Official Protocol Title:	A Phase 1, Open-label, Multicenter Study to Assess Safety, Tolerability, PK, and Efficacy of MK-6598 as Monotherapy and in Combination With Pembrolizumab in Participants With Advanced Solid Tumors
NCT Number:	NCT05594043
Document Date:	01-Feb-2023

Title Page

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Protocol Title: A Phase 1, Open-label, Multicenter Study to Assess Safety, Tolerability, PK, and Efficacy of MK-6598 as Monotherapy and in Combination With Pembrolizumab in Participants With Advanced Solid Tumors

Protocol Number: 001-02

Compound Number: MK-6598

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	162743

Approval Date: 01 February 2023

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 02	01-FEB-2023	To incorporate revisions based on health authority feedback.
Amendment 01	13-SEP-2022	To correct the required duration of contraception and pregnancy testing during and following treatment with MK-6598.
Original Protocol	23-AUG-2022	Not applicable

PROTOCOL AMENDMENT SUMMARY OF CHANGES

Amendment: 02

Overall Rationale for the Amendments:

To incorporate revisions based on health authority feedback.

Summary of Changes Table:

Section # and Name	Description of Change	Brief Rationale
1.3.1 Schedule of Activities – Screening and Treatment Period 1.3.2 Schedule of Activities – For Crossover Participants	Added detail about the requirements for participants being considered for treatment beyond progression and crossover treatment.	To clarify protocol requirements about repeat informed consent and eligibility review.
6.6.4.4 Treatment Beyond Progression (Optional)	Revised this section to clarify and add detail about treatment beyond progression.	
6.6.2 Definition of Dose-limiting Toxicity	Revised the DLT definition and list of possible toxicities that will be considered a DLT.	To broaden the DLT definition to include any of the listed toxicities considered related to any study intervention by investigator assessment. To clarify the list of toxicities and capture any Grade 3 or Grade 4 nonhematologic laboratory value lasting more than 72 hours as a DLT.

Section # and Name	Description of Change	Brief Rationale
6.6.3 Guidelines for Dose Modification due to Adverse Events for MK-6598	Revised Table 6 MK-6598 Dose Modification and Treatment Discontinuation Guidelines for Drug-related Adverse Events.	MK-6598 will be permanently discontinued in the event of a Grade 4 nonhematologic 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).
6.6.4 Immune-related Events and Toxicity Modifications (Withhold, Treat, Discontinue)	Revised Table 8 Dose Modification and Toxicity Management Guidelines for Immune-related Adverse Events Associated with Pembrolizumab Monotherapy or IO Combinations (pembrolizumab + MK-6598).	To clarify that IO combinations refers to pembrolizumab + MK-6598.
5.1 Inclusion Criteria	Revised the adequate renal function cutoff value for CrCl or GFR to 60 mL/min in Table 3 Adequate Organ Function Laboratory Values.	To ensure participant safety until the routes of elimination of MK-6598 have been identified.
5.2 Exclusion Criteria	Added exclusion criterion number 21 to exclude participants with a QTc >470 msec.	To ensure participant safety until the effect of MK-6598 on the QT interval has been characterized.
6.5.2 Prohibited Concomitant Medications	Added medications that prolong the QT/QTc interval to the list of prohibited concomitant medications.	

Section # and Name	Description of Change	Brief Rationale
1.3.1 Schedule of Activities – Screening and Treatment Period 8.3.3 Electrocardiograms	Added ECG collections corresponding with blood collection for PK analysis. Removed details from Section 8.3.3 that are described more clearly in the SoA.	To monitor ECG at the expected C_{max} after the first dose and the expected steady state for MK-6598.
1.3.4 Schedule of Activities – PK Sample Collection 3 Hypotheses, Objectives, and Endpoints 8.6.2 Blood Collection for Pembrolizumab	Added sample collection for pembrolizumab PK.	In response to an FDA request.
6.6.4.4.2 Crossover	Added to the crossover eligibility that the participant must have completed the DLT evaluation period.	For consistency across protocol sections.
1.3.1 Schedule of Activities – Screening and Treatment Period 1.3.2 Schedule of Activities – For Crossover Participants	Added notes that Day 1 is always when a dose is administered and the scheduling window is for the visit day, unless otherwise indicated.	For clarity.

Section # and Name	Description of Change	Brief Rationale
1.3.1 Schedule of Activities – Screening and Treatment Period	Removed the Day 15 visit and associated assessments during Cycles 3 to 5. Added ECOG assessments on Day 15 of Cycles 1 and 2. Removed PT/INR and aPTT or PTT from Day 1 of Cycles 2+.	To correct errors and streamline the study assessments.
1.3.1 Schedule of Activities – Screening and Treatment Period 1.3.2 Schedule of Activities – For Crossover Participants 1.3.3 Schedule of Activities – Discontinuation, End of Treatment, and Follow-up	Added note to the Vital Signs rows: If the systolic blood pressure changes more than 10 mm Hg from the previous cycle, then blood pressure should be performed 5 minutes apart in triplicate. This was already stated in Section 8.3.2, but repeated in the SoAs for clarity.	For clarity.
1.3.1 Schedule of Activities – Screening and Treatment Period 1.3.2 Schedule of Activities – For Crossover Participants	Added a pregnancy test requirement for Day 1 of each cycle.	To provide more detailed pregnancy testing requirements.
8.3.5 Pregnancy Testing	Editorial revisions.	For clarity.

Section # and Name	Description of Change	Brief Rationale
1.3.4 Schedule of Activities – PK Sample Collection	Moved all details for PK sample collection to this new section and SoA table. Added sample collection windows. Added a Safety Follow-up blood sample collection for consistency with Section 8.6.1.	To present the PK sample collection schedule more clearly.
1.3.1 Schedule of Activities – Screening and Treatment Period	Increased the interval for collecting a pre-treatment tumor biopsy from Day -6 to Day -14.	For additional flexibility.
4.3.1.3 Dose Finding Using a Modified Toxicity Probability Interval Design	Added a clarifying statement that dose-escalation and de-escalation decisions depend on the number of participants with at least 1 DLT, not the number of DLTs.	For clarity.
4.4 Beginning and End-of-Study Definition	Added details about when the overall study ends and the definition of the local start of study in the EEA.	To align with EU CTR.
4.4.1 Clinical Criteria for Early Study Termination	Editorial revisions.	For clarity and to remove redundancy.
5 Study Population	Added a clarifying paragraph.	To refer to the Code of Conduct for Clinical Trials and restate that the collection and use of demographic data will follow all local laws and participant confidentiality guidelines while supporting the study of the disease, its related factors, and the IMP under investigation.

Section # and Name	Description of Change	Brief Rationale
5.1 Inclusion Criteria	Revisions to inclusion criterion number 5 for HIV-infected participants.	For clarity and to provide additional detail about AIDS-defining opportunistic infections and the combination ART regimen.
	Deleted the note from the end of Table 3.	The note was unnecessary.
	Revisions to inclusion criteria number 8, 9, and 10.	For clarity and to ensure gender inclusive language.
5.2 Exclusion Criteria	Revisions to exclusion criteria numbers 1, 8, 14, and 17.	For clarity and to remove redundancy.
	Added a note to exclusion criterion number 2.	To allow participants with low-risk early stage prostate cancer (as further defined in the exclusion).
	Replaced exclusion criterion number 12.	The previous exclusion about pregnancy or breastfeeding, or expecting to conceive or father children, was redundant (see inclusion criteria numbers 9 and 10); the current exclusion is required as participants with HIV may be eligible for this study.
	Revisions to exclusion criterion number 13.	For clarity and to remove unnecessary additional requirements.
6.7 Intervention After the End of the Study	Moved language from Section 4.4 to Section 6.7 about participants enrolling in an extension study using pembrolizumab, if available.	Section 6.7 is a more appropriate location for this information.

Section # and Name	Description of Change	Brief Rationale
7.3 Lost to Follow-up	Deleted the last bulleted note.	To allow a participant to be considered lost to follow-up as appropriate for the study.
8.1.6 Assignment of Screening Number	Added text about pre-trial screening logs.	To allow collection of pre-trial screening logs by the Sponsor.
8.1.7 Assignment of Treatment/Randomization Number Throughout Document	Removed references to randomization.	The study design does not include randomization.
8.1.12 Participants With Treated HIV	Added this new section.	To provide instructions on the management of participants with treated HIV.
8.4.1 Time Period and Frequency for Collecting AE, SAE, and Other Reportable Safety Event Information (Table 10) 10.3.4 Additional Events Reported	Clarified that new cancer and overdose AEs require reporting within 5 calendar days (SAEs are still reported with 24 hours).	For consistency throughout the protocol.
8.4.5 Pregnancy and Exposure During Breastfeeding	Added requirement that any pregnancy that occurs during the study in a nonparticipant whose sexual partner is a participant capable of producing ejaculate is reportable to the Sponsor.	To ensure gender inclusive language and collection of nonparticipant pregnancy information.

Section # and Name	Description of Change	Brief Rationale
8.5 Treatment of Overdose	Added clarification that the Sponsor must be contacted in the event of an MK-6598 overdose.	For clarity.
8.8.1 Planned Genetic Analysis Sample Collection	Added instructions on when to collect the planned genetic analysis sample.	For clarity.
8.10.3 Participants Discontinued From Study Intervention but Continuing to be Monitored in the Study	Added information about discontinuation visits.	For clarity.
10.5 Appendix 5: Contraceptive Guidance	Editorial revisions and formatting corrections.	For clarity and to ensure gender inclusive language.
Throughout Document	Minor administrative, formatting, grammatical, and typographical changes were made throughout the document.	To ensure clarity and accurate interpretation of the protocol.

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Confidential

1 PROTOCOL SUMMARY

1.1 Synopsis

Protocol Title: A Phase 1, Open-label, Multicenter Study to Assess Safety, Tolerability, PK, and Efficacy of MK-6598 as Monotherapy and in Combination With Pembrolizumab in Participants With Advanced Solid Tumors

Short Title: Phase 1 Study of MK-6598 in Advanced Solid Tumors

Acronym: Not applicable.

Hypotheses, Objectives, and Endpoints:

MK-6598 will be assessed in participants with advanced or recurrent/refractory tumors.

Objectives	Endpoints
Primary	
• To assess the safety and tolerability and to establish a preliminary recommended Phase 2 dose (RP2D) of MK-6598 administered as monotherapy and in combination with pembrolizumab infusion	• Dose-limiting toxicity (DLT) • Adverse event (AE) • Discontinuing study intervention due to an AE
Secondary	
• To evaluate the pharmacokinetics (PK) of MK-6598 administered orally as monotherapy and in combination with pembrolizumab • To evaluate the pharmacodynamics of MK-6598 administered orally as monotherapy and in combination with pembrolizumab	• PK parameters including area under the curve (AUC), minimum concentration (C_{min}) and maximum concentration (C_{max}) • Tumor phenylpyruvate concentrations.

Overall Design:

Study Phase	Phase 1
Primary Purpose	Treatment
Indication	Treatment of participants with advanced solid tumors
Population	Participants with advanced or recurrent/refractory 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 5 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:

The overall sample size for this study is expected to be approximately 90 (45 per arm). The maximum total sample size could be approximately 168. The actual sample size depends on the safety profiles and number of doses studied.

Intervention Groups and Duration:

<table>
<tr><td>Intervention Groups</td><td>
<table>
<tr><th>Inter-vention Group Name</th><th>Drug</th><th>Dose Strength</th><th>Dose Frequency</th><th>Route of Adminis-tration</th><th>Regimen/ Treatment Period</th><th>Use</th></tr>
<tr><td>Arm 1</td><td>MK-6598</td><td>25 mg and 100 mg tablets</td><td>QD</td><td>oral</td><td>Continuous</td><td>Test Product</td></tr>
<tr><td rowspan="2">Arm 2</td><td>MK-6598</td><td>25 mg and 100 mg tablets</td><td>QD</td><td>oral</td><td>Continuous</td><td>Test Product</td></tr>
<tr><td>Pembrolizumab</td><td>100 mg/vial</td><td>Q3W</td><td>IV</td><td>35 cycles</td><td>Test product</td></tr>
<tr><td colspan="7">IV=intravenous; Q3W=every 3 weeks; QD=daily.</td></tr>
</table>
Other current or former name(s) or alias(es) for study intervention(s) are as follows: pembrolizumab; MK-3475; KEYTRUDA®
</td></tr>
<tr><td>Total Number of Intervention Groups/ Arms</td><td>2</td></tr>
<tr><td>Duration of Participation</td><td>Each participant will participate in the study for approximately 2.5 years 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 35 cycles (approximately 2 years) or until radiographically documented disease progression per RECIST 1.1 confirmed by site, unacceptable AEs, illness preventing further treatment, investigator’s decision to discontinue the participant, pregnancy of the participant, withdrawal of consent or administrative reasons requiring treatment discontinuation.

Participants assigned to receive monotherapy MK-6598 (Arm 1) may be eligible to receive combination therapy in the Crossover Phase after experiencing radiographically confirmed disease progression per RECIST 1.1 if deemed medically appropriate by the investigator in consultation with the Sponsor as described in Sections 4.1 and 6.6.4.4.</td></tr>
</table>

	After the end-of-treatment visit, each participant will be followed for the occurrence of AEs and spontaneously reported pregnancy as described in Section 8.4.1. All participants will be followed for progression-free survival then overall survival until death, withdrawal of consent, becoming lost to follow-up or end of the study.

Study Governance Committees:

Executive Oversight Committee	No
Data Monitoring Committee	No
Clinical Adjudication Committee	No
Study governance considerations are outlined in Appendix 1.	

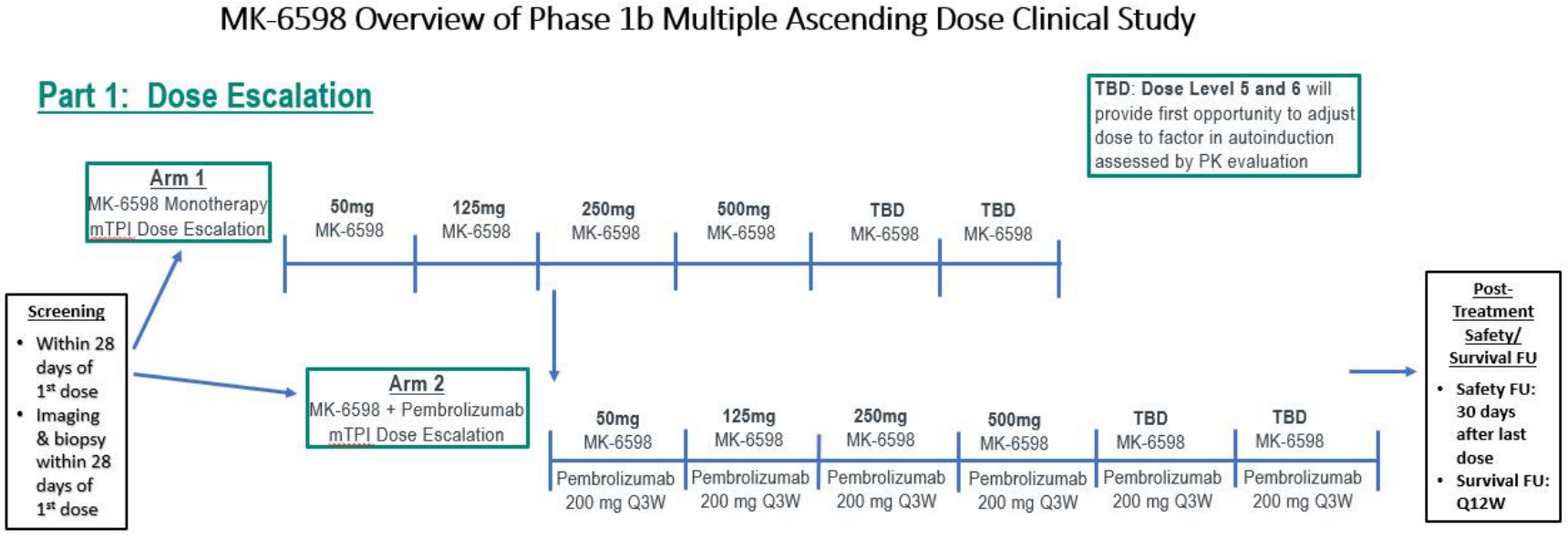
Study Accepts Healthy Volunteers: No

A list of abbreviations is in Appendix 8.

1.2 Schema

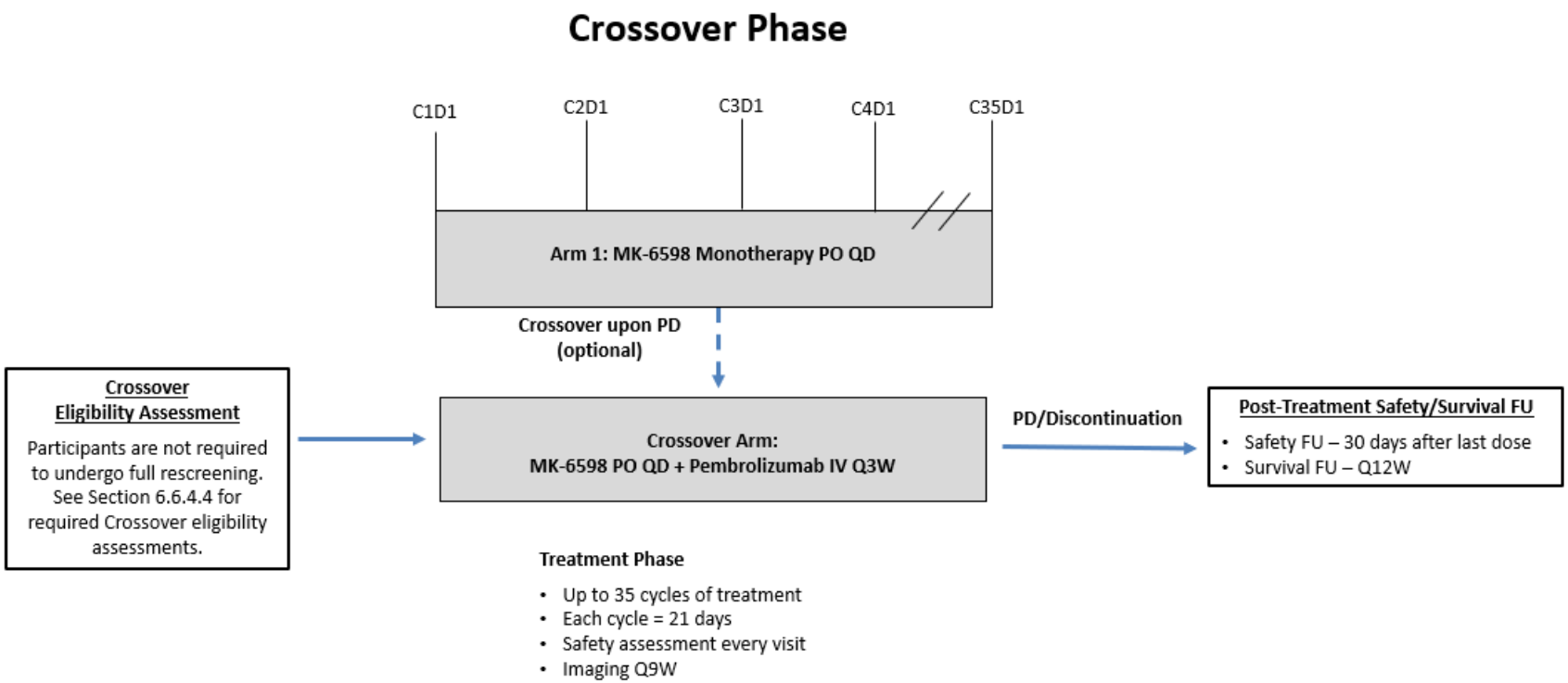
The study design is depicted in Figure 1.

Figure 1 Study Design



DLT=dose-limiting toxicity; mTPI=modified toxicity probability interval; FU=follow-up; PK=pharmacokinetics; Q3W=every 3 weeks; Q12W=every 12 weeks; TBD=to be determined.

MK-6598 will be administered in multiple ascending dose levels. The escalation of doses will be staggered, first as monotherapy then in combination with pembrolizumab as monotherapy dose cohorts clear for DLT.



C=Cycle; D=Day; FU=follow-up; IV=intravenously; PD=progressive disease; PO=oral; Q3W=every 3 weeks; Q9W=every 9 weeks; Q12W=every 12 weeks; QD=daily; RECIST=Response Evaluation Criteria In Solid Tumors.

Participants assigned to receive monotherapy MK-6598 (Arm 1) may be eligible to receive combination therapy in the Crossover Phase after experiencing radiographically confirmed disease progression per RECIST 1.1 if deemed medically appropriate by the investigator in consultation with the Sponsor as described in Sections 4.1 and 6.6.4.4.

Part 2 of this study (Expansion Phase in multiple indications in select tumor types) will be initiated through a protocol amendment.

1.3 Schedule of Activities

1.3.1 Schedule of Activities – Screening and Treatment Period

Activity	Screening	Treatment									Notes
Cycle (21-days)		**C1**					**C2**		**C3 to 5**	**≥C6**	
Treatment Day		**1**	**2**	**8**	**9**	**15**	**1**	**15**	**1**	**1**	**Day 1 is always when a dose is administered**
Scheduling Window (Days)	**Day -28 to Day -1**	**±0**	**±0**	**±1**	**±1**	**±1**	**±3**	**±1**	**±3**	**±3**	**Window is for visit day unless otherwise indicated. Procedure windows may vary**
Administrative Procedures											
Informed Consent	X										Tests (including tumor imaging) performed prior to consent as part of routine clinical management are acceptable if performed within the specified timeframe. Reconsent with ICF addendum(s) before crossover treatment or treatment beyond progression.
Informed Consent for FBR	X										
Inclusion/Exclusion criteria	X										Participants considered for crossover treatment are required to undergo eligibility review (see Section 6.6.4.4)
Treatment Assignment		X									
Issue Participant Identification Card	X	X									

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Activity	Screening	Treatment									Notes
Cycle (21-days)		**C1**					**C2**		**C3 to 5**	**≥C6**	
Treatment Day		**1**	**2**	**8**	**9**	**15**	**1**	**15**	**1**	**1**	**Day 1 is always when a dose is administered**
Scheduling Window (Days)	**Day -28 to Day -1**	**±0**	**±0**	**±1**	**±1**	**±1**	**±3**	**±1**	**±3**	**±3**	**Window is for visit day unless otherwise indicated. Procedure windows may vary**
Demographics and Medical History	X										
Oncology Disease Details and Prior Oncologic Treatment	X										
Prior and Concomitant Medications	X	X	X	X	X	X	X	X	X	X	
MK-6598 Dispensed to Participants		X					X		X	X	
Participants Return Unused MK-6598 Tablets							X		X	X	
MK-6598 Daily Dose Administered		X	X	X	X	X	X	X	X	X	To be administered after required blood sample collections (Central Laboratory Assessments, below). MK-6598 will be witnessed in the clinic on these visit days.
Pembrolizumab Administration (Arm 2 only)		X					X		X	X	For Arm 2 participants, refer to the Pharmacy Manual for the order in which treatments are to be administered.

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Activity	Screening	Treatment									Notes
Cycle (21-days)		**C1**					**C2**		**C3 to 5**	**≥C6**	
Treatment Day		**1**	**2**	**8**	**9**	**15**	**1**	**15**	**1**	**1**	**Day 1 is always when a dose is administered**
Scheduling Window (Days)	**Day -28 to Day -1**	**±0**	**±0**	**±1**	**±1**	**±1**	**±3**	**±1**	**±3**	**±3**	**Window is for visit day unless otherwise indicated. Procedure windows may vary**
Efficacy Procedures											
Tumor Imaging (CT or MRI as Indicated) (RECIST 1.1, Response Assessment)	X								X	X	At 9 weeks (± 7 days), and then every 9 weeks thereafter (± 7 days) until completion or progression.
Clinical/Safety Assessments and Procedures											
Full Physical Examination	X										
Height	X										
Directed Physical Examination		X					X		X	X	At the investigator's discretion.
Vital Signs	X	X	X	X	X	X	X	X	X	X	Temperature, pulse rate, respiratory rate, and blood pressure. If the systolic blood pressure changes more than 10 mm Hg from the previous cycle, then blood pressure should be performed 5 min apart in triplicate.

Activity	Screening	Treatment									Notes
Cycle (21-days)		**C1**					**C2**		**C3 to 5**	**≥C6**	
Treatment Day		**1**	**2**	**8**	**9**	**15**	**1**	**15**	**1**	**1**	**Day 1 is always when a dose is administered**
Scheduling Window (Days)	**Day -28 to Day -1**	**±0**	**±0**	**±1**	**±1**	**±1**	**±3**	**±1**	**±3**	**±3**	**Window is for visit day unless otherwise indicated. Procedure windows may vary**
12-lead ECG	X	X		X		X	X			X[a]	Cycle 1 Days 1, 8, and 15: perform ECG after MK-6598 dosing at 30 min (±5 min), 45 min (±5 min), 60 min (±5 min), and 2 hrs (±15 min) (corresponding with blood collection for PK analysis). Note: If the ECG at 45 min can only be performed within 10 min of either the 30 min or 60 min ECG, then it is considered redundant and the ECG at 45 min may be omitted. A single, resting (at least 10 min) ECG will be collected predose MK-6598 on C1D1, C2D1, and [a] then once every 5 cycles.
ECOG Performance Status	X	X[a]				X	X	X	X	X	[a] Not required if screening assessment performed ≤72 hrs before C1D1. Can be assessed within 72 hrs of next study visit.
AE Monitoring	X	X	X	X	X	X	X	X	X	X	

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Activity	Screening	Treatment									Notes
Cycle (21-days)		**C1**					**C2**		**C3 to 5**	**≥C6**	
Treatment Day		**1**	**2**	**8**	**9**	**15**	**1**	**15**	**1**	**1**	**Day 1 is always when a dose is administered**
Scheduling Window (Days)	**Day -28 to Day -1**	**±0**	**±0**	**±1**	**±1**	**±1**	**±3**	**±1**	**±3**	**±3**	**Window is for visit day unless otherwise indicated. Procedure windows may vary**
Local Laboratory Assessments											
CBC with Differential	X	X	X				X		X	X	Tests do not have to be repeated at C1 if the screening laboratory tests were within 72 hrs before the first dose of study medication and within acceptable limits. [a] Thyroid testing to be performed at every other cycle (predose on Day 1 of cycles where these samples are collected) during the treatment period.
Chemistry Panel	X	X	X				X		X	X	
Thyroid Function Testing: T_4 or FT_4, T_3 or FT_3, TSH	X								X[a]	X[a]	
PT/INR and aPTT or PTT	X	X									As clinically indicated, for participants on anticoagulant therapy.
Pregnancy Test for POCBP Only (Urine or Serum hCG)	X	X					X		X	X	To be collected within 24 hrs (urine)/72 hrs (serum) of C1D1. Additional testing may be done more frequently when clinically indicated and/or per local regulations (Inclusion Criterion 10).
Urinalysis	X										Assessment by dipstick is allowed.

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Activity	Screening	Treatment									Notes
Cycle (21-days)		**C1**					**C2**		**C3 to 5**	**≥C6**	
Treatment Day		**1**	**2**	**8**	**9**	**15**	**1**	**15**	**1**	**1**	**Day 1 is always when a dose is administered**
Scheduling Window (Days)	**Day -28 to Day -1**	**±0**	**±0**	**±1**	**±1**	**±1**	**±3**	**±1**	**±3**	**±3**	**Window is for visit day unless otherwise indicated. Procedure windows may vary**
Central Laboratory Assessments											
Blood for MK-6598 PK Analysis (Arm 1 and Arm 2)	See Section 1.3.4 for details										
Blood for pembrolizumab PK Analysis (Arm 2 only)											
Biomarker Assessments											
Blood for Genetic Analysis		X									Draw predose before study intervention administration.
Tumor Tissue Collection											
Archival or Newly Obtained Tissue Collection	X										An archival tissue sample is preferred. If archival tissue is not available, a new biopsy will be obtained. Collected tissue will be used for exploratory objectives and biomarker research.

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Activity	Screening	Treatment									Notes
Cycle (21-days)		**C1**					**C2**		**C3 to 5**	**≥C6**	
Treatment Day		**1**	**2**	**8**	**9**	**15**	**1**	**15**	**1**	**1**	**Day 1 is always when a dose is administered**
Scheduling Window (Days)	**Day -28 to Day -1**	**±0**	**±0**	**±1**	**±1**	**±1**	**±3**	**±1**	**±3**	**±3**	**Window is for visit day unless otherwise indicated. Procedure windows may vary**
Tumor Biopsy	X[a]						X[b]				[a] Mandatory. Must be collected Days -14 to -1. [b] Mandatory. Must be collected predose and within 3 days before study intervention administration on C2D1.

AE=adverse event; aPTT=activated partial thromboplastin time; C=cycle; CBC=complete blood cell (count); CT=computed tomography; D=day; ECG=electrocardiogram; ECOG=Eastern Cooperative Oncology Group; FBR=future biomedical research; FT_3=free triiodothyronine; FT_4=free thyroxine; hCG=human chorionic gonadotropin; hrs=hours; INR=international normalized ratio; min=minutes; MRI=magnetic resonance imaging; PK=pharmacokinetic(s); POCBP=participant of childbearing potential; PT=prothrombin time; PTT=partial thromboplastin time; RECIST 1.1=Response Evaluation Criteria In Solid Tumors version 1.1; T_3=triiodothyronine; T_4=thyroxine; TSH=thyroid-stimulating hormone.

1.3.2 Schedule of Activities – For Crossover Participants

Activity	Treatment			Notes
Cycle (21-days)	**C1 and C2**	**C3 to 5**	**≥C6**	
Treatment Day	**1**	**1**	**1**	**Day 1 is always when a dose is administered.**
Scheduling Window (Days)	**±0[a]**	**±3**	**±3**	**Window is for visit day unless otherwise indicated. Procedure windows may vary.** **[a] Scheduling window for Cycle 2 Day 1 is ±3 days.**
Administrative Procedures				
Informed Consent	X			Reconsent with ICF addendum(s) before crossover treatment or treatment beyond progression. Tests performed prior to consent as part of routine clinical management or as part of the initial treatment phase are acceptable if performed within the specified timeframe.
Inclusion/Exclusion Criteria	X			Participants considered for crossover treatment are required to undergo eligibility review.
Prior and Concomitant Medications	X	X	X	
MK-6598 Dispensed to Participants	X	X	X	
Participants Return Unused MK-6598 Tablets	X	X	X	
MK-6598 Daily Dose Administered	X	X	X	Study treatments to be administered after collection of required blood samples (see Central Laboratory Assessments below). MK-6598 administration will be witnessed in the clinic on these visit days.
Pembrolizumab Administration	X	X	X	Refer to the Pharmacy Manual for the order in which treatments are to be administered.

Activity	Treatment			Notes
Cycle (21-days)	**C1 and C2**	**C3 to 5**	**≥C6**	
Treatment Day	**1**	**1**	**1**	**Day 1 is always when a dose is administered.**
Scheduling Window (Days)	**±0[a]**	**±3**	**±3**	**Window is for visit day unless otherwise indicated. Procedure windows may vary.** **[a] Scheduling window for Cycle 2 Day 1 is ±3 days.**
Efficacy Procedures				
Tumor Imaging (CT or MRI as Indicated) (RECIST 1.1, Response Assessment)	X[a]	X	X	At 9 weeks (± 7 days), and then every 9 weeks thereafter (± 7 days) until completion or progression. [a] Scan at C1D1 only if the last scan was >28 days prior to first crossover dose. This scan will be used to re-baseline the tumors.
Clinical/Safety Assessments and Procedures				
Directed Physical Examination	X	X	X	At the investigator's discretion.
Vital Signs	X	X	X	Temperature, pulse rate, respiratory rate, and blood pressure. If the systolic blood pressure changes more than 10 mm Hg from the previous cycle, then blood pressure should be performed 5 min apart in triplicate.
12-lead ECG	X[a]		X[b]	Perform a single, resting (at least 10 min) ECG on C1D1. [a] ECG does not have to be repeated in C1 if the DC ECG from the initial treatment phase was completed within 21 days of the crossover first dose. ECGs will be collected before MK-6598 dosing, and [b] then once every 5 cycles.
ECOG Performance Status	X[a]	X	X	[a] Not required if screening assessment performed within 7 days before C1D1. Can be assessed within 7 days of next study visit.
AE Monitoring	X	X	X	

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Activity	Treatment			Notes
Cycle (21-days)	**C1 and C2**	**C3 to 5**	**≥C6**	
Treatment Day	**1**	**1**	**1**	**Day 1 is always when a dose is administered.**
Scheduling Window (Days)	**±0[a]**	**±3**	**±3**	**Window is for visit day unless otherwise indicated. Procedure windows may vary.** **[a] Scheduling window for Cycle 2 Day 1 is ±3 days.**
Local Laboratory Assessments				
CBC with Differential	X	X	X	Repeat at C1 only if the last evaluation was done >72 hrs before the first crossover dose.
Chemistry Panel	X	X	X	
Thyroid Function Testing: T_4 or FT_4, T_3 or FT_3, TSH	X[a]	X[a]	X[a]	[a] Thyroid testing to be performed at every other cycle (predose on Day 1 of cycles where these samples are collected) during the treatment period.
PT/INR and aPTT or PTT	X			As clinically indicated, for participants on anticoagulant therapy.
Pregnancy Test for POCBP Only (Urine or Serum hCG)	X	X	X	To be collected within 24 hrs (urine)/72 hrs (serum) of C1D1. Additional testing may be done more frequently when clinically indicated and/or per local regulations (Inclusion Criterion 10).
Urinalysis	X			Assessment by dipstick is allowed.

AE=adverse event; aPTT=activated partial thromboplastin time; C=cycle; CBC=complete blood cell (count); CT=computed tomography; D=day; DC=discontinuation; ECG=electrocardiogram; ECOG=Eastern Cooperative Oncology Group; FT_3=free triiodothyronine; FT_4=free thyroxine; hCG=human chorionic gonadotropin; hrs=hours; INR=international normalized ratio; min=minutes; MRI=magnetic resonance imaging; POCBP=participant of childbearing potential; PT=prothrombin time; PTT=partial thromboplastin time; RECIST 1.1=Response Evaluation Criteria In Solid Tumors version 1.1; T_3=triiodothyronine; T_4=thyroxine; TSH=thyroid-stimulating hormone.

1.3.3 Schedule of Activities – Discontinuation, End of Treatment, and Follow-up

DC / EOT / Follow-up SoA					
	EOT / DC	**Safety Follow-up**	**Imaging Follow-up**	**Survival Follow-up**	**Notes**
Treatment Day	**At Treatment Discontinuation**	**30 Days After Last Dose**	**Every 12 Weeks**	**Every 12 Weeks**	
Visit Window (Days)	**±7**	**±7**	±14	±14	
Administrative Procedures					
Prior and Concomitant Medication	X	X			
New Anticancer Therapy Status	X	X	X	X	
Survival Status Monitoring				X	Survival Follow-up will occur every 12 weeks (± 14 days) after discontinuation from imaging follow-up. On request, participants may also be contacted for survival status at any time.
Efficacy Procedures					
Tumor Imaging (CT or MRI as Indicated) (RECIST 1.1 Response Assessment)	X		X		All imaging should be performed at time of discontinuation. Evaluation window ± 4 weeks. Additional imaging as clinically indicated. If imaging was performed within 4 weeks before EOT, imaging does not need to be performed at EOT.

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DC / EOT / Follow-up SoA					
	EOT / DC	**Safety Follow-up**	**Imaging Follow-up**	**Survival Follow-up**	**Notes**
Treatment Day	**At Treatment Discontinuation**	**30 Days After Last Dose**	**Every 12 Weeks**	**Every 12 Weeks**	
Visit Window (Days)	**±7**	**±7**	±14	±14	
Clinical/Safety Assessments and Procedures					
Full Physical Examination	X	X			
Vital Signs	X	X			Temperature, pulse rate, respiratory rate, and blood pressure. If the systolic blood pressure changes more than 10 mm Hg from the previous cycle, then blood pressure should be performed 5 min apart in triplicate.
12-lead ECG	X	X			
ECOG Performance Status	X	X			
AE Monitoring	X	X			
Local Laboratory Assessments					
CBC with Differential	X	X			
Chemistry Panel	X	X			
Thyroid Function Testing: T_4 or FT_4, T_3, or FT_3, TSH	X				
Pregnancy Test for POCBP Only (Urine or Serum)	X	X	see note		As clinically indicated and/or per local regulations for 120 days after last dose of pembrolizumab or 42 days after the last dose of MK-6598, whichever is longer (see Section 8.3.5 and Inclusion Criterion 10).

AE=adverse event; CBC=complete blood cell (count); CT=computed tomography; DC=discontinuation; ECG=electrocardiogram; ECOG=Eastern Cooperative Oncology Group; EOT=end of treatment; FT_3=free triiodothyronine; FT_4=free thyroxine; min=minutes; MRI=magnetic resonance imaging; POCBP=participant of childbearing potential; RECIST 1.1=Response Evaluation Criteria In Solid Tumors version 1.1; SoA=schedule of activities; T_3=triiodothyronine; T_4=thyroxine; TSH=thyroid-stimulating hormone.

1.3.4 Schedule of Activities – PK Sample Collection

Activity	**Treatment**														**Notes**
Cycle (21-days)	**C1**					**C 2**	**C 5**	**C 8**	**C 10**	**C 15**	**C 20**	**C 25**	**C 30**	**C 35**	**Safety Follow-up**	
Treatment Day	**1**	**2**	**8**	**9**	**15**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**30 Days After Last Dose**	
Scheduling Window (Days)	**±0**	**±0**	**±1**	**±1**	**±1**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±7**	
Blood for MK-6598 PK Analysis (Arm 1 and Arm 2)	X[a]	X	X[a]	X	X[a]	X	X		X	X	X	X	X	X	X	Collect predose (within 2 hrs) before MK-6598 administration. [a] In addition to predose, collect postdose at 30 min (±5 min), 45 min (±5 min), 60 min (±5 min), 2 hrs (±15 min), and 6 hrs (±15 min)
Blood for pembrolizumab PK Analysis (Arm 2 only)	X[a]					X[a]	X[a]	X[b]							X	[a] Collect predose (within 24 hrs) before pembrolizumab infusion and 30 min (±5 min) after oral dosing with MK-6598 [b] Collect predose only (within 24 hours) before pembrolizumab infusion

C=cycle; hrs=hours; min=minutes; PK=pharmacokinetic(s).

2 INTRODUCTION

MK-6598 is a novel small molecule inhibitor of the immunosuppressive enzyme IL4I1 for use as a single-agent therapy or in combination with pembrolizumab or other oncology therapeutics across multiple tumor indications. This is a FIH, dose-escalation, and dose finding study to assess the safety and tolerability of MK-6598, both as monotherapy and in combination with pembrolizumab in Part 1 of the study. Part 2 will be added as a protocol amendment. Refer to the MK-6598 IB for further information.

2.1 Study Rationale

IL4I1, which was identified after treating splenocytes with the cytokine interleukin-4 [Chu, C. C. 1997], is a secreted extracellular enzyme involved in oxidative deamination of aromatic L-amino acids to produce H_2O_2 and other metabolites [Molinier-Frenkel, V., et al 2019]. Excess H_2O_2 in the TME suppresses T-cell activity and prevents antitumor immunity. Degradation of essential amino acids by IL4I1 further constrains the antitumor immune response by restricting infiltrating immune cell metabolism.

It is hypothesized that inhibition of IL4I1 will alleviate T-cell suppression in the TME to allow increased antitumor immune response either alone or in combination with pembrolizumab. Preclinical data show that IL4I1 is differentially expressed in tumors as compared with normal tissue and, consistent with its role as an inducible negative feedback mechanism, IL4I1 expression is higher in GEP high tumors (ie, T-cell inflamed tumors) compared to GEP low tumors. Overall, IL4I1 has been found to be highly expressed in ovarian, endometrial cancers and B cell lymphomas. IL4I1 is also expressed and secreted by myeloid cells, among other cell types, providing an opportunity to target a T cell suppression mechanism that arises from both tumor cells themselves as well as myeloid components of the TME.

It is hypothesized that inhibition of IL4I1 will improve PD-1/L1 efficacy in combination therapy or for patients who have previously received a PD-1/L1 inhibitor. It could also be combined with other modalities and may have monotherapy activity.

2.2 Background

2.2.1 Pharmaceutical and Therapeutic Background

2.2.1.1 MK-6598 Pharmaceutical and Therapeutic Background

Cellular and molecular interactions in the TME drive tumor growth and malignant progression [Hanahan, D. 2022]. Infiltration and activation of cellular components of the innate and adaptive immune system restricts this growth and progression, representing an opportunity to promote antitumor immunity [Anandappa, A. J., et al 2020] The high metabolic needs of activated T cells make them particularly susceptible to biochemical modifications in the TME. Components of the evolutionarily conserved host response to infection, including upregulation of LAAOs such as IL4I1, can alter T-cell metabolism and impact antitumor immunity.

Tumors upregulate immune-suppressive pathways that can be therapeutically targeted. While immune therapies targeting PD-1/L1, including pembrolizumab, have transformed cancer treatment, suppressed T-cell inflammation in the TME is associated with resistance to immunotherapy. Developing treatments that restore T-cell activity in the TME and allow greater effectiveness of immunotherapy remain a significant unmet medical need.

MK-6598 is a novel, potent, orally available small molecule inhibitor of the immunosuppressive IL4I1 enzyme (IC_{50} = 14 nM) with complete selectivity over its nearest neighbor amine oxidases (MAO-A, MAO-B, LSD1 >5000-fold) as well as all potential off-targets tested.

Inhibition of IL4I1 activity prevents accumulation of the immunosuppressive metabolite H_2O_2, which impacts tumor growth. Genetic knockout of IL4I1 in the Ret model of spontaneous melanoma delayed tumor development and metastasis [Bod, L., et al 2018]. In a second study using chimeric mice reconstituted with IL4I1 knockout progenitor bone marrow cells, another group demonstrated that loss of IL4I1 resulted in suppressed progression of the Eu-TCL1 model of chronic lymphocytic leukemia [Sadik, A., et al 2020], Conversely, forced expression of IL4I1 in an immunogenic variant of the B16 melanoma model caused tumors to develop in over 50% of recipients whereas none of the mice in the control arm without IL4I1 expression developed tumors [Lasoudris, F., et al 2011].Together, these data link IL4I1 activity with tumor growth and immune evasion.

IL4I1 and downstream metabolites such as phenylpyruvate are differentially expressed at both the mRNA and protein level in tumors compared with normal tissue. Notably, phenylpyruvate is readily detected in human tumor biopsies but rarely, if ever, detected in matched normal tissue. Bioinformatic analysis of pembrolizumab response data, The Cancer Genome Atlas, and Moffitt Cancer Center databases revealed elevated expression in GEP high tumors. These preclinical data suggest a therapeutic window for targeting a critical and inducible suppressor of antitumor immunity. Production of IL4I1 by myeloid cells in addition to tumor cells offers another mechanism to enhance antitumor immunity across tumor types and potentially independent of tumor IL4I1 expression.

MK-6598 may demonstrate efficacy as monotherapy in cancers where IL4I1 is active. The mechanism of T-cell suppression by IL4I1 via generation of H_2O_2 is independent of checkpoints such as PD-1 and therefore it is anticipated that MK-6598 will be effective in combination with agents that act in the TME to promote T-cell activity, such as pembrolizumab. The specific populations intended for MK-6598 plus pembrolizumab combination therapy are those that have evidence of relatively high IL4I1 expression in the tumor and where pembrolizumab is either a SOC or undergoing investigational trials.

Refer to the IB for detailed background information on MK-6598.

2.2.2 Preclinical and Clinical Studies

2.2.2.1 Preclinical Studies

Refer to MK-6598 IB for details.

2.2.3 Ongoing Clinical Studies

There are no ongoing studies with MK-6598.

2.2.3.1 MK-6598 Clinical Studies

This is a FIH study of MK-6598 and there are no clinical data yet available. Please refer to the MK-6598 IB and the pembrolizumab IB for detailed background information.

2.2.4 Information on Other Study-related Therapy

Refer to the pembrolizumab IB for information.

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.

MK-6598 nonclinical studies showed mild changes in BP, HR, and ECG tracings at high doses in animal models.

The combination of MK-6598 and pembrolizumab has the potential to increase the frequency and/or severity of immune-related toxicities compared with each agent individually.

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

MK-6598 will be assessed in participants with advanced or recurrent/refractory tumors.

Objectives	Endpoints
Primary	
• To assess the safety and tolerability and to establish a preliminary recommended Phase 2 dose (RP2D) of MK-6598 administered as monotherapy and in combination with pembrolizumab infusion	• Dose-limiting toxicity (DLT) • Adverse event (AE) • Discontinuing study intervention due to an AE

Objectives	Endpoints
Secondary	
• To evaluate the pharmacokinetics (PK) of MK-6598 administered orally as monotherapy and in combination with pembrolizumab • To evaluate the pharmacodynamics of MK-6598 administered orally as monotherapy and in combination with pembrolizumab	• PK parameters including area under the curve (AUC), minimum concentration (C_{min}) and maximum concentration (C_{max}) • Tumor phenylpyruvate concentrations.
Tertiary/Exploratory	
• To evaluate ORR, PFS, and DOR of participants treated with MK-6598 both as monotherapy and in combination with pembrolizumab using RECIST 1.1 as assessed by the investigator	• Objective response (OR): A confirmed complete response (CR) or partial response (PR) • Progression-free survival (PFS): The time from allocation to the first documented disease progression or death due to any cause, whichever occurs first • Duration of response (DOR): 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 a CR or PR.
• To evaluate overall survival of participants treated with MK-6598 both as monotherapy and in combination with pembrolizumab.	• Overall survival (OS): The time from first study treatment to the date of death due to any cause.
• 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-6598 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

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Objectives	Endpoints
• To evaluate the PK of pembrolizumab administered in combination with MK-6598.	• PK parameters including AUC, C_{min}, and C_{max}

4 STUDY DESIGN

4.1 Overall Design

MK-6598-001 is a FIH Phase 1 multicenter, 2-arm, open-label dose-escalation and dose confirmation study, to evaluate the safety, tolerability, PK, and efficacy of MK-6598 as monotherapy (Arm 1) and in combination with pembrolizumab (Arm 2) in adult participants with advanced or metastatic solid tumors. In Arm 1 and Arm 2, MK-6598 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. It is planned that on completion of the dose escalation and establishment of a RP2D, a cohort expansion phase in 3 to 5 selected tumor types will be initiated through a protocol amendment.

A RP2D will be determined by tolerability and PK at each dose, with the assumptions that the highest tolerated dose that meets or exceeds the target C_{trough} and pharmacodynamic endpoints for MK-6598 will be most effective. On-study biopsies will be included during dose escalation or at the RP2D to demonstrate target engagement by measuring changes in tumor phenylpyruvate concentrations. The RP2D may be used in combination with pembrolizumab in expansion cohorts in specific tumor indications. The selection of indications for cohort expansion will be guided by the state of the science at the time.

Participants who experience radiographically confirmed disease progression per RECIST 1.1 on monotherapy with MK-6598 (Arm 1) may, at the investigator's discretion and after consultation with the Sponsor, cross over to receive combination treatment of MK-6598 and pembrolizumab. Participants who cannot tolerate MK-6598 are not permitted to cross over and receive monotherapy pembrolizumab.

Treatment beyond disease progression will be at the discretion of the investigator whether to continue a participant on study intervention until repeat imaging is obtained. This clinical judgment decision should be based on the participant's overall clinical condition, including performance status, clinical symptoms, and laboratory data. Participants may continue to receive study intervention until tumor assessment is repeated ≥4 weeks later in order to confirm PD by RECIST 1.1 per site assessment.

A participant may not cross over from Arm 1 (monotherapy) to combination therapy with pembrolizumab until that participant has completed the DLT evaluation period (ie, 21 days) in Arm 1. Participants who are considered for crossover to combination treatment will not have a second screening visit; however, participants will be evaluated to ensure eligibility prior to crossing over (see Section 6.6.4.4 for details). All assessments required to determine eligibility for initial study entry must be repeated within the defined screening procedure

timeframes to confirm continued treatment eligibility. However, screening assessments obtained for Arm 1 may be used for crossover eligibility determination if the assessments were obtained within the specific timeframes prior to the first crossover dose. An additional tumor biopsy specimen is not required. Once eligibility is confirmed these participants will undergo the scheduled activities outlined in the Crossover SoA (Section 1.3.2). Participants may receive the highest dose of MK-6598 evaluated in Arm 2 that has already demonstrated safety and tolerability in combination with pembrolizumab (DLT evaluation period completed for that combination dose) at the time of crossover.

Participants who cross over to combination treatment will be eligible to receive up to 35 cycles (approximately 2 years) of pembrolizumab, irrespective of the number of cycles of MK-6598 received in monotherapy, depending on the state of the study.

Crossover participants will not be included in the mTPI dose-escalation determination for Arm 2, as that specific dose level cohort must have already demonstrated 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.

There will be no intraparticipant dose escalation in this study. The definition of DLTs and criteria for dose modification of MK-6598 are outlined in Section 6.6.2 and Section 6.6.3, respectively. Pembrolizumab will be administered at a fixed dose of 200 mg every 3 weeks, which will not be modified except in case of AEs associated with pembrolizumab (Section 6.6.4). Refer to Section 6.6.4.4 for more detailed information on cross over and maximum dose permitted.

There is no protocol-defined limit on the number of treatment cycles for MK-6598. Participants may receive a maximum of 35 cycles of pembrolizumab.

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

4.2 Scientific Rationale for Study Design

4.2.1 Rationale for Endpoints

4.2.1.1 Efficacy Endpoints

Efficacy is a tertiary/exploratory objective in Part 1 of this FIH study. The ORR of MK-6598 as assessed by the investigator when used as monotherapy and in combination with pembrolizumab will be evaluated by RECIST 1.1. PFS, DOR, and OS will also be evaluated as tertiary/exploratory objectives.

4.2.1.1.1 Response Rate Assessed by RECIST Version 1.1

RECIST 1.1 will be used to determine the OR. Although traditional RECIST 1.1 references a maximum of 5 target lesions in total and 2 per organ, this protocol has implemented a modification to RECIST 1.1 to allow a maximum of 10 target lesions in total and 5 per organ (see Section 8.2.1.5).

4.2.1.2 Safety Endpoints

The primary objective of this study is to characterize the safety and tolerability of MK-6598 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-6598 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-6598 after administration as a single agent, and to characterize the PK profile of MK-6598 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 pharmacodynamics, and safety and exploratory endpoint data to help assess future dosing strategies for MK-6598.

PK will not be collected during the Crossover Phase.

4.2.1.4 Pharmacodynamic Endpoints

4.2.1.4.1 Target Engagement

LAAOs like IL4I1 catabolize essential amino acids in a healthy biological setting to help contain autotrophic microorganisms and highly proliferative cells such as newly activated T cells. In doing so, these enzymes produce toxic metabolites that act as anti-infectives and pro-apoptotic factors. IL4I1 specifically deaminates phenylalanine releasing phenylpyruvate, H_2O_2, and ammonia. During cancer development, IL4I1-secreting cells infiltrate the TME to facilitate immune escape, ultimately limiting T-cell proliferation and restraining the natural antitumor response. In addition, some cancer cells express elevated levels of IL4I1 compared with adjacent normal tissue. Administration of MK-6598 is expected to inhibit/decrease the enzymatic activity of IL4I1 and therefore reduce tumor phenylpyruvate levels. As a proxy for this biological phenomenon, tumor phenylpyruvate levels will be measured via liquid chromatography-mass spectrometry. The Sponsor hypothesizes that a discernable decrease

from baseline to on-treatment tumor samples will be identified due to IL4I1 activity and target engagement.

4.2.1.5 Planned Exploratory Biomarker Research

The mechanism of action of many antitumor agents is not completely understood and much remains to be learned regarding how best to leverage new drugs in treating patients. Thus, to aid future patients, it is important to investigate the determinants of response or resistance to cancer 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 antineoplastic 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 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/or blood RNA analyses

Both genome-wide and targeted mRNA expression profiling and sequencing in tumor tissue and/or in blood may be performed to define gene signatures that correlate to clinical response to treatment with antitumor therapies. Specific gene sets (ie, those capturing interferon-gamma transcriptional pathways) may be evaluated and new signatures may be identified.

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

Proteomics and IHC using blood and/or tumor

Tumor and/or blood samples from this study may undergo proteomic analyses (eg, PD-L1 IHC). 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 antitumor 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 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.

4.2.1.6 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

Translational pharmacokinetics and pharmacodynamics modeling was used to predict the human plasma C_{trough} target and efficacious dose by leveraging preclinical in vivo data and in vitro MLR data. Since an in vivo efficacy model was not available, in vitro MLR assay using primary human cells was used. The translational modeling strategy was implemented based on 4 steps. The first step was evaluation of MK-6598 dose response in the MLR assay where 2 pharmacodynamic biomarkers (IFN-γ and phenylpyruvate) were simultaneously analyzed.

Increased levels of IFN-γ indicated immunomodulation due to IL4i1 inhibition, while reduced phenylpyruvate levels phenylpyruvate indicated inhibition of IL4i1 activity. The MLR assay was used to define the percentage of phenylpyruvate inhibition that leads to meaningful immunomodulation. Next, estimated in vivo potency from modeling of tumor exposure and phenylpyruvate reduction was used to calculate the plasma C_{trough} anticipated to achieve the pharmacodynamic target. Then, human pharmacokinetic parameters were calculated using intrinsic clearance from in vitro human Hepatopac® to estimate MK-6598 clearance, incorporating human plasma protein binding, blood to plasma ratio and hepatocyte binding. Data from rat and dog used to estimate volume of distribution incorporating species differences in plasma protein binding. Bioavailability was estimated using a combination of preclinical species data and predicted human clearance. These estimations were used to predict the dose required to achieve the target plasma C_{trough}. Finally, because of the likelihood of CYP3A4 enzyme induction and the expectation that metabolism of MK-6598 by CYP3A4 is the major route of clearance, a physiology-based PK model was also used to predict dose with and without autoinduction.

4.3.1 Starting Dose for This Study

4.3.1.1 Rationale for Starting and Maximum Dose of MK-6598

The predicted dose of 50 mg QD is selected to achieve sustained inhibition of tumor IL4I1 of at least 70%. This level of inhibition is hypothesized to rescue tumoral T-cell activity, alone and in combination with pembrolizumab. In order to ensure a high degree of pharmacological coverage it is desirable to investigate higher doses of MK-6598 that achieve IC_{90}, predicted to occur at a dose of 270 mg to >2 g, depending on CYP3A4 autoinduction. Alternate doses and dosing regimens/frequency for MK-6598 may be explored based on the totality of the data.

4.3.1.2 Rationale for Dose Interval and Escalation Increments

The starting dose and dosing interval of MK-6598 are based on an integration of nonclinical toxicological, pharmacological, and efficacy data (see Table 1).

Table 1 Rationale for Dose Escalation Increments

Dose	Rationale
50 mg	Predicted 70% IL4I1 inhibition, no CYP3A4 autoinduction (est. 47 mg)
125 mg	Predicted 70% inhibition with CYP3A4 autoinduction (est. 110 mg)
250 mg	Predicted 90% inhibition, no CYP3A4 autoinduction (est. 273 mg)
500 mg and TBD (2 dose levels)	Approach to predicted 90% inhibition with autoinduction (est. >2 g) will be assessed as the study is ongoing.
CYP3A4=cytochrome P450 3A4; est.=estimated; IL4I1= Interleukin 4-induced 1; TBD=to be determined.	

Dose finding will proceed with a model-based dose mTPI approach with 3 to 14 participants treated per dose level using dose increment increases of 30% to 100% of the prior dose.

In cohorts of participants treated with a combination of MK-6598 and pembrolizumab, doses of MK-6598 used in combination with pembrolizumab will be at least 1 to 2 dose levels behind the monotherapy dose and will not exceed the MTD/MAD for monotherapy. Since MK-6598 and pembrolizumab both activate T cells, there is a risk of overlapping toxicities. If an MTD/MAD for the monotherapy arm is established, the dose of MK-6598 in combination with pembrolizumab may continue escalation up to that dose.

4.3.1.3 Dose Finding Using a Modified Toxicity Probability Interval Design

Dose finding will follow the mTPI design [Ji, Y., et al 2007] with a target DLT rate of 30%. Dose-escalation and de-escalation decisions are based on the mTPI design and depend on the number of participants enrolled and number of participants with at least 1 DLT 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 2, 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 2). 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 2). 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. and Wang, S.-J. 2013] will be used to estimate the DLT rates across doses. The dose with an estimated DLT rate closest to 30% will be treated as a preliminary MTD. The totality of the data will be considered before a dose is selected to carry forward to Part 2 and the escalation schedule may be adjusted based on PK, pharmacodynamic, and safety data emerging throughout the study to determine the RP2D. The preliminary RP2D of MK-6598 in the combination arm (Arm 2) will not exceed, but may be equal to, the preliminary RP2D in the MK-6598 monotherapy arm (Arm 1).

Note that although 30% was the target toxicity rate used to generate the guidelines in Table 2, the observed rates of participants with DLTs at the MTD may be slightly above or below 30%.

Table 2 Dose-finding Rules per mTPI Design

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

D=De-escalate to the next lower dose; DLT=dose-limiting toxicity; DU=The current dose is unacceptably toxic; E=Escalate to the next higher dose; mTPI=modified Toxicity Probability Interval; S=Stay at the current dose.

Target toxicity rate = 30%

Flat noninformative prior Beta (1,1) is used as a prior and ε1=ε2=0.03[Ji, Y., et al 2007] [Ji, Y. and Wang, S.-J. 2013] [Ji, Y., et al 2010].

Confidential

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 (Section 7.3).

For purposes of analysis and reporting, the overall study ends when the Sponsor receives the last laboratory test result or at the time of final contact with the last participant, whichever comes last.

If the study includes countries in the EEA, the local start of the study in the EEA is defined as FSR in any Member State.

4.4.1 Clinical Criteria for Early Study Termination

The clinical study may be terminated early if the extent (incidence and/or severity) of emerging effects is such that the risk/benefit ratio to the study population as a whole is unacceptable. In addition, further recruitment in the study or at (a) particular study site(s) may be stopped as described in Appendix 1.10.

5 STUDY POPULATION

As stated in the Code of Conduct for Clinical Trials (Appendix 1.1) this study includes participants of varying age (as applicable), race, ethnicity, and sex (as applicable). The collection and use of these demographic data will follow all local laws and participant confidentiality guidelines while supporting the study of the disease, its related factors, and the IMP under investigation.

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

5.1 Inclusion Criteria

An individual is eligible for inclusion in the study if the individual meets all of the following criteria:

Type of Participant and Disease Characteristics

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

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

3. Must have one or more discrete malignant lesions that are amenable to a minimum of 2 separate biopsies.

   Note: Participants should only be enrolled if during the screening assessment the investigator deems the biopsy of such lesions to be medically safe.

4. Have a baseline tumor sample that can be submitted for analysis. Details pertaining to archival tumor tissue submission can be found in the Laboratory Manual.

5. 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. It is advised that participants must not have had any AIDS-defining opportunistic infections within the past 12 months

   d. 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) and agree to continue ART throughout the study.

   e. The combination ART regimen must not contain any antiretroviral medications that interact with CYP3A4 inhibitors/inducers/substrates (https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers)

6. Performance status of 0 or 1 on the ECOG Performance Scale.

7. Adequate organ function as defined in Table 3. Specimens must be collected within 72 hours before the start of study intervention.

Table 3 Adequate Organ Function Laboratory Values

System	Laboratory Value
Hematological	
Absolute neutrophil count	>1500/mcL (>1000/mcL for lymphoma participants)
Platelets	>100,000/mcL (>75,000/mcL for lymphoma participants)
Hemoglobin	>9 g/dL or >5.6 mmol/L[a] (>8 g/dL or >5.0 mmol/L for lymphoma participants)
Renal	
Measured or calculated[b] CrCl or GFR	≥60 mL/min for measured or calculated CrCl Or ≥60 mL/min for GFR
Hepatic	
Total bilirubin	≤1.5 x ULN OR direct bilirubin ≤ULN for participants with total bilirubin levels >1.5 x ULN
AST (SGOT) and ALT (SGPT)	<2.5 X ULN or ≤5 × ULN for participants with liver metastases
Coagulation	
International Normalized Ratio (INR) or Prothrombin Time (PT)	<1.5 X ULN unless participant is receiving anticoagulant therapy
Activated Partial Thromboplastin Time (aPTT)	<1.5 X ULN unless participant is receiving anticoagulant therapy

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

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

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

Demographics

8. Is an individual of any sex/gender of at least 18 years of age at the time of providing informed consent.

Participants Assigned Male Sex at Birth

9. If capable of producing sperm, the participant agrees to the following during the intervention period and for at least the time needed to eliminate each study intervention after the last dose of study intervention. The length of time required to continue contraception for each study intervention is as follows:

    a. MK-6598: 102 days

    b. Pembrolizumab: no contraception measures are required

- Refrains from donating sperm

PLUS either:

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

OR

- Uses contraception as detailed below 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 review):

  – Uses a penile/external condom when having penile-vaginal intercourse with a nonparticipant of childbearing potential who is not currently pregnant PLUS partner use of an additional contraceptive method, as a condom may break or leak. Note: Participants capable of producing ejaculate whose partner is pregnant or breastfeeding must agree to use a penile/external condom during each episode of sexual activity in which the partner is at risk of drug exposure via ejaculate.

  – Contraceptive use by participants capable of producing sperm should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies. If the contraception requirements in the local label for any of the study interventions are more stringent than the requirements above, the local label requirements are to be followed.

Participants Assigned Female Sex at Birth

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

- Is not a POCBP

OR

- Is a POCBP and:

  – Uses a contraceptive method that is highly effective (with a failure rate of <1% per year), with low user dependency, or is abstinent from penile-vaginal 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 the time needed to eliminate each study intervention after the last dose of study intervention. The participant agrees not to donate eggs (ova, oocytes) to others or freeze/store eggs during this period for the purpose of reproduction. The length of time required to continue contraception for each study intervention is:

  ◦ MK-6598: 42 days

- Pembrolizumab: 120 days

– 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 POCBPs should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies. If the contraception requirements in the local label for any of the study interventions are more stringent than the requirements above, the local label requirements are to be followed.

– Has a negative highly sensitive pregnancy test (urine or serum as required by local regulations) within 24 hours (for urine test) or 72 hours (for serum test) 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 the time needed to eliminate study intervention after the last dose of study intervention. The length of time required for each study intervention is:

- MK-6598: 42 days

- Pembrolizumab: 120 days

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

Informed Consent

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

5.2 Exclusion Criteria

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

Medical Conditions

1. Received prior systemic anticancer therapy including investigational agents within 4 weeks before the first dose of study intervention, or has not recovered to CTCAE Version 5.0 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. Known additional malignancy that is progressing or has required active treatment within the past 2 years.

   Note: Participants with basal cell carcinoma of the skin, squamous cell carcinoma of the skin, or carcinoma in situ, excluding carcinoma in situ of the bladder, that have undergone potentially curative therapy are not excluded. Participants with low-risk early-stage prostate cancer (T1-T2a, Gleason score ≤6, and PSA <10 ng/mL) either treated with definitive intent or untreated in active surveillance with stable disease are not excluded.

3. 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. A severe hypersensitivity (≥Grade 3) reaction to treatment with a monoclonal antibody/ components of the study intervention.

5. Active infection requiring therapy.

6. History of interstitial lung disease.

7. History of (noninfectious) pneumonitis that required steroids or current pneumonitis.

8. Active autoimmune disease that has required systemic treatment in the past 2 years. Replacement therapy (eg, thyroxine, insulin, or physiologic corticosteroid) is allowed.

9. Has known hepatitis B or C infections, or known to be positive for HBsAg/HBV DNA or hepatitis C antibody or RNA. Active hepatitis C is defined by a known positive Hep C Ab result and known quantitative HCV RNA results greater than the lower limits of detection of the assay.

   Note: No testing for hepatitis B, or hepatitis C is required unless mandated by local health authority.

10. 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.

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

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

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

Prior/Concomitant Therapy

14. Received prior radiotherapy within 2 weeks of start of study intervention, has radiation-related toxicities requiring corticosteroids, or had a history of radiation pneumonitis.

    Note: Two weeks or fewer of palliative radiotherapy for non-CNS disease is permitted. The last radiotherapy treatment must have been performed at least 7 days before the first dose of study intervention.

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

    Note: Any licensed COVID-19 vaccine (including for Emergency Use) in a particular country is allowed as long as they are mRNA vaccines, adenoviral vaccines, or inactivated vaccines. Investigational vaccines (ie, those not licensed or approved for Emergency Use) are not allowed.

16. 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 co-inhibitory T-cell receptor (eg, CTLA-4, OX 40, CD137), and was discontinued from that treatment due to a ≥Grade 3 irAE.

Prior/Concurrent Clinical Study Experience

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

18. Received medications, foods, or herbal supplements considered strong inhibitors of CYP3A4, strong inducers of CYP3A4, substrates of CYP3A4 with a narrow therapeutic index within 2 weeks of study start (Table 5).

Diagnostic Assessments

19. Has a diagnosis of immunodeficiency or is receiving chronic systemic steroid therapy (in dosing exceeding 10 mg daily of prednisone equivalent) or any other form of immunosuppressive therapy within 7 days before the start of study treatment.

    Note: Participants that require intermittent use of nonsystemic steroids such as ocular, inhaled, intranasal, topical steroids, or local are not excluded.

Other Exclusions

20. Has had an allogeneic tissue/solid organ transplant in the last 5 years or has evidence of graft-versus-host disease.

21. Has a QTc of >470 msec.

5.3 Lifestyle Considerations

5.3.1 Meals and Dietary Restrictions

MK-6598 may be taken with or without food.

Foods that are CYP3A inhibitors should 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-6598 and for the entire duration of the study. Consumption of CYP3A4 inhibitors, such as grapefruit juice, may significantly increase the levels of MK-6598 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-6598. A partial list of examples of CYP3A inhibitors is provided in Section 6.5.2.

5.3.2 Caffeine, Alcohol, and Tobacco Restrictions

No restrictions are required.

5.3.3 Activity Restrictions

No restrictions are required.

5.4 Screen Failures

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

5.5 Participant Replacement Strategy

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-6598 or pembrolizumab amounts in Cycle 1 (eg, if the pembrolizumab infusion had to be discontinued due to an infusion reaction) and did not experience a DLT.

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 (ie, MK-6598 and pembrolizumab) 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 4.

Table 4 Study Interventions

Arm Name	Arm Type	Inter-vention Name	Intervention Type	Dose Formulation	Unit Dose Strength(s)	Dosage Level(s)	Route of Adminis-tration	Regimen/ Treatment Period	Use	IMP or NIMP/ AxMP	Sourcing
Arm 1	Experi-mental	MK-6598	Drug	Tablet	25 mg tablet 100 mg tablet	50 mg 125mg 250 mg 500 mg	Oral	Continuous	Test Product	IMP	Central
Arm 2	Experi-mental	MK-6598	Drug	Tablet	25 mg tablet 100 mg tablet	50 mg 125mg 250 mg 500 mg	Oral	Continuous	Test Product	IMP	Central
Arm 2	Experi-mental	MK-3475	Biological/ Vaccine	Vial	100 mg/vial	200 mg	IV Infusion	Q3W	Test Product	IMP	Central

EEA=European Economic Area; IMP=investigational medicinal product; IV=intravenous; NIMP/AxMP =noninvestigational/auxiliary medicinal product; Q3W=every 3 weeks.

The classification of IMP and NIMP/AxMP 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 and NIMP/AxMP may exist. In these circumstances, local legislation is followed.

All supplies indicated in Table 4 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.

6.2 Preparation/Handling/Storage/Accountability

6.2.1 Dose Preparation

Details on preparation and administration of MK-6598 (and pembrolizumab) are provided in the appropriate Pharmacy Manual.

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 IRT. Participants will be allocated to 1 of 2 intervention arms: MK-6598 monotherapy (Arm 1) or MK-6598 in combination with pembrolizumab (Arm 2) using an IRT in Part 1.

In Part 1 of the study, intervention will be allocated by nonrandom assignment. Enrollment into the MK-6598 + pembrolizumab combination intervention arm (Arm 2) will begin once a dose escalation decision has been made in MK-6598 monotherapy (Arm 1). The starting dose of MK-6598 in the combination arm (Arm 2) will be at least 2 levels below the dose being tested in the MK-6598 monotherapy arm. When both intervention arms are open for enrollment, IRT will alternate participant assignment as appropriate between Arm 1 and 2 starting with Arm 1. 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.

Participants who cross over from monotherapy (Arm 1) to combination therapy (Arm 2) may receive the highest dose of MK-6598 evaluated in Arm 2 that has already demonstrated safety and tolerability in combination with pembrolizumab (DLT evaluation period completed for that combination dose) at the time of crossover.

Refer to Section 6.6.4.4 here for more detailed information on crossover and maximum dose permitted.

6.3.2 Stratification

There is no stratification.

6.3.3 Blinding

This study is conducted as open label; therefore, there is no blinding. 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.

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

Refer to Section 6.6.4 for dose modification and toxicity management for irAEs associated with pembrolizumab and for other allowed dose interruptions of pembrolizumab.

Interruptions from the protocol-specified administration require consultation between the investigator and the Sponsor and written documentation of the collaborative decision on participant management.

Because participants self-administer MK-6598 at home, compliance with study intervention will be assessed at each visit. Compliance will be assessed by direct questioning during the site visits and documented in the source documents and eCRF. Deviations from the prescribed dosage regimen should be recorded in the eCRF.

A record of the number of MK-6598 tablets 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 eCRF.

When participants are dosed with pembrolizumab at the site, they will receive study intervention directly from the investigator or designee, under medical supervision. The date and time of each dose administered in the clinic will be recorded in the source documents and recorded in the eCRF. The dose of study intervention and study participant ID will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study intervention.

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.

6.5.1 Acceptable Concomitant Medications

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, OTC products, herbal supplements, and IV medications and fluids. If changes occur during the study period, documentation of drug dosage, frequency, route, and date should also be included on the eCRF.

All concomitant medications received within 28 days 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.

6.5.2 Prohibited Concomitant Medications

Participants are prohibited from receiving the following therapies during the Screening and Treatment Phases of this study:

- Antineoplastic systemic chemotherapy or biological therapy
- Immunotherapy not specified in this protocol
- Chemotherapy not specified in this protocol
- Investigational agents other than pembrolizumab or MK-6598
- Enzyme inducers, or substrates listed in Table 5.
- 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: Injectable killed vaccines are allowed.

  Note: Any licensed COVID-19 vaccine (including for Emergency Use) in a particular country is allowed in the study as long as they are mRNA vaccines, adenoviral vaccines, or inactivated vaccines. These vaccines will be treated just as any other concomitant therapy. Investigational vaccines (ie, those not licensed or approved for Emergency Use) are not allowed.

- Systemic glucocorticoids are prohibited except for the following purposes:
  - To modulate symptoms of an AE that is suspected to have an immunologic etiology
  - As needed for the prevention of emesis
  - Premedication for IV contrast allergies
  - Short-term oral or IV use in doses >10 mg/day prednisone equivalent for asthma or COPD exacerbations
  - For chronic systemic replacement not to exceed 10 mg/day prednisone equivalent
- Other glucocorticoid use.

  The following glucocorticoid use is allowed:

  - For topical use or ocular use

- Intraarticular joint use
- For inhalation in the management of asthma or COPD

- Medications that prolong the QT/QTc interval
- 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 5 during the study 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 5 Examples of Prohibited Study Medications and Other Substances

Strong 3A4 Inducers[a,d]	**Strong CYP3A4 Inhibitors**[b,d]	**Moderate CYP3A4 Inhibitors**[b,d]	**CYP3A4 *or CYP2C8* 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]

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 and CYP2C8 substrates with narrow therapeutic range refers to drugs whose exposure-response indicates that increases in their exposure levels by the concomitant use of CYP3A4 or CYP2C8 inhibitors may lead to serious safety concerns. For specific information, see the Classification of Substrates tables available at: https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers.

[d] Compiled from the in vivo inhibitors and inducers, inhibitor classification, and substrate classification tables available at: https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-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.

6.5.3 Rescue Medications and Supportive Care

There are no rescue medications specified for this study.

Medications required to treat AEs or concurrent illnesses other than those prohibited in Section 6.5.2 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 5).

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.

6.5.3.1 Supportive Care for MK-6598

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

6.5.3.2 Supportive Care for Pembrolizumab

Participants should receive appropriate supportive care measures as deemed necessary by the treating investigator. Suggested supportive care measures for the management of AEs with potential immunologic etiology are outlined along with the dose modification guidelines in Section 6.6. Where appropriate, these guidelines include the use of oral or IV treatment with corticosteroids, as well as additional anti-inflammatory agents if symptoms do not improve with administration of corticosteroids. Note that several courses of steroid tapering may be necessary as symptoms may worsen when the steroid dose is decreased. For each disorder, attempts should be made to rule out other causes such as metastatic disease or bacterial or viral infection, which might require additional supportive care. The treatment guidelines are intended to be applied when the investigator determines the events to be related to pembrolizumab.

Note: If after the evaluation of the event, it is determined not to be related to pembrolizumab, the investigator does not need to follow the treatment guidance. Refer to Section 6.6 for guidelines regarding dose modification and supportive care.

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

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-6598 (and pembrolizumab) are provided in the appropriate Pharmacy/Procedures Manual.

Participants should be instructed to take MK-6598 every 24 hours. On clinic days when PK samples are scheduled, dosing should be delayed until arrival at the clinic and until the predose PK sample has been collected.

The reason for any variability in administration outside of the protocol-specified window should be documented in the participant's chart and recorded on the eCRFs.

Every effort should be made to begin the first dose of study intervention on the day of treatment assignment, but if this is not achieved, study intervention should be initiated no later than 3 days after the date of treatment assignment.

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 unless the investigator assessment determines the toxicity to be clearly due to the underlying disease or extraneous causes.

- 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
  - Grade 4 anemia should be considered a DLT, regardless of duration
- 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 lasting <3 days without use of antiemetics or antidiarrheals per standard of care; Grade 3 rash lasting <3 days without use of corticosteroids or anti-inflammatory agents per standard of care.
- Any Grade 3 or Grade 4 nonhematologic laboratory value should be considered a DLT if:
  - Clinically significant medical intervention is required to treat the participant, or
  - The abnormality leads to hospitalization, or
  - The abnormality persists for >72 hours
  - The abnormality results in a DILI (see Section 8.4.7 for criteria)

- The following exceptions are not considered DLTs:
  - Grade 3 electrolyte abnormality that lasts <24 hours to 72 hours, is not clinically complicated, and resolves spontaneously or responds to conventional medical interventions
  - ≥Grade 3 amylase or lipase that is not associated with symptoms or clinical manifestations of pancreatitis
  - Isolated Grade 3 elevation of ALT and/or AST that resolves to Grade 1 or lower or baseline within 72 hours
- 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 the MK-6598 doses as a result of drug-related AEs during the first cycle.
- Grade 5 toxicity.

6.6.3 Guidelines for Dose Modification due to Adverse Events for MK-6598

AEs (both nonserious and serious) associated with MK-6598 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.

The CTCAE Version 5.0 must be used to grade the severity of AEs. The investigator may attribute each toxicity event to MK-6598 alone, to pembrolizumab alone, or to the combination, and modify the dose according to Table 6 and Table 7. If a dose modification for toxicity occurs with MK-6598, the dose may not be re-escalated to the dose that preceded the dose modification. Dose modifications are always based on the previous cycle. Refer to Section 6.6.4.4 for details.

Participants may have up to 2 dose modifications of MK-6598 throughout the course of the study, as described in Table 6. 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). Since MK-6598 and pembrolizumab both activate T cells, there is a risk of overlapping irAE. For irAEs in MK-6598 monotherapy, please follow the guidance below in Table 7. Exceptional circumstances to following the dose modification tables below may be considered after consultation with the Sponsor.

Table 6 MK-6598 Dose Modification and Treatment Discontinuation Guidelines for Drug-related Adverse Events

Toxicity	Hold Treatment	Criteria for Restarting Treatment	Dose/Schedule for Restarting Treatment	Criteria for Discontinuation after Consultation with Sponsor
Hematological Toxicities:				
• Any Grade 1 hematological toxicity	No	N/A	N/A	N/A
• Any Grade 2 hematological toxicity, or Grade 3 toxicity that persists for ≤5 days	Per medical assessment of the investigator	If treatment held, may be restarted when AE resolves back to baseline or to Grade 1.	Per medical assessment of the investigator: may decrease dose by 1 dose level.	If AE persists for 12 weeks without resolution 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

Toxicity	Hold Treatment	Criteria for Restarting Treatment	Dose/Schedule for Restarting Treatment	Criteria for Discontinuation after Consultation with Sponsor
• 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 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
• Any Grade 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	Permanently discontinue	NA	NA
AE=adverse event; N/A=not applicable.				

If toxicity does not resolve to Grade 0 to 1 within 12 weeks after last intervention, MK-6598 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.)

6.6.3.1 Dose Modification and Toxicity Management for Immune-related AEs Associated with MK-6598 Monotherapy

As there is no prior clinical experience with MK-6598, it is unknown whether MK-6598 may be associated with immune-related AEs. Nevertheless, the following treatment guidance is provided in the event of immune-related AEs due to MK-6598 monotherapy. These irAEs should be managed with treatment interruption and administration of corticosteroids and/or other supportive care as detailed in Table 7.

Table 7 Dose Modification and Toxicity Management for Immune-related AEs Associated with MK-6598 Monotherapy

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. MK-6598 monotherapy 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 MK-6598 monotherapy has been withheld, treatment may resume after the irAE decreased to ≤ Grade 1 after corticosteroid taper.

irAEs	Toxicity Grade (CTCAE v5.0)	Action With MK-6598 Monotherapy	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		

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irAEs	Toxicity Grade (CTCAE v5.0)	Action With MK-6598 Monotherapy	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]		

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irAEs	Toxicity Grade (CTCAE v5.0)	Action With MK-6598 Monotherapy	Corticosteroid and/or Other Therapies	Monitoring and Follow-up
Hypothyroidism	Grade 2	Continue	• Initiate thyroid replacement hormones (eg, levothyroxine or liothyronine) per standard of care	• Monitor for signs and symptoms of thyroid disorders
	Grade 3 or 4	Withhold until clinically stable or permanently discontinue [d]		
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	Asymptomatic cardiac enzyme elevation with clinical suspicion of myocarditis (which was previously myocarditis Grade 1 using CTCAE v4.0)	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		

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irAEs	Toxicity Grade (CTCAE v5.0)	Action With MK-6598 Monotherapy	Corticosteroid and/or Other Therapies	Monitoring and Follow-up
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		

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; 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 MK-6598 monotherapy is at the discretion of the investigator.

[e] Events that require discontinuation include, but are not limited to, encephalitis and other clinically important irAEs (eg, vasculitis and sclerosing cholangitis).

6.6.4 Immune-related Events and Toxicity Modifications (Withhold, Treat, Discontinue)

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

AEs associated with pembrolizumab monotherapy or IO combination (pembrolizumab + MK-6598) 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 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 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 AE to a single component is likely to be difficult. Therefore, while the investigator may attribute a toxicity event to pembrolizumab monotherapy or IO combinations, pembrolizumab monotherapy or IO combinations must be held according to the criteria in the Dose Modification and Toxicity Management Guidelines for Immune-Related Adverse Events.

In cases where the toxicity is attributed to pembrolizumab or IO combinations, re-initiation of pembrolizumab as a monotherapy may be considered after communication with, and agreement by, the Sponsor.

Holding Study Interventions:

When study interventions are administered in combination and if the AE is considered immune-related, pembrolizumab monotherapy 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 or IO combinations.

Restarting Study Interventions:

Participants may restart pembrolizumab monotherapy 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 or IO combinations may be restarted at the discretion of the investigator.

Dose Modification and Toxicity Management Guidelines for irAEs associated with pembrolizumab monotherapy 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 (pembrolizumab + MK-6598)

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 or IO combinations (pembrolizumab + MK-6598) 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 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 or IO Combinations (pembrolizumab + MK-6598)	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		

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irAEs	Toxicity Grade (CTCAE v5.0)	Action With Pembrolizumab Monotherapy or IO Combinations (pembrolizumab + MK-6598)	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]		

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irAEs	Toxicity Grade (CTCAE v5.0)	Action With Pembrolizumab Monotherapy or IO Combinations (pembrolizumab + MK-6598)	Corticosteroid and/or Other Therapies	Monitoring and Follow-up
Hypothyroidism	Grade 2	Continue	• Initiate thyroid replacement hormones (eg, levothyroxine or liothyronine) per standard of care	• Monitor for signs and symptoms of thyroid disorders
	Grade 3 or 4	Withhold until clinically stable or permanently discontinue [d]		
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	Asymptomatic cardiac enzyme elevation with clinical suspicion of myocarditis (which was previously myocarditis Grade 1 using CTCAE v4.0)	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		

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irAEs	Toxicity Grade (CTCAE v5.0)	Action With Pembrolizumab Monotherapy or IO Combinations (pembrolizumab + MK-6598)	Corticosteroid and/or Other Therapies	Monitoring and Follow-up
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		

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 or IO combinations is at the discretion of the investigator or treating physician. If control achieved or ≤ Grade 2, pembrolizumab monotherapy 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).

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

Pembrolizumab monotherapy or IO combinations 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 or IO combinations associated infusion reactions are provided in Table 9.

The actions of slowing or interrupting infusion and/or initiating interventions are not indicated for Grade 1 infusion-related reaction events per CTCAE Version 5.0. However, the investigator is advised to provide supportive care to the participant per their judgment and treat if deemed appropriate. The investigator may adjust treatment for Grade 1 infusion-related reactions to include: slowing or interrupting the infusion, treating the reaction, and/or pretreating prior to subsequent infusions.

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).

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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
CTCAE=Common Terminology Criteria for Adverse Events; h=hour; IO=immune-oncology; IV=intravenous; NCI=National Cancer Institute; NSAIDs= nonsteroidal anti-inflammatory drugs; po=orally. 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 Version 5.0 at http://ctep.cancer.gov		

6.6.4.3 Other Allowed Dose Interruption(s) for Pembrolizumab

Pembrolizumab may be interrupted for situations other than treatment-related AEs such as medical or surgical events and/or unforeseen circumstances not related to study intervention. However, study intervention is to be restarted within 42 days of the previously administered dose, unless otherwise discussed with the Sponsor. The reason for study intervention interruption is to be documented in the participant's study record.

6.6.4.4 Treatment Beyond Progression (Optional)

Disease progression must be determined by imaging and meet the criteria for progression as defined by RECIST 1.1. Treatment beyond progression is optional, is at the discretion of the investigator, and requires the Sponsor's approval.

Treatment Beyond Progression Eligibility

Participants considered for treatment beyond progression are required to undergo eligibility review and meet the following eligibility criteria:

- Participants must have adequate organ function as indicated by the laboratory values in Table 3
- Participants must have an ECOG performance status of 0 or 1
- The participant meets all of the inclusion criteria and none of the exclusion criteria
- The participant received at least one dose of MK-6598
- No other criteria for discontinuation were met (See Section 7.1)
- The treatment phase of the study is still ongoing

6.6.4.4.1 Treatment Beyond Progression Remaining on Current Therapy

The participant must be reconsented and the risks and benefits of continuing study treatment after disease progression should be reviewed prior to performing any related procedures.

6.6.4.4.2 Crossover

Participants with disease progression during treatment with MK-6598 in the monotherapy arm may be eligible to participate in the Crossover Phase of the study to receive combination treatment. Participants who permanently discontinue MK-6598 monotherapy due to an AE, withdrawal of consent, or for any reason other than disease progression are not eligible for crossover. Crossover is optional, is at the discretion of the investigator, and requires the Sponsor's approval.

Imaging must be completed to establish a new baseline for the Crossover Phase. The scan used to determine disease progression may be used as the crossover baseline scan if it is within 28 days of Crossover Phase Cycle 1. If crossover is being considered, the participant must be reconsented and the risks and benefits of continuing study treatment after disease progression should be reviewed prior to performing any crossover related procedures.

Although intraparticipant dose escalation is not allowed, at crossover, the participant may be eligible to receive the highest dose of MK-6598 that has passed the DLT evaluation period in the combination treatment arm at the time of crossover. If that dose is higher than the MK-6598 dose the participant was receiving in the monotherapy arm, the increase in dose will be allowed only if the participant did not experience any drug-related AEs at the dose of MK-6598 the participant was receiving in the monotherapy arm. If that dose is lower than the MK-6598 dose the participant was receiving in the monotherapy arm, the MK-6598 dose the participant will receive in the combination treatment arm after crossover will be de-escalated to the highest dose of MK-6598 that has passed an initial DLT evaluation period in the combination treatment arm.

Crossover Eligibility

Participants considered for crossover treatment are required to undergo crossover eligibility review and meet the following eligibility criteria for crossover:

- Participants must have adequate organ function as indicated by the laboratory values in Table 3
- Participants must have an ECOG performance status of 0 or 1
- The participant meets all of the inclusion criteria and none of the exclusion criteria
- The participant received at least one dose of MK-6598
- The participant has completed the DLT evaluation period (ie, 21 days) in Arm 1
- No other criteria for discontinuation were met (See Section 7.1)
- The treatment phase of the study is still ongoing

Participants who cross over to the combination treatment arm will not be counted toward the total number of participants in the combination cohort for DLT evaluation. The first dose of study treatment in the combination treatment arm should be administered no earlier than 21 days (3 weeks) and no later than 42 days (6 weeks) from the last dose of MK-6598 in the monotherapy arm unless otherwise discussed with and approved by the Sponsor.

Participants who cross over to combination treatment will be eligible to receive up to 35 cycles (approximately 2 years) of combination treatment irrespective of the number of cycles of MK-6598 received in monotherapy.

The study procedures to be completed in the Crossover Treatment Phase and their timing are in Section 1.3.2. Efficacy data from participants who cross over into the combination arm will be presented separately and will include all events starting from the date of the first dose of combination study treatment.

6.7 Intervention After the End of the Study

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

6.8 Clinical Supplies Disclosure

This is an open-label study; 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.

6.9.1 Study Site Retention Samples

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 8.10.3.

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 prior to 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 which, 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 (after obtaining informed consent addendum and Sponsor communication, the investigator may elect to continue treatment beyond confirmed disease progression).

    - Participants who experience radiographically confirmed disease progression per RECIST 1.1 on monotherapy may be allowed to cross over to combination therapy at

the discretion of the investigator and after consultation with the Sponsor. Participants will only be considered for crossover treatment if they meet the crossover criteria listed in Section 6.6.4.4.)

- Any progression or recurrence of malignancy, or any occurrence of another malignancy that requires active treatment.
- Intercurrent illness that prevents further administration of treatment.
- Investigator's decision to discontinue 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.

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.

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 decisions must be made by an investigator who is a qualified physician.
- 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 providing document informed consent may be used for screening or baseline purposes provided the procedures meet 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.
- The maximum amount of blood collected from each participant over the duration of the study will be listed in the Procedures Manual.
- Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

8.1 Administrative and General Procedures

8.1.1 Informed Consent

The investigator or 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.

If the investigator recommends the participant to cross over to combination treatment, then 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. The medical history will collect all active conditions and any condition diagnosed within the prior 10 years that the investigator considers to be clinically important. Any cancer other than the cancer under study will be recoded as medical history even if diagnosed greater than 10 years prior to enrollment. Details regarding the disease for which the participant has enrolled in this study will be recorded separately and not listed as medical history.

The investigator or qualified designee will obtain historic and current details of the participant's cancer under study. This information will include, but is not limited to, date of diagnosis, stage, histology, locations of primary and metastatic lesions as applicable.

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 starting study intervention. Treatment for the disease for which the participant has enrolled in this study will be recorded separately and not listed as a prior medication. However, treatment for a cancer other than the one under study will be recorded as concomitant medication regardless of the time since enrollment.

In addition to systemic/local treatment and vaccines the investigator or qualified designee will review and record all other treatments for the cancer under study including radiation and surgeries. Additional information collected on these treatments will include, but is not limited to, dates of administration, reason for therapy, reason for discontinuation, and response.

8.1.5.2 Concomitant Medications

The investigator or qualified designee will record medication, if any, taken by the participant during the study and through the Safety Follow-up period. In addition, new medications started during the Crossover Phase through the Crossover Safety Follow-up period should be recorded.

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

All new anticancer therapy, including radiation and surgeries, initiated after the study start must be recorded in the appropriate 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 allocation. Each participant will be assigned only 1 screening number. Screening numbers must not be reused for different participants.

Any participant who is screened multiple times will retain the original screening number assigned at the initial screening visit. Specific details on the screening/rescreening visit requirements are provided in Section 8.10.1. Pre-trial screening logs may be collected for review by the Sponsor. If applicable, any information that would make the participant identifiable will be removed.

A new screening number will not be assigned to participants who are evaluated for crossover.

8.1.7 Assignment of Treatment/Randomization Number

All eligible participants will be allocated centrally through IRT, by nonrandom assignment, to either Arm 1 or Arm 2. The treatment/allocation number identifies the participant for all procedures occurring after treatment allocation. Once a treatment/allocation number is assigned to a participant, it can never be reassigned to another participant even if the participant was never treated with study treatment.

A single participant cannot be assigned more than one treatment/allocation number. The procedures for obtaining an allocation number from the Sponsor are outlined in the IRT Manual.

Participants who cross over to combination therapy will not receive a new treatment/allocation number.

8.1.8 Study Intervention Administration

Oral Medication MK-6598:

During on-site visits when PK is collected, 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 other visits and nonvisit days, MK-6598 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. The site will then dispense the required amount for the next cycle.

Refer to Section 6.1 for dose and treatment details.

For Infusion Pembrolizumab:

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.

8.1.8.1 Timing of Dose Administration

The Pharmacy Manual contains instructions for the order in which treatments are to be administered for combination treatment.

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 reason for any variability in drug administration outside the protocol-specified window should be documented in the participant's medical chart and recorded on the eCRFs.

8.1.8.2 Timing of Administration for MK-6598

Participants may take MK-6598 at the same time every day; however, on days a PK sample is collected the participant will need to hold their daily dose until instructed to administer it by the site staff. See the SoA (Section 1.3.4) for PK collection details.

MK-6598 will be administered orally at the same time once every day and documented in the participant's medical chart and recorded on the eCRFs.

8.1.8.3 Timing of Administration for Pembrolizumab

Pembrolizumab (200 mg) will be administered as a 30-minute IV infusion Q3W (Arm 2 only). Sites should make every effort to target infusion timing to be as close to 30 minutes as possible. However, given the variability of infusion pumps from site to site, a window of -5 minutes and +10 minutes is permitted (ie, infusion time is 30 minutes: -5 min/+10 min). The Pharmacy Manual contains specific instructions for pembrolizumab preparation of the infusion fluid and administration.

The first dose of pembrolizumab should be administered on Cycle 1 Day 1. All subsequent cycles of study treatment may be administered up to 3 days before or 3 days after the scheduled Day 1 of each cycle due to administrative reasons per the investigator's judgment. All study interventions will begin on Day 1 of each cycle after all predose study procedures and assessments have been completed as detailed in the SoA (Section 1.3). All study interventions will be administered on an outpatient basis. The Pharmacy Manual contains specific instructions for pembrolizumab storage 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 and Section 8.10.3.

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.

8.1.12 Participants With Treated HIV

Participants should be comanaged by a HIV specialist and the investigator during the study, including monitoring of HIV viral load, CD4+ T-cell count, and additional supportive care measures.

8.2 Efficacy/Immunogenicity Assessments

8.2.1 Tumor Imaging 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, 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. 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 scan 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.

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

Bone scans may be performed to evaluate bone metastases. Any supplemental scans performed to support a positive or negative bone scan, such as plain X-rays should be entered on the appropriate eCRFs.

8.2.1.1 Initial Tumor Scans

Initial tumor scans at Screening must be performed within 28 days prior to the date of allocation. Any scans obtained after Cycle 1 Day 1 cannot be included in the screening assessment. The site must review screening scans to confirm the participant has measurable disease per RECIST 1.1.

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

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

8.2.1.2 Tumor Scans During the Study

The first on-study scan should be performed at 9 weeks (±7 days) from the date of allocation. Subsequent tumor scans should be performed every 9 weeks (±7 days) or more frequently if clinically indicated. 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, until the start of new non-study anticancer treatment, withdrawal of consent, or death, whichever occurs first. If the participant crosses over to combination therapy, scans will continue as described in Section 8.2.1.4.

OR 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.

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 baseline).

8.2.1.3 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 8.2.1.2.

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

- disease progression as defined by RECIST 1.1 unless the participant crosses over to receive combination treatment.
- the start of a new non-study anticancer treatment
- pregnancy
- death
- withdrawal of consent
- the end of the study

8.2.1.4 Crossover Tumor Scans

The crossover baseline tumor scan(s) must be performed within 28 days before receiving the first dose of pembrolizumab in the crossover phase. If the last scan performed during the initial treatment phase is within 28 days of Crossover Cycle 1, that scan can be used as the baseline scan for the crossover phase.

The first on-study scan should be performed at 9 weeks (±7 days) from the date of cross over. Subsequent tumor scans should be performed every 9 weeks (±7 days) or more frequently if clinically indicated 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, until the start of new anticancer treatment, withdrawal of consent, or death, whichever occurs first.

OR 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.

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 baseline).

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 cross over, refer to Section 8.2.1.2.

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

- disease progression as defined by RECIST 1.1
- the start of a new anticancer treatment
- pregnancy
- death
- withdrawal of consent
- the end of the study

8.2.1.5 RECIST 1.1 Assessment of Disease

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.

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. In addition, the following is to occur:
    - continue scans per protocol schedule (the next scheduled scan should be ≥4 weeks from most recent scan acquired) until any of these conditions are met:
        - the start of a new anticancer treatment
        - pregnancy

- death
- withdrawal of consent
- the end of the study

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. Height will be measured at Screening only.

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 examinations 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 require a full physical examination as defined in Section 1.3, the investigator or qualified designee will perform a directed physical examination as clinically indicated prior to 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 and during the follow-up period as specified in the SoA. Vital signs include temperature, pulse, respiratory rate, and blood pressure.

If the systolic blood pressure changes more than 10 mm Hg from the previous cycle, then blood pressure should be performed 5 minutes apart in triplicate.

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 during the screening period should be recorded as medical history. Additional ECGs may be performed as clinically necessary.

Abnormal ECGs should be further investigated according to standard of care such as serum troponin, an echocardiogram, MUGA, or stress test.

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, urinalysis and other assessments are specified in Appendix 2.

Laboratory tests for screening should be performed within 72 hours 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.

8.3.5 Pregnancy Testing

- Pregnancy testing:

  - Pregnancy testing requirements for study inclusion are described in Section 5.1.

  - Pregnancy testing (urine or serum) should be conducted at every protocol treatment cycle, as per SoA.

  - Pregnancy testing (urine or serum) should be conducted for the time required to eliminate systemic exposure after the last dose of each study intervention and should correspond with the time frame for the participant's contraception, as noted in Section 5.1. The length of time required to continue pregnancy testing for each study intervention is:

    - MK-6598: 42 days

    - MK-3475: 120 days

  - 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 participant'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, prior to the administration of each dose of study intervention, and during the follow-up period as specified in the SoA.

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.

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 the investigator 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 10.

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

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

Type of Event	**Reporting Time Period:** Consent to Allocation/ Randomization	**Reporting Time Period:** Allocation/ Randomization/ 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	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
New Cancer (that is not the cancer under study)	Report if: – due to intervention – causes exclusion	Report all	Not required	Within 5 calendar days of learning of event (unless SAE)
Overdose	Report if: – receiving placebo run-in or other run-in medication	Report all	Not required	Within 5 calendar days of learning of event (unless SAE)

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) or a pregnancy that occurs during the study in a nonparticipant whose sexual partner is a participant capable of producing ejaculate is 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 that the 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

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

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

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

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 includes:

Potential DILI events defined as 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-6598 by ≥20% of the indicated dose. No specific information is available on the treatment of overdose of MK-6598. In the event of overdose, MK-6598 may be discontinued and the participant should be observed closely for signs of toxicity. Appropriate supportive treatment should be provided if clinically indicated.

The Sponsor must be contacted in the event of an MK-6598 overdose.

For this study, an overdose of pembrolizumab will be defined as any dose of 1000 mg or greater.

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

8.6.1 Blood Collection for Plasma MK-6598

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 the Safety Follow-up visit.

8.6.2 Blood Collection for Pembrolizumab

Sample collection, storage, and shipment instructions for serum 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 the Safety Follow-up visit.

8.7 Pharmacodynamics

Tumor phenylpyruvate levels will be measured via liquid chromatography-mass spectrometry. Refer also to Section 4.2.1.4.1.

8.8 Biomarkers

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

- Blood for Genetic Analysis
- 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

The planned genetic analysis sample should be drawn for planned analysis of the association between genetic variants in DNA and drug response. This sample will not be collected at the site if there is either a local law or regulation prohibiting collection, or if the IRB/IEC does not approve the collection of the sample for these purposes. If the sample is collected,

leftover extracted DNA will be stored for FBR if the participant provides documented informed consent for FBR. If the planned genetic analysis is not approved, but FBR is approved and consent is given, this sample will be collected for the purpose of FBR.

The planned genetic analysis sample should be obtained pre-dose on Day 1 but may be collected at the next scheduled blood draw, if needed. Sample collection, storage, and shipment instructions for planned genetic analysis samples will be in the Operations/Laboratory Manual.

8.8.2 Tumor Tissue for Biomarker Analysis

During the screening period,

- A mandatory tumor core biopsy of a tumor lesion, which was not previously irradiated, must be collected for each participant.

AND

- The participant must submit an archival tumor tissue sample. Archival tissue is preferred but if archival tissue is not available, then a new biopsy will be obtained.

During Treatment period at C2D1,

- A mandatory tumor core biopsy must be collected within 3 days before dose administration.

Details pertaining to tumor tissue submissions can be found in the Laboratory Manual.

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 (including any extracted material from samples).

8.10 Visit Requirements

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

8.10.1 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 5.1. 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 provides documented informed

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 unless indicated otherwise in the SoA.

If the results of a Screening procedure will be outside the approved 28-day window due to delay in dosing caused by a stagger to allow for tolerability assessment between participants, the participant's dosing can proceed after discussion with the investigator and Sponsor approval.

Participants considered for crossover treatment will not have a separate crossover screening visit. All assessments needed to determine the participant's eligibility for crossover can be done as part of the initial treatment discontinuation visit if they will be completed within the prescribed time before starting crossover treatment.

8.10.2 Treatment Period

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

8.10.3 Participants Discontinued From Study Intervention but 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.

If the decision to discontinue a participant from study intervention is made after study intervention has been held, then the discontinuation visit should occur as soon as possible.

Participants who crossover will have two discontinuation visits: one after the initial treatment and one after combination treatment.

8.10.3.1 Safety Follow-up Visit

Participants will be required to return to the clinic for the Safety Follow-up visit approximately 30 days after the last dose of study treatment or before initiating a new anticancer therapy, whichever occurs first. If the Safety Follow-up visit occurs less than 30 days after the last dose of study treatment, a subsequent follow up phone call should be made 30 calendar days after the last dose of study treatment to determine if any AEs occurred since the last study visit.

After treatment discontinuation, participants will be monitored for AEs for 30 calendar days and SAEs for 90 calendar days after the last administration of the investigational product (30 calendar days if the participant initiates new anticancer therapy). Participants with an

ongoing AE at the time of treatment discontinuation will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up.

If the End of Treatment visit occurs 30 days from the last dose of study treatment, at the time of the mandatory Safety Follow-up visit, the End of Treatment visit procedures and any additional Safety Follow-up procedures should be performed.

Participants who are eligible for crossover with pembrolizumab may have up to 2 Safety Follow-up visits: 1 after the Initial Treatment and 1 after crossover treatment. However, if a participant crosses over within 30 days from the last dose in their initial treatment phase, a separate visit is not needed.

8.10.3.2 Efficacy Follow-up Visits

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

8.10.3.3 Survival Follow-up Contacts

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

The Sponsor may request survival status be assessed at additional time points during the course of the study. For example, these additional time points may be requested before an efficacy interim analysis, and/or final analysis. All participants who are not known to have died before the request for these additional survival status time points will be contacted at that time.

8.10.4 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. Upon Sponsor notification, all participants who do not/will not have a scheduled study visit or study contact during the Sponsor-defined time period will be contacted for their vital status.

9 STATISTICAL ANALYSIS PLAN

This section outlines the statistical analysis strategies and procedures for the primary and secondary analyses of the study. Exploratory 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 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.

9.1 Statistical Analysis Plan Summary

Full details are in the SAP, Sections 9.2 to 9.12.

Study Design Overview	Phase 1 study of MK-6598 monotherapy (Arm 1) and MK-6598 in combination with pembrolizumab (Arm 2) in participants with advanced/metastatic solid tumors or lymphomas. The study applies a mTPI design for dose finding.
Intervention Assignment	Participants will be allocated centrally through IRT by nonrandom assignment.
Analysis Populations	Safety (Primary): APaT PK/Pharmacodynamic (Secondary): Per Protocol Efficacy (Exploratory): FAS
Primary Endpoint(s)	• DLT • AE • Discontinuing study intervention due to an AE
Secondary Endpoints	• PK parameters including AUC, C_{min}, and C_{max} • Tumor phenylpyruvate concentrations
Statistical Methods for Efficacy/Immunogenicity/ Pharmacokinetic Analyses	PK parameters of study medicines will be summarized by planned visit and time for each dose separately. Summary statistics will be provided for the quantity of phenylpyruvate in the tumor.
Statistical Methods for Safety Analyses	Summary statistics will be provided for the safety endpoints as appropriate. The pool-adjacent-violators algorithm [Ji, Y., et al 2007] will be used to estimate the DLT rates across doses. The estimate of the DLT rate among participants treated at RP2D of MK-6598 and the 90% Bayesian credible intervals for the estimate will be provided for each treatment arm.
Interim Analyses	An interim analysis may be conducted to enable future study planning at the Sponsor's discretion. Data will be examined on a continuous basis to allow for dose-finding decisions.
Multiplicity	No multiplicity adjustment is planned in this Phase 1 study.
Sample Size and Power	The overall sample size for this study depends on the observed DLT profiles of MK-6598 monotherapy and MK-6598 in combination with pembrolizumab. A target sample size of 90 participants will be used for study planning purposes.

9.2 Responsibility for Analyses/In-house Blinding

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

The 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 exploratory endpoints in this study. Details of the analysis plan will be documented in the sSAP. A description of efficacy measures is provided in Section 4.2.1.1.

PK endpoints include serum concentrations of MK-6598, as well as derived PK parameters.

Pharmacodynamic endpoints include tumor phenylpyruvate concentrations.

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 endpoints is provided in Section 4.2.1.2.

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.

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 6.6.2 for details.

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. To assess change from baseline, a baseline measurement is also required.

Safety data from participants who experienced disease progression in the monotherapy arm and crossed over into the combination arm will be presented separately.

9.5.2 Pharmacokinetic/Pharmacodynamic Analysis Populations

The per protocol population will be used for the analysis of PK and pharmacodynamic 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 baseline scan that showed measurable disease by the investigator's assessment, and who were administered at least 1 dose of study intervention.

Efficacy data from participants who experienced disease progression in the monotherapy arm and crossed over into the combination arm will be presented separately.

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.

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., et al 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

Tumor phenylpyruvate levels will be summarized by planned visit and time for each dose separately.

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

9.7 Interim Analyses

An interim analysis may be conducted to enable future study planning at the Sponsor's discretion. Data will be examined on a continuous basis to allow for dose-finding decisions.

9.8 Multiplicity

There will be no multiplicity control in this study as this is an open-label nonrandomized study.

9.9 Sample Size and Power Calculations

The sample size for this Phase 1 study is expected to be approximately 90 (45 per arm). The maximum total sample size is 168. The actual sample size depends on the safety profiles and number of doses studied. For example, if 6 participants are enrolled in each dose level up to the highest dose level of 14 participants, then 44 participants will be enrolled in each arm for a total of 88 participants.

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 and number of days for which the participant receives the study intervention.

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 Committees Structure

None.

10.1.5 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.

10.1.6 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.

10.1.7 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.

10.1.8 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.

10.1.9 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.

10.1.10 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 11 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 11 Protocol-required Safety Laboratory Assessments

Hematology	Comprehensive Chemistry Panel	Urinalysis	Other
Hematocrit	Albumin	Blood	Pregnancy test (urine or serum)[a]
Hemoglobin	Alkaline phosphatase	Glucose	PT/INR
Platelet count	ALT	Protein	aPTT or PTT
WBC (total and differential)[d]	AST	Specific gravity	Total T_3 (or Free T_3 [FT_3]), Total T_4 (or Free T_4 [FT_4]), and TSH[b,c]
RBC	Bicarbonate	Microscopic examination, if abnormal results are noted	
Absolute lymphocyte count[d]	Calcium		
	Chloride		
Absolute neutrophil count[d]	Creatinine		
	Glucose		
	Phosphorus		
	Potassium		
	Sodium		
	Total bilirubin		
	Direct bilirubin		
	Total protein		
	Blood urea nitrogen or urea		

ALT=alanine aminotransferase; aPTT=activated partial thromboplastin time; AST=aspartate aminotransferase; PT/INR=prothrombin time/international normalized ratio; PTT=partial thromboplastin time; RBC=red blood cell; T3=triiodothyronine; T4=thyroxine; TSH=thyroid 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 should submit the sample to the central laboratory for testing. 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.

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 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."

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

Additional events that require reporting

In addition to the above criteria, AEs meeting either of the below criteria, although not serious per ICH definition, are reportable to the Sponsor.

- Is a new cancer (that is not the cancer under study) as noted in Section 8.4.1
- 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.

Assessment of causality

- Did the study intervention cause the AE?

- The determination of the likelihood that the study intervention 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 study intervention and the AE; the greater the correlation with the components and their respective elements (in number and/or intensity), the more likely the study intervention caused the AE:**

    - **Exposure:** Is there evidence that the participant was actually exposed to the study intervention such as: reliable history, acceptable compliance assessment (pill count,

diary, etc), expected pharmacologic effect, or measurement of drug/metabolite in bodily specimen?

- **Time Course:** Did the AE follow in a reasonable temporal sequence from administration of the study intervention? 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 study intervention discontinued or dose/exposure/frequency reduced?

  - If yes, did the AE resolve or improve?

  - If yes, this is a positive dechallenge.

  - If no, this is a negative dechallenge.

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

- **Rechallenge:** Was the participant re-exposed to the study intervention 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) study intervention(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 STUDY INTERVENTION, OR IF RE-EXPOSURE TO THE STUDY INTERVENTION 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 study intervention 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 study intervention relationship).

    - Yes, there is a reasonable possibility of study intervention relationship:

        - There is evidence of exposure to the study intervention. The temporal sequence of the AE onset relative to the administration of the study intervention is reasonable. The AE is more likely explained by the study intervention than by another cause.

    - No, there is not a reasonable possibility of study intervention relationship:

        - Participant did not receive the study intervention OR temporal sequence of the AE onset relative to administration of the study intervention is not reasonable OR the AE is more likely explained by another cause than the study intervention. (Also entered for a participant with overdose without an associated AE.)

- The investigator must review and provide an assessment of causality for each AE/SAE and document this in the medical notes.

- 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

Participants of Childbearing Potential (POCBP)

A participant assigned female sex at birth is considered fertile and capable of becoming pregnant 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.

Participants assigned female sex at birth who are in the following categories are not capable of becoming pregnant and, therefore, not considered POCBP:

- Premenarchal
- Premenopausal 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
  - 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 participants assigned female sex at birth who are not using hormonal contraception or HRT. However, in the absence of 12 months of amenorrhea, confirmation with 2 FSH measurements in the postmenopausal range is required.
  - Participants assigned female sex at birth who are on HRT and whose menopausal status is in doubt will be required to use one of the nonhormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

10.5.2 Contraception Requirements

Contraceptives allowed during the study include:
Highly Effective Contraceptive Methods That Have Low User Dependency [a] *Failure rate of <1% per year when used consistently and correctly.*
IUS [b, c] Progestogen-only subdermal contraceptive implant [a, c] Nonhormonal IUD Bilateral tubal occlusion
Azoospermic partner (vasectomized or secondary to medical cause) All sexual partner(s) of the POCBP must be azoospermic. The participant must provide verbal confirmation of partner azoospermia during Medical History. If not, an additional highly effective method of contraception should be used. A spermatogenesis cycle is approximately 90 days.
Sexual Abstinence Sexual abstinence is considered a highly effective method only if defined as refraining from penile-vaginal intercourse with partner(s) capable of producing sperm 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.
[a] If locally required, in accordance with CTFG guidelines, acceptable contraceptive implants are limited to those which inhibit ovulation. [b] IUS is a progestin-releasing IUD. [c] Penile/external condoms must be used in addition to POCBP's hormonal contraception. Note: Tubal occlusion includes tubal ligation.

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 8.9 will be used in various experiments to understand:

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

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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
AE(s)	Adverse event(s)
AIDS	acquired immunodeficiency syndrome
ALT	alanine aminotransferase
APaT	All-Participants-as-Treated
ART	antiretroviral therapy
BP	blood pressure
C_{max}	maximum concentration
C_{min}	Minimum concentration
CNS	central nervous system
CONSORT	Consolidated Standards of Reporting Trials
COPD	chronic obstructive pulmonary disease
CR	complete response
CrCl	creatinine clearance
CRF	Case Report Form
CSR	Clinical Study Report
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTFG	Clinical Trial Facilitation Group
CTLA-4	cytotoxic T-lymphocyte-associated protein 4
C_{trough}	trough concentration
CYP	cytochrome P450
DILI	drug-induced liver injury
DLT	dose-limiting toxicity
DMC	Data Monitoring Committee
DNA	deoxyribonucleic acid
DOR	duration of response
ECG	electrocardiogram
ECI	event of clinical interest
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic Case Report Form
EDC	electronic data collection
EEA	European Economic Area
ELISA	enzyme-linked immunosorbent assay
EMA	European Medicines Agency
EU CTR	European Union Clinical Trials Regulation
FAS	Full Analysis Set
FBR	future biomedical research
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act
FIH	first in human
FSH	follicle-stimulating hormone
FSR	first site ready

Abbreviation	Expanded Term
GCP	Good Clinical Practice
GEP	gene-expression profile
GFR	glomerular filtration rate
H_2O_2	hydrogen peroxide
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
hCG	human chorionic gonadotropin
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HR	heart rate
HRT	hormone replacement therapy
IB	Investigator's Brochure
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
IFN-γ	interferon-gamma
IL4I1	interleukin 4-induced 1
IND	Investigational New Drug
IO	immune-oncology
irAE(s)	immune-related AE(s)
IRB	Institutional Review Board
IRT	interactive response technology
IUD	intrauterine device
IUS	intrauterine hormone-releasing system
IV	intravenous
LAAO	L-amino acid oxidase
LAM	lactational amenorrhea method
LLOQ	lower limit of quantitation
LSD1	Lysine-specific demethylase 1
MAD	maximum administered dose
MAO-A	monoamine oxidase A
MAO-B	monoamine oxidase B
MLR	mixed lymphocyte reaction
MRI	magnetic resonance imaging
MSI	microsatellite instability
MTD	maximum tolerated dose
mTPI	modified Toxicity Probability Interval
MUGA	multigated acquisition scan
NCI	National Cancer Institute
OR	objective response
ORR	objective response rate
OS	overall survival

Confidential

Abbreviation	Expanded Term
OTC	over-the-counter
PD	progressive disease
PD-1	programmed cell death 1 protein
PD-L1	programmed cell death ligand 1
PD-L2	programmed cell death ligand 2
PFS	progression free survival
PK	pharmacokinetic
PKCθ	protein kinase C-theta
po	orally
POCBP	participant of childbearing potential
PR	partial response
Q3W	every 3 weeks
QD	daily
RECIST	Response Evaluation Criteria In Solid Tumors
RNA	ribonucleic acid
RP2D	recommended Phase 2 dose
SAE	serious adverse event
SAP	Statistical Analysis Plan
SLAB	Supplemental laboratory test(s)
SoA	schedule of activities
SOC	standard of care
sSAP	supplemental Statistical Analysis Plan
SUSAR	suspected unexpected serious adverse reaction
TME	tumor microenvironment
ULN	upper limit of normal

Confidential

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