Official Protocol Title:	A Phase 1, Open-Label, Multicenter Study to Assess the Safety and Tolerability of mRNA-5671/V941 as a Monotherapy and in Combination with Pembrolizumab in Participants with KRAS Mutant Advanced or Metastatic Non-Small Cell Lung Cancer, Colorectal Cancer or Pancreatic Adenocarcinoma
NCT number:	NCT03948763
Document Date:	24 March 2022

Title Page

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Protocol Title: A Phase 1, Open-Label, Multicenter Study to Assess the Safety and Tolerability of mRNA-5671/V941 as a Monotherapy and in Combination with Pembrolizumab in Participants with KRAS Mutant Advanced or Metastatic Non-Small Cell Lung Cancer, Colorectal Cancer or Pancreatic Adenocarcinoma

Protocol Number: 001-08

Compound Number: V941

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):

IND	17861

Approval Date: 24 March 2022

Sponsor Signatory

Typed Name:
Title:

Date

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

Investigator Signatory

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

Typed Name:
Title:

Date

DOCUMENT HISTORY

Document	Date of Issue	Overall Rationale
Amendment 8	24-MAR-2022	To transition ongoing study participants, who are on active treatment with pembrolizumab in the post-treatment follow-up phase, into a pembrolizumab extension study before the close out of this study.
Amendment 7	24-JUN-2021	To update the dose modification and toxicity management guidelines for irAEs.
Amendment 6	23-JAN-2020	Defined the KRAS and HLA testing criteria, reduced the number of PBMC assessments, and modified the sample size.
Amendment 5	24-JUL-2019	Added leukaphereses in Part 2; clarified KRAS testing approach, buccal swab sampling, tumor biopsies, and additional consent after progression.
Amendment 4	22-MAR-2019	Updated protocol for the new formulation (removed STING) and the corresponding dose level changes
Amendment 3	27-APR-2018	Changes to the timing of pre-screening and screening procedures and other administrative changes.
Amendment 2	19-MAR-2018	Generated by Merck
Amendment 1	23-JAN-2018	Generated by Moderna; addressed regulatory authority feedback.
Original Protocol	08-DEC-2017	Original protocol; Moderna.

PROTOCOL AMENDMENT SUMMARY OF CHANGES

Amendment: 001-08

Overall Rationale for the Amendments:

To transition ongoing study participants, who are on active treatment with pembrolizumab in the post-treatment follow-up phase, into a pembrolizumab extension study before the close out of this study.

Summary of Changes Table:

Section # and Name	Description of Change	Brief Rationale
1.1 Synopsis 1.2 Schema 4.1 Overall Design 4.4 Beginning and End of Study Definition 6.3.1 Intervention Assignment 6.7 Intervention After the End of the Study 7.2 Participant Withdrawal From the Study 8.11.4 End of Treatment/Discontinuation Visit 8.11.5.3 Survival Follow-up Visits	Added language to give participants in the post-treatment phase an option to discontinue this study and transition into a pembrolizumab extension study. Provided details regarding randomization number (Section 6.3.1)	To allow for the participants to rollover into a pembrolizumab extension study before the close out of this study. Also, to clarify that participants in survival follow-up phase will not be rolled-over.

Section # and Name	Description of Change	Brief Rationale
1.3 Schedule of Activities (SoA)	Clarification to period of treatment end	To identify possibility of discontinuation and activities associated with discontinuation.
1.1 Synopsis 6.1 Study Intervention(s) Administered	Updated the "Use" column in Intervention Groups table and Study Interventions table with "Test Product" or Comparator" for all the Arms. Updated the "Arm Type" column in Study Interventions table with "Experimental" or "Active Comparator" for all the Arms, and also added a footnote pertaining to IMP and NIMP/AxMP.	To align with the European Union Clinical Trial Regulation requirements.
1.1 Synopsis 5.1 Inclusion Criteria 8.1.1 Informed Consent 8.1.1.1 General Informed Consent 8.4.1 Time Period and Frequency for Collecting AE, SAE, and Other Reportable Safety Event Information 10.1.7 Data Quality Assurance	Updated the 'signed informed consent' to 'documented informed consent'	Legal language update to address new study needs as a result of COVID-19.
4.2.1.6 Planned Exploratory Biomarker Research	Added an "or" to the text "tumor and/*or* blood RNA Analyses."	To ensure exploratory biomarker section allows flexibility.

Section # and Name	Description of Change	Brief Rationale
5.2 Exclusion Criteria 6.5.2 Prohibited Concomitant Medications	Edited to include reference to COVID-19.	Provide additional information regarding COVID-19 and other vaccines.
8.1.9.1 Withdrawal From Future Biomedical Research 10.6 Appendix 6: Collection and Management of Specimens for Future Biomedical Research	Sponsor mailbox address corrected to clinical.specimen.management@MSD.com and minor updates made to the text	Correction to the Sponsor mailbox address per the latest company norms and text changes made for clarity and better readability
10.6 Appendix 6: Collection and Management of Specimens for Future Biomedical Research	Added superscripted footnotes 3 and 4 corresponding to existing “13. References” at the end of the appendix.	Appendix 6 contains references (at the bottom of the appendix, “13. References” numbered 1-4). These references have corresponding footnotes in the text/headings.
8.3.5 Pregnancy Test	Renumbered (previously Section 8.3.4.2)	Created new section heading.
8.4.1 Time Period and Frequency for Collecting AE, SAE, and Other Reportable Safety Event Information	Provided an exception for positive pregnancy test at screening.	Clarification of reportable pregnancy.
Document History	Updated document column	To align with protocol formatting standards.
Global	Minor administrative and formatting changes were made.	For clarity and better readability.

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1 PROTOCOL SUMMARY

1.1 Synopsis

Protocol Title: A Phase 1, Open-Label, Multicenter Study to Assess the Safety and Tolerability of mRNA-5671/V941 as a Monotherapy and in Combination with Pembrolizumab in Participants with KRAS Mutant Advanced or Metastatic Non-Small Cell Lung Cancer, Colorectal Cancer or Pancreatic Adenocarcinoma

Short Title: A Phase 1 Study of mRNA-5671/V941 as Monotherapy and in Combination with Pembrolizumab

Hypotheses, Objectives, and Endpoints:

There will be no hypothesis testing in this study.

The objectives and endpoints apply to the study population of male and female participants at least 18 years of age with advanced/metastatic solid tumors who have received, or been intolerant to, or been ineligible for, all treatments known to confer clinical benefit.

Primary Objectives	Primary Endpoints
- To determine the safety and tolerability of mRNA-5671/V941 as monotherapy and in combination with pembrolizumab infusion and to establish a preliminary recommended Phase 2 dose of mRNA-5671/V941 in combination with pembrolizumab infusion	- Dose-limiting toxicity (DLT) - Adverse event (AE) - Discontinuing study treatment due to an AE
Secondary Objectives	Secondary Endpoints
- To evaluate objective response rate (ORR) as assessed by the investigator based on RECIST 1.1 and iRECIST following administration of mRNA-5671/V941 as a monotherapy and in combination with pembrolizumab	- Objective response is a confirmed complete response (CR) or partial response (PR)
- To evaluate the immunogenicity of mRNA-5671/V941 as a monotherapy and in combination with pembrolizumab	- Presence of and changes in the quantity of mutant KRAS specific T cells in the blood

Overall Design:

Study Phase	Phase 1
Primary Purpose	Treatment
Indication	Dose Escalation: The treatment of KRAS 4MUT+ (G12D, G12V, G13D, or G12C) solid tumors Cohort Expansion: The treatment of patients with HLA types HLA-A11:01 and/or HLA-C08:02 (and/or potentially other additional HLA types to be specified in the Procedures Manual) and mutated KRAS (G12D, G12V, G13D or G12C) advanced or metastatic NSCLC, non-MSI-H CRC, or pancreatic adenocarcinoma.
Population	Participants with advanced/metastatic solid tumors. Note: Sponsor changed the terminology referring to individuals who take part in clinical trials to "Participant" from the previously used term "Subject." For the purpose of any trial-related documents using the previous terminology, the term "Participant" is equivalent to "Subject."
Study Type	Interventional
Intervention Model	Dose Escalation This is a 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 3 years from the time the first participant (or their legally acceptable representative) provides documented informed consent until the last participant's last study-related contact.

Number of Participants:

Approximately 100 participants will be allocated.

Intervention Groups and Duration:

Intervention Groups

Intervention Group Name	Drug	Dose Strength	Dose Frequency	Route of Admin	Regimen/ Treatment Period/ Vaccination Regimen	Use
Arm A: mRNA-5671/V941 monotherapy	mRNA-5671/V941	DL 1: 1.0 mg DL -1: 0.40 mg DL -2: 0.20 mg DL -3: 0.10 mg	Q3W	IM	9 cycles	Test product
Arm B: mRNA-5671/V941 + pembrolizumab	mRNA-5671/V941	DL 1: 1.0 mg DL -1: 0.40 mg DL -2: 0.20 mg DL -3: 0.10 mg	Q3W	IM	9 cycles	Test product
	Pembrolizumab	200 mg	Q3W	IV	35 cycles	Comparator

DL=dose level; DL -1=first dose reduction; DL -2=second dose reduction; DL -3=third dose reduction; Q3W=every 3 weeks; IM=intramuscularly; IV=intravenously.

Participants may receive up to 9 doses total of mRNA-5671/V941 in either the monotherapy or combination arm. Dose Levels DL -1, DL -2, and DL -3 will only be enrolled in the event that DLTs are observed in the starting dose (1.0 mg), per the mTPI design.

Total Number	Depending on the observation of DLTs during Part A, the study will consist of ≤9 total intervention groups (up to 8 in Part A and 1 for Part B).

Duration of Participation	Each participant will participate in the study from the time the participant signs the Informed Consent Form (ICF) through the final protocol-specified contact. After a pre-screening phase of up to 21 days (Part 2) and a screening phase of up to 28 days, each participant will be assigned to receive study intervention until disease progression is radiographically documented and, when clinically appropriate, confirmed by the site per modified Response Evaluation Criteria in Solid Tumors 1.1 for immune-based therapeutics (iRECIST), unacceptable adverse event(s) (AEs), intercurrent illness that prevents further administration of treatment, investigator's decision to withdraw the participant, noncompliance with study intervention or procedure requirements or administrative reasons requiring cessation of treatment, or until the participant has received 35 administrations of pembrolizumab (approximately 2 years). After the end of treatment, each participant will be followed for the occurrence of AEs and spontaneously reported pregnancy as described under Section 8.4. Participants on treatment with pembrolizumab monotherapy in the post-treatment phase are discontinued and may be enrolled in to a pembrolizumab extension study. 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, and confirmed by the site per iRECIST, initiating a non-study 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.

Study Governance Committees:

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

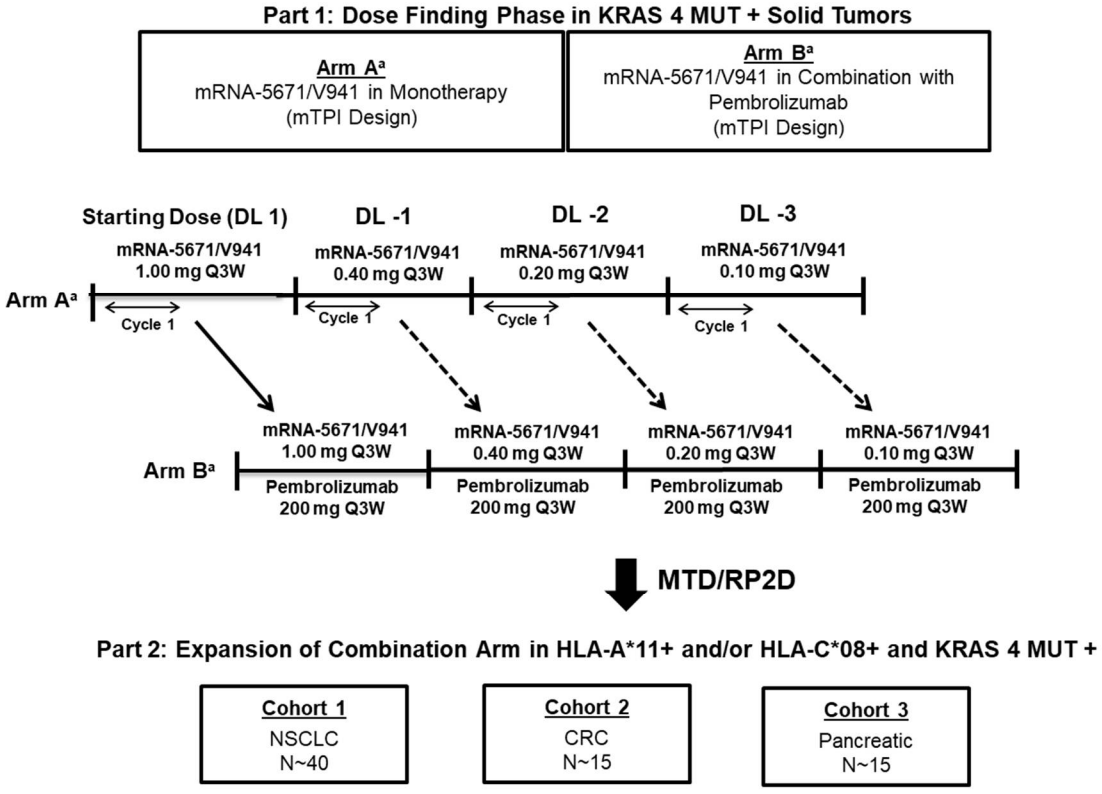
Study Accepts Healthy Volunteers: No

A list of abbreviations used in this document can be found in Appendix 9.

1.2 Schema

The dose finding and expansion study design is depicted in Figure 1.

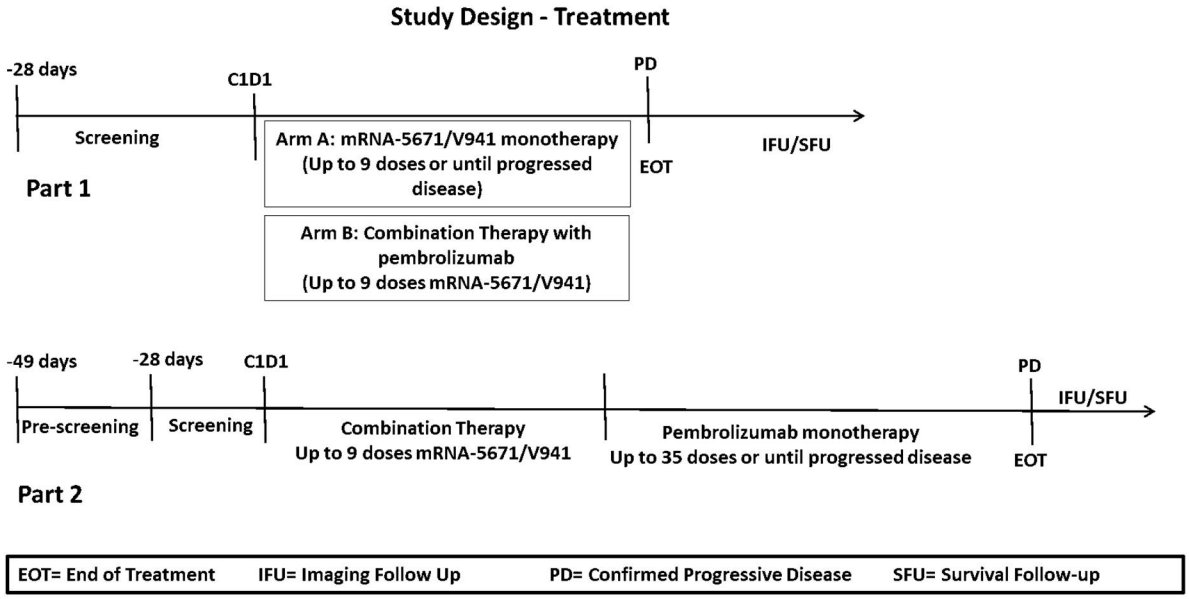
Figure 1 Study Design (Dose De-escalation and Expansion)



a. Patients may receive up to 9 total doses of mRNA-5671/V941 in either the monotherapy or combination arm. Dose Levels DL -1, DL -2, and DL -3 will only be enrolled in the event that DLTs are observed in the starting dose (1.0 mg), per the mTPI design.

The treatment course for the study is depicted in Figure 2.

Figure 2 Study Design (Treatment Course)



Participants on active treatment with pembrolizumab monotherapy in the post-treatment phase are discontinued and may be enrolled in to a pembrolizumab extension study. Participants in survival follow-up phase will not be rolled-over.

1.3 Schedule of Activities (SoA)

1.3.1 Schedule of Activities for Monotherapy Arm A (mRNA-5671/V941 alone) in Part 1

Schedule of Activities for Monotherapy Arm A (mRNA-5671/V941 alone) in Part 1											
Trial Period:	Screening Phase	Treatment Phase (3-Week Cycles)					End of Treatment (EOT) / Discontinuation	Post-Treatment Phase			Notes
Treatment Cycle/Title:	Screening	1		2	3-9			Safety Follow-up	Imaging Follow-up	Survival Follow-up	
Treatment Day of Cycle:		1	2	1	1	8	At time of treatment discontinuation	30 days post last dose of study treatment	Every 9 weeks	Every 12 weeks	
Scheduled Window (Days):	-28 to -1			+3	±3	±3	<14	+14	±7	±7	
Administrative Procedures											
Informed Consent	X										
Informed Consent for Future Biomedical Research	X										Optional
Participant Identification Card	X										
Inclusion/Exclusion Criteria	X										
Demographic and Medical History	X										
Prior/Concomitant Medication Review	X	X	X	X	X	X*	X	X			*only applicable if participant has a required visit for collection of Pharmacokinetics/Pharmacodynamics/ Biomarkers sample(s)
Treatment Allocation		X									
Anti-cancer therapy information collection							X	X	X		
Study Medication Administration											
mRNA-5671/V941 IM Administration		X		X	X						

Schedule of Activities for Monotherapy Arm A (mRNA-5671/V941 alone) in Part 1											
Trial Period:	Screening Phase	Treatment Phase (3-Week Cycles)					End of Treatment (EOT) / Discontinuation	Post-Treatment Phase			Notes
Treatment Cycle/Title:	Screening	1		2	3-9			Safety Follow-up	Imaging Follow-up	Survival Follow-up	
Treatment Day of Cycle:		1	2	1	1	8	At time of treatment discontinuation	30 days post last dose of study treatment	Every 9 weeks	Every 12 weeks	
Scheduled Window (Days):	-28 to -1			+3	±3	±3	<14	+14	±7	±7	
Efficacy Procedures											
Tumor Imaging and Response Assessment	X				X		X		X		Imaging will be obtained via CT, PET/CT, or MRI. Medical Photography for cutaneous lesions (if applicable) should be obtained on the same schedule as imaging. On study imaging should be performed every 9 weeks (± 7 days) and EOT imaging should be performed at time of treatment discontinuation (± 4 weeks).
Survival Status		⟷								X	After investigator determined PD or start of new anticancer treatment. In addition, upon Sponsor request, participants may be contacted for survival status at any time during the course of the study.
Safety Procedures											
Full Physical Examination	X	X					X				It is not necessary to repeat C1D1 testing if the Screening testing was performed within 3 days prior to C1D1.
Height	X										
Weight	X	X		X	X		X	X			
Directed Physical Examination			X	X	X	X*		X			*only applicable if participant has a required visit for collection of Pharmacokinetics/ Pharmacodynamics/Biomarkers sample(s)
Vital Signs	X	X	X	X	X	X*	X	X			VS: heart rate, respiratory rate, blood pressure, temperature *only applicable if participant has a required visit for collection of Pharmacokinetics/ Pharmacodynamics/ Biomarkers sample(s)
12-lead Electrocardiograph (ECG)	X										

Schedule of Activities for Monotherapy Arm A (mRNA-5671/V941 alone) in Part 1											
Trial Period:	Screening Phase	Treatment Phase (3-Week Cycles)					End of Treatment (EOT) / Discontinuation	Post-Treatment Phase			Notes
Treatment Cycle/Title:	Screening	1		2	3-9			Safety Follow-up	Imaging Follow-up	Survival Follow-up	
Treatment Day of Cycle:		1	2	1	1	8	At time of treatment discontinuation	30 days post last dose of study treatment	Every 9 weeks	Every 12 weeks	
Scheduled Window (Days):	-28 to -1			+3	±3	±3	<14	+14	±7	±7	
Eastern Cooperative Oncology Group (ECOG) Performance Status	X	X		X	X		X	X			It is not necessary to repeat C1D1 testing if the Screening testing was performed within 3 days prior to C1D1.
Adverse Events Reporting	X	X	X	X	X	X*		X			AEs will be followed until the 30-day follow up visit and SAEs will be followed for 120 days after last dose of study medication. *only applicable if participant has a required visit for collection of Pharmacokinetics/ Pharmacodynamics/ Biomarkers sample(s)
Clinical Laboratory Assessments											
Serum (hCG; women of child-bearing potential [WOCBP] only) or Urine Pregnancy Test (WOCBP only)	X	X									Screening and within 72 hours prior to the first dose of study treatment. Additional urine/serum pregnancy tests may be performed if clinically warranted, or as defined by local regulations. If a urine pregnancy test cannot be confirmed as negative, a serum pregnancy test is required and should be negative.
Human immunodeficiency virus (HIV), hepatitis B and C screen (per site SOP)	X										Assessment should be based on history unless testing is required by local regulation.
Urinalysis	X						X				
Hematology	X	X		X	X		X	X			
Comprehensive Chemistry Panel	X	X		X	X		X	X			

Schedule of Activities for Monotherapy Arm A (mRNA-5671/V941 alone) in Part 1											
Trial Period:	Screening Phase	Treatment Phase (3-Week Cycles)					End of Treatment (EOT) / Discontinuation	Post-Treatment Phase			Notes
Treatment Cycle/Title:	Screening	1		2	3-9			Safety Follow-up	Imaging Follow-up	Survival Follow-up	
Treatment Day of Cycle:		1	2	1	1	8	At time of treatment discontinuation	30 days post last dose of study treatment	Every 9 weeks	Every 12 weeks	
Scheduled Window (Days):	-28 to -1			+3	±3	±3	<14	+14	±7	±7	
Prothrombin (PT)/International Normalized Ratio (INR) and Activated Partial Thromboplastin Time (aPTT)	X	X		X				X			Additional testing may be performed for participants who are on warfarin-based anticoagulants at the discretion of the Investigator.
Pharmacokinetics/Pharmacodynamics/Biomarkers (Please refer to Procedures Manual)											
Blood for Genetic Analyses		X									Collect predose C1D1
Blood for RNA Analyses		X		X							Collect predose on C1D1 and predose on C2D1.
Peripheral Blood Mononuclear Cells (PBMC) for Immunogenicity Assessment		X			X	X					Collect predose on Day 1 of C1, and on both Day 8 of C4 and on Day 1 of C6.
Plasma for ctDNA		X			X		X				Collect plasma samples predose on Day 1 of C1, C4, and C9, and at EOT.
Blood for T-Cell receptor (TCR) repertoire (DNA)		X				X					Collect predose on Day 1 of C1 predose on Day 8 of C4.
Tumor Tissue Collection											
Archival Tumor Sample	X										Please refer to Procedures Manual.

1.3.2 Schedule of Activities for Combination Therapy Arm B (mRNA-5671/V941 + pembrolizumab) in Part 1 and Part 2

Schedule of Activities for Combination Therapy Arm B (mRNA-5671/V941 + pembrolizumab) in Part 1 and Part 2													
Trial Period:	Screening Phase		Treatment Phase (3-Week Cycles)						End of Treatment (EOT) / Discontinuation	Post-Treatment Phase			Notes
Treatment Cycle/Title:	Pre-screening*	Screening	1		2	3-9		10 to 35		Safety Follow-up	Imaging Follow-up	Survival Follow-up	* Pre-screening is only applicable for Part 2 and does not apply to Part 1
Treatment Day of Cycle:			1	2	1	1	8	1	At time of treatment discontinuation	30 days post last dose of study treatment	Every 9 weeks	Every 12 weeks	
Scheduled Window (Days):	-49 to -28	-28 to -1			+3	±3	±3	± 3	<14	+14	±7	±7	
Administrative Procedures													
Informed Consent	X*	X											*Must be obtained before any HLA or other testing in Pre-screening is performed (Part 2)
Informed Consent for Future Biomedical Research		X											Optional
Participant Identification Card		X											
Inclusion/Exclusion Criteria		X											
Demographic and Medical History		X											
Prior/Concomitant Medication Review		X	X	X	X	X	X*	X	X	X			*only applicable if participant has a required visit for collection of Pharmacokinetics/ Pharmacodynamics/ Biomarkers sample(s)
Treatment Allocation			X										
Anti-cancer therapy Information collection									X	X	X		
Study Medication Administration													
mRNA-5671/V941 IM Administration			X		X	X							
Pembrolizumab infusion (IV)			X		X	X		X					

Schedule of Activities for Combination Therapy Arm B (mRNA-5671/V941 + pembrolizumab) in Part 1 and Part 2													
Trial Period:	Screening Phase		Treatment Phase (3-Week Cycles)						End of Treatment (EOT) / Discontinuation	Post-Treatment Phase			Notes
Treatment Cycle/Title:	Pre-screening*	Screening	1		2	3-9		10 to 35		Safety Follow-up	Imaging Follow-up	Survival Follow-up	* Pre-screening is only applicable for Part 2 and does not apply to Part 1
Treatment Day of Cycle:			1	2	1	1	8	1	At time of treatment discontinuation	30 days post last dose of study treatment	Every 9 weeks	Every 12 weeks	
Scheduled Window (Days):	-49 to -28	-28 to -1			+3	±3	±3	± 3	<14	+14	±7	±7	
Efficacy Procedures													
Tumor Imaging and Response Assessment		X				X		X	X		X		Imaging will be obtained via CT, PET/CT, or MRI. Medical Photography for cutaneous lesions (if applicable) should be obtained on the same schedule as imaging. On study imaging should be performed every 9 weeks (± 7 days) and EOT imaging should be performed at time of treatment discontinuation (± 4 weeks).
Survival Status			←						→			X	After investigator determined PD or start of new anticancer treatment. In addition, upon Sponsor request, participants may be contacted for survival status at any time during the course of the study.
Safety Procedures													
Full Physical Examination		X	X						X				It is not necessary to repeat C1D1 testing if the Screening testing was performed within 3 days prior to C1D1.
Height		X											
Weight		X	X		X	X		X	X	X			
Directed Physical Examination				X	X	X	X*	X		X			*only applicable if participant has a required visit for collection of Pharmacokinetics/ Pharmacodynamics/ Biomarkers sample(s)
Vital Signs		X	X	X	X	X	X*	X	X	X			VS: heart rate, respiratory rate, blood pressure, temperature *only applicable if participant has a

Schedule of Activities for Combination Therapy Arm B (mRNA-5671/V941 + pembrolizumab) in Part 1 and Part 2													
Trial Period:	Screening Phase		Treatment Phase (3-Week Cycles)						End of Treatment (EOT) / Discontinuation	Post-Treatment Phase			Notes
Treatment Cycle/Title:	Pre-screening*	Screening	1		2	3-9		10 to 35		Safety Follow-up	Imaging Follow-up	Survival Follow-up	* Pre-screening is only applicable for Part 2 and does not apply to Part 1
Treatment Day of Cycle:			1	2	1	1	8	1	At time of treatment discontinuation	30 days post last dose of study treatment	Every 9 weeks	Every 12 weeks	
Scheduled Window (Days):	-49 to -28	-28 to -1			+3	±3	±3	± 3	<14	+14	±7	±7	
													required visit for collection of Pharmacokinetics/Pharmacodynamics/Biomarkers sample(s)
12-lead ECG		X											
ECOG Performance Status		X	X		X	X		X	X	X			It is not necessary to repeat C1D1 testing if the Screening testing was performed within 3 days prior to C1D1.
Adverse Events Reporting		X	X	X	X	X	X*	X	X	X			AEs will be followed until the 30-day follow up visit and SAEs will be followed for 120 days after last dose of study medication. *only applicable if participant has a required visit for collection of PK/Pharmacodynamics/Biomarkers sample(s)
Clinical Laboratory Assessments													
Review of prior local tumor KRAS mutational testing results	X												If not already tested as per routine standard of care, tumor KRAS mutational testing may be performed, but only with Sponsor approval. Please refer to Procedures Manual.
HLA testing (Part 2 only)	X												In Part 1, no sample is collected. In Part 2, the required HLA type must be confirmed in Pre-screening. If routine standard of care KRAS testing has not been performed prior to Pre-screening, Sponsor approval is needed for HLA testing and KRAS mutation testing in Pre-screening. Please refer to

Schedule of Activities for Combination Therapy Arm B (mRNA-5671/V941 + pembrolizumab) in Part 1 and Part 2													
Trial Period:	Screening Phase		Treatment Phase (3-Week Cycles)						End of Treatment (EOT) / Discontinuation	Post-Treatment Phase			Notes
Treatment Cycle/Title:	Pre-screening*	Screening	1		2	3-9		10 to 35		Safety Follow-up	Imaging Follow-up	Survival Follow-up	* Pre-screening is only applicable for Part 2 and does not apply to Part 1
Treatment Day of Cycle:			1	2	1	1	8	1	At time of treatment discontinuation	30 days post last dose of study treatment	Every 9 weeks	Every 12 weeks	
Scheduled Window (Days):	-49 to -28	-28 to -1			+3	±3	±3	± 3	<14	+14	±7	±7	
													Procedures Manual.
Serum (hCG; WOCBP only) or Urine Pregnancy Test (WOCBP only)		X	X										Screening and within 72 hours prior to the first dose of study treatment. Additional urine/serum pregnancy tests may be performed if clinically warranted, or as defined by local regulations. If a urine pregnancy test cannot be confirmed as negative, a serum pregnancy test is required and should be negative.
HIV, hepatitis B and C screen (per site SOP)		X											Assessment should be based on history unless testing is required by local regulation.
Urinalysis		X							X				
Hematology		X	X		X	X		X	X	X			
Comprehensive Chemistry Panel		X	X		X	X		X	X	X			
PT/INR and aPTT		X	X		X					X			Additional testing may be performed for participants who are on warfarin-based anticoagulants at the discretion of the Investigators.
Thyroid Function (T3, or FT3, FT4, and TSH)		X	X			X		X	X				Every other cycle (ie, Cycles 1, 3, 5, 7, etc.),
Pharmacokinetics/Pharmacodynamics/Biomarkers (Please refer to Procedures Manual)													
Blood for Genetic Analyses			X										Collect predose on C1D1
Blood for RNA Analysis			X		X								Collect predose on C1D1 and predose on C2D1.
Serum for Pembrolizumab Pharmacokinetics			X		X	X		X		X			Collect predose at Cycles 1, 2, 4, 8 and every 4 cycles thereafter. May be collected ≤24 hours prior to dosing.

Schedule of Activities for Combination Therapy Arm B (mRNA-5671/V941 + pembrolizumab) in Part 1 and Part 2												
Trial Period:	Screening Phase		Treatment Phase (3-Week Cycles)						End of Treatment (EOT) / Discontinuation	Post-Treatment Phase			Notes
Treatment Cycle/Title:	Pre-screening*	Screening	1		2	3-9		10 to 35		Safety Follow-up	Imaging Follow-up	Survival Follow-up	* Pre-screening is only applicable for Part 2 and does not apply to Part 1
Treatment Day of Cycle:			1	2	1	1	8	1	At time of treatment discontinuation	30 days post last dose of study treatment	Every 9 weeks	Every 12 weeks	
Scheduled Window (Days):	-49 to -28	-28 to -1			+3	±3	±3	± 3	<14	+14	±7	±7	
													Collect postdose at Cycles 1 & 2: Sample drawn within 30 minutes after end of pembrolizumab infusion.
Serum for Anti-pembrolizumab Antibodies			X		X	X		X		X			Collect predose at cycles 1, 2, 4, 8 and every 4 cycles thereafter. May be collected ≤24 hours prior to dosing.
PBMC for Immunogenicity Assessment			X			X	X						Collect predose on Day 1 of C1 (unless a screening leukapheresis is collected); and on both Day 8 of C4 and on Day 1 of C6 (unless a leukapheresis is collected on Day 8 of C4).
Leukapheresis		X					X						Leukaphereses during Screening and on Day 8 of C4 are optional and may only be performed if the leukapheresis pack can be processed appropriately. Refer to Procedures Manual for collection instructions.
Plasma for ctDNA			X			X		X	X				Collect plasma samples predose on Day 1 of C1, C4, C9, and C12, and at EOT.
Blood for T-Cell receptor (TCR) repertoire (DNA)			X				X						Collect predose on Day 1 of C1 and predose on Day 8 of C4.
Tumor Tissue Collection													
Archival Tumor Sample		X											Please refer to Procedures Manual.

1.3.3 Schedule of Activities for Crossover Participants

Schedule of Activities for Crossover Participants											
Trial Period:	Screening Phase	Treatment Phase (3-Week Cycles)					End of Treatment (EOT) / Discontinuation	Post-Treatment Phase			Notes
Treatment Cycle/Title:	Screening	1	2	3-9		10 to 35		Safety Follow-up	Imaging Follow-up	Survival Follow-up	
Treatment Day of Cycle:		1	1	1	8	1	At time of treatment discontinuation	30 days post last dose of study treatment	Every 9 weeks	Every 12 weeks	
Scheduled Window (Days):	-28 to -1		+3	±3	±3	±3	<14	+14	±7	±7	
Administrative Procedures											
Informed Consent	X										Review ICFs at crossover Screening visit.
Informed Consent for Future Biomedical Research	X										Optional
Inclusion/Exclusion Criteria	X										
Prior/Concomitant Medication Review	X	X	X	X	X*	X	X	X			*only applicable if participant has a required visit for collection of Pharmacokinetics/Pharmacodynamics/Biomarkers sample(s)
Anti-cancer therapy Information collection							X	X	X		
Study Medication Administration											
mRNA-5671/V941 IM Administration		X	X	X							Participants who had PD prior to completion of 9 doses of mRNA-5671/V941 in Arm A will receive their remaining doses of mRNA-5671/V941 in crossover (total of 9 doses).
Pembrolizumab infusion (IV)		X	X	X		X					Participants who completed 9 doses of mRNA-5671/V941 will receive pembrolizumab monotherapy up to total 35 cycles.
Efficacy Procedures											
Tumor Imaging and Response Assessment	X			X		X	X		X		Imaging will be obtained via CT, PET/CT, or MRI. Medical Photography for cutaneous lesions (if applicable) should be obtained on the same schedule as imaging. On study imaging should be performed every 9 weeks (±7 days) and EOT imaging should be performed at time of treatment discontinuation (±4

Schedule of Activities for Crossover Participants											
Trial Period:	Screening Phase	Treatment Phase (3-Week Cycles)					End of Treatment (EOT) / Discontinuation	Post-Treatment Phase			Notes
Treatment Cycle/Title:	Screening	1	2	3-9		10 to 35		Safety Follow-up	Imaging Follow-up	Survival Follow-up	
Treatment Day of Cycle:		1	1	1	8	1	At time of treatment discontinuation	30 days post last dose of study treatment	Every 9 weeks	Every 12 weeks	
Scheduled Window (Days):	-28 to -1		+3	±3	±3	±3	<14	+14	±7	±7	
											weeks). Screening imaging will not need to be performed if previous imaging was performed within 4 weeks.
Survival Status		←								→ X	After investigator determined PD or start of new anticancer treatment. In addition, upon Sponsor request, participants may be contacted for survival status at any time during the course of the study.
Safety Procedures											
Full Physical Examination	X	X					X				It is not necessary to repeat C1D1 testing if the Screening testing was performed within 3 days prior to C1D1.
Weight	X	X	X	X		X	X	X			
Directed Physical Examination			X	X	X*	X		X			*only applicable if participant has a required visit for collection of Pharmacokinetics/Pharmacodynamics/ Biomarkers sample(s)
Vital Signs	X	X	X	X	X*	X	X	X			VS: heart rate, respiratory rate, blood pressure, temperature *only applicable if participant has a required visit for collection of Pharmacokinetics/Pharmacodynamics/ Biomarkers sample(s)
12-lead ECG	X										
ECOG Performance Status	X	X	X	X		X	X	X			
Adverse Events Reporting	X	X	X	X	X*	X	X	X			AEs will be followed until the 30-day follow up visit and SAEs will be followed for both 30 day and 120 days after last dose of study medication. *only applicable if participant has a required visit for collection of Pharmacokinetics/Pharmacodynamics/ Biomarkers sample(s)
Clinical Laboratory Assessments											
Serum (hCG; WOCBP only) or Urine	X	X									Screening and within 72 hours prior to the first dose of study treatment. Additional urine/serum pregnancy tests may be performed if clinically warranted, or as

Schedule of Activities for Crossover Participants											
Trial Period:	Screening Phase	Treatment Phase (3-Week Cycles)					End of Treatment (EOT) / Discontinuation	Post-Treatment Phase			Notes
Treatment Cycle/Title:	Screening	1	2	3-9		10 to 35		Safety Follow-up	Imaging Follow-up	Survival Follow-up	
Treatment Day of Cycle:		1	1	1	8	1	At time of treatment discontinuation	30 days post last dose of study treatment	Every 9 weeks	Every 12 weeks	
Scheduled Window (Days):	-28 to -1		+3	±3	±3	±3	<14	+14	±7	±7	
Pregnancy Test (WOCBP only)											defined by local regulations. If a urine pregnancy test cannot be confirmed as negative, a serum pregnancy test is required and should be negative.
Urinalysis	X						X				
Hematology	X	X	X	X		X	X	X			
PT/INR and aPTT	X	X	X					X			Additional testing may be done to participants who are on warfarin-based anticoagulants at the discretion of the Investigators.
Comprehensive Chemistry Panel	X	X	X	X		X	X	X			
Thyroid Function (T3, or FT3, FT4, and TSH)	X	X		X		X	X				Every other cycle (ie, Cycles 1, 3, 5, 7, etc.)
Pharmacokinetics/Pharmacodynamics/Biomarkers (Please refer to Procedures Manual)											
Serum for Pembrolizumab Pharmacokinetics		X	X	X		X		X			Collect predose at Cycles 1, 2, 4, 8 and every 4 cycles thereafter. May be collected ≤24 hours prior to dosing. Collect postdose at Cycles 1 & 2: Sample drawn within 30 min. after end of pembrolizumab infusion.
Serum for Anti-pembrolizumab Antibodies		X	X	X		X		X			Collect predose at Cycles 1, 2, 4, 8 and every 4 cycles thereafter. May be collected ≤24 hours prior to dosing.
PBMC for Immunogenicity Assessment		X		X	X						Collect predose on Day 1 of C1 and on both Day 8 of C4 and on Day 1 of C6.
Plasma for ctDNA		X		X		X	X				Collect predose on Day 1 for C1, C4, C9, and C12, and at EOT.
Blood for T-Cell receptor (TCR) repertoire (DNA)		X			X						Collect predose on Day 1 of C1 and per-dose on Day 8 of C4.

2 INTRODUCTION

mRNA-5671/V941 contains an mRNA Drug Substance that encodes 4 antigens containing KRAS mutations (G12D, G12V, G13D, G12C). mRNA-5671/V941 is under study for the treatment of solid tumors as monotherapy and as combination therapy with pembrolizumab. This is a first-in-human, dose-escalation, and dose-finding study to assess the safety and tolerability of mRNA-5671/V941, both as monotherapy and as combination therapy with pembrolizumab. Refer to the mRNA-5671/V941 IB for further information.

2.1 Study Rationale

Recent breakthroughs in cancer immunotherapy (eg, checkpoint inhibitors and chimeric antigen receptor T-cell therapies) have demonstrated that long-lasting, curative-intent antitumor activity can be achieved in patients with metastatic epithelial cancers by activating specific antitumor T cells. The steps required for proliferation, migration, and activation of T cells in a successful antitumor response have been described as the "Cancer Immunity Cycle" [Chen, D. S. 2013]. Furthermore, it has become apparent that when an effective T-cell response occurs, the antitumor T cells recognize peptide fragments presented by major histocompatibility complex (MHC) that harbor cancer-specific somatic mutations. In the vast majority of cases, these mutations appear to be randomly occurring passenger mutations that are present only in that individual patient's cancer, as opposed to oncogenic driver mutations. However, finding oncogenic driver mutations that encode targetable T-cell epitopes has considerable therapeutic implications: (a) driver mutations are subject to positive selection, as they confer survival advantages for the tumor, and (b) such epitopes would be shared between patients, enabling a more straightforward approach to developing therapeutic interventions.

The most frequently mutated oncogene in cancer is KRAS, which is mutated in approximately 30% of epithelial cancers, primarily lung cancers, colorectal cancers (CRC) and pancreatic cancers [Pylayeva-Gupta, Y., et al 2011]. The 4 most prevalent KRAS mutant antigens in these 3 malignancies are G12D, G12V, G13D, and G12C, which constitute 80% to 90% of the KRAS mutations [Prior, I. A., et al 2012] [Cox, A. D., et al 2014]. KRAS has multiple downstream signaling pathways, and although drugs have been developed to target individual pathway components, direct inhibition of KRAS could be more efficacious. Unfortunately, direct inhibition of KRAS has proven clinically challenging; despite significant efforts, no successful KRAS targeted cancer therapy has been developed yet [Kempf, E., et al 2016].

KRAS mutations occur in approximately 40% of CRCs. The presence of a KRAS mutation in CRC confers a worse prognosis for patients [Lee, D. W., et al 2015]. KRAS mutations also mediate primary resistance to anti-epidermal growth factor receptor (EGFR) monoclonal antibodies, such that treatment with these monoclonal antibodies is not indicated in this population. Chemotherapy remains the first line of treatment for metastatic CRC patients. Various oxaliplatin and irinotecan-based regimens have been shown to prolong survival, but none are administered with curative intent. Anti–programmed cell death protein 1 (PD-1) therapies alone are not effective in metastatic CRC except in rare cases of mismatch repair

deficient/microsatellite instability-high (MSI-H) tumors [Boland, C. R. 2010] [Le, D. T., et al 2015] [Lee, D. W., et al 2015], [Ashktorab, H., et al 2016]. Many single agent and combination trials with various immunotherapy agents are being investigated to overcome these limitations.

Pancreatic adenocarcinoma is one of the deadliest cancers, with 5-year overall survival of less than 5%. While some improvements have been made in both the adjuvant and neo-adjuvant setting over the past 10 years, success has been measured only in months. The only curative option remains surgery; however, less than 20% of patients are eligible to undergo surgery at the time of diagnosis, and the rate of relapse is high in those that have undergone surgical resection [Zeitouni, D., et al 2016]. In approximately 98% of cases of pancreatic adenocarcinomas, mutated KRAS is one of the oncogenic drivers; approximately 90% of those KRAS mutations involve 1 of 4 target alleles: G12C, G12V, G12D, and G13D [Prior, I. A., et al 2012] [Cox, A. D., et al 2014]. Many attempts have been made to target KRAS and the RAS-MEK-ERK pathway in pancreatic cancer, but there has not been much success [Jamieson, D., et al 2016] [Ning, C., et al 2017]. Advances in immunotherapy for pancreatic cancer have also been impeded by challenges that include the dense stromal nature of the tissue, the inability of effector cells to penetrate the tumor microenvironment, and substantial local immune suppression.

While previous efforts have been made to generate a therapeutic cancer vaccine that targets mutant KRAS, based on observations that mutated KRAS peptides can be recognized in the context of HLA-A2 (the most prevalent MHC class I molecules in Caucasians), these have not been effective to date. Our interest in generating a therapeutic vaccine to target mutant KRAS resulted from a recent manuscript that describes KRAS-mutant specific T cells mediating significant antitumor efficacy [Tran, E., et al 2016] in the context of HLA-C08:02 and preclinical data that demonstrated that HLA-A11:01 can present KRAS G12D peptides [Wang, Q. J., et al 2016].

The Sponsor is developing a new mRNA-based therapeutic vaccine technology that allows for induced production of a broad array of secreted, membrane-bound, and intracellular proteins both in cell culture and in many animal models and humans. Vaccination with antigen-encoding mRNA is an attractive technology platform for the delivery of mutant KRAS antigens because the therapeutic vaccine can deliver multiple mutations in a single vaccination. These mutations are endogenously translated and enter into the natural cellular antigen processing and presentation pathway. Moreover, this mRNA-based therapeutic vaccine technology, which is delivered IM, overcomes the challenges commonly associated with DNA-based therapeutic vaccines, such as risk of genome integration or the high doses and devices needed for administration (eg, electroporation). mRNA-5671/V941 is a therapeutic KRAS vaccine developed to elicit an antitumor T-cell response in patients' KRAS mutated cancers, in particular non-small cell lung cancer (NSCLC), non-MSI-H CRC and pancreatic cancer. This therapeutic vaccine is a concatemer that consists of the 4 most prevalent KRAS mutant antigens (G12D, G12V, G13D, and G12C) in these cancers; these 4 point mutations address 80% to 90% of the KRAS mutations present in these 3 malignancies [Prior, I. A., et al 2012] [Cox, A. D., et al 2014].

Recent breakthroughs in cancer immunotherapy (eg, checkpoint inhibitors and chimeric antigen receptor-T-cell therapies) have demonstrated that powerful antitumor responses can be achieved by activating large numbers of T cells in a variety of cancer settings. In particular, immune checkpoint blockade is a broadly applicable therapeutic approach, and treatment with agents targeting this mechanism has led to remarkable clinical benefit for patients with metastatic melanoma, NSCLC, bladder cancer, renal cancer, and head and neck squamous cell carcinoma (HNSCC). Multiple checkpoint inhibitor biologic agents (eg, pembrolizumab) are currently approved for human use in these cancer types, including agents that target cytotoxic T lymphocyte–associated antigen 4 (CTLA-4); PD-1; and its ligand, programmed death ligand 1 (PD-L1). Pembrolizumab (Keytruda™) is a potent humanized immunoglobulin G4 monoclonal antibody with high specificity of binding to the PD-1 receptor, thus inhibiting its interaction with PD-L1 and programmed cell death ligand 2 (PD-L2). Based on preclinical in vitro data, pembrolizumab has a high affinity and potent receptor blocking activity for PD-1. Inhibitory receptors and their ligands play complementary roles in down-regulating adaptive immunity; pembrolizumab overcomes T-cell exhaustion in peripheral tissues [Sharma, P. 2015]. Although it is clear that single agent checkpoint inhibitor therapy can provide significant benefit for certain patients, many patients have incomplete or no response to this therapy. Thus, an unmet need remains for new treatment options, especially ones that can be used in combination with first generation breakthrough immunotherapies.

mRNA-5671/V941 is a novel therapeutic vaccine that is hypothesized to enhance the antitumor immune activity of the PD-1-blocking antibody pembrolizumab. Therefore, mRNA-5671/V941 may have the potential to provide benefit in terms of increased efficacy in patients with a variety of advanced solid malignancies with unmet need.

While emerging data support the use of PD-1 inhibitors such as pembrolizumab in tumors in which PD-L1 expression can be demonstrated, there remains a strong rationale for the potential utility of combinations that include PD-1 inhibitors, even in putatively PD-L1 “negative” tumors [Topalian, S. L., et al 2016]. Mechanistically, there is an adaptive component to PD-L1 expression by tumors, ie, tumors may initially appear PD-L1 negative but upregulate PD-L1 expression in response to IFNγ secretion by infiltrating tumor lymphocytes [Taube, J. M., et al 2012]. Finally, recent preclinical data explicitly demonstrate the ability of a therapeutic cancer vaccine to induce PD-L1 expression in PD-L1–low tumors, leading to intratumor infiltration of CD8+ T cells when given in combination with a PD-1 inhibitor [Soares, K. C., et al 2015]. Thus, there is a scientific rationale for the combination of a therapeutic vaccine with pembrolizumab in patients whose tumors do not express PD-L1.

For patients with advanced disease and no available standard therapies, treatment with mRNA-5671/V941 and pembrolizumab is considered acceptable, as mRNA-5671/V941 may enhance the pembrolizumab response beyond that seen in prior studies. Many patients in the refractory setting currently receive investigational immunotherapy targeting the PD-1/PD-L1 axis, such as pembrolizumab, regardless of PD-L1 status.

2.2 Background

Refer to the Investigator's Brochure (IB) for detailed background information on mRNA-5671/V941, and the IB/approved labeling for detailed background information on pembrolizumab. This is a first-in-human (FIH) study.

Pembrolizumab is a potent humanized immunoglobulin G4 (IgG4) 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 pembrolizumab Investigator's Brochure.

2.2.1 mRNA-5671/V941 Pharmaceutical and Therapeutic Background

2.2.1.1 In Vivo Pharmacology

mRNA-5671/V941 contains an mRNA Drug Substance that encodes 4 antigens containing KRAS mutations (G12D, G12V, G13D, G12C), formulated in an SM-102 lipid nanoparticle (LNP).

Recent data from the Yang laboratory at the National Cancer Institute demonstrated that coimmunization with 10–amino acid peptides spanning the G12D and G12V mutations of KRAS and a class II helper peptide derived from hepatitis B virus core 128–140 could invoke T-cell responses specific for the respective mutations in mice transgenic for the human HLA-A11:01 class I allele [Wang, Q. J., et al 2016]. Data that showed the superior immunogenicity of KRAS G12D using a therapeutic mRNA vaccine encoding KRAS G12D relative to peptide vaccination was obtained in collaboration with the Yang lab. Furthermore, cluster of differentiation 8 (CD8) T cells specific to KRAS G12D and G12V were detected when HLA-A11:01 knock-in mice were immunized with mRNA-5671/V941.

2.2.1.2 Toxicology

To support the proposed V941-001 Phase 1 clinical study, the safety and tolerability of mRNA-5671/V941 was evaluated in a Good Laboratory Practices (GLP)-compliant 1-month toxicity study, in Sprague Dawley rats at 0.01, 0.03, and 0.10 mg per dose via intramuscular (IM) injection administered weekly for a total of 5-doses, followed by a 2-week treatment-free period. The mRNA was formulated in a LNP consisting of 4 lipids (SM-102, PEG2000-DMG, DSPC, and cholesterol). Doses of 0.01, 0.03 and 0.10 mg per dose tested in the rat toxicology study approximate to human equivalent doses (HED) of 0.34, 1.03 and 3.40 mg, respectively (based on group mean body weight of 0.328 kg in rats, and using an average human body weight of 70 kg), and thus approximate to margins of 0.34-, 1.03-, and 3.40-fold over the human starting dose of 1.0 mg. The Sponsor has determined the no-observed

adverse effect level (NOAEL) to be 0.03 mg/week based on low severity and incidence of the clinical and microscopic findings at this dose in rats, as summarized below. The related mRNA-4157/V940 therapeutic vaccine, a personalized therapeutic cancer vaccine developed using the same mRNA technology platform, has also been evaluated in Phase 1 clinical trials and is formulated in a LNP consisting of the same 4 lipids (SM-102, PEG2000-DMG, DSPC and cholesterol) and has been well-tolerated in patients up to 1 mg intramuscularly (Section 4.3.2). Therefore, the proposed starting dose for the V941-001 clinical study of 1.0 mg is expected to be similarly tolerated as mRNA-4157/V940. The Sponsor intends the clinical starting dose to achieve some level of pharmacological activity; therefore, the use of a NOAEL from the GLP rat toxicity study allows interpretation of the anticipated risk of toxicity from the mRNA and lipid formulation at this dose. The NOAEL of 0.03 mg achieved in rat GLP study converted to an HED represents a 1.03-fold safety margin compared to the proposed starting dose of 1.0 mg. The findings in the rat GLP study are further summarized below.

The results of this GLP-compliant, repeat-dose toxicity study of mRNA-5671/V941 in rats indicated that mRNA-5671/V941 administered weekly by IM injection at 0.01, 0.03, and 0.10 mg per dose for a total of 5 doses was well tolerated at all dose levels (no mRNA-5671/V941 related mortality observed). Weekly administration of mRNA-5671/V941 to Sprague Dawley rats (both male and female) was associated with a dose-dependent slight to mild decreases in body weight gain which correlated with slightly reduced food consumption. Dose-dependent changes consistent with an inflammatory response were noted in clinical observations at the injection site (described as injection site being swollen and firm to touch with associated erythema), clinical pathology parameters (eg, increased white blood cells (WBC) parameters driven predominantly by neutrophils as well as mild increases in fibrinogen, globulin). Additional findings suggestive of inflammation at the high-dose (0.10 mg/dose) consisted of minimal to mild increases in body temperature and serum cytokines (eg, MCP-1, interferon γ-induced protein 10, IL-6, and macrophage inflammatory protein 1α). Dose-related target organ effects were also generally consistent with local and systemic inflammation and occurred at the injection site, bone marrow, the inguinal and/or popliteal lymph nodes, the connective tissue surrounding the sciatic nerve, the spleen, and the liver of rats. At the end of a 2-week treatment-free period, all findings were fully recovered with the exception of findings associated with local and systemic inflammation at the injection site, popliteal/inguinal lymph node, the connective tissue surrounding the sciatic nerve, bone marrow and the liver which were considered to be partially recovered and were characteristically minimal to mild in severity and showed evidence of continued resolution.

This rat GLP study involved a more dose-dense regimen (weekly) compared to the proposed human dosing frequency of every 3 weeks which is intended to align with the pembrolizumab dosing schedule; importantly, a more aggressive regimen than the intended clinical dosing frequency was selected for the toxicology studies to thoroughly characterize drug product toxicity. The mRNA-5671/V941 therapeutic vaccine to be administered in the Phase 1 study consists of only an mRNA-encoding KRAS antigen formulated in a LNP. The LNP formulation constituents utilized in the GLP rat study were generally similar to the composition of the LNP formulation intended for use in the Phase 1 study. KRAS is a mutated human epitope highly dependent on human HLA in order to elicit a specific immune

response; therefore, the sequence tested in the rat GLP toxicology study represented a human-based sequence of mRNA-encoding KRAS that will be used in the clinical study, and was manufactured in a similar manner to how mRNA-5671/V941 will be manufactured in this clinical study. Of note, the version of mRNA-5671/V941evaluated in the rat GLP study included an mRNA-encoding KRAS antigen as well as an mRNA component encoding a constitutively active STING since the Sponsor initially intended to evaluate the immunogenic potential of both these components together. However, the present Phase 1 clinical study will only evaluate the immunogenic potential of mRNA-encoding KRAS (without an mRNA-encoding STING).

The Sponsor also characterized toxicology endpoints in a nonterminal exploratory monkey study by administering an mRNA-encoding model antigen expected to be immunogenic to monkeys (HPV16 E6/E7 mRNA) by IM injection on Day 1 and 15 at 100 µg/dose. Further, since the Sponsor previously intended to evaluate a drug product with mRNA-encoding constitutively active STING antigen, the monkey study assessed potential for any differential effects attributed to an mRNA-encoding constitutively active STING antigen individually or combined with HPV16 E6/E7 mRNA. Reversibility of findings was assessed during a 2-week treatment-free period. The results indicated that a mRNA-based therapeutic vaccine containing STING mRNA alone or in combination with an mRNA-encoding antigen (HPV16 E6/E7) was well tolerated at 100 µg/dose and there were no test article-related mortalities, clinical observations, no local reactions at the site of administration or changes in body weight or food consumption during the study or changes in serum chemistry. Changes in hematology, coagulation, d-dimer, c-reactive protein, complement and cytokine were consistent with an inflammatory response. These changes were generally absent after a 2-week treatment-free period, suggesting a reversibility of the effect. Hematology, coagulation, d-dimer, c-reactive protein, Bb fragment, C3a and C5B9, cytokine data sets indicate no significant differences between an mRNA therapeutic vaccine with or without STING mRNA. Based on available nonclinical data, removal of STING mRNA from the drug product is likely to be subtractive and result in an equivalent or decreased toxicology profile for an mRNA-encoding KRAS only therapeutic vaccine compared to an mRNA-encoding KRAS and STING.

The novel lipid component of the LNP formulation, SM-102 was not genotoxic when tested in a bacterial reverse mutation (Ames) test or an in vitro micronucleus test. Results of an in vivo micronucleus study performed in the Sprague Dawley rat completed with a similar mRNA-based vaccine (mRNA-1706 encoding the Zika virus prME polypeptide), that was formulated with the same LNPs as mRNA-5671/V941 are considered weakly positive at doses in excess of 2 mg/kg via the intravenous (IV) route of administration. These observations are unlikely to indicate a risk to humans after IM administration due to minimal systemic exposure.

Overall, the nonclinical toxicity of mRNA-5671/V941 formulated in a LNP consisting of 4 lipids (SM-102, PEG2000-DMG, DSPC, and cholesterol) was considered adequately assessed in a GLP-compliant, repeat-dose toxicity study with weekly administration by IM injection at 0.01, 0.03, and 0.10 mg per dose for a total of 5 doses followed by a 2-week treatment-free period. The nonclinical toxicity of the lipid nanoparticle (LNP), the mRNA

chemistry and any differential effects with or without STING mRNA were assessed in nonclinical models. Any immunological effects of KRAS antigen expression are likely to be participant-specific and are more adequately assessed clinically. Based on available nonclinical data, removal of STING mRNA from the drug product is likely to be subtractive and result in an equivalent or decreased toxicology profile for an mRNA-encoding KRAS therapeutic vaccine only compared to an mRNA-encoding KRAS and STING. Therefore, the NOAEL of 0.03 mg achieved in rat GLP study converted to an HED represents a 1.03-fold safety margin compared to the proposed starting dose of 1.0 mg.

2.2.2 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 (Tregs) 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 advanced solid tumors.

2.2.3 Ongoing Clinical

2.2.3.1 mRNA-5671/V941 Clinical Studies

This is the first clinical trial with mRNA-5671/V941.

2.2.3.2 Pembrolizumab (MK-3475) 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.

mRNA-5671/V941 is a novel therapeutic vaccine that is hypothesized to enhance the antitumor immune activity of the PD-1-blocking antibody pembrolizumab. Therefore, mRNA-5671/V941 may potentially provide benefits in terms of increased efficacy in participants with a variety of advanced KRAS mutant solid malignancies with unmet need.

mRNA-5671/V941 encodes for the 4 KRAS mutations (G12D/G12V/G13D/G12C), which are not seen in normal healthy human cells. This approach allows the T cells to be trained and then target the mutated cancer cells, which enables cell killing. The fact that these mutations are not found in normal cells potentially reduces the risk of an autoimmune reaction against healthy tissue.

Risk to participants who receive mRNA-5671/V941 is expected to be low and to primarily involve mild to moderate ISRs (eg, swelling and erythema), which have been observed in animal studies and are generally observed and expected for other IM administered therapeutic vaccines. These local reactions may consist of transient and dose-dependent pain, swelling, and erythema. Possible mild to moderate systemic reactions, which are also transient, may include fever, fatigue, chills, headache, myalgia, and arthralgia. In addition, other adverse events (AEs) that have been generally associated with approved IM administered therapeutic vaccines have included mild hematological and clinical chemistry abnormalities that are usually reversible.

Participants who receive mRNA-5671/V941 could experience signs and symptoms consistent with a complement activation-related pseudoallergy (CARPA) response, which has been observed with the administration of approved liposomal products, contrast agents, pegylated proteins, and antibodies [Szebeni, J. 2014], as well as small interfering RNA products formulated in LNPs [Coelho, T., et al 2013] [Fitzgerald, K. 2014]. The signs and symptoms of CARPA resemble those of an acute hypersensitivity reaction. However, complement activation is far less likely to be associated with clinical signs for LNP products such as

mRNA-5671/V941, which are administered IM at a much lower dose, on a mg/kg basis, than other clinical entities that cause CARPA in humans and nonclinical species.

Pembrolizumab is approved for use in multiple cancer types, and is under investigation in several phases of clinical development for many more. Despite much progress in the field of immune-oncology therapeutics, an unmet medical need exists, as not all participants respond to pembrolizumab monotherapy, most responses are not complete, and it is only approved for use in limited tumor types. Combining pembrolizumab with mRNA-5671/V941 may allow more participants to derive greater clinical benefit than with pembrolizumab monotherapy. This study intends to assess the safety, tolerability, and immunogenicity of mRNA-5671/V941 as a monotherapy and in combination with pembrolizumab in participants with advanced or metastatic KRAS+ solid tumors, and to determine the recommended phase 2 dose (RP2D) of mRNA-5671/V941 to be used in combination with pembrolizumab.

The anticipated toxicities of mRNA-5671/V941 (primarily ISRs) are not expected to overlap or synergize with the known and well-characterized safety profile of pembrolizumab. However, all safety findings will be closely monitored and reviewed by the Sponsor.

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

3 HYPOTHESIS, OBJECTIVES, AND ENDPOINTS

There will be no hypothesis testing in this study.

The objectives and endpoints apply to the study population of male and female participants at least 18 years of age with advanced/metastatic solid tumors who have received, or been intolerant to, or been ineligible for, all treatments known to confer clinical benefit.

Objectives	Endpoints
Primary	
• To determine the safety and tolerability of mRNA-5671/V941 as monotherapy and in combination with pembrolizumab infusion and to establish a preliminary recommended Phase 2 dose of mRNA-5671/V941 in combination with pembrolizumab infusion	• Dose-limiting toxicity (DLT) • Adverse event (AE) • Discontinuing study treatment due to an AE

Objectives	Endpoints
Secondary	
• To evaluate objective response rate (ORR) as assessed by the investigator based on RECIST 1.1 and iRECIST following administration of mRNA-5671/V941 as a monotherapy and in combination with pembrolizumab	• Objective response is a confirmed complete response (CR) or partial response (PR)
• To evaluate the immunogenicity of mRNA-5671/V941 as a monotherapy and in combination with pembrolizumab	• Presence of and changes in the quantity of mutant KRAS specific T cells in the blood
Tertiary/Exploratory	
• To evaluate progression-free survival (PFS) as assessed by investigator based on RECIST 1.1 and iRECIST and overall survival (OS) following administration of mRNA-5671/V941 as a monotherapy and in combination with pembrolizumab	• PFS is time from the first dose of study medication to the first documented disease progression or death due to any cause, whichever occurs first • OS is the time from the first dose of study medication to death due to any cause
• To evaluate changes in relevant immunogenic and pharmacodynamic biomarkers	• Expression of immune markers • T-cell receptor (TCR) clonality and diversity in blood
• To characterize changes in circulating levels of tumor cell DNA (ctDNA) in plasma	• ctDNA plasma levels
• To evaluate the PK of pembrolizumab	• PK parameters including area under the curve (AUC), maximum concentration (C_{max}), and minimum concentration (C_{min})
• 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 mRNA-5671/V941	• 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 multicenter, worldwide, open label, nonrandomized, Phase 1 study of mRNA-5671/V941, as monotherapy and in combination with pembrolizumab in participants with KRAS 4MUT+ (G12D, G12V, G13D or G12C) solid tumors in the dose finding and confirmation phase, and in combination with pembrolizumab in participants with HLA types HLA-A11:01 and/or HLA-C08:02 (and/or potentially other additional HLA types to be specified in the Procedures Manual) with advanced or metastatic KRAS 4MUT+ (G12D, G12V, G13D or G12C) NSCLC, non-MSI-H CRC, or pancreatic adenocarcinoma in the cohort expansion phase.

This study will evaluate the safety, tolerability, and preliminary efficacy of mRNA-5671/V941 as monotherapy (Arm A), and in combination with pembrolizumab (Arm B). There are 2 parts in this study, dose finding and confirmation (Part 1) and tumor cohort expansion (Part 2), which will include 3 cohorts.

In Pre-screening (Part 1 and Part 2), local tumor testing results will be reviewed to identify potential participants with any of the required 4 tumor KRAS mutations (G12D, G12V, G13D or G12C). For Part 2 only, potential participants will also be tested for the required HLA types HLA-A11:01 and/or HLA-C08:02 (and/or potentially other additional HLA types as specified in the Procedures Manual).

The selected participant population for Part 1 will then be screened and allocated to receive mRNA-5671/V941 as monotherapy (Arm A) or mRNA-5671/V941 in combination with pembrolizumab (Arm B) using an interactive voice response system/integrated web response system (IVRS/IWRS). mRNA-5671/V941 will be administered intramuscularly (IM) every 3 weeks (Q3W) on Day 1 of a 21-day cycle. In Arm B, pembrolizumab will be administered intravenously (IV) Q3W on Day 1 of each cycle.

In Part 1 of the study, a modified Toxicity Probability Interval (mTPI) design [Ji, Y. 2013] will be used to identify the recommended Phase 2 dose (RP2D) of mRNA-5671/V941 in Arm A (mRNA-5671/V941 as a single agent), and to identify and confirm the RP2D in Arm B (mRNA-5671/V941 in combination with pembrolizumab). The 1.0 mg dose level (DL 1) of mRNA-5671/V941 will be evaluated independently in each arm. DL -1, DL -2 & DL -3 (0.40 mg, 0.20 mg, and 0.10 mg, respectively) may be used as alternative dose levels should the 1.0 mg dose level prove to be intolerable. Lower and/or higher doses of mRNA-5671/V941 may be explored depending on the combined safety, pharmacokinetic (PK), and pharmacodynamic data available at each dose level. The dose of pembrolizumab in Part 1/Arm B and in Part 2 will remain constant at 200 mg every 3 weeks.

Participants will be enrolled to receive mRNA-5671/V941 monotherapy (Arm A) at the 1.0 mg dose level. Treatment allocation will be accomplished by nonrandom assignment. Enrollment in Arm B (mRNA-5671/V941 in combination with pembrolizumab at the 1.0 mg DL 1 will begin once the DLT observation period for Arm A has been completed and the

1.0 mg DL 1 dose has been deemed safe. If dose reductions to DL -1, DL -2, or DL -3 in Arm A are required, then Arm B enrollment at the reduced dose level in combination with pembrolizumab will only be initiated once that mRNA-5671/V941 dose has been deemed safe. The final number of participants enrolled in Part 1 will depend on the empirical safety observations (DLT), and what dose is ultimately identified as the RP2D using the mTPI design.

Dose finding and confirmation in Arm B will end after 14 participants have been treated at any of the selected doses (which may include the optional doses). The pool adjacent-violators algorithm [Ji, Y. 2013] will be used to estimate the DLT rates across doses in each treatment arm under the assumption of monotonicity between DLT rates and dose levels. The dose with an estimated DLT rate closest to 30% may be treated as a preliminary RP2D. The totality of the data will be considered before deciding on the dose(s) to carry forward to Part 2. The RP2D of mRNA-5671/V941 in the combination arm (Arm B) will not exceed, but may equal, the RP2D in the mRNA-5671/V941 monotherapy arm (Arm A).

In Part 2, participants with advanced solid tumors who have received various prior lines of therapy will be enrolled into each of the following 3 expansion cohorts for the following tumor types: 40 participants with advanced/metastatic NSCLC, 15 participants with non-MSI-H CRC, and 15 participants with pancreatic adenocarcinoma. Participants must have tumor KRAS G12D, G12V, G13D, or G12C mutations, as determined by local testing, and must also have confirmed HLA types HLA-A11:01 and/or HLA-C08:02 (and/or potentially other additional HLA types to be specified in the Procedures Manual). Part 2 will further evaluate safety and efficacy of mRNA-5671/V941 in combination with pembrolizumab at the mRNA-5671/V941 RP2D defined in Part 1 Arm B.

The final RP2D for future studies will be confirmed using all available safety information (including early and late toxicities from Parts 1 and 2), as well as immunogenicity and pharmacodynamic data, and preliminary efficacy assessments.

Participants on active treatment with pembrolizumab monotherapy in the post-treatment phase are discontinued and may be enrolled in to a pembrolizumab extension study. Participants in survival follow-up phase will not be rolled-over.

Preliminary efficacy will be evaluated using objective response rate (ORR) assessed by the investigator based on the Response Evaluation Criteria In Solid Tumors version 1.1 (RECIST 1.1) as a secondary objective. Progression-free survival (PFS) based on RECIST 1.1 as assessed by the investigator and overall survival (OS) will be evaluated as exploratory objectives. ORR and PFS will be also assessed by modified Response Evaluation Criteria in Solid Tumors 1.1 for immune-based therapeutics (iRECIST).

Participants will be monitored carefully for the development of adverse events AEs, and for clinical and/or radiographic evidence of disease progression according to RECIST 1.1. However, iRECIST may be used by the investigator for treatment decisions. In participants who have initial evidence of radiological progressive disease by RECIST 1.1, it will be at the discretion of the investigator whether to continue a participant on study treatment until repeat

imaging is obtained. This clinical judgment decision should be based on the participant's overall clinical condition, including performance status, clinical symptoms, and laboratory data. Participants may continue to receive study treatment until tumor assessment is repeated 4 to 8 weeks later in order to confirm progressive disease by iRECIST per site assessment.

Adverse events (AEs) will be evaluated by the investigator, according to criteria outlined in the National Cancer Institute (NCI) Common Toxicity Criteria for Adverse Events (CTCAE), version 4.0, to establish the safety and tolerability of mRNA-5671/V941 when administered as monotherapy or in combination with pembrolizumab as per the primary objective of this study.

There will be no intraparticipant dose escalation for participants enrolled in this study. The definition of DLTs and criteria for dose modification of mRNA-5671/V941 and pembrolizumab are outlined in Sections 6.6.1 to 6.6.4. Pembrolizumab will be administered at a fixed dose of 200 mg every 3 weeks.

Participants may receive study treatment with mRNA-5671/V941 (Arm A and Arm B) for up to 9 cycles and with pembrolizumab (Arm B) for up to 35 cycles (24 months). Participants will be treated until progressive disease, unacceptable toxicity, intercurrent illness that prevents further administration of treatment, investigator's decision to withdraw treatment, participant withdrawal of consent, pregnancy of the participant, noncompliance with trial treatment or procedure requirements, participant completes treatment, or administrative reasons requiring cessation of treatment, at which point they will be discontinued from the study.

Participants in Part 1 Arm A who develop progressive disease during therapeutic vaccination monotherapy or within 6 months after completing therapeutic vaccination monotherapy may be eligible to crossover and receive pembrolizumab, at the investigator's discretion and after consultation with and approval by the Sponsor.

1. Participants who have not completed 9 doses of mRNA-5671/V941 as monotherapy at the time of progressive disease may be eligible to crossover and complete the remaining therapeutic vaccine doses as part of combination therapy with pembrolizumab. The first dose of combination treatment will not occur until after the 21-day Cycle 1 of mRNA-5671/V941 monotherapy treatment is completed.

2. Participants who have completed 9 doses of mRNA-5671/V941 as monotherapy may be eligible to crossover and receive pembrolizumab as monotherapy if:

    a. They have radiologic evidence of progressive disease within 6 months after completing mRNA-5671/V941 monotherapy, AND

    b. Have not started subsequent anti-neoplastic therapy.

Participants may continue receiving crossover treatment until disease progression, unacceptable toxicity, intercurrent illness that prevents further administration of treatment, investigator's decision to withdraw treatment, participant withdrawal of consent, pregnancy

of the participant, noncompliance with trial treatment or procedure requirements, administrative reasons requiring cessation of treatment, or the completion of 35 cycles of pembrolizumab treatment. These participants' safety and efficacy data will be analyzed separately than that of the participants enrolled in Arm B.

All participants will be followed for at least 30 days after their last dose of mRNA-5671/V941 or pembrolizumab therapy for AE monitoring. Serious adverse events (SAE) will be collected for120 days after discontinuation of study treatment, 30 days if the participant initiates new anticancer therapy less than 30 days after study treatment discontinuation, or the day new anticancer therapy is initiated if between 30 days and 120 days after study treatment discontinuation. Participants with an ongoing AE of Grade >1 at the time of treatment discontinuation will be followed until resolution of the AE to Grade 0-1, until considered stable by the treating physician, or until beginning a new anticancer therapy, whichever occurs first.

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

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

Specific procedures to be performed during the study, 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

4.2.1 Rationale for Endpoints

4.2.1.1 Efficacy Endpoints

4.2.1.1.1 Response Rate Assessed by RECIST version 1.1

RECIST 1.1 will be used to determine the objective 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 pembrolizumab Section 8.2.1.5. Immunotherapeutic agents such as 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 exploratory efficacy analyses when specified.

4.2.1.2 Safety Endpoints

The primary objective of this trial is to characterize the safety and tolerability of mRNA-5671/V941 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 and DLTs further defined in Section 6.6.2. Safety will be assessed by quantifying the toxicities and grades of toxicities experienced by participants who have received mRNA-5671/V941 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

An exploratory objective of this study is to characterize the pharmacokinetic (PK) profile of pembrolizumab following administration as combination therapy with mRNA-5671/V941. The serum concentrations of pembrolizumab will serve as the primary readout for the PK, and these data will be used to derive PK parameters of pembrolizumab when administered in

combination. Furthermore, the results of these analyses will be used in conjunction with the pharmacodynamics, and safety and exploratory endpoint data to help assess future dosing strategies.

4.2.1.4 Pharmacodynamic Endpoints

4.2.1.4.1 Immunogenicity

A secondary objective of this study is to evaluate the immunogenicity of mRNA-5671/V941 when administered alone and in combination with pembrolizumab. This will be assessed by quantifying the presence of and changes in KRAS-specific T cells in peripheral blood. Exploratory immunogenicity endpoints may also include changes in immune markers as assessed by gene expression analyses and the clonality and diversity of TCRs in the blood.

4.2.1.5 Antidrug Antibodies (ADA)

Formation of antidrug antibodies (ADA) can potentially confound drug exposures at therapeutic doses and prime for subsequent infusion-related toxicity. Antidrug (pembrolizumab) antibody response at the beginning of each cycle will be determined to understand drug metabolism, exposure, and safety. The incidence of ADA and neutralizing ADA will be evaluated and summarized over time by dose. Correlations between the presence/absence of positivity for antidrug antibodies and PK and pharmacodynamic markers, activity, and safety of mRNA-5671/V941 and/or pembrolizumab will be explored.

4.2.1.6 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 mRNA expression profiling and sequencing in tumor tissue and/or in blood may be performed to define gene signatures that correlate to clinical response to treatment with 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.

4.2.1.6.1 Planned Genetic Analysis

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

DNA samples will be used for research related to the study intervention(s), the disease under study, and related diseases. They may also be used to develop tests/assays including diagnostic tests related to the disease under study, related diseases, and study intervention(s). Genetic research may consist of the analysis of 1 or more candidate genes or the analysis of genetic markers throughout the genome [or analysis of the entire genome] (as appropriate).

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

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

4.2.1.7 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 (ribonucleic acid [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 6.

4.3 Justification for Dose

4.3.1 Rationale for Pembrolizumab Dose

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 pharmacokinetic [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.

4.3.2 Rationale for Starting and Maximum Dose of mRNA-5671/V941

The planned clinical starting dose for mRNA-5671/V941 is 1.0 mg. The selection of this starting dose is based on support by the safety and tolerability of the 1.0 mg dose of the similarly formulated mRNA-4157/V940 personalized therapeutic cancer vaccine that has been evaluated in clinical trials. Overall, based on HED, the NOAEL of 0.03 mg achieved in the rat GLP study converted to a human equivalent dose represents an approximate 1.03-fold safety margin compared to the proposed human starting dose of 1.0 mg. Therefore, the 1.0 mg starting dose is supported by the nonclinical safety and tolerability demonstrated in the mRNA-5671/V941 GLP-compliant 1-month toxicity study as well as based on the clinical experience from the related mRNA-4157/V940 therapeutic vaccine developed using the same mRNA technology platform. mRNA-4157/V940 has been evaluated in Phase 1 clinical trials and is formulated in a LNP consisting of the same 4 lipids (SM-102, PEG2000-DMG, DSPC and cholesterol). It has been well-tolerated in patients up to 1.0 mg intramuscularly.

mRNA-4157/V940 is currently in Phase 1 development, both as monotherapy and in combination with pembrolizumab. Each patient's mRNA-4157/V940 therapeutic vaccine consists of a single mRNA that encodes up to 34 neoantigens designed specifically to each individual patient's tumor mutanome and HLA type. The Phase 1 first in human study of mRNA-4157-P101 (NCT03313778) is currently ongoing. This study is an open-label, Phase 1, multicenter dose-escalation, First-In-Human study of mRNA-4157/V940 monotherapy in participants with resected solid tumors (Part A) who are in the adjuvant setting (ie, status post-resection); mRNA-4157/V940 in combination with pembrolizumab in participants with unresectable (locally advanced or metastatic) solid tumors (Part B, C); and mRNA-4157/V940 in combination with pembrolizumab in melanoma participants who are in the adjuvant setting (Part D).

As of 31-DEC-2019, mRNA-4157/V940 has been dosed to 75 patients in total, 15 patients as monotherapy and 60 patients in combination with pembrolizumab at multiple dose levels. Of those, 44 patients received mRNA-4157/V940 at a dose level of 1 mg in combination with pembrolizumab. There were no dose limiting toxicities reported at any dose levels, including the 1 mg dose. While the tumor antigens encoded by the mRNAs of mRNA-4157/V940 personalized therapeutic cancer vaccine do differ from those encoded by the mRNA of mRNA-5671/V941 (encoding mutated KRAS epitopes), mRNA-5671/V941 is expected to have a similar clinical tolerability profile to mRNA-4157/V940 as both therapeutic vaccines are intended for IM delivery to patients with advanced cancers and both consist of similar mRNA nucleotide chemistry formulated for delivery in a lipid nanoparticle (LNP) formulation with overall comparable ratios of constituents (including the cationic lipid SM-102, PEG-DMG, etc.). Any dose limiting toxicities that might occur during the DLT observation period would be anticipated to be due to the LNP, independent of the identity of the encapsulated mRNA; as such, the available clinical experience with mRNA-4157 up to

1.0 mg supports the initiation of clinical dosing for evaluation of therapeutic benefit to advanced cancer patients with mRNA-5671/V941 at 1.0 mg.

As described in the repeat-dose GLP toxicology studies in outbred Sprague Dawley rats, the no observed adverse effect level (NOAEL) is to be 0.03 mg based on low severity and incidence of the clinical and microscopic findings at this dose in rats. Therefore, the proposed human starting dose of 1.0 mg represents an approximate 1.03-fold safety margin. The Sponsor considers this a sufficient safety margin for the 1.0 mg starting dose in this clinical study, especially given that the 1.0 mg mRNA-4157/V940 dose has been well tolerated clinically.

In summary, 44 patients have been dosed at the 1.0 mg dose level with mRNA-4157/V940, a therapeutic IM vaccine similar in formulation to mRNA-5671/V941 and expected to exhibit a safety profile similar to that of mRNA-5671/V941. This dose of mRNA-4157/V940 has been found to be safe in human cancer patients, supporting a starting dose for mRNA-5671/V941 of 1.0 mg.

Nine cycles of mRNA-5671/V941 are planned in order to boost the intended tumor-killing T-cell population over an extended period of time by promoting optimal development of T effector memory cells [Knudsen, M. L., et al 2014]. The 21-day cycle allows for maximal contraction of the antigen-specific $CD8^+$ T-cell response before boosting, which has been found to produce the best maintenance of $CD8^+$ T cells with high recall capacity. From a safety perspective, the Sponsor assessed the toxicity of mRNA-5671/V941 in outbred Sprague Dawley® rats at 0.01, 0.03, and 0.10 mg per dose via IM injection administered weekly for a total of 5 doses, followed by a 14-day post-study recovery period. This preclinical weekly injection schedule is 3-fold more dose-dense over time than the clinical dosing schedule in this study and thus provides an additional margin to avoid potential cumulative toxicity. The Sponsor considers this Q3W 9 dose regimen appropriate for mRNA-5671/V941.

4.3.3 Rationale for Dose Interval and De-escalation Increments

The human starting dose and dosing interval of mRNA-5671/V941 are based on an integration of nonclinical toxicological, pharmacological, and efficacy data, as well as on safety data from the similarly formulated mRNA-4157/V940 therapeutic vaccine, as described in Section 4.3.2. Dose de-escalation decisions will be made according to mTPI, based on 3 dosing outcomes, ie, underdosing, proper dosing, or overdosing. In the case of overdosing at 1.0 mg, mTPI will recommend de-escalating the dose level using model-based inference on the toxicity probability. If required, mTPI dose de-escalation will follow approximately half-log increments, rounded up to the next 0.10 mg (ie, 0.40 mg [DL -1], 0.20 mg [DL -2], and 0.10 mg [DL -3] doses). The mTPI dose evaluation scheme is consistent with US Food and Drug Administration (FDA) guidance for early-phase clinical trials involving cellular and gene therapy products [U.S. Department of Health and Human Services 2015].

In tumor cohorts of participants treated with a combination of mRNA-5671/V941 and pembrolizumab, the dose of mRNA-5671/V941 to be used in combination with pembrolizumab must have been deemed safe as monotherapy based on mTPI evaluation and will not exceed the maximum tolerated dose (MTD)/ maximum administered dose (MAD) for monotherapy. If an MTD/MAD for the monotherapy arm is established, the dose of mRNA-5671/V941 in combination with pembrolizumab may continue up to that dose.

4.3.4 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% (a different DLT rate may be considered in participants evaluable for DLT). 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. It is to be noted that participants in the dose finding phase will not be restricted by HLA type.

A minimum of 3 participants are required at each dose. However, depending on the accrual rate, 3, 4, 5, or 6 participants may be enrolled within 7-14 days 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 trial due to unacceptable toxicity, respectively. For example, if 0 out of 3 participants at a given dose level develop a DLT, then the dose can escalate to the next level. If 2 participants out of 3 develop a DLT, the dose will be de-escalated to the next lower dose level. If 3 out of 3 participants develop a DLT, this indicates an unacceptable toxicity at this dose. The dose should be de-escalated, and the current dose will not be explored further. If 1 out of 3 participants at a given dose level develops a DLT, then additional participants should be enrolled at that dose level following the rules below.

When adding participants to a dose level in response to a “stay” decision, the 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 trial. An E decision at the highest dose level will result in staying at that level. During dose finding, it may be acceptable to deescalate 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 Part 2, and the escalation schedule may be adjusted based on pharmacodynamic, PK, and safety data emerging throughout the trial. The preliminary RP2D of mRNA-5671/V941 in the combination arm (Arm B) will not exceed, but may be equal to, the preliminary RP2D in the mRNA-5671/V941 monotherapy arm (Arm A).

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

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

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).

Participants on active treatment with pembrolizumab monotherapy in the post-treatment phase are discontinued and may be enrolled in to a pembrolizumab extension study. Participants in the survival follow-up phase will not be rolled-over.

4.4.1 Clinical Criteria for Early Study Termination

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

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

2. In addition to DLT and dose de-escalation criteria defined in the dose finding phase of the study, if, in the expansion cohorts**,** toxicities observed meet the definition of a DLT and occur in >33% of the total number of enrolled participants, the study will pause, and an expedited ad hoc safety evaluation will be assessed by the Sponsor prior to further enrollment in the study.

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

4. Poor adherence to protocol and regulatory requirements.

5. 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 mRNA-5671/V941 or pembrolizumab.

5 STUDY POPULATION

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

5.1 Inclusion Criteria

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

1. **All participants:** Have a histologically confirmed advanced or metastatic KRAS 4MUT+ (G12D, G12V, G13D or G12C) solid tumor identified by local laboratory testing, and who have received, or been intolerant to, or ineligible for all treatment known to confer clinical benefit.

   Note: If local tumor KRAS mutation testing has not previously been performed as standard of care, such testing may be conducted on study in Pre-screening to determine eligibility, but only if discussed with and approved by the Sponsor.

   Part 2 only: Have a histologically confirmed advanced or metastatic NSCLC, non-MSI-H CRC, or pancreatic adenocarcinoma, and confirmed HLA types HLA-A11:01 and/or HLA-C08:02 (and/or potentially other additional HLA types to be specified in the Procedures Manual).

   NSCLC: Participants must have been tested for mutations affecting EGFR and/or anaplastic lymphoma kinase (ALK). Participants with ALK or EGFR-positive NSCLC must have had recurrent or progressive disease (PD) after treatment with the corresponding inhibitor and current standard of care, in any sequence.

   Non-MSI-H CRC: Participant tumors must have been locally tested for MSI and have been found to be non-MSI-H.

Demographics

2. Participant is Male or Female.

3. Participant is at least 18 years of age, at the time of providing documented informed consent.

Male Participants

4. A male participant must agree to use 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

5. 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

6. The participant (or legally acceptable representative if applicable) provides documented informed consent for the study. The participant may also provide consent for future biomedical research. However, the participant may participate in the main study without participating in future biomedical research.

Additional Categories

7. Have measurable disease per RECIST 1.1 as assessed by the local site investigator/radiology. Lesions situated in a previously irradiated area are considered measurable if progression has been demonstrated in such lesions. **For Part 1 only:** Cutaneous lesions can be considered in addition to imaging, but measurable disease should be defined by radiologic assessment.

8. Have an evaluable archival tumor sample to submit for analysis. Formalin-fixed, paraffin embedded (FFPE) tissue blocks are preferred to slides.

   Note: If submitting unstained cut slides, newly cut slides should be submitted to the testing laboratory within 14 days from the date slides are cut. Details pertaining to tumor tissue submission can be found in the Procedures Manual.

9. Have adequate organ function as defined in the following table (Table 2). Specimens must be collected within 7 days prior to the start of study intervention.

Table 2 Adequate Organ Function Laboratory Values

System	Laboratory Value
Hematological	
Absolute neutrophil count (ANC)	≥1500/μL
Platelets	≥100 000/μL
Hemoglobin	≥9.0 g/dL or ≥5.6 mmol/L[1]
Renal	
Creatinine OR Measured or calculated[2] creatinine clearance (GFR can also be used in place of creatinine or CrCl)	≤1.5 × ULN OR ≥30 mL/min for participant with creatinine levels >1.5 × institutional ULN
Hepatic	
Total bilirubin	≤1.5 ×ULN OR direct bilirubin ≤ULN for participants with total bilirubin levels >1.5 × ULN
AST (SGOT) and ALT (SGPT)	≤2.5 × ULN (≤5 × ULN for participants with liver metastases)
Coagulation	
International normalized ratio (INR) OR prothrombin time (PT) Activated partial thromboplastin time (aPTT)	≤1.5 × ULN unless participant is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants

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

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

[2]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.

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

In order to be eligible to crossover from Arm A into Arm B in Part 1 of this trial, the participant must meet the following criteria:

11. Have radiographic disease progression as defined by RECIST v1.1 on Arm A mRNA-5671/V941 monotherapy and have Sponsor approval for crossover.

5.2 Exclusion Criteria

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

Medical Conditions

1. A WOCBP who has a positive urine pregnancy test within 72 hours prior to randomization or treatment allocation (see Appendix 5). If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required.

   Note: In the event that 72 hours have elapsed between the screening pregnancy test and the first dose of study treatment, another pregnancy test (urine or serum) must be performed and must be negative in order for participant to start receiving study medication.

2. Has an active infection requiring therapy.

3. Has a history of interstitial lung disease.

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

5. Has conditions, 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.

6. Has not fully recovered from any effects of major surgery or has evidence of 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.

Prior/Concomitant Therapy

7. 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, non-cytotoxic small molecule therapeutics within 5 half-lives (or 2 weeks, whichever is longer) prior to the first dose of study treatment, 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.

8. Has received a live-virus vaccine within 30 days of planned treatment start. Seasonal flu vaccines that do not contain live virus are permitted. Refer to Section 6.5 for information on COVID-19 vaccines.

9. Has received hematopoietic colony-stimulating growth factors (eg, granulocyte-colony stimulating factor, erythropoietin, granulocyte-macrophage-colony stimulating factor, macrophage-colony stimulating factor) within 2 weeks prior to the first dose of study intervention.

10. Discontinued from therapy with an anti-PD-1, anti-PD-L1, or anti-PD-L2 agent or with an agent directed to another stimulatory or co-inhibitory T-cell receptor (TCR; eg, CTLA-4, OX 40, and CD137) due to a Grade 3 or higher immune-related adverse event (irAE).

Prior/Concurrent Clinical Study Experience

11. Is currently participating in or has participated in a study of an investigational agent or has used an investigational device within 28 days prior to the first dose of study intervention.

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

Diagnostic Assessments

12. Has a diagnosis of immunodeficiency or is receiving chronic systemic steroid therapy (in dosing exceeding 10 mg daily of prednisone equivalent) or any other form of immunosuppressive therapy within 7 days prior the first dose of study drug.

13. Has a known additional malignancy that is progressing or has required active treatment within the past 2 years.

    Note: Participants with basal cell carcinoma of the skin, squamous cell carcinoma of the skin, or carcinoma in situ (eg, breast carcinoma, cervical cancer in situ) that have undergone potentially curative therapy are not excluded.

14. Has known active CNS metastases and/or carcinomatous meningitis. Participants with previously treated brain metastases may participate provided they are radiologically stable, (ie, without evidence of progression) for at least 4 weeks by repeat imaging (note that the repeat imaging should be performed during study screening), clinically stable and without requirement of steroid treatment for at least 14 days prior to first dose of study intervention.

15. Has severe hypersensitivity (≥Grade 3) to pembrolizumab and/or any of its excipients.

16. Has a history of (non-infectious) pneumonitis that required steroids or has current pneumonitis.

17. Has a known history of Hepatitis B (defined as Hepatitis B surface antigen [HBsAg] reactive) or known active Hepatitis C virus (defined as HCV RNA [qualitative] is detected) infection.

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

18. Has a known history of HIV.

    Note: No testing for HIV is required unless mandated by local health authority.

19. Has a known psychiatric or substance abuse disorder that would interfere with cooperating with the requirements of the study.

Other Exclusions

20. 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 intervention.

21. Has had an allogenic tissue/solid organ transplant.

5.3 Lifestyle Considerations

5.3.1 Meals and Dietary Restrictions

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

5.3.2 Contraception

Pembrolizumab and/or mRNA-5671/V941 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.

5.3.3 Pregnancy

If a participant inadvertently becomes pregnant while on treatment, 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 experience (eg, death, abortion, congenital anomaly, or other disabling or life-threatening complication to the mother or newborn). The study Investigator will make every effort to obtain permission to follow the outcome of the pregnancy and report the condition of the fetus or newborn to the Sponsor. If a male participant impregnates his female partner, the study personnel at the site must be informed immediately and the pregnancy must be reported to the Sponsor and followed as described in Section 8.4.

5.3.4 Use in Nursing Women

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

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 Cycle 1. Participants are considered nonevaluable and will be replaced if:

- They are allocated but not treated.
- They discontinue from the trial prior to completing all the safety evaluations for reasons other than treatment-related adverse events during Cycle 1 in the dose finding phase of the study (Part 1).
- They receive less than 100% of the total mRNA-5671/V941 or less than 90% of the total pembrolizumab infusion in Cycle 1 (eg, if the infusion had to be discontinued due to an infusion reaction) and did not experience a DLT.

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

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

6 STUDY INTERVENTION

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

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

6.1 Study Intervention(s) Administered

The study intervention(s) to be used in this study are outlined in Table 3.

Table 3 Study Interventions

Arm Name	Arm Type	Intervention Name	Type	Dose Formulation	Unit Dose Strength(s)	Dosage Level(s)	Route of Administration	Regimen/ Treatment Period/ Vaccination Regimen	Use	IMP or NIMP/ AxMP	Sourcing
Arm A – mRNA-5671/ V941 mono-therapy	Experimental	mRNA-5671/V941	Biological/Vaccine	Ampule	1.0 mg/mL	DL 1: 1.00 mg DL -1: 0.40 mg DL -2: 0.20 mg DL -3: 0.10 mg	IM	Q3W for up to 9 cycles	Test Product	IMP	Provided centrally by the Sponsor
Arm B and Cross-over mRNA-5671/ V941 + pembrolizumab	Experimental	mRNA-5671/V941	Biological/Vaccine	Ampule	1.0 mg/mL	DL 1: 1.00 mg DL -1: 0.40 mg DL -2: 0.20 mg DL -3: 0.10 mg	IM	Q3W for up to 9 cycles	Test Product	IMP	Provided centrally by the Sponsor
Arm B and Cross-over mRNA-5671/ V941 + pembrolizumab	Active Comparator	Pembrolizumab	Biological/Vaccine	Ampule	25 mg/mL	200 mg	IV Infusion	Q3W for up to 35 cycles	Comparator	IMP	Provided centrally by the Sponsor

AxMP=auxiliary medicinal product; DL=dose level; IMP=investigational medicinal product; NIMP=non-investigational medicinal product; Q3W=every 3 weeks.

Participants may receive up to 9 total doses of mRNA-5671/V941 in either the monotherapy or combination arm.
Dose Levels DL -1, DL -2, and DL -3 will only be enrolled in the event that DLTs are observed in the starting dose (1.0 mg), per the mTPI design.

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

All study interventions will be administered on an outpatient basis.

All products indicated in Table 3 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 intervention.

6.1.1 mRNA-5671/V941 Administration

For all participants, mRNA-5671/V941 will be administered by IM injection into the deltoid or thigh muscle (deltoid preferred). The Pharmacy Manual contains specific instructions for the preparation and administration of mRNA-5671/V941.

6.1.2 Pembrolizumab Administration

For participants receiving mRNA-5671/V941 in combination with pembrolizumab, pembrolizumab will be administered at the study site as a 30-minute IV infusion of a 200 mg fixed dose on Day 1 of each 3-week (21-day) cycle 30 to 60 minutes following the administration of mRNA-5671/V941. Sites should make every effort to keep infusion duration as close to 30 minutes as possible. However, given the variability of infusion pumps from site to site, a window of 25 to 40 minutes is permitted for infusion duration. The Pharmacy Manual contains specific instructions for the preparation of the pembrolizumab infusion and administration of the infusion solution.

6.2 Preparation/Handling/Storage/Accountability

6.2.1 Dose Preparation

Details on preparation and administration of mRNA-5671/V941 and pembrolizumab are provided in the Pharmacy Manual.

There are no specific calculations or evaluations required to be performed in order to administer the proper dose to each participant. The rationale for selection of doses to be used in this study is provided in Section 4.3.

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 occur centrally using an interactive voice response system/integrated web response system (IVRS/IWRS). There are 2 treatment arms. Participants will be allocated to 1 of 2 treatment arms: mRNA-5671/V941 monotherapy (Arm A) or mRNA-5671/V941 in combination with pembrolizumab (Arm B) using an IVRS/IWRS in Part 1.

In Part 1 of the study, treatment will be allocated by nonrandom assignment. Enrollment into DL1 in Arm B will begin once all participants in DL1 Arm A complete the DLT evaluation (1 cycle) and DL1 of Arm A has been demonstrated to be safe and tolerable in this cohort. If/when both treatment arms are open for enrollment, IVRS/IWRS will alternate participant assignment between Arm A and Arm B starting with Arm A. An observation period of at least 7 days will occur between treatment initiation for the first participant and second participant within each dose level. A new dose cohort at DL -1, -2, or -3 may open for enrollment without delay once the 21-day DLT observation period of the previous dose cohort is completed and a dose de-escalation decision is made.

Participants on Arm A, who have radiological evidence of disease progression may be allowed to crossover to Arm B, at the investigator's discretion and after consultation with and approval by the Sponsor. Cohort assignment of crossover participants will be determined

at time of crossover by the Sponsor based on safety evaluation of the combination therapy cohorts. Refer to Section 4.1 for more information regarding eligibility for crossover.

When Part 2 is open for enrollment, IVRS/IWRS will assign participants to 1 of 3 cohorts by tumor type.

In a situation where reallocation/rerandomization of participants is planned (eg, study extension periods), the reallocation/rerandomization will be based on a new allocation/randomization schedule; however, each participant will retain his/her original treatment/randomization number. Only the study intervention regimen associated with the reallocation/rerandomization period or phase may change.

6.3.2 Stratification

In Part 1 of the study, no stratification based on age, sex, or other characteristics will be used.

In Part 2 of the study, treatment allocation will be stratified according to the following factors:

1. Tumor type: Non-Small Cell Lung Cancer, Colorectal Cancer or Pancreatic Adenocarcinoma

6.3.3 Blinding

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

6.4 Study Intervention Compliance

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

Interruptions from the protocol-specified treatment plan for more than 12 weeks 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 or vaccinations specifically prohibited in the exclusion criteria are not allowed during the ongoing study. If there is a clinical indication for any medication or vaccination specifically prohibited, discontinuation from study therapy or vaccination may be required. The investigator should discuss any questions regarding this with the Sponsor's Clinical Director. The final decision on any supportive therapy or vaccination rests with the investigator and/or the participant's primary physician. However, the decision to continue the participant on study intervention requires the mutual agreement of the investigator, the Sponsor, and the participant.

6.5.1 Acceptable Concomitant Medications

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 intervention, should be discussed with the Sponsor Clinical Director or designee.

6.5.2 Prohibited Concomitant Medications

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

- Antineoplastic systemic chemotherapy or biological therapy not specified in this protocol
- Immunotherapy not specified in this protocol
- Chemotherapy not specified in this protocol
- Investigational agents other than pembrolizumab or mRNA-5671/V941
- Radiation therapy

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

- Live vaccines within 30 days prior to the first dose of study intervention 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, 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.

  Note: Any licensed COVID-19 vaccine (including for Emergency Use) in a particular country is allowed in the study as long as they are mRNA vaccines, adenoviral vaccines, or inactivated vaccines. These vaccines will be treated just as any other concomitant therapy.

  Investigational vaccines (ie, those not licensed or approved for Emergency Use) are not allowed.

- Systemic glucocorticoids for any purpose other than to modulate symptoms from an ECI that is suspected to have an immunologic etiology. The use of physiologic doses of corticosteroids may be approved after consultation with and approval by the Sponsor.

- Granulocyte-colony stimulating factors and erythropoietin should not be used prophylactically during the DLT evaluation period. Use of prophylactic colony stimulating factors may be considered thereafter following consultation with and approval by the Sponsor.

Participants who, in the assessment of the Investigator, require the use of any of the aforementioned treatments for clinical management should be removed from the study.

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

All concomitant medications received within 28 days prior to the first dose of study intervention and up to 30 days after the last dose of study intervention should be recorded. Concomitant medications administered 30 days after the last dose of study intervention should be recorded for SAEs and events of clinical interest (ECIs) as defined in Section 8.4.

6.5.3 Rescue Medications and Supportive Care

6.5.3.1 mRNA-5671/V941 Supportive Care Guidelines

Participants should receive appropriate supportive care measures for adverse experiences potentially associated with mRNA-5671/V941 administration as deemed necessary by the treating investigator including, but not limited to, the item(s) outlined below.

Management of Cytokine Release Syndrome (CRS): Cytokine release syndrome is defined in CTCAE v4 as a disorder characterized by nausea, headache, tachycardia, hypotension, rash, and shortness of breath. CRS occurs when lymphocytes (B cells, T cells, and/or natural killer cells) and/or myeloid cells (macrophages, dendritic cells, and monocytes) become activated and release inflammatory cytokines [Lee, D. W., et al 2014]. In addition to the symptomatology defined under CTCAE, CRS may present with fever, chills, myalgias, and malaise [Lee, D. W., et al 2014]. Table 4 shows treatment guidelines for participants who experience CRS.

Table 4 Cytokine Release Syndrome Treatment Guidelines

NCI CTCAE Grade	Treatment	Premedication at subsequent dosing
Grade 1 Mild reaction: Therapy interruption not indicated. Intervention not indicated.	Increase monitoring of vital signs and oxygen saturation, as medically indicated, until the participant is deemed medically stable in the opinion of the Investigator	None
Grade 2 Therapy interruption indicated but responds promptly to symptomatic treatment (eg, NSAIDS, narcotics, IV fluids). Prophylactic medications indicated for ≤ 24 hours	Increase monitoring of vital signs and oxygen saturation, as medically indicated, until the participant is deemed medically stable in the opinion of the Investigator Additional appropriate medical therapy may include, but is not limited to: IV fluids NSAIDS Acetaminophen Narcotics Oxygen Perform fever work-up to exclude infectious etiologies; treat neutropenia if present	Participant may be premedicated 1.5 hours (± 30 minutes) prior to mRNA-5671/V941 administration with acetaminophen 500 to 1000 mg PO (or equivalent dose of antipyretic)
Grade 3 Prolonged (eg, not rapidly responsive to symptomatic medication); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae (eg, renal impairment, pulmonary infiltrates)	Additional appropriate medical therapy may include, but is not limited to: IV fluids NSAIDS Acetaminophen Narcotics Oxygen Pressors Corticosteroids Anti-IL6 (eg, tocilizumab) Empiric antibiotics Participants with ≥ Grade 3 CRS need to be monitored very closely, likely in an intensive care setting	For Grade 3 CRS, discuss with Sponsor prior to restart of mRNA-5671/V941 treatment. Participant may be premedicated 1.5 hours (± 30 minutes) prior to mRNA-5671/V941 administration with acetaminophen 500 to 1000 mg PO (or equivalent dose of antipyretic)
Grade 4 Life-threatening consequences; pressor or ventilatory support indicated	Additional appropriate medical therapy may include, but is not limited to: IV fluids NSAIDS Acetaminophen Narcotics Oxygen Pressors Corticosteroids Anti-IL6 (eg, tocilizumab) Empiric antibiotics Participants with ≥ Grade 3 CRS need to be monitored very closely, likely in an intensive care setting	Permanently discontinue mRNA-5671/V941 in participants who develop Grade 4 CRS

6.5.3.2 Pembrolizumab Supportive Care Guidelines

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, Table 5. Where appropriate, these guidelines include the use of oral or IV treatment with corticosteroids, as well as additional anti-inflammatory agents if symptoms do not improve with administration of corticosteroids. Note that several courses of steroid tapering may be necessary as symptoms may worsen when the steroid dose is decreased. For each disorder, attempts should be made to rule out other causes such as metastatic disease or bacterial or viral infection, which might require additional supportive care. The treatment guidelines are intended to be applied when the investigator determines the events to be related to 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 5 in Section 6.6 for guidelines regarding dose modification and supportive care.

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

6.6 Dose Modification (Escalation/Titration/Other)

6.6.1 Dose Administration/Escalation

6.6.1.1 Dose Administration (Preparation)

Details on preparation and administration mRNA-5671/V941 and pembrolizumab are provided in the appropriate Pharmacy or Procedures 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 21 days from the first dose of study treatment (Cycle 1). Participants will be monitored for DLTs during treatment with mRNA-5671/V941 as a monotherapy as well as in when mRNA-5671/V941 is administered in combination with pembrolizumab.

For dose-escalation decisions, an evaluable participant is defined as a participant who meets one of the following criteria:

- Receives any amount of an mRNA-5671/V941 dose alone or in combination with a pembrolizumab dose and experiences a DLT during Cycle 1.

- Receives 100% of an mRNA-5671/V941 dose in Arm A, Cycle 1 or 100% of an mRNA-5671/V941 dose and/or ≥ 90 % of a pembrolizumab dose in Arm B, Cycle 1, is followed up for ≥ 21 days after the first dose of study treatment, and does not experience a DLT.

Participants who are not considered to be evaluable may be replaced (Section 5.5).

The occurrence of any of the following toxicities will be considered a DLT if judged by the investigator to be possibly related to administration of either mRNA-5671/V941 monotherapy or mRNA-5671/V941 in combination with pembrolizumab (ie, the toxicity is not attributable to the disease or disease-related processes under investigation or other causes):

1. Grade 4 nonhematologic toxicity (ie. Not a laboratory finding).

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

3. Grade 4 thrombocytopenia of any duration

4. Grade 3 thrombocytopenia associated with clinically significant bleeding

5. 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 that does not require anti-emetics or anti-diarrheals per standard of care; Grade 3 rash that does not require corticosteroids or anti-inflammatory agents per standard of care.

6. Any Grade 3 or Grade 4 nonhematologic laboratory value that meets one of the following criteria:

   - Clinically significant medical intervention is required to treat the participant.
   - The abnormality leads to hospitalization.
   - The abnormality persists for >1 week.
   - The abnormality results in a drug-induced liver injury.

   The following are exceptions: clinically nonsignificant, treatable, or reversible laboratory abnormalities, such as those related to liver function and uric acid.

7. Febrile neutropenia Grade 3 or Grade 4:

   - Grade 3 is defined as absolute neutrophil count (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.

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

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

10. Grade 5 toxicity

11. Any other toxicity that is clinically significant and/or unacceptable and is judged to be a DLT by the investigator in collaboration with the Sponsor.

6.6.3 Dose Modification of mRNA-5671/V941

Individual participant dose modifications of mRNA-5671/V941 (dose increases or dose reductions) are not permitted in the study, unless the participant is crossing over to Arm B, which may result in a reduced dose of mRNA-5671/V941, if a lower dose is determined to be the safe dose in combination. If the participant requires a delay in pembrolizumab dosing, administration of mRNA-5671/V941 may also be delayed based on an assessment of relationship to study treatment(s). Any irAEs associated with mRNA-5671/V941 will follow the same guidelines presented in Table 5.

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

Dose Modification and Toxicity Management for Immune-related AEs Associated with Pembrolizumab or Study Interventions

AEs associated with pembrolizumab or study interventions exposure may represent an immune-related response. These irAEs may occur shortly after the first dose or several months after the last dose of pembrolizumab or study interventions 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 or study interventions, 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.

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

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

General instructions:

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

irAEs	Toxicity Grade (CTCAEv4.0)	Action With Pembrolizumab Monotherapy, Coformulations or IO Combinations	Corticosteroid and/or Other Therapies	Monitoring and Follow-up
Pneumonitis	Grade 2	Withhold	• Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper	• Monitor participants for signs and symptoms of pneumonitis • Evaluate participants with suspected pneumonitis with radiographic imaging and initiate corticosteroid treatment • Add prophylactic antibiotics for opportunistic infections
	Recurrent Grade 2 or Grade 3 or 4	Permanently discontinue		
Diarrhea / Colitis	Grade 2 or 3	Withhold	• Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper	• Monitor participants for signs and symptoms of enterocolitis (ie, diarrhea, abdominal pain, blood or mucus in stool with or without fever) and of bowel perforation (ie, peritoneal signs and ileus)

irAEs	Toxicity Grade (CTCAEv4.0)	Action With Pembrolizumab Monotherapy, Coformulations or IO Combinations	Corticosteroid and/or Other Therapies	Monitoring and Follow-up
	Recurrent Grade 3 or Grade 4	Permanently discontinue		• 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.
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	
T1DM or Hyperglycemia	New onset T1DM or Grade 3 or 4 hyperglycemia associated with evidence of β-cell failure	Withhold [a]	• Initiate insulin replacement therapy for participants with T1DM • Administer anti-hyperglycemic in participants with hyperglycemia	• Monitor participants for hyperglycemia or other signs and symptoms of diabetes
Hypophysitis	Grade 2	Withhold	• Administer corticosteroids and initiate hormonal replacements as clinically indicated	• Monitor for signs and symptoms of hypophysitis (including hypopituitarism and adrenal insufficiency)
	Grade 3 or 4	Withhold or permanently discontinue [a]		

irAEs	Toxicity Grade (CTCAEv4.0)	Action With Pembrolizumab Monotherapy, Coformulations or IO Combinations	Corticosteroid and/or Other Therapies	Monitoring and Follow-up
Hyperthyroidism	Grade 2	Continue	• Treat with non-selective beta-blockers (eg, propranolol) or thionamides as appropriate	• Monitor for signs and symptoms of thyroid disorders
	Grade 3 or 4	Withhold or Permanently discontinue [a]		
Hypothyroidism	Grade 2-4	Continue	• Initiate thyroid replacement hormones (eg, levothyroxine or liothyronine) per standard of care	• Monitor for signs and symptoms of thyroid disorders
Nephritis and renal dysfunction	Grade 2	Withhold	• Administer corticosteroids (prednisone 1-2 mg/kg or equivalent) followed by taper	• Monitor changes of renal function
	Grade 3 or 4	Permanently discontinue		
Myocarditis	Grade 1	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 2, 3 or 4	Permanently discontinue		

irAEs	Toxicity Grade (CTCAEv4.0)	Action With Pembrolizumab Monotherapy, Coformulations or IO Combinations	Corticosteroid and/or Other Therapies	Monitoring and Follow-up
All Other irAEs	Persistent Grade 2	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology or exclude other causes
	Grade 3	Withhold or discontinue [b]		
	Recurrent Grade 3 or Grade 4	Permanently discontinue		

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

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

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

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

Dose Modification and Toxicity Management of Infusion Reactions Related to Pembrolizumab

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

Table 6 Guidelines for Pembrolizumab Infusion Reaction Dose Modification and Treatment

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 hrs.	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/hr to 50 mL/hr). 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 1.5 h (±30 minutes) prior to infusion of pembrolizumab with: Diphenhydramine 50 mg PO (or equivalent dose of antihistamine). Acetaminophen 500 to 1000 mg PO (or equivalent dose of analgesic).

NCI CTCAE Grade	Treatment	Premedication at Subsequent Dosing
Grades 3 or 4 Grade 3: Prolonged (ie, not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms 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

Pembrolizumab 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 participant's study record.

6.7 Intervention After the End of the Study

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

Participants on active treatment with pembrolizumab monotherapy in the post-treatment phase are discontinued and may be enrolled in to a pembrolizumab extension study.

6.8 Clinical Supplies Disclosure

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

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 8.11.4.

Participants may discontinue study intervention at any time for any reason or be dropped 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 interrupts study intervention administration for more than 12 consecutive weeks (exception if the Sponsor approves treatment continuation).
- 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.
- Unacceptable adverse experiences as described in Section 8.4.
- Intercurrent illness other than another malignancy that prevents further administration of study intervention.
- Confirmed radiographic disease progression outlined in Section 8.2.1.5 (exception if the Sponsor approves treatment continuation)
- Any progression or recurrence of any malignancy, or any occurrence of another malignancy that requires active treatment
- Noncompliance with study intervention or procedure requirements

- Recurrent Grade 2 pneumonitis
- Completion of 35 treatments (approximately 2 years) with pembrolizumab

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.

Participants on active treatment with pembrolizumab monotherapy in the post-treatment phase are discontinued and may be enrolled in to a pembrolizumab extension study. Participants in the survival follow-up phase will not be rolled-over.

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 decisions must be made by an investigator who is a qualified physician.

- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.

- Procedures conducted as part of the participant's routine clinical management (eg, blood count) and obtained before 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, can be found in the Procedures Manual.

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

8.1 Administrative and General Procedures

8.1.1 Informed Consent

The investigator or medically qualified designee (consistent with local requirements) must obtain documented informed consent from each potential participant or their legally acceptable representative prior to participating in this clinical study or 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 documented informed consent is in place.

8.1.1.1 General Informed Consent

Informed consent given by the participant or their legally acceptable representative must be documented on a consent form. The form must include the study protocol number, study

protocol title, dated signature, and agreement of the participant (or his/her legally acceptable representative) and of the person conducting the consent discussion.

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

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

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

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

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

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 will be reviewed by the investigator 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 starting the study. Treatment for the disease for which the participant has enrolled in this study will be recorded separately and not listed as a prior medication.

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 trial 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 monitored by the investigator and/or study staff. The total volume of trial treatment infused will be compared to the total volume prepared to determine compliance with each dose administered. More details regarding the administration of mRNA-5671/V941 and pembrolizumab can be found in the accompanying Procedures Manual and Pharmacy Manual.

8.1.8.1 Timing of Dose Administration

Refer to Sections 6.1 and 6.2.1 for details regarding administration of study intervention.

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/Discontinuation 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.

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@MSD.com). Subsequently, the participant's consent for future biomedical research will be withdrawn. A letter will be sent from the Sponsor to the investigator confirming the withdrawal. It is the responsibility of the investigator to inform the participant of completion of withdrawal. Any analyses in progress at the time of request for withdrawal or already performed prior to the request being received by the Sponsor will continue to be used as part of the overall research study data and results. No new analyses would be generated after the request is received.

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

8.1.10 Participant Blinding/Unblinding

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

8.1.11 Calibration of Equipment

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

8.2 Efficacy Assessments

8.2.1 Tumor Imaging and Assessment of Disease

Tumor imaging should be acquired by computed tomography (CT, strongly preferred). Magnetic resonance imaging (MRI) should be used when CT is contraindicated or for imaging in the brain. The same imaging technique regarding modality and use of contrast should be used in a participant throughout the trial 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).

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

8.2.1.1 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 28 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 magnetic resonance imaging (MRI) if MRI was used at prior imaging, or confirmed by computed tomography (CT) imaging if CT used at prior imaging) for at least 4 weeks prior to the first dose of trial treatment. Any neurologic symptoms must have returned to baseline and participants must have no evidence of new or enlarging brain metastases, and have not used steroids for brain metastases for at least 14 days prior to trial initiation as per local site assessment. This exception does not include carcinomatous meningitis, as participants with carcinomatous meningitis are excluded regardless of clinical stability.

8.2.1.2 Tumor Imaging During the Study

The first on study imaging assessment should be performed at 9 weeks (63 days ± 7 days) from the date of allocation. Subsequent tumor imaging should be performed every 9 weeks or more frequently if clinically indicated. Imaging timing should follow calendar days and should not be adjusted for delays in cycle starts. Imaging should continue to be performed until disease progression is identified by the Investigator, the start of new anticancer treatment, withdrawal of consent, or death, whichever occurs first.

PR and CR should be confirmed by a repeat imaging assessment. The imaging for confirmation of response may be performed at the earliest 4 weeks after the first indication of response, or at the next scheduled scan (ie, 9 weeks later), whichever is clinically indicated. Participants will then return to regular scheduled imaging every 9 weeks, starting with the next scheduled imaging time point. Participants who receive additional imaging for confirmation do not need to undergo the next scheduled tumor imaging if it is less than 4 weeks later; tumor imaging may resume at the subsequent scheduled imaging time point.

Per iRECIST (Section 8.2.1.5), 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 8.2.1.5. 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.

8.2.1.3 End-of-Treatment and Follow-up Tumor Imaging

For 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 intervention due to documented disease progression, this is the final required tumor imaging if the investigator elects not to implement iRECIST.

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

8.2.1.4 RECIST 1.1 Assessment of Disease

RECIST 1.1 will be used by investigator assessment as the primary measure for assessment of tumor response, date of disease progression, and as a basis for all protocol guidelines related to disease status (eg, discontinuation of study intervention). Although RECIST 1.1

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

8.2.1.5 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 the investigator to assess tumor response and progression, and make treatment decisions. When clinically stable, participants should not be discontinued until progression is confirmed by the investigator, working with local radiology, according to the rules outlined in Appendix 8. This allowance to continue treatment despite initial radiologic PD takes into account the observation that some participants can have a transient tumor flare in the first few months after the start of immunotherapy, and then experience subsequent disease response. This data will be captured in the clinical database.

Clinical stability is defined as the following:

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

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

If the investigator decides to continue treatment, the participant may continue to receive study intervention and the tumor assessment should be repeated 4 to 8 weeks later to confirm PD by iRECIST, per investigator assessment. In order to continue to receive study intervention after initial radiologic PD, the participant must sign an additional informed consent form (see Section 8.1.1.1).

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

If a participant has confirmed radiographic progression (iCPD) as defined in Appendix 8, study intervention should be discontinued; however, if the participant is achieving a clinically meaningful benefit, an exception to continue study intervention may be considered following consultation with the Sponsor. In this case, if study intervention is continued, tumor imaging should continue to be performed following the intervals as outlined in Section 8.2.1.2.

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

Table 7 Imaging and Treatment Requirements 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 intervention at the investigator's discretion while awaiting confirmatory tumor imaging by site by iRECIST.	Repeat imaging at 4 to 8 weeks to confirm PD per investigator's discretion only.	Discontinue treatment
Repeat tumor imaging confirms PD (iCPD) by iRECIST per investigator assessment.	No additional imaging required.	Discontinue treatment (exception is possible upon consultation with Sponsor).	No additional imaging required.	Not applicable
Repeat tumor imaging shows iUPD by iRECIST per investigator assessment.	Repeat imaging at 4 to 8 weeks to confirm PD. May occur at next regularly scheduled imaging visit.	Continue study intervention at the investigator's discretion.	Repeat imaging at 4 to 8 weeks to confirm PD per investigator's discretion only.	Discontinue treatment
Repeat tumor imaging shows iSD, iPR, or iCR by iRECIST per investigator assessment.	Continue regularly scheduled imaging assessments.	Continue study intervention at the investigator's discretion.	Continue regularly scheduled imaging assessments.	May restart study intervention if condition has improved and/or clinically stable per investigator's discretion. Next tumor imaging should occur according to the regular imaging schedule.
iCPD=iRECIST confirmed progressive disease; iCR=iRECIST complete response; iPR=iRECIST partial response; iRECIST=modified Response Evaluation Criteria in Solid Tumors 1.1 for immune-based therapeutics; iSD=iRECIST stable disease; iUPD=iRECIST unconfirmed progressive disease; PD=progressive disease; RECIST 1.1=Response Evaluation Criteria in Solid Tumors 1.1.				

8.2.2 Eastern Cooperative Oncology Group (ECOG) Performance Scale

The investigator or qualified designee will assess ECOG status as indicated 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 the Procedures Manual.

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

8.3.1 Physical Examinations

8.3.1.1 Full Physical Examination

The investigator or qualified designee will perform a complete physical exam during the Screening period. Clinically significant abnormal findings should be recorded as medical history. The time points for full physical exam are described in the SoA. After the first dose of trial 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 Examination

For visits that do not require a full physical exam per the SoA, the investigator or qualified designee will perform a directed physical exam as clinically indicated prior to the administration of the study intervention. New clinically significant abnormal findings should be recorded as AEs.

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

8.3.2 Vital Signs

The investigator or qualified designee will take vital signs when indicated in the SoA. Vital signs include temperature, pulse, respiratory rate, weight, and blood pressure. Height will be measured at Screening only.

8.3.3 Electrocardiograms

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

8.3.4 Clinical Safety Laboratory Assessments

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

- The investigator or medically qualified designee (consistent with local requirements) must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the 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.

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

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 7 days prior to the first dose of study treatment. An exception is hepatitis and thyroid serologies, which may be performed within 28 days prior to first dose. Predose laboratory safety tests can be conducted up to 72 hours prior to dosing.

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

8.3.5 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 or the first dose of study intervention. If a urine test is positive or not evaluable, a serum test will be required. Participants must be excluded/discontinued from the study in the event of a positive test result. Repeated pregnancy test (such as monthly testing) may be conducted if required by local regulations.

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 3.

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

The investigator and any designees are responsible for detecting, documenting, and reporting events that meet the definition of an AE or SAE as well as other reportable safety events. Investigators 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 participant provides documented informed consent, but before intervention allocation/randomization, must be reported by the investigator if the participant is receiving placebo run-in or other run-in treatment, if the event cause the participant to be excluded from the study, or is the result of a protocol-specified intervention, including, but not limited to washout or discontinuation of usual therapy, diet, or a procedure.

- All AEs from the time of intervention allocation/randomization through 30 days after cessation of study intervention must be reported by the investigator.
- All AE meeting serious criteria, from the time of intervention allocation/randomization through 120 days after cessation of study intervention or 30 days after cessation of study intervention if the participant initiates new anticancer therapy, whichever is earlier, must be reported by the investigator.

- All pregnancies and exposure during breastfeeding, from the time of intervention allocation/randomization through 120 days following cessation of study intervention, or 30 days after cessation of study intervention if the participant initiates new anticancer therapy must be reported by the investigator.
- Additionally, any SAE brought to the attention of an investigator at any time outside the time specified above must be reported immediately to the Sponsor if the event is considered related to study intervention.

Investigators are not obligated to actively seek AE or SAE 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 8.

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

Table 8 Reporting Time Periods and 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/therapeutic 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 and/or SAE 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 are reportable to the Sponsor.

All reported pregnancies must be followed to the completion/termination of the pregnancy. Pregnancy outcomes of spontaneous abortion, missed abortion, benign hydatidiform mole, blighted ovum, fetal death, intrauterine death, miscarriage, and stillbirth must be reported as serious events (Important Medical Events). If the pregnancy continues to term, the outcome (health of infant) must also be reported.

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 that 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:

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

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

   *Note: These criteria are based upon available regulatory guidance documents. The purpose of the criteria is to specify a threshold of abnormal hepatic tests that 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 this study, an overdose of pembrolizumab will be defined as any dose of 1000 mg or greater (≥5 times the indicated dose).

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

For this study, an overdose of mRNA-5671/V941 will be defined as any dose exceeding the prescribed dose for mRNA-5671/V941 by ≥20% of the indicated dose.

No specific information is available on the treatment of overdose of mRNA-5671/V941. In the event of overdose, the participant should be observed closely for signs of toxicity. Appropriate supportive treatment should be provided if clinically indicated. If desired by the investigator, resumption of treatment should be discussed with the clinical monitor.

8.6 Pharmacokinetics

To further evaluate pembrolizumab immunogenicity and pembrolizumab exposure in this indication, and also to evaluate exposure of the proposed dosing regimen, sample collections for analysis of antidrug antibodies (ADA) and PK are currently planned as shown in the SoA. Blood samples will be obtained to measure PK of serum pembrolizumab. The pembrolizumab serum maximum concentration (C_{max}) and minimum concentration (C_{min}) at planned visits and times will be summarized. If ongoing ADA and/or PK results continue to be consistent with existing ADA and/or PK data from other pembrolizumab clinical studies, it may be decided to discontinue or reduce further sample collection in this study. Should this occur, it will be communicated by an administrative memo.

Pharmacokinetic data will also be analyzed using nonlinear mixed effects modeling. Based on PK data obtained in this study as well as PK data obtained from other studies, a population PK analysis will be performed to characterize PK parameters (clearance [CL], volume of distribution [V]) and evaluate the effect of extrinsic and intrinsic factors to support proposed dosing regimen. Pharmacokinetic data will also be used to explore the exposure response relationships for pembrolizumab antitumor activity/efficacy as well as safety in the proposed participant population, if feasible. The results of these analyses, if performed, will be reported separately.

8.6.1 Blood Collection for PK, ADA, and Biomarkers

8.6.1.1 Blood Collection for PK

Sample collection, storage, and shipment instructions for serum samples will be provided in the Procedures Manual. Pharmacokinetic samples should be drawn according to the PK collection schedule for all participants. Every effort should be taken to collect samples at 30 days after end of study intervention.

8.6.1.2 Blood Collection for Antidrug Antibodies

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

8.6.1.3 Blood Collection for Biomarkers

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

8.7 Pharmacodynamics

Sample collection, storage, and shipment instructions for pharmacodynamic samples will be 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:

- DNA for future research
- Leftover tumor
- Leftover RNA
- Leftover Peripheral Blood Mononuclear Cells from immunogenicity assessment
- Leftover blood from Blood for TCR (DNA) analysis
- Leftover plasma or derivative from ctDNA analysis
- Leftover serum from PK and ADA analyses

8.9 Planned Genetic Analysis Sample Collection

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

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

8.10 Biomarkers

8.10.1 Pre-screening Biomarker Samples

8.10.1.1 Tumor KRAS Mutation Testing

Routine standard of care tumor KRAS mutation assessment by local testing should have been performed prior to consideration for study participation and should be used for eligibility determination. If a patient is being considered for participation in Part 2 of this study and tumor KRAS mutation testing has not been previously performed, Sponsor consultation should occur. Sponsor approval would subsequently be required in order to perform local testing for tumor KRAS mutations on study in Pre-screening (see the Procedures Manual).

8.10.1.2 Human Leukocyte Antigen Typing

Participants with KRAS mutated tumors being considered for enrollment in Part 2 of the study must undergo HLA typing during Pre-screening. Details regarding HLA testing can be found in the Procedures Manual. Results from this testing must be received by the site before a participant can be entered into the Screening phase for Part 2 of the study.

Note: If the patient has not undergone prior local tumor KRAS mutation testing, the timing of HLA testing in relation to KRAS mutation testing in Pre-screening (if on-study KRAS mutation testing has been approved by the Sponsor) must also be discussed with and approved by the Sponsor.

8.10.2 Archival Tumor Sample

All participants must provide an archival tumor sample during the Screening phase in order to be eligible for the study. KRAS mutational analysis, as well as other analyses, will be performed utilizing this sample. Details regarding the collection, shipment, and/or storage of these samples can be found in the Procedures Manual.

8.10.3 Blood Samples

Blood should be collected predose at the timepoints outlined in Section 1.3 – Schedule of Activities. Further details are provided in the Procedures Manual.

8.10.4 Immunogenicity Assessment

The assessment of immunogenicity of the mRNA-5671/V941 therapeutic vaccine is a secondary objective of this study.

8.10.4.1 PBMC Collection

Whole blood will be collected at specified time points from each study participant for isolation and cryopreservation of PBMC for immunogenicity assessment (unless a leukapheresis pack has been collected at a comparable time point [Section 8.10.4.2]). These PBMC will be utilized in immune assays to assess responses against KRAS mutant epitopes potentially induced by vaccination with mRNA-5671/V941. Further details are provided in the Procedures Manual.

8.10.4.2 Leukapheresis

Participants receiving combination therapy (mRNA-5671/V941 + pembrolizumab) either in Arm B of Part 1 or in Part 2 may undergo optional leukapheresis during Screening and on Day 8 of Cycle 4, but only if the clinical site has the capability to perform this procedure and facilities are available to isolate and cryopreserve PBMC from the collected leukapheresis within the specified time window (see the Procedures Manual for details). These collected cells will be utilized for immune assays to evaluate the immunological response against KRAS mutant epitopes potentially induced and expanded by vaccination with mRNA-

5671/V941. Additional details regarding the collection, storage, and/or shipment of the collected leukapheresis pack can be found in the Procedures Manual.

In the event that a screening leukapheresis is collected from a given participant, the screening whole blood sample for isolation of PBMC for immunogenicity assessment should not be drawn from that participant. Similarly, if a Day 8 Cycle 4 leukapheresis is collected, the whole blood collections for isolation of PBMC for immunogenicity assessment on both Day 8 of Cycle 4 and Day 1 of Cycle 6 should not be performed.

8.10.5 Exploratory Analyses

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

- Archival tumor tissue
- Blood for Genetic Analysis
- Blood for PBMC immunogenicity assessment
- Blood for RNA analysis
- Blood for TCR (DNA)
- Blood for ctDNA 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 Pre-screening (Part 2 only)

For Part 2 of the study, approximately 50 days prior to treatment allocation, potential participants will undergo pre-screening procedures to determine their eligibility based on results of prior local tumor KRAS mutational testing (see Section 8.10.1.1) and on HLA typing (see Section 8.10.1.2).

Pre-screening procedures are to be completed within 21 days prior to screening procedure initiation. Pre-screening procedures may be repeated if needed after consultation with and approval by the Sponsor. Once Part 2 eligibility requirements regarding KRAS mutational status and HLA type are confirmed, potential participants should have screening procedures performed without delay.

8.11.2 Screening

Approximately 28 days prior to treatment allocation, potential participants will be evaluated to determine that they fulfill the entry requirements of the study. 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 clinical management are acceptable in lieu of a screening test if performed within the specified time frame. Screening procedures are to be completed within 28 days prior to the first dose of study intervention except for the following:

- Laboratory tests are to be performed within 7 days prior to the first dose of study intervention. An exception is hepatitis testing 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 intervention.
- 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).
- Baseline radiological evaluations must be done within 28 days prior to the first dose of study intervention.
- Archival tumor sample collection may have occurred at any point prior to the first dose of study intervention.

Participants may be rescreened after initially failing to meet the inclusion/exclusion criteria. Results from assessments during the initial screening period are acceptable in lieu of a repeat screening test if performed within the specified time frame and the corresponding inclusion/exclusion criteria is met. Participants who are rescreened will retain their original screening number. Assessments performed as part of the screening evaluations and within 3 days prior to the first dose of study treatment are not required to be repeated on Day 1 of Cycle 1.

8.11.3 Treatment Period/Vaccination Visit

Visit requirements are outlined in the SoA. Specific procedure-related details are provided in Section 8.1.

8.11.4 End of Treatment/Discontinuation Visit

The End of Treatment/Discontinuation Visit should occur at the time study intervention is discontinued for any reason. If the Discontinuation Visit occurs 30 days from the last dose of study intervention, at the time of the mandatory Safety Follow-up Visit, the Discontinuation

Visit procedures and any additional Safety Follow-up procedures should be performed. Visit requirements are outlined in Section 1.3. Additional details regarding participant withdrawal and discontinuation are presented in Section 7.

Participants on active treatment with pembrolizumab monotherapy in the post-treatment phase are discontinued and may be enrolled in to a pembrolizumab extension study. Participants in the survival follow-up phase will not be rolled-over.

8.11.5 Post-treatment Visit

8.11.5.1 Safety Follow-up Visit

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

All AEs that occur prior to the Safety Follow-up Visit should be recorded (up to 30 days following end of treatment). Participants with an AE of Grade >1 will be followed until the resolution of the AE to Grade 0-1 or until the beginning of a new anticancer therapy, whichever occurs first. SAEs that occur within 120 days of the end of treatment or before initiation of a new anticancer treatment should also be followed and recorded.

8.11.5.2 Imaging Follow-up Visit(s)

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

8.11.5.3 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 every 12 weeks to assess for survival status until death, withdrawal of consent, or the end of the study, whichever occurs first.

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

Participants on active treatment with pembrolizumab monotherapy in the post-treatment phase are discontinued and may be enrolled in to a pembrolizumab extension study. Participants in the survival follow-up phase will not be rolled-over.

8.11.6 Survival Status

To ensure current and complete survival data is available at the time of database locks, updated survival status may be requested during the course of the study by the Sponsor. For example, updated survival status may be requested prior to but not limited to an external Data Monitoring Committee (eDMC) review, interim and/or final analysis. Upon Sponsor notification, all participants who do not/will not have a scheduled study visit or study contact during the Sponsor defined time period will be contacted for their survival status (excluding participants that 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

Full details are in the Statistical Analysis Plan (SAP), Sections 9.2 to 9.12.

Study Design Overview	Phase 1 trial of mRNA-5671/V941 monotherapy (Arm A) and mRNA-5671/V941 in combination with pembrolizumab (Arm B) in participants with advanced/metastatic solid tumors. The study applies a modified TPI design for dose finding.
Treatment Assignment	Participants will be allocated centrally through IVRS/IWRS to single agent mRNA-5671/V941 and mRNA-5671/V941 coadministered with pembrolizumab.
Analysis Populations	Safety (Primary): All-Subjects-as-Treated (AsaT) Pharmacodynamic (Secondary): Per-Protocol (PP) Efficacy (Secondary and Exploratory): Full Analysis Set (FAS)
Primary Endpoint(s)	• Dose-limiting toxicity (DLT) • Adverse event (AE) • Discontinuing study treatment due to an AE
Secondary Endpoints	• Objective response is a confirmed CR or PR. • Presence of and changes in the quantity of mutant KRAS-specific T cells in the blood.
Statistical Methods for Efficacy/ Immunogenicity/	ORR in participants treated with mRNA-5671/V941 monotherapy (Arm A) and mRNA-5671/V941 in combination with pembrolizumab (Arm B) will be estimated using an exact method based on the binomial distribution (Clopper-

Pharmacokinetic Analyses	Pearson interval) together with its 95% confidence interval. Methods for the rest of the efficacy analyses are documented in the sSAP. Summary statistics will be provided for the immunogenicity parameters.
Statistical Methods for Safety Analyses	Summary statistics will be provided for the safety endpoints as appropriate. The pool-adjacent-violators-algorithm [Ji Y, Li Y, Bekele BN 2007] will be used to estimate the DLT rates across doses. The estimate of the DLT rate among participants treated at RP2D of mRNA-5671/V941 and the 80% Bayesian credible intervals for the estimate will be provided for each treatment arm.
Interim Analyses	An interim analysis for part 2 will be conducted after about 60% of enrollment in each tumor cohort.
Multiplicity	No multiplicity adjustment is planned in this Phase 1 trial.
Sample Size and Power	The overall sample size for this study depends on the observed DLT profiles of mRNA-5671/V941 monotherapy and mRNA-5671/V941 in combination with pembrolizumab. A target sample size of 100 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 trial is open-label, ie, participants, investigators, and Sponsor personnel will be aware of participant treatment assignment after each participant is enrolled and treatment is assigned. Allocation to treatment will not be randomized.

9.3 Hypotheses/Estimation

Objectives and hypotheses of the study are outlined in Section 3 – Objectives/Hypotheses and Endpoints.

9.4 Analysis Endpoints

9.4.1 Efficacy/Immunogenicity Endpoints

Objective response rate is the secondary endpoint in this study. Objective response rate is defined as the proportion of participants in the analysis population who experience complete response (CR) or partial response (PR) using RECIST 1.1 criteria as assessed by investigator review.

Other efficacy endpoints (eg, PFS, OS) are exploratory endpoints in this trial and details of the analysis plan will be documented in the sSAP. Progression-free survival (PFS) is defined as the time from the first dose of study medication to the first documented disease progression (PD), using RECIST 1.1 criteria as assessed by investigator review, or death due to any cause, whichever occurs first. Overall survival (OS) is defined as the time from the

first dose of study medication to death due to any cause. Participants who did not die will be censored on the date of last study assessment or contact.

Immunogenicity endpoints may include the following: 1) Presence of and changes in the quantity of mutant KRAS-specific T cells in the blood and 2) TCR clonality and diversity in the blood.

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 – Safety Assessments.

9.5 Analysis Populations

9.5.1 Safety Analysis Populations

The All-Subjects-as-Treated (AsaT) population will be used for the analysis of safety data in this study. The AsaT population consists of all participants who received at least 1 dose of study treatment.

The DLT evaluable population includes AsaT participants that meet the criteria for DLT evaluability (eg, finished Cycle 1 without a DLT or experienced a DLT in Cycle 1). See Section 6.6.2 for details.

At least 1 laboratory or vital sign measurement obtained 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.

Data from participants who crossover from monotherapy to the combination therapy will be presented separately.

9.5.2 Pharmacokinetic/Immunogenicity Analysis Populations

The Per-Protocol (PP) population will be used for the analysis of PK and immunogenicity 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 Full Analysis Set (FAS) population will be used for the analyses of secondary and exploratory efficacy data in this study. It consists of participants with centrally-confirmed tumor KRAS mutations, with a baseline scan that demonstrated measurable disease by the investigator's assessment, and who were administered at least 1 dose of study medicine. Participants from the dose finding phase in the combination arm (Arm B) who are treated at the RP2D and meet the dose expansion eligibility criterion will be pooled together with participants enrolled in the dose expansion in a supportive analysis.

Data from participants who crossover from monotherapy to the combination therapy 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 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. Laboratory tests, vital signs, and other safety endpoints will be summarized as appropriate.

Dose limiting toxicities will be listed and summarized by dose level. The pool adjacent violators-algorithm [Ji Y, Li Y, Bekele BN 2007], which forces the DLT rate estimates to be nondecreasing with increasing dose levels and pools adjacent violators for weighted estimates by sample size, will be used to estimate the DLT rates across doses in each treatment arm. The estimate of the DLT rate among participants treated at the RP2D and the 80% Bayesian credible interval based on a prior distribution of Beta (1,1) for the estimate will be provided.

9.6.2 Statistical Methods for Efficacy Analysis

ORR, along with the confidence interval, will be estimated using an exact method based on the binomial distribution (Clopper-Pearson method). The statistical methods for other efficacy endpoints are exploratory nature and will be documented in the sSAP.

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

Pharmacokinetic parameters of pembrolizumab will be summarized by planned visit and time for each dose separately.

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

9.7 Interim Analyses

Due to low prevalence of KRAS mutant and selected HLA typing population, the accrual is expected to be slow. A futility analysis will be conducted after about 60% of enrollment in each tumor cohort. For example, if no response is observed among the 9 participants in the non-MSI-H CRC or pancreatic cohort, or less than 7 responses out of 24 participants in the NSCLC cohort, enrollment to the tumor cohort may be stopped. The totality of data across the cohorts will be assessed to stop the trial early for futility.

9.8 Multiplicity

There will be no multiplicity control in this study.

9.9 Sample Size and Power Calculations

The planned total sample size for Part 1 dose finding is approximately 30 participants. The actual sample size could be less given that the therapeutic vaccine is expected to have a tolerable toxicity profile. The planned sample size for Part 2 efficacy expansion is 70 participants (40 for NSCLC, 15 for non-MSI-H CRC and 15 for pancreatic).

While there is no formal hypothesis testing in this study, preliminary efficacy in the Part 2 expansion will be assessed with the pruning and pooling method [Chen, C., et al 2016]. With 70 participants by the aforementioned allocation, the study has approximately 83% power for detecting a 15% improvement of ORR over historical control (pembrolizumab monotherapy) in at least 1 of the 3 tumor indications, while controlling the Type I error for the global null hypothesis under 5%. The ORR for historical control in the KRAS mutated population is assumed to be 1% for non-MSI-H CRC, 1% for pancreatic adenocarcinoma, and 20 to 25% for NSCLC.

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 trial. 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 (Institutiona 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 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.

10.1.5 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.

10.1.6 Compliance with Law, Audit, and Debarmen

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.

10.1.7 Data Quality Assurance

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

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

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

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

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

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

Study monitors will perform ongoing source data review and verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

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

10.1.8 Source Documents

Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. 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.

10.1.9 Study and Site Closure

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

In the event the Sponsor prematurely terminates a particular study site, the Sponsor will promptly notify that study site's IRB/IEC.

10.2 Appendix 2: Clinical Laboratory Tests

- The tests detailed in Table 9 will be performed by the local laboratory.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5.1 and Section 5.2 of the protocol.
- Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.

Table 9 Protocol-required Safety Laboratory Assessments

Hematology	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]
RBC	Bicarbonate	Microscopic exam, if abnormal results are noted	
Absolute lymphocyte count[c]	Calcium		
Absolute neutrophil count[c]	Chloride		
	Creatinine		Anti-HCV[d]
	Glucose		HCV viral load[d]
	Phosphorus		Anti-HBs[d]
	Potassium		HbsAg[d]
	Sodium		Anti-HBc (total and IgM)[d]
	Total bilirubin		HbeAg[d]
	Direct bilirubin		Anti-Hbe[d]
	Total protein		HIV testing[d]
	Blood urea nitrogen		

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. T3 is preferred; if not available, Free T3 may be tested.
c. Report % or absolute results per standard of practice. Report the results in the same manner throughout the study.
d. Assessment should be based on history unless testing is required by local regulation.

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."

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 4.0. Any AE that changes CTCAE grade over the course of a given episode will have each change of grade recorded on the AE CRFs//worksheets.

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

    - Grade 2: Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental 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 IRB/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 10 during the protocol-defined time frame in Section 5.1.

Table 10 Highly Effective Contraception Methods

Highly Effective Contraceptive Methods That Are User Dependent[a] *Failure rate of <1% per year when used consistently and correctly.*
● Combined (estrogen- and progestogen- containing) hormonal contraception[b,c] ○ Oral ○ Intravaginal ○ Transdermal ○ Injectable
● Progestogen only hormonal contraception[b,c] ○ Oral ○ Injectable
Highly Effective Methods That Have Low User Dependency *Failure rate of <1% per year when used consistently and correctly.*
● Progestogen- only contraceptive implant[b,c] ● Intrauterine hormone-releasing system (IUS)[b] ● Intrauterine device (IUD) ● Bilateral tubal occlusion
● Vasectomized partner A vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.
● Sexual abstinence Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.
[a] Use should be consistent with local regulations regarding the use of contraceptive methods for participants of clinical studies. [b] Typical use failure rates are higher than perfect-use failure rates (ie, when used consistently and correctly). [c] If hormonal contraception efficacy is potentially decreased due to interaction with study intervention, condoms must be used in addition to the hormonal contraception during the intervention period and for at least 120 days 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. Additional pregnancy testing will be performed as indicated in the SoA, and 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

1. Definitions

a. Biomarker: A biological molecule found in blood, other body fluids, or tissues that is a sign of a normal or abnormal process or of a condition or disease. A biomarker may be used to see how well the body responds to a treatment for a disease or condition.[1]

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

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

d. DNA: Deoxyribonucleic acid.

e. RNA: Ribonucleic acid.

2. Scope of Future Biomedical Research[3, 4]

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

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

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

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

3. Summary of Procedures for Future Biomedical Research[3, 4]

a. Participants for Enrollment

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

b. Informed Consent

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

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

c. eCRF Documentation for Future Biomedical Research Specimens

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

d. Future Biomedical Research Specimen(s)

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

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

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

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

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

5. Biorepository Specimen Usage[3, 4]

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

6. Withdrawal From Future Biomedical Research[3, 4]

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

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

7. Retention of Specimens[3, 4]

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

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

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

8. Data Security[3, 4]

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

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

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

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

10. Future Biomedical Research Study Population[3, 4]

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

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

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

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

12. Questions

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

13. References

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

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

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

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

10.7 Appendix 7: Country-specific Requirements

Not Applicable

10.8 Appendix 8: Description of the iRECIST Process for Assessment of Disease Progression

Assessment at Screening and Prior to RECIST 1.1 Progression

Until radiographic disease progression based on RECIST 1.1, there is no distinct iRECIST assessment.

Assessment and Decision at RECIST 1.1 Progression

For participants who show evidence of radiological PD by RECIST 1.1 as determined by the investigator, the investigator will decide whether to continue a participant on study intervention until repeat imaging is obtained (using iRECIST for participant management (see Table 7). This decision by the investigator should be based on the participant's overall clinical condition.

Clinical stability is defined as the following:

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

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

If the investigator decides to continue treatment, the participant may continue to receive study intervention and the tumor assessment should be repeated 4 to 8 weeks later to confirm PD by iRECIST, per investigator assessment.

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 – Non-target.

Assessment at the Confirmatory Imaging

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

Confirmation of Progression

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

- Any of the factors that were the basis for the iUPD at the previous visit show worsening
    - For target lesions, worsening is a further increase in the sum of diameters of ≥5 mm, compared to any prior iUPD time point
    - For nontarget lesions, worsening is any significant growth in lesions overall, compared to a prior iUPD time point; this does not have to meet the “unequivocal” standard of RECIST 1.1
    - For new lesions, worsening is any of these:
        - An increase in the new lesion sum of diameters by ≥5 mm from a prior iUPD time point
        - Visible growth of new 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 imaging proceeds in an identical manner, with possible outcomes of iCPD, iUPD, and iSD/iPR/iCR.

Resolution of iUPD

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

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

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

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

Management Following the Confirmatory Imaging

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

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

Detection of Progression at Visits After Pseudo-progression Resolves

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

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

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

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

Additional details about iRECIST are provided in the iRECIST publication [Seymour, L., et al 2017].

10.9 Appendix 9: Abbreviations

Abbreviation	Definition
Abscopal	a phenomenon in the treatment of metastatic cancer where localized treatment of a tumor causes not only a shrinking of the treated tumor, but also a shrinking of tumors outside the scope of the localized treatment.
ADA	anti-drug antibody
ADME	absorption, distribution, metabolism, and excretion
AE	adverse event
ALK	anaplastic lymphoma kinase
ALT	alanine aminotransferase
AMP	adenosine monophosphate
ANC	absolute neutrophil count
aPTT	activated partial thromboplastin time
ART	anti-retroviral therapy
AsaT	all-subjects-as-treated
AST	aspartate aminotransferase
ATD	accelerated titration design
AUC	area under the curve
C	cycle
CARPA	complement activation-related pseudoallergy
CBC	complete blood count
CBR	carbonyl reductase
CD	cluster of differentiation (eg, CD3, CD8, CD28)
CDN	cyclic dinucleotide
cGAMP	cyclic GMP-AMP
cGAS	cyclic (guanosine monophosphate-adenosine monophosphate)
C_{max}	maximum plasma concentration
C_{min}	minimum plasma concentration
CNS	central nervous system
CONSORT	Consolidated Standards of Reporting Trials
COVID	Coronavirus disease
CR	complete response
CRC	colorectal cancer
CrCl	creatinine clearance
CRF/eCRF	case report form/electronic case report form
CRS	cytokine release syndrome
CT	computed tomography
CTCL	cutaneous T-cell lymphoma
CTCAE	Common Terminology Criteria for Adverse Events
ctDNA	circulating tumor DNA
CTLA-4	cytotoxic T lymphocyte-associated antigen 4
CXCL11	C-X-C motif chemokine 11
CxCy	Cycle x Day y
DILI	drug-induced liver injury
DLT	dose-limiting toxicity
DNA	deoxynucleic acid
ECG	electrocardiograph

Abbreviation	Definition
ECI	event of clinical interest
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EDC	electronic data capture
EGFR	epidermal growth factor receptor
EMA	European Medicines Agency
EOT	end of treatment
FAS	Full Analysis Set
FBR	future biomedical research
FDA	U.S. Food and Drug Administration
FDAA	Food and Drug Administration Amendments Act
FDG	fluorodeoxyglucose
FIH	first-in-human
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMP	guanosine monophosphate
GRI	growth rate inhibition
GVHD	graft-versus-host disease
HbsAg/HBV	Hepatitis B surface antigen/Hepatitis B virus
HCV	Hepatitis C virus
hCG	human chorionic gonadotropin
HED	human equivalent doses
HIV	human immunodeficiency virus
HLA	human leukocyte antigen
HLA-A	human leukocyte antigen A
HLA-C	human leukocyte antigen C
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IFN	interferon
IFNα	interferon alpha
IFNγ	interferon gamma
Ig	immunoglobulin
IgG4	immunoglobulin G4
IHC	immunohistochemistry
IL-6	interleukin-6
IM	intramuscular
INR	international normalized ratio
IP-10	interferon gamma-induced protein 10
irAE	immune-related adverse event
IRF3	interferon regulatory transcription factor-3
iRECIST	immune Response Evaluation Criteria In Solid Tumors
ISCL	International Society for Cutaneous Lymphomas
IT	intratumoral
IV	intravenous
IVD	in vitro diagnostic

Abbreviation	Definition
IVRS/IWRS	integrated web response system
IWG	International Working Group
KRAS	Kirsten RAt Sarcoma
LDH	lactate dehydrogenase
LLOQ	less than the limit of detection
LNP	lipid nanoparticle
mAb	monoclonal antibody
MAD	maximum administered dose
MCP-1	monocyte chemoattractant protein-1
MCP-2	monocyte chemoattractant protein-2
MHC	major histocompatibility complex
MIP-1α	macrophage inflammatory protein-1 alpha
MRI	magnetic resonance imaging
mRNA	messenger ribonucleic acid
MRI	magnetic resonance imaging
MSD	Merck Sharp & Dohme
MSI	microsatellite instability
MSI-H	microsatellite instability-high
mSWAT	modified Severity Weighted Assessment Tool
MTD	maximum tolerated dose
mTPI	modified toxicity probability interval
NCI	National Cancer Institute
NF-κB	nuclear factor-κB
NOAEL	no-observed adverse effect level
NSCLC	non-small-cell lung cancer
ORR	objective response rate
OS	overall survival
OTC	over-the-counter
PBMC	peripheral blood mononuclear cell
PD	progressive disease
PD-1	programmed cell death protein 1
PD-L1	programmed cell death-1 ligand 1
PD-L2	programmed cell death-1 ligand 2
PET	positron emission tomography
PFS	progression-free survival
PK	pharmacokinetic
PO	per os (by mouth)
PP	per-protocol
PR	partial response
PT	prothrombin time
Q1W	once a week
Q3W	every three weeks
RECIST	Response Evaluation Criteria In Solid Tumors
RNA	ribonucleic acid
RP2D	recommended Phase 2 dose
SAE	serious adverse events
SNP	single nucleotide polymorphism

Abbreviation	Definition
SoA	schedule of activities
SOP	standard operating procedure
SPD	sum of the products of the greatest diameters
sSAP	Supplemental Statistical Analysis Plan
STING	stimulator of interferon genes
SUSAR	suspected unexpected serious adverse reactions
TBK1	tumor necrosis factor receptor-associated factors (TRAF)-associated nuclear factor (NF)-κB activator
TCR	T-cell receptor
TNF-α	tumor necrosis factor-alpha
TSH	thyroid stimulating hormone
ULN	upper limit of normal
VS	vital signs
WOCBP	women of childbearing potential
WT	wild-type

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