Official Protocol Title:	A Phase 1/Phase 2 Study to Evaluate the Safety and Tolerability of MK-1088 as Monotherapy and in Combination with Pembrolizumab in Participants with Advanced Solid Tumors
NCT number:	NCT05394350
Document Date:	29-Jun-2022

Title Page

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Protocol Title: A Phase 1/Phase 2 Study to Evaluate the Safety and Tolerability of MK-1088 as Monotherapy and in Combination with Pembrolizumab in Participants with Advanced Solid Tumors

Protocol Number: 002-01

Compound Number: MK-1088

Sponsor Name:

Merck Sharp & Dohme LLC
(hereafter called the Sponsor or MSD)

Legal Registered Address:

126 East Lincoln Avenue

P.O. Box 2000

Rahway, NJ 07065 USA

Regulatory Agency Identifying Number(s):

IND	160204
EudraCT	2021-006712-93

Approval Date: 29 June 2022

Sponsor Signatory

Typed Name: Title:	Date

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

Investigator Signatory

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

Typed Name: Title:	Date

DOCUMENT HISTORY

Document	Date of Issue	Overall Rationale
Amendment 01	29-JUN-2022	Address agency comments
Original Protocol	15-DEC-2021	Not applicable

PROTOCOL AMENDMENT SUMMARY OF CHANGES

Amendment: 01

Overall Rationale for the Amendments:

The rationale for this amendment is to address agency feedback.

Summary of Changes Table:

Section # and Name	Description of Change	Brief Rationale
1.3.1.1 Part 1, Arms 1 and 2, and Arm 1 Crossover to Arm 2: Screening Through End-of-Treatment Phase	Table 1: Modified the Scheduling Window for some of the scheduled visits	Updated for clarity
	Provides clarity in the Notes and in footnotes for Cycle 1 and Cycle 2 evaluation collection in relation to intervention administration	Updated for clarity
5.1.1 Inclusion Criteria for Arm 1 and Arm 2	Inclusion Criterion number 8: Table 4: Adjusted renal evaluations and related laboratory values	Update addresses agency feedback
5.2.1 Exclusion Criteria for Arm 1 and Arm 2	Exclusion Criterion number 16: Provides specific details regarding clinically significant cardiovascular disease	Update addresses agency feedback
	EC number 17: Provides new criteria: QTcF	Update addresses agency feedback
	EC number 18: Provides new criteria: stem cell or organ transplant	Provides clarity for eligibility

Section # and Name	Description of Change	Brief Rationale
	EC number 23: Deleted text due to conflicting language	Provides clarity for eligibility
	EC number 24: Revised text to reduce redundancy	Provides clarity for eligibility
	EC number 26: Revised text to clarify conflicting language	Provides clarity for eligibility
	EC number 28: Provides new criterion: recovery from surgery or ongoing complications	Provides clarity for eligibility
5.3.1 Meals and Dietary Restrictions	Update provides guidance for fasting requirements.	Update addresses agency feedback
5.3.3 Activity Restrictions	Update aligns with the IB content.	Update aligns with information provided in the most current MK-1088 IB
4.1 Overall Design	Updated language to indicate 'adjusted' mTPI	Update addresses agency feedback
4.3.1.2 Rationale for Dose Interval and Escalation Increments	Updated language to indicate 'adjusted' mTPI	Update addresses agency feedback
4.3.1.3 Dose Finding Using a Modified Toxicity Probability Interval Design	Updated language in text and also Table 3 (Dose-finding Rules per Adjusted mTPI Design) to show the change in some actions/rules for given DLTs and AEs	Update addresses agency feedback

Section # and Name	Description of Change	Brief Rationale
6.3.1 Intervention Assignment	Updated language to indicate 'adjusted' mTPI	Update addresses agency feedback
6.5 Concomitant Therapy	Table 6: Removed reference to CYP2C8	CYP2C8 substrates are permitted, not prohibited, as concomitant therapy
6.6.3 Cohort Expansion	Updated language to indicate 'adjusted' mTPI	Update addresses agency feedback
9.1 Statistical Analysis Plan Summary	Updated language to indicate 'adjusted' mTPI	Update addresses agency feedback
10.2 Appendix 2: Clinical Laboratory Tests	Updated to state laboratory evaluations are performed locally, not centrally.	Provides correct language
	Table 12: Updated footnotes for lab evaluation collection and analysis	Provides clarity
Title Page	Updated the corporate name address	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.
10.1.1 Code of Conduct for Clinical Trials	Updated the corporate name and address	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.

Section # and Name	Description of Change	Brief Rationale
8.4 Adverse Events, Serious Adverse Events, and Other Reportable Safety Events	Update instructs the investigators to document if an SAE was associated with a medication error, misuse, or abuse	Per REGULATION (EU) No 536/2014 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL
10.3.1 Definitions of Medication Error, Misuse, and Abuse	This is a new section that provides definitions for medication error, misuse, and abuse	Per REGULATION (EU) No 536/2014 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL

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1 PROTOCOL SUMMARY

1.1 Synopsis

Protocol Title: A Phase 1/Phase 2 Study to Evaluate the Safety and Tolerability of MK-1088 as Monotherapy and in Combination with Pembrolizumab in Participants with Advanced Solid Tumors

Short Title: Phase 1/Phase 2 Study of MK-1088 as Monotherapy and in Combination with Pembrolizumab in Participants with Solid Tumors

Acronym:

Hypotheses, Objectives, and Endpoints:

In male and female participants with advanced/metastatic solid tumors:

Objectives	Endpoints
Primary	
• To determine the safety and tolerability and to establish a preliminary maximum tolerated dose/recommended Phase 2 dose of MK-1088 administered as monotherapy and in combination with pembrolizumab infusion in Part 1	• Dose-limiting toxicity (DLT) • Adverse events (AE) • Discontinuing study intervention due to an AE
Secondary	
• To evaluate the PK of MK-1088 administered as monotherapy and in combination with pembrolizumab infusion in Part 1 and in Part 2	• PK parameters including AUC and C_{max}
• To evaluate the antitumor activity (objective response rate [ORR] based on PCWG-modified RECIST 1.1 [prostate cancer participants only] or RECIST 1.1 [all other participants]) of MK-1088 as assessed by the investigator when used as monotherapy and in combination with pembrolizumab in Part 1 and in Part 2	• Objective response (OR) is a complete response (CR) or partial response (PR)

Overall Design:

Study Phase	Phase 1/Phase 2
Primary Purpose	Treatment
Indication	Treatment of advanced/metastatic solid tumors
Population	Participants with advanced/metastatic solid tumors
Study Type	Interventional
Intervention Model	Parallel This is a multi-site study.
Type of Control	No treatment control
Study Blinding	Unblinded Open-label
Blinding Roles	No Blinding
Estimated Duration of Study	The Sponsor estimates that the study will require approximately 3 years from the time the first participant (or their legally acceptable representative) provides documented informed consent until the last participant's last study-related contact.

Number of Participants:

Approximately 80 participants will be allocated for participation in Part 1 of this study.

Intervention Groups and Duration:

Intervention Groups

Intervention Group Name	Drug	Dose Strength	Dose Frequency	Route of Administration	Regimen/ Treatment Period/ Vaccination Regimen	Use
Part 1: Arm 1 and Arm 2	MK-1088	50 mg, 100 mg,	QD	Oral	Day 1 to Day 21 of each treatment cycle for up to 35 cycles	Experimental
Part 1: Arm 2 **Part 2:** (to be specified)	Pembrolizumab (MK-3475)	100 mg per vial	Q3W	Intravenous	Day 1 of each treatment cycle for up to 35 cycles	Experimental
Part 2: (to be specified)	MK-1088	50 mg, 100 mg	This will be based on the RP2D from Part 1	Oral	Day 1 to Day 21 of each treatment cycle for up to 35 cycles	Experimental

Total Number of Intervention Groups/ Arms

Total number of Intervention Groups: 2

Duration of Participation

Each participant will participate in the study for up to approximately 28 months from the time the participant provides documented informed consent through the final contact. After a screening phase of up to 28 days, each participant will receive assigned intervention for up to 24 months. After the end of treatment, each participant will be followed for a minimum of 30 days.

During Part 1 (Dose Escalation and Confirmation), participants will receive treatment with MK-1088 as monotherapy (Arm 1) or as combination therapy with pembrolizumab (Arm 2). Study treatment will begin on Day 1 of each 21-day cycle. Participants enrolled in Arm 1 and in Arm 2 may continue treatment for up to 35 cycles (approximately 2 years) from the start of treatment.

Participants in Arm 1 who experience disease progression by either clinical or radiographic evaluation, may cross over into Arm 2, provided they meet eligibility criteria. Participants who cross over to combination treatment will be eligible to receive a maximum of 35 cycles of combination treatment irrespective of the number of cycles of MK-1088 received in monotherapy."

	After the end of treatment, each participant will be followed for the occurrence of AEs and spontaneously reported pregnancy. All participants, except for those who withdraw consent or are lost to follow-up, will be followed up for survival. Participants who experience confirmed disease progression or start a new anticancer therapy, will move into the Survival Follow-up Phase and should be contacted every 12 weeks to assess for survival status until death, withdrawal of consent, or the end of the study, whichever occurs first.

Study Governance Committees:

Executive Oversight Committee	No
Data Monitoring Committee	No
Clinical Adjudication Committee	No

There are no governance committees for this study.

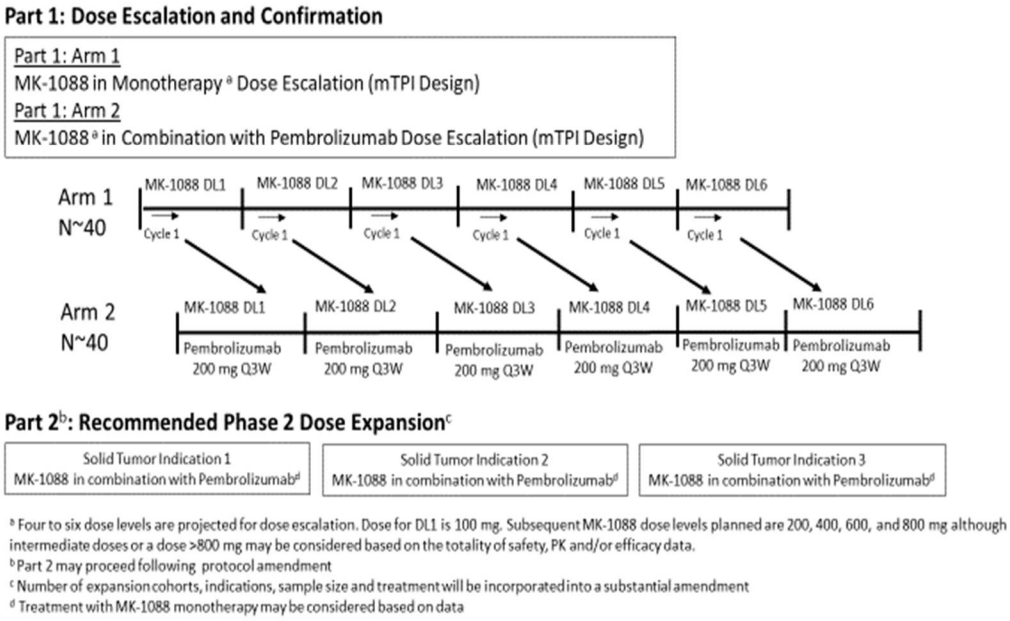
Study Accepts Healthy Volunteers: No

Abbreviations are not spelled out at first use. A list of abbreviations used in this document is in Appendix 8. Note that “subject” or “participant” may be used to refer to individuals enrolled in clinical trials.

1.2 Schema

The study design is depicted in Figure 1.

Figure 1 Part 1 Study Design: Dose Escalation and Confirmation of MK-1088 as a Single Agent (Arm 1) and in Combination with Pembrolizumab (Arm 2); Part 2: Dose Expansion in 3 Selected Solid Tumor Cohorts



Abbreviations: DL = dose level; mTPI = modified Toxicity Probability Interval; N = participant population size; PK = pharmacokinetic; Q3W = every 3 weeks;

1.3 Schedule of Activities

1.3.1 Schedule of Activities for Part 1: Dose Escalation and Confirmation for Arm 1 (MK-1088 Monotherapy) and Arm 2 (MK-1088 in Combination With Pembrolizumab), and for Arm 1 Crossover to Arm 2

1.3.1.1 Part 1, Arms 1 and 2, and Arm 1 Crossover to Arm 2: Screening Through End-of-Treatment Phase

Table 1 Schedule of Activities: Screening through End-of-Treatment Phase for Part 1, Arm 1 and Arm 2, and Arm 1 Crossover to Arm 2

Study Phase	**Screening Phase** [a]	**Treatment Phase (3-Week Cycles)**												**End of Treatment /Discon-tinuation**	**Notes**
Treatment Cycle/Title:	Screening (Visit 1)	Cycle 1				Cycle 2				Cycle 3			Cycles 4 to 35		
Treatment Days per Cycle:	Up to 28 days before Day 1 Cycle 1	Day 1[b]	Day 2[c]	Day 8	Day 15	Day 1	Day 2[c]	Day 8	Day 15	Day 1	Day 8	Day 15	Day 1	At time of treatment discon-tinuation	Treatment Phase: Procedures, assessments, and samples are collected **predose unless otherwise specified**.
Scheduling Window (Days)	-28 to -1	0	0	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	+3	
Administrative Procedures															
Informed Consent	X														Documented IC must be obtained before performing protocol-specific procedures. Participants may elect to continue study treatment beyond disease progression and will require additional consent.
Informed Consent for Optional Future Biomedical Research	X														This is optional for the participant.
Inclusion/Exclusion Criteria	X														
Participant Identification Card	X	X													Update with the treatment number at the time of treatment allocation.
Demography and Medical History	X														

Study Phase	**Screening Phase** [a]	**Treatment Phase (3-Week Cycles)**												**End of Treatment /Discon-tinuation**	**Notes**
Treatment Cycle/Title:	Screening (Visit 1)	Cycle 1				Cycle 2				Cycle 3			Cycles 4 to 35		
Treatment Days per Cycle:	Up to 28 days before Day 1 Cycle 1	Day 1[b]	Day 2[c]	Day 8	Day 15	Day 1	Day 2[c]	Day 8	Day 15	Day 1	Day 8	Day 15	Day 1	At time of treatment discon-tinuation	Treatment Phase: Procedures, assessments, and samples are collected **predose unless otherwise specified**.
Scheduling Window (Days)	-28 to -1	0	0	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	+3	
Prior/Concomitant Medication Review	X	X		X	X	X		X	X	X	X	X	X	X	
Treatment Allocation		X													Treatment allocation may occur up to 3 days before C1D1.
Part 1 Arm 1 and Arm 2: MK-1088 Administration/Dispense		X				X				X			X		MK-1088: taken orally QD from D1 through D21 of each treatment cycle.
Part 1 Arm 2: Pembrolizumab Administration		X				X				X			X		Pembrolizumab: administered IV Q3W on D1 of each treatment cycle.
Anticancer Therapy Status														X	Any changes in new treatment will be collected.
Disease Status														X	
Clinical Procedures/Assessments															
Full Physical Examination	X													X	
Directed Physical Examination		X		X	X	X				X			X		
Height	X														
Weight	X	X				X				X				X	
Vital Signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	Obtain heart rate, respiratory rate, blood pressure, temperature.
12-lead Electrocardiogram	X	X	X			X	X								**C1D1 and C2D1:** Obtain predose and 2 hrs postdose. **C1D2 and C2D2:** Obtain predose.

Study Phase	**Screening Phase** [a]	**Treatment Phase (3-Week Cycles)**												**End of Treatment /Discon-tinuation**	**Notes**
Treatment Cycle/Title:	Screening (Visit 1)	Cycle 1				Cycle 2				Cycle 3			Cycles 4 to 35		
Treatment Days per Cycle:	Up to 28 days before Day 1 Cycle 1	Day 1[b]	Day 2[c]	Day 8	Day 15	Day 1	Day 2[c]	Day 8	Day 15	Day 1	Day 8	Day 15	Day 1	At time of treatment discon-tinuation	Treatment Phase: Procedures, assessments, and samples are collected **predose unless otherwise specified**.
Scheduling Window (Days)	-28 to -1	0	0	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	+3	
ECOG Performance Status	X	X				X				X			X	X	Obtain within 72 hrs before the first dose of study intervention on D1 of each cycle.
AE Monitoring	X	←	—	—	—	—	—	—	—	—	—	—	→	X	
Tumor Imaging Response Assessment (PCWG-modified RECIST 1.1 for prostate cancer participants; RECIST 1.1 for all other participants)	X	←	- -	- -	- -	- -	- -	- -	- -	- -	- -	- -	→	X	Treatment phase schedule: • Obtain every 9 weeks (±7 days) • After 54 weeks, obtain every 12 weeks (±7 days)
Prostate cancer participants only: Bone Scan	X	←	- -	- -	- -	- -	- -	- -	- -	- -	- -	- -	→	X	Tc99 bone scintigraphy (nuclear medicine bone scan) is required at screening and on-study at all protocol-required tumor assessment visits and when clinically indicated. Tumor assessments visits: • Obtain every 9 weeks (±7 days) • After 54 weeks, obtain every 12 weeks (±7 days)

Study Phase	**Screening Phase** [a]	**Treatment Phase (3-Week Cycles)**												**End of Treatment /Discon-tinuation**	**Notes**
Treatment Cycle/Title:	Screening (Visit 1)	Cycle 1				Cycle 2				Cycle 3			Cycles 4 to 35		
Treatment Days per Cycle:	Up to 28 days before Day 1 Cycle 1	Day 1[b]	Day 2[c]	Day 8	Day 15	Day 1	Day 2[c]	Day 8	Day 15	Day 1	Day 8	Day 15	Day 1	At time of treatment discon-tinuation	Treatment Phase: Procedures, assessments, and samples are collected **predose unless otherwise specified**.
Scheduling Window (Days)	-28 to -1	0	0	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	+3	
Non-prostate cancer participants: Bone Scan	X	◄----------											----------►	X	Examples of acceptable scans: nuclear medicine bone scan, PET scan, PET-CT, etc. Obtain at screening for participants with history of bone metastases or if bone metastases are suspected. Obtain when clinically indicated or to confirm CR when bone metastases were present at screening.
CT/MRI chest, abdomen, pelvis	X	◄----------											----------►	X	Obtain at screening for all participants, at protocol-required tumor assessment visits, and when clinically indicated. Tumor assessment visits: • Every 9 weeks (±7 days) • After 54 weeks, obtain every 12 weeks (±7 days)
Brain Scan	X	◄----------											----------►	X	Required at screening for participants with known history of brain metastases or if brain metastases are suspected. On study, obtain when clinically indicated or to confirm CR when brain metastases were present at screening.

Study Phase	**Screening Phase** [a]	**Treatment Phase (3-Week Cycles)**												**End of Treatment /Discon-tinuation**	**Notes**
Treatment Cycle/Title:	Screening (Visit 1)	Cycle 1				Cycle 2				Cycle 3			Cycles 4 to 35		
Treatment Days per Cycle:	Up to 28 days before Day 1 Cycle 1	Day 1[b]	Day 2[c]	Day 8	Day 15	Day 1	Day 2[c]	Day 8	Day 15	Day 1	Day 8	Day 15	Day 1	At time of treatment discon-tinuation	Treatment Phase: Procedures, assessments, and samples are collected **predose unless otherwise specified**.
Scheduling Window (Days)	-28 to -1	0	0	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	+3	
Vital Status		◄----------											----------►	X	Participants may be contacted for survival information at any time during the study, on Sponsor request.
Laboratory Procedures / Assessments															
Comprehensive Chemistry Panel	X	X		X	X	X		X	X	X		X	X	X	
Hematology	X	X		X	X	X		X	X	X		X	X	X	
Urinalysis	X														Microscopic analysis is required if dipstick results are abnormal.
HIV, hepatitis B and C screen (per site SOP)	X														Screening requirements are based on history and local regulations. Refer to Sections 5.1 and 5.2.
PT/INR and aPTT or PTT	X														Perform at screening, then as clinically indicated.
Thyroid Function Tests (TSH, T3 or free T3, free T4)	X	X				X							X	X	After C2D1: testing will be performed D1 of every other cycle (ie, C4, C6, C8, etc.)
Prostate cancer participants only: PSA	X	X				X				X			X	X	

Study Phase	**Screening Phase** [a]	**Treatment Phase (3-Week Cycles)**												**End of Treatment /Discon-tinuation**	**Notes**
Treatment Cycle/Title:	Screening (Visit 1)	Cycle 1				Cycle 2				Cycle 3			Cycles 4 to 35		
Treatment Days per Cycle:	Up to 28 days before Day 1 Cycle 1	Day 1[b]	Day 2[c]	Day 8	Day 15	Day 1	Day 2[c]	Day 8	Day 15	Day 1	Day 8	Day 15	Day 1	At time of treatment discon-tinuation	Treatment Phase: Procedures, assessments, and samples are collected **predose unless otherwise specified**.
Scheduling Window (Days)	-28 to -1	0	0	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	+3	
Pregnancy test for WOCBP only: urine or serum β-hCG	X	X				X				X			X		Perform a highly sensitive pregnancy test (urine or serum per local guidelines) within 24 hrs before C1D1. If screening collection is conducted within this timeframe, no need to repeat for C1D1. Pregnancy test should be performed before each treatment cycle (24 hrs for urine and 72 hrs for serum test). Obtain urine pregnancy test as indicated; if test is positive or cannot be confirmed as negative, a serum pregnancy test is required. Additional pregnancy testing may be conducted if required by local regulations or if clinically indicated.
Pharmacokinetics / Pharmacodynamics / Future Biomedical Research / Biomarkers															
Blood for Genetic Analysis		X													Predose: See Section 8.8.

Study Phase	**Screening Phase** [a]	**Treatment Phase (3-Week Cycles)**												**End of Treatment /Discon-tinuation**	**Notes**
Treatment Cycle/Title:	Screening (Visit 1)	Cycle 1				Cycle 2				Cycle 3			Cycles 4 to 35		
Treatment Days per Cycle:	Up to 28 days before Day 1 Cycle 1	Day 1[b]	Day 2[c]	Day 8	Day 15	Day 1	Day 2[c]	Day 8	Day 15	Day 1	Day 8	Day 15	Day 1	At time of treatment discon-tinuation	Treatment Phase: Procedures, assessments, and samples are collected **predose unless otherwise specified**.
Scheduling Window (Days)	-28 to -1	0	0	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	+3	
Plasma for MK-1088 PK assay		X	X			X	X			X			X	X	On the day(s) of sample collection, participants must not take study medication until the predose PK and biomarker (Section 8.8) sample collections are complete. Document the time of the last MK-1088 dose (ie, at home) taken before PK collection. **C1D1 and C2D1:** Obtain predose and 1, 2, 4, and 8 hrs postdose. **C1D2 and C2D2:** Obtain predose (24 hrs after D1 dosing for C1 and C2) **C3, C4 and every 4 cycles** (ie, C4, C8, etc): Obtain predose
Blood for Serum Biomarker Analysis		X				X				X					Obtain predose
Blood for RNA Analyses		X				X				X					Obtain predose
Tumor Tissue Collection															
Archival or Newly Obtained Tumor Tissue Collection	X														See detailed tissue collection requirements in the Procedure/Lab Manual. Participants in Arm 1 who cross over to Arm 2 do not need to provide an additional sample.

AE=adverse event; aPTT= activated partial thromboplastin time; β-hCG=beta-human chorionic gonadotropin; C=Cycle; CR=complete response; CT=computed tomography; D=Day; ECOG=Eastern Cooperative Oncology Group; HIV= human immunodeficiency virus; MRI=magnetic resonance imaging; PCWG=Prostate Cancer Working Group; PET= positron emission tomography; PK=pharmacokinetic; PSA=prostate-specific antigen; PT/INR=prothrombin time/international normalized ratio; PTT= partial thromboplastin time; Q3W=every 3 weeks; QD=once daily; RECIST=Response Evaluation Criteria In Solid Tumors; RNA=ribonucleic acid; SOP=standard operating procedure; TSH=thyroid-stimulating hormone; WOCBP=women of childbearing potential.

[a] Arm 1 crossover to Arm 2: Screening assessments obtained during Arm 1 may be eligible for crossover screening for Arm 2 if the assessments were obtained within 28 days before Arm 2 treatment initiation.

[b] Laboratory tests should be performed within 3 days before the first dose of study intervention. An exception is hepatitis and thyroid serologies, which may be performed within 28 days before the first dose. Please refer to Section 8.3.4.1 for details.

[c] C1D2 and C2D2 evaluations must be obtained withjn 24 hours after study intervention administration for C1D1 and C2D1.

1.3.1.2 Part 1, Arms 1 and 2, and Arm 1 Crossover to Arm 2: Posttreatment Phase

Table 2 Schedule of Activities: Posttreatment Phase for Part 1, Arm 1 and Arm 2, and Arm 1 Crossover to Arm 2

Study Phase:	**Posttreatment**				**Notes**
Title:	Safety Follow-up		Imaging Follow-up	Survival Follow-up	
Timing/frequency for Follow-up:	30 days after the last dose of study medication	Arm 2 only: 90 days after the last dose of pembrolizumab	Every 12 weeks	Every 12 weeks	
Scheduling Window (Days):	±7	±7	±7	±7	
Administrative Procedures					
Concomitant Medication Review	X	X			Arm 2: 90-day follow-up can be performed with a telephone call.
Anticancer Therapy Status	X			X	Any changes in new treatment will be collected.
Disease Status	X		X	X	See Sections 8.11.4.2 and 8.11.4.3.
Clinical Procedures / Assessments					
Full Physical Examination	X				
Vital Signs	X				Obtain heart rate, respiratory rate, blood pressure, temperature.
ECOG Performance Status	X				
AE Reporting	←----------------------------→				Arm 2: 90-day follow-up can be performed with a telephone call.
Vital Status	←--------------------------------------→				On 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 vital status.
Tumor Imaging Response Assessment			X		PCWG-modified RECIST 1.1 for prostate cancer participants; RECIST 1.1 for all other participants. Use the same type of scans obtained during treatment phase.
Laboratory Procedures / Assessments					
Comprehensive Chemistry Panel	X				
Hematology	X				
Thyroid Function Tests (TSH, T3 or free T3, free T4)	X				
Pharmacokinetics					
Plasma for MK-1088 PK	X				

AE=adverse event; ECOG=Eastern Cooperative Oncology Group; PCWG=Prostate Cancer Working Group; PK=pharmacokinetic; RECIST= Response Evaluation Criteria In Solid Tumors; TSH=thyroid-stimulating hormone.

2 INTRODUCTION

MK-1088 is a novel small molecule that is a dual antagonist of the adenosine A_{2A} and A_{2B} receptors. MK-1088 is under study for the treatment of solid tumors as monotherapy and as combination therapy with pembrolizumab. This is a dose-escalation and dose-finding study to assess the safety and tolerability of MK-1088, both as monotherapy and as combination therapy with pembrolizumab. The FIH single ascending dose study of MK-1088 in healthy volunteers (PN001) completed study enrollment on 01-JUN-2021. Refer to the MK-1088 IB for further information.

2.1 Study Rationale

Immunotherapy has dramatically improved treatment rates of some cancers. However, tumors have several mechanisms to limit an immune response and escape immunosurveillance. An immune suppressive TME contributes to the lack of response or resistance to T-cell immune checkpoint inhibitors such as pembrolizumab and ipilimumab [Chen DS, Mellman I. 2013]. Along with indoleamine 2,3-dioxygenase, arginase, and transforming growth factor-beta, adenosine and its receptors represent a key pathway contributing to an immune suppressive environment in tumors and allow tumors to escape from immune responses [Smyth, M. J., et al 2016] [Leone, R. D., et al 2015] [Hatfield, S. M. 2016]. Therefore, an adenosine rich TME represents a major barrier for effective tumor immunotherapy and needs to be overcome to achieve more effective and broader clinical efficacy.

MK-1088 is a potent small molecule antagonist of the A_{2A} and A_{2B} receptors. Dual A_{2A}R and A_{2B}R antagonists may improve the immune status in the TME by both removing the suppression of T-cell effector functions via A_{2A}R and blocking the inhibitory effects of myeloid cells via A_{2B}R [Iannone, R., et al 2013] [Sorrentino, C., et al 2016] [Sitkovsky, M. V. 2020]. Internal preclinical data show that MK-1088 administration led to significant antitumor efficacy as a single agent in the mouse syngeneic CT26 tumor model. Furthermore, in the mouse syngeneic CM3 tumor model (Cloudman S-91 melanoma), treatment with MK-1088 in combination with anti-PD-1 muDX400 monoclonal antibody led to significant antitumor efficacy compared with treatment with MK-1088 alone, supporting the scientific rationale for this study.

This is the first trial of MK-1088 in oncology patients, preceded by a FIH single ascending dose study of MK-1088 in healthy volunteers. The study will evaluate the safety, tolerability, PK, and pharmacodynamics of escalating doses of MK-1088 in monotherapy and in combination with pembrolizumab in participants with advanced solid tumors who have not responded to conventional therapy. The effect of MK-1088 on tumor size will also be explored.

Clinical proof-of-concept for adenosine receptor antagonism is emerging. There has been some early signal of efficacy both in monotherapy and in combination with anti-PD-L1 specifically in mCRPC [Lim, E. A., et al 2020] [Buisseret, L., et al 2020]. These data support the potential for meaningful clinical activity in the mCRPC population by targeting adenosine signaling inhibition. Other disease indications with some early signal of efficacy

both in monotherapy and in combination with anti-PD-1/anti-PD-L1 include NSCLC [Chiappori, A., et al 2018] [Chiappori, A. 2018] and mCRC [Cecchini, M., et al 2020], among others. Additional clinical data supporting the role of the adenosine pathway in cancer therapy were recently presented. CD73 is involved in the generation of adenosine from adenosine diphosphate. Data with an anti-CD73 monoclonal antibody in combination with an anti-PD-L1 agent have shown promising efficacy in the treatment of Stage III NSCLC following chemoradiation over anti-PD-L1 agents alone [Martinez-Marti, A., et al 2021].

2.2 Background

Refer to the IB/approved labeling for detailed background information on MK-1088, and the MK-3475 IB for detailed background information on pembrolizumab.

2.2.1 Pharmaceutical and Therapeutic Background

2.2.1.1 MK-1088 Pharmaceutical and Therapeutic Background

MK-1088 is a novel small molecule antagonist of the A_{2A} and A_{2B} receptors. Based on in vitro data, MK-1088 has potent binding affinity for human A_{2A} and A_{2B} receptors and lower affinity for human A_1 and A_3 receptors. MK-1088 has an acceptable preclinical safety profile and is in clinical development as an oral immunotherapy for advanced solid tumors. This small molecule is being developed as a cancer immunotherapeutic with the potential to be used as monotherapy or to be combined with KEYTRUDA® (pembrolizumab; a humanized anti-PD-1 receptor antibody), to increase antitumor efficacy in participants with various tumor indications.

A_{2A} is expressed on T cells whereas A_{2A} and A_{2B} are expressed on myeloid cells, and thus development of a dual antagonist represents a single agent to target different cell types in the TME. Agonism of A_{2A} directly suppresses T-cell proliferation and cytokine production, and agonism of A_{2B} activates myeloid cells to produce immunosuppressive factors that secondarily inhibit T-cell function. Adenosine levels in the TME can be orders of magnitude higher than in normal tissues (reported to be 10 – 100 µM vs 10 – 100 nM). These concentrations are far above the Kd of adenosine for A_{2A} and at times above its Kd for A_{2B} as well (reported to be 300 nM and 15 µM, respectively). An A_{2A}/A_{2B} dual antagonist would provide coverage under high adenosine levels in the TME at baseline or during anti-PD-1 treatment or any other therapy that induces tumor cell death. That A_{2B} is expressed on myeloid cells suggests that benefit would be seen in tumors with high myeloid infiltrate or in combination with treatments that induce myeloid infiltration.

Significant antitumor efficacy, shown by tumor growth inhibition with MK-1088 as a single agent, was observed in the CT26 mouse syngeneic tumor model, which is known to express moderate levels of A_{2A}R by RNA sequencing. These data provide the rationale to pursue MK-1088 as monotherapy. In addition to the CT26 model, the antitumor activity of the A_{2A}/A_{2B} dual antagonist MK-1088 was tested as a single agent and in combination with the murinized anti-PD-1 antibody, muDX400 in the CM3, Renca, and MCA205 mouse syngeneic tumor models.

Adenosine promotes immunosuppression in the TME via its effects on both innate and adaptive immune cells as outlined above. Therefore, relief of this adenosine-mediated immunosuppression may potentiate T-cell activation and improve efficacy of T-cell targeted therapies such as pembrolizumab, even in tumors that do not normally respond to PD-1 antagonist alone. This would suggest that removal of immune suppression induced by MK-1088 combined with the T-cell checkpoint inhibitor, pembrolizumab, can offer substantially augmented antitumor efficacy than either treatment alone. This scientific rationale provides justification to pursue MK-1088 and pembrolizumab as combination therapy.

2.2.1.2 Pembrolizumab (MK-3475) Pharmaceutical and Therapeutic Background

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

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

The structure of murine PD-1 has been resolved [Zhang, X., et al 2004]. PD-1 and its family members are type I transmembrane glycoproteins containing an IgV–type domain responsible for ligand binding and a cytoplasmic tail responsible for the binding of signaling molecules. The cytoplasmic tail of PD-1 contains 2 tyrosine-based signaling motifs, an immunoreceptor tyrosine-based inhibition motif, and an immunoreceptor tyrosine-based switch motif. 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 CD3ζ, PKCθ, and ZAP70, which are involved in the CD3 T-cell signaling cascade [Okazaki, T., et al 2001] [Chemnitz, J. M., et al 2004] [Sheppard, K-A, et al 2004], [Riley, J. L. 2009]. The mechanism by which PD-1 down-modulates T-cell responses is similar to, but distinct from, that of CTLA-4, because both molecules regulate an overlapping set of signaling proteins [Parry, R. V., et al 2005] [Francisco, L. M., et al 2010]. As a consequence, the PD-1/PD-L1 pathway is an attractive target for therapeutic intervention in advanced/metastatic solid tumors.

2.2.2 Preclinical and Clinical Studies

Please refer to the MK-1088 IB for a description of preclinical evaluations of MK-1088. Please refer to the current pembrolizumab IB/approved labeling for a description of preclinical and clinical evaluations of pembrolizumab.

2.2.3 Ongoing Clinical Studies

Please refer to the current pembrolizumab IB/approved labeling for a description of ongoing clinical evaluations of pembrolizumab.

2.2.3.1 MK-1088 Clinical Studies

The FIH study for MK-1088 was PN001, a single ascending dose study in healthy volunteers to assess the safety, tolerability, and PK of MK-1088. This study completed enrollment and achieved LPLV on 01-JUN-2021. The FIH study in healthy volunteers afforded the advantage of rapid dose escalation into the therapeutic dose range in the subsequent Phase 1/Phase 2 study in oncology patients while also offering more comprehensive and reliable measurement of MK-1088 plasma exposures to thoroughly characterize the PK of MK-1088. Single doses of 1, 3, 10, 25, 50, 100, 150, and 224 mg of MK-1088 were evaluated in PN001. Doses up to 224 mg were generally well tolerated, with no major AEs and SAEs observed at the dose range of 1 to 224 mg. Increases in blood pressure of up to 14 mm Hg along with increases in heart rate of up to approximately 2 to 13 bpm were observed over the dose range of 10 to 224 mg. One participant at the highest dose of 224 mg had a greater systolic blood pressure/heart rate response than others (3× mean) and diastolic blood pressure increase similar to mean but did not report any associated symptoms.

Plasma exposures in PN001 were generally dose proportional at the 1 to 224 mg dose range, with observed median T_{max} of 2 hours and apparent terminal $t_{1/2}$ between 6 to 11 hours. The minimum C_{trough} concentration target of 0.3 µM corresponding to >99% TE for A_{2A} and >80% for A_{2B} was successfully achieved at a single dose of 150 mg while the aspirational trough target of 1 µM corresponding to >99% for A_{2A} and >90% for A_{2B} was attained at both the 12- and 24-hour time points at a dose of 224 mg of MK-1088, enabling QD dosing of MK-1088 in Phase 1b. Furthermore, no food effect was observed at the 50 mg dose. Data from this FIH study were applied to inform the starting dose and dose levels for PN002 based on overall safety, tolerability profile, and PK of MK-1088 from PN001.

Please refer to the IB for further details.

2.2.3.2 Pembrolizumab (MK-3475) Clinical Studies [redacted]

Ongoing clinical studies with pembrolizumab are being conducted in multiple solid tumors. In addition, multiple combinations with pembrolizumab are also being investigated. Refer to pembrolizumab IB for study details.

2.3 Benefit/Risk Assessment

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

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

3 HYPOTHESES, OBJECTIVES, AND ENDPOINTS

In male and female participants with advanced/metastatic solid tumors:

Objectives	Endpoints
Primary	
• To determine the safety and tolerability and to establish a preliminary maximum tolerated dose/recommended Phase 2 dose of MK-1088 administered as monotherapy and in combination with pembrolizumab infusion in Part 1	• Dose-limiting toxicity (DLT) • Adverse events (AE) • Discontinuing study intervention due to an AE
Secondary	
• To evaluate the PK of MK-1088 administered as monotherapy and in combination with pembrolizumab infusion in Part 1 and in Part 2	• PK parameters including AUC and C_{max}
• To evaluate the antitumor activity (objective response rate [ORR] based on PCWG-modified RECIST 1.1 [prostate cancer participants only] or RECIST 1.1 [all other participants]) of MK-1088 as assessed by the investigator when used as monotherapy and in combination with pembrolizumab in Part 1 and in Part 2	• Objective response (OR) is a complete response (CR) or partial response (PR)

Objectives	Endpoints
Tertiary/Exploratory	
• To evaluate progression-free survival (PFS) and overall survival (OS) of participants treated with MK-1088 both as monotherapy and in combination with pembrolizumab. In solid tumors, assessment will be based on RECIST 1.1 as assessed by the investigator. Metastatic prostate cancer response assessments will also use PCWG criteria.	• PFS: the time from treatment allocation to the first documented disease progression or death due to any cause, whichever is first • OS: The time from treatment allocation to death due to any cause
• To evaluate the duration of response (DOR) per RECIST 1.1 as assessed by the investigator	• DOR is defined as the time from the first documented evidence of CR or PR until progressive disease (PD) or death due to any cause, whichever occurs first, in participants demonstrating PR or CR
• To identify molecular (genomic, metabolic and/or proteomic) biomarkers that may be indicative of clinical response/resistance, safety, pharmacodynamic activity, and/or the mechanism of action of MK-1088 as monotherapy and in combination with pembrolizumab	• Molecular (genomic, metabolic and/or proteomic) determinants of response or resistance to treatments, using blood and/or tumor tissue

4 STUDY DESIGN

4.1 Overall Design

This is a multicenter, global, open-label, nonrandomized Phase 1/Phase 2 study of MK-1088 in monotherapy and in combination with pembrolizumab in participants with a histologically or cytologically confirmed diagnosis of advanced solid tumor who have received, been intolerant to, or have been ineligible for treatment known to confer clinical benefit.

This study will evaluate the safety, tolerability, and preliminary efficacy of MK-1088 monotherapy administration (Arm 1), and in combination with pembrolizumab (Arm 2). There are 2 parts in this study, dose escalation and confirmation (Part 1) (Section 6.6.2) and cohort expansion (Part 2) (Section 6.6.3).

Participants will receive MK-1088 in monotherapy (Arm 1) or in combination with pembrolizumab (Arm 2). In Arm 1 and Arm 2, MK-1088 will be administered po QD every

day of a 21-day cycle. In Arm 2, pembrolizumab will be administered IV Q3W, on Day 1 of each cycle.

In Part 1 of the study, an adjusted mTPI design [Ji, Y. 2013] will be used to identify and confirm the RP2D of MK-1088 in Arm 1 (MK-1088 as a single agent), and in Arm 2 (MK-1088 in combination with pembrolizumab). Four to 6 dose levels of MK-1088 are planned to be evaluated independently in each arm, in the dose range of 100 to 800 mg QD. Intermediate and/or higher doses of MK-1088 than those indicated may be explored depending on the totality of the data, including safety and PK, available at each dose level. BID dosing may also be explored based on tolerability and/or PK data. If applicable, BID dosing will be implemented in treatment arms introduced in an amendment. The dose of pembrolizumab in Arm 2 will remain constant at 200 mg Q3W.

Participants will be allocated centrally through IVRS. Arm 1 monotherapy slots will be filled first to generate monotherapy safety data before enrolling participants at that dose in Arm 2. After Arm 2 combination therapy has opened, slots in Arm 1 at a higher MK-1088 dose than Arm 2, if available, will be allocated first before Arm 2 slots are assigned. If both arms are open at the same dose of MK-1088, then allocation to Arm 1 or Arm 2 will be alternated.

Participants will be initially enrolled to receive MK-1088 in monotherapy (Arm 1). Enrollment in Arm 1 (MK-1088 in monotherapy) at DL2 will begin once all participants complete Cycle 1 at DL1 of Arm 1 and a dose-escalation decision has been made. Enrollment in Arm 2 (MK-1088 in combination with pembrolizumab) at DL1 may begin after all participants complete Cycle 1 at DL1 of Arm 1 and a dose-escalation decision has been made. Thus, the starting dose of MK-1088 in the combination arm will be at least 1 level below the dose level being tested concurrently in the MK-1088 monotherapy arm. The final number of participants enrolled in Part 1 will depend on the empirical safety observations (DLT), and what dose is ultimately identified as the RP2D using the adjusted mTPI design.

Based on the adjusted mTPI design, it is anticipated that data from 14 participants at a dose level will provide sufficient data to declare an MTD or RP2D. However, should there be clinical PK or safety reasons, additional participants and/or dose levels may be evaluated. The pool-adjacent-violators algorithm [Ji Y, Li Y, Bekele BN 2007] will be used to estimate the DLT rates across doses in each treatment arm under the assumption of monotonicity between DLT rates and dose levels. The dose with an estimated DLT rate closest to 30% may be treated as a preliminary RP2D. The totality of the data will be considered before deciding on the dose(s) to carry forward to Part 2. The RP2D of MK-1088 in the combination arm (Arm 2) may equal, but will not exceed, the RP2D in the MK-1088 monotherapy arm (Arm 1).

In Part 2, safety and efficacy of MK-1088 in combination with pembrolizumab at the RP2D defined in Part 1 Arm 2 will be assessed. At least 3 indication-specific expansion cohorts are planned based on evolving data and will be incorporated into an amendment before initiating Part 2. Additional lower and/or higher doses of MK-1088 in combination with pembrolizumab may also be explored in Part 2. The final RP2D for future studies will be confirmed using all available safety information (including early and late toxicities from

Parts 1 and 2), as well as PK and pharmacodynamic data, and preliminary efficacy assessments.

Preliminary efficacy will be evaluated using ORR assessed by the investigator based on PCWG-modified RECIST 1.1 or RECIST 1.1 as a secondary objective. PFS based on PCWG-modified RECIST 1.1 or RECIST 1.1 as assessed by the investigator and OS will be evaluated as exploratory objectives.

Intermittent data assessments may be conducted to enable future study planning and dosing decisions.

Participants will be monitored carefully for the development of AEs, and for clinical and/or radiographic evidence of disease progression according to PCWG-modified RECIST 1.1 or RECIST 1.1. If a participant has evidence of radiological PD by PCWG-modified RECIST 1.1 or RECIST 1.1, it will be at the discretion of the investigator whether to continue a participant on study intervention. This clinical judgment decision should be based on the participant's overall clinical condition, including performance status, clinical symptoms, and laboratory data.

AEs will be evaluated by the investigator, according to criteria outlined in the NCI CTCAE, version 5.0, to establish the safety and tolerability of MK-1088 when administered in monotherapy or in combination with pembrolizumab per the primary objective of this study.

There will be no intraparticipant dose escalation for participants enrolled in this study. The definition of DLTs and criteria for dose modification of MK-1088 are outlined in Section 6.6.2. Pembrolizumab will be administered at a fixed dose of 200 mg Q3W, which will not be modified.

Participants may receive study intervention (monotherapy in Arm 1 or combination with pembrolizumab in Arm 2) for up to 35 cycles (~24 months). Participants will be treated until PD, unacceptable toxicity, intercurrent illness that prevents further administration of treatment, investigator's decision to withdraw treatment, participant withdrawal of consent, pregnancy of the participant, noncompliance with study intervention or procedure requirements, participant completes treatment, or administrative reasons requiring cessation of treatment, at which point they will be discontinued from the study.

Participants who progress by radiographic evaluation on monotherapy with MK-1088 (Arm 1) may, at the investigator's discretion and after consultation with the Sponsor, cross over to combination treatment arm of MK-1088 and pembrolizumab (Arm 2).

A participant may not cross over from Arm 1 (monotherapy) into Arm 2 (combination therapy with pembrolizumab) until that participant has completed the DLT evaluation period (ie, 21 days) in Arm 1. Participants who are eligible for crossover from Arm 1 to Arm 2 will complete the Arm 2 screening phase to ensure eligibility. In participants who cross over to Arm 2, screening assessments obtained for Arm 1 may be eligible for crossover screening if the assessments were obtained within 28 days before Arm 2 treatment initiation; an additional tumor biopsy specimen is not required. These participants will continue to undergo

their scheduled activities. Participants may receive the highest dose of MK-1088 that has already shown safety and tolerability in combination with pembrolizumab (DLT evaluation period completed for that combination dose).

Participants who are eligible to receive combination treatment due to radiographically confirmed PD while in Arm 1, will not be included in the adjusted mTPI dose-escalation determination for Arm 2, as that specific dose level cohort must have already shown safety and tolerability. However, their data may be included retrospectively in determination of the RP2D for the combination treatment. These participants' safety and efficacy data will be analyzed separately from that of the participants enrolled in Arm 2. Once they discontinue from any part of the study, participants will be treated at the discretion of the physician.

Participants who cross over to combination treatment will be eligible to receive a maximum of 35 cycles of combination treatment irrespective of the number of cycles of MK-1088 received in monotherapy.

Participants who discontinued monotherapy in Arm 1 due to a DLT are not eligible for crossover to Arm 2.

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

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

Specific procedures to be performed during the study, including prescribed times and associated visit windows, are outlined in Section 1.3 (Table 1, Table 2) of the SoA. Details of each procedure are provided in Section 8.

4.2 Scientific Rationale for Study Design

MK-1088 is a novel small molecule antagonist dually targeting the A_{2A} and A_{2B} receptors. Inhibition of adenosine signaling in the TME can decrease the immunosuppressive signals on immune cells, thus resulting in their activation against tumor cells. Combining MK-1088 with pembrolizumab has the potential to overcome resistance and/or deepen the antitumor response to PD-1 blockade alone. In the dose-escalation, safety phase of this trial, participants with any advanced solid tumor are eligible for enrollment. In the expansion phase of the study, participants with specific solid tumors will be selected based on all available preclinical and clinical data and any preliminary clinical efficacy data of MK-1088 in monotherapy and in combination with pembrolizumab.

4.2.1 Rationale for Endpoints

4.2.1.1 Efficacy Endpoints

One of the secondary endpoints is antitumor activity based on PCWG-modified RECIST 1.1 or RECIST 1.1 criteria as determined by the investigator. ORR is an acceptable measure of clinical benefit that demonstrates superiority of a new antineoplastic therapy, especially if the magnitude of the effect is large and the therapy has an acceptable risk/benefit profile. The use of PCWG-modified RECIST 1.1 or RECIST 1.1 to assess ORR is typically considered acceptable by regulatory authorities.

Tumor response will be assessed using PCWG-modified RECIST 1.1 or RECIST 1.1 as assessed by investigator (see Section 8.2.5). Antitumor activity will be measured through such tertiary endpoints as PFS, OS, and DOR, which are described further in Section 9.4.1.

4.2.1.1.1 Response Rate Assessed by RECIST Version 1.1

PCWG-modified RECIST 1.1 or RECIST 1.1 will be used by the local site when determining eligibility (Section 8.2.2) and by the principal investigator when assessing scans for efficacy measures (Sections 8.2.3 and 8.2.4). PCWG-modified RECIST 1.1 or RECIST 1.1 will be used to determine the objective response. Although RECIST 1.1 references a maximum of 5 target lesions in total and 2 per organ, this protocol has implemented a PCWG-modified RECIST 1.1 and modified RECIST 1.1 to allow a maximum of 10 target lesions in total and 5 per organ (Section 8.2.5).

4.2.1.2 Safety Endpoints

The primary objective of this study is to characterize the safety and tolerability of MK-1088 as monotherapy and as combination therapy with pembrolizumab in participants with advanced/metastatic solid tumors. The primary safety analysis will be based on participants who experience toxicities as defined by CTCAE Version 5.0 criteria. Safety will be assessed by quantifying the toxicities and grades of toxicities experienced by participants who have received MK-1088 as monotherapy and in combination with pembrolizumab.

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

4.2.1.3 Pharmacokinetic Endpoints

A secondary objective of this study is to characterize the PK profile of MK-1088 after administration as a single agent, and to characterize the PK profile of MK-1088 and pembrolizumab after administration as combination therapy. The serum concentrations of these agents will serve as the primary readout for the PK, and these data will be used to derive PK parameters of the agents when administered alone and in combination. Furthermore, the results of these analyses will be used in conjunction with the safety and exploratory endpoint data to help assess future dosing strategies for MK-1088.

4.2.1.4 Planned Exploratory Biomarker Research

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

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

This research may evaluate whether genetic variation within a clinical study population correlates with response to the treatment(s) under evaluation. If genetic variation is found to predict efficacy or 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 to interpret tumor-specific DNA mutations. Finally, MSI may be evaluated as this is an important biomarker for some cancers (ie, colorectal cancer).

Genetic (DNA) analyses from tumor

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

Tumor and blood RNA analyses

Both genome-wide and targeted mRNA expression profiling and sequencing in tumor tissue and in blood may be performed to define gene signatures that correlate to clinical response to treatment with pembrolizumab or other immunotherapies. Pembrolizumab induces a response in tumors that likely reflects an inflamed/immune phenotype. Specific immune-related gene sets (ie, those capturing interferon-gamma transcriptional pathways) may be evaluated and new signatures may be identified. Individual genes related to the immune system may also be

evaluated (eg, IL-10). MicroRNA profiling may also be pursued as well as exosomal profiling.

Proteomics 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 IVD device has been developed for use with pembrolizumab in NSCLC. Preliminary data indicates that this association may also be true in additional cancer types (ie, triple negative breast cancer, head and neck, and gastric). Additional tumor or blood-derived proteins may also correlate with response to pembrolizumab. Therefore, tumor tissue may be subjected to proteomic analyses using a variety of platforms that could include, but are not limited to, immunoassays and liquid chromatography/mass spectrometry. This approach could identify novel protein biomarkers that could aid in patient selection for pembrolizumab (MK-3475) therapy.

Other blood-derived biomarkers

In addition to expression on the tumor tissue, PD-L1 and other tumor derived proteins can be shed from tumor and released into the blood. Assays such as ELISA measure such proteins in serum. Correlation of expression with response to pembrolizumab therapy may identify new approaches for predictive biomarkers in blood, representing a major advance from today's reliance on assessing tumor biomarkers. This research would serve to develop such assays for future clinical use.

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

4.2.1.5 Future Biomedical Research

The Sponsor will conduct FBR on specimens for which consent was provided during this study. 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 FBR.

Such research is for biomarker testing to address emergent questions not described elsewhere in the protocol and will only be conducted on specimens from appropriately consented participants. The objective of collecting/retaining specimens for FBR 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 FBR research are presented in Appendix 6.

4.3 Justification for Dose

The planned dose of pembrolizumab for this study is 200 mg Q3W. Based on the totality of data generated in the Keytruda development program, 200 mg Q3W is 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

4.3.1 Starting Dose for This Study

4.3.1.1 Rationale for Starting and Maximum Dose of MK-1088

The planned starting dose of MK-1088 is 100 mg po QD. This starting dose was informed by the results of the FIH study MK-1088 PN001, which is a randomized, placebo controlled, double-blind, single ascending dose trial conducted in healthy males and females of non-child-bearing potential to determine the safety and tolerability of MK-1088 as well as to characterize the PK of MK-1088 that can achieve acceptable exposure and trough concentrations for the desired level of target engagement of the A_{2A} and A_{2B} receptors. The study was conducted with a tablet formulation (platform tablet of 40% drug load spray-dried intermediate in hydroxypropyl methylcellulose acetate succinate LF) in Belgium.

Data from this study was incorporated into a pharmacokinetic model to project the anticipated pharmacokinetic profile for daily dosing and projected tolerable starting dose that balances safety with potential benefits.

The 100 mg dose is approximately 2-fold lower than the highest dose tested in PN001. Based on in vitro profiling, high levels of A_{2A} inhibition (>99% TE) and A_{2B} inhibition (>90% TE) are expected at a trough concentration of approximately 1 μM in the absence of adenosine. While this trough concentration was achieved by a single dose of 224 mg in PN001, changes in blood pressure/heart rate measurements in an individual subject, and a general trend for increased blood pressure and heart rate measurement over baseline values with increasing MK-1088 dose was noted. A starting dose of 100 mg was recommended as a conservative approach at which pharmacological activity for MK-1088 is expected to be observed (>90% TE for A_{2A} and >80% TE for A_{2B}) and comprehensive evaluation of the safety profile upon

repeat dosing in an oncology patient population will be enabled. A 100 mg single dose was well tolerated in healthy volunteers and this starting dose provides the ability to have appropriate monitoring of patients after repeat dosing, before steadily increasing the dose. Exposures have increased dose proportionately up to 224 mg single doses in MK-1088 PN001.

The maximum planned dose of MK-1088 is 800 mg po QD although higher doses may be explored if safety and tolerability permit. In addition to inhibiting A_{2A}, dosing to this level is projected to achieve significant inhibition of A_{2B} comparable to levels that more selective A_{2B} inhibitors can achieve, even in the presence of high levels of adenosine expected to exist in the TME. Dose escalation to this planned maximum dose and/or higher doses are dependent on tolerability as observed during the adjusted mTPI dose-escalation design and if MK-1088 exposures continue to increase with dose.

4.3.1.2 Rationale for Dose Interval and Escalation Increments

The human starting dose and dosing interval of MK-1088 are based on an integration of nonclinical toxicological, pharmacological, and efficacy data. Dose-finding will proceed with a model-based adjusted mTPI approach with 3 to 14 participants treated per dose level using dose increment increases of approximately 30% to 100% of the prior dose.

In cohorts of participants treated with a combination of MK-1088 and pembrolizumab, doses of MK-1088 used in combination with pembrolizumab will be at least 1 to 2 dose levels behind the monotherapy dose and will not exceed the MTD/RP2D for monotherapy. If an MTD/RP2D for the monotherapy arm is established, the dose of MK-1088 in combination with pembrolizumab may continue escalation up to that dose.

4.3.1.3 Dose Finding Using a Modified Toxicity Probability Interval Design

Further dose-finding will follow the adjusted mTPI design [Ji, Y. 2013] with a target DLT rate of 30%. Dose-escalation and deescalation decisions are based on the adjusted mTPI design and depend on the number of participants enrolled and number of DLTs observed at the current dose level.

A minimum of 3 participants are required at each dose. However, depending on the accrual rate, 3, 4, 5, or 6 participants may be enrolled within 7 to 14 days of the opening of a dose cohort. In Table 3, the columns indicate the numbers of participants treated at the current dose level, and the rows indicate the numbers of participants experiencing DLT. The entries of the table are the dose-finding decisions: E, S, D, and DU represent escalating the dose, staying at the same dose, de-escalating the dose, and excluding the dose from the study due to unacceptable toxicity, respectively. For example, if 0 of 3 participants at a given dose level develop a DLT, then the dose can escalate to the next level. If 2 participants of 3 develop a DLT, the dose will be de-escalated to the next lower dose level. If 3 of 3 participants develop a DLT, this indicates an unacceptable toxicity at this dose. The dose should be de-escalated and the current dose will not be explored further. If 1 of 3 participants at a given dose level develop a DLT, then additional participants should be enrolled at that dose level following the rules below.

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

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

After 14 participants have been enrolled at any of the tested doses (including intermediate doses), dose-finding will stop if the mTPI table indicates "S" for staying at current dose. Otherwise, up to 14 new participants may be enrolled at a lower dose if "D" or "DU" is indicated, or at a higher dose if "E" is indicated.

The pool-adjacent-violators algorithm [Ji Y, Li Y, Bekele BN 2007] will be used to estimate the DLT rates across doses. The dose with an estimated DLT rate closest to 30% will be treated as a preliminary MTD. However, the totality of the data will be considered before deciding on the dose(s) to carry forward to Part 2. The dose-escalation schedule may be adjusted based on pharmacodynamic, PK, and safety data emerging throughout the study. The preliminary RP2D of MK-1088 in the combination arm (Arm 2) will not exceed, but may be equal to, the preliminary RP2D in the MK-1088 monotherapy arm (Arm 1).

Note that although 30% was the target toxicity rate used to generate the guidelines in Table 3, the observed rates of participants with DLTs at the MTD may be slightly above or below 30%). When selecting the RP2D of the monotherapy and combination therapy, the totality of the safety data (eg, duration, reversibility, severity, and nature of the DLTs and AEs) will be evaluated.

Table 3 Dose-finding Rules per Adjusted mTPI Design

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

D = De-escalate to the next lower dose; DLT = dose-limiting toxicity; DU = Current dose is unacceptably toxic; E = Escalate to the next higher dose; mTPI = modified Toxicity Probability Interval; S = Stay at the current dose;.
Adjusted from the mTPI table with target toxicity rate = 30%.
Flat noninformative prior Beta (1,1) is used as a prior and ε1=ε2=0.03[Ji Y, Li Y, Bekele BN 2007] [Ji, Y. 2013] [Ji, Y., et al 2010]

4.4 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).

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

4.4.1 Clinical Criteria for Early Study Termination

Recruitment in the study or at (a) particular study site(s) may be stopped due to insufficient compliance with the protocol, GCP and/or other applicable regulatory requirements, procedure-related problems or the number of discontinuations for administrative reasons is too high.

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

1. Incidence or severity of adverse drug reactions in this or other studies suggest a potential health hazard to participants

2. Plans to modify or discontinue the development of the study drug

Ample notification will be provided in the event of Sponsor decision to no longer supply MK-1088 or pembrolizumab.

5 STUDY POPULATION

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

5.1 Inclusion Criteria

A participant will be eligible for inclusion in the study if the participant meets the following criteria:

5.1.1 Inclusion Criteria for Arm 1 and Arm 2

The inclusion criteria apply to all participants unless otherwise indicated.

Type of Participant and Disease Characteristics

1. The participant must have a histologically or cytologically confirmed diagnosis of advanced/metastatic **solid tumor** by pathology report and have received, have been intolerant to, or have been ineligible for treatment known to confer clinical benefit.

   For metastatic castrate-resistant prostate cancer (mCRPC) only:

   - Must have previously received docetaxel, prior treatment with one other chemotherapy is allowed as well as up to 2 second-generation hormonal manipulations.

   - Have prostate cancer progression within 6 months before screening, as determined by the investigator, by one of the following:

     a. PSA progression using local laboratory values as defined by a minimum of 2 rising PSA levels with an interval of ≥1 week between each assessment where the PSA value at screening should be ≥2 ng/mL.

     b. Radiographic disease progression in soft tissue based on PCWG-modified RECIST 1.1 or RECIST 1.1 criteria with or without PSA progression.

     c. Radiographic disease progression in bone defined as the appearance of 2 or more new bone lesions on bone scan with or without PSA progression.

Note: Subjects with prostate cancer lesions solely confined to prostate without evidence of metastasis cannot be reliably imaged and therefore are not eligible for study

2. Disease per PCWG-modified RECIST 1.1 for mCRPC or measurable disease per 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 shown in such lesions.

   Note: Lesions situated in the brain are not considered measurable disease and may be considered as nonmeasurable only.
   Note: Subjects with prostate cancer lesions solely confined to prostate without evidence of metastasis cannot be reliably imaged and therefore are not eligible for study

   For participants with metastatic castrate-resistant prostate cancer:

   a. Have PCWG-modified RECIST 1.1 measurable (soft tissue) prostate cancer on CT or MRI scans as assessed by the local site/investigator/radiology

   OR

   b. Detectable bone metastases by whole body bone scintigraphy as per PCWG guidance (see Section 10.9, Appendix 9)

Demographics

3. Is male or female, from minimum of 18 years of age inclusive, at the time of providing informed consent.

Male Participants

4. If male, agrees to the following during the intervention period and for at least 7 days after the last dose of MK-1088:

- Abstains from heterosexual intercourse as their preferred and usual lifestyle (abstinent on a long-term and persistent basis) and agrees to remain abstinent

  OR

- Uses contraception unless confirmed to be azoospermic (vasectomized or secondary to medical cause, documented from the site personnel's review of the participant's medical records, medical examination, or medical history interview) as detailed below:

  - Uses a male condom plus partner use of an additional contraceptive method when having penile-vaginal intercourse with a WOCBP who is not currently pregnant.
    Note: Men with a pregnant or breastfeeding partner must agree to remain abstinent from penile-vaginal intercourse or use a male condom during each episode of penile-vaginal penetration.

- Contraceptive use by men should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.

Female Participants

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

- Not a WOCBP

  OR

- A WOCBP and:

  - Uses a contraceptive method that is highly effective (with a failure rate of <1% per year), with low user dependency, 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 7 days after the last dose of MK-1088 and for at least 120 days after the last dose of pembrolizumab, whichever occurs last after the last dose of study intervention. The investigator should evaluate the potential for contraceptive method failure (ie, noncompliance, recently initiated) in relationship to the first dose of study intervention. Contraceptive use by women should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.

  - Has a negative highly sensitive pregnancy test ([urine or serum] as required by local regulations) within 24 hours 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 8.3.5.

  - Abstains from breastfeeding during the study intervention period and for at least 7 days after study intervention with MK-1088 or 120 days from the last dose of pembrolizumab.

  - Medical history, menstrual history, and recent sexual activity has been reviewed by the investigator to decrease the risk for inclusion of a woman with an early undetected pregnancy.

Informed Consent

6. The participant (or legally acceptable representative) has provided documented informed consent/assent for the study. The participant may also provide consent/assent for FBR. However, the participant may participate in the study without participating in FBR.

Additional Categories

7. Archival tumor tissue sample or newly obtained core needle biopsy of a tumor lesion not previously irradiated has been provided. Details pertaining to tumor tissue submission can be found in the Procedures or Laboratory Manual.

8. Adequate organ function as defined in Table 4. Specimens must be collected within 72 hours before the start of study intervention.

Table 4 Adequate Organ Function Laboratory Values

System	Laboratory Value
Hematological	
Absolute neutrophil count (ANC)	≥1500/µL
Platelets	≥100 000/µL
Hemoglobin	≥9.0 g/dL or ≥5.6 mmol/L[a]
Renal	
Measured or calculated[b] creatinine clearance	≥30 mL/min
Hepatic	
Total bilirubin	≤1.5 ×ULN OR direct bilirubin ≤ULN for participants with total bilirubin levels >1.5 × ULN
AST (SGOT) and ALT (SGPT)	≤2.5 × ULN (≤5 × ULN for participants with liver metastases)
Coagulation	
International normalized ratio (INR) OR prothrombin time (PT) Activated partial thromboplastin time (aPTT)	≤1.5 × ULN unless participant is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants

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

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

[b] Creatinine clearance (CrCl) must be calculated using Cockcroft Gault formula.

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

9. Have an ECOG Performance Status of 0 to 1 assessed within 72 hours before the first dose of study intervention.

10. HIV-infected participants must have well controlled HIV on ART, defined as:

    a. Participants on ART must have a CD4+ T-cell count >350 cells/mm^3 at the time of screening.

b. Participants on ART must have achieved and maintained virologic suppression defined as confirmed HIV RNA level below 50 or the LLOQ (below the limit of detection) using the locally available assay at the time of screening and for at least 12 weeks before screening.

c. Participants on ART must have been on a stable regimen, without changes in drugs or dose modification, for at least 4 weeks before study entry (Day 1).

d. The combination ART regimen must not contain any antiretroviral medications other than: abacavir, dolutegravir, emtricitabine, lamivudine, raltegravir, rilpivirine, or tenoforvir.

11. Participants who are HBsAg positive are eligible if they have received HBV antiviral therapy for at least 4 weeks and have undetectable HBV viral load before treatment allocation.

    Note: Participants should remain on antiviral therapy throughout study intervention and follow local guidelines for HBV antiviral therapy post completion of study intervention.

    Hepatitis B screening tests are not required unless:

    - Known history of HBV infection
    - As mandated by local health authority

12. Participants with history of HCV infection are eligible if HCV viral load is undetectable at screening.

    Note: Participants must have completed curative antiviral therapy at least 4 weeks before treatment allocation.

    Hepatitis C screening tests are not required unless:

    - Known history of HCV infection
    - As mandated by local health authority

13. Be able to swallow and retain oral medication and must not have any clinically significant gastrointestinal abnormalities that may alter absorption.

5.2 Exclusion Criteria

The participant must be excluded from the study if the participant meets the following criteria:

5.2.1 Exclusion Criteria for Arm 1 and Arm 2

The exclusion criteria apply to all participants unless otherwise indicated.

Medical Conditions

1. Has had chemotherapy, definitive radiation, or biological cancer therapy within 4 weeks (2 weeks for palliative radiation) before the first dose of study intervention, 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 immune-related AEs). Participants receiving ongoing replacement hormone therapy for endocrine immune-related AEs will not be excluded from participation in this study.

2. Has a history of a second malignancy, unless potentially curative treatment has been completed with no evidence of malignancy for 2 years.

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

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

4. Has had a severe hypersensitivity reaction to treatment with a monoclonal antibody/components of the study intervention.

5. Has an active infection requiring therapy.

6. Has a history of interstitial lung disease.

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

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

9. Has concurrent active Hepatitis B (defined as HBsAg positive and/or detectable HBV DNA) and Hepatitis C virus (defined as anti-HCV Ab positive and detectable HCV RNA) infection.

   Note: Hepatitis B and C screening tests are not required unless:

   - Known history of HBV and HCV infection
   - As mandated by local health authority

10. HIV-infected participants with a history of Kaposi's sarcoma and/or Multicentric Castleman's Disease.

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

12. Has known psychiatric or substance abuse disorders that would interfere with the participant's ability to cooperate with the requirements of the study.

13. Is pregnant or breastfeeding, or expecting to conceive or father children within the projected duration of the study, starting with the screening visit through the duration of contraception after the last dose of study intervention.

14. 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 intervention administration. Surgery requiring regional/epidural anesthesia must be completed at least 72 hours before first study intervention administration and participants should be recovered.

15. Has a history or current evidence of a GI condition (eg, inflammatory bowel disease, Crohn's disease, ulcerative colitis) or impaired liver function or diseases that in the opinion of the investigator may significantly alter the absorption or metabolism of oral medications; 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.

16. Has clinically significant cardiovascular disease within 12 months from first dose of study intervention, including NYHA Class III or IV congestive heart failure, unstable angina, myocardial infarction, cerebral vascular accident, or cardiac arrhythmia associated with hemodynamic instability. Note: Medically controlled arrhythmia would be permitted.

17. Has a QTcF >470 msec.

18. History of an allogeneic stem cell transplant or a solid organ transplant.

Prior/Concomitant Therapy

19. Has received prior therapy with an anti-PD-1, anti-PD-L1, or anti-PD-L2 agent or with an agent directed to another stimulatory or coinhibitory T-cell receptor (eg, CTLA-4, OX-40, CD137), AND was discontinued from that treatment due to a Grade 3 or higher irAE.

20. Has received prior A_{2A} or A_{2B} receptor antagonist therapy.

21. Currently receiving strong/moderate CYP3A4 inducers or inhibitors.

22. Currently receiving H2 blockers or proton-pump inhibitors.

23. Has received prior systemic anticancer therapy including investigational agents within 4 weeks before allocation.

    Note: Participants must have recovered from all AEs due to previous therapies to ≤Grade 1 or baseline. Participants with ≤Grade 2 neuropathy may be eligible. Participants with endocrine-related AEs Grade ≤2 requiring treatment or hormone replacement may be eligible.

24. Has received prior radiotherapy within 2 weeks of start of study intervention, or had radiation-related toxicities requiring corticosteroids.

    Note: Two or fewer weeks of palliative radiotherapy for non-CNS disease, with a 1-week washout, is permitted.

25. Has received a live or live-attenuated vaccine within 30 days before the first dose of study intervention. Administration of killed vaccines are allowed.

    Refer to Section 6.5 for information on COVID-19 vaccines.

Prior/Concurrent Clinical Study Experience

26. Has received an investigational agent or has used an investigational device within 4 weeks prior to intervention administration.

Other Exclusions

27. Has a “superscan” bone scan. This is defined as an intense symmetric activity in the bones and diminished renal parenchymal activity on screening bone scan such that the presence of additional metastases in the future could not be evaluated.

28. Has not adequately recovered from major surgery or has ongoing surgical complications.

5.3 Lifestyle Considerations

5.3.1 Meals and Dietary Restrictions

Participants are required to fast 2 hours predose and 1 hour postdose.

Foods that are CYP3A inhibitors must not be consumed during the study. Grapefruit and star fruit are known to be CYP3A inhibitors, and should not be consumed for 2 weeks before the first dose of MK-1088 and for the entire duration of the study. Consumption of CYP3A4 inhibitors, such as grapefruit juice, may significantly increase the levels of MK-1088 and cause increased toxicity. St. John's Wort is a CYP3A inducer, and the consumption of St. John's Wort or products containing St. John's Wort may reduce the levels of MK-1088. A partial list of examples of CYP3A inhibitors is provided in Section 6.5.

5.3.2 Caffeine, Alcohol, and Tobacco Restrictions

No restrictions are required.

5.3.3 Activity Restrictions

Patients should avoid prolonged exposure to sun.

5.4 Screen Failures

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

Participants who fail screening may be rescreened for eligibility after consultation between the investigator and the Sponsor and written documentation of the collaborative decision on participant management.

5.5 Participant Replacement Strategy

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

- They are allocated, but not treated.
- They discontinue from the study without the occurrence of a DLT, before completing all the safety evaluations for reasons other than treatment-related AEs.

- They receive less than 75% of the total MK-1088 (or pembrolizumab infusion, if appropriate) in Cycle 1 (eg, if the infusion had to be discontinued due to an infusion reaction) and did not experience a DLT.

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

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

6 STUDY INTERVENTION

Study intervention is defined as any investigational intervention(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 intervention[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 before dosing the replacement participant. Clinical supplies will be affixed with a clinical label in accordance with regulatory requirements.

6.1 Study Intervention(s) Administered

The study intervention(s) to be used in this study are outlined in Table 5.

Table 5 Study Interventions

Arm Name	Arm Type	Inter-vention Name	Inter-vention Type	Dose Formulation	Unit Dose Strength(s)	Planned Dosage Level(s)	Route of Adminis-tration	Regimen/ Treatment Period	Use	IMP/ NIMP	Sourcing
Part 1: Arm 1 and Arm 2	Experi mental	MK-1088	Drug	Tablet	50 mg, 100 mg	DL1: 100 mg DL2: 200 mg DL3: 400 mg DL4: 600 mg DL5: 800 mg	Oral	Day 1 to Day 21 of each treatment cycle for up to 35 cycles; QD dosing	Experi mental	IMP	Provided centrally by the Sponsor
Part 1: Arm 2	Experi mental	Pembro-lizumab (MK-3475)	Drug	Solution for Infusion	100 mg per Vial	200 mg	IV Infusion	Day 1 of each treatment cycle for up to 35 cycles; Q3W dosing	Experi mental	IMP	Provided centrally by the Sponsor
Part 2: (To be speci-fied)	Experi mental	MK-1088	Drug	Tablet	50 mg 100 mg	Will be based on the RP2D from Part 1	Oral	Day 1 to Day 21 of each treatment cycle for up to 35 cycles; QD dosing	Experi mental	IMP	Provided centrally by the Sponsor
Part 2: (To be speci-fied)	Experi mental	Pembro-lizumab (MK-3475)	Drug	Solution for Infusion	100 mg per Vial	200 mg	IV Infusion	Day 1 of each treatment cycle for up to 35 cycles; Q3W dosing	Experi mental	IMP	Provided centrally by the Sponsor

DL=dose level; EEA=European Economic Area; IMP=investigational medicinal product; IV=intravenous; NIMP=noninvestigational medicinal product; QD=once daily; Q3W=every 3 weeks; RP2D=recommended Phase 2 dose.

The classification of IMP and NIMP in this table is based on guidance issued by the European Commission and applies to countries in the EEA. Country differences with respect to the definition/classification of IMP/NIMP may exist. In these circumstances, local legislation is followed.

Part 2 Arm Names will be specified in an amendment once the RP2D is determined in Part 1.

All supplies indicated in Table 5 will be provided per the "Sourcing" column depending on local country operational requirements. If local sourcing, every attempt should be made to source these supplies from a single lot/batch number where possible (eg, not applicable in the case where multiple lots or batches may be required due to the length of the study, etc).

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

Throughout the study, the first intake of MK-1088 will occur at the trial site on Day 1 of each cycle for Arm 1 and Arm 2 (shortly before the pembrolizumab infusion in Arm 2). MK-1088 will be administered orally, once daily. While in the clinic setting, pembrolizumab will be administered through an IV infusion as described in the Pharmacy Manual. Subsequent dosing of MK-1088 will be administered once daily QD by the participant (ie, unsupervised at their home) at approximately the same time each day, until Day 1 of the next cycle. For the MK-1088 dose on Day 2 of Cycles 1 and 2, the participant should refrain from MK-1088 administration until required study procedures on this day (eg, blood draw for MK-1088 PK assay) have been completed.

6.1.1 Medical Devices

Not applicable.

6.2 Preparation/Handling/Storage/Accountability

6.2.1 Dose Preparation

Details on preparation and administration of MK-1088 (and pembrolizumab) are provided in the appropriate Pharmacy/Procedures Manual.

Concomitant chemotherapeutic/immunotherapeutic agents will be prepared and administered per the approved product label(s).

6.2.2 Handling, Storage, and Accountability

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

Only participants enrolled in the study may receive study intervention, and only authorized site staff may supply or administer study intervention. All study interventions 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 intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).

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

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

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

6.3 Measures to Minimize Bias: Randomization and Blinding

6.3.1 Intervention Assignment

Intervention allocation will occur centrally using an IVRS. There are 2 intervention arms. Participants will be allocated to 1 of 2 intervention arms: MK-1088 monotherapy (Arm 1) or MK-1088 in combination with pembrolizumab (Arm 2) using an IVRS in Part 1.

Participants will be allocated centrally through IVRS. Arm 1 monotherapy slots will be filled first to generate monotherapy safety data before enrolling participants at that dose in Arm 2. After Arm 2 combination therapy has opened, slots in Arm 1 at a higher MK-1088 dose than Arm 2, if available, will be allocated first before Arm 2 slots are assigned. If both arms are open at the same dose of MK-1088, then assignment to Arm 1 or Arm 2 will be alternated.

In Part 1 of the study, intervention will be allocated by nonrandom assignment. Enrollment into the MK-1088 in combination with pembrolizumab combination intervention arm (Arm 2) may begin once all participants complete 1 cycle of MK-1088 monotherapy (Arm 1) at DL1, complete the DLT evaluation period, and a dose-escalation decision to the next dose level has been made. This ensures that the starting dose of MK-1088 in the combination arm will be at least one dose level below that being tested concurrently in the MK-1088 monotherapy arm. If both Arm 1 and Arm 2 are open for enrollment at different doses Arm 1 will be allocated first. If, according to the adjusted mTPI algorithm, a dose de-escalation is recommended in Arm 1 (MK-1088 monotherapy) resulting in both monotherapy and combination arms open at the same dose, IVRS will alternate participant assignment between Arm 1 and 2 starting with Arm 1. For example, if the guidance of the adjusted mTPI indicates a dose de-escalation to the prior dose level of 200 mg after at least 3 DLT-evaluable participants at the 400 mg dose cohort of Arm 1 (MK-1088 monotherapy) have completed Cycle 1 and the 200 mg dose cohort of Arm 2 (MK-1088 in combination with pembrolizumab) is enrolling, then both arms are open for enrollment at the same dose. In that situation, the first participant will be allocated to Arm 1, the second participant will be allocated to Arm 2, the third participant will be allocated to Arm 1, etc. An observation period of at least 24 hours will occur between intervention initiation in participants enrolled within each dose level. Each new dose cohort will open for enrollment without delay once

the 21-day DLT observation period of the previous dose cohort is completed and a dose-escalation decision is made.

When Part 2 is open for enrollment, IVRS will allocate participants by tumor type.

6.3.2 Stratification

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

6.3.3 Blinding

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

6.4 Study Intervention Compliance

If there are interruptions in the study intervention schedule or infusion/injection was stopped, the details of and reason for any interruption or infusion/injection cessation of study intervention will be documented in the participant's medical record.

- When participants self-administer study intervention(s) at home, compliance with study intervention will be assessed at each visit. Compliance will be assessed by direct questioning and counting returned tablets during the site visits and documented in the source documents and CRF. Deviation(s) from the prescribed dosage regimen should be recorded in the CRF.

- A record of the number of MK-1088 tablets dispensed to and taken by each participant must be maintained and reconciled with study intervention and compliance records. Intervention start and stop dates, including dates for intervention delays and/or dose reductions will also be recorded in the CRF.

Refer to Section 6.6.1 for Dose Modification and Toxicity Management Guidelines for irAEs associated with pembrolizumab monotherapy, coformulations, or IO combinations and for other allowed dose interruptions.

6.5 Concomitant Therapy

Medications or vaccinations specifically prohibited in the exclusion criteria are not allowed during the ongoing study. If there is a clinical indication for any medication or vaccination specifically prohibited, discontinuation from study intervention may be required. The investigator is to discuss prohibited medication/vaccination with the Sponsor's 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 intervention requires the mutual agreement of the investigator, the Sponsor, and the participant.

The following medications and vaccinations are prohibited during the study:

- Antineoplastic systemic chemotherapy or biological therapy

- Participants with mCRPC should not remain on androgen receptor blockers such as enzalutamide, abiraterone, nilutamide, etc. Participants are allowed to remain on GnRH/ LHRH agents after progression as part of standard of care (as allowed by local regulations).
- Immunotherapy not specified in this protocol
- Chemotherapy not specified in this protocol
- Investigational agents other than pembrolizumab
- Radiation therapy

  Note: Radiation therapy to a symptomatic solitary lesion or to the brain may be allowed at the investigator's discretion after the DLT observation period for the participant to be considered evaluable for DLT.
- Live or live-attenuated vaccines within 30 days before the first dose of study intervention and while participating in the study.

  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 except when used for the following purposes:
  - To modulate symptoms of an AE that is suspected to have an immunologic etiology
  - For the prevention of emesis
  - To premedicate for IV contrast allergies
  - To treat COPD exacerbations (only short-term oral or IV use in doses >10 mg/day prednisone equivalent)
  - For chronic systemic replacement not to exceed 10 mg/day prednisone equivalent
- Other glucocorticoid use except when used for the following purposes:
  - For topical use or ocular use
  - Intraarticular joint use
  - For inhalation in the management of asthma or COPD

- H2 Blockers or PPI

  The participant must not take H2 blockers or PPI during the trial from 5 days before the start of the study treatment to 5 days after the last administration of MK-1088. The investigator should use their medical judgment when a participant presents with an H2 blocker or PPI treatment or call the Sponsor Clinical Director for clarification.

  Of note, antacids, such as calcium carbonate or aluminum hydroxide-based product, will be allowed during the study, and are recommended to be taken either 4 hours before or after dosing of MK-1088.

- Strong/moderate inhibitors/inducers/substrates of the CYP3A4 enzymes.

  Investigators should check an actively updated list of drugs that are clinically relevant substrates, inducers or inhibitors of cytochrome P450, including CYP3A4 (http://medicine.iupui.edu/clinpharm/ddis/table.asp) as well as the product labeling of these compounds for reference.

  CYP3A4 inhibitors/inducers/substrates are listed below. The participant must not take the treatments listed in Table 6 during the trial after the start of the study treatment. Since this list is not comprehensive, the investigator should use their medical judgment when a participant presents with a medication not on the list or call the Sponsor Clinical Director for clarification.

Table 6 Examples of Medications, Supplements, and Other Substances Prohibited During the Trial

Strong 3A4 Inducers[a,d]	**Strong CYP3A4 Inhibitors**[b,d]	**Moderate CYP3A4 Inhibitors**[b,d]	**CYP3A4 Substrates With Narrow Therapeutic Range**[c,d]
carbamazepine phenobarbital phenytoin rifabutin rifampin troglitazone	indinavir nelfinavir ritonavir clarithromycin itraconazole ketoconazole nefazodone atazanavir saquinavir telithromycin	amprenavir aprepitant diltiazem erythromycin fluconazole fosamprenavir verapamil grapefruit juice	alfentanil[c] ergotamine[c] diergotamine[c] cyclosporine[c] fentanyl[c] pimozide[c] quinidine[c] sirolimus[c] tacrolimus[c] astemizole[c,e] terfenadine[c,e] cisapride[c,e] paclitaxel[c] repaglinide[c] lurasidone[c]

Strong 3A4 Inducers[a,d]	Strong CYP3A4 Inhibitors[b,d]	Moderate CYP3A4 Inhibitors[b,d]	CYP3A4 Substrates With Narrow Therapeutic Range[c,d]

Abbreviation: CYP = cytochrome P450.

[a] Strong 3A4 inducers listed are those that decrease plasma AUC values of 3A4 substrates by 30% or higher.

[b] Moderate inhibitors are defined as causing a ≥2- but <5-fold increase in the AUC values or 50-80% decrease in clearance of sensitive CYP3A substrates when the inhibitors were given at the highest approved dose and the shortest dosing interval in clinical evaluations. Strong inhibitors are defined as causing a ≥5-fold increase in the plasma AUC values or more than 80% decrease in clearance.

[c] CYP3A4 substrates with narrow therapeutic range refers to drugs whose exposure-response indicates that increases in their exposure levels by the concomitant use of CYP3A4 inhibitors may lead to serious safety concerns. For specific information, see the Classification of Substrates tables available at: ***http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ (then click "Drug Development and Drug Interactions: Table of Substrates, Inhibitors and Inducers")***

[d] Compiled from the in vivo inhibitors and inducers, inhibitor classification, and substrate classification tables available at: ***http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ (then click "Drug Development and Drug Interactions: Table of Substrates, Inhibitors and Inducers")*** and from the CYP450 drug interaction table (accessed ***June 2012***) available at: http://medicine.iupui.edu/clinpharm/DDIs/table.aspx

[e] Not available in the United States, and limited availability in the European Union.

If the investigator determines that a participant requires any of the aforementioned treatments for any reason, study intervention must be discontinued.

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

All concomitant medications received within 28 days before the first dose of study intervention and up to 30 days after the last dose of study intervention should be recorded. All concomitant medications administered during SAEs or ECIs are to be recorded. SAEs and ECIs are defined in Section 8.4.

Prohibited medications should not be used during the treatment phase of the study.

6.5.1 MK-1088 Supportive Care

Medications required to treat AEs or concurrent illnesses, other than those listed as prohibited, (Section 6.5), are allowed during the study. These include antiemetics, growth factors, and other supportive care medications. Contraceptive medications as described in Appendix 5 are allowed.

Any supportive care cancer treatment should not be CYP3A4 inhibitors/inducers (Table 6).

Every medication taken by the participant during the study and the reason for use must be recorded in the eCRF. Note that the use of any concomitant medication must relate to the documented medical history, prophylaxis, or an AE of the participant.

6.5.2 Rescue Medications and Supportive Care

No rescue or supportive medications are specified for use in this study.

6.5.3 Pembrolizumab Supportive Care

Participants should receive appropriate supportive care measures as deemed necessary by the treating investigator including, but not limited to, the items outlined below.

Suggested supportive care measures for the management of AEs with potential immunologic etiology are outlined along with the dose modification guidelines in Section 6.6.

6.6 Dose Modification (Escalation/Titration/Other)

6.6.1 Dose Administration/Escalation

6.6.1.1 Dose Administration (Preparation)

Details on preparation and administration of MK-1088 (and pembrolizumab) are provided in the appropriate Pharmacy/Procedures Manual.

6.6.2 Definition of Dose-limiting Toxicity

All toxicities will be graded using NCI CTCAE Version 5.0 based on the investigator assessment.

The DLT window of observation will be during Cycle 1.

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

- Grade 4 nonhematologic toxicity (not laboratory).
- Grade 4 hematologic toxicity lasting ≥7 days, except thrombocytopenia:

  Grade 4 thrombocytopenia of any duration

  Grade 3 thrombocytopenia associated with clinically significant bleeding
- Any nonhematologic AE ≥Grade 3 in severity should be considered a DLT, with the following exceptions: Grade 3 fatigue lasting ≤3 days; Grade 3 diarrhea, nausea, or

vomiting without use of antiemetics or antidiarrheals per standard of care; Grade 3 rash without use of corticosteroids or anti-inflammatory agents per standard of care.

- Any Grade 3 or Grade 4 nonhematologic 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 DILI (see Section 8.4.7 for criteria)

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

- Febrile neutropenia Grade 3 or Grade 4:

  Grade 3 is defined as ANC <1000/mm^3 with a single temperature of >38.3 degrees C (101 degrees F) or a sustained temperature of ≥38 degrees C (100.4 degrees F) for more than 1 hour.

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

- Prolonged delay (>2 weeks) in initiating Cycle 2 due to intervention-related toxicity.

- Any intervention-related toxicity that causes the participant to discontinue intervention during Cycle 1.

- Missing >25% of MK-1088 doses as a result of drug-related AEs during the first cycle.

- Grade 5 toxicity.

6.6.3 Cohort Expansion

In Part 2 of the study, approximately 30 additional participants will be treated in each of the cohorts of participants with select advanced tumors. Participants in these cohorts will be treated at the RP2D identified using the adjusted mTPI design in Arm 2 of Part 1 (MK-1088 in combination with pembrolizumab). The dose of pembrolizumab in Arm 2 will remain fixed at 200 mg Q3W. Part 2 may proceed after a protocol amendment.

Part 2 will begin once an RP2D for Arm 2 has been identified. When Part 2 is open for enrollment, IVRS will assign participants to 1 of the cohorts by tumor type.

6.6.4 Guidelines for Dose Modification due to Adverse Events for MK-1088

Adverse events (both nonserious and serious) associated with MK-1088 and pembrolizumab exposure may represent an immunologic etiology. These AEs may occur shortly after the first dose or several months after the last dose of treatment.

For individual participants, dose delays and modifications of study treatment will be based on treatment-related toxicity, laboratory test results before treatment administration, and clinical assessments.

Participants may have up to 2 dose modifications of MK-1088 throughout the course of the study, as described in Table 7. Participants at dose level 1 who require dose reduction may reduce their dose to 50 mg. Participants who require dose reductions below 50 mg should be discontinued from study treatment. If further toxicity occurs or the criteria for resuming treatment are not met, the participant must be discontinued from the study intervention. If a participant experiences several toxicities and there are conflicting recommendations, follow the most conservative dose adjustment recommended (dose reduction appropriate to the most severe toxicity). Dose reductions are not permitted during the DLT evaluation period.

The NCI CTCAE, version 5.0 must be used to grade the severity of AEs. The investigator may attribute each toxicity event to MK-1088 alone, to pembrolizumab alone, or to the combination. However, dose modifications should be implemented according to Table 7, Table 8, and Table 9 regardless of investigator/Sponsor causality assessment and attribution to either or both drugs, unless clearly related to disease progression or intercurrent illness. If an irAE is observed in a participant enrolled on Arm 2, dose modifications for both pembrolizumab and MK-1088 should be followed according to the Grade associated with the AE in the respective dose-modification tables. If a participant experiences several toxicities and there are conflicting recommendations, follow the most conservative dose adjustment guidance.

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

Table 7 MK-1088 Monotherapy: Dose Modification and Treatment Discontinuation Guidelines for Treatment Emergent Adverse Events

Toxicity	Hold Treatment	Criteria for Restarting Treatment	Dose/Schedule for Restarting Treatment	Criteria for Discontinuation after Consultation with Sponsor
Hematological Toxicities:				
• Any Grade 1 hematological toxicity	No	N/A	N/A	N/A
• Any Grade 2 hematological toxicity, or Grade 3 toxicity that persists for ≤5 days	Per medical assessment of the investigator	If treatment held, may be restarted when AE resolves back to baseline or to Grade 1.	Per medical assessment of the investigator: may decrease dose by 1 dose level.	If AE persists for 12 weeks without resolution after reduction in dose
• Any Grade 3 hematologic toxicity that persists for >5 days, or Grade 4 hematological toxicity • Febrile neutropenia • Grade 3 thrombocytopenia of any duration if associated with bleeding	Yes	Treatment may be restarted when AE resolves back to baseline or to Grade 1.	Decrease dose by 1 dose level.	If AE persists for 12 weeks without resolution after reduction in dosing schedule Permanent discontinuation should be considered for any severe or life-threatening event.
Nonhematological Toxicities:				
• Toxicity	Hold treatment	Criteria for restarting treatment	Dose/schedule for restarting treatment	Criteria for discontinuation after consultation with Sponsor
• Any Grade 1 nonhematological toxicity • Grade 2 alopecia • Grade 2 fatigue	No	N/A	N/A	N/A
• Any Grade 2 nonhematological toxicity except Grade 2 alopecia and Grade 2 fatigue	Per medical assessment of the investigator	If treatment held, may be restarted when AE resolves back to baseline or to Grade 1.	Per medical assessment of the investigator: may decrease dose by 1 dose level.	If AE persists for 12 weeks without resolution after reduction in dose
• Any Grade 3 or 4 nonhematological toxicity (not including laboratory, unless clinically significant medical intervention is required to treat the participant, or the abnormality leads to hospitalization, or the abnormality persists for >1 week)	Yes	Treatment may be restarted when AE resolves back to baseline or to Grade 1.	Decrease dose by 1 dose level.	If AE persists for 12 weeks without resolution after reduction in dose. Permanent discontinuation should be considered for any severe or life-threatening event.

AE=adverse event; N/A=not applicable.

If toxicity does not resolve to Grade 0 to 1 within 12 weeks after last intervention, MK-1088 should be discontinued after consultation with the Sponsor.

With investigator and Sponsor agreement, participants with a laboratory AE still at Grade 2 after 12 weeks may continue intervention in the study only if asymptomatic and controlled.

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

Dose reductions are not permitted during Cycle 1.

Pembrolizumab treatment will be modified for the AEs described Section 6.6.5.

6.6.5 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.

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 8.

Table 8 Dose Modification and Toxicity Management Guidelines for Immune-related Adverse Events Associated with Pembrolizumab Monotherapy 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 (CTCAE v5.0)	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 to 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
	Recurrent Grade 2, Grade 3 or 4	Permanently discontinue		
Diarrhea/Colitis	Grade 2 or 3	Withhold	• Administer corticosteroids (initial dose of 1 to 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 (CTCAE v5.0)	Action With Pembrolizumab Monotherapy, Coformulations or IO Combinations	Corticosteroid and/or Other Therapies	Monitoring and Follow-up
AST or ALT Elevation or Increased Bilirubin	Grade 2 [a]	Withhold	• Administer corticosteroids (initial dose of 0.5 to 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 to 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 antihyperglycemic 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 nonselective 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 (CTCAE v5.0)	Action With Pembrolizumab Monotherapy, Coformulations or IO Combinations	Corticosteroid and/or Other Therapies	Monitoring and Follow-up
Hypothyroidism	Grade 2, 3 or 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 increased creatinine or acute kidney injury	Grade 2	Withhold	• Administer corticosteroids (prednisone 1 to 2 mg/kg or equivalent) followed by taper	• Monitor changes of renal function
	Grade 3 or 4	Permanently discontinue		
Neurological Toxicities	Grade 2	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 3 or 4	Permanently discontinue		
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		
Exfoliative Dermatologic Conditions	Suspected SJS, TEN, or DRESS	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology or exclude other causes
	Confirmed SJS, TEN, or DRESS	Permanently discontinue		
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 based on the event [e]		
	Recurrent Grade 3 or Grade 4	Permanently discontinue		

irAEs	Toxicity Grade (CTCAE v5.0)	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: encephalitis and other clinically important irAEs (eg, vasculitis and sclerosing cholangitis).

Dose Modification and Toxicity Management of Infusion Reactions Related to Pembrolizumab Monotherapy, Coformulations or IO Combinations (MK-1088)

Pembrolizumab monotherapy, coformulations or IO combinations (MK-1088) may cause severe or life-threatening infusion reactions including severe hypersensitivity or anaphylaxis. Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion. Dose modification and toxicity management guidelines on pembrolizumab monotherapy, coformulations or IO combinations (MK-1088) associated infusion reactions are provided in Table 9.

Table 9 Pembrolizumab Monotherapy or IO Combinations 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 intervention.	Participant may be premedicated 1.5 h (±30 min) prior to infusion of study intervention with: Diphenhydramine 50 mg PO (or equivalent dose of antihistamine). Acetaminophen 500 to 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 after 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 intervention.	No subsequent dosing
h=hour; IV=intravenous; CTCAE=Common Terminology Criteria for Adverse Events; NCI=National Cancer Institute; NSAIDs=nonsteroidal anti-inflammatory drugs. Note: Appropriate resuscitation equipment should be available at the bedside and a physician readily available during the period of drug administration. For further information, please refer to the CTCAE v5.0 at http://ctep.cancer.gov		

6.7 Intervention After the End of the Study

There is no study-specified intervention after the end of the study.

6.8 Clinical Supplies Disclosure

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

6.9 Standard Policies

Not applicable.

7 DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT WITHDRAWAL

7.1 Discontinuation of Study Intervention

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

As certain data on clinical events beyond study intervention 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 intervention. Therefore, all participants who discontinue study intervention before completion of the protocol-specified treatment period will still continue to participate in the study as specified in Section 1.3 and Section 8.11.3, or if available, Protocol Clarification Letter.

Participants may discontinue study intervention at any time for any reason or be discontinued from the study intervention at the discretion of the investigator should any untoward effect occur. In addition, a participant may be discontinued from study intervention by the investigator or the Sponsor if study intervention is inappropriate, the study plan is violated, or for administrative and/or other safety reasons.

A participant must be discontinued from study intervention, 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 intervention.
- Any prolonged interruption of study intervention beyond the permitted periods, for irAE management or other allowed dose interruptions, as noted in Section 6.6.1, require Sponsor consultation before restarting treatment. If treatment will not be restarted, the participant will continue to be monitored in the study and the reason for discontinuation of study intervention will be recorded in the medical record.
- The participant has a medical condition or personal circumstance that, in the opinion of the investigator and/or Sponsor, placed the participant at unnecessary risk from continued administration of study intervention.
- The participant has a confirmed positive serum pregnancy test.
- Radiographic disease progression outlined in Section 8.2.3 (after obtaining informed consent addendum and Sponsor communication, the investigator may elect to continue treatment beyond disease progression).
- Any progression or recurrence of malignancy, or any occurrence of another malignancy that requires active treatment.
- Intercurrent illness other than another malignancy as noted above that prevents further administration of treatment.

- 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 6.6.

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

Arm 1 participants who progress on monotherapy MK-1088 may crossover into Arm 2 at the screening phase if they have completed the DLT evaluation period and a dose level in Arm 2 has shown safety and tolerability.

7.2 Participant Withdrawal From the Study

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

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

Specific details regarding procedures to be performed at the time of withdrawal from the study, as well as specific details regarding withdrawal from FBR, are outlined in Section 8.1.9. The procedures to be performed should a participant repeatedly fail to return for scheduled visits and/or if the study site is unable to contact the participant are outlined in Section 7.3.

7.3 Lost to Follow-up

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

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

- The investigator or designee must make every effort to regain contact with the participant at each missed visit (eg, telephone calls and/or a certified letter to the participant's last known mailing address or locally equivalent methods). These contact attempts should be documented in the participant's medical record.

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

8 STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarized in the SoA.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- The investigator is responsible for ensuring that procedures are conducted by appropriately qualified (by education, training, and experience) staff. Delegation of study-site personnel responsibilities will be documented in the Investigator Trial File Binder (or equivalent).
- All study-related medical (or dental) decisions must be made by an investigator who is a qualified physician (or dentist when appropriate).
- 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 used for screening or baseline purposes provided the procedure met the protocol-specified criteria and were performed within the time frame defined in the SoA.
- Additional evaluations/testing may be deemed necessary by the investigator and or the Sponsor for reasons related to participant safety. In some cases, such evaluation/testing may be potentially sensitive in nature (eg, HIV, hepatitis C), 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.

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

8.1 Administrative and General Procedures

8.1.1 Informed Consent

The investigator or 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.

8.1.1.1 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 their 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 their 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.

8.1.1.2 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 their 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.

8.1.2 Inclusion/Exclusion Criteria

All inclusion and exclusion criteria will be reviewed by the investigator, who is a qualified physician, to ensure that the participant qualifies for the study.

8.1.3 Participant Identification Card

All participants will be given a participant identification card identifying them as participants in a research study. The card will contain study-site contact information (including direct telephone numbers) to be 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, 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.

8.1.4 Medical History

A medical history will be obtained by the investigator or qualified designee. Medical history will include all active conditions, and any condition diagnosed within the prior 10 years that are considered to be clinically important. Details regarding the disease for which the participant has enrolled in the 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).

8.1.5 Prior and Concomitant Medications Review

8.1.5.1 Prior Medications

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

8.1.5.2 Concomitant Medications

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

All medications related to reportable SAEs and ECIs should be recorded as defined in Section 8.4.

All new anticancer therapy initiated after the study start must be recorded in the eCRF. If a participant initiates another anticancer therapy other than the assigned study intervention(s), the study intervention(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 study intervention, the 30-day Safety Follow-up Visit should occur before the first dose of the new therapy.

8.1.6 Assignment of Screening Number

All consented participants will be given a unique screening number that will be used to identify the participant for all procedures that occur before intervention allocation. Each participant will be assigned only 1 screening number. Screening numbers must not be reused for different participants.

8.1.7 Assignment of Treatment/Randomization Number

All eligible participants will be allocated, by nonrandom assignment, and will receive a treatment/randomization number. The treatment/randomization number identifies the participant for all procedures occurring after treatment allocation. The assigned screening number will become the participants' treatment/randomization number. Once a treatment/randomization number is assigned to a participant, it can never be reassigned to another participant.

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

8.1.8 Study Intervention Administration

Study intervention should begin within 3 days of treatment allocation.

8.1.8.1 Timing of Dose Administration

For infusion:

Study intervention(s) will be administered by the investigator and/or study staff according to the specifications within the Pharmacy Manual. The total volume of study intervention infused will be compared with the total volume prepared to determine compliance with each dose administered.

Oral medication:

During on-site visits, study intervention(s) will be administered by the investigator and/or study staff according to the specifications within the Pharmacy Manual. The administration, the dose, the time of administration, as well as any immediate reactions at the time of intake will be documented in the eCRF.

For nonvisit days, MK-1088 will be taken at home. The participant will note the number of tablets taken, the time of administration, as well as any reactions including the date/time.

When a participant attends a study visit, they will bring any unused tablets.

8.1.8.2 Timing of Administration for MK-1088

MK-1088 is a tablet administered orally once a day from Day 1 to Day 21 of each treatment cycle. The reason for any variability in administration of MK-1088 outside the protocol-

specified window should be documented in the participant's medical chart and recorded on the eCRFs.

Every effort should be made to begin the first dose of study intervention on the day of allocation, but if this is not achieved, study intervention should be initiated no later than 3 days from the date of allocation. All subsequent cycles of study intervention 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 interventions will begin on Day 1 of each cycle after all predose study procedures and assessments have been completed as detailed in Section 1.3.

The Pharmacy Manual contains specific instructions for MK-1088 dose calculation and administration.

8.1.8.3 Timing for Administration of Pembrolizumab

For those subjects enrolled in Arm 2 (MK-1088 and pembrolizumab), study treatment with pembrolizumab should be administered on Day 1 of each cycle after all procedures/assessments have been completed as detailed in the SoA (Section 1.3). All study treatments of pembrolizumab will be administered on an outpatient basis. Study treatment of pembrolizumab may be administered up to 3 days before or after the scheduled Day 1 of each cycle due to administrative reasons except for C1D1, where the window is +3 days from allocation.

Please refer to the Pharmacy Manual for specific instructions regarding preparation of the pembrolizumab infusion fluid, and administration.

8.1.9 Discontinuation and Withdrawal

Participants who discontinue study intervention before completion of the treatment period should be encouraged to continue to be followed for all remaining study visits as outlined in the SoA (Section 1.3) and Section 8.11.3.

Participants who withdraw from the study should be encouraged to complete all applicable activities scheduled for the final study visit at the time of withdrawal. Any AEs that are present at the time of withdrawal should be followed in accordance with the safety requirements outlined in Section 8.4.

8.1.9.1 Withdrawal From Future Biomedical Research

Participants may withdraw their consent for FBR. Participants may withdraw consent at any time by contacting the study investigator. If medical records for the study are still available, the investigator will contact the Sponsor using the designated mailbox (clinical.specimen.management@MSD.com). Subsequently, the participant's consent for FBR 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 before the request being received by the Sponsor will continue to be used as part of the overall research study data and results. No new analyses would be generated after the request is received.

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

8.1.10 Participant Blinding/Unblinding

This is an open-label study; there is no blinding for this study. The emergency unblinding call center will be available so that a health care provider can obtain information about study intervention in emergency situations where the investigator is not available.

8.1.11 Calibration of Equipment

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

8.2 Efficacy/Immunogenicity Assessments

8.2.1 Tumor Scans and Assessment of Disease

Throughout this section, the term 'scan' refers to any medical imaging data used to assess tumor burden and may include cross-sectional imaging (such as CT or MRI), medical photography, bone imaging, or other methods as specified in this protocol.

In addition to survival, efficacy will be assessed based on evaluation of scan changes in tumor burden over time, until the participant is discontinued from the study or goes into survival follow-up. The process for scan collection and retention and/or transfer can be found in the SIM.

Tumor scans by CT are strongly preferred. 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 should be used in a participant throughout the study to optimize the reproducibility of the assessment of existing and new tumor burden and improve the accuracy of the response assessment based on scans.

Note: For the purposes of assessing tumor scans, the term "investigator" refers to the local investigator at the site and/or the radiological reviewer at the site or at an offsite facility.

Brain imaging is required at screening for participants with a history of brain metastases or when clinically indicated and on-study when clinically indicated or to confirm CR when brain metastases were present at screening.

- If brain scans are performed, magnetic resonance imaging is preferred; however, CT imaging will be acceptable, if MRI is medically contraindicated.

Prostate Cancer

Bone scintigraphy (eg, nuclear medicine bone scan, Tc99 bone scan, bone scan, etc.) of the whole body is required for all participates at screening and on-study for all scheduled imaging visits and to confirm PCWG-modified RECIST 1.1 bone PD.

- Other bone imaging modalities (eg, FDG-PET, PET, PSMA PET, MRI, SPECT, etc.) cannot be a substitute for the bone scan (see Appendix 9, Section 10.9).

Non-Prostate Cancer

Bone imaging (e.g. bone scan, PET scan, etc.) should be performed to evaluate bone metastases when clinically indicated at screening and on-study or to confirm CR when bone metastases were present at screening.

8.2.2 Initial Tumor Scans

Initial tumor scans at screening must be performed within 28 days before the date of allocation. Any scans obtained after Cycle 1 Day 1 cannot be included in the screening assessment. The investigator must review screening scans to confirm the participant has measurable disease per RECIST 1.1, for mCRPC participants by PCWG-modified RECIST 1.1.

If brain scans are required to document the stability of existing metastases, the brain scan should be acquired during screening. The specific methods permitted for this study are described in the SIM.

Bone scintigraphy (eg, Tc99 bone scan, etc.) is required for all participants with prostate cancer. For all other participants, bone imaging (eg, bone scan, PET scan, etc.) is required only when clinically symptomatic (eg, with new bone pain, etc.).

8.2.3 Tumor Scans During the Study

The first on-study scan should be performed at 9 weeks (63 days ±7 days) from the C1D1 date. Subsequent tumor scans should be performed every 9 weeks (63 days ±7 days) or more frequently if clinically indicated. After 54 weeks (378 days ±7 days), participants who remain on treatment will have scans performed every 12 weeks (84 days ±7 days). Scan timing should follow calendar days and should not be adjusted for delays in cycle starts.

Scans are to be performed until disease progression is identified by the investigator, withdrawal of consent, pregnancy, or death, whichever occurs first.

Objective response should be confirmed by a repeat scan performed at least 4 weeks after the first indication of a response is observed. Participants will then return to the regular scan schedule, starting with the next scheduled time point. Participants who receive additional scans for confirmation do not need to undergo the next scheduled scan if it is fewer than 4 weeks later; scans may resume at the subsequent scheduled time point.

For non-prostate cancer participants, on-study brain or bone scans should be performed if clinically indicated or to confirm CR (if other lesions indicate CR and brain or bone lesions existed at screening).

For prostate cancer participants, radiographic progression will be determined according to PCWG-modified RECIST 1.1. Disease progression in bone lesions should be confirmed by another bone scan ≥6 weeks after site assessed first radiographic evidence of bone disease progression.

8.2.4 End of Treatment and Follow-up Tumor Scans

If participants discontinue study intervention, tumor scans should be performed at the time of discontinuation (±4 week window) unless previous scans were obtained within 4 weeks of discontinuation. If participants discontinue study intervention due to documented disease progression, this is the final required tumor scan.

If participants discontinue study intervention without documented disease progression, every effort is to be made to monitor disease status by acquiring tumor scans using the same schedule calculated from the date of allocation, refer to Section 8.2.3.

Scans are to be continued until one of the following conditions are met:

- Disease progression as defined by RECIST 1.1 or PCWG-modified RECIST 1.1
- The start of a new anticancer treatment
- Pregnancy
- Death
- Withdrawal of consent
- The end of the study

8.2.5 RECIST 1.1 and PCWG-modified RECIST 1.1 Assessment of Disease

For participants other than those with prostate cancer, RECIST 1.1 will be used as the primary measure for assessment of tumor response, date of disease progression, and as a basis for all protocol guidelines related to disease status (eg, discontinuation of study intervention). 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.

For participants with prostate cancer, the primary measure for assessment of tumor response, date of disease progression and as the basis for all protocol guidelines related to disease status (eg, discontinuation of study intervention) will be PCWG-modified RECIST 1.1. Assessment of treatment response in the soft tissue will be according to RECIST 1.1, modified as above. Assessment of treatment response in the bone will be according to the rules of PCWG as described in Appendix 9.

Soft tissue response and bone response assessments will be combined to produce an overall radiographic response, as shown in Table 10.

Table 10 Overall Radiographic Response per PCWG-modified RECIST 1.1

Soft Tissue Response	**Bone Scan Result**	**PCWG-modified RECIST 1.1 Time Point Response Entered into CRF**
PD	Any	**PD**
Any	PD	**PD**
Any (except PD)	PDu	**PDu**
NE	Non-PD, NED or NE	**NE**
NED	NE	**NE**
NED	Non-PD	**Non-CR/Non-PD**
NED	NED	**NED**
SD	Non-PD, NED, or NE[a]	**SD**
Non-CR/Non-PD	Non-PD, NED, or NE[a]	**Non-CR/Non-PD**
PR	Non-PD, NED or NE*	**PR**
CR	Non-PD or NE*	**PR** (if target lesions were present at screening)
		Non-CR/Non-PD (if no target lesions at screening)
CR	NED	**CR**

Abbreviations: CR = complete response; CRF = case report form; NE = nonevaluable; NED = no evidence of disease; PCWG = Prostate Cancer Working Group; PD = progressive disease; PDu = progressive disease unconfirmed; PR= partial response; RECIST 1.1 = Response Evaluation Criteria in Solid Tumors Version 1.1; SD = Stable disease.

[a] If the bone scan is entirely missing or was not conducted, and bone lesions were present at screening, then the overall response is NE.

For all participants (prostate cancer and non-prostate cancer), if disease progression is established by the investigator, the process continues as follows:

- Investigator judgment will determine action
- If the participant is clinically stable and study intervention is to continue, communication with the Sponsor is required and a reconsent addendum must be signed
- Obtain scans per original protocol schedule

For the purpose of this decision process, lack of clinical stability is defined as:

- Unacceptable toxicity
- Clinical signs or symptoms indicating clinically significant disease progression
- Decline in performance status
- Rapid disease progression or threat to vital organs or critical anatomical sites (eg, CNS metastasis, respiratory failure due to tumor compression, spinal cord compression) requiring urgent alternative medical intervention

8.3 Safety Assessments

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

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

8.3.1 Physical Examinations

A complete physical examination will be conducted by an investigator or medically qualified designee (consistent with local requirements) per institutional standard. Height and weight will also be measured and recorded.

A brief directed physical examination will be conducted by an investigator or medically qualified designee (consistent with local requirements) per institutional standard .

Investigators should pay special attention to clinical signs related to previous serious illnesses.

8.3.1.1 Full Physical Examination

The investigator or qualified designee will perform a complete physical examination during the screening period. Clinically significant abnormal findings should be recorded as medical

history. The time points for full physical exams are described in Section 1.3. After the first dose of study intervention, new clinically significant abnormal findings should be recorded as AEs.

Investigators should pay special attention to clinical signs related to previous serious illnesses.

8.3.1.2 Directed Physical Examination

For cycles that do not required a full physical examination as defined in Section 1.3, the investigator or qualified designee will perform a directed physical examination as clinically indicated before study intervention administration. New clinically significant abnormal findings should be recorded as AEs.

Investigators should pay special attention to clinical signs related to previous serious illnesses.

8.3.2 Vital Signs

The investigator or qualified designee will take vital signs at screening, before the administration of each dose of study intervention at study visits and during the follow-up period as specified in the SoA. Vital signs include temperature, heart rate, respiratory rate, and blood pressure. Height will be measured at Visit 1 only. Weight will be measured at Visit 1; Day 1 of Cycles 1, 2, and 3; and during follow-up as specified in the SoA.

8.3.3 Electrocardiograms

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

8.3.4 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 or medically qualified designee (consistent with local requirements) 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 nonprotocol-specified laboratory assessments performed at the institution's local laboratory require a change in study participant management or are

considered clinically significant by the investigator (eg, SAE or AE or dose modification), then the results must be recorded in the appropriate CRF (eg, SLAB).

- For any laboratory tests with values considered clinically significantly abnormal during participation in the study or within 30 days after the last dose of study intervention, 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.

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

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

Laboratory tests should be performed within 3 days before the first dose of study intervention. An exception is hepatitis and thyroid serologies, which may be performed within 28 days before the first dose. After Cycle 1, predose laboratory safety tests can be conducted up to 72 hours before dosing unless otherwise noted on the flow charts.

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

See the Operations/Laboratory Manual for additional details.

8.3.5 Pregnancy Testing

- Pregnancy testing:
  - Pregnancy testing requirements for study inclusion are described in Section 5.1.
  - Pregnancy testing ([urine or serum] as required by local regulations) should be conducted at monthly intervals during intervention.
  - Pregnancy testing ([urine or serum] as required by local regulations) should be conducted at the end of relevant systemic exposure and correspond with the time frame for female participant contraception in Section 5.1.

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.

8.3.6 Eastern Cooperative Oncology Group Performance Status

The ECOG Performance Status is standardized criteria to measure how cancer impacts level of functioning (performance status) in terms of ability to care for oneself, daily activity, and physical ability (walking, working, etc.) with grades 0 to 5.

The investigator or qualified designee will assess ECOG status at screening, before the administration of each dose of study intervention at study visits, and during the follow-up period as specified in the SoA (Section 1.3).

8.4 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 3.

Progression of the cancer under study is not considered an AE unless it results in hospitalization or death as described in Section 8.4.6 and Appendix 3.

Adverse events, 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 and any designees are responsible for detecting, documenting, and reporting events that meet the definition of an AE or SAE as well as other reportable safety events. Investigators need to document if an SAE was associated with a medication error, misuse, or abuse. Investigators remain responsible for following up AEs, SAEs, and other reportable safety events for outcome according to Section 8.4.3.

The investigator, who is a qualified physician, will assess events that meet the definition of an AE or SAE as well as other reportable safety events with respect to seriousness, intensity/toxicity and causality.

Adverse events will not be collected for participants during the prescreening 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.

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

All AEs, SAEs, and other reportable safety events that occur after the participant provides documented informed consent, but before intervention allocation, 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 through 30 days after cessation of study intervention must be reported by the investigator.

- All AEs meeting serious criteria, from the time of intervention allocation 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 through the time required to eliminate systemic exposure after cessation of study intervention as described in Sections 5.1 and 8.3.5, 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 AEs or SAEs or other reportable safety events in former study participants. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study intervention or study participation, the investigator must promptly notify the Sponsor.

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

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

Table 11 Reporting Time Periods and Time Frames 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	Time Frame to Report Event and Follow-up Information to Sponsor:
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
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: - participant has been exposed to any protocol-specified intervention (eg, procedure, washout or run-in treatment including placebo run-in) Exception: A positive pregnancy test at the time of initial screening is not a reportable event.	Report all	Previously reported – Follow to completion/ termination; report outcome	Within 24 hours of learning of event
ECI (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
ECI (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

DILI=drug-induced liver injury; ECI=event of clinical interest; NSAE=nonserious adverse event; SAE=serious adverse event.

8.4.2 Method of Detecting AEs, SAEs, and Other Reportable Safety Events

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

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

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All AEs, SAEs, and other reportable safety events, including pregnancy and exposure during breastfeeding, ECIs, cancer, and overdose will be followed until resolution, stabilization, until the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3). In addition, the investigator will make every attempt to follow all nonserious AEs that occur in allocated participants for outcome. Further information on follow-up procedures is given in Appendix 3.

8.4.4 Regulatory Reporting Requirements for SAE

Prompt notification (within 24 hours) by the investigator to the Sponsor of SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention 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 intervention under clinical investigation. The Sponsor will comply with country-specific regulatory requirements and global laws and regulations relating to safety reporting to regulatory authorities, IRB/IECs, and investigators.

Investigator safety reports must be prepared for SUSARs according to local regulatory requirements and Sponsor policy and forwarded to investigators as necessary.

An investigator who receives an investigator safety report describing an SAE or other specific safety information (eg, summary or listing of SAE) from the Sponsor will file it along with the IB and will notify the IRB/IEC, if appropriate according to local requirements.

8.4.5 Pregnancy and Exposure During Breastfeeding

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

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

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.

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

Progression of the cancer under study is not considered a reportable event unless it results in hospitalization or death.

8.4.7 Events of Clinical Interest

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

Events of clinical interest for this study include:

3. An overdose of Sponsor's product, as defined in Section 8.5.

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

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

8.5 Treatment of Overdose

For purposes of this study, an overdose will be defined as any dose exceeding the prescribed dose for MK-1088 by ≥20% of the indicated dose. No specific information is available on the treatment of overdose of MK-1088. In the event of overdose, MK-1088 may be discontinued and the participant should be observed closely for signs of toxicity. Appropriate supportive treatment should be provided if clinically indicated.

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

8.6 Pharmacokinetics

To further evaluate MK-1088 exposure in this indication, and also to evaluate exposure of the proposed dosing regimen, sample collections for analysis of PK are currently planned as shown in Section 1.3. Blood samples will be obtained to measure PK of serum MK-1088. The MK-1088 serum C_{max} and C_{min} at planned visits and times will be summarized. Blood samples collected may be stored and further analysis may be performed, if required.

On the day(s) of sample collection, participants must not take study medication until the predose PK and biomarker (Section 8.8) sample collections are complete. Every effort should be taken by the investigative center to document the time of the last MK-1088 dose (ie, at home) before PK collection.

8.6.1 Blood Collection for Plasma MK-1088

Sample collection, storage, and shipment instructions for plasma samples will be provided in the Operations/Laboratory 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.

8.7 Pharmacodynamics

Pharmacodynamic parameters will not be evaluated in this study.

8.8 Biomarkers

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

- Blood (DNA) for genetic analysis
- Blood for serum biomarker analyses
- Blood for RNA analyses
- Archival or newly obtained tumor tissue

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

8.8.1 Planned Genetic Analysis Sample Collection

Sample collection, storage, and shipment instructions for planned genetic analysis samples will be provided in the Procedures Manual. Samples should be collected for planned analysis of associations between genetic variants in germline/tumor DNA and drug response. If a documented law or regulation prohibits (or local IRB/IEC does not approve) sample collection for these purposes, then such samples should not be collected at the corresponding sites. Leftover DNA extracted from planned genetic analysis samples will be stored for FBR only if participant signs the FBR consent.

8.9 Future Biomedical Research Sample Collection

If the participant provides documented informed consent for FBR, the following specimens will be obtained as part of FBR:

- Leftover samples listed in Section 8.8

8.10 Health Economics Medical Resource Utilization and Health Economics

This section is not applicable.

8.11 Visit Requirements

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

8.11.1 Screening

Approximately 28 days before treatment allocation, potential participants will be evaluated to determine that they fulfill the entry requirements as set forth in Section 1.3. Screening procedures may be repeated after consultation with the Sponsor.

Documented informed consent must be provided before performing any protocol-specific procedure. Results of a test performed before the participant signing consent as part of routine clinical management are acceptable in lieu of a screening test if performed within the specified time frame. Screening procedures are to be completed within 28 days before the first dose of study intervention.

8.11.2 Treatment Period/Vaccination Visit

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

8.11.3 Discontinued Participants Continuing to be Monitored in the Study

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

8.11.4 Posttreatment Visit

Participants will be required to return to the clinic approximately 30 days after the last dose of study intervention for the poststudy visit. If the poststudy visit occurs less than 30 days after the last dose of study intervention, a subsequent follow-up telephone call should be

made at 30 days post the last dose of study intervention to determine if any AEs have occurred since the poststudy clinic visit.

8.11.4.1 Safety Follow-up Visit

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

All AEs that occur before the Safety Follow-up Visit should be recorded (up to 30 days after the end of treatment).

8.11.4.2 Efficacy Follow-up Visits

Participants who complete the protocol-required cycles of study intervention or who discontinue study intervention for a reason other than disease progression will begin Efficacy Follow-up. Participants who discontinue study intervention for reasons other than PD should continue with imaging assessments per the protocol-defined schedule until: (1) radiographic PD is assessed by the investigator, (2) initiation of a new anticancer treatment, (3) death, (4) withdrawal of consent, (5) pregnancy, or (6) study conclusion or early termination, whichever occurs first. Follow-up should be assessed as defined in Section 8.11.4.3, to monitor disease status. Information regarding poststudy anticancer treatment will be collected if new treatment is initiated. Participants who completed all efficacy assessments and/or will not have further efficacy assessments must enter survival follow-up.

8.11.4.3 Survival Follow-up Contacts

Participant survival follow-up status will be assessed approximately every 12 weeks to assess for survival status until death, withdrawal of consent, or the end of the study, whichever occurs first.

The first survival follow-up assessment should be scheduled as described below:

- For participants who discontinue treatment intervention and who will not enter Efficacy Follow-up, the first survival follow-up contact will be scheduled 12 weeks after the Discontinuation Visit and/or Safety Follow-up Visit (whichever is last).

- For participants who completed assessments in Efficacy Follow-up, the first survival follow-up contact will be scheduled 12 weeks after the last efficacy assessment follow-up visit has been performed.

8.11.5 Poststudy

Participants will be required to return to clinic approximately 30 days after the last dose of study intervention for the poststudy visit. If the poststudy visit occurs less than 30 days after the last dose of study intervention, a subsequent follow-up telephone call should be made at

30 days post the last dose of study intervention to determine if any AEs have occurred since the poststudy clinic visit.

8.11.6 Vital Status

To ensure current and complete survival information (vital status) is available at the time of database locks, updated vital status may be requested during the study by the Sponsor. For example, updated vital status may be requested before but not limited to, an eDMC review, interim and/or final analysis. On 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 vital status.

9 STATISTICAL ANALYSIS PLAN

9.1 Statistical Analysis Plan Summary

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

If, after the study has begun, changes are made to primary and/or secondary objectives, or the statistical methods related to those objectives, then the protocol will be amended (consistent with ICH Guideline E9). Changes to exploratory or other nonconfirmatory analyses made after the protocol has been finalized, but before the conduct of any analyses, will be documented in the sSAP as needed and referenced in the CSR for the study. Post hoc exploratory analyses will be clearly identified in the CSR.

Full details are in the SAP, Section 9.2 through 9.12.

Study Design Overview	Phase 1/Phase 2 study of MK-1088 monotherapy (Arm 1) and MK-1088 in combination with pembrolizumab (Arm 2) in participants with advanced/metastatic solid tumors. The study applies an adjusted mTPI design for dose-finding.
Intervention Assignment	Participants will be allocated centrally through IVRS by nonrandom assignment.
Analysis Populations	• Safety (Primary): All-Participants-as-Treated • PK (Secondary): Per-Protocol • Efficacy (Secondary and Exploratory): Full Analysis Set
Primary Endpoint(s)	• Dose-limiting toxicity • Adverse event • Discontinuing study treatment due to an AE
Secondary Endpoints	• PK parameters including AUC, C_{min}, and C_{max} • ORR based on RECIST 1.1 as assessed by the investigator

Statistical Methods for Efficacy/ Immunogenicity/ Pharmacokinetic Analyses	• ORR based on RECIST 1.1 will be estimated using an exact method based on the binomial distribution (Clopper-Pearson interval). • Exploratory efficacy (eg, PFS, OS, and DOR) analyses are documented in the sSAP. • PK parameters of study medicines will be summarized by planned visit and time for each dose separately.
Statistical Methods for Safety Analyses	Summary statistics will be provided for the safety endpoints as appropriate. The pool-adjacent-violators algorithm [Ji Y, Li Y, Bekele BN 2007] will be used to estimate the DLT rates across doses. The estimate of the DLT rate among participants treated at RP2D of MK-1088 and the 90% Bayesian credible intervals for the estimate will be provided for each treatment arm.
Interim Analyses	No interim analyses are planned. Data will be examined on a continuous basis to allow for dose-finding decisions.
Multiplicity	No multiplicity adjustment is planned.
Sample Size and Power	The overall sample size for this study depends on the observed DLT profiles of MK-1088 monotherapy and MK-1088 in combination with pembrolizumab. A target sample size of 80 participants in Part 1 will be used for study planning purposes. Sample size for Part 2 Expansion will be determined once the RP2D is determined.

9.2 Responsibility for Analyses/In-house Blinding

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

The study is open-label (ie, participants, investigators, and Sponsor personnel will be aware of participant intervention assignment after each participant is enrolled and treatment is assigned). Participants will be allocated by nonrandom assignment.

9.3 Hypotheses/Estimation

Objectives and hypotheses of the study are outlined in Section 3.

9.4 Analysis Endpoints

9.4.1 Efficacy/Immunogenicity/Pharmacokinetics Endpoints

Efficacy endpoints are secondary (ORR) and exploratory (PFS, OS, and DOR) endpoints in this study. The ORR is defined as the percentage of participants who achieve a confirmed CR

or PR per PCWG-modified RECIST 1.1 or RECIST 1.1 as assessed by the investigator. Participants without response assessment will be counted as nonresponders. Details of the analysis plan will be documented in the sSAP for the exploratory objectives. A description of efficacy measures is provided in Section 8.2.

Pharmacokinetic endpoints include plasma concentrations of MK-1088 (and pembrolizumab), as well as derived PK parameters.

9.4.2 Safety Endpoints

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

A description of safety measures is provided in Section 8.3.

9.5 Analysis Populations

9.5.1 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 intervention. Participants who receive the incorrect study intervention will be summarized according to the actual study intervention they receive.

The DLT-evaluable population includes APaT participants that meet the criteria for DLT evaluability (eg, finished Cycle 1 without a DLT or experienced a DLT in Cycle 1). See Section 5.5 for details. Participants who are DLT nonevaluable will be eligible for inclusion in other analysis populations if they meet the respective criteria.

At least 1 laboratory or vital sign measurement obtained after at least 1 dose of study intervention is required for inclusion in the analysis of each specific parameter. A baseline measurement is also required to assess change from baseline.

Safety data from participants who experienced disease progression in the monotherapy arm and crossed over into the combination arm will be summarized in their initial monotherapy dose group until the time of cross over and will be summarized separately thereafter.

9.5.2 Pharmacokinetic Analysis Populations

The per-protocol population will be used for the analysis of PK and target engagement data in this study. The per-protocol population consists of the subset of participants who complied with the protocol sufficiently to ensure that their data will be likely to show 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 per-protocol analysis dataset.

9.5.3 Efficacy Analysis Populations

The FAS population will be used for the analyses of efficacy data in this study. It consists of all participants with a screening/baseline scan that showed measurable disease by the investigator's assessment, and who were administered at least 1 dose of study intervention. Participants who receive the incorrect study intervention will be summarized according to the actual study intervention they receive.

Efficacy data from participants who experienced disease progression in the monotherapy arm and crossed over into the combination arm will be summarized in their initial monotherapy dose group until the time of cross over and will be summarized separately thereafter.

9.6 Statistical Methods

This section describes the statistical methods that address the primary and secondary objectives. Methods related to exploratory endpoints will be described in the sSAP.

9.6.1 Statistical Methods for Efficacy Analysis

The statistical methods for efficacy analyses will be documented in the sSAP.

ORR will be estimated using an exact method based on the binomial distribution (Clopper-Pearson interval).

9.6.2 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.

AEs will be summarized by counts and frequencies for each dose level. Laboratory tests, vital signs, and other safety endpoints will be summarized as appropriate.

DLTs will be listed and summarized by dose level. The pool-adjacent-violators algorithm [Ji Y, Li Y, Bekele BN 2007], which forces the DLT rate estimates to be nondecreasing with increasing dose levels and pools adjacent violators for weighted estimates by sample size, will be used to estimate the DLT rates across doses in each treatment arm. The estimate of the DLT rate among participants treated at the RP2D and the 90% Bayesian credible interval based on a prior distribution of Beta (1,1) for the estimate will be provided.

9.6.3 Summaries of Baseline Characteristics, Demographics, and Other Analyses

9.6.3.1 Demographic and Baseline Characteristics

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

9.6.3.2 Pharmacokinetic and Pharmacodynamic Modeling Analysis

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

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

9.7 Interim Analyses

No interim analyses are planned. Data will be examined on a continuous basis to allow for dose-finding decisions.

9.8 Multiplicity

There will be no multiplicity adjustment since no hypothesis testing will be conducted.

9.9 Sample Size and Power Calculations

With a maximum sample size of 14 at each dose level, the overall sample size for this Phase 1/Phase 2 study is expected to be approximately 80. The actual sample size depends on the safety profiles and number of doses studied.

9.10 Subgroup Analyses

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

9.11 Compliance (Medication Adherence)

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

9.12 Extent of Exposure

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

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

10.1.1 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.

10.1.2 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 their 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, frequently 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.

10.1.3 Data Protection

The Sponsor will conduct this study in compliance with all applicable data protection regulations.

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 that would make the participant identifiable will not be transferred.

The participant must be informed that their 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 their 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.

10.1.3.1 Confidentiality of Data

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

10.1.3.2 Confidentiality of Participant Records

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

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

10.1.3.3 Confidentiality of IRB/IEC Information

The Sponsor is required to record the name and address of each IRB/IEC that reviews and approves this study. The Sponsor is also required to document that each IRB/IEC meets regulatory and ICH GCP requirements by requesting and maintaining records of the names

and qualifications of the IRB/IEC members and to make these records available for regulatory agency review upon request by those agencies.

10.1.4 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 ICMJE authorship requirements.

10.1.5 Compliance with Study Registration and Results Posting Requirements

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

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

10.1.6 Compliance with Law, Audit, and Debarment

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

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

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

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

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

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

10.1.7 Data Quality Assurance

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

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

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

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

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

The Sponsor or designee is responsible for the data management of this study including quality checking of the data.

Study monitors will perform ongoing source data review and verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the

study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

Records and documents, including participants' documented informed consent, 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.

10.1.8 Source Documents

Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. The investigator/institution should maintain adequate and accurate source documents and study records that include all pertinent observations on each of the site's participants. Source documents and data should be attributable, legible, contemporaneous, original, accurate, and complete. Changes to source data should be traceable, should not obscure the original entry, and should be explained if necessary (eg, via an audit trail). 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/institution may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

10.1.9 Study and Site Closure

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

In the event the Sponsor prematurely terminates a particular study site, the Sponsor or designee will promptly notify that study site's IRB/IEC as specified by applicable regulatory requirement(s).

10.2 Appendix 2: Clinical Laboratory Tests

- The tests detailed in Table 12 will be performed by the local laboratory.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5 of the protocol.
- Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.

Table 12 Protocol-required Safety Laboratory Assessments

Hematology	Comprehensive Chemistry Panel	Urinalysis	Other
Hematocrit	Albumin	Blood	Pregnancy test (serum or urine)[a]
Hemoglobin	Alkaline phosphatase	Glucose	
Platelet count	ALT	Protein	Total T3 (or Free T3 [FT3]), Total T4 (or Free T4 [FT4]), and TSH[b,c]
WBC (total and differential)[d]	AST	Specific gravity	
	Bicarbonate	Microscopic examination or, other standard diagnostic evaluation (if blood or protein is abnormal)	
RBC	Calcium		Anti-HCV[e]
Absolute lymphocyte count[d]	Chloride		HCV viral load[c,e]
	Creatinine		HCV genotype[c,e]
	Glucose		anti-HBs[c, e]
Absolute neutrophil count[d]	Phosphorus		HBsAg[e]
	Potassium		Anti-HBc (total and IgM)[c,e]
	Sodium		HBeAg[c, e]
PT/INR	Total bilirubin		anti-HBe[c,e]
aPTT or PTT	Direct bilirubin		HBV viral load[c,e]
	Total protein		GGT[f]
	Blood urea nitrogen (or Urea)		PSA

ALT=alanine aminotransferase; aPTT=activated partial thromboplastin time; AST=aspartate aminotransferase; BUN=blood urea nitrogen; GGT=gamma-glutamyl transpeptidase; HBc= hepatitis B core; HBe= hepatitis Be; HBeAg=hepatitis B e-antigen; HBs=hepatitis B surface; HBsAg=hepatitis B surface antigen; HCV=hepatitis C virus; IgM=immunoglobulin M; PT/INR=prothrombin time/international normalized ratio; PTT=partial thromboplastin time; RBC=red blood cell; T3=triiodothyronine; T4=thyroxine; TSH=thryroid stimulating hormone; WBC=white blood cell.

[a] Perform on women of childbearing potential only 72 hours before Day 1 of Cycle 1. Pregnancy tests must be repeated before every cycle if required or as specified per local regulatory guidance.

[b] T3 is preferred; if not available, Free T3 may be tested.

[c] If the local laboratory is unable to perform these tests, the site may send the samples to another laboratory certified to perform the test. Details are provided in the Procedure Manual.

[d] Report % or absolute results per standard of practice. Report the results in the same manner throughout the study.

[e] Tests are required for participants with known history or if local regulation mandates the testing.

[f] GGT is required as clinically indicated.

Investigators must document their review of each laboratory safety report.

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

10.3.1 Definitions of Medication Error, Misuse, and Abuse

Medication error

This is an unintended failure in the drug treatment process that leads to or has the potential to lead to harm to the patient.

Misuse

This refers to situations where the medicinal product is intentionally and inappropriately used not in accordance with the terms of the product information.

Abuse

This corresponds to the persistent or sporadic, intentional excessive use of a medicinal product for a perceived psychological or physiological reward or desired nontherapeutic effect.

10.3.2 Definition of AE

AE definition

- An AE is any untoward medical occurrence in a clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention.

- 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 intervention.

- Note: For purposes of AE definition, study intervention (also referred to as Sponsor's product) includes any pharmaceutical product, biological product, vaccine, diagnostic agent, medical device, combination product, or protocol specified procedure whether investigational or marketed (including placebo, active comparator product, or run-in intervention), manufactured by, licensed by, provided by, or distributed by the Sponsor for human use in this study.

Events meeting the AE definition

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator.

- Exacerbation of a chronic or intermittent preexisting condition including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after study intervention 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 intervention or a concomitant medication.
- For all reports of overdose (whether accidental or intentional) with an associated AE, the AE term should reflect the clinical symptoms or abnormal test result. An overdose 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). Progression of the cancer under study is not a reportable event. Refer to Section 8.4.6 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 preexisting disease(s) or condition(s) present or detected at the start of the study that do not worsen.
- Surgical procedure(s) planned prior to informed consent to treat a preexisting condition that has not worsened.
- Refer to Section 8.4.6 for protocol-specific exceptions.

10.3.3 Definition of SAE

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

An SAE is defined as any untoward medical occurrence that, at any dose:

a. Results in death

b. Is life-threatening

- The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

c. Requires inpatient hospitalization or prolongation of existing hospitalization

- Hospitalization is defined as an inpatient admission, regardless of length of stay, even if the hospitalization is a precautionary measure for continued observation. (Note: Hospitalization for an elective procedure to treat a preexisting condition that has not worsened is not an SAE.) A preexisting condition is a clinical condition that is diagnosed prior to the use of an MSD product and is documented in the participant'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) that 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 1 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.

10.3.4 Additional Events Reported in the Same Manner as SAE

Additional events that require reporting in the same manner as SAE

In addition to the above criteria, AEs meeting either of the below criteria, although not serious per ICH definition, are reportable to the Sponsor in the same time frame as SAEs to meet certain local requirements. Therefore, these events are considered serious by the Sponsor for collection purposes.

- Is a new cancer (that is not a condition of the study)
- Is associated with an overdose

10.3.5 Recording AE and SAE

AE and SAE recording

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

Assessment of intensity /toxicity

- 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 CTCAE, version 5.0. Any AE that changes CTCAE grade over the course of a given episode will have each change of grade recorded on the AE CRFs/worksheets.
    - Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.

- Grade 2: Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL.

- Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL.

- Grade 4: Life threatening consequences; urgent intervention indicated.

- Grade 5: Death related to AE.

Assessment of causality

- Did the Sponsor's product cause the AE?

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

- **The following components are to be used to assess the relationship between the Sponsor's product and the AE; the greater the correlation with the components and their respective elements (in number and/or intensity), the more likely the Sponsor's product caused the AE:**

  - **Exposure:** Is there evidence that the participant was actually exposed to the Sponsor's product such as: reliable history, acceptable compliance assessment (pill count, diary, etc), expected pharmacologic effect, or measurement of drug/metabolite in bodily specimen?

  - **Time Course:** Did the AE follow in a reasonable temporal sequence from administration of the Sponsor's product? Is the time of onset of the AE compatible with a drug-induced effect (applies to studies with IMP)?

  - **Likely Cause:** Is the AE not reasonably explained by another etiology such as underlying disease, other drug(s)/vaccine(s), or other host or environmental factors.

  - **Dechallenge:** Was the Sponsor's product discontinued or dose/exposure/frequency reduced?

    - If yes, did the AE resolve or improve?

    - If yes, this is a positive dechallenge.

    - If no, this is a negative dechallenge.

(Note: This criterion is not applicable if: (1) the AE resulted in death or permanent disability; (2) the AE resolved/improved despite continuation of the Sponsor's product; (3) the study is a single-dose drug study; or (4) Sponsor's product(s) is/are only used 1 time.)

- **Rechallenge:** Was the participant re-exposed to the Sponsor's product in this study?
  - If yes, did the AE recur or worsen?
  - If yes, this is a positive rechallenge.
  - If no, this is a negative rechallenge.

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

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

- **Consistency with study intervention 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 their 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 their 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 1 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 AE causality to the combination regimen or to a single agent of the combination. In general, causality attribution should be assigned to the combination regimen (ie, to all agents in the regimen). However, causality attribution may be assigned to a single agent if in the investigator's opinion, there is sufficient data to support full attribution of the AE 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.

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

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

- The primary mechanism for reporting to the Sponsor will be the EDC tool.

  - Electronic reporting procedures can be found in the EDC data entry guidelines (or equivalent).

  - If the electronic system is unavailable for more than 24 hours, then the site will use the paper AE Reporting form.

- Reference Section 8.4.1 for reporting time requirements.

- The site will enter the SAE data into the electronic system as soon as it becomes available.
- After the study is completed at a given site, the EDC tool will be taken off-line to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the EDC tool has been taken off-line, then the site can report this information on a paper SAE form or by telephone (see next section).
- Contacts for SAE reporting can be found in the Investigator Study File Binder (or equivalent).

SAE reporting to the Sponsor via paper CRF

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

10.4 Appendix 4: Medical Device and Drug-device Combination Products: Product Quality Complaints/Malfunctions: Definitions, Recording, and Follow-up

Not applicable.

10.5 Appendix 5: Contraceptive Guidance

10.5.1 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.

10.5.2 Contraception Requirements

Contraceptives allowed during the study include[a]:
Contraceptives allowed during the study include[a]:
Highly Effective Contraceptive Methods That Have Low User Dependency *Failure rate of <1% per year when used consistently and correctly.*
• Progestogen-only subdermal contraceptive implant[b,c] • IUS[c,d] • 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.
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] If locally required, in accordance with CTFG guidelines, acceptable contraceptive implants are limited to those which inhibit ovulation. [c] Male condoms must be used in addition to female participant hormonal contraception. [d] 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).

10.6 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[3, 4]

The specimens consented and/or collected in this study as outlined in Section 8.8 will be used in various experiments to understand:

a. The biology of how drugs/vaccines work

b. Biomarkers responsible for how a drug/vaccine enters and is removed by the body

c. Other pathways with which drugs/vaccines may interact

d. 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[3, 4]

a. Participants for Enrollment

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

b. Informed Consent

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

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

c. eCRF Documentation for Future Biomedical Research Specimens

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

d. Future Biomedical Research Specimen(s)

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

4. Confidential Participant Information for Future Biomedical Research[3, 4]

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

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

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

5. Biorepository Specimen Usage[3, 4]

Specimens obtained for the Sponsor will be used for analyses using good scientific practices. Analyses using the future biomedical research specimens may be performed by the Sponsor, or an additional third party (eg, a university investigator) designated by the Sponsor. The investigator conducting the analysis will follow the Sponsor's privacy and confidentiality requirements. Any contracted third party analyses will conform to the specific scope of analysis outlined in 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[3, 4]

Participants may withdraw their consent for FBR and ask that their biospecimens not be used for FBR. Participants may withdraw consent at any time by contacting the study investigator. If medical records for the study 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 study use only. If specimens were collected from study participants specifically for FBR, 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 before the request being received by the Sponsor will continue to be used as part of the overall research study data and results. No new analyses would be generated after the request is received.

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

7. Retention of Specimens[3, 4]

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

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

to Sponsor policies and procedures and this destruction will be documented in the biorepository database.

8. Data Security[3, 4]

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

9. Reporting of Future Biomedical Research Data to Participants[3, 4]

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[3, 4]

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

11. Risks Versus Benefits of Future Biomedical Research[3, 4]

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

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

12. Questions

Any questions related to the future biomedical research should be emailed directly to clinical.specimen.management@MSD.com.

13. References

1. National Cancer Institute [Internet]: Available from https://www.cancer.gov/publications/dictionaries/cancer-terms?cdrid=45618

2. International Council on Harmonisation [Internet]: E15: Definitions for Genomic Biomarkers, Pharmacogenomics, Pharmacogenetics, Genomic Data and Sample Coding Categories. Available from http://www.ich.org/products/guidelines/efficacy/efficacy-single/article/definitions-for-genomic-biomarkers-pharmacogenomics-pharmacogenetics-genomic-data-and-sample-cod.html

3. Industry Pharmacogenomics Working Group [Internet]: Understanding the Intent, Scope and Public Health Benefits of Exploratory Biomarker Research: A Guide for IRBs/IECs and Investigational Site Staff. Available at http://i-pwg.org/

4. Industry Pharmacogenomics Working Group [Internet]: Pharmacogenomics Informational Brochure for IRBs/IECs and Investigational Site Staff. Available at http://i-pwg.org/

10.7 Appendix 7: Country-specific Requirements

Not applicable

10.8 Appendix 8: Abbreviations

Abbreviation	Expanded Term
ADL	activities of daily living
AE	adverse event
ALT	alanine aminotransferase
APaT	All-Participants-as-Treated
ART	anti-retroviral therapy
AST	aspartate aminotransferase
AUC	area under the curve
BID	twice daily
CD	cluster of differentiation
CD3ζ	CD3 zeta
C_{max}	maximum plasma concentration
C_{min}	minimum plasma concentration
CNS	central nervous system
CONSORT	Consolidated Standards of Reporting Trials
COPD	chronic obstructive pulmonary disease
CR	complete response
CRF	Case Report Form
CSR	Clinical Study Report
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTCAE 5.0	Common Terminology Criteria for Adverse Events, Version 5.0
CTFG	Clinical Trial Facilitation Group
CTLA-4	cytotoxic T-lymphocyte-associated protein 4
C_{trough}	trough (minimum) concentration
CYP	cytochrome P450
DILI	drug-induced liver injury
DLT	dose-limiting toxicity
DNA	deoxyribonucleic acid
DOR	duration of response
DU	current dose is unacceptably toxic
ECG	electrocardiogram
ECI	event of clinical interest
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic Case Report Form
EDC	electronic data collection
eDMC	electronic Data Monitoring Committee
ELISA	enzyme-linked immunosorbent assay
EMA	European Medicines Agency
FAS	Full Analysis Set
FBR	future biomedical research
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act
FIH	first-in-human

Abbreviation	Expanded Term
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GI	gastrointestinal
GM-CSF	Granulocyte Macrophage Colony-Stimulating Factor
HbA1c	hemoglobin A1c
HBcAb	hepatitis B core antibody
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
hCG	human chorionic gonadotropin
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HRT	hormone replacement therapy
IB	Investigator's Brochure
IC	Informed Consent
ICF	Informed Consent Form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ICMJE	International Committee of Medical Journal Editors
IEC	Independent Ethics Committee
Ig	immunoglobulin
IgV	immunoglobulin-variable
IHC	immunohistochemistry
IMP	investigational medicinal product
IND	Investigational New Drug
IO	immune-oncology
irAEs	immune-related AEs
IRB	Institutional Review Board
IUD	intrauterine device
IUS	intrauterine hormone-releasing system
IV	intravenous
IVD	in vitro diagnostic
IVRS	interactive voice response system
LAM	lactational amenorrhea method
LLOQ	lower limit of quantification
LPLV	last participant last visit
MRI	magnetic resonance imaging
mRNA	messenger RNA
MSI	microsatellite instability
MTD	maximum tolerated dose
mTPI	modified Toxicity Probability Interval
NCI	National Cancer Institute
NIMP	noninvestigational medicinal product
NSCLC	non–small cell lung cancer
NYHA	New York Health Association
OR	objective response

Abbreviation	Expanded Term
ORR	objective response rate
OS	overall survival
PBPK	physiologically based PK
PCWG	Prostate Cancer Working Group
PD-1	programmed cell death 1 protein
PD-L1	programmed cell death ligand 1
PD-L2	programmed cell death ligand 2
PET	positron emission tomography
PFS	progression-free survival
PK	pharmacokinetic
PKCθ	protein kinase C-theta
PN	protocol number
po	orally
PP	Per-Protocol
PPI	proton-pump inhibitors
PQC	product quality complaint
PR	partial response
PSA	prostate-specific antigen
Q2W	every 2 weeks
Q3W	every 3 weeks
QD	once daily
QTcF	corrected QT interval by Fridericia
RECIST	Response Evaluation Criteria In Solid Tumors
RNA	ribonucleic acid
RP2D	recommended Phase 2 dose
SAE	serious adverse event
SAP	Statistical Analysis Plan
SIM	Site Imaging Manual
SLAB	Supplemental laboratory test(s)
SoA	schedule of activities
SOP	Standard Operating Procedures
sSAP	supplemental Statistical Analysis Plan
SUSAR	suspected unexpected serious adverse reaction
$t_{1/2}$	half life
TE	target engagement
T_{max}	time to maximum plasma concentration
TME	tumor microenvironment
ULN	upper limit of normal
US(A)	United States (of America)
WOCBP	woman/women of childbearing potential
ZAP70	zeta-chain-associated protein kinase

10.9 Appendix 9: Prostate Cancer Working Group Criteria

1. Description of the Prostate Cancer Working Group (PCWG) Process for Assessment of Bone Lesions

The rules for evaluation of response and progression based on bone lesions were created by the Prostate Cancer Working Group, and published as part of both PCWG2 and PCWG3[Scher, H. I., et al 2016]. All bone lesions are evaluated according to these rules, including assessment at screening and evaluation of response.

2. Imaging Methods

The PCWG rules were designed based on the radionuclide (Tc-99m) bone scintigraphy. Other modalities, including FDG-PET, sodium fluoride PET, bone MRI, etc. may have individual advantages, but the PCWG rules were not created with the performance characteristics of these methods in mind and should not be used instead of radionuclide bone scan.

Only bone lesions seen by bone scan may be followed for assessment of tumor treatment response. Bone disease seen by CT only (not visible on bone scan) is presumed not to represent active disease and should not be documented as a bone lesion (sclerotic lesions seen on CT may represent healed disease or nonmalignant confounders such as bone infarcts or other benign findings).

3. Documentation of Bone Lesions at Baseline

At screening, individual bone lesions may be recorded as non-target lesions only, and the number of bone lesions should be noted.

4. Assessment of Bone Response at Subsequent Imaging Time Points

At all follow-up time points, bone disease will be classified as PD, PDu, Non-PD, NED, or NE. The definitions are summarized in Table 13, and described in more detail below.

Table 13 Bone Response Abbreviations and Associated Definitions

Bone Response	Definition
PD	Progressive disease: 2 new lesions, not flare, persistent
PDu	Progressive disease unconfirmed: Temporary marker of possible PD, to be updated to PD or non-PD once a subsequent scan is available. If this is the final visit, the visit response will remain PDu, but is updated to PD during analysis by the Sponsor.
Non-PD	Non-progressive disease: At least one bone lesion present, but not enough to trigger PD
NE	Non-evaluable: Status of bone lesions cannot be determined (scan quality, scan missing, etc.)
NED	No evidence of disease: No lesions seen on bone scan

Abbreviations: NE=non-evaluable; NED=no evidence of disease; Non-PD=non-progressive disease; PD=progressive disease; PDu=progressive disease unconfirmed

5. Descriptions of Bone Response Categories

5.1 No Evidence of Disease

No lesions seen on bone scan at this visit. Either none were seen at screening, or all completely resolved on subsequent imaging.

5.2 Non-progression (Non-PD)

At least one bone lesion is present on the scan at this visit, but the conditions for progression have not been met, because there are not at least 2 new lesions present.

5.3 Unconfirmed Progressive Disease (PDu)

At least 2 new bone lesions are present, but an additional scan is required for confirmation. This response category is meant as a placeholder that reflects temporary uncertainty, and is updated to PD or non-PD once a subsequent bone scan is available.

5.4 Progressive Disease (PD)

At least 2 new bone lesions are present, which have been confirmed to not represent flare or any other confounder (see below), and which are persistent for at least 6 weeks. The new bone lesions do not all have to appear at the same time. Thus if one new lesion appears at visit N, and another new lesion at visit N+1, visit N+1 is considered to represent PD.

5.5 Confirmation of Progression

Radiographic progression of bone lesions is defined as the appearance of ≥ 2 new bone lesions on radionuclide bone scan. When ≥ 2 new bone lesions are first observed, this is classified as PD-U, which marks the possibility of progression that will be resolved by the next scan.

5.5.1 For new lesions within the flare window (<12 weeks)

After a scan classified as PDu within the first 12 weeks of treatment, if the next bone scan outside the flare window shows at least 2 additional new bone lesions (in addition to the new lesions seen on the prior scan), the initial progression is considered confirmed, and the bone scan response updated to PD. Because this requires at least 2 new lesions, followed by another 2 new lesions, this is known as the "2+2 rule".

If the next bone scan outside the flare window does not show at least 2 additional new bone lesions, the lesions seen on the prior scan within the flare window are considered to be preexisting lesions that became more visible because of the tumor flare phenomenon.

- The bone response at the prior visit is updated to non-PD.
- The bone lesions seen within the flare window are ignored for the purposes of counting new lesions at later timepoints, since they were not new. This may be referred to as "re-baselining".

5.5.2 For new lesions outside the flare window (> 12 weeks)

After a scan classified as PDu after the first 12 weeks of treatment, if at least 2 of the new lesions seen on that scan persist on the next bone scan performed at least 6 weeks later, this confirms the initial progression. The prior response is then updated to PD. If the new lesions have disappeared on this later scan, the prior response is updated to non-PD because these lesions are presumed to be nonmalignant in nature. No rebaselining of lesions will occur in this scenario.

5.6 Superscan

A "superscan" occurs when there is diffuse skeletal involvement by tumor, such that individual bone lesions are not distinguishable. The bone scan may initially appear normal, because the increase bone uptake may be uniform, but can be distinguished by the faint or absent activity in the kidneys and urinary tract.

If there is a true superscan at screening, identifying individual new bone lesions, and determining progression based on bone lesions, may be impossible.

If a superscan occurs after screening, the participant's bone response will be recorded as PD. No subsequent imaging will be required for confirmation, because a superscan is extremely unlikely to be caused by benign conditions or tumor flare.

5.7 Management Following Confirmed Progressive Disease

If repeat imaging does confirm PD, participants will be discontinued from study treatment.

Note: If a participant has confirmed radiographic progression as defined above, but the participant is achieving a clinically meaningful benefit, an exception to continue study treatment may be considered after consultation with the Sponsor. In this case, if study treatment is continued, tumor imaging should continue (reference the efficacy section of the protocol).

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