Official Protocol Title:	A Phase 1/1b, Open-label Clinical Study of Intratumoral/ Intralesional Administration of MK-4621/JetPEI as Monotherapy or in Combination with Pembrolizumab (MK-3475) in Participants with Advanced/Metastatic or Recurrent Solid Tumors
NCT number:	NCT03739138
Document Date:	27-OCT-2020

Title Page

THIS PROTOCOL AMENDMENT AND ALL OF THE INFORMATION RELATING TO IT ARE CONFIDENTIAL AND PROPRIETARY PROPERTY OF MERCK SHARP & DOHME CORP., A SUBSIDIARY OF MERCK & CO., INC., NJ, U.S.A. (MSD).

Protocol Title: A Phase 1/1b, Open-label Clinical Study of Intratumoral/Intralesional Administration of MK-4621/JetPEI as Monotherapy or in Combination with Pembrolizumab (MK-3475) in Participants with Advanced/Metastatic or Recurrent Solid Tumors

Protocol Number: 002-04

Compound Number: MK-4621

Sponsor Name:

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

Legal Registered Address:

One Merck Drive

P.O. Box 100

Whitehouse Station, New Jersey, 08889-0100, U.S.A.

Regulatory Agency Identifying Number(s):

EudraCT	2018-000845-37

Approval Date: 27 October 2020

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
MK-4621-002-04	27-Oct-2020	The overall rationale for the amendment is to allow eligible participants who are still ongoing in the study to continue to receive treatment for up to 35 cycles of treatment with pembrolizumab or be followed for survival through enrollment in a pembrolizumab extension study.
MK-4621-002-03-V2	22-Mar-2019	This amendment (-03) was updated to correct an error in the document footer.
MK-4621-002-03	21-Mar-2019	The main purpose for the amendment is to remove testing for GLDH from Arms 1 and 2.
MK-4621-002-02	19-Sep-2018	To clarify the order of recruitment to the different arms of the study and the maximum duration of treatment with MK-4621/JetPEI.
MK-4621-002-01	26-Jul-2018	To provide for more frequent pregnancy testing; to clarify risk associated with MK-4621 with regard to contraception, pregnancy, and breastfeeding; and to extend the prohibition of live vaccines from 3 months after the end of the study treatment.
MK-4621-002-00	29-May-2018	Original protocol.

PROTOCOL AMENDMENT SUMMARY OF CHANGES

Amendment: 04

Overall Rationale for the Amendments:

The overall rationale for the amendment is to allow eligible participants who are still ongoing in the study to continue to receive treatment for up to 35 cycles of treatment with pembrolizumab or be followed for survival through enrollment in a pembrolizumab extension study.

Summary of Changes Table:

Section # and Name	Description of Change	Brief Rationale
1 Synopsis 1.2 Schema 4.4 Beginning and End of Study Definition	Language was added to allow eligible participants who are still ongoing in the study to continue to receive treatment for up to 35 cycles of treatment with pembrolizumab or be followed for survival through enrollment in a pembrolizumab extension study.	This change will allow this study to be closed.

Table of Contents

LIST OF TABLES

LIST OF FIGURES

1 PROTOCOL SUMMARY

1.1 Synopsis

Protocol Title: A Phase 1/1b, Open-label Clinical Study of Intratumoral/Intralesional Administration of MK-4621/JetPEI as Monotherapy or in Combination with Pembrolizumab (MK-3475) in Participants with Advanced/Metastatic or Recurrent Solid Tumors

Short Title: Phase 1/1b Open-label Study of MK-4621/JetPEI by IT Injection

Acronym: Not applicable.

Hypotheses, Objectives, and Endpoints:

Primary Objectives	Primary Endpoints
- Objective: To evaluate the safety and tolerability and to establish a preliminary recommended Phase 2 dose (RP2D) of MK-4621/JetPEI administered as monotherapy and in combination with pembrolizumab	- Dose-limiting toxicity (DLT) - Adverse events (AEs) - Study intervention discontinuations due to AEs
Secondary Objectives	Secondary Endpoints
- Objective: To evaluate the pharmacokinetics (PK) of MK-4621/JetPEI administered as monotherapy and in combination with pembrolizumab	- PK parameters of MK-4621/JetPEI, including area under the curve (AUC), minimum concentration (Cmin), maximum concentration (Cmax)
- Objective: To evaluate the objective response rate (ORR) as assessed by the investigator based on Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST 1.1) and modified RECIST 1.1 for immune-based therapeutics (iRECIST) of MK-4621/JetPEI administered as monotherapy and in combination with pembrolizumab	- Objective response is a confirmed complete response (CR) or partial response (PR)

Overall Design:

Study Phase	Phase 1/1b
Primary Purpose	Treatment
Indication	The treatment of participants with advanced/metastatic or recurrent solid tumors.
Population	Participants with any histologically- or cytologically-confirmed advanced/metastatic solid tumor by pathology report who have received or been intolerant to all treatment known to confer clinical benefit
Study Type	Interventional
Intervention Model	This is a mono- and combination-therapy, dose-finding and dose-confirmation, multi-site study.
Type of Control	No treatment control
Study Blinding	Unblinded Open-label
Masking	No Masking
Estimated Duration of Study	The Sponsor estimates that the study will require approximately 2.5 years from the time the first participant signs the informed consent until the last participant's last study-related telephone call or visit.

Number of Participants:

Approximately 72 participants will be enrolled in the dose-escalation/dose-confirmation part of the study. The final number of participants enrolled in the study will depend on the empirical safety data (DLT observations, in particular, at which dose the modified Toxicity Probability Interval (mTPI) design is triggered, and at which dose the preliminary RP2D is identified). The approximate number of participants in Arm 1 is 8, in Arm 2 is 32, and in Arm 3 is 32.

Intervention Groups and Duration:

Inter-vention Groups

Inter-vention Group Name	Drug	Dose Strength	Dose Frequency	Route of Admin.	Regimen/ Treatment Period/	Use
Arm 1	MK-4621/JetPEI	0.8 mg	q1w	Intratumoral via visual inspection for cutaneous lesions, and via ultrasound guidance for subcutaneous lesions, as needed	Days 1, 8, and 15 of each 21-day cycle	Experi-mental
Arm 2	Pembrolizumab	200 mg	q3w	IV infusion	Day 1 of each 21-day cycle	Experi-mental
	MK-4621/ JetPEI [a]	Range: 0.4 mg to 0.8 mg [b]	q1w	Intratumoral via visual inspection for cutaneous lesions, and via ultrasound guidance for subcutaneous lesions, as needed	Days 1, 8 and 15 of each 21-day cycle	Experi-mental
Arm 3	Pembrolizumab	200 mg	q3w	IV infusion	Day 1 of each 21-day cycle beginning with Cycle 2	Experi-mental
	MK-4621/ JetPEI [a]	Range: 0.2 mg to 0.8 mg [b]	q3w	Intratumoral (Visceral) via ultrasound or cross-sectional imaging (CT/MRI) guidance for liver lesions, as needed.	Day 1 of each 21-day cycle	Experi-mental

[a] MK-4621/JetPEI will be administered within 0.5 to 4 hours following completion of pembrolizumab IV infusion, as applicable.
[b] Dose levels will be determined based on emerging safety data.

Total Number	3 Arms
Duration of Participation	Each participant will participate in the study for approximately 2.5 years from the time the participant signs the Informed Consent Form (ICF) through the final contact. After a screening phase of up to 28 days, each participant will be assigned to receive study treatment until disease progression is radiographically documented and, when clinically appropriate, confirmed by the site per iRECIST for treated participants, unacceptable AEs, intercurrent illness that prevents further administration of treatment, investigator's decision to withdraw the participant, noncompliance with study treatment or procedure requirements or administrative reasons requiring cessation of treatment, or until the participant has received 35 administrations of pembrolizumab (approximately 2 years). Participants who progress by either clinical or radiographic evaluation on monotherapy with MK-4621/JetPEI (Arm 1) may cross over into the combination therapy arm (Arm 2), provided that they meet crossover eligibility criteria. After the end of treatment, each participant will be followed for the occurrence of AEs and spontaneously reported pregnancy as described in Section 8.4. Participants who discontinue for reasons other than radiographic disease progression will have post-treatment follow-up imaging for disease status until disease progression is documented radiographically per RECIST 1.1, confirmed by the site per iRECIST (for participants treated with pembrolizumab), initiating a nonstudy cancer treatment, withdrawing consent, or becoming lost to follow-up. All participants will be followed by telephone for overall survival until death, withdrawal of consent, or the end of the study, whichever occurs first. Once participants have achieved the study objectives, they will be discontinued from this study and may be enrolled into an extension study to continue protocol-defined assessments and treatment with pembrolizumab monotherapy, as appropriate.

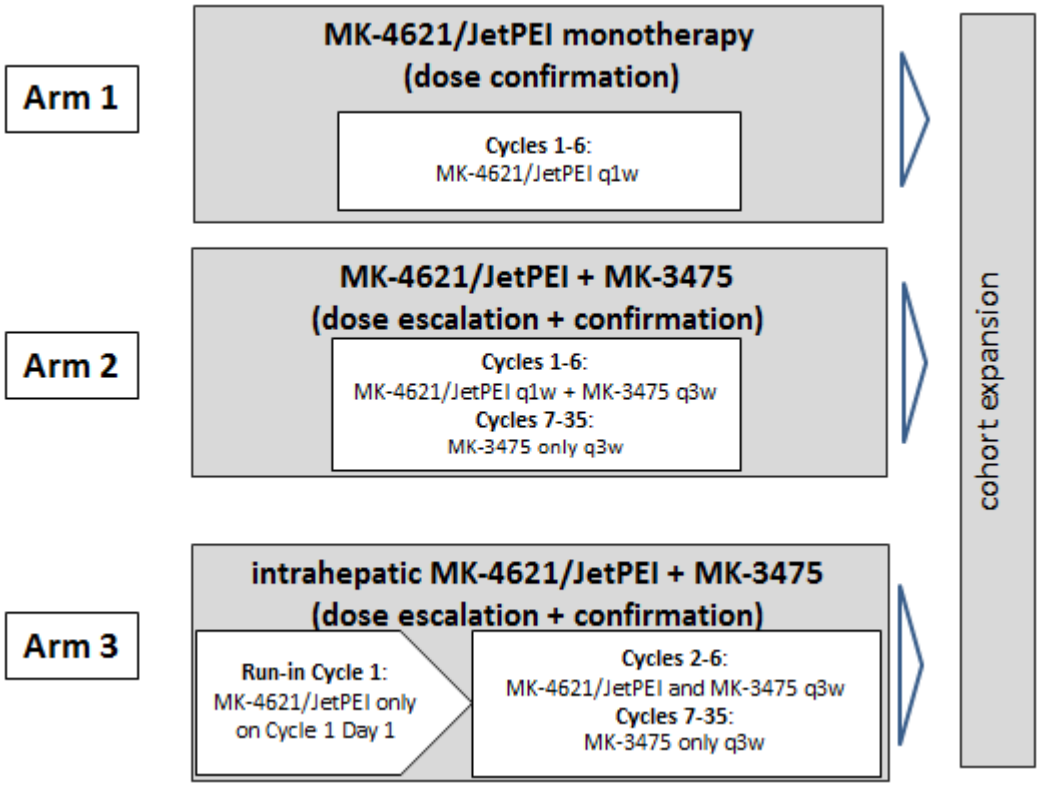
Study Governance Committees:

Steering Committee	No
Executive Oversight Committee	No
Data Monitoring Committee	No
Clinical Adjudication Committee	No
There are no governance committees in this study.	

Study Accepts Healthy Volunteers: No

A list of abbreviations used in this document can be found in Appendix 8.

1.2 Schema



NOTE: Participants who progress by either clinical or radiographic evaluation on monotherapy with MK-4621/JetPEI (Arm 1) may cross over into the combination therapy arm (Arm 2), provided that they meet crossover eligibility criteria.

NOTE: Once participants have achieved the study objectives, they will be discontinued from this study and may be enrolled into an extension study to continue protocol-defined assessments and treatment with pembrolizumab monotherapy, as appropriate.

Figure 1 Overall Study Design

1.3 Schedule of Activities (SoA)

1.3.1 Schedule of Activities for the Initial Screening (Arms 1, 2, and 3) and Crossover Screening (Arm 1 to Arm 2)

Study Period	Initial and Crossover Screening	Notes
Visit Days	**-28 to -1**	
Administrative Procedures		
Informed Consent	X	Written informed consent must be obtained prior to performing any protocol-specific procedures. Tests performed prior to consent as part of routine clinical management are acceptable if performed within the specified timeframe.
Informed Consent for Future Biomedical Research (FBR) (Optional)	X	Consent for FBR is not required to participate in the study. Any leftover biomarker samples will be stored for FBR if the participant signs the FBR consent. Detailed instructions for the collection and management of FBR specimens are provided in the Procedure Manual.
Inclusion/Exclusion Criteria	X	
Participant Identification Card	X	
Demographics and Medical History	X	For crossover, update only.
Oncology Disease Status and Prior Oncology Treatment History	X	
Prior Medication	X	
Clinical Procedures/Assessments		
Tumor Imaging, RECIST 1.1, and iRECIST Response Assessment	X	Baseline tumor imaging (CT or MRI) as indicated for tumor type and/or medical photography of cutaneous lesions should be performed within 28 days of enrollment. Please refer to Imaging Manual for detailed information.
Medical Photography (Cutaneous Lesions)	X	
Physical Examination	X	A full physical examination should be done at screening.
Height	X	
Weight	X	
Vital Signs	X	Includes temperature, pulse, respiratory rate, blood pressure, and oxygen (O_2) saturation.
ECOG Performance Status	X	To be performed within 7 days prior to the first dose of study intervention.
12-Lead Electrocardiogram	X	
Adverse Event Monitoring	X	All adverse events that occur after the consent form is signed but before treatment allocation must be reported by the investigator if the event causes the participant to be excluded from the study or is the result of a protocol-specified intervention. There is to be continuous AE reporting from the time of treatment allocation.

Study Period	Initial and Crossover Screening	Notes
Visit Days	**-28 to -1**	
Laboratory Procedures/Assessments		
CBC with Differential	X	Perform all screening clinical laboratory tests within 72 hours of treatment initiation. Exceptions are hepatitis, HIV and thyroid serologies, which may be performed within 28 days prior to first dose. Participants on anticoagulant therapy should be monitored throughout the study. GLDH is to be collected for Arm 3 only. Thyroid function: Total T4 and T3 are preferred over FT4 and FT3.
Chemistry Panel	X	
PT/INR and PTT or aPTT	X	
LDH, GGT, GLDH	X	
Lipase and Amylase	X	
Thyroid Function Testing (T4 or FT4, T3 or FT3, TSH)	X	
Urinalysis	X	
Pregnancy test for WOCBP only (urine or serum β-hCG)	X	Perform within 72 hours prior to C1D1. Urine pregnancy test to be performed as indicated; if test is positive or cannot be confirmed as negative, a serum pregnancy test is required. Additional pregnancy testing can be conducted if required by local regulations or if clinically indicated. Refer to Appendix 7 for country-specific requirements.
HIV/Hepatitis B and C Screen	X	Include HCV antibody or HCV RNA (qualitative) and HBsAg. HIV, and Hepatitis B and C by history are acceptable for exclusion, unless testing is required by local regulations. Refer to Appendix 7 for country-specific requirements.
Laboratory Procedures/Assessments – CENTRAL		
Blood for RNA Analyses	X	Collect **blood** for RNA samples (Arm 1, Arm 2, and Arm 3) at **initial and crossover screening**.
Serum for Cytokine/Chemokine Analyses and C-Reactive Protein (CRP)[3]	X	Collect **blood** for serum for cytokine/chemokine analyses and C-Reactive Protein (CRP) samples at **initial and crossover screening**.
Pretreatment Tumor Biopsies	X	Initial Screening (Arm 1 and Arm 2) and Crossover Screening (Arm 1 to Arm 2): Required at **initial screening as the predose samples** (including the tumor lesion that is intended for treatment with IT administration of MK-4621/JetPEI, as well as on the distant, discrete lesion that is not intended for IT administration of MK-4621/JetPEI), up to 72 hours prior to treatment. Initial Screening (Arm 3): Biopsy and MK-4621/JetPEI injection should be done at the same procedure in 1 tumor on C1D1 (details see SoA for Arm 3)

NOTE: Participants who progress by either clinical or radiographic evaluation on monotherapy with MK-4621/JetPEI (Arm 1) may cross over into the combination therapy arm (Arm 2), provided that they meet crossover eligibility criteria.

aPTT=activated partial thromboplastin time; β-hCG= β-human chorionic gonadotropin; CT=computed tomography; ECOG=Eastern Cooperative Oncology Group; GGT=gamma glutamyl transferase; GLDH=glutamate dehydrogenase; HCV= hepatitis C virus; INR=International Normalized Ratio; IT=intratumoral; LDH=lactate dehydrogenase; MRI=magnetic resonance imaging; PET=positron emission tomography; PT=prothrombin time; PTT=partial thromboplastin time; TSH=thyroid stimulating hormone; WOCBP=women of childbearing potential.

1.3.2 Schedule of Activities for the Treatment Period

1.3.2.1 Schedule of Activities for the Treatment Period for Arm 1

Study Period	Treatment Period Cycle = 21 days									Notes
Visit Timing	Cycle 1			Cycle 2			Cycles ≥3			**For all cycles:** Up to 6 cycles of treatment with MK-4621/JetPEI
Visit Day (Days)	1	8	15	1	8	15	1	8	15	
Visit Window	+3	±1	±1	+3	±3	±3	±3	±3	±3	
Arm 1: MK-4621/JetPEI Monotherapy										
MK-4621/JetPEI Administration	X	X	X	X	X	X	X	X	X	Study treatment may be administered up to 3 days after the scheduled Day 1 of each treatment cycle.
24-Hour Inpatient Observation Period (Discretionary)	X									A 24-hour inpatient observation period following MK-4621/JetPEI administration on Day 1 of Cycles 1-6 will be at the discretion of the investigator for Arm 1.
Clinical Procedures/Assessments										
Tumor Imaging, RECIST 1.1, and iRECIST Response Assessment	⟷									Tumor imaging (CT or MRI) as indicated for tumor type and/or medical photography of cutaneous lesions should be performed every 9 weeks (± 7 days) after the first dose, **following calendar days**, and should not be adjusted for delays in cycle starts. Continue imaging schedule until disease progression, discontinuation, or the start of anticancer treatment. Please refer to Imaging Manual for detailed information on medical photography.
Medical Photography (Cutaneous Lesions)	⟷									
Physical Examination	X	X	X	X	X	X	X	X	X	Directed physical examinations may be performed unless a full examination is deemed necessary.
Weight	X						X			Every other cycle (ie, Cycles 1, 3, and 5).
tal Signs (temperature, pulse, respiratory rate, blood pressure, and oxygen (O_2) saturation)	X	X	X	X	X	X	X	X	X	To be measured within 1 h (± 30 min) prior to dosing, and 2, 4, and 6 hours after MK-4621/JetPEI administration in Cycle 1. For Cycle 2 to Cycle 6, to be measured within 1 h (± 30 min) prior to dosing, and 2 and 4 hours after MK-4621/JetPEI administration.
ECOG Performance Status	X			X			X			Performed within 72 hours prior to MK-4621/JetPEI dosing on Day 1 of each cycle.
12-Lead Electrocardiogram	X			X			X			Performed within 72 hours prior to MK-4621/JetPEI dosing on Day 1 of each cycle. Postdose ECG will be obtained within 30 minutes after following MK-4621/JetPEI administration on Day 1 of each cycle up to Cycle 4.
Concomitant Medication	X	X	X	X	X	X	X	X	X	
Adverse Events	⟷									Continuous AE reporting from the time of treatment allocation.

Study Period	Treatment Period Cycle = 21 days									Notes
Visit Timing	**Cycle 1**			**Cycle 2**			**Cycles ≥3**			**For all cycles:** Up to 6 cycles of treatment with MK-4621/JetPEI
Visit Day (Days)	**1**	**8**	**15**	**1**	**8**	**15**	**1**	**8**	**15**	
Visit Window	**+3**	**±1**	**±1**	**+3**	**±3**	**±3**	**±3**	**±3**	**±3**	
Survival Status	←								→	Upon Sponsor request, participants may be contacted for survival status at any time during the course of the study.
Laboratory Procedures/Assessments										
CBC with Differential	X	X	X	X	X	X	X	X	X	Perform all scheduled clinical laboratory tests within 72 hours prior to the start of each cycle. Screening procedures/sample collections done within this timeframe do not need to be repeated for the Cycle 1, Day 1 time point. Participants on anticoagulant therapy should be monitored throughout the study. Thyroid function: After Cycle 1, samples are collected every other cycle (ie, Cycles 2, 4, 6, etc.). Total T4 and T3 are preferred over FT4 and FT3.
Chemistry Panel	X	X	X	X	X	X	X	X	X	
PT/INR and PTT or aPTT	X			X			X			
LDH, GGT	X			X			X			
Lipase and Amylase	X			X			X			
Thyroid Function Testing (T4 or FT4, T3 or FT3, TSH)	X			X			X			
Urinalysis	X			X			X			
Pregnancy test for WOCBP only (urine or serum β-hCG)	X									Perform within 72 hours prior to C1D1. Urine pregnancy test to be performed as indicated; if test is positive or cannot be confirmed as negative, a serum pregnancy test is required. Additional pregnancy testing can be conducted if required by local regulations or clinically indicated. Refer to Appendix 7 for country-specific requirements.
Laboratory Procedures/Assessments – CENTRAL										
Pharmacokinetics for MK-4621	X			X						Collect **predose** samples 1-8 h before MK-4621/JetPEI administration on C1D1 and C2D1. Collect **postdose** samples on C1D1 and C2D1: end of IT injection (up to +5 min), 0.5 h (±5 min), 1.0 h (±10 min), 2 h (±15 min), 4 h (±15 min), and 6 h (±15 min) after MK-4621/JetPEI IT administration. Additional **postdose** samples will be collected at **24 h (± 4 h)** after MK-4621/JetPEI IT administration on C1D1 only.
Blood for T Cell Repertoire (TCR)	X			X			X			Collect **blood** for TCR samples at -4 to 0 h **predose** of MK-4621/JetPEI on Day 1 of Cycle 1 (C1D1), Cycle 2 (C2D1), Cycle 3 (C3D1), and Cycle 5 (C5D1).

Study Period	Treatment Period Cycle = 21 days									Notes
Visit Timing	**Cycle 1**			**Cycle 2**			**Cycles ≥3**			**For all cycles:** Up to 6 cycles of treatment with MK-4621/JetPEI
Visit Day (Days)	**1**	**8**	**15**	**1**	**8**	**15**	**1**	**8**	**15**	
Visit Window	**+3**	**±1**	**±1**	**+3**	**±3**	**±3**	**±3**	**±3**	**±3**	
Blood for RNA Analyses	X			X						Collect **blood** for RNA samples -4 to 0 h **predose**, and 6 h (±15 min) **postdose** of MK-4621/JetPEI on Day 1 of Cycle 1 (C1D1) and Cycle 2 (C2D1).
Serum for Cytokine/Chemokine Analyses and C-Reactive Protein (CRP)	X			X			X			Collect **blood** for serum cytokine/chemokine analyses and C-Reactive Protein (CRP) samples at -4 to 0 h **predose** of MK-4621/JetPEI on Day 1 of every cycle. **C**ollect **blood** for serum cytokine/chemokine analyses and C-Reactive Protein (CRP) samples at 2 h (±15 min), 6 h (±15 min), and **24 h (±4 h) postdose** of MK-4621/JetPEI on Day 1 of Cycle 1 (C1D1) and Cycle 2 (C2D1). Collect samples at the same time as for MK-4621/JetPEI PK when feasible.
Blood for Genetic Analyses	X									Collect prior to treatment.
On-treatment Tumor Biopsy							X			Required post administration of MK-4621/JetPEI including 2 biopsy samples of both the injected and noninjected tumors **where predose biopsy samples are collected** on **C3D1 (Week 7)**. Biopsy samples will be collected 5 h (±2 h) prior to MK-4621/JetPEI injection. All participants will have the option to provide 2 additional biopsy samples of both the injected and uninjected tumors on **C5D1 (Week 13)**.

aPTT=activated partial thromboplastin time; β-hCG= β-human chorionic gonadotropin; CT=computed tomography; ECOG=Eastern Cooperative Oncology Group; GGT=gamma glutamyl transferase; INR=International Normalized Ratio; IT=intratumoral; LDH=lactate dehydrogenase; MRI=magnetic resonance imaging; PET=positron emission tomography; PT=prothrombin time; WOCBP=women of childbearing potential.

1.3.2.2 Schedule of Activities for the Treatment Period for Arm 2

Study Period	Treatment Period Cycle = 21 days									Notes
Visit Timing	**Cycle 1**			**Cycles 2-6**			**Cycles ≥7**			**For all cycles:** Up to 35 cycles of treatment with pembrolizumab and up to 6 cycles of treatment with MK-4621/JetPEI.
Visit Day (Days)	**1**	**8**	**15**	**1**	**8**	**15**	**1**	**8**	**15**	
Visit Window	**+3**	**±1**	**±1**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	
Arm 2: MK-4621/JetPEI and Pembrolizumab Combination Therapy										
Pembrolizumab Administration	X			X			X			In Cycle 2, study treatment may be administered up to 3 days after the scheduled Day 1. Beginning in Cycle 3, study treatment may be administered up to 3 days before or after the scheduled Day 1. MK-4621/JetPEI will be administered within 0.5 to 4 h after completion of the pembrolizumab infusion. See Pharmacy Manual. Participants who crossover to Arm 2 will receive combination therapy at the highest dose of MK-4621/JetPEI with pembrolizumab that has been cleared for DLT in Arm 2 at the time of crossover. Participants who cross over from Arm 1 to Arm 2 are eligible for up to 35 cycles of treatment with pembrolizumab therapy and up to a cumulative total of 6 cycles of treatment with MK-4621/JetPEI inclusive of the MK-4621/JetPEI cycles received in Arm 1 and Arm 2.
MK-4621/JetPEI Administration	X	X	X	X	X	X				
24-Hour Inpatient Observation Period	X			X[a]						There will be a 24-hour inpatient observation period following MK-4621/JetPEI administration on C1D1, which may be extended to 48 hours at the discretion of the investigator, per local Institutional Review Board, Ethics Review Committee, and/or Health Authority mandate. For Cycles 2-6, a 24-hour inpatient observation period following MK-4621/JetPEI administration will be at the discretion of the investigator.

Study Period	Treatment Period Cycle = 21 days									Notes
Visit Timing	**Cycle 1**			**Cycles 2-6**			**Cycles ≥7**			**For all cycles:** Up to 35 cycles of treatment with pembrolizumab and up to 6 cycles of treatment with MK-4621/JetPEI.
Visit Day (Days)	**1**	**8**	**15**	**1**	**8**	**15**	**1**	**8**	**15**	
Visit Window	**+3**	**±1**	**±1**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	
Clinical Procedures/Assessments										
Tumor Imaging, RECIST 1.1, and iRECIST Response Assessment	←	—	—	—	—	—	—	—	→	Tumor imaging (CT or MRI) as indicated for tumor type and/or medical photography of cutaneous lesions should be performed every 9 weeks (± 7 days) after the first dose, **following calendar days**, and should not be adjusted for delays in cycle starts. Continue imaging schedule until disease progression, discontinuation, or the start of anticancer treatment. Please refer to Imaging Manual for detailed information om medical photography.
Medical Photography (Cutaneous Lesions)	←	—	—	—	—	—	—	—	→	
Physical Examination	X	X	X	X	X	X	X			Directed physical examinations may be performed unless a full examination is deemed necessary.
Weight	X			X			X			Every other cycle (ie, Cycles 1, 3, 5, 7, etc.).
Vital Signs (temperature, pulse, respiratory rate, blood pressure, and oxygen (O_2) saturation)	X	X	X	X	X	X	X			To be measured within 1 h (± 30 min) prior to dosing, and 2, 4, and 6 hours after MK-4621/JetPEI administration in Cycle 1. For Cycle 2 to Cycle 6, to be measured within 1 h (± 30 min) prior to dosing, and 2 and 4 hours after MK-4621/JetPEI administration. For Cycle 7 and beyond, to be measured within 1 h (± 30 min) prior to dosing with pembrolizumab on Day 1 only of every cycle.
ECOG Performance Status	X			X			X			Performed within 72 hours prior to MK-4621/JetPEI dosing on Day 1 of each cycle.
12-Lead Electrocardiogram	X			X						Performed within 72 hours prior to MK-4621/JetPEI dosing on Day 1 of each cycle. Postdose ECG will be obtained within 30 minutes after following MK-4621/JetPEI administration on Day 1 of each cycle up to Cycle 4.
Concomitant Medication	X	X	X	X	X	X	X			
Adverse Events	←	—	—	—	—	—	—	—	→	Continuous AE reporting from the time of treatment allocation.
Survival Status	←	—	—	—	—	—	—	—	→	Upon Sponsor request, participants may be contacted for survival status at any time during the course of the study.

Study Period	Treatment Period Cycle = 21 days									Notes
Visit Timing	**Cycle 1**			**Cycles 2-6**			**Cycles ≥7**			**For all cycles:** Up to 35 cycles of treatment with pembrolizumab and up to 6 cycles of treatment with MK-4621/JetPEI.
Visit Day (Days)	**1**	**8**	**15**	**1**	**8**	**15**	**1**	**8**	**15**	
Visit Window	**+3**	**±1**	**±1**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	
Laboratory Procedures/Assessments										
CBC with Differential	X	X	X	X	X	X	X			Perform all scheduled clinical laboratory tests within 72 hours prior to the start of each cycle. Screening procedures/sample collections done within this timeframe do not need to be repeated for the Cycle 1, Day 1 time point. Participants on anticoagulant therapy should be monitored throughout the study. Thyroid function: After Cycle 1, samples are collected every other cycle (ie, Cycles 2, 4, 6, etc.). Total T4 and T3 are preferred over FT4 and FT3.
Chemistry Panel	X	X	X	X	X	X	X			
PT/INR and PTT or aPTT	X			X			X			
LDH, GGT	X			X			X			
Lipase and Amylase	X			X			X			
Thyroid Function Testing (T4 or FT4, T3 or FT3, TSH)	X			X			X			
Urinalysis	X			X			X			
Pregnancy test for WOCBP only (urine or serum β-hCG)	X									Perform within 72 hours prior to C1D1. Urine pregnancy test to be performed as indicated; if test is positive or cannot be confirmed as negative, a serum pregnancy test is required. Additional pregnancy testing can be conducted if required by local regulations or clinically indicated. Refer to Appendix 7 for country-specific requirements.
Laboratory Procedures/Assessments – CENTRAL										
Anti-pembrolizumab Antibody	X			X			X			Collect samples **predose** 0 to 4 h before pembrolizumab IV infusion on C1D1, C2D1, C4D1, and on Day 1 of every 4 cycles thereafter (ie, C8, C12, etc.). Collect with plasma samples for MK-4621/JetPEI PK when feasible.
Pharmacokinetics for MK-4621	X			X						Collect **predose** samples 1-8 h before MK-4621/JetPEI administration on C1D1 and C2D1 (ie, before any drug administration of pembrolizumab and MK-4621/JetPEI) Collect **postdose** samples on C1D1 and C2D1 at the following time points: end of IT injection (up to +5 min), 0.5 h (±5 min), 1.0 h (±10 min), 2 h (±15 min), 4 h (±15 min), and 6 h (±15 min) after MK-462/JetPEI 1 IT administration. Additional **postdose** samples will be collected at **24 h (± 4 h)** after MK-4621/JetPEI IT administration on C1D1 only.

Study Period	Treatment Period Cycle = 21 days									Notes
Visit Timing	**Cycle 1**			**Cycles 2-6**			**Cycles ≥7**			**For all cycles:** Up to 35 cycles of treatment with pembrolizumab and up to 6 cycles of treatment with MK-4621/JetPEI.
Visit Day (Days)	**1**	**8**	**15**	**1**	**8**	**15**	**1**	**8**	**15**	
Visit Window	**+3**	**±1**	**±1**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	
Pharmacokinetics for Pembrolizumab PK	X			X			X			Collect samples **predose** 0 to 4 h before pembrolizumab IV infusion on C1D1, C2D1, C4D1, and on Day 1 of every 4 cycles thereafter (ie, C8, C12, etc.). Collect **postdose** samples at 0.5 h (±5 min) after MK-4621/JetPEI administration on C1D1, C2D1, and C4D1 in Arm 2. Collect with plasma samples for MK-4621/JetPEI PK when feasible.
Blood for T Cell Repertoire (TCR)	X			X						Collect **blood** for TCR samples at -4 to 0 h **predose** of MK-4621/JetPEI on Day 1 of Cycle 1 (C1D1), Cycle 3 (C3D1), and Cycle 5 (C5D1).
Blood for RNA Analyses	X			X						Collect **blood** for RNA samples -4 to 0 h **predose**, and 6 h (±15 min) **postdose** of MK-4621/JetPEI on Day 1 of Cycle 1 (C1D1) and Cycle 2 (C2D1).
Serum for Cytokine/Chemokine Analyses and C-Reactive Protein (CRP)	X			X						Collect **blood** for serum cytokine/chemokine analyses and C-Reactive Protein (CRP)samples at -4 to 0 h **predose** of MK-4621/JetPEI on Day 1 of every cycle. **C**ollect **blood** for serum for Cytokine/Chemokine Analyses and C-Reactive Protein (CRP) samples at 2 h (±15 min), 6 h (±15 min), and **24 h (±4 h) postdose** of MK-4621/JetPEI on Day 1 of Cycle 1 (C1D1) and Cycle 2 (C2D1). Collect samples at the same time as for MK-4621/JetPEI PK when feasible.
Blood for Genetic Analyses	X									Collect prior to treatment
On-treatment Tumor Biopsy				X						Required post administration of MK-4621/JetPEI (including 2 biopsy samples of both the injected and noninjected tumors **where predose biopsy samples are collected** on **C3D1 (Week 7)**. Biopsy samples will be collected 5 h (±2 h) prior to MK-4621/JetPEI injection. All participants will have the option to provide 2 additional biopsy samples of both the injected and uninjected tumors on **C5D1 (Week 13)**.

aPTT=activated partial thromboplastin time; β-hCG= β-human chorionic gonadotropin; CT=computed tomography; ECOG=Eastern Cooperative Oncology Group; GGT=gamma glutamyl transferase; INR=International Normalized Ratio; IT=intratumoral; LDH=lactate dehydrogenase; MRI=magnetic resonance imaging; PET=positron emission tomography; PT=prothrombin time; WOCBP=women of childbearing potential.

1.3.2.3 Schedule of Activities for the Treatment Period for Arm 3

Study Period	Treatment Period Cycle = 21 days									Notes
Visit Timing	Cycle 1			Cycles 2-6			Cycles ≥7			**For all cycles:** Up to 35 cycles of treatment with pembrolizumab and up to 6 cycles of treatment with MK-4621/JetPEI.
Visit Day (Days)	1	8	15	1	8	15	1	8	15	
	+3	±3	±3	±3	±3	±3	±3	±3	±3	
Arm 3: MK-4621/JetPEI and Pembrolizumab Combination Therapy (Intrahepatic)										
Pembrolizumab Administration				X			X			Beginning in Cycle 2, study treatment may be administered up to 3 days before or after the scheduled Day 1. MK-4621/JetPEI will be administered within 0.5 to 4 h after completion of the pembrolizumab infusion. See Pharmacy Manual.
MK-4621/JetPEI Administration	X			X						
24-Hour Inpatient Observation Period	X			X						There will be a 24-hour inpatient observation period following MK-4621/JetPEI administration on C1D1 and following MK-4621/JetPEI and pembrolizumab administration on C2D1, which may be extended to 48 hours at the discretion of the investigator, per local Institutional Review Board, Ethics Review Committee, and/or Health Authority mandate. For Cycles 3-6, a 24-hour inpatient observation period following MK-4621/JetPEI administration will be at the discretion of the investigator.
Clinical Procedures/Assessments										
Tumor Imaging, RECIST 1.1, and iRECIST Response Assessment	←								→	Tumor imaging (CT or MRI) as indicated for tumor type (and medical photography in the case of the presence of cutaneous lesions) should be performed every 9 weeks (± 7 days) after the first dose, **following calendar days**, and should not be adjusted for delays in cycle starts. Continue imaging schedule until disease progression, discontinuation, or the start of anticancer treatment. Please refer to Imaging Manual for detailed information on medical photography.
Medical Photography (Cutaneous Lesions)	←								→	
Physical Examination	X	X	X	X	X	X	X			Directed physical examinations may be performed unless a full examination is deemed necessary.
Weight	X			X			X			Every other cycle (ie, Cycles 1, 3, 5, 7, etc.).

Study Period	Treatment Period Cycle = 21 days									Notes
Visit Timing	**Cycle 1**			**Cycles 2-6**			**Cycles ≥7**			**For all cycles:** Up to 35 cycles of treatment with pembrolizumab and up to 6 cycles of treatment with MK-4621/JetPEI.
Visit Day (Days)	**1**	**8**	**15**	**1**	**8**	**15**	**1**	**8**	**15**	
	+3	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	
Vital Signs (temperature, pulse, respiratory rate, blood pressure, and oxygen (O_2) saturation)	X	X	X	X	X	X	X			To be measured within 1 h (± 30 min) prior to dosing, and 2, 4, and 6 hours after MK-4621/JetPEI administration in Cycle 1 and Cycle 2. For Cycle 3 to Cycle 6, to be measured within 1 h (± 30 min) prior to dosing, and 2 and 4 hours after MK-4621/JetPEI administration. For Cycle 7 and beyond, to be measured within 1 h (± 30 min) prior to dosing with pembrolizumab on Day 1 only of every cycle.
ECOG Performance Status	X			X			X			Performed within 72 hours prior to MK-4621/JetPEI dosing on Day 1 of each cycle.
12-Lead Electrocardiogram	X			X						Performed within 72 hours prior to MK-4621/JetPEI dosing on Day 1 of each cycle. Postdose ECG will be obtained within 30 minutes after following MK-4621/JetPEI administration on Day 1 of each cycle up to Cycle 4.
Concomitant Medication	X	X	X	X	X	X	X			
Adverse Events	←								→	Continuous AE reporting from the time of treatment allocation.
Survival Status	←								→	Upon Sponsor request, participants may be contacted for survival status at any time during the course of the study.
Laboratory Procedures/Assessments										
CBC with Differential	X	X	X	X	X	X	X			Perform all scheduled clinical laboratory tests within 72 hours prior to the start of each cycle. Screening procedures/sample collections done within this timeframe do not need to be repeated for the Cycle 1, Day 1 time point. Participants on anticoagulant therapy should be monitored throughout the study. Thyroid function: After Cycle 1, samples are collected every other cycle (ie, Cycles 2, 4, 6, etc.). Total T4 and T3 are preferred over FT4 and FT3.
Chemistry Panel	X	X	X	X	X	X	X			
PT/INR and PTT or aPTT	X	X	X	X	X	X	X			
LDH, GGT, GLDH	X			X			X			
Lipase and Amylase	X			X			X			
Thyroid Function Testing (T4 or FT4, T3 or FT3, TSH)	X			X			X			
Urinalysis	X			X			X			
Pregnancy test for WOCBP only (urine or serum β-hCG)	X									Perform within 72 hours prior to C1D1. Urine pregnancy test to be performed as indicated; if test is positive or cannot be confirmed as negative, a serum pregnancy test is required. Monthly testing should be conducted per local regulations. Refer to Appendix 7 for country-specific requirements

Study Period	Treatment Period Cycle = 21 days									Notes
Visit Timing	Cycle 1			Cycles 2-6			Cycles ≥7			**For all cycles:** Up to 35 cycles of treatment with pembrolizumab and up to 6 cycles of treatment with MK-4621/JetPEI.
Visit Day (Days)	1	8	15	1	8	15	1	8	15	
	+3	±3	±3	±3	±3	±3	±3	±3	±3	
Laboratory Procedures/Assessments – CENTRAL										
Anti-Pembrolizumab Antibody				X			X			Collect samples **predose** 0 to 4 h before pembrolizumab IV infusion on C2D1, C3D1, C5D1, and on Day 1 of every 4 cycles thereafter (ie, C9, C13, etc.). Collect with plasma samples for MK-4621/JetPEI PK when feasible.
Pharmacokinetics for MK-4621	X			X						Collect **predose** samples 1-8 h before MK-4621/JetPEI administration on C1D1, C2D1 and C3D1 (ie, before any drug administration of pembrolizumab and MK-4621/JetPEI) Collect **postdose** samples on C1D1, C2D1, and C3D1 at the following time points: end of IT injection (up to +5 min), 0.5 h (±5 min), 1.0 h (±10 min), 2 h (±15 min), 4 h (±15 min), and 6 h (±15 min) after MK-4621/JetPEI IT administration. Additional **postdose** samples will be collected at **24 h (± 4 h)** after MK-4621/JetPEI IT administration on C1D1 only.
Pharmacokinetics for Pembrolizumab PK				X			X			Collect samples **predose** 0 to 4 h before pembrolizumab IV infusion on C2D1, C3D1, C5D1, and on Day 1 of every 4 cycles thereafter (ie, C9, C13, etc.). Collect **postdose** samples at 0.5 h (±5 min) after MK-4621/JetPEI administration on C2D1, C3D1, and C5D1. Collect with plasma samples for MK-4621/JetPEI PK when feasible

Study Period	Treatment Period Cycle = 21 days									Notes
Visit Timing	Cycle 1			Cycles 2-6			Cycles ≥7			**For all cycles:** Up to 35 cycles of treatment with pembrolizumab and up to 6 cycles of treatment with MK-4621/JetPEI.
Visit Day (Days)	1	8	15	1	8	15	1	8	15	
	+3	±3	±3	±3	±3	±3	±3	±3	±3	
Blood for T Cell Repertoire (TCR)	X			X						Collect **blood** for TCR samples at -4 to 0 h **predose** of MK-4621/JetPEI on Day 1 of Cycle 1 (C1D1), Cycle 3 (C3D1), Cycle 4 (C4D1), and Cycle 6 (C6D1).
Blood for RNA Analyses	X			X						Collect **blood** for RNA samples -4 to 0 h **predose**, and 6 h (±15 min) **postdose** of MK-4621/JetPEI on Day 1 of Cycle 1 (C1D1), Cycle 2 (C2D1), and Cycle 3 (C3D1).
Serum for Cytokine/Chemokine Analyses and C-Reactive Protein (CRP)	X			X						Collect **blood** for serum cytokine/chemokine analyses and C-Reactive Protein (CRP) samples at -4 to 0 h **predose** of MK-4621/JetPEI on Day 1 of every cycle. Collect **blood** for serum cytokine/chemokine analyses and C-Reactive Protein (CRP) at 2 h (±15 min), 6 h (±15 min), and **24 h (±4 h) postdose** of MK-4621/JetPEI on Day 1 of Cycle 1 (C1D1), Cycle 2 (C2D1), and Cycle 3 (C3D1). Collect samples at the same time as for MK-4621/JetPEI PK when feasible.
Blood for Genetic Analyses	X									Collect prior to treatment.
On-treatment Tumor Biopsy	X			X			X			Two required biopsy samples will be collected on C1D1 and C4D1 from the same injected tumor. Biopsy collection procedure will be done at the same time as MK-4621/JetPEI injection at these 2 time points. All participants will have the option to provide 1 additional biopsy sample of the injected tumor on **C6D1 (Week 16)**. Biopsy collection procedure will be done at the same time as MK-4621/JetPEI injection.

aPTT=activated partial thromboplastin time; β-hCG= β-human chorionic gonadotropin; CT=computed tomography; ECOG=Eastern Cooperative Oncology Group; GGT=gamma glutamyl transferase; INR=International Normalized Ratio; IT=intratumoral; LDH=lactate dehydrogenase; MRI=magnetic resonance imaging; PET=positron emission tomography; PT=prothrombin time; WOCBP=women of childbearing potential.

1.3.3 Schedule of Activities for the End of Treatment and Post-Treatment Follow-Up Periods

Study Period	End of Treatment (EOT)/ Discontinuation	Post-Treatment Follow-Up			Notes
		Safety	Disease Status	Survival	
Visit Timing	Treatment Discontinuation	30 days after the last dose	Every 9 weeks	Approximately every 12 weeks	
Visit Window (Days)		+ 7	±7	±14	
Administrative / Clinical Procedures / Assessments					
Concomitant Medication	X	X			
Physical Examination	X	X			A directed physical examination may be done unless a full examination is deemed necessary.
Weight	X	X			
12-Lead ECG		X			
Vital Signs	X	X			Measurements include temperature, pulse, respiratory rate, blood pressure, and O_2 saturation.
ECOG Performance Status	X	X			Evaluation before study drug administration
Adverse Event Monitoring	X	X			After treatment discontinuation, participants will be monitored for AEs for 30 days and SAEs for 90 days (30 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.
Tumor Imaging, RECIST 1.1 and iRECIST Response Assessment	X		X		Posttreatment tumor imaging every 9 weeks starting from the first dose of study treatment until new anticancer treatment
Medical Photography (Cutaneous Lesions)	X				
New Anticancer Therapy Status		X	X		
Survival Status	←	→		X	Upon Sponsor request, participants may be contacted for survival status at any time during the course of the study. After confirmed disease progression, each participant will be contacted by telephone for survival until participant withdrawal of consent, becoming lost to follow-up, death, or the end of the study.
Laboratory Procedures/Assessments – LOCAL					
CBC with Differential	X	X			
Chemistry Panel	X	X			
Thyroid Function Testing (T4, FT4, T3, FT3, TSH)		X			
Lipase and Amylase	X	X			

Study Period	End of Treatment (EOT)/ Discontinuation	Post-Treatment Follow-Up			Notes
		Safety	Disease Status	Survival	
Visit Timing	Treatment Discontinuation	30 days after the last dose	Every 9 weeks	Approximately every 12 weeks	
Visit Window (Days)		+ 7	±7	±14	
Pregnancy test for WOCBP only (urine or serum β-hCG)		X			
Laboratory Procedures/Assessments					
Anti-Pembrolizumab Antibody	X				Only for pembrolizumab-treated participants.
Pharmacokinetics for Pembrolizumab PK (Arm 2, Arm 3)	X				

CT=computed tomography; ECOG=Eastern Cooperative Oncology Group; GGT=gamma glutamyl transferase; IT=intratumoral; LDH=lactate dehydrogenase; MRI=magnetic resonance imaging; PET=positron emission tomography; WOCBP=women of childbearing potential.

2 INTRODUCTION

In the past few years significant progress has been made in the field of immunotherapy. In particular antibodies targeting immune checkpoints have yielded impressive improvements in clinical outcomes for a range of tumor types. Despite this the majority of advanced cancer patients do not respond to immunotherapy, due to local immune tolerance at the tumor, absence of effector cells, or the development of resistance through a variety of adaptive mechanisms. MK-4621 (RGT-100) is a double-stranded 5'-triphosphate RNA that binds to Retinoic acid Inducible Gene I (RIG-I), a cytosolic receptor of the innate immune system, for intratumoral/intralesional injection. In preclinical experiments, MK-4621/JetPEI injection activates RIG-I, which induces a potent innate as well as adaptive immune response. The immune activation is accompanied by the induction of apoptosis in tumor cells. In nonmalignant cells, stimulation of RIG-I leads to a secretion of type I interferons, but not to apoptosis. Tumor antigens released during apoptosis can enhance antitumor immune response. In combination, these mechanisms lead to antitumor effects in injected tumor and untreated metastases (abscopal effect). Strong immune activation and release of neoantigens allows for a vaccination-like effect.

Treatment of relapsed/refractory malignancies represents a substantial challenge for clinical oncologists and there is a large area of unmet medical need for more effective therapy. As shown in preclinical studies, MK-4621/JetPEI has a potential to improve efficacy when used as a monotherapy or in combination with an anti-PD-1 inhibitor and other immunomodulatory agents.

2.1 Study Rationale

Limited efficacy of immune checkpoint inhibitors (ICI) has been recently elucidated in numerous clinical studies. Therefore, there is a great unmet need for agents that are able to enhance the effect of ICIs. Based on the results of preclinical experiments, multifaceted antitumor mechanisms of MK-4621/JetPEI can be exploited to overcome tumor resistance to ICI via direct stimulation of innate and adaptive immunity, in situ vaccination effects, and reprogramming tumor microenvironment. MK-4621/JetPEI is positioned to be the first--in-class RIG-I agonist in oncology.

MK-4621/JetPEI (originally RGT100-PEI, developed by Rigontec) represents a double-stranded triphosphate RNA that binds to and activates RIG-I, a cytosolic receptor molecule that results in the induction of a potent innate as well as adaptive antitumoral immune responses. Preclinical experiments have demonstrated broad antitumoral activity in multiple in vivo models.

The empirical rationale for combining MK-4621/JetPEI with PD-1 ICI is based on the data from experiments in anti-PD-1-resistant syngeneic mouse tumor models in which the combination of these agents enhanced antitumor responses compared with monotherapy treatment. It was also shown that MK-4621/JetPEI upregulated PD-1 expression and resulted in increased activity when combined with a PD-1 inhibitor. For further details please refer to the MK-4621 Investigator's Brochure (IB).

PD-1 blockade by pembrolizumab can exhibit a protective effect on a newly generated immune cell effectors in hostile tumor microenvironment and prevent inhibition of immune response. Therefore, a combination of the 2 treatment strategies can potentially enhance an antitumor response.

The rationale for an intrahepatic intratumoral arm of MK-4621/JetPEI is to expand the tumor location for IT therapy to deeper and visceral organs such as the liver.

This Phase 1/1b multicenter, open label, dose escalation and confirmation study will evaluate the safety, tolerability, and preliminary antitumor activity of intratumoral/intralesional injections of MK-4621/JetPEI in participants with advanced or recurrent tumors.

Results from this study will support further clinical development of MK-4621/JetPEI. The study will be performed in compliance with the protocol, International Council for Harmonisation (ICH), Good Clinical Practice (GCP), and local regulatory requirements. Aspects of the study concerned with manufacture and labelling of MK-4621/JetPEI will meet the requirements of Good Manufacturing Practice.

2.2 Background

Refer to the IBs for detailed background information on MK-4621/JetPEI and pembrolizumab.

MK-4621/JetPEI (originally RGT100-PEI, developed by Rigontec) is a double-stranded triphosphate RNA that binds to and activates RIG-I, a cytosolic receptor molecule that results in the induction of a potent innate as well as adaptive antitumoral immune responses. Preclinical experiments have demonstrated broad antitumoral activity in multiple in vivo models.

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

2.2.1 Pharmaceutical and Therapeutic Background

2.2.1.1 MK-4621/JetPEI Pharmaceutical and Therapeutic Background

Retinoic acid–inducible gene I is a cytosolic receptor molecule that was initially discovered as a sensor for viral RNAs.

Because RIG-I is a cytosolic receptor, various agents have been investigated to efficiently deliver MK-4621 into the cytosol. In vivo-jetPEI™ (Polyplus Transfection) has been identified as the most efficient delivery agent. A stable formulation procedure to generate stable and defined particles for storage has been developed as ready-to-use dispersion. In vivo-jetPEI™ has been tested in several clinical studies for the delivery of DNA in gene therapy studies. This linear polyethylenimine agent is regarded as an excipient and has a Drug Master File placed at the United States Food and Drug Administration (FDA) for the use in clinical studies.

2.2.1.2 Mechanism of Action

Although the expression of many receptors of the innate immune system is restricted to a certain subset of cells (eg, only in dendritic cells), RIG-I is ubiquitously expressed. This observation is in line with its pivotal role in antiviral defense against RNA viruses, a system that must be functional in virtually all somatic cells. RIG-I activation in tumor cell lines triggers cells death, whereas nonmalignant cells showed only marginal reduction in cell viability. Subsequent studies reveal that RIG-I stimulation initiates the mitochondrial apoptosis pathway, which is preferentially due to the induction of the pro-apoptotic BH3-only proteins Puma and Noxa in RIG-I–stimulated cells. The same pro-apoptotic signal was also observed in nonmalignant cells but these cells were comparatively less sensitive to apoptosis induction than melanoma cells, as the upregulation of endogenous Bcl-xL rescued primary cells from RIG-I–mediated pro-apoptotic signal. Because Bcl-xL is dysregulated in most tumor cells it can no longer serve as a rescue mechanism.

Apart from the direct immune-activating effect of RIG-I agonists in immune cells, RIG-I activation in tumor cells leads to formation of immune-activating exosomes. These exosomes contain the RIG-I agonist and express the natural killer (NK) cell receptor ligand BAG6 on the surface. Thereby they trigger a NK cell-mediated cytotoxicity as well.

Several studies revealed that breaking the local dominance of myeloid-derived suppressor cell within the tumor microenvironment was a key step to effective antitumor immunity. Interferon α (IFNα), one of the lead cytokines produced after RIG-I activation, can potently induce myeloid-derived suppressor cell differentiation. Thereby they exhibit a significantly reduced T-cell suppressive phenotype. The immunosuppressive tumor microenvironment is converted into a T-cell–promoting environment and this conversion facilitates the generation of a T-cell–dependent antitumor immune response.

Taken together, the RIG-I–dependent antitumor activity can be exploited as immunotherapy due to its multifaceted mechanism of action: direct activation if immune effector cells, induction of immunogenic cell death in tumor cells, release of immune-activating exosomes to promote tumor-specific natural killer cell cytotoxicity, reprogramming of tumor microenvironment to facilitate the antitumor immune response (see Figure 2). Local effects are most efficiently induced by high concentration of MK-4621/JetPEI in tumor that can be achieved by intratumoral administration.

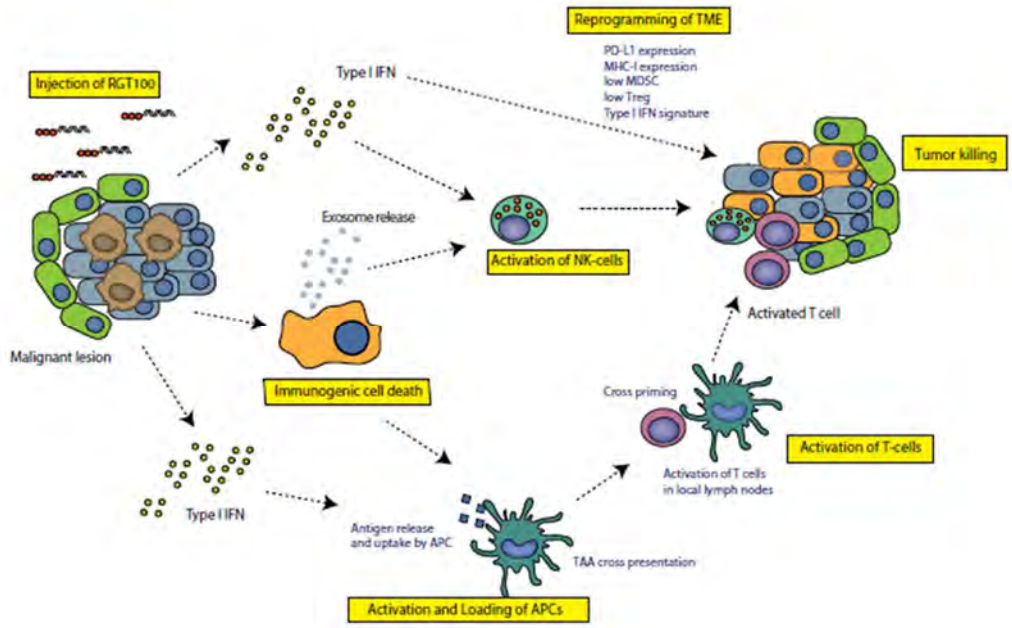


Figure 2 Schematic Representation of MK-4621/JetPEI Mechanism of Action

2.2.1.3 Preclinical Studies of MK-4621/JetPEI

Please refer to the MK-4621 IB for a description of preclinical evaluations.

2.2.1.4 Pembrolizumab Pharmaceutical and Therapeutic Background

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

The PD-1 receptor-ligand interaction is a major pathway hijacked by tumors to suppress immune control. The normal function of PD-1, expressed on the cell surface of activated T cells under healthy conditions, is to down-modulate unwanted or excessive immune responses, including autoimmune reactions. PD-1 (encoded by the gene Pdcd1) is an immunoglobulin (Ig) superfamily member related to cluster of differentiation 28 (CD28) and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) that has been shown to negatively

regulate antigen receptor signaling upon engagement of its ligands (PD-L1 and/or PD-L2) [Greenwald, R. J., et al 2005] [Okazaki, T., et al 2001].

The structure of murine PD-1 has been resolved [Zhang, X., et al 2004]. PD-1 and its family members are type I transmembrane glycoproteins containing an Ig-variable–type (IgV-type) domain responsible for ligand binding and a cytoplasmic tail responsible for the binding of signaling molecules. The cytoplasmic tail of PD-1 contains 2 tyrosine-based signaling motifs, an immunoreceptor tyrosine-based inhibition motif, and an immunoreceptor tyrosine-based switch motif. Following T-cell stimulation, PD-1 recruits the tyrosine phosphatases, SHP-1 and SHP-2, to the immunoreceptor tyrosine-based switch motif within its cytoplasmic tail, leading to the dephosphorylation of effector molecules such as CD3 zeta (CD3ζ), protein kinase C-theta (PKCθ), and zeta-chain-associated protein kinase (ZAP70), which are involved in the CD3 T-cell signaling cascade [Okazaki, T., et al 2001] [Chemnitz, J. M., et al 2004] [Sheppard, K-A, et al 2004] [Riley, J. L. 2009]. The mechanism by which PD-1 down-modulates T cell responses is similar to, but distinct from, that of CTLA-4, because both molecules regulate an overlapping set of signaling proteins [Parry, R. V., et al 2005] [Francisco, L. M., et al 2010]. As a consequence, the PD-1/PD-L1 pathway is an attractive target for therapeutic intervention in solid tumors. Please refer to the current pembrolizumab IB for a description of preclinical and clinical evaluations of pembrolizumab.

2.2.2 Ongoing Clinical Studies

2.2.2.1 MK-4621/JetPEI Clinical Studies

One first-in-human and first-in-class study is currently being performed with MK-4621/JetPEI (Study MK-4621-001). This is a Phase 1/1b, open-label, dose-escalation study in participants with advanced solid tumors. A conventional 3+3 design was used and the dose has been safely escalated up to 0.8 mg. Fifteen participants have been treated and no DLTs have occurred. Related AEs have been mainly fever reactions up to Grade 3.

2.2.2.2 Pembrolizumab Clinical Studies

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

2.3 Benefit/Risk Assessment

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

Potential risks associated with the administration of MK-4621/JetPEI based on nonclinical data may include the following:

- Local reactions at the injected tumor site (swelling, induration, and erythema)

- Altered liver function (increases in alanine transaminase [ALT], aspartate transaminase [AST], and lactate dehydrogenase [LDH], decreases in erythrocyte counts, hemoglobin levels, and hematocrit)

- Immune-related adverse events (irAEs) (including colitis, hepatitis, impaired thyroid function) or fever, chills, muscle aches, fatigue, headache, diarrhea, nausea and vomiting, and low blood pressure based on the fact that the mode of action of MK-4621/JetPEI is based upon activation of the immune system.

For intrahepatic administration of MK-4621/JetPEI in Arm 3, there is an increased risk associated with the procedure (eg, bleeding, liver damage).

Additional details regarding specific benefits and risks for participants participating in this clinical study may be found in the accompanying MK-4621 and pembrolizumab IBs and ICF documents.

3 HYPOTHESIS, OBJECTIVES, AND ENDPOINTS

Objectives	Endpoints
Primary	
• Objective: To evaluate the safety and tolerability and to establish a preliminary recommended Phase 2 dose (RP2D) of MK-4621/JetPEI administered as monotherapy and in combination with pembrolizumab	• Dose-limiting toxicity (DLT) • Adverse events (AEs) • Study intervention discontinuations due to AEs
Secondary	
• Objective: To evaluate the pharmacokinetics (PK) of MK-4621/JetPEI administered as monotherapy and in combination with pembrolizumab	• PK parameters of MK-4621/JetPEI, including area under the curve (AUC), minimum concentration (C_{min}), maximum concentration (C_{max})
• Objective: To evaluate the objective response rate (ORR) as assessed by the investigator based on Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST 1.1) and modified RECIST 1.1 for immune-based therapeutics (iRECIST) of MK-4621/JetPEI administered as monotherapy and in combination with pembrolizumab	• Objective response is a complete response (CR) or partial response (PR)

Tertiary/Exploratory	
• Objective: To evaluate progression-free survival (PFS) as assessed by the investigator based on RECIST 1.1 and iRECIST, and overall survival (OS) for participants administered MK-4621/JetPEI as monotherapy and in combination with pembrolizumab	• OS is the time from the first dose of study intervention to death due to any cause. • PFS is the time from first dose of study intervention to the first documented disease progression or death due to any cause, whichever occurs first.
• Objective: To evaluate the pharmacokinetics (PK) of pembrolizumab administered in combination with MK-4621/JetPEI	• PK parameters of pembrolizumab including minimum concentration (C_{min}) and maximum concentration (C_{max})
• Objective: To evaluate the development of circulating anti-pembrolizumab antibodies, as appropriate, following administration of MK-4621/JetPEI alone and in combination with pembrolizumab	• Antidrug antibody levels
• Objective: To identify molecular (genomic, metabolic and/or proteomic) biomarkers that may be indicative of clinical response/resistance, safety, pharmacodynamic activity, and/or the mechanism of action of MK-4621/JetPEI as monotherapy and in combination with pembrolizumab	• Germline genetic variation, genetic (DNA) mutations from tumor, tumor and blood RNA variation, proteomics and IHC, and other biomarkers.

4 STUDY DESIGN

4.1 Overall Design

This is a Phase 1/1b, dose-escalation, nonrandomized, multicenter, open-label study of MK-4621/JetPEI as monotherapy and in combination with pembrolizumab in participants with advanced/metastatic solid tumors.

For Arm 1 (MK-4621/JetPEI monotherapy dose confirmation and cohort expansion) and Arm 2 (MK-4621/JetPEI + pembrolizumab, dose escalation, dose confirmation, and cohort expansion), the study will enroll participants with cutaneous, subcutaneous, and/or nodal lesions that are amenable to IT injection by visual inspection or ultrasound guidance. Participants need to have 1 measurable lesion that is amenable to IT injection and biopsy, 1 measurable discrete and/or distant lesion (bystander lesion) that is amenable to biopsy to

evaluate any abscopal effect, as well as 1 measurable noninjected, nonbiopsied lesion for RECIST assessment. Arm 2 will be opened for enrollment prior to Arm 1.

For Arm 3 (intrahepatic administration of MK-4621/JetPEI, dose escalation, dose confirmation, and cohort expansion), the study will enroll participants with liver metastases/lesions that are amenable to injection via ultrasound or cross-sectional imaging (CT/MRI) guidance. Participants need to have 1 measurable lesion that is amenable to IT injection and biopsy and 1 measurable noninjected, nonbiopsied discrete and/or distant lesion for RECIST assessment. Enrollment into Arm 3 will only start once the dose escalation of Arm 2 has reached the highest dose level (0.8 mg) and this has been cleared for DLT.

Each treatment cycle is 21 days. In Arm 1 (dose confirmation), MK-4621/JetPEI dosing is q1w for each 21-day cycle. In Arm 2, MK-4621/JetPEI dosing is q1w for each 21-day cycle. In Arm 3, MK-4621/JetPEI will be injected q3w in combination with pembrolizumab. Pembrolizumab in Arm 2 and Arm 3 (post run-in phase) will be administered at a fixed dose 200 mg q3w. See Section 8.1.11 for a detailed description of mandatory and discretionary observation periods. For each dose level (DL), the first participant will start treatment at least 7 days before the next participant of the dose level is treated. Further participants should start treatment at least 3 days apart. This allows initial assessment of safety by the treating investigator and to detect potential major safety risks with a certain dose level prior to exposing more participants to this dose.

In Arm 1, the dose of 0.8 mg will be used to start the mTPI part to confirm this highest dose tested in the dose escalation study (MK-4621-001). In the event of any DLT, it may be decided to down-escalate 1 dose level (to 0.6 mg). The DLT period will last 1 cycle (3 weeks). Dose escalation of MK-4621/JetPEI in Arm 2 will start with 0.4 mg, the second dose level cleared for DLT in the MK-4621-001, and will proceed to the dose level of 0.6 mg and then to the highest dose of 0.8 mg based on emerging safety and tolerability data. The DLT evaluation period will be 21 days (1 cycle). Treatment allocation between Arms 1 and 2 is described in Section 6.3.1. In Arm 3, the initial dose will be 0.2 mg and dose escalation will go up to 0.4, 0.6, and 0.8 mg. The DLT evaluation period will be 42 days (2 cycles: 1 cycle in monotherapy and 1 cycle in combination therapy) (see Section 6.6.2 for more details).

The decision on further dose escalation in Arms 2 and 3 may be made based on the entirety of the data from the study. Each participant will be monitored for DLTs over the DLT evaluation period. For each dose level, an assessment will be made of the safety and tolerability data in order to define the next dose level to be tested. Once a preliminary maximum tolerated dose/maximum administered dose (MTD/MAD) has been determined in the mTPI phase, expansion cohorts may be implemented to expand to a total of 40 participants to obtain additional PK/pharmacodynamic data, confirm RP2D, and explore antitumor activity in particular tumor types. Tumor indications will be specified based on safety and efficacy data as well as feasibility derived from the dose escalation/confirmation phase. Several factors will be considered to define particular tumor types for cohort expansion. Based on the data accumulated to date (internally as well as in the peer-reviewed

literature), gene expression profile (GEP), and mutational load (ML) can provide a rationale for pembrolizumab combination. Both biomarkers have been shown to be strong independent predictors of response to PD-1 inhibitors. Tumor types of particular interest are those in which pembrolizumab demonstrated only modest clinical success. Tumors known for the high rate of response to PD-1/PD-L1 blockade (eg, melanoma) can serve as a reference for MK-4621/JetPEI efficacy when it is used in a monotherapy regimen.

The safety data from individual participants will be closely followed by the principal/sub-investigator and the Sponsor on an ongoing basis and shared at regular safety teleconferences (typically biweekly). The safety and tolerability of all participants, including those undergoing DLT evaluation, as well as those who have completed DLT evaluation, will be reviewed prior to the start of the next dose level at dose escalation/dose confirmation decision meetings. The Sponsor and principal/sub-investigators will jointly assess the appropriateness of predetermined protocol dose escalation/dose confirmation rules (refer to Section 4.3) based on safety and tolerability data at the completion of each dose level, and prior to the opening of enrollment for the next dose level. The joint committee of Sponsor and principal/sub-investigators will render the formal decision regarding subsequent dose level to be tested in the participants, and a memorandum will be sent to each site to communicate the specified next dose level. Participants will be enrolled and allocated via Interactive Response Technology (IRT) according to the dose escalation and confirmation mTPI guidelines outlined in Section 4.3. The dose at each cohort will be specified via IRT. Cohorts will be opened or closed through IRT to ensure correct dosing in each cohort.

Duration of the treatment with MK-4621/JetPEI is limited to 6 cycles. Participants may continue on treatment with pembrolizumab for up to 35 cycles (approximately 2 years) from the start of treatment. Treatment with either of the agents may continue until discontinuation criteria are fulfilled (see Section 7). Treatment allocation will be accomplished by nonrandom assignment through an interactive response technology (IRT).

Participants who progress by either clinical or radiographic evaluation on monotherapy with MK-4621/JetPEI (Arm 1) may cross over into the combination therapy arm (Arm 2), provided that they meet crossover eligibility criteria in Section 1.3.1. Participants who cross over from Arm 1 to Arm 2 will enter Arm 2 at Screening and will be allocated to a combination dose level cohort in Arm 2 through an IRT. Participants who cross over from Arm 1 to Arm 2 are eligible for up to 35 cycles of treatment with pembrolizumab therapy and up to a cumulative total of 6 cycles of treatment with MK-4621/JetPEI, inclusive of cycles received in Arm 1 and Arm 2. Participants who crossover to Arm 2 will receive combination therapy at the highest dose of MK-4621/JetPEI with pembrolizumab that has been cleared for DLT in Arm 2 at the time of crossover.

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

Adverse events will be evaluated according to criteria outlined in the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0.

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

4.2 Scientific Rationale for Study Design

MK-4621/JetPEI is being developed for the treatment of solid tumors. This is the first-in-class RIG-I agonist being evaluated in clinical study designed to assess the safety, tolerability, PK, and PD of escalating doses of MK-4621/JetPEI when used as monotherapy and in combination with pembrolizumab in participants with advanced/refractory solid tumors.

The study exposes a small number of participants to each dose of MK-4621/JetPEI alone or in combination with pembrolizumab and enrolls different participants for each cohort. A low starting dose is used to evaluate safety with minimal risk to participants.

All safety and tolerability data will be evaluated, before escalating to the next dose in a new cohort.

The mTPI design is considered a safe design for a dose-escalation study in this population.

Frequent assessments of safety will be conducted to support the primary objective for conducting the study.

Tumor response will also be assessed to support the secondary and exploratory objectives of the study.

4.2.1 Rationale for Endpoints

4.2.1.1 Efficacy Endpoints

Efficacy endpoints in this study include ORR (secondary endpoint), PFS and OS (exploratory endpoints).

ORR is a commonly used endpoint in oncology studies to estimate preliminary efficacy and used for futility assessments. PFS and OS are also standard endpoints in oncology to further evaluate efficacy of tested interventions.

Tumor response will be assessed by investigators using RECIST 1.1 and iRECIST.

4.2.1.1.1 Response Rate Assessed by RECIST 1.1

RECIST 1.1 will be used to determine the treatment response. 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.

4.2.1.1.2 Response Rate Assessed by Modified Response Evaluation Criteria in Solid Tumors 1.1 for Immune-based Therapeutics (iRECIST)

RECIST 1.1 will be adapted to account for the unique tumor response characteristics seen following treatment with MK-4621/JetPEI ± pembrolizumab (Section 8.2.5). Immunotherapeutic agents such as MK-4621/JetPEI ± pembrolizumab may produce antitumor effects by potentiating endogenous cancer-specific immune responses. The response patterns seen with such an approach may extend beyond the typical time course of responses seen with cytotoxic agents, and patients treated with pembrolizumab may manifest a clinical response after an initial increase in tumor burden or even the appearance of new lesions. Thus, standard RECIST 1.1 may not provide an accurate response assessment of immunotherapeutic agents such as pembrolizumab. Based on an analysis of participants with melanoma enrolled in KEYNOTE-001 (KN001), 7% of evaluable participants experienced delayed or early tumor pseudo-progression. Of note, participants who had progressive disease (PD) by RECIST 1.1 but not by the immune-related response criteria [Wolchok, J. D., et al 2009] had longer overall survival than participants with PD by both criteria [Hodi, F. S., et al 2014]. Additionally, the data suggest that RECIST 1.1 may underestimate the benefit of pembrolizumab in approximately 15% of participants. These findings support the need to apply a modification to RECIST 1.1 that takes into account the unique patterns of atypical responses in immunotherapy and enables treatment beyond initial radiographic progression, if the participant is clinically stable.

Modified RECIST 1.1 for immune-based therapeutics (iRECIST) assessment has been developed and published by the RECIST Working Group, with input from leading experts from industry and academia, along with participation from the US Food and Drug Administration and the European Medicines Agency [Seymour, L., et al 2017]. The unidimensional measurement of target lesions, qualitative assessment of nontarget lesions, and response categories are identical to RECIST 1.1, until progression is seen by RECIST 1.1. However, if a participant is clinically stable, additional imaging may be performed to confirm radiographic progression. iRECIST will be used by investigators to assess tumor response and progression and make treatment decisions as well as for secondary efficacy analyses where specified.

For further information on iRECIST, see Section 8.2.5.

4.2.1.2 Safety Endpoints

The primary objective of this study is to characterize the safety and tolerability of MK-4621/JetPEI 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 4.0 criteria. Safety will be assessed by quantifying the toxicities and grades of toxicities experienced by participants who have received MK-4621/JetPEI as monotherapy and in combination with pembrolizumab.

For adverse events, 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 pharmacokinetic (PK) profile of MK-4621/JetPEI following administration as a single agent and in combination with pembrolizumab. An exploratory objective is to characterize the pharmacokinetic profile of pembrolizumab following administration as combination therapy. The plasma 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, safety, and exploratory endpoint data to help assess future dosing strategies for MK-4621/JetPEI as monotherapy or in combination with pembrolizumab.

4.2.1.4 Target Engagement and Pharmacodynamic Endpoints

Given the nature of RIG-I as an intracellular receptor and its ubiquitous expression in many cell types, there is no direct target engagement biomarker. Downstream exploratory pharmacodynamic biomarkers in tumor tissue and blood will be assessed for pathway activation.

4.2.1.5 Planned Exploratory Biomarker Research

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

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

This research may evaluate whether genetic variation within a clinical study population correlates with response to the treatment(s) under evaluation. If genetic variation is found to predict efficacy or AEs, the data might inform optimal use of therapies in the patient population. Furthermore, it is important to evaluate germline DNA variation across the genome in order to interpret tumor-specific DNA mutations. Finally, microsatellite instability

(MSI) may be evaluated as this is an important biomarker for some cancers (ie, colorectal cancer).

Genetic (DNA) analyses from tumor

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

Tumor and blood RNA analyses

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

Proteomics and immunohistochemistry (IHC) using blood or tumor

Tumor and blood samples from this study may undergo proteomic analyses (eg, PD-L1 IHC). PD-L1 protein level in tumor sections, assessed by IHC, has been shown to correlate with response to pembrolizumab in patients with NSCLC, and an in vitro diagnostic (IVD) device has been developed for use with pembrolizumab in NSCLC. Preliminary data indicates that this association may also be true in additional cancer types (ie, triple negative breast cancer, head and neck, and gastric). Additional tumor or blood-derived proteins may also correlate with response to pembrolizumab. Therefore, tumor tissue may be subjected to proteomic analyses using a variety of platforms that could include but are not limited to immunoassays and liquid chromatography/mass spectrometry. This approach could identify novel protein biomarkers that could aid in patient selection for pembrolizumab (MK-3475) therapy.

Other blood-derived biomarkers

In addition to expression on the tumor tissue, PD-L1 and other tumor derived proteins can be shed from tumor and released into the blood. Assays such as enzyme-linked immunoassay

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

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

4.2.1.6 Future Biomedical Research

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

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

4.3 Justification for Dose

4.3.1 Starting Dose for This Study

4.3.1.1 Rationale for Starting and Maximum Dose of MK-4621

Based on the pharmacodynamic data and the dose/tumor size correlation observed (refer to MK-4621 IB, Section 4.2.1.4), 0.2 mg MK-4621/JetPEI can be considered a pharmacologically active dose for intratumoral injection when extrapolated from tumors in mice to a human lesion with a diameter of 20 mm.

Accordingly, a starting dose (DL1) of 1 mL (0.2 mg) of MK-4621/JetPEI was considered for the first-in-human clinical study of intratumoral/intralesional injection (MK-4621-001) into cutaneous or hepatic lesions. Local administration is limited by maximum injection volumes feasible in target tumor tissue. The concentration of the MK-4621 particles in the injection dispersion is fixed to 0.2 mg/mL to achieve stable complexes. Therefore, the maximum dose of MK-4621/JetPEI per tumor is planned to be a maximum injectate of 4 mL (0.8 mg). This reflects also experience with other compounds that are applied intratumorally.

Results from the 4-week toxicity studies in mice and cynomolgus monkeys suggest the following no-observed-adverse-effect levels (NOAELs) and human equivalent doses (HEDs) after IV administration of MK-4621/JetPEI:

- NOAEL/MTD in mice=1.6 mg/kg IV → HED=0.13 mg/kg
- NOAEL in cynomolgus monkeys=0.16 mg/kg → HED=0.05 mg/kg
- MTD in cynomolgus monkeys=1.5 mg/kg → HED=0.5 mg/kg

Leakage of MK-4621/JetPEI from the lesion after intratumoral injection is expected to be marginal because, after intratumoral injection in mice, 100% of the compound remained local (refer to MK-4621 IB, Section 4.2.1.4). However, for the calculation of safety margins, complete leakage (eg, accidental administration into a blood vessel) was used as a worst case assumption. A theoretical complete leakage from a cutaneous lesion was mimicked in the subcutaneous toxicity studies. Local toxicity after direct injection into the liver was not examined, but results from a preliminary biodistribution study showed that most MK-4621/JetPEI is found in the liver after IV injection. Therefore, the IV toxicity data can be used to extrapolate the safety of leakage into healthy liver tissue.

Thus, assuming a theoretical complete systemic ad hoc exposure after intratumoral administration, a starting dose of 1 mL (0.2 mg MK-4621/JetPEI) in a 60-kg human (0.0033 mg/kg) would lead to the following safety factors (calculated with unrounded raw data):

- Safety factor for mouse NOAEL/MTD: 0.13/0.0033=40
- Safety factor for cynomolgus monkey NOAEL: 0.05/0.0033=15
- Safety factor for cynomolgus monkey MTD: 0.5/0.0033=150

Of note, the safety factor of 40 for the mouse has been calculated based on the NOAEL/MTD of 1.6 mg/kg (HED=0.13 mg/kg) observed in the pivotal 4-week toxicity study. Nevertheless, in single-dose IV studies in mice (LPT studies 32867 and 33090) at a dose of 2 mg/kg (HED=0.16 mg/kg) or 3 mg/kg MK-4621/JetPEI, acute clinical signs and mortality were observed within 2 hours after administration of MK-4621/JetPEI. Therefore, the safety factor for the minimum lethal dose is 48. Because this safety factor is based on the worst case assumption of complete leakage, it is considered acceptable for the intended patient population with advanced cancer.

4.3.1.2 Rationale for Fixed Dose of Pembrolizumab

The planned dose of pembrolizumab for this study is 200 mg every 3 weeks (q3w). Based on the totality of data generated in the Keytruda development program, 200 mg q3w is the appropriate dose of pembrolizumab for adults across all indications and regardless of tumor type. As outlined below, this dose is justified by:

- Clinical data from 8 randomized studies demonstrating flat dose- and exposure-efficacy relationships from 2 mg/kg q3w to 10 mg/kg every 2 weeks (q2w),
- Clinical data showing meaningful improvement in benefit-risk including overall survival at 200 mg q3w across multiple indications, and
- Pharmacology data showing full target saturation in both systemic circulation (inferred from PK data) and tumor (inferred from physiologically-based PK [PBPK] analysis) at 200 mg q3w.

Among the 8 randomized dose-comparison studies, a total of 2262 participants were enrolled with melanoma and non-small cell lung cancer (NSCLC), covering different disease settings (treatment naïve, previously treated, PD-L1 enriched, and all-comers) and different treatment settings (monotherapy and in combination with chemotherapy). Five studies compared 2 mg/kg q3w versus 10 mg/kg q3w (KN001 Cohort B2, KN001 Cohort D, KN002, KN010, and KN021), and 3 studies compared 10 mg/kg q3w versus 10 mg/kg q2w (KN001 Cohort B3, KN001 Cohort F2 and KN006). All of these studies demonstrated flat dose- and exposure-response relationships across the doses studied representing an approximate 5- to 7.5-fold difference in exposure. The 2 mg/kg (or 200 mg fixed-dose) q3w provided similar responses to the highest doses studied. Subsequently, flat dose-exposure-response relationships were also observed in other tumor types including head and neck cancer, bladder cancer, gastric cancer, and classical Hodgkin Lymphoma, confirming 200 mg q3w as the appropriate dose independent of the tumor type. These findings are consistent with the mechanism of action of pembrolizumab, which acts by interaction with immune cells, and not via direct binding to cancer cells.

Additionally, pharmacology data clearly show target saturation at 200 mg q3w. First, PK data in KN001 evaluating target-mediated drug disposition (TMDD) conclusively demonstrated saturation of PD-1 in systemic circulation at doses much lower than 200 mg q3w. Second, a PBPK analysis was conducted to predict tumor PD-1 saturation over a wide range of tumor penetration and PD-1 expression. This evaluation concluded that pembrolizumab at 200 mg q3w achieves full PD-1 saturation in both blood and tumor.

Finally, population PK analysis of pembrolizumab, which characterized the influence of body weight and other participant covariates on exposure, has shown that the fixed-dosing provides similar control of PK variability as weight based dosing, with considerable overlap in the distribution of exposures from the 200 mg q3w fixed dose and 2 mg/kg q3w dose. Supported by these PK characteristics, and given that fixed-dose has advantages of reduced dosing complexity and reduced potential of dosing errors, the 200 mg q3w fixed-dose was selected for evaluation across all pembrolizumab protocols.

4.3.1.3 Rationale for Dose Interval and Escalation Increments

The human starting dose and dosing interval of MK-4621/JetPEI are based on an integration of nonclinical toxicological, pharmacological, and efficacy data. Dose finding will proceed with a model-based mTPI approach with 3-14 participants treated per dose level using dose

increment increases of 30% to 100% of the prior dose. Planned dose levels (DL) are DL1=0.2 mg (1 mL), DL2=0.4 mg (2 mL), DL3=0.6 mg (3 mL), and DL4=0.8 mg (4 mL). Arm 1 will start at DL4 (0.8 mg), as DLs 1-3 have already been found to be tolerable in Study MK-4621-001, as reflected in Section 4.1 - Study Design. After careful evaluation of all safety data it may be decided to further escalate to a higher dose as well as to use an intermediate dose level.

4.3.1.4 Dose Finding Using a Modified Toxicity Probability Interval Design

Dose finding will follow the mTPI design [Ji Y, Li Y, Bekele BN 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 DLTs observed at the current dose level.

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

When adding participants to a dose level in response to a “stay” decision, the number of additional participants to be enrolled is capped to minimize the exposure to a dose that may be unacceptably toxic (denoted as DU in Table 1). Secondly, to determine how many more participants can be enrolled at the dose level, one can count steps in diagonal direction (down and to the right) from the current cell to the first cell marked DU. For example, if 1 of 3 participants have experienced a DLT at a given dose level, no more than an additional 3 participants should be enrolled at this dose level until additional DLT data are available. This is because this dose level would be considered unacceptably toxic if all 3 of the additional participants experience a DLT (ie, 4/6 participants with DLT in Table 1). 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. 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. However, the totality of the data will be considered before deciding on the dose(s) to carry forward to the dose-expansion phase of the study, and the escalation schedule may be adjusted based on PD, PK, and safety data emerging throughout the study. The preliminary RP2D of MK-4621/JetPEI in the combination arm (Arm 2) will not exceed, but may be equal to, the preliminary RP2D in the MK-4621/JetPEI monotherapy arm (Arm 1).

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

Table 1 Dose-finding Rules per mTPI Design

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

E = Escalate to the next higher dose; S = Stay at the current dose; D = De-escalate to the next lower dose; DU = The current dose is unacceptably toxic.
Target toxicity rate = 30%.
Flat noninformative prior Beta (1,1) is used as a prior and ε1=ε2=0.03[Ji Y, Li Y, Bekele BN 2007], [Ji, Y. 2013], [Ji, Y., et al 2010]

4.4 Beginning and End of Study Definition

The overall study begins when the first participant signs the ICF. The overall study ends when the last participant completes the last study-related telephone-call or visit, withdraws from the study, or is lost to follow-up (ie, the participant is unable to be contacted by the investigator).

Once participants have achieved the study objectives, they will be discontinued from this study and may be enrolled into an extension study to continue protocol-defined assessments and treatment with pembrolizumab monotherapy, as appropriate.

4.4.1 Clinical Criteria for Early Study Termination

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

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

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

3. Poor adherence to protocol and regulatory requirements

4. Quality or quantity of data recording is inaccurate or incomplete

Ample notification will be provided in the event of Sponsor decision to no longer supply MK-4621/JetPEI or pembrolizumab.

5 STUDY POPULATION

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

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

5.1 Inclusion Criteria

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

1. Have a 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. For Arms 1 and 2: have 3 lesions as defined below:

    - at least 1 cutaneous or subcutaneous lesion that is amenable to injection and biopsy (lesion 1). This injectable lesion must be measurable as defined by the

response criteria (RECIST 1.1): ≥ 1 cm in longest diameter for nonnodal lesion, or ≥ 1.5 cm in short axis for a nodal lesion. The longest diameter for an injectable lesion must be ≤ 10 cm. In case of multiple coalescing, superficial lesions the longest diameter in aggregate should be ≥ 1 cm and ≤ 10 cm.

- at least 1 discrete noninjected, nonbiopsied lesion that is measurable as defined by the response criteria (RECIST 1.1): ≥1 cm in longest diameter for non-nodal lesions, or ≥1.5 cm in the short axis for nodal lesions (lesion 2).
- at least 1 discrete and/or distant noninjected lesion amenable for biopsy (lesion 3).

3. For Arm 3 only: Have metastatic liver and/or liver lesion involvement that does not exceed one third of the total liver volume in participants to be treated by liver IT injection. Hepatocellular carcinoma participants are excluded from eligibility of intratumoral liver injection. For Arm 3, at least 2 lesions have to be identified as described below:

    - at least 1 liver lesion amenable to image-guided intratumoral injection and biopsy via ultrasound guidance or cross-sectional imaging (CT/MRI) guidance and must be measurable as defined by the response criteria (RECIST 1.1) ≥ 1 cm in longest diameter. The longest diameter for an injectable lesion must be ≥ 1 cm and ≤ 10 cm (lesion 1).
    - at least 1 other discrete noninjected, nonbiopsied lesion that is measurable as defined by the response criteria (RECIST 1.1): ≥1 cm in longest diameter (lesion 2).

4. Submit an evaluable baseline tumor sample for analysis before start of treatment from: the lesion to be injected (lesion 1 in Arm 1, 2, and 3); and from a discrete noninjected lesion (lesion 3 in Arms 1 and 2) for assessing potential abscopal effects. Details pertaining to tumor tissue submission can be found in the Procedures Manual.

5. Have a performance status of 0 or 1 on the Eastern Cooperative Oncology Group (ECOG) Performance Scale.

6. Demonstrate adequate organ function as defined in Table 2. Specimens must be collected within 72 hours prior to the start of study treatment.

Table 2 Adequate Organ Function Laboratory Values

System	Laboratory Value
Hematological	
Absolute neutrophil count	≥1,500/mcL
Platelets	≥100,000/mcL
Hemoglobin	≥9 g/dL or ≥5.6 mmol/L[a]
Renal	
Serum creatinine or creatinine clearance (CrCl) (measured or calculated)[b] or Glomerular Filtration Rate (GFR) in place of CrCl	≤1.5 X ULN or ≥30 mL/min for participant with creatinine levels >1.5 X ULN
Hepatic	
Total bilirubin (serum)	≤1.5 × ULN or Direct bilirubin ≤ULN for participants with total bilirubin levels >1.5 × ULN
AST (SGOT) and ALT (SGPT)	≤2.5 × ULN or ≤3 × ULN for participants with liver metastases
Coagulation	
International Normalized Ratio (INR) or Prothrombin Time (PT) Activated Partial Thromboplastin Time (aPTT)	<1.5 × ULN (unless participant is receiving anticoagulant therapy, in which case PT/INR or aPTT should be within the therapeutic range of intended use of anticoagulants)

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

Demographics

Male Participants

7. A male participant must agree to use a form of contraception as detailed in Appendix 5 of this protocol during the treatment period and for at least 120 days after the last dose of study intervention and refrain from donating sperm during this period.

Female Participants

8. A female participant is eligible to participate if she is not pregnant (Appendix 5), not breastfeeding, and at least 1 of the following conditions applies:

   a) Not a woman of childbearing potential (WOCBP) as defined in Appendix 5.

      OR

   b) A WOCBP who agrees to follow the contraceptive guidance in Appendix 5 during the treatment period and for at least 120 days after the last dose of study intervention.

Informed Consent

9. The participant (or legally acceptable representative if applicable) provides written informed consent for the study. The participant may also provide consent for Future Biomedical research (FBR). However, the participant may consent to the main study without participating in FBR.

5.2 Exclusion Criteria

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

Medical Conditions

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

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

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

3. Has hepatocellular carcinoma (for Arm 3 only).

4. Has clinically active central nervous system (CNS) metastases and/or carcinomatous meningitis. Participants with previously treated brain or meningeal metastases may participate and be eligible for treatment provided they are stable and asymptomatic

(without evidence of progression by MRI scan of the brain separated by at least 4 weeks after treatment), have no evidence of new or enlarging brain metastases, are evaluated within 4 weeks prior to first study treatment administration, and are off immunosuppressive doses of systemic steroids at least 2 weeks prior to enrollment.

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

6. Has an active infection requiring therapy.

7. Has a history of interstitial lung disease.

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

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

10. Participants with known human immunodeficiency virus (HIV) and/or Hepatitis B or C infections, or known to be positive for Hepatitis B surface antigen (HBsAg)/Hepatitis B virus (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.

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

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

13. Is pregnant or breastfeeding, or expecting to conceive or father children within the projected duration of the study, starting with the screening visit through 120 days after the last dose of study treatment.

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

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

Prior/Concomitant Therapy

16. Has received a live-virus vaccine within 30 days of planned treatment start. Seasonal flu vaccines that do not contain live virus are permitted.

Prior/Concurrent Clinical Study Experience

17. Is currently participating and receiving study therapy in a study of an investigational agent or has participated and received study therapy in a study of an investigational agent or has used an investigational device within 28 days of administration of MK-4621/JetPEI.

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

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

Diagnostic Assessments

Other Exclusions

18. Has a history of re-irradiation for squamous cell carcinoma of head and neck (SCCHN) at the projected injection site.

19. Has a tumor(s) in direct contact or encases a major blood vessel and has ulceration and/or fungation onto the skin surface at the projected injection site.

20. Has undergone prior allogeneic hematopoietic stem cell transplantation within the last 5 years.

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

5.3 Lifestyle Considerations

5.3.1 Meals and Dietary Restrictions

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

5.3.2 Caffeine, Alcohol, and Tobacco Restrictions

There are no restrictions on consumption of caffeine or tobacco. Reasonable alcohol consumption is allowed but patients with alcohol abuse should not be enrolled into the study.

5.3.3 Activity

There are no restrictions on activity.

5.3.4 Contraception

Pembrolizumab or MK-4621/Jet/PEI may have adverse effects on a fetus in utero. Refer to Appendix 5 for approved methods of contraception.

Participants should be informed that taking the study medication may involve unknown risks to the fetus (unborn baby) if pregnancy were to occur during the study. In order to participate in the study, participants of childbearing potential must adhere to the contraception requirement (Appendix 5) from the day of study medication initiation (or 14 days prior to the initiation of study medication for oral contraception) throughout the study period up to 120 days after the last dose of study medication. If there is any question that a participant of childbearing potential will not reliably comply with the requirements for contraception, that participant should not be entered into the study.

5.3.5 Pregnancy

If a participant inadvertently becomes pregnant while on treatment with pembrolizumab or MK-4621/JetPEI, the participant will be immediately discontinued from study intervention. The site will contact the participant at least monthly and document the participant's status until the pregnancy has been completed or terminated. The outcome of the pregnancy will be reported to the Sponsor without delay and within 24 hours if the outcome is a serious adverse event (SAE) (eg, death, abortion, congenital anomaly, or other disabling or life-threatening complication to the mother or newborn). The study investigator will make every effort to obtain permission to follow the outcome of the pregnancy and report the condition of the fetus or newborn to the Sponsor. If a male participant impregnates his female partner, the study personnel at the site must be informed immediately and the pregnancy must be reported to the Sponsor and followed as described in Section 8.4.5.

5.3.6 Use in Nursing Women

It is unknown whether pembrolizumab or MK-4621/JetPEI is excreted in human milk. Because many drugs are excreted in human milk, and because of the potential for serious adverse reactions in the nursing infant, participants who are breastfeeding are not eligible for enrollment.

5.4 Screen Failures

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

5.5 Participant Replacement Strategy

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

- They are allocated but not treated
- They discontinue from the study prior to completing all the safety evaluations for reasons other than treatment-related adverse events
- They receive less than 75% of the total MK-4621/JetPEI injection or pembrolizumab infusion in Cycle 1 (Cycles 1 and 2 for Arm 3) (eg, if the infusion had to be discontinued due to an infusion reaction) and did not experience a DLT.

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

If a participant experiences a DLT during DLT evaluation period, study treatment may be discontinued following discussion between the sponsor and investigator. However, if the participant is deriving clinical benefit from the study treatment, 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 will be packaged to support enrollment. Clinical supplies will be affixed with a clinical label in accordance with regulatory requirements.

6.1 Study Intervention(s) Administered

The study treatments to be used in this study are outlined in Table 5.

The formulation for MK-4621/JetPEI is the same as that used in the first-in-human study MK-4621-001.

All products indicated in Table 5 will be provided centrally by the Sponsor or locally by the study site, subsidiary or designee, depending on local country operational or regulatory requirements.

For any commercially available product that is provided by the study site, subsidiary, or designee, every attempt will be made to source these supplies from a single lot/batch number. The study site is responsible for recording the lot number, manufacturer, and expiry date for any locally purchased product as per local guidelines unless otherwise instructed by the Sponsor.

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

6.1.1 Intratumoral Injection

In Arms 1 and 2, MK-4621/JetPEI will be administered by intratumoral injection into cutaneous, subcutaneous, and/or nodal lesions that are visible, palpable, or detectable by ultrasound guidance. In Arm 3, MK-4621/JetPEI will be administered by injection into liver metastasis/lesions by ultrasound or cross-sectional imaging guidance (CT/MRI). This injectable lesion must be a measurable target lesion as defined by the response criteria (RECIST 1.1):, ≥ 1 cm in longest diameter for non-nodal lesion, or ≥ 1.5 cm in short axis for a nodal lesion.

The injectable target lesion at the initiation of the treatment must be sufficiently sized to allow for injection of a total volume of the respective dose level as per the judgment of the treating physician in accordance with the minimum lesion diameters provided in Table 3.

Table 3 Determination of Minimum Target Lesion Diameter at Treatment Initiation by Dose Level

Dose Level		**Maximum Injection Volume per Treatment Visit**	**Minimum Target Lesion Diameter at Treatment Initiation**
1	0.2 mg	1 mL	≥1 cm
2	0.4 mg	2 mL	≥2 cm
3	0.6 mg	3 mL	≥3 cm
4	0.8 mg	4 mL	≥4 cm

Maximum MK-4621/JetPEI injection volume should be administered to a single sufficiently sized target lesion at treatment initiation. Injected tumor area should consist of vital tumor tissue (avoid injection into areas with significant necrosis). Injected, single, sufficiently-sized target lesion at treatment initiation should be the same lesion that underwent pretreatment biopsy. If dose cannot be fully injected into the single biopsied target lesion planned for treatment initiation according to treating physician's assessment, discuss with Sponsor before treatment initiation.

If at a certain point after treatment initiation a dose cannot be fully injected into the single target lesion identified at the start of treatment (eg, due to tissue induration, tumor shrinkage or similar), it is permissible to split the dose and inject the remaining amount of MK-4621/JetPEI into another accessible target lesion(s). The volume of injectate delivered to each target lesion will be based on the longest dimension of the target lesion, as shown in Table 4, and on the number of target lesions injected. If there are multiple target lesions of similar size, then up to a maximum of 4 target lesions may be injected per treatment visit, with a minimum injectate volume of 1 mL per lesion, and a total injectate volume less than or equal to the maximum volume set for the dose level. Documentation of dose volume administered per target lesion will be obtained.

Table 4 Determination of MK-4621/JetPEI Injection Volume for Injections Administered in More Than one Target Lesion Upon Change in Lesion Diameter After Initial Treatment

Target Lesion Size (longest dimension)	Injection Volume
≥4 cm	4 mL
≥ 3 cm to < 4 cm	3 mL
≥2 cm to < 3 cm	2 mL
≥1 cm to < 2 cm	1 mL

Regarding prioritization of target lesions to be injected at a treatment visit, any new or progressing lesion should be injected first, followed by injection of another accessible lesion(s) in order of size, as permitted by total volume determined for dose level per treatment visit. In Arms 1 and 2, if no other target lesion is accessible for injection, the remaining amount may alternatively be injected subcutaneously into the tissue immediately surrounding the target lesion, if assessed feasible by the treating physician. In Arm 3, injection into different liver target lesions is permitted only, but not into peritumoral liver tissue.

It is desirable to administer the full dose of MK-4621/JetPEI at each treatment date throughout a treatment cycle, when feasible. If a remaining amount cannot be injected

according to treating physician's assessment, this amount needs to be documented for each injection as described in the Pharmacy Manual.

For lesions that are no longer visible following treatment, discuss with Sponsor for continued injection. Distant bystander lesion(s) assessed for "abscopal" response should not be injected unless approved by the Sponsor Medical Monitor or designee. Deviation from the injectate volumes specified in Table 3 and in Table 4 for individual target lesions may be permitted upon approval by the Sponsor Medical Monitor or designee under selected scenarios; eg, allocating the total injectate volume among multiple target lesions rather than delivering the entire volume to the largest target lesion.

Details on dose calculation, preparation, and administration of MK-4621/JetPEI are provided in the Pharmacy Manual.

Table 5 Study Intervention(s)

Arm Name	Arm Type	Intervention Name	Type	Dose Formulation	Unit Dose Strength(s)	Dosage Level(s)	Route of Administration	Regimen/Treatment Period	Use	IMP/ NIMP	Sourcing
Arm 1	Experimental	MK-4621/ JetPEI	Drug	Dispersion for injection	0.2 mg/mL	0.8 mg = 4 mL	Intratumoral	q1w for each 21-day cycle	Experimental	IMP	Provided centrally by Sponsor
Arm 2	Experimental	MK-4621/ JetPEI	Drug	Dispersion for injection	0.2 mg/mL	0.4 to 0.8 mg = 2-4 mL[a, b]	Intratumoral	q1w for each 21-day cycle	Experimental	IMP	Provided centrally by Sponsor
Arm 2	Experimental	Pembrolizumab	Drug	Solution for infusion	25 mg/mL	200 mg = 8 mL	Intravenous	q3w	Experimental	IMP	Provided centrally by Sponsor
Arm 3	Experimental	MK-4621/ JetPEI	Drug	Dispersion for injection	0.2 mg/mL	0.4 to 0.8 mg = 2-4 mL[a, b]	Intratumoral	q3w for each 21-day cycle	Experimental	IMP	Provided centrally by Sponsor
Arm 3	Experimental	Pembrolizumab	Drug	Solution for infusion	25 mg/mL	200 mg = 8 mL	Intravenous	q3w beginning Cycle 2	Experimental	IMP	Provided centrally by Sponsor

[a] In Arms 2 and 3, MK-4621/JetPEI will be administered within 0.5-4 hours following completion of pembrolizumab IV infusion.
[b] Dose levels will be determined based on emerging safety data.

Definition Investigational Medicinal Product (IMP) and Non- Investigational Medicinal Product (NIMP) is based on guidance issued by the European Commission. Regional and/or Country differences of the definition of IMP/NIMP may exist. In these circumstances, local legislation is followed.

All supplies indicated in Table 5 will be provided per the "Sourcing" row depending upon local country operational requirements. Every attempt should be made to source these supplies from a single lot/batch number. The study site is responsible for recording the lot number, manufacturer, and expiry date for any locally purchased product per local guidelines unless otherwise instructed by the Sponsor.

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

6.1.2 Medical Devices

Not applicable.

6.2 Preparation/Handling/Storage/Accountability

6.2.1 Dose Preparation

The investigational medical product in this study is MK-4621, which is a double-stranded 3-phosphate-RNA that binds to RIG-I; in vivo jetPEI™ is the delivery vehicle. MK-4621/JetPEI will be applied intratumorally/intralesionally. MK-4621/JetPEI will be provided as ready-to-use formulation in 10-mL vials with an extractable volume of at least 5 mL. Details on preparation and administration of MK-4621/JetPEI (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

Treatment allocation will be accomplished by nonrandom assignment by IRT. Arm 1 and Arm 2 may not be opened for enrollment at the same time. When Arms 1 and 2 are open for enrollment simultaneously, IRT will alternate participant assignment between Arm 1 and Arm 2, with consideration of eligible lesion size for dose level. During the dose-confirmation phase, in the event that both Arms 1 and 2 are open for enrollment of participants, IRT will distribute successive participants across the treatment arms/dose-levels. Each new dose-level will open for enrollment without delay once the DLT evaluation period of the previous dose cohort is completed and a dose escalation decision has been made. For example, once the 0.8 mg dose cohort of Arm 1 (MK-4621/JetPEI monotherapy) and the 0.4 mg dose cohort of Arm 2 (MK-4621/JetPEI + pembrolizumab) are open for enrollment, the first participant will be allocated to Arm 1, the second participant will be allocated to Arm 2, the third participant will be allocated to Arm 1, etc.

The enrollment to Arm 3 is independent of Arms 1 and 2 due to different location of injectable tumor, and will be opened after the DLT evaluation period is cleared at the highest dose for the first 3 participants in Arm 2. If all 3 arms are open for enrollment, participants with tumors located predominantly in the liver, accessible for intrahepatic injection and not suitable for Arms 1 and 2 will be enrolled into Arm 3. Otherwise, priority will be given to Arms 1 and 2.

For Arms 2 and 3, an observation period of at least 24 hours will occur after treatment initiation in participants enrolled within each dose level. Each new dose cohort will open for enrollment without delay once DLT evaluation period of the previous dose cohort is completed and a dose-escalation decision is made.

6.3.2 Stratification

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

6.3.3 Blinding

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

6.4 Study Intervention Compliance

Interruptions from the protocol specified treatment plan for >12 weeks between MK-4621/JetPEI or pembrolizumab doses for nondrug-related or administrative reasons require consultation between the investigator and the Sponsor and written documentation of the collaborative decision on participant management.

6.5 Concomitant Therapy

Medications specifically prohibited in the exclusion criteria are not allowed during the ongoing study. If there is a clinical indication for any medication specifically prohibited, discontinuation from study treatment may be required. The investigator should discuss any questions regarding this with the Sponsor. The final decision on any supportive therapy rests with the investigator and/or the participant's primary physician. However, the decision to continue the participant on study treatment requires the mutual agreement of the investigator, the Sponsor, and the participant.

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 except for those that are prohibited as described in Section 6.5.2. All concomitant medication will be recorded on the case report form (CRF) including all prescription, over-the-counter (OTC), herbal supplements, and IV medications and fluids. If changes occur during the study period, documentation of drug dosage, frequency, route, and date may also be included on the CRF.

Anticoagulants or antiplatelet agents are allowed however may be discontinued temporarily for the biopsy and injection procedures; benefit/risk of the interruption needs to be weighed by the investigator. The timing and duration of the interruption and further management will be done according to the sites routine procedures. Coagulation parameter should be carefully monitored and the potential bleeding risk of the intrahepatic administration of the drug needs to be taken into consideration.

All concomitant medications received within 28 days before the first dose of study treatment and 30 days after the last dose of study treatment should be recorded. Concomitant medications administered after 30 days after the last dose of study treatment should be recorded for SAEs and ECIs as 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 (including retreatment for post-complete response relapse) 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 MK-4621/JetPEI and pembrolizumab
- Radiation therapy

  Note: Radiation therapy to a symptomatic solitary lesion or to the brain may be allowed at the investigator's discretion after the DLT evaluation period.

- Live vaccines within 30 days prior to the first dose of study treatment and while participating in the study. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, varicella/zoster, yellow fever, rabies, Bacillus Calmette–Guérin (BCG), and typhoid vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed; however, intranasal influenza vaccines (eg, FluMist®) are live attenuated vaccines and are not allowed.
- Systemic glucocorticoids for any purpose other than to modulate symptoms from an adverse event of suspected immunologic etiology. The use of physiologic doses of corticosteroids may be approved after consultation with the Sponsor.

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

6.5.3 Rescue Medications and Supportive Care

6.5.3.1 MK-4621/JetPEI Supportive Care

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

- Pyrexia: Fever reactions are expected during treatment with MK-4621/JetPEI. Investigators may treat the fever with their standard antipyretics (eg, paracetamol) at their discretion. Pretreatment with antipyretics is also allowed in a case in which a participant showed a fever reaction after an earlier injection. This pretreatment is also at the discretion of the investigator.

Hypersensitivity is seen as a potential safety risk in general with novel compounds. In addition (based upon published preclinical experiences) the excipient PEI and its variants are seen as a potential source for hypersensitivity reactions. Therefore, it is recommended to monitor all participants carefully for any such potential reaction and to take appropriate measures where seen as needed (eg, premedication) as per treating physician's assessment. In case any such hypersensitivity reaction (infusion-related reaction [IRR]; anaphylaxis/ anaphylactoid reactions or other cytokine release-related events and similar) may occur within the first 48 hours of injection that presents as AE ≥Grade 2, the participant should

receive medication according to the institutions local policies. A premedication with methylprednisolone, an antihistamine and an H2-blocker may appear recommendable with subsequent injections to avoid any such IRR if seen as recommendable by the investigator. Treatment shall be permanently discontinued in any case of Grade 4 hypersensitivity reaction.

In the first 15 participants, local reactions at the injection site have been seen, as well as fever reactions and fatigue, mainly Grade 1. A Grade 3 fever reaction occurred once and resolved in less than 24 hours. Grade 3 fatigue was also reported.

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

6.5.3.2 Pembrolizumab Supportive Care

Participants should receive appropriate supportive care measures as deemed necessary by the treating investigator. Suggested supportive care measures for the management of AEs with potential immunologic etiology are outlined along with the dose modification guidelines in Section 6.6.5.2, Table 7. Where appropriate, these guidelines include the use of oral or IV treatment with corticosteroids, as well as additional anti-inflammatory agents if symptoms do not improve with administration of corticosteroids. Note that several courses of steroid tapering may be necessary as symptoms may worsen when the steroid dose is decreased. For each disorder, attempts should be made to rule out other causes such as metastatic disease or bacterial or viral infection, which might require additional supportive care. The treatment guidelines are intended to be applied when the investigator determines the events to be related to 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 Table 7 in Section 6.6.5.2 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-4621/JetPEI and pembrolizumab are provided in the appropriate Pharmacy Manual.

6.6.2 Definition of Dose-limiting Toxicity

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

The DLT window of observation will be during Cycle 1 for Arms 1 and 2. For Arm 3, the DLT evaluation period will be the first 2 cycles (ie, the first monotherapy run-in cycle [Cycle 1]) and the first combination therapy cycle [Cycle 2]).

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

1. Grade 4 nonhematologic toxicity (not laboratory).

2. Grade 4 hematologic toxicity lasting ≥7 days, except thrombocytopenia:

   - Grade 4 thrombocytopenia of any duration

   - Grade 3 thrombocytopenia associated with clinically significant bleeding

3. Any nonhematologic AE ≥Grade 3 in severity should be considered a DLT, with the following exceptions: Grade 3 fatigue lasting ≤3 days; Grade 3 diarrhea, nausea, or vomiting without use of antiemetics or antidiarrheals per standard of care; Grade 3 rash without use of corticosteroids or anti-inflammatory agents per standard of care; Grade 3, drug-related fever that resolves within 24 hours.

4. Any Grade 3 or Grade 4 nonhematologic laboratory value if:

   - Clinically significant medical intervention is required to treat the participant, or

   - The abnormality leads to hospitalization, or

   - The abnormality persists for >1 week; or

   - The abnormality results in a Drug-induced Liver Injury (DILI) (see Sections 8.4.1 and 8.4.7 for criteria)

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

5. Febrile neutropenia Grade 3 or Grade 4:

   - Grade 3 is defined as ANC <1000/mm3 with a single temperature of >38.3°C (101°F) or a sustained temperature of ≥38°C (100.4°F) for more than 1 hour.

- Grade 4 is defined as ANC <1000/mm3 with a single temperature of >38.3°C (101°F) or a sustained temperature of ≥38°C (100.4°F) for more than 1 hour, with life-threatening consequences and urgent intervention indicated.

6. Prolonged delay (>2 weeks) in initiating Cycle 2 due to treatment-related toxicity.
7. Any treatment-related toxicity that causes the participant to discontinue treatment during Cycle 1, or Cycles 1 and 2 for Arm 3.
8. Missing >2 injections of MK-4621/JetPEI doses in Arms 1 and 2 and >1 injection in Arm 3 as a result of drug-related AE(s) during the first cycle of Arms 1 or 2 or the first 2 cycles of Arm 3, respectively.
9. Grade 5 toxicity.

The following toxicities will not be considered as DLTs:

1. Grade 3 AE of tumor flare (defined as local pain, irritation, or rash localized at sites of known or suspected tumor) or injection procedure related local pain that is clinically manageable as per investigator's assessment.
2. Grade 3 injection/hypersensitivity reactions that resolve to Grade ≤ 1 within 24 hours.

6.6.3 Crossover Treatment Phase (Optional)

Participants with disease progression following treatment with MK-4621/JetPEI in the monotherapy arm (Arm 1) may be eligible to participate in the crossover treatment phase of this study and cross over to Arm 2. Participants who permanently discontinue MK-4621/JetPEI 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.

Eligibility criteria for crossover include:

- Participants must have disease progression following treatment with MK-4621/JetPEI in the monotherapy arm (Arm 1)

  Note: Disease progression must be assessed by imaging study using RECIST 1.1 and be confirmed by iRECIST, as assessed by the site. Participants with overt progression before confirmed PD may initiate crossover upon Sponsor consultation on a case-by-case basis. The imaging that confirms the progression will be used to establish a new baseline for the crossover phase.

- Participants must have adequate organ function as indicated by the laboratory values in Table 2;
- Participants must have no evidence of new or enlarging brain metastases; and
- Participants must have an ECOG performance status of 0 or 1.

If crossover is being considered, the participant must be re-consented 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-4621/JetPEI that has passed the DLT evaluation period in the combination treatment arm at the time of crossover. The participant will receive the highest dose of MK-4621/JetPEI that has passed an initial DLT evaluation period in the combination treatment arm. Participants who cross over to the combination treatment arm will not be counted toward the total number of participants in the 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-4621/JetPEI in the monotherapy arm unless otherwise discussed with the Sponsor.

The study procedures are to be completed in the crossover treatment phase and safety and efficacy data from participants who crossover 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.

6.6.4 Timing of Dose Administration

Arm 1: MK-4621/JetPEI will be administered once weekly in each cycle, for a maximum duration of 6 cycles. A cycle is defined as 3 weeks.

Arm 2: Pembrolizumab will be administered once every 3 weeks starting with D1C1. MK-4621/JetPEI will be injected intratumorally once weekly for each cycle. The injection will be done 0.5-4 hours after the infusion of pembrolizumab.

Arm 3: Run-in Phase (Cycle 1): MK-4621/JetPEI as monotherapy will be administered on Day 1 of Cycle 1.

Combination Phase (Cycles 2-6): Pembrolizumab and MK-4621/JetPEI will be administered once every 3 weeks. On Day 1 of each cycle, MK-4621/JetPEI will be injected 0.5-4 hours after pembrolizumab.

If neither pembrolizumab treatment nor MK-4621/JetPEI treatment can be performed on the Treatment Cycle Day 1, the Treatment Cycle will not be initiated. If either pembrolizumab treatment or MK-4621/JetPEI treatment can be performed on the Treatment Cycle Day 1, the Treatment Cycle will be initiated. If treatment cannot be performed within the given time window during a Treatment Cycle, the dose is missed and will not be replaced; the participant will continue with the next visit according to the Treatment Cycle schedule.

The reason for any variability in administration of MK-4621/JetPEI and pembrolizumab outside of the protocol-specified window should be documented in the participant's chart and recorded on the electronic Case Report Forms (eCRFs). All study treatments will begin on Day 1 of each cycle after all predose study procedures and assessments have been completed

as detailed in Section 1.3, Schedule of Activities. The Pharmacy Manual contains specific instructions for dose calculation, reconstitution, and preparation of MK-4621/JetPEI, and administration.

6.6.5 Guidelines for Dose Modification for MK-4621/JetPEI and/or Pembrolizumab due to Adverse Events

Adverse events (both nonserious and serious) associated with MK-4621/JetPEI and pembrolizumab exposure may represent an immunologic etiology. These adverse events may occur shortly after the first dose or several months after the last dose of treatment.

The CTCAE must be used to grade the severity of adverse events. The investigator may attribute each toxicity event to MK-4621/JetPEI 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-4621/JetPEI, the dose may not be re-escalated to the dose that preceded the dose modification. Dose modifications are always based on the previous cycle.

Reduction or holding of 1 agent and not the other agent is appropriate if, in the opinion of the investigator, the toxicity is clearly related to 1 of the study treatments. For example, in the combination arm (Arm 2), if MK-4621/JetPEI is held due to an AE attributed to that drug, then pembrolizumab may continue to be administered. Appropriate documentation is required regarding to which drug the investigator is attributing the AE. If, in the opinion of the investigator, the toxicity is related to the combination of 2 agents, then both drugs should be held according to recommended dose modifications.

6.6.5.1 Dose Modification for MK-4621/JetPEI

Participants may have up to 2 dose modifications of MK-4621/JetPEI 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 treatment. 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).

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

Table 6 MK-4621/JetPEI Dose Modification and Treatment Discontinuation Guidelines for Drug-related Adverse Events

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

In case toxicity does not resolve to Grade 0-1 within 12 weeks after last treatment, MK-4621/JetPEI should be discontinued after consultation with the Sponsor.

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

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

6.6.5.2 Dose Modification for Pembrolizumab

Dose modification and toxicity management for immune-related AEs associated with pembrolizumab

Adverse events associated with pembrolizumab exposure may represent an immunologic etiology. These immune-related AEs (irAEs) may occur shortly after the first dose or several months after the last dose of pembrolizumab treatment and may affect more than one body system simultaneously. Therefore, early recognition and initiation of treatment is critical to reduce complications. Based on existing clinical study data, most irAEs were reversible and could be managed with interruptions of pembrolizumab, administration of corticosteroids, and/or other supportive care. For suspected irAEs, ensure adequate evaluation to confirm etiology or exclude other causes. Additional procedures or tests such as bronchoscopy, endoscopy, skin biopsy may be included as part of the evaluation. Based on the severity of irAEs, withhold or permanently discontinue pembrolizumab and administer corticosteroids. Dose modification and toxicity management guidelines for irAEs associated with pembrolizumab are provided in Table 7.

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

General instructions:

1. Corticosteroid taper should be initiated upon AE improving to Grade 1 or less and continue to taper over at least 4 weeks.
2. For situations where pembrolizumab has been withheld, pembrolizumab can be resumed after AE has been reduced to Grade 1 or 0 and corticosteroid has been tapered. Pembrolizumab should be permanently discontinued if AE does not resolve within 12 weeks of last dose or corticosteroids cannot be reduced to ≤10 mg prednisone or equivalent per day within 12 weeks.
3. For severe and life-threatening irAEs, IV corticosteroid should be initiated first followed by oral steroid. Other immunosuppressive treatment should be initiated if irAEs cannot be controlled by corticosteroids.

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

Immune-related AEs	Toxicity Grade or Conditions (CTCAEv4.0)	Action Taken with Pembrolizumab	irAE Management with Corticosteroid and/or Other Therapies	Monitor and Follow-up
AST / ALT Elevation or Increased Bilirubin	Grade 2	Withhold	• Administer corticosteroids (initial dose of 0.5- 1 mg/kg prednisone or equivalent) followed by taper	• Monitor with liver function tests (consider weekly or more frequently until liver enzyme value returned to baseline or is stable
	Grade 3 or 4	Permanently discontinue	• Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper	
Type 1 Diabetes Mellitus (T1DM) or Hyperglycemia	Newly onset T1DM or Grade 3 or 4 hyperglycemia associated with evidence of β-cell failure	Withhold	• Initiate insulin replacement therapy for participants with T1DM • Administer 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[1]		
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[1]		
Hypothyroidism	Grade 2-4	Continue	• Initiate thyroid replacement hormones (eg, levothyroxine or liothyronine) per standard of care	• Monitor for signs and symptoms of thyroid disorders.
Nephritis and Renal Dysfunction	Grade 2	Withhold	• Administer corticosteroids (prednisone 1-2 mg/kg or equivalent) followed by taper.	• Monitor changes of renal function
	Grade 3 or 4	Permanently discontinue		

Immune-related AEs	Toxicity Grade or Conditions (CTCAEv4.0)	Action Taken with Pembrolizumab	irAE Management with Corticosteroid and/or Other Therapies	Monitor and Follow-up
Myocarditis	Grade 1 or 2	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 3 or 4	Permanently discontinue		
All Other Immune-related AEs	Intolerable/ persistent Grade 2	Withhold	• Based on type and severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 3	Withhold or discontinue based on the type of event. Events that require discontinuation include and not limited to:Guillain-Barre Syndrome, encephalitis		
	Grade 4 or recurrent Grade 3	Permanently discontinue		

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

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

Dose modification and toxicity management of infusion-reactions related to pembrolizumab

Pembrolizumab may cause severe or life-threatening infusion-reactions including severe hypersensitivity or anaphylaxis. Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion. Dose modification and toxicity management guidelines on pembrolizumab associated infusion reaction are provided in Table 8.

Table 8 Pembrolizumab Infusion Reaction Dose Modification and Treatment Guidelines

NCI CTCAE Grade	Treatment	Premedication at Subsequent Dosing
Grade 1 Mild reaction; infusion interruption not indicated; intervention not indicated	Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator.	None
Grade 2 Requires therapy or infusion interruption but responds promptly to symptomatic treatment (eg, antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for ≤24 h	**Stop Infusion.** Additional appropriate medical therapy may include but is not limited to: IV fluids Antihistamines NSAIDs Acetaminophen Narcotics Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator. If symptoms resolve within 1 hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (eg, from 100 mL/h to 50 mL/h). Otherwise dosing will be held until symptoms resolve and the participant should be premedicated for the next scheduled dose. Participants who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further study drug treatment.	Participant may be premedicated 1.5h (± 30 minutes) prior to infusion of pembrolizumab with: diphenhydramine 50 mg po (or equivalent dose of antihistamine and/or H2 blocker). Paracetamol (acetaminophen) 500-1000 mg po (or equivalent dose of analgesic).

NCI CTCAE Grade	Treatment	Premedication at Subsequent Dosing
Grades 3 or 4 Grade 3: Prolonged (ie, not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (eg, renal impairment, pulmonary infiltrates) Grade 4: Life-threatening; pressor or ventilatory support indicated	**Stop Infusion.** Additional appropriate medical therapy may include but is not limited to: Epinephrine** IV fluids Antihistamines NSAIDs Acetaminophen Narcotics Oxygen Pressors Corticosteroids Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator. Hospitalization may be indicated. **In cases of anaphylaxis, epinephrine should be used immediately. **Participant is permanently discontinued from further study drug treatment.**	No subsequent dosing
Appropriate resuscitation equipment should be available at the bedside and a physician readily available during the period of drug administration. For further information, please refer to the Common Terminology Criteria for Adverse Events v4.0 (CTCAE) at http://ctep.cancer.gov		

Other allowed dose interruption for pembrolizumab or MK-4621/JetPEI

Pembrolizumab or MK-4621/JetPEI may be interrupted for situations other than treatment-related AEs such as medical / surgical events or logistical reasons not related to study therapy. Participants should be placed back on study therapy within 3 weeks of the scheduled interruption, unless otherwise discussed with the Sponsor. The reason for interruption should be documented in the patient's study record.

6.7 Intervention After the End of the Study

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

6.8 Clinical Supplies Disclosure

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

7 DISCONTINUATION OF STUDY 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 prior to completion of the protocol-specified treatment period will still continue to participate in the study as specified in Section 1.3 and Section 8.12.

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. Specific details regarding procedures to be performed at study intervention discontinuation are provided in Section 8.1.9.

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.
- 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.
- Confirmed radiographic disease progression outlined in Section 8.2 (exception if the Sponsor approves treatment continuation, or if a participant progresses on Arm 1 and crosses over to Arm 2).
- Unacceptable adverse experiences as described in Section 8.3.
- Use of prohibited concomitant medications as described in Section 6.5.2.
- Progression or recurrence of any malignancy, or any occurrence of another malignancy that requires active treatment.
- Intercurrent illness other than another malignancy as noted above that prevents further administration of treatment.

- Investigator's decision to discontinue treatment.
- Recurrent Grade 2 pneumonitis.
- Completion of 6 cycles of treatment with MK-4621/JetPEI in Arm 1 or 35 treatments with pembrolizumab in Arms 2 and 3. Participants who cross over from Arm 1 to Arm 2 are eligible for up to 35 cycles of treatment with pembrolizumab therapy and up to a cumulative total of 6 cycles of treatment with MK-4621/JetPEI, inclusive of the MK-4621/JetPEI cycles received in Arm 1 and Arm 2.

Participants may discontinue from one of the study medications (Arm 2 and 3) but continue with the other study medication if considered reasonable by the investigator.

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

7.2 Participant Withdrawal From the Study

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

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

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

7.3 Lost to Follow-up

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

- The site must attempt to contact the participant and reschedule the missed visit. If the participant is contacted, the participant should be counseled on the importance of maintaining the protocol-specified visit schedule.
- The investigator or designee must make every effort to regain contact with the participant at each missed visit (eg, telephone calls and/or a certified letter to the participant's last known mailing address or locally equivalent methods). These contact attempts should be documented in the participant's medical record.
- Note: A participant is not considered lost to follow-up until the last scheduled visit for the individual participant. The missing data for the participant will be managed via the prespecified statistical data handling and analysis guidelines.

8 STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarized in the SoA.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- The investigator is responsible for ensuring that procedures are conducted by appropriately qualified or trained staff. Delegation of study site personnel responsibilities will be documented in the Investigator Trial File Binder (or equivalent).
- All study-related medical (or dental) decisions must be made by an investigator who is a qualified physician (or dentist when appropriate).
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the participant's routine clinical management (eg, blood count) and obtained before signing of ICF may be utilized for screening or baseline purposes provided the procedure met the protocol-specified criteria and were performed within the time frame defined in the SoA.
- Additional evaluations/testing may be deemed necessary by the investigator and or the Sponsor for reasons related to participant safety. In some cases, such evaluation/testing may be potentially sensitive in nature (eg, HIV, Hepatitis C), and thus local regulations may require that additional informed consent be obtained from the participant. In these cases, such evaluations/testing will be performed in accordance with those regulations.

The maximum amount of blood collected from each participant, including any extra assessments that may be required over the duration of the study, will not exceed 500 mL (refer to 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 consent from each potential participant or each participant's legally acceptable representative prior to participating in a clinical study or future biomedical

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

8.1.1.1 General Informed Consent

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

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

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

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

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

8.1.1.2 Consent and Collection of Specimens for Future Biomedical Research

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

8.1.2 Inclusion/Exclusion Criteria

All inclusion and exclusion criteria (Sections 5.1 and 5.2) will be reviewed by the investigator who is a qualified physician or qualified designee to ensure that the participant qualifies for the study.

8.1.3 Participant Identification Card

All participants will be given a participant identification card identifying them as participants in a research study. The card will contain study site contact information (including direct telephone numbers) to be 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 written informed consent. At the time of intervention allocation/ randomization, site personnel will add the intervention/randomization number to the participant identification card.

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

8.1.4 Medical History

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

8.1.5 Prior and Concomitant Medications Review

8.1.5.1 Prior Medications

The investigator or qualified designee will review prior medication use, including any protocol-specified washout requirement, and record prior medication taken by the participant within 28 days before first dose of study medication. Treatment for the disease for which the participant has been enrolled in this study will be recorded separately and should not be listed in prior medications.

8.1.5.2 Concomitant Medications

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

All medications related to reportable SAEs and events of clinical interest (ECIs) should be recorded as defined in Section 8.4.

All new anticancer therapy initiated after the study start must be recorded in the eCRF. If a participant initiates another anticancer therapy other than the assigned study treatment(s), the study treatment(s) should be discontinued and the participant will move into the survival follow-up phase; if a participant initiates a new anticancer therapy within 30 days after the last dose of the study treatment, 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 prior to intervention allocation. Each participant will be assigned only 1 screening number. Screening numbers must not be re-used for different participants.

8.1.7 Assignment of Treatment/Randomization Number

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

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

8.1.8 Study Intervention Administration

Administration of study medication will be witnessed by the investigator and/or study staff. The total volume of study treatment injected and/or infused will be compared to the total volume prepared to determine compliance with each dose administered.

Study treatment will begin on Cycle 1 Day 1, once all predose assessments have been completed.

See Section 6 for a description of treatment modifications. Instructions for preparing and administering study intervention will be provided in the Pharmacy Manual.

8.1.8.1 Timing of Dose Administration

In Arm 1 (monotherapy), MK-4621/JetPEI will be administered on Days 1, 8, and 15 of the of each cycle. Each participant may undergo up to 6 cycles of MK-4621/JetPEI treatment in Arm 1.

In Arm 2, MK-4621/JetPEI will be administered on Days 1, 8, and 15 of each 21-day cycle. MK-4621/JetPEI will be administered within 0.5 to 4 hours following completion of pembrolizumab IV infusion. Each participant may undergo up to 6 cycles of MK-4621/JetPEI treatment in Arm 2.

For Arm 3, MK-4621/JetPEI will be administered on Day 1 of each 21-day cycle. MK-4621/JetPEI will be administered within 0.5 to 4 hours following completion of pembrolizumab IV infusion. Each participant may undergo up to 6 cycles of MK-4621/JetPEI treatment in Arm 3.

In Arms 2 and 3, pembrolizumab 200 mg will be administered as an IV infusion on Day 1 of each 21-day cycle (except for Cycle 1 of Arm 3). Participants may continue treatment with pembrolizumab for up to a total of 35 cycles (approximately 2 years).

In Cycle 2, study intervention may be administered up to 3 days after the scheduled Day 1. Beginning in Cycle 3, study treatment may be administered up to 3 days before or after the scheduled Day 1. Dosing interruptions are permitted in the case of medical/surgical events or logistical reasons that are not related to study therapy (eg, elective surgery, unrelated medical events, participant vacation, and/or holidays). Participants should be placed back on study

therapy within 3 weeks of the scheduled interruption, unless otherwise discussed with the Sponsor Medical Monitor or designee. The reason for interruption should be documented in the participant's study record.

8.1.9 Discontinuation and Withdrawal

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

When a participant withdraws from participation in the study, all applicable activities scheduled for the End of Treatment Visit should be performed (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 and Section 8.12.2.1. The investigator or study coordinator must notify the Sponsor when a participant has been discontinued/withdrawn from the study and/or treatment. If a participant discontinues for any reason at any time during the course of the study and/or treatment, the participant may be asked to return to the clinic (or be contacted) for a poststudy visit as per the number of days described in Section 8.4 and Section 8.12.2.1 to have the applicable procedures conducted. However, the investigator may decide to perform the poststudy procedures at the time of discontinuation or as soon as possible after discontinuation. If the poststudy visit occurs prior to the safety follow-up timeframe as specified in Section 8.4.1, the investigator should perform a follow-up telephone call at the end of the follow-up period (Section 8.4.1.) to determine if any AEs have occurred since the poststudy clinic visit. Any AEs that are present at the time of discontinuation/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 future biomedical research. Participants may withdraw consent at any time by contacting the principal investigator for the main study. If medical records for the main study are still available, the investigator will contact the Sponsor using the designated mailbox (clinical.specimen.management@merck.com). Subsequently, the participant's consent for future biomedical research will be withdrawn. A letter will be sent from the Sponsor to the investigator confirming the withdrawal. It is the responsibility of the investigator to inform the participant of completion of withdrawal. Any analyses in progress at the time of request for withdrawal or already performed prior to the request being received by the Sponsor will continue to be used as part of the overall research study data and results. No new analyses would be generated after the request is received.

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

8.1.10 Participant Blinding/Unblinding

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

8.1.11 Domiciling

Participants will report to the clinical research unit (CRU) on Cycle 1 Day 1. For Arm 1, on Day 1 of Cycles 1-6, a 24-hour inpatient observation period following MK-4621/JetPEI administration will be at the discretion of the investigator. All participants in Arm 2 will undergo at least a 24-hour observation period following first dose administration on C1D1, which may be extended to 48 hours at the discretion of the investigator. For Arm 2, on Day 1 of Cycles 2-6, a 24-hour inpatient observation period following MK-4621/JetPEI administration will be at the discretion of the investigator. All participants in Arm 3 will undergo at least a 24-hour observation period following dose administration on C1D1 and C2D1, which may be extended to 48 hours at the discretion of the investigator. For Arm 3, on Day 1 of Cycles 3-6, a 24-hour inpatient observation period following MK-4621/JetPEI administration will be at the discretion of the investigator. For all the required inpatient observation periods, observation time may be extended to 48 hours at the discretion of the investigator, per local Institutional Review Board, Ethics Review Committee, and/or Health Authority mandate. This requirement may be waived at the discretion of the Sponsor and will be communicated to sites via a memorandum.

8.1.12 Calibration of Equipment

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

8.2 Efficacy/Immunogenicity Assessments

8.2.1 Tumor Imaging and Assessment of Disease

RECIST 1.1 and iRECIST assessment will be done on the basis of both injected and noninjected lesions. Injecting a lesion after treatment has begun will not render it “nonevaluable” for response assessment purposes.

The initial PET/CT scan or MRI for solid tumor imaging as well as medical photography for cutaneous lesions must be performed within 28 days prior to enrollment, and the site study team must confirm that the participant has measurable disease as defined by RECIST 1.1.

Tumor imaging should be acquired by computed tomography (CT, strongly preferred). MRI should be used when CT is contraindicated or for imaging in the brain. The same imaging technique regarding modality and use of contrast media should be used in a participant throughout the study to optimize the visualization of existing and new tumor burden.

Required anatomical images as well as the process for image collection and transmission to the central imaging vendor can be found in the Site Imaging Manual (SIM).

A central imaging vendor will be made available for possible future independent review.

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

8.2.2 Initial Tumor Imaging

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

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 42 days prior to the date of allocation.

Participants with previously treated brain metastases may participate provided they have stable brain metastases, ie, without evidence of progression by imaging (confirmed by MRI if MRI was used at prior imaging, or confirmed by CT imaging if CT used at prior imaging) for at least 4 weeks prior to the first dose of study treatment. Any neurologic symptoms must have returned to baseline and participants must have no evidence of new or enlarging brain metastases, and have not used steroids for brain metastases for at least 28 days prior to 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.

8.2.3 Tumor Imaging During the Study

The first on-study imaging assessment should be performed at 9 weeks (±7 days) from the date of allocation. Subsequent tumor imaging should be performed every 9 weeks (±7 days) or more frequently if clinically indicated. Imaging timing should follow calendar days and should not be adjusted for delays in cycle starts. Imaging should continue to be performed until disease progression is identified by the investigator, the start of new anticancer treatment, withdrawal of consent, death, or the end of the study, whichever occurs first.

Per iRECIST (Section 8.2.5), disease progression should be confirmed by the site 4 to 8 weeks after site-assessed first radiologic evidence of PD in clinically stable participants. Participants who have unconfirmed disease progression may continue on treatment at the discretion of the investigator until progression is confirmed provided they have met the conditions detailed in Section 8.2.5. Participants who receive confirmatory imaging do not need to undergo the next scheduled tumor imaging if it is less than 4 weeks later; tumor imaging may resume at the subsequent scheduled imaging time point if clinically stable. Participants who have confirmed disease progression by iRECIST, as assessed by the site, will discontinue the treatment. Exception is detailed in Section 8.2.5.

8.2.4 End of Treatment and Follow-up Tumor Imaging

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

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

8.2.5 iRECIST Assessment of Disease

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

For participants who show evidence of radiological PD by RECIST 1.1, as determined by the investigator, the investigator will decide whether to continue a participant on study intervention until repeat imaging is obtained (using iRECIST for participant management, see Table 9). This decision by the investigator should be based on the participant's overall condition.

Clinical stability is defined as the following:

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

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

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

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

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

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

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

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

Assessment at the Confirmatory Imaging

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

Confirmation of progression

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

- Any of the factors that were the basis for the initial iUPD show worsening:
    - For target lesions, worsening is a further increase in the sum of diameters of ≥5mm, compared to any prior iUPD timepoint.

- For nontarget lesions, worsening is any significant growth in lesions overall, compared to a prior iUPD timepoint; this does not have to meet the "unequivocal" standard of RECIST 1.1
- For new lesions, worsening is any of these:
  - An increase in the new lesion sum of diameters by ≥5mm from a prior iUPD timepoint
  - Visible growth of new nontarget lesions
  - The appearance of additional new lesions
  - Any new factor appears that would have triggered PD by RECIST 1.1.

Persistent iUPD

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

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

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

Resolution of iUPD

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

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

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

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

Management following the confirmatory imaging

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

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

Detection of progression at visits after pseudoprogression resolves

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

- Target lesions
    - Sum of diameters reaches the PD threshold (20% & 5 mm increase from nadir) either for the first time, or after resolution of previous pseudoprogression. The nadir is always the smallest SOD seen during the entire study, either before or after an instance of pseudoprogression.
- Nontarget lesions
    - If nontarget lesions have never shown unequivocal progression, their doing so for the first time results in iUPD.
    - If nontarget lesions had shown previous unequivocal progression, and this progression has not resolved, iUPD results from any significant further growth of nontarget lesions, taken as a whole.
- New lesions
    - New lesions appear for the first time
    - Additional new lesions appear
    - Previously identified new target lesions show an increase of ≥5 mm in the new lesion sum of diameters, from the nadir value of that sum
    - Previously identified nontarget lesions show any significant growth

If any of the events above occur, the overall response for that visit is iUPD, and the iUPD evaluation process (see Assessment at the Confirmatory Imaging above) is repeated. Progression must be confirmed before iCPD can occur.

The decision process is identical to the iUPD confirmation process for the initial PD, with one exception: if new lesions occurred at a prior instance of iUPD, and at the confirmatory imaging the burden of new lesions has increased from its smallest value (for new target lesions, the sum of diameters is ≥5 mm increased from its nadir), then iUPD cannot resolve to iSD or iPR. It will remain iUPD until either a decrease in the new lesion burden allows resolution to iSD or iPR, or until a confirmatory factor causes iCPD.

Additional details about iRECIST are provided in the iRECIST publication.

Table 9 Imaging and Treatment After First Radiologic Evidence of Progressive Disease

	Clinically Stable		Clinically Unstable	
	Imaging	Treatment	Imaging	Treatment
First radiologic evidence of PD by RECIST 1.1	Repeat imaging at 4 to 8 weeks to confirm PD	May continue study treatment at the local site investigator's discretion while awaiting confirmatory tumor imaging by site by iRECIST.	Repeat imaging at 4 to 8 weeks to confirm PD per physician discretion only	Discontinue treatment
Repeat tumor imaging confirms PD (iCPD) by iRECIST, per local assessment	No additional imaging required	Discontinue treatment (exception is possible upon consultation with Sponsor)	No additional imaging required	N/A
Repeat tumor imaging shows iUPD by iRECIST, per local assessment	Repeat imaging at 4-8 weeks to confirm PD. May occur at next regularly scheduled imaging visit.	Continue study treatment at the local site investigator's discretion	Repeat imaging at 4-8 weeks to confirm PD per physician discretion only	Discontinue treatment
Repeat tumor imaging shows iSD, iPR, or iCR by iRECIST, per local assessment	Continue regularly scheduled imaging assessments	Continue study treatment at the local site investigator's discretion	Continue regularly scheduled imaging assessments	May restart study treatment if condition has improved and/or clinically stable per investigator's discretion. Next tumor imaging should occur according to the regular imaging schedule
If progression has been centrally verified, further management by the study site, based on iRECIST. Any further imaging should still be submitted to the vendor, but no rapid review will occur. iCPD=immune confirmed progressive disease; iUPD=immune unconfirmed progressive disease; iCR=immune complete response; iRECIST=immune-related response evaluation criteria in solid tumors; PD=progressive disease; PFS=progression-free survival; iPR=immune partial response; iSD=immune stable disease.				

8.2.6 Eastern Cooperative Oncology Group (ECOG) Performance Scale

The investigator or qualified designee will assess ECOG status at screening, prior to the administration of study treatment on Day 1 of every cycle, and during the follow-up period as specified in the SoA.

8.3 Safety Assessments

Details regarding specific safety procedures/assessments to be performed in this study are provided. 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 Section 8.

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

8.3.1 Physical Examinations

8.3.1.1 Full Physical Exam

The investigator or qualified designee will perform a complete physical exam during the screening period, including height and weight. Height will be measured at Visit 1 only. Clinically significant abnormal findings should be recorded as medical history. The time points for full physical exam are described in the SoA. After the first dose of study treatment, 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 Exam

For cycles that do not required a full physical exam per the Schedule of Activities, the investigator or qualified designee will perform a directed physical exam as clinically indicated prior to study treatment administration. New clinically significant abnormal findings should be recorded as AEs.

8.3.2 Vital Signs

The investigator or qualified designee will take vital signs at screening, prior and after the administration of study treatment and during the follow-up period as specified in the SoA. Vital signs include temperature, pulse, respiratory rate, blood pressure, and oxygen saturation.

8.3.3 Electrocardiograms

A standard 12-lead ECG will be performed using local standard procedures. The timing of ECGs is specified in the Schedule of Activities in Section 1.3. Clinically significant abnormal findings should be recorded as medical history before study treatment and as an AE

if occurring under study treatment. Additional ECGs may be performed as clinically necessary.

8.3.4 Clinical Safety Laboratory Assessments

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

- The investigator or medically qualified designee (consistent with local requirements) must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the case report form (CRF). The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.

- All protocol-required laboratory assessments, as defined in Appendix 2, must be conducted in accordance with the Procedures Manual and the SoA.

- If laboratory values from nonprotocol specified laboratory assessments performed at the institution’s local laboratory require a change in study participant management or are considered clinically significant by the investigator (eg, SAE or AE or dose modification), then the results must be recorded in the appropriate CRF (eg, SLAB).

- For any laboratory tests with values considered clinically significantly abnormal during participation in the study or within 30 days after the last dose of study intervention, every attempt should be made to perform repeat assessments until the values return to normal or baseline or if a new baseline is established as determined by the investigator.

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

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

Laboratory tests for screening should be performed within 3 days prior to the first dose of study treatment. An exception is hepatitis, HIV and thyroid serologies, which may be performed within 28 days prior to first dose. After Cycle 1, predose laboratory safety tests can be conducted up to 72 hours prior to 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 prior to administration of each dose of study treatment. Unresolved abnormal laboratory values that are drug-related AEs should be followed until resolution. Laboratory tests do not need to be repeated after the end of treatment if laboratory results are within normal range.

8.3.4.2 Pregnancy Test

All women who are being considered for participation in the study, and who are not surgically sterilized or postmenopausal, must be tested for pregnancy within 72 hours prior to Cycle 1 of study treatment. If a urine test is positive or not evaluable, a serum test will be required. Participants must be excluded/discontinued from the study in the event of a positive or borderline-positive test result.

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

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

Progression of the cancer under study is not considered an AE as described in Section 8.4.6 and Appendix 4.

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 remain responsible for following up AE, 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 consent form is signed but before treatment allocation/randomization must be reported by the investigator if the participant is receiving placebo run-in or other run-in treatment, if the event 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 treatment allocation/randomization through 30 days following cessation of study intervention must be reported by the investigator.
- All AEs meeting serious criteria, from the time of treatment allocation/randomization through 90 days following cessation of study intervention or 30 days following 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 treatment allocation/randomization through 120 days following cessation of study intervention, or 30 days following 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 of the time period specified above must be reported immediately to the Sponsor if the event is considered drug-related.

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

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

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

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

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

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

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All AE, SAE, and other reportable safety events including pregnancy and exposure during breastfeeding, events of clinical interest (ECI), cancer, and overdose will be followed until resolution, stabilization, until the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3). In addition, the investigator will make every attempt to follow all nonserious AEs that occur in randomized participants for outcome. Further information on follow-up procedures is given in Appendix 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. All AEs will be reported to regulatory authorities, IRB/IECs, and investigators in accordance with all applicable global laws and regulations (ie, per ICH Topic E6 (R2) Guidelines for Good Clinical Practice [GCP]).

Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSARs) according to local regulatory requirements and Sponsor policy and forwarded to investigators as necessary.

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

8.4.5 Pregnancy and Exposure During Breastfeeding

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

All reported pregnancies must be followed to the completion/termination of the pregnancy. Pregnancy outcomes of spontaneous abortion, missed abortion, benign hydatidiform mole, blighted ovum, fetal death, intrauterine death, miscarriage, and stillbirth must be reported as

serious events (Important Medical Events). If the pregnancy continues to term, the outcome (health of infant) must also be reported.

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

8.4.7 Events of Clinical Interest (ECIs)

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

Events of clinical interest for this study include:

- An overdose of Sponsor's product, as defined in Section 8.5, that is not associated with clinical symptoms or abnormal laboratory results.

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

*Note: These criteria are based upon available regulatory guidance documents. The purpose of the criteria is to specify a threshold of abnormal hepatic tests that must trigger 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-4621/JetPEI by ≥20% of the indicated dose or a pembrolizumab dose of ≥ 1000 mg (≥ 5 times the indicated dose). No specific information is available on the treatment of overdose of MK-4621/JetPEI or pembrolizumab. In the event of overdose, MK-4621/JetPEI or pembrolizumab should be discontinued and the participant should be

observed closely for signs of toxicity. Appropriate supportive treatment should be provided if clinically indicated.

8.6 Pharmacokinetics

To evaluate the immunogenicity (ADA) and exposure of pembrolizumab and exposure of MK-4621/JetPEI in this indication, sample collections for analysis of anti-drug antibodies (ADA) and PK are currently planned as shown in the SoA. Blood samples for PK and ADA collected may be stored only at this time. Further analysis may be performed if required. If ongoing PK and/or ADA sampling is deemed to be unnecessary by the Sponsor, it may be reduced or discontinued.

8.6.1 Blood Collection for Plasma MK-4621/JetPEI

Blood sample collection, processing, storage, and shipment instructions are provided in the Procedures Manual. Pharmacokinetic samples should be drawn according to the PK collection schedule for all participants (Section 1.3 - Schedule of Activities).

Time points may be changed or eliminated based on emerging PK data.

8.6.2 Blood Collection for Anti-pembrolizumab Antibodies

Sample collection, storage, and shipment instructions for serum samples are provided in the procedure manual. Anti-pembrolizumab antibody samples should be drawn according to the ADA collection schedule for all participants (Section 1.3 Schedule of Activities). Simultaneous PK sampling is required for interpretation of ADA analysis. Time points may be changed or eliminated based on emerging ADA data.

8.7 Pharmacodynamics

Blood, serum, and tumor biopsy sample collection, storage, and shipment instructions for pharmacodynamics analysis are provided in the Procedure Manual.

8.7.1 Blood for Pharmacodynamic Markers

The time points for pharmacodynamic sampling are described in Section 1.3 – Schedule of Activities.

8.7.2 Tumor Biopsy

8.7.2.1 Pretreatment Tumor Biopsy

All participants will be required to provide a sample biopsy of the tumor to be injected with MK-4621/JetPEI and a sample biopsy from a distant, discrete noninjected site at initial screening as the predose samples. This predose tumor biopsy at screening will be performed on both the tumor lesion that is intended for treatment with IT administration of MK-4621/JetPEI, as well as on the distant, discrete lesion that is not intended for

IT administration of MK-4621/JetPEI. Predose tumor biopsies (injected and noninjected tumors) should be collected on the same day as treatment, but if this is not possible, must be collected within 72 hours prior to treatment.

The samples will be obtained by either punch biopsy (according to sites routine procedure) for cutaneous lesions, ultrasound-guided biopsy for subcutaneous lesions, or image-guided biopsy, such as CT-guided biopsy, for additional lesions. Method of biopsy will be per guidance of the investigator as well as with discussion with the Sponsor. Biopsies obtained during this study will be submitted as formalin-fixed, paraffin-embedded samples. Instructions for tissue collection, processing, and shipment are provided in the Procedures Manual.

8.7.2.2 Posttreatment Tumor Biopsy

Post administration of MK-4621/JetPEI, all participants will be required to provide 2 biopsy samples of both the injected and noninjected tumors where predose biopsy samples are collected (see above in pretreatment tumor biopsy collection) on C3D1 (Week 7) in Arm 1 and Arm 2 and on C4D1 (Week 8) in Arm 3.

All participants will have the option to provide 2 additional biopsy samples of both the injected and uninjected tumors on C5D1 (Week 13) in Arm 1 and Arm 2, and on C6D1 (Week 16) in Arm 3, unless deemed medically unsafe by the investigator.

Sample collection and processing are the same as for pretreatment tumor biopsy (Section 8.7.2.1). Instructions for tissue collection, processing, and shipment are provided in the Procedures Manual.

8.8 Future Biomedical Research Sample Collection

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

Leftover samples listed in 8.10 – Biomarkers.

8.9 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 future biomedical research if the participant signs the future biomedical research consent. If the planned genetic analysis is not approved, but future biomedical research is approved and consent is given, this sample will be collected for the purpose of future biomedical research.

8.10 Biomarkers

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

- Blood for Genetic Analysis
- Serum for Cytokine/Chemokine Analyses and C-Reactive Protein (CRP)Blood for T cell repertoire (TCR)
- Blood for RNA analysis
- Pre-treatment Tumor Biopsy
- Post-treatment Biopsy

8.10.1 Planned Genetic Analysis Sample Collection

Sample collection, storage and shipment instructions for planned genetic analysis samples will be provided in the Procedures Manual. The timing of collection of samples is provided in Section 1.3 – Schedule of Activities.

8.10.2 Blood Collection for Antidrug Antibodies

Sample collection, storage and shipment instructions for serum samples will be provided in the procedure manual. Anti-pembrolizumab antibody samples should be drawn according to the ADA collection schedule for all participants (Section 1.3.1). Every effort should be taken to collect samples at 30 days after end of study treatment for ADA. Simultaneous PK sampling is required for interpretation of ADA analysis.

8.11 Visit Requirements

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

8.11.1 Screening

Approximately 28 days prior to treatment allocation/randomization, potential participants will be evaluated to determine that they fulfill the entry requirements as set forth in Section 5. Screening procedures may be repeated after consultation with the Sponsor.

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

- Laboratory tests are to be performed within 72 hours prior to the first dose of study treatment. An exception is hepatitis, HIV and thyroid serologies, which may be done up to 28 days prior to the first dose of study intervention.

- Evaluation of ECOG is to be performed within 7 days prior to the first dose of study treatment.

- For women of reproductive potential, a urine or serum pregnancy test will be performed within 72 hours prior to the first dose of study intervention. If urine pregnancy results cannot be confirmed as negative, a serum pregnancy test will be required (performed by the local study site laboratory). Additional pregnancy testing can be conducted if required by local regulations or if clinically indicated. Refer to Appendix 7 for country-specific requirements.

8.12 Treatment Period

Visit requirements are outlined in Section 1.3 – Schedule of Activities. Specific procedure-related details are provided above in Section 8 – Study Assessments and Procedures.

8.12.1 Discontinued Participants Continuing to be Monitored in the Study

The Discontinuation Visit should occur at the time study treatment is discontinued for any reason. If the Discontinuation Visit occurs 30 days from the last dose of study treatment, at the time of the mandatory Safety Follow up Visit, the Discontinuation Visit procedures and any additional Safety Follow-up procedures should be performed. Visit requirements are outlined in Section 1.3 - Schedule of Activities. Additional details regarding participant withdrawal and discontinuation are presented in Section 8 – Discontinuation/Withdrawal Criteria.

8.12.2 Poststudy

Participants will be required to return to clinic approximately 14 days after the last dose of study intervention for the poststudy visit. If the poststudy visit occurs less than 14 days after the last dose of study intervention, a subsequent follow-up telephone call should be made at 14 days post the last dose of study intervention to determine if any AEs have occurred since the poststudy clinic visit.

8.12.2.1 Safety Follow-up Visit

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

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

8.12.2.2 Imaging Follow-up Visit(s)

Participants who discontinue treatment for reasons other than confirmed 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 anti-cancer treatment, (3) death, (4) withdrawal of consent, or (5) study conclusion or early termination, whichever occurs first.

8.12.2.3 Survival Follow-up Visits

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

8.12.3 Survival Status

To ensure current and complete survival data is available at the time of database locks, updated survival status may be requested during the course of the study by the Sponsor. Upon Sponsor notification, all participants who do not/will not have a scheduled study visit or study contact during the Sponsor-defined time period will be contacted for their survival status (excluding participants who have a previously recorded death event in the collection tool).

9 STATISTICAL ANALYSIS PLAN

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

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

9.1 Statistical Analysis Plan Summary

This section contains a brief summary of the statistical analyses for this study. Full details are in the Statistical Analysis Plan (SAP), Section 9.2 through Section 9.9.

Study Design Overview	Phase 1/1b study of MK-4621/JetPEI monotherapy (Arm 1), MK-4621/JetPEI in combination with pembrolizumab (Arm 2), and MK-4621/JetPEI in combination with pembrolizumab via visceral IT injection (Arm 3) in participants with advanced/metastatic solid tumors. The study applies a modified TPI design for dose finding.
Treatment Assignment	After initial enrollment (screening), participants will be allocated centrally through IRT by nonrandom assignment to single agent MK-4621/JetPEI (Arm 1), MK-4621/JetPEI via cutaneous IT injection coadministered with pembrolizumab (Arm 2), and MK-4621/JetPEI via visceral IT injection coadministered with pembrolizumab Arm 3 based on eligibility for open dose levels.
Analysis Populations	Safety (Primary): All-Participants-as-Treated (APaT) and DLT-evaluable (DLTe) PK (Secondary): Per-Protocol (PP) Efficacy (Secondary): Full Analysis Set (FAS)
Primary Endpoint(s)	• Dose-limiting toxicity (DLT) • Adverse event (AE) • Discontinuing study treatment due to an AE
Secondary Endpoints	PK parameters of MK-4621/JetPEI monotherapy and MK-4621/JetPEI in combination with pembrolizumab; PK parameters of pembrolizumab in combination with MK-4621/JetPEI; ORR based on RECIST 1.1 and iRECIST.
Statistical Methods for Efficacy/ Pharmacokinetic Analyses	ORR will be estimated using an exact method based on the binomial distribution (Clopper-Pearson interval). Exploratory efficacy analyses (eg, PFS and OS) are documented in the sSAP. PK parameters of study medicines will be summarized by planned visit and time for each dose separately.
Statistical Methods for Safety Analyses	Summary statistics will be provided for the safety endpoints as appropriate. The pool-adjacent-violators-algorithm [Ji Y, Li Y, Bekele BN 2007] will be used to estimate the DLT rates across doses. The estimate of the DLT rate among participants treated at MTD/MAD of MK-4621/JetPEI and the 80% Bayesian credible intervals for the estimate will be provided for each treatment arm.

Interim Analyses	Interim analyses may be conducted to enable future study planning at the Sponsor's discretion and data will be examined on a continuous basis to allow for dose-finding decisions.
Multiplicity	No multiplicity adjustment is planned in this Phase 1/1b study.
Sample Size and Power	The overall sample size for this study depends on the observed DLT profiles of MK-4621/JetPEI monotherapy (Arm 1) and MK-4621/JetPEI in combination with pembrolizumab (Arms 2 and 3). A target sample size of 72 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 treatment assignment after each participant is enrolled and treatment is assigned. Participants will be allocated by nonrandom assignment.

9.3 Hypotheses/Estimation

Objectives of the study are outlined in Section 3.

9.4 Analysis Endpoints

9.4.1 Efficacy/Pharmacokinetics Endpoints

Preliminary efficacy will be evaluated using ORR and PFS, assessed by the investigator based on the RECIST 1.1 or iRECIST, and OS. ORR is a secondary endpoint in this study. PFS and OS are exploratory endpoints. Details of the analysis plan will be documented in the sSAP. A description of efficacy measures is provided in Section 8.2.

ORR is defined as the proportion of participants who have achieved confirmed CR or PR. PFS is defined as the time from the first dose of study treatment to the first documented disease progression or death due to any cause, whichever occurs first. OS is defined as the time from the first dose of study treatment to death due to any cause. Participants who do not die will be censored on the date of the last study assessment or contact.

Pharmacokinetic endpoints include PK exposure of MK-4621/JetPEI and pembrolizumab, as well as derived PK parameters.

The exploratory evaluation of biomarkers to be measured in this study is described in Section 8.10.

9.4.2 Safety Endpoints

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

A description of safety measures is provided in Section 8.3 and Section 8.4.

9.5 Analysis Populations

9.5.1 Safety Analysis Populations

The All-Participants-as-Treated (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 treatment. In case of treatment administration errors, participants will be analyzed according to the treatment they actually received.

The DLT-evaluable (DLTe) population includes APaT participants who meet the criteria for DLT evaluability (eg, finished the DLT evaluation period without a DLT or experienced a DLT in the DLT evaluation period). See Section 6.6.2 for details. Safety data from crossover participants will also be presented separately.

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

9.5.2 Pharmacokinetic Analysis Populations

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

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 demonstrated measurable disease by the investigator's assessment, and who were administered at least 1 dose of study medicine. Efficacy data from crossover participants 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

ORR will be estimated using an exact method based on the binomial distribution (Clopper-Pearson interval). The statistical methods for analyses of PFS and OS will be documented in the sSAP. All efficacy analysis will be done by treatment arm and dose level of MK-4621/JetPEI for the dose-escalation/dose-confirmation part and by tumor type for the expansion cohorts.

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.

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

Dose-limiting toxicities will be listed and summarized by dose level of MK-4621/JetPEI and treatment arm. The pool adjacent violators-algorithm [Ji Y, Li Y, Bekele BN 2007], which forces the DLT rate estimates to be nondecreasing with increasing dose levels and pools adjacent violators for weighted estimates by sample size, will be used to estimate the DLT rates across doses in each treatment arm. The estimate of the DLT rate among participants treated at the MTD/MAD and the 80% Bayesian credible interval based on a prior distribution of Beta (1,1) for the estimate will be provided for each treatment arm.

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

Concentrations of study medicines will be summarized by planned visit and time for each dose separately

9.7 Interim Analyses

Interim analyses may be conducted to enable future study planning at the Sponsor's discretion and 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.

9.9 Sample Size and Power Calculations

The actual sample size for Arm 1, Arm 2, and Arm3 of study is dependent on the number of dose levels tested and emerging safety data following mTPI design (refer to Section 4.3.1.4). The mTPI phase will have up to 3 to 6 participants in the first cohort at each dose level, and based on the occurrence of DLTs, up to 14 participants may be enrolled per dose level. Assuming all dose levels are tolerable and 4 dose levels are to be tested in Arm 2 and Arm 3, the overall sample size for the dose-escalation/dose-confirmation part of this Phase 1/1b study is expected to be up to approximately 72 participants (approximately 8 participants in Arm 1, 32 participants on Arm 2, and 32 participants in Arm 3, assuming 6 participants at each dose level and 8 more participants at the MTD/MAD). Enrollment of additional participants in the expansion cohorts will be specified in a future protocol amendment.

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 treatment will be collected during the study. Any deviation from protocol-directed administration will be reported.

9.12 Extent of Exposure

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

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

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

10.1.1 Code of Conduct for Clinical Trials

Merck Sharp and Dohme Corp., a subsidiary of Merck & Co., Inc. (MSD)

Code of Conduct for Interventional Clinical Trials

I. Introduction

A. Purpose

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

B. Scope

Highest ethical and scientific standards shall be endorsed for all clinical interventional investigations sponsored by MSD irrespective of the party (parties) employed for their execution (eg, 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 (ie, participant population, duration, statistical power) must be adequate to address the specific purpose of the trial. Participants must meet protocol entry criteria to be enrolled in the trial.

2. Site Selection

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

3. Site Monitoring/Scientific Integrity

Investigative trial sites are monitored to assess compliance with the trial protocol and general principles of Good Clinical Practice (GCP). MSD reviews clinical data for accuracy, completeness, and consistency. Data are verified versus source documentation according to standard operating procedures. Per MSD policies and procedures, if fraud, scientific/research misconduct, or serious GCP-noncompliance is suspected, the issues

are investigated. When necessary, the clinical site will be closed, the responsible regulatory authorities and ethics review committees notified.

B. Publication and Authorship

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

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

III. Participant Protection

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

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

B. Safety

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

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

C. Confidentiality

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

D. Genomic Research

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

IV. Financial Considerations

A. Payments to Investigators

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

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

B. Clinical Research Funding

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

C. Funding for Travel and Other Requests

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

10.1.3 Data Protection

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

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

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

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 report form data. By signing the consent form, the participant agrees to this process. If study documents will be photocopied during the process of verifying worksheet/CRF information, the participant will be identified by unique code only; full names/initials will be masked prior to transmission to the Sponsor.

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

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

Not applicable.

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 International Committee of Medical Journal Editors authorship requirements.

10.1.6 Compliance with Study Registration and Results Posting Requirements

Under the terms of the Food and Drug Administration Amendments Act (FDAAA) of 2007 and the European Medicines Agency (EMA) clinical trial Directive 2001/20/EC, the Sponsor of the study is solely responsible for determining whether the study and its results are subject to the requirements for submission to http://www.clinicaltrials.gov, www.clinicaltrialsregister.eu or other local registries. MSD, as Sponsor of this study, will review this protocol and submit the information necessary to fulfill these requirements. MSD entries are not limited to FDAAA or the EMA clinical trial directive mandated trials. Information posted will allow participants to identify potentially appropriate studies for their disease conditions and pursue participation by calling a central contact number for further information on appropriate study locations and 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, International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use GCP: Consolidated Guideline and other generally accepted standards of good clinical practice); and all applicable federal, state and local laws, rules and regulations relating to the conduct of the clinical 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 Studies.

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 signed ICF, pertaining to the conduct of this study must be retained by the investigator for 15 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

10.1.9 Source Documents

Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.

Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

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 will promptly notify that study site's IRB/IEC.

10.2 Appendix 2: Clinical Laboratory Tests

- The tests detailed in Table 11 will be performed by the local laboratory. Laboratory samples that cannot be processed locally may be sent to the central 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 (serum or urine)[a]
Hemoglobin	Alkaline phosphatase	Glucose	PT/INR
Platelet count	Alanine aminotransferase	Protein	aPTT or PTT
WBC (total and differential)[d]	Aspartate aminotransferase	Specific gravity	Total T3 (or Free T3 [FT3]), Total T4 (or Free T4[FT4]), and TSH[b,c]
RBC	Bicarbonate[d]	Microscopic exam, if abnormal results are noted	Anti-HCV
Absolute lymphocyte count[e]	Calcium		HCV viral load[c]
	Chloride		HCV genotype[c]
Absolute neutrophil count[e]	Creatinine		anti-HBs[c]
	Glucose		
	Phosphorus		HBsAg
	Potassium		Anti-HBc (total and IgM)[c]
	Sodium		HBeAg[c]
	Total bilirubin		anti-HBe[c]
	Direct bilirubin		HBV viral load[c]
	Total protein		Anti-HDV [c]
	Amylase		HIV
	Lipase		
	GLDH[c]		
	GGT[c]		
	Blood urea nitrogen (BUN)/ Urea[f]		

a. Perform on women of childbearing potential only 72 hours prior to Day 1 of Cycle 1. Pregnancy tests must be repeated prior to every cycle if required or as specified per local regulatory guidance.
b. Total T3 and T4 are preferred; if not available, free T3 and T4 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. If bicarbonate/CO_2 is not done as part of standard of care in your region, then these tests do not need to be performed.
e. Report % or absolute results per standard of practice. Report the results in the same manner throughout the study.
f. Blood urea nitrogen is preferred; if not available urea may be tested

BUN=blood urea nitrogen; GGT=gamma glutamyl transferase; GLDH=glutamate dehydrogenase; HIV=human immunodeficiency virus;

The investigator (or medically qualified designee) 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 Definition of AE

AE definition

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

- NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a study intervention.

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

Events meeting the AE definition

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

- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.

- New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study.

- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.

- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication.

- For all reports of overdose (whether accidental or intentional) with an associated AE, the AE term should reflect the clinical symptoms or abnormal test result. An overdose without any associated clinical symptoms or abnormal laboratory results is reported using the terminology "accidental or intentional overdose without adverse effect."

- Any new cancer (that is not a condition of the study). Progression of the cancer under study is not a reportable event. Refer to Section 8.4.6 for additional details.

Events NOT meeting the AE definition

- Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.
- Surgery planned prior to informed consent to treat a pre-existing condition that has not worsened.
- Refer to Section 8.4.7 for protocol-specific exceptions.

10.3.2 Definition of SAE

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

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

a. **Results in death**

b. **Is life-threatening**

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

c. **Requires inpatient hospitalization or prolongation of existing hospitalization**

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

10.3.3 Additional Events Reported in the Same Manner as SAE

Additional events that require reporting in the same manner as SAE

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

- Is a new cancer (that is not a condition of the study)

- Is associated with an overdose

10.3.4 Recording AE and SAE

AE and SAE recording

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory, and diagnostics reports) related to the event.

- The investigator will record all relevant AE/SAE information on the AE CRFs/worksheets at each examination.

- It is not acceptable for the investigator to send photocopies of the participant's medical records to the Sponsor in lieu of completion of the AE CRF page.

- There may be instances when copies of medical records for certain cases are requested by the Sponsor. In this case, all participant identifiers, with the exception of the participant number, will be blinded on the copies of the medical records before submission to the Sponsor.

- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of intensity

- An event is defined as "serious" when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, not when it is rated as severe.

The investigator will make an assessment of intensity for each AE and SAE (and other reportable safety event) according to the NCI Common Terminology for Adverse Events (CTCAE), version 4. Any AE that changes CTCAE grade over the course of a given episode will have each change of grade recorded on the AE CRFs /worksheets.

Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.

Grade 2: Moderate; minimal, local, or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living (ADL).

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

Grade 4: Life threatening consequences; urgent intervention indicated.

Grade 5: Death related to AE.

Assessment of causality

- Did the Sponsor's product cause the AE?

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

likelihood of a relationship between the test product and the AE based upon the available information.

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

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

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

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

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

  If yes, did the AE resolve or improve?

  If yes, this is a positive dechallenge.

  If no, this is a negative dechallenge.

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

  Rechallenge: Was the participant re-exposed to the Sponsor's product in this study?

  If yes, did the AE recur or worsen?

  If yes, this is a positive rechallenge.

  If no, this is a negative rechallenge.

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

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

- Consistency with study intervention profile: Is the clinical/pathological presentation of the AE consistent with previous knowledge regarding the Sponsor's product or drug class pharmacology or toxicology?

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

    - Use the following scale of criteria as guidance (not all criteria must be present to be indicative of a Sponsor's product relationship).

        Yes, there is a reasonable possibility of Sponsor's product relationship:

            There is evidence of exposure to the Sponsor's product. The temporal sequence of the AE onset relative to the administration of the Sponsor's product is reasonable. The AE is more likely explained by the Sponsor's product than by another cause.

        No, there is not a reasonable possibility of Sponsor's product relationship:

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

- For each AE/SAE, the investigator must document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.

- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to the Sponsor. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the Sponsor.

- The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.

- The causality assessment is 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.

10.3.5 Reporting of AE, SAE, and Other Reportable Safety Events to the Sponsor

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

- The primary mechanism for reporting to the Sponsor will be the electronic data collection (EDC) tool.

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

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

        - Reference Section 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 Incidents: Definition and Procedures for Recording, Evaluating, Follow-up, and Reporting

Not applicable.

10.5 Appendix 5: Contraceptive Guidance and Pregnancy Testing

10.5.1 Definitions

Women of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile.

Women in the following categories are not considered WOCBP:

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

Note: Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.

- Postmenopausal female
  - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
- A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormone replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, confirmation with 2 FSH measurements in the postmenopausal range is required.
  - Females on HRT and whose menopausal status is in doubt will be required to use 1 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

Male Participants

Male participants with female partners of childbearing potential are eligible to participate if they agree to 1 of the following during the protocol defined time frame in Section 5.1:

- Be abstinent from penile-vaginal intercourse as their usual and preferred lifestyle (abstinent on a long term and persistent basis) and agree to remain abstinent.
- Use a male condom plus partner use of an additional contraceptive method when having penile-vaginal intercourse with a WOCBP who is not currently pregnant.

  The following are not acceptable methods of contraception:

  - Periodic abstinence (calendar, symptothermal, postovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhoea method (LAM).
  - Male condom with cap, diaphragm, or sponge with spermicide.
  - Male and female condom cannot be used together.

  Note: Men with a pregnant or breastfeeding partner must agree to remain abstinent from penile-vaginal intercourse or use a male condom during each episode of penile penetration.

Female Participants

Female participants of childbearing potential are eligible to participate if they agree to consistent and correct use of a highly effective method of contraception as described in Table 12 during the protocol-defined time frame in Section 5.1.

Female Participants

Female participants of childbearing potential are eligible to participate if they agree to use a highly effective method of contraception that has a low user dependency consistently and correctly as described in Table 12 during the protocol-defined time frame in Section 5.1.

Table 12 Highly Effective Contraceptive Methods That Have Low User Dependency

Highly Effective Methods That Have Low User Dependency *Failure rate of <1% per year when used consistently and correctly.*
• Progestogen-only contraceptive implant [a, b] • Intrauterine hormone-releasing system (IUS) [b] • Intrauterine device (IUD) • Bilateral tubal occlusion
• Vasectomized partner A vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.
• Sexual abstinence Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatment. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.
Notes: Use should be consistent with local regulations regarding the use of contraceptive methods for participants of clinical studies. a) If locally required, in accordance with Clinical Trial Facilitation Group (CTFG) guidelines, acceptable contraceptive implants are limited to those which inhibit ovulation. b) If hormonal contraception efficacy is potentially decreased due to interaction with study treatment, condoms must be used in addition to the hormonal contraception during the treatment period and for at least [120 days, corresponding to time needed to eliminate study treatment plus 30 days for study treatments with genotoxic potential] after the last dose of study intervention.

If locally required, in accordance with Clinical Trial Facilitation Group (CTFG) guidelines, acceptable hormonal contraceptives are limited to those which inhibit ovulation.

10.5.3 Pregnancy Testing

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

Following initiation of treatment additional pregnancy testing will be performed monthly during the treatment period, if required locally, and at 90 days after the last dose of study intervention, as required locally.

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

10.6 Appendix 6: Collection and Management of Specimens for Future Biomedical Research

- Definitions

1. 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.

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

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

4. DNA: Deoxyribonucleic acid.

5. RNA: Ribonucleic acid.

- **Scope of Future Biomedical Research**

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

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

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

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

- **Summary of Procedures for Future Biomedical Research**.

1. Participants for Enrollment

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

2. 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.

3. 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.

4. 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.

- **Confidential Participant Information for Future Biomedical Research**

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

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

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

- **Biorepository Specimen Usage**

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

- **Withdrawal From Future Biomedical Research**

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

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

- **Retention of Specimens**

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

  Specimens from the study site will be shipped to a central laboratory and then shipped to the Sponsor-designated biorepository. If a central laboratory is not utilized in a particular study, the study site will ship directly to the Sponsor-designated biorepository. The

specimens will be stored under strict supervision in a limited access facility which operates to assure the integrity of the specimens. Specimens will be destroyed according to Sponsor policies and procedures and this destruction will be documented in the biorepository database.

- **Data Security**

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

- **Reporting of Future Biomedical Research Data to Participants**

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

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

- **Future Biomedical Research Study Population**

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

- **Risks Versus Benefits of Future Biomedical Research**

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

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

- **Questions**

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

- **References**

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

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

  - 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/

  - 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

Germany

Section 1.3.1 Schedule of Activities for Initial Screening (Arms 1, 2, and 3) and Crossover Screening (Arm 1 to Arm 2)

Assessment	Note
HIV/Hepatitis B and C Screen	Include HCV antibody or HCV RNA (qualitative) and HBsAg. HIV, and Hepatitis B and C by history are acceptable for exclusion; testing for HIV, Hepatitis B or Hepatitis C is required at screening.
Pregnancy test for WOCBP only (urine or serum β-hCG)	Perform within 72 hours prior to C1D1. Urine pregnancy test to be performed as indicated; if test is positive or cannot be confirmed as negative, a serum pregnancy test is required. Monthly pregnancy testing should be conducted as per local regulations, or as clinically indicated.

Section 1.3.2 Schedule of Activities for the Treatment Period

Assessment	Note
Pregnancy test for WOCBP only (urine or serum β-hCG)	Perform within 72 hours prior to C1D1. Urine pregnancy test to be performed as indicated; if test is positive or cannot be confirmed as negative, a serum pregnancy test is required. Monthly pregnancy testing should be conducted as per local regulations, or as clinically indicated.

Section 5.2 Exclusion Criteria

10. Participants with known human immunodeficiency virus (HIV) and/or Hepatitis B or C infections, or known to be positive for Hepatitis B surface antigen (HBsAg)/Hepatitis B virus (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. Testing for HIV, Hepatitis B or Hepatitis C is required at screening.

Section 8.7.2.1 Pretreatment Biopsy

Only ultrasound-guided biopsies will be taken.

Section 8.7.2.2 Posttreatment Biopsy

Only ultrasound-guided biopsies will be taken.

Section 8.11.1 Screening

For women of reproductive potential, a urine or serum pregnancy test will be performed within 72 hours prior to the first dose of study intervention. If urine pregnancy results cannot be confirmed as negative, a serum pregnancy test will be required (performed by the local study site laboratory). Monthly pregnancy testing should be conducted as per local regulations, or as clinically indicated.

Appendix 2 Clinical Laboratory Tests

Other Screening Tests: Serology (HIV RNA, hepatitis B surface antigen [HBsAg], and hepatitis C virus antibody).

Appendix 5 Contraceptive Guidance and Pregnancy Testing

Pregnancy Testing

WOCBP should only be included after a negative highly sensitive urine or serum pregnancy test. Monthly pregnancy testing should be conducted as per local regulations.

United Kingdom

Sections 1.3.2.1, 1.3.2.2, and 1.3.2.3 - Schedule of Activities for the Treatment Period

Assessment	**Note**
Pregnancy test for WOCBP only (urine or serum β-hCG)	Perform within 72 hours prior to C1D1. Urine pregnancy test to be performed as indicated; if test is positive or cannot be confirmed as negative, a serum pregnancy test is required. Thereafter, pregnancy testing should be performed approximately monthly.

Section 6.5.2 – Prohibited Concomitant Medications

- Live vaccines within 30 days prior to the first dose of study treatment while participating in the study and for 3 months after the end of study treatment. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, varicella/zoster, yellow fever, rabies, Bacillus Calmette–Guérin (BCG), and typhoid vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed; however, intranasal influenza vaccines (eg, FluMist®) are live attenuated vaccines and are not allowed.

Section 8.3.4.2 – Pregnancy Testing

All women who are being considered for participation in the study, and who are not surgically sterilized or postmenopausal, must be tested for pregnancy within 72 hours prior to Cycle 1 of study treatment. If a urine test is positive or not evaluable, a serum test will be required. Participants must be excluded/discontinued from the study in the event of a positive or borderline-positive test result. During study treatment, pregnancy testing should be repeated approximately monthly and then again 30 days after the last study dose of study treatment.

Section 8.11.1 Screening

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

Appendix 2 Clinical Laboratory Tests

Footnote to Table 11 reads:

a. Perform on women of childbearing potential only 72 hours prior to Day 1 of Cycle 1. Pregnancy tests must be repeated approximately monthly.

Appendix 5 Contraceptive Guidance and Pregnancy Testing

Pregnancy Testing

Following initiation of treatment additional pregnancy testing will be performed approximately monthly during study treatment period, and at 30 days after the last dose of study intervention, as required locally.

10.8 Appendix 8: Abbreviations

Abbreviation	Expanded Term
AE	adverse event
aPTT	activated partial thromboplastin time
ADA	anti-drug antibodies
ALT	alanine transaminase
ANC	absolute neutrophil count
APaT	All-Participants-as-Treated
AST	aspartate transaminase
AUC	area under the curve
BCG	Bacillus Calmette–Guérin
CD28	cluster of differentiation 28
CD3ζ	CD3 zeta
C_{max}	maximum concentration
C_{min}	minimum concentration
CNS	central nervous system
CONSORT	Consolidated Standards of Reporting Trials
CR	complete response
CRF	case report form
CRP	C-reactive protein
CRU	clinical research unit
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
DL	dose level
DL1	starting dose
DILI	drug-induced liver injury
DLT	dose-limiting toxicity
DLTe	DLT evaluable
DNA	deoxyribonucleic acid
ECG	electrocardiogram
ECI	event of clinical interest
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EDC	electronic data collection
ELISA	enzyme-linked immunoassay
EMA	European Medicines Agency
FAS	full analysis set
FBR	Future Biomedical Research
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GEP	gene expression profile
GFR	glomerular filtration rate
GGT	gamma glutamyl transferase
GLDH	glutamate dehydrogenase
HBsAG	hepatitis B surface antigen
HBV	hepatitis B virus

Abbreviation	Expanded Term
HED	human equivalent dose
HIV	human immunodeficiency virus
HRT	hormone replacement therapy
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Conference on Harmonization
ICI	immune checkpoint inhibitors
iCR	immune complete response
IEC	Independent Ethics Committee
IFNα	interferon α
Ig	immunoglobulin
IHC	immunohistochemistry
INR	international normalized ratio
iPR	immune partial response
irAE	immune‑related adverse event
iRECIST	immune-related RECIST
IRR	infusion-related reaction
IRB	Institutional Review Board
IRT	interactive response technology
iSD	immune stable disease
IT	intratumoral
IUD	intrauterine device
iUPD	immune unconfirmed progressive disease
IUS	intrauterine hormone-releasing system
IV	intravenous
IVD	in vitro diagnostic (device)
LDH	lactate dehydrogenase
mAb	monoclonal antibody
MAD	maximum administered dose
ML	mutational load
MRI	magnetic resonance imaging
mRNA	messenger RNA
MSI	microsatellite instability
mTPI	modified Toxicity Probability Interval
MTD	maximum tolerated dose
NCI	National Cancer Institute
NK	natural killer
NOAEL	no observed adverse effect level
NSCLC	non-small cell lung cancer
ORR	objective response rate
OS	overall survival
OTC	over-the-counter
PBPK	physiologically-based Pharmacokinetics
PD	progressive disease
PD 1	programmed cell death 1
PD-L1	programmed cell death ligand 1
PD-L2	programmed cell death ligand 2
PET	positron emission tomography
PFS	progression free survival
PK	pharmacokinetic
PKCθ	protein kinase C-theta

Abbreviation	Expanded Term
PP	per-protocol
PR	partial response
PT	prothrombin time
PTT	partial thromboplastin time
q1w	every week
q2w	every 2 weeks
q3w	every 3 weeks
RECIST	Response Evaluation Criteria in Solid Tumors
RIG-I	Retinoic acid Inducible Gene I
RNA	ribonucleic acid
SAE	serious adverse event
SAP	Statistical Analysis Plan
SCCHN	squamous cell carcinoma of head and neck
SIM	Site Imaging Manual
SoA	Schedule of Activities
SOD	sum of the diameters
sSAP	supplemental Statistical Analysis Plan
SUSAR	suspected unexpected serious adverse reaction
TCR	T cell repertoire
T1DM	Type 1 diabetes mellitis
TMDD	Target-mediated drug disposition
TSH	thyroid-stimulating hormone
ULN	upper limit of normal
WOCBP	woman/women of childbearing potential
ZAP70	zeta-chain-associated protein kinase

11 REFERENCES

[Disis, M. L. 2010]	Disis ML. Immune regulation of cancer. J Clin Oncol 2010;28(29):4531-8.	[058SQL]
[Dudley, M. E., et al 2005]	Dudley ME, Wunderlich JR, Yang JC, Sherry RM, Topalian SL, Restifo NP, et al. Adoptive cell transfer therapy following non-myeloablative but lymphodepleting chemotherapy for the treatment of patients with refractory metastatic melanoma. J Clin Oncol 2005;23(10):2346-57.	[00VMPR]
[Hunder, N. N., et al 2008]	Hunder NN, Wallen H, Cao J, Hendricks DW, Reilly JZ, Rodmyre R, et al. Treatment of metastatic melanoma with autologous CD4+ T cells against NY-ESO-1. N Engl J Med 2008;358(25):2698-703.	[00VMPX]
[Greenwald, R. J., et al 2005]	Greenwald RJ, Freeman GJ, Sharpe AH. The B7 family revisited. Annu Rev Immunol 2005;23:515-48.	[00VMQL]
[Okazaki, T., et al 2001]	Okazaki T, Maeda A, Nishimura H, Kurosaki T, Honjo T. PD-1 immunoreceptor inhibits B cell receptor-mediated signaling by recruiting src homology 2-domain-containing tyrosine phosphatase 2 to phosphotyrosine. Proc Natl Acad Sci U S A 2001;98(24):13866-71.	[00VMQ6]
[Zhang, X., et al 2004]	Zhang X, Schwartz J-CD, Guo X, Bhatia S, Cao E, Chen L, et al. Structural and functional analysis of the costimulatory receptor programmed death-1. Immunity 2004;20:337-47.	[00VMQJ]
[Chemnitz, J. M., et al 2004]	Chemnitz JM, Parry RV, Nichols KE, June CH, Riley JL. SHP-1 and SHP-2 associate with immunoreceptor tyrosine-based switch motif of programmed death 1 upon primary human T cell stimulation, but only receptor ligation prevents T cell activation. J Immunol 2004;173:945-54.	[00VMPN]
[Sheppard, K-A, et al 2004]	Sheppard K-A, Fitz LJ, Lee JM, Benander C, George JA, Wooters J, et al. PD-1 inhibits T-cell receptor induced phosphorylation of the ZAP70/CD3zeta signalosome and downstream signaling to PKCtheta. FEBS Lett. 2004;574:37-41.	[00VMQC]

[Riley, J. L. 2009]	Riley JL. PD-1 signaling in primary T cells. Immunol Rev 2009;229:114-25.	[00VMQ9]
[Parry, R. V., et al 2005]	Parry RV, Chemnitz JM, Frauwirth KA, Lanfranco AR, Braunstein I, Kobayashi SV, et al. CTLA-4 and PD-1 receptors inhibit T-cell activation by distinct mechanisms. Mol Cell Biol 2005;25(21):9543-53.	[00VMQ7]
[Francisco, L. M., et al 2010]	Francisco LM, Sage PT, Sharpe AH. The PD-1 pathway in tolerance and autoimmunity. Immunol Rev 2010;236:219-42.	[058SQP]
[Wolchok, J. D., et al 2009]	Wolchok JD, Hoos A, O'Day S, Weber JS, Hamid O, LebbéC, et al. Guidelines for the evaluation of immune therapy activity in solid tumors: immune-related response criteria. Clin Cancer Res 2009;15(23):7412-20.	[00VMNZ]
[Hodi, F. S., et al 2014]	Hodi FS, Ribas A, Daud A, Hamid O, Robert C, Kefford R, et al. Patterns of response in patients with advanced melanoma treated with Pembrolizumab (MK-3475) and evaluation of immune-related response criteria (irRC). J Immunother Cancer. 2014;2(Suppl 3):P103.	[0465RW]
[Seymour, L., et al 2017]	Seymour L, Bogaerts J, Perrone A, Ford R, Schwartz LH, Mandrekar S, et al. iRECIST: guidelines for response criteria for use in trials testing immunotherapeutics. Lancet Oncol. 2017 Mar;18(3):e143-52.	[04P9RV]
[Ji Y, Li Y, Bekele BN 2007]	Ji Y, Li Y, Bekele BN. Dose-finding in phase l clinical trials based on toxicity probability intervals. Clin Trials 2007;4:235-44.	[03TFYL]
[Ji, Y. 2013]	Ji Y, Wang S-J. Modified toxicity probability interval design: a safer and more reliable method than the 3 + 3 design for practical phase I trials. J Clin Oncol 2013;31:1-12.	[03FL3C]
[Ji, Y., et al 2010]	Ji Y, Liu P, Li Y, Bekele BN. A modified toxicity probability interval method for dose-finding trials. Clin Trials. 2010;7:653-63.	[04WC92]