Official Protocol Title:	A Phase 2, Randomized Clinical Study of Intravenous or Intratumoral Administration of V937 in Combination with Pembrolizumab (MK-3475) Versus Pembrolizumab Alone in Participants with Advanced/Metastatic Melanoma
NCT number:	NCT04152863
Document Date:	25-October-2022

Title Page

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Protocol Title: A Phase 2, Randomized Clinical Study of Intravenous or Intratumoral Administration of V937 in Combination with Pembrolizumab (MK-3475) Versus Pembrolizumab Alone in Participants with Advanced/Metastatic Melanoma

Protocol Number: 011-06

Compound Number: V937

Sponsor Name:

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

Legal Registered Address:

126 East Lincoln Avenue

P.O. Box 2000

Rahway, NJ 07065 USA

Regulatory Agency Identifying Number(s):

IND	14547
EudraCT	2019-002034-36

Approval Date: 25 October 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 6	25-OCT-2022	V937-011 is going to be discontinued due to the Sponsor's development decision. The overall rationale for this amendment is to allow eligible participants who are receiving pembrolizumab may be enrolled in a pembrolizumab extension study to continue receiving pembrolizumab monotherapy for up to 35 cycles.
Amendment 5	22-JUN-2022	Merck Sharp & Dohme Corp. underwent an entity name and address change to Merck Sharp & Dohme LLC, Rahway, NJ, USA. This conversion resulted only in an entity name change and update to the address.
Amendment 4	23-JUN-2021	To update the dose modification and toxicity management guidelines for irAEs.
Amendment 3	10-DEC-2020	To remove C1D1 collection of blood/serum samples from Arm 3 and all biopsies from Arm 3.
Amendment 2	26-AUG-2020	To remove the collection of throat swabs or sputum samples from close contacts or health care workers related to viral transmission of V937 from participants, to address Health Authority requests, and to provide additional clarifications.
Amendment 1	09-JUL-2020	The overall rationale for this amendment is to change the timing of PBMC collection to Day 1 of Cycle 3, and to indicate it is to be performed only at selected study site(s).
Original Protocol	19-JUN-2019	Not applicable

PROTOCOL AMENDMENT SUMMARY OF CHANGES

Amendment: 06

Overall Rationale for the Amendments:

V937-011 is going to be discontinued due to the Sponsor's development decision. The overall rationale for this amendment is to allow eligible participants who are receiving pembrolizumab may be enrolled in a pembrolizumab extension study to continue receiving pembrolizumab monotherapy for up to 35 cycles.

Summary of Changes Table:

Section # and Name	Description of Change	Brief Rationale
1.1 Synopsis – Duration of Participation 1.2 Schema 1.3 Schedule of Activities (SoA) 6.7 Intervention After the End of the Study	Language was added to allow eligible participants who are ongoing in the study to continue to receive treatment for up to 35 cycles of treatment with pembrolizumab or be followed for survival through enrollment in a pembrolizumab extension study.	These changes will allow this study to be closed.
1.1 Synopsis – Number of Participants 1.2 Schema 9.1 Statistical Analysis Plan Summary 9.9 Sample Size and Power Calculations	Added language indicating the total planned enrollment number may not be met due to early study discontinuation.	The study may not enroll the planned 135 participants due to early study termination.

Section # and Name	Description of Change	Brief Rationale
1.3.2 Schedule of Activities for the Treatment Period – Arm 1 (IV Pembro + IV V937) 1.3.3 Schedule of Activities for the Treatment Period – Arm 2 (IV Pembro + ITu V937) 1.3.4 Schedule of Activities for the Treatment Period – Arm 3 (Pembrolizumab Monotherapy) 1.3.5 Schedule of Activities for the End of Treatment and Posttreatment Follow-up Periods	Removed sample collections for urinalysis, V937 PK (RNA), pembrolizumab PK, neutralizing V937 antibodies, antipembrolizumab antibodies, blood for ctDNA analysis, biomarker analysis, blood for genetic analyses, and tumor biopsy.	Due to early study termination, collection of central laboratory samples is no longer required.
1.3.5 Schedule of Activities for the End of Treatment and Posttreatment Follow-up Periods 8.10.4 Posttreatment Visit	Removed survival status monitoring and columns corresponding to the "Posttreatment Phase" from SoA. Added language specifying that the Safety Follow-up, Imaging Follow-up and Survival Follow-up visits are not required upon early study closure.	Due to early study termination, completion of the 30-day Safety Follow-up visit, posttreatment Imaging visits, and Survival Follow-up visits are no longer required. Participants deriving benefit from pembrolizumab will be given the opportunity to transfer to a pembrolizumab extension study, if available, upon study closure, and will be monitored following the SoA of the pembrolizumab extension study.

Section # and Name	Description of Change	Brief Rationale
8.6 Pharmacokinetics	Added statements related to analysis of samples if study is terminated early	Update collection information due to early study termination.
1.1 Synopsis 6.1 Study Intervention(s) Administered	Updated Intervention Groups and Duration and Table 7 to reflect proper nomenclature for study interventions.	To align with the EU CTR
4.4 Beginning and End of Study Definition	New paragraph added for overall study end clarification and EEA on local start for member states.	To align with the EU CTR
8.4 Adverse Events (AEs), Serious Adverse Events (SAEs), and Other Reportable Safety Events 10.3.1 Definitions of Medication Error, Misuse, and Abuse	Added language related to investigator documenting SAEs related to medication error, misuse, abuse, and their definition Added new section	To align with the EU CTR
8.5 Treatment of Overdose	Removed discontinuation statement in the event of overdose	Treatment interruption until AE resolution and then resumption is appropriate
10.7 Country-specific requirements Norway	Country-specific criteria has been added for 'Planned Genetic analysis Sample Collection'	To clarify country-specific requirement

Section # and Name	Description of Change	Brief Rationale
Throughout Document	Minor administrative, formatting, grammatical, and typographical changes were made throughout the document	To ensure clarity and accurate interpretation of the intent of the protocol

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1 PROTOCOL SUMMARY

1.1 Synopsis

Protocol Title: A Phase 2, Randomized Clinical Study of Intravenous or Intratumoral Administration of V937 in Combination with Pembrolizumab (MK-3475) Versus Pembrolizumab Alone in Participants with Advanced/Metastatic Melanoma

Short Title: Phase 2 Randomized Study of V937 Administered IV or ITu with Pembrolizumab Versus Pembrolizumab Alone

Acronym: Not applicable.

Hypotheses, Objectives, and Endpoints:

Hypotheses are aligned with objectives in the Objectives and Endpoints table.

Throughout this protocol, the term RECIST 1.1 refers to modification to RECIST 1.1 to include a maximum of 10 target lesions and a maximum of 5 target lesions per organ.

In males and females with advanced/metastatic melanoma who are antiprogrammed cell death (ligand) 1 [anti-PD-(L)1]-treatment-naïve:

Primary Objectives	Primary Endpoints
- Objective: To evaluate the objective response rate (ORR) of participants treated with IV V937 administered in combination with pembrolizumab, ITu V937 administered in combination with pembrolizumab, or pembrolizumab alone per Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST 1.1) by blinded independent central review (BICR). - Hypothesis: V937 administered either IV in combination with pembrolizumab or ITu in combination with pembrolizumab results in a superior ORR per RECIST 1.1 based on BICR, compared to pembrolizumab alone.	- Objective response is a confirmed complete response (CR) or partial response (PR)

Secondary Objectives	Secondary Endpoints
- To evaluate progression free survival (PFS), and duration of response (DOR) of participants treated with IV V937 in combination with pembrolizumab, ITu V937 in combination with pembrolizumab, or pembrolizumab alone per RECIST 1.1 by blinded independent central review (BICR).	- PFS, defined as the time from randomization to the first documented progressive disease (PD) or death from any cause, whichever occurs first. - DOR, defined as the time from the first documented evidence of CR or PR until progressive disease (PD) or death due to any cause, whichever occurs first, in participants demonstrating CR or PR
- To evaluate ORR, PFS, and DOR of participants treated with IV V937 in combination with pembrolizumab, ITu V937 in combination with pembrolizumab, or pembrolizumab alone, per RECIST 1.1, as assessed by the investigator.	- Objective response - PFS - DOR
- To evaluate OS of participants treated with IV V937 in combination with pembrolizumab, ITu V937 in combination with pembrolizumab, or pembrolizumab alone.	- OS, defined as the time from randomization to the date of death from any cause
- Objective: To assess the safety and tolerability of participants treated with IV V937 in combination with pembrolizumab, ITu V937 in combination with pembrolizumab, or pembrolizumab alone.	- Adverse events (AEs) - Discontinuing study intervention due to an AE

Overall Design:

Study Phase	Phase 2
Primary Purpose	Treatment
Indication	The treatment of participants with advanced/metastatic melanoma
Population	Participants with histologically or cytologically confirmed advanced/metastatic melanoma by pathology report who have not received PD-(L)1 antibody.
Study Type	Interventional
Intervention Model	Parallel This is a multi-site study.
Type of Control	Active comparator
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 135 participants will be randomly assigned in a 1:1:1 ratio to the following intervention arms: Arm 1 (IV pembro + IV V937); Arm 2 (IV pembro + ITu V937); Arm 3 (IV pembro alone).

Due to early termination of this study, the total enrollment number may be less than 135 participants.

Intervention Groups and Duration:

Intervention Groups

Inter-vention Group Name	Drug	Dose Strength	Dose Frequency	Route of Administration	Regimen/ Treatment Period/ Vaccination Regimen	Use
Arm 1	V937[a]	1 X 10^9 $TCID_{50}$	q2d in Cycle 1 (4 doses); then q3w	IV infusion	Days 1, 3, 5, and 8 of Cycle 1 (28-day cycle); Day 1 of Cycles 2-8 (21-day cycles)	Test Product
	pembro-lizumab	200 mg	q3w	IV infusion	Day 8 of Cycle 1 (28-day cycle) Day 1 of each subsequent 21-day cycle	
Arm 2	V937 [a]	3 X 10^8 $TCID_{50}$	q2d in Cycle 1 (4 doses); then q3w	ITu administration via visual inspection for cutaneous lesions, and via ultrasound guidance for subcutaneous lesions, as needed	Days 1, 3, 5, and 8 of Cycle 1 (28-day cycle); Day 1 of Cycles 2-8 (21-day cycles)	Test Product
	pembro-lizumab	200 mg	q3w	IV infusion	Day 8 of Cycle 1 (28-day cycle) Day 1 of each subsequent 21-day cycle	
Arm 3	pembro-lizumab	200 mg	q3w	IV infusion	Day 8 of Cycle 1 (28-day cycle) Day 1 of each subsequent 21-day cycle	SoC

[a] In Arms 1 and 2, V937 will be administered within 0.5-4 h following completion of pembrolizumab IV infusion.
ITu=intratumoral; IV=intravenous; q2d=every 2 days; q3w=every 3 weeks; SoC=standard of care; $TCID_{50}$=50% tissue culture infectious dose.

Other current or former name(s) or alias(es) for study intervention(s) are as follows: V937: Coxsackievirus A21 (CVA21); CAVATAK®; CAV21.

Total Number: 3 arms

Duration of Participation	Each participant will participate in the study for approximately 2 years from the time the participant provides documented informed consent through the final contact. After a screening phase of up to 28 days, each participant will be receiving assigned intervention for up to approximately 2 years. 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 screening phase of up to 28 days, each participant will be assigned to receive study intervention until disease progression is radiographically documented, confirmed by the site per modified Response Evaluation Criteria in Solid Tumors 1.1 for immune-based therapeutics (iRECIST), when clinically appropriate, unacceptable adverse event(s) (AEs), intercurrent illness that prevents further administration of treatment, investigator's decision to discontinue the participant, or administrative reasons requiring cessation of treatment, or until the participant has received 35 administrations of pembrolizumab (approximately 2 years). Participants will receive up to 8 cycles (11 administrations) of V937, unless any of the above apply. 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 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 when clinically appropriate, confirmed by the site per iRECIST (for participants treated with pembrolizumab), the start of a new anti-cancer treatment, withdrawal of consent, pregnancy, death, or loss to follow-up. All participants will be followed by telephone for overall survival until death, withdrawal of consent, or the end of the study. Due to discontinuation of V937-011, participants who have completed or discontinued V937 treatment and are only receiving pembrolizumab may be enrolled in a pembrolizumab extension study, if available, to continue pembrolizumab monotherapy for up to 35 cycles from first pembrolizumab dose on V937-011 and to be monitored per the extension study as appropriate.

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.	

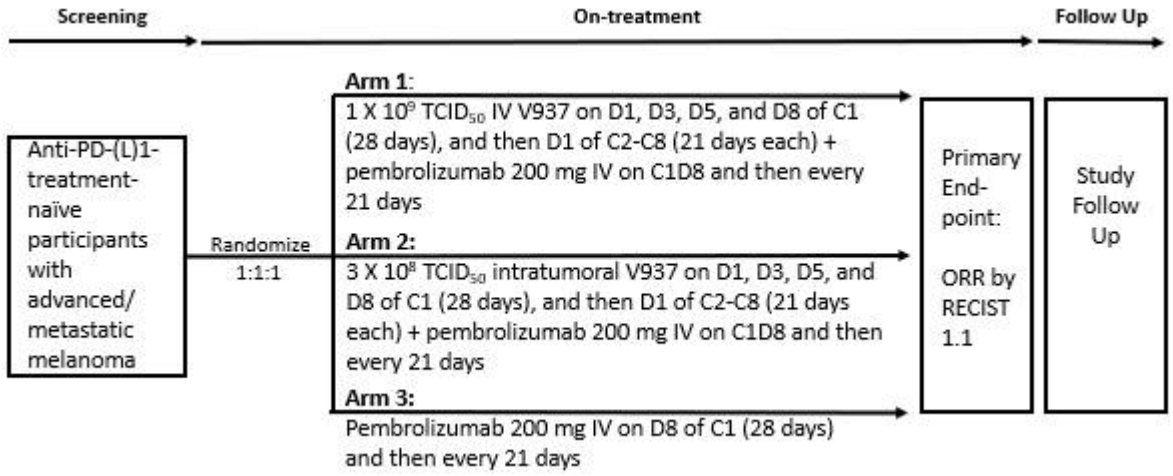
Study Accepts Healthy Volunteers: No

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

1.2 Schema

The study design is depicted in Figure 1. Due to discontinuation of V937-011, participants who have completed or discontinued V937 treatment and are only receiving pembrolizumab may be enrolled in a pembrolizumab extension study, if available, to continue pembrolizumab monotherapy for up to 35 cycles from first pembrolizumab dose on V937-011 and to be monitored per the extension study as appropriate. Due to early study termination of this study, the total enrollment number may be less than 135 participants.

Figure 1 Study Schema



C=cycle; D=day; IV=intravenous; ORR=objective response rate; PD-(L)1=programmed cell death (ligand) 1; RECIST=Response Evaluation Criteria in Solid Tumors, version 1.1; $TCID_{50}$=50% tissue culture infectious dose.

1.3 Schedule of Activities (SoA)

It should be noted that there are variations to certain sections within the protocol that are based on country-specific regulations. These variations are organized by country and addressed in Appendix 7.

Due to discontinuation of V937-011, participants who have completed or discontinued V937 treatment and are only receiving pembrolizumab may be enrolled in a pembrolizumab extension study, if available, to continue pembrolizumab monotherapy for up to 35 cycles from first pembrolizumab dose on V937-011 and to be monitored per the extension study as appropriate.

1.3.1 Schedule of Activities for Screening

Table 1 Study Schedule of Activities for Screening

Study Period	**Screening**	**Notes**
Visit Days	**-28 to -1**	
Administrative Procedures		
Informed Consent	X	Documented informed consent must be obtained prior to performing any protocol-specific procedures. Tests performed prior to consent as part of routine clinical management are acceptable if performed within the specified timeframe.
Informed Consent for Future Biomedical Research (FBR) (Optional)	X	Consent for FBR is not required to participate in the study. Any leftover biomarker samples will be stored for FBR if the participant (or their legally acceptable representative) provides documented informed consent for FBR. Detailed instructions for the collection and management of FBR specimens are provided in the Procedures Laboratory Manual. This is optional for the participant.
Inclusion/Exclusion Criteria	X	
Participant Identification Card	X	Add the allocation or randomization number at the time of allocation or randomization.
Demographics and Medical History	X	
Oncology Disease Status and Prior Oncology Treatment History	X	
Mutational Status / Tumor Genetic Alteration(s)	X	Tumor genetic alteration(s) per standard of care, by history if available, as determined by local testing results.
Prior Medication	X	

Study Period	Screening	Notes
Visit Days	**-28 to -1**	
Clinical Procedures/Assessments		
Tumor Imaging, RECIST 1.1 Response Assessment	X	Baseline tumor imaging (CT or MRI as indicated for tumor type) and/or medical photography of cutaneous lesions should be performed within 28 days of enrollment. Please refer to Imaging Manual for detailed information.
Medical Photography (Cutaneous Lesions)	X	
Brain Imaging	X	Participants with previously treated brain metastases must undergo brain imaging within 28 days prior to the first dose of study treatment, with local confirmation that no new or untreated brain metastases are present.
Physical Examination	X	A full physical examination should be done at screening.
Height	X	
Weight	X	
Vital Signs	X	Includes temperature, pulse, respiratory rate, and blood pressure.
ECOG Performance Status	X	To be performed within 72 h prior to dosing.
12-Lead Electrocardiogram	X	
AE Monitoring	X	All AEs that occur after the consent form is signed but before treatment allocation must be reported by the investigator if the event causes the participant to be excluded from the study or is the result of a protocol-specified intervention. There is to be continuous AE reporting from the time of treatment allocation.
Laboratory Procedures/Assessments - LOCAL		
CBC with Differential	X	Perform all screening clinical laboratory tests within 72 h of treatment initiation with the exception of thyroid and hepatitis testing. Participants on anticoagulant therapy should be monitored throughout the study. Thyroid function: Total T4 and T3 are preferred over FT4 and FT3.
Chemistry Panel	X	
PT/INR and PTT or aPTT	X	
LDH, AST, ALT	X	
Thyroid Function Testing (T4 or FT4, T3 or FT3, TSH)	X	
Urinalysis	X	

Study Period	Screening	Notes
Visit Days	**-28 to -1**	
Pregnancy test for WOCBP only (urine or serum hCG)	X	Perform within 72 h prior to C1D1. Urine pregnancy test to be performed as indicated; if test is positive or cannot be confirmed as negative, a serum pregnancy test is required. Additional pregnancy testing can be conducted if required by local regulations or if clinically indicated.
HIV, Hepatitis B and C Screen	X	Acceptable to be based on history unless testing is required by local regulation. Include HCV antibody or HCV RNA (qualitative) and HBsAg. No testing for Hepatitis B and Hepatitis C is required unless mandated by local health authority.
AE=adverse event; aPTT=activated partial thromboplastin time; ALT=alanine aminotransferase; AST=aspartate aminotransferase; C=Cycle; CBC=complete blood count; CT=computed tomography; D=Day; ECOG=Eastern Cooperative Oncology Group; FBR=future biomedical research; F=free; HBsAg=hepatitis B surface antigen; hCG=human chorionic gonadotropin; HCV=hepatitis C virus; HIV=human immunodeficiency virus; INR=International Normalized Ratio; LDH=lactate dehydrogenase; MRI=magnetic resonance imaging; PT=prothrombin time; PTT=partial thromboplastin time; RECIST 1.1=Response Evaluation Criteria in Solid Tumors, version 1.1; RNA=ribonucleic acid; T3=triiodothyronine; T4=thyroxine; TSH=thyroid-stimulating hormone; WOCBP=women of childbearing potential.		

1.3.2 Schedule of Activities for the Treatment Period – Arm 1 (IV Pembro + IV V937)

Table 2 Study Schedule of Activities for the Treatment Period – Arm 1 (IV Pembro + IV V937)

Study Period	**Treatment Period**						**Notes**
Visit Timing	**Cycle 1 (28 days)**				**Cycle 2-8 (21 days)**	**Cycles ≥9 (21 days)**	**For all cycles:** Up to 35 cycles of treatment with pembrolizumab and up to 8 cycles (ie, 11 doses) of treatment with V937. Cycle 1 is 28 days and all subsequent cycles are 21 days.
Visit Day (Days)	**1**	**3**	**5**	**8**	**1**	**1**	
Visit Window	**±0**	**±1**	**±1**	**±1**	**+3**	**±3**	**The visit window is +3 days for C2D1 and ±3 days for Day 1 of subsequent cycles.**
Intervention Randomization	X						Randomization can occur up to 3 days prior to C1D1.
Participant Identification Card	X						Participant identification card to be updated with treatment number at the time of treatment randomization.
Pembrolizumab Administration				X	X	X	For the first 4 doses of V937, a window of 24 h for dosing will be allowed to accommodate weekends. In Cycle 2, study treatment may be administered up to 3 days after the scheduled Day 1. Beginning in Cycle 3, study treatments may be administered up to 3 days before or after the scheduled Day 1. For Cycles 2-8, V937 will be infused IV over 30 min at 0.5 to 4 h after a 200-mg dose of pembrolizumab infused over 30 min. For administration details, see Pharmacy Manual.
V937 Administration	X	X	X	X	X		

Study Period	Treatment Period						Notes
Visit Timing	**Cycle 1 (28 days)**				**Cycle 2-8 (21 days)**	**Cycles ≥9 (21 days)**	**For all cycles:** Up to 35 cycles of treatment with pembrolizumab and up to 8 cycles (ie, 11 doses) of treatment with V937. Cycle 1 is 28 days and all subsequent cycles are 21 days.
Visit Day (Days)	**1**	**3**	**5**	**8**	**1**	**1**	
Visit Window	**±0**	**±1**	**±1**	**±1**	**+3**	**±3**	**The visit window is +3 days for C2D1 and ±3 days for Day 1 of subsequent cycles.**
Clinical Procedures/Assessments							
Tumor Imaging, RECIST 1.1, and iRECIST Response Assessment	←					→	Tumor imaging (CT or MRI) as indicated for tumor type and/or medical photography of cutaneous lesions should be performed every 9 weeks (± 7 days) after the first dose of pembrolizumab for the first 54 weeks then every 12 weeks thereafter, **following calendar days**, and should not be adjusted for delays in cycle starts. Continue imaging schedule until disease progression, discontinuation, or the start of new anticancer treatment. Please refer to Imaging Manual for detailed information on medical photography.
Medical Photography (Cutaneous Lesions)	←					→	
Physical Examination	X	X	X	X	X	X	Directed physical examinations may be performed unless a full examination is deemed necessary. To be performed on Days 1, 3, 5, and 8 of Cycle 1; on Day 1 of every cycle thereafter.
Weight	X				X	X	Every other cycle (ie, Cycles 1, 3, 5, 7, 9, etc.).
Vital Signs (temperature, pulse, respiratory rate, and blood pressure)	X	X	X	X	X	X	To be measured within 1 h (± 30 min) prior to dosing of V937, and 2, 4, and 6 h (± 30 min for each timepoint) after V937 administration in Cycle 1. For Cycle 2 to Cycle 8, to be measured within 1 h (± 30 min) prior to dosing of V937, and 2 and 4 h (± 30 min for each timepoint) after V937 administration. For Cycle 9 and beyond, to be measured within 1 h (± 30 min) prior to dosing with pembrolizumab on Day 1 of every cycle.
ECOG Performance Status	X				X	X	Performed within 72 h prior to V937 dosing on Day 1 of each cycle.

Study Period	**Treatment Period**						**Notes**
Visit Timing	**Cycle 1 (28 days)**				**Cycle 2-8 (21 days)**	**Cycles ≥9 (21 days)**	**For all cycles:** Up to 35 cycles of treatment with pembrolizumab and up to 8 cycles (ie, 11 doses) of treatment with V937. Cycle 1 is 28 days and all subsequent cycles are 21 days.
Visit Day (Days)	**1**	**3**	**5**	**8**	**1**	**1**	
Visit Window	**±0**	**±1**	**±1**	**±1**	**+3**	**±3**	**The visit window is +3 days for C2D1 and ±3 days for Day 1 of subsequent cycles.**
Concomitant Medication	X	X	X	X	X	X	
AEs	⟷						Continuous AE reporting from the time of treatment allocation.
Survival Status	⟷						Upon Sponsor request, participants may be contacted for survival status at any time during the course of the study.
Laboratory Procedures/Assessments – LOCAL							
CBC with Differential	X			X	X	X	Perform all scheduled clinical laboratory tests within 72 h prior to the start of each cycle. Screening procedures/sample collections done within this time frame do not need to be repeated for the Cycle 1, Day 1 timepoint. For PT/INR/PTT/aPTT: Only as clinically indicated Participants on anticoagulant therapy should be monitored throughout the study. Thyroid function: After Cycle 1, samples are collected every other cycle (ie, Cycles 2, 4, 6, etc.). Total T4 and T3 are preferred over FT4 and FT3. The participant may be dosed while thyroid function tests are pending.
Chemistry Panel	X			X	X	X	
PT/INR and PTT or aPTT	X				X	X	
LDH, AST, ALT	X				X	X	
Thyroid Function Testing (T4 or FT4, T3 or FT3, TSH)	X				X	X	
PBMC Collection					X		Optional collection on C3D1 to be performed at selected study site(s) in the US only.

Study Period	**Treatment Period**						**Notes**
Visit Timing	**Cycle 1 (28 days)**				**Cycle 2-8 (21 days)**	**Cycles ≥9 (21 days)**	**For all cycles:** Up to 35 cycles of treatment with pembrolizumab and up to 8 cycles (ie, 11 doses) of treatment with V937. Cycle 1 is 28 days and all subsequent cycles are 21 days.
Visit Day (Days)	**1**	**3**	**5**	**8**	**1**	**1**	
Visit Window	**±0**	**±1**	**±1**	**±1**	**+3**	**±3**	**The visit window is +3 days for C2D1 and ±3 days for Day 1 of subsequent cycles.**
Pregnancy test for WOCBP only (urine or serum hCG)	X				X		Perform within 72 h prior to C1D1. Urine pregnancy test to be performed as indicated; if test is positive or cannot be confirmed as negative, a serum pregnancy test is required. Additional pregnancy testing can be conducted if required by local regulations or clinically indicated.

AE=adverse event; ALT=alanine aminotransferase; aPTT=activated partial thromboplastin time; AST=aspartate aminotransferase; C=Cycle; CBC=complete blood count; CT=computed tomography; C_{trough}=trough concentration; D=Day; ECOG=Eastern Cooperative Oncology Group; F=free; hCG=human chorionic gonadotropin; INR=International Normalized Ratio; iRECIST=modified RECIST 1.1 for immune-based therapeutics; IV=intravenous; LDH=lactate dehydrogenase; MRI=magnetic resonance imaging; PBMC=peripheral blood mononuclear cells; PT=prothrombin time; PTT=partial thromboplastin time; RECIST 1.1=Response Evaluation Criteria in Solid Tumors, version 1.1; T3=triiodothyronine; T4=thyroxine; TSH=thyroid-stimulating hormone; WOCBP=women of childbearing potential.

1.3.3 Schedule of Activities for the Treatment Period – Arm 2 (IV Pembro + ITu V937)

Table 3 Study Schedule of Activities for the Treatment Period – Arm 2 (IV Pembro + ITu V937)

Study Period	**Treatment Period**						**Notes**
Visit Timing	**Cycle 1 (28 days)**				**Cycle 2-8 (21 days)**	**Cycles ≥9 (21 days)**	**For all cycles:** Up to 35 cycles of treatment with pembrolizumab and up to 8 cycles (ie, 11 doses) of treatment with V937. Cycle 1 is 28 days and all subsequent cycles are 21 days.
Visit Day (Days)	**1**	**3**	**5**	**8**	**1**	**1**	
Visit Window	**±0**	**±1**	**±1**	**±1**	**+3**	**±3**	**The visit window is +3 days for C2D1 and ±3 days for Day 1 of subsequent cycles.**
Intervention Randomization	X						Randomization can occur up to 3 days prior to C1D1.
Participant Identification Card	X						Participant identification card to be updated with treatment number at the time of treatment randomization.
Pembrolizumab Administration				X	X	X	For the first 4 doses of V937, a window of 24 h for dosing will be allowed to accommodate weekends. In Cycle 2, study treatment may be administered up to 3 days after the scheduled Day 1. Beginning in Cycle 3, study treatments may be administered up to 3 days before or after the scheduled Day 1. For Cycles 2-8, V937 will be injected ITu 0.5 to 4 h after a 200-mg dose of pembrolizumab infused over 30 min. For administration details, see Pharmacy Manual.
V937 Administration	X	X	X	X	X		

Study Period	Treatment Period						Notes
Visit Timing	**Cycle 1 (28 days)**				**Cycle 2-8 (21 days)**	**Cycles ≥9 (21 days)**	**For all cycles:** Up to 35 cycles of treatment with pembrolizumab and up to 8 cycles (ie, 11 doses) of treatment with V937. Cycle 1 is 28 days and all subsequent cycles are 21 days.
Visit Day (Days)	**1**	**3**	**5**	**8**	**1**	**1**	
Visit Window	**±0**	**±1**	**±1**	**±1**	**+3**	**±3**	**The visit window is +3 days for C2D1 and ±3 days for Day 1 of subsequent cycles.**
Clinical Procedures/Assessments							
Tumor Imaging, RECIST 1.1, and iRECIST Response Assessment	←					→	Tumor imaging (CT or MRI) as indicated for tumor type and/or medical photography of cutaneous lesions should be performed every 9 weeks (± 7 days) after the first dose of pembrolizumab for the first 54 weeks then every 12 weeks thereafter, **following calendar days**, and should not be adjusted for delays in cycle starts. Continue imaging schedule until disease progression, discontinuation, or the start of new anticancer treatment. Please refer to Imaging Manual for detailed information on medical photography.
Medical Photography (Cutaneous Lesions)	←					→	
Physical Examination	X	X	X	X	X	X	Directed physical examinations may be performed unless a full examination is deemed necessary. To be performed on Days 1, 3, 5, and 8 of Cycle 1; on Day 1 of every cycle thereafter.
Weight	X				X	X	Every other cycle (ie, Cycles 1, 3, 5, 7, 9, etc.).
Vital Signs (temperature, pulse, respiratory rate, and blood pressure)	X	X	X	X	X	X	To be measured within 1 h (± 30 min) prior to dosing of V937, and 2, 4, and 6 h (± 30 min for each time point) after V937 administration in Cycle 1. For Cycle 2 to Cycle 8, to be measured within 1 h (± 30 min) prior to dosing of V937, and 2 and 4 h (± 30 min for each time point) after V937 administration. For Cycle 9 and beyond, to be measured within 1 h (± 30 min) prior to dosing with pembrolizumab on Day 1 of every cycle.

Study Period	**Treatment Period**						**Notes**
Visit Timing	**Cycle 1 (28 days)**				**Cycle 2-8 (21 days)**	**Cycles ≥9 (21 days)**	**For all cycles:** Up to 35 cycles of treatment with pembrolizumab and up to 8 cycles (ie, 11 doses) of treatment with V937. Cycle 1 is 28 days and all subsequent cycles are 21 days.
Visit Day (Days)	**1**	**3**	**5**	**8**	**1**	**1**	
Visit Window	**±0**	**±1**	**±1**	**±1**	**+3**	**±3**	**The visit window is +3 days for C2D1 and ±3 days for Day 1 of subsequent cycles.**
ECOG Performance Status	X				X	X	Performed within 72 h prior to V937 dosing on Day 1 of each cycle.
Concomitant Medication	X	X	X	X	X	X	
AEs	⟷						Continuous AE reporting from the time of treatment allocation.
Survival Status	⟷						Upon Sponsor request, participants may be contacted for survival status at any time during the course of the study.
Laboratory Procedures/Assessments – LOCAL							
CBC with Differential	X			X	X	X	Perform all scheduled clinical laboratory tests within 72 h prior to the start of each cycle. Screening procedures/sample collections done within this time frame do not need to be repeated for the Cycle 1, Day 1 timepoint. For PT/INR/PTT/aPTT: Only as clinically indicated Participants on anticoagulant therapy should be monitored throughout the study. Thyroid function: After Cycle 1, samples are collected every other cycle (ie, Cycles 2, 4, 6, etc.). Total T4 and T3 are preferred over FT4 and FT3. The participant may be dosed while thyroid function tests are pending.
Chemistry Panel	X			X	X	X	
PT/INR and PTT or aPTT	X				X	X	
LDH, AST, ALT	X				X	X	
Thyroid Function Testing (T4 or FT4, T3 or FT3, TSH)	X				X	X	
PBMC Collection					X		Optional collection on C3D1 to be performed at selected study site(s) in the US only.

Study Period	Treatment Period						Notes
Visit Timing	**Cycle 1 (28 days)**				**Cycle 2-8 (21 days)**	**Cycles ≥9 (21 days)**	**For all cycles:** Up to 35 cycles of treatment with pembrolizumab and up to 8 cycles (ie, 11 doses) of treatment with V937. Cycle 1 is 28 days and all subsequent cycles are 21 days.
Visit Day (Days)	**1**	**3**	**5**	**8**	**1**	**1**	
Visit Window	**±0**	**±1**	**±1**	**±1**	**+3**	**±3**	**The visit window is +3 days for C2D1 and ±3 days for Day 1 of subsequent cycles.**
Pregnancy test for WOCBP only (urine or serum hCG)	X						Perform within 72 h prior to C1D1. Urine pregnancy test to be performed as indicated; if test is positive or cannot be confirmed as negative, a serum pregnancy test is required. Additional pregnancy testing can be conducted if required by local regulations or clinically indicated.

AE=adverse event; ALT=alanine aminotransferase; aPTT=activated partial thromboplastin time; AST=aspartate aminotransferase; C=Cycle; CBC=complete blood count; CT=computed tomography; C_{trough}=trough concentration; D=Day; ECOG=Eastern Cooperative Oncology Group; F=free; hCG=human chorionic gonadotropin; INR=International Normalized Ratio; iRECIST=modified RECIST 1.1 for immune-based therapeutics; ITu=intratumoral; IV=intravenous; LDH=lactate dehydrogenase; MRI=magnetic resonance imaging; PBMC=peripheral blood mononuclear cells; PT=prothrombin time; PTT=partial thromboplastin time; RECIST 1.1=Response Evaluation Criteria in Solid Tumors, version 1.1; T3=triiodothyronine; T4=thyroxine; TSH=thyroid-stimulating hormone; WOCBP=women of childbearing potential.

1.3.4 Schedule of Activities for the Treatment Period – Arm 3 (Pembrolizumab Monotherapy)

Table 4 Study Schedule of Activities for the Treatment Period – Arm 3 (IV Pembro Alone)

Study Period	**Treatment Period**						**Notes**
Visit Timing	**Cycle 1 (28 days)**				**Cycles 2-8 (21 days)**	**Cycles ≥9 (21 days)**	**For all cycles:** Up to 35 cycles of treatment with pembrolizumab. Cycle 1 is 28 days and all subsequent cycles are 21 days.
Visit Day (Days)	**1**	**3**	**5**	**8**	**1**	**1**	
Visit Window	**±0**	**±1**	**±1**	**±1**	**+3**	**±3**	**The visit window is +3 days for C2D1 and ±3 days for Day 1 of subsequent cycles.**
Intervention Randomization	X						Randomization can occur up to 3 days prior to C1D1.
Participant Identification Card	X						Participant identification card to be updated with treatment number at the time of treatment randomization.
Pembrolizumab Administration				X	X	X	
Clinical Procedures/Assessments							
Tumor Imaging, RECIST 1.1, and iRECIST Response Assessment	←					→	Tumor imaging (CT or MRI) and/or medical photography of cutaneous lesions should be performed every 9 weeks (± 7 days) after the first dose for the first 54 weeks then every 12 weeks thereafter, **following calendar days**, and should not be adjusted for delays in cycle starts. Continue imaging schedule until disease progression, discontinuation, or the start of new anticancer treatment. Please refer to Imaging Manual for detailed information on medical photography.
Medical Photography (Cutaneous Lesions)	←					→	
Physical Examination				X	X	X	Directed physical examinations may be performed unless a full examination is deemed necessary. To be performed on Day 8 of Cycle 1 and Day 1 of every cycle thereafter.

Study Period	**Treatment Period**						**Notes**
Visit Timing	**Cycle 1 (28 days)**				**Cycles 2-8 (21 days)**	**Cycles ≥9 (21 days)**	**For all cycles:** Up to 35 cycles of treatment with pembrolizumab. Cycle 1 is 28 days and all subsequent cycles are 21 days.
Visit Day (Days)	**1**	**3**	**5**	**8**	**1**	**1**	
Visit Window	**±0**	**±1**	**±1**	**±1**	**+3**	**±3**	**The visit window is +3 days for C2D1 and ±3 days for Day 1 of subsequent cycles.**
Weight				X	X	X	Every other cycle (ie, Cycles 1, 3, 5, 7, 9, etc.).
Vital Signs (temperature, pulse, respiratory rate, and blood pressure)				X	X	X	To be measured within 1 h (± 30 min) prior to dosing with pembrolizumab on C1D8 and Day 1 of each subsequent cycle.
ECOG Performance Status				X	X	X	Performed within 72 h prior to dosing with pembrolizumab on C1D8 and Day 1 of each subsequent cycle.
Concomitant Medication	X			X	X	X	
AEs	⟷						Continuous AE reporting from the time of treatment allocation.
Survival Status	⟷						Upon Sponsor request, participants may be contacted for survival status at any time during the course of the study.
Laboratory Procedures/Assessments - LOCAL							
CBC with Differential				X	X	X	Perform all scheduled clinical laboratory tests within 72 h prior to the start of dosing in each cycle. Screening procedures/sample collections done within this time frame do not need to be repeated for the Cycle 1, Day 8 time point.
Chemistry Panel				X	X	X	
PT/INR and PTT or aPTT				X	X	X	
LDH, AST, ALT				X	X	X	

Study Period	**Treatment Period**						**Notes**
Visit Timing	**Cycle 1 (28 days)**				**Cycles 2-8 (21 days)**	**Cycles ≥9 (21 days)**	**For all cycles:** Up to 35 cycles of treatment with pembrolizumab. Cycle 1 is 28 days and all subsequent cycles are 21 days.
Visit Day (Days)	**1**	**3**	**5**	**8**	**1**	**1**	
Visit Window	**±0**	**±1**	**±1**	**±1**	**+3**	**±3**	**The visit window is +3 days for C2D1 and ±3 days for Day 1 of subsequent cycles.**
Thyroid Function Testing (T4 or FT4, T3 or FT3, TSH)				X	X	X	For PT/INR/PTT/aPTT: Only as clinically indicated Participants on anticoagulant therapy should be monitored throughout the study. Thyroid function: After Cycle 1, samples are collected every other cycle (ie, Cycles 2, 4, 6, etc.). Total T4 and T3 are preferred over FT4 and FT3. The participant may be dosed while thyroid function tests are pending.
PBMC Collection					X		Optional collection on C3D1 to be performed at selected study site(s) in the US only.
Pregnancy test for WOCBP only (urine or serum hCG)				X			Perform within 72 h prior to C1D8. Urine pregnancy test to be performed as indicated; if test is positive or cannot be confirmed as negative, a serum pregnancy test is required. Additional pregnancy testing can be conducted if required by local regulations or clinically indicated.

AE=adverse event; ALT=alanine aminotransferase; aPTT=activated partial thromboplastin time; AST=aspartate aminotransferase; C=Cycle; CBC=complete blood count; CT=computed tomography; C_{trough}=trough concentration; D=Day; ECOG=Eastern Cooperative Oncology Group; F=free; hCG=human chorionic gonadotropin; INR=International Normalized Ratio; iRECIST IV=intravenous; LDH=lactate dehydrogenase; MRI=magnetic resonance imaging; PBMC=peripheral blood mononuclear cells; PT=prothrombin time; PTT=partial thromboplastin time; RECIST 1.1=Response Evaluation Criteria in Solid Tumors, version 1.1; T3=triiodothyronine; T4=thyroxine; TSH=thyroid-stimulating hormone; WOCBP=women of childbearing potential.

Samples to be collected on C1D1 “predose” and “postdose” are to be calculated relative to an arbitrary timepoint as there is no dosing of pembrolizumab on C1D1. Samples will provide an untreated, controlled set to assess variability without treatment.

1.3.5 Schedule of Activities for the End of Treatment and Posttreatment Follow-up Periods

Table 5 Study Schedule of Activities for the End of Treatment and Posttreatment Follow-up Periods

Study Period	End of Treatment/ Discontinuation	Notes
Visit Timing		
Visit Window (Days)	**±7**	
Administrative Procedures		
Concomitant Medication	X	
Efficacy Procedures		**See Imaging Manual – All imaging visits have a ± 7-day window**
Tumor Imaging, RECIST 1.1, and iRECIST Response Assessment	X	
Medical Photography (Cutaneous Lesions)	X	
New Anticancer Therapy Status	X	
Safety Assessments and Procedures		**See Procedures Manual for collection and management of samples.**
AE Monitoring	X	
Full Physical Examination	X	
Weight	X	
Vital Signs	X	Temperature, pulse, respiratory rate, and blood pressure
ECOG Performance Status	X	
CBC with Differential	X	
Chemistry Panel	X	
AE=adverse event; CBC=complete blood count; ECOG=Eastern Cooperative Oncology Group; iRECIST=immune-based RECIST; LDH=lactate dehydrogenase; RECIST 1.1=Response Evaluation Criteria In Solid Tumors version 1.1;		

2 INTRODUCTION

Significant progress has been made in the field of immunotherapy to treat cancer. Antibodies targeting immune checkpoints have yielded impressive improvements in clinical outcomes for a range of tumor types. Despite this however, many advanced cancer patients do not respond to immunotherapy alone, due to local immune tolerance at the tumor, absence of effector cells, and/or the development of resistance through a variety of adaptive mechanisms [Park, Y. J., et al 2018] [Sharma, P., et al 2017]. Various combinations in clinical studies, such as with conventional chemotherapy, dual T-cell checkpoint blockade (CTLA-4), second-generation immunotherapy targets (TIGIT, LAG3, TIM-3, etc.), cancer vaccines, and oncolytic viruses, simultaneously targeting different components of tumor development/progression have the potential to significantly enhance efficacy, response rates, and durability relative to single-agent first- and second-generation immunotherapies (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6115503/).

V937 is a novel oncolytic viral therapy and is being developed for intratumoral (ITu)/intralesional, intravesicular, and intravenous (IV) administration to treat advanced cancers.

The use of oncolytic viruses for the treatment of cancer gained significant momentum, with several oncolytic viruses in Phase 2 and Phase 3 clinical evaluations [Kaufman, H. L. 2010] [Rowan, K. 2010] [Senzer, N. N., et al 2009], reinforcing the potential of this novel method for the treatment of malignancy.

Essential to the rationale for the use of an oncolytic virus is a differential infectivity between normal cells and neoplastic cells. An oncolytic virus may accomplish this by different mechanisms, including the capacity to employ an intracellular selective process to replicate in a cancer cell with an inability to replicate in normal cells, as is the case with reovirus [Forsyth, P., et al 2008] [Harrington, K. J., et al 2010] and genetically altered vaccinia [Liu, T. C., et al 2008] [Merrick, A. E., et al 2009] and herpes simplex viruses [Senzer, N. N., et al 2009].

A second mechanism by which oncolytic viruses may achieve this destructive targeting of cancer cells compared to normal cells is based on the interplay with innate as well as adaptive immune responses. It is essential for the control of a viral infection to have both innate and adaptive immune responses functioning. It is well documented that cancer cells have abnormal interferon responses due to unique metabolic pathways. A normal interferon response limits the ability of viruses to replicate as well as spread to adjacent cells. This interferon-governed response is deficient in cancer cells, giving the oncolytic virus an advantage in growth and spread when infecting cancer cells [Krishnamurthy, S., et al 2006] [Stojdl, D. F., et al 2000].

A third mechanism by which an oncolytic virus can achieve this differential in killing cancer cells, and the mechanism primarily utilized by coxsackievirus A21, is based on viral receptor surface expression. By targeting a viral receptor or receptor complex that is present or over-expressed on the surface of cancer cells compared to being absent or under-expressed

on normal cells, degrees of selective cell destruction can, in principle, be achieved [Anderson, B. D., et al 2004].

While the primary mode of action of oncolytic viruses is the direct lytic infection of the target cancer cell, there is increasing evidence that suggests a viral infection within a tumor will cause a migration into the tumor of immune modulating cells and an inflammatory response. Such an inflammatory response in the tumor, involving dendritic cells and cytotoxic T cells, may stimulate a cell-based immune response against a patient's cancer.

V937 is under study for the treatment of solid tumors as monotherapy and as combination therapy with pembrolizumab and other immune checkpoint inhibitors. This is a Phase 2 study to assess the efficacy, safety, and tolerability of V937 administered both ITu and IV as combination therapy with pembrolizumab versus pembrolizumab alone.

2.1 Study Rationale

Advanced/metastatic melanoma cause significant morbidity and mortality. Melanoma is the most serious form of skin cancer and strikes adults of all ages. In 2008, the 5-year prevalence of melanoma in the European Union (EU) is approximately 159,000 patients with an incidence of approximately 41,000 per year and approximately 11,000 deaths annually as described in the World Health Organization (WHO) Europe region [Ferlay, J., et al 2010]. Melanoma accounts for approximately 5% of all new cases of cancer in the United States (US), and the incidence of melanoma continues to rise by almost 3% per year in the US. This translates to 76,000 new cases a year with 9000 associated deaths. The male-to-female incidence ratio of melanoma is 1.4:1, respectively [Siegel, R., et al 2012]. The 5-year survival rate is 15% once patients have progressed to late-stage disease [American Cancer Society 2012].

There is a great unmet medical need for therapeutic agents that can enhance the effect of immunotherapy. Nonclinical studies investigating the coadministration of ITu or IV V937 with 2 different immunostimulatory antibodies showed that, regardless of the method of administration, V937 used in combination with antiprogrammed cell death (PD)-1 and/or anti-CTLA-4 blocking antibodies was generally well tolerated in immunocompetent mouse models of melanoma and NSCLC, with gross observations not revealing AEs relating to the agents tested. These studies were the basis for subsequent clinical studies assessing V937 in combination with different checkpoint inhibitors.

Previous clinical studies have demonstrated that V937 has antitumor activity and good tolerability in both monotherapy (CALM study) and in combination with checkpoint inhibitor such as pembrolizumab for both ITu and IV settings (CAPRA and STORM [KN200] studies).

In the CAPRA study, patients with advanced melanoma who were naïve to prior checkpoint inhibitor exposure received the combination of ITu V937 and pembrolizumab. Although the study is ongoing, an overall response rate of 59% (16/27) has been observed. Five Grade 3 or greater AEs related to pembrolizumab were reported in 4 participants, with AEs related to

V937 limited to Grade 1 or 2 in severity. In summary, the combination of ITu V937 and pembrolizumab was well tolerated.

In the STORM study (KN200), V937 administered IV as monotherapy can induce viral replication in NSCLC, metastatic bladder carcinoma, and melanoma. When given in combination with pembrolizumab, tumor responses were observed in the NSCLC and metastatic bladder cancer expansion cohorts. No DLTs were noted, and AEs related to V937 or pembrolizumab were mainly Grade 1 or 2 in severity. Four Grade 3 events related to V937 were reported in 3 participants, or 4% (3/85) of participants treated. Nineteen Grade 3 AEs related to pembrolizumab were reported in 9 participants, or 11% (9/85) of treated participants. The ability to administer V937 systemically via IV infusion would make possible treatment for patients with cancers that are not accessible for ITu therapy.

The current study is a randomized study to assess whether ITu and/or IV administration of V937 in combination with pembrolizumab is superior to pembrolizumab alone in anti-PD-(L)1-treatment-naive patients with melanoma (with accessible tumors).

2.2 Background

V937 (coxsackievirus A21 [CVA21]; CAVATAK; CAV21) is a live oncolytic virus preparation derived from the non-genetically altered prototype Kuykendall strain of coxsackievirus A21 that has been propagated in cell cultures. Coxsackievirus is a nonenveloped virus with positive single-stranded RNA and 4 capsid proteins and is a naturally occurring human enterovirus. V937 has an acceptable preclinical safety profile and is in clinical development as an intratumoral (ITu), intravesicular, and IV immunotherapy for advanced malignancies. For more details on specific refer to the V937 Investigator's Brochure (IB).

Pembrolizumab is a potent humanized immunoglobulin G4 (IgG4) monoclonal antibody (mAb) with high specificity of binding to the 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 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 IB.

2.2.1 V937 Pharmaceutical and Therapeutic Background

The primary focus of the V937 development program is to assess the safety and efficacy of the virus in the treatment of advanced solid tumor and other malignancies where ICAM-1/ DAF receptor expression occurs. Coxsackievirus A21 is a naturally occurring enterovirus that can cause the common cold [Zeichhardt, H. 2004]. V937 used in the current nonclinical and clinical studies is the prototype Kuykendall strain, which has not been genetically modified.

Coxsackievirus A21 belongs to the Enterovirus genus of the Picornaviridae family, which consists of more than 70 serologically distinguishable strains of virus that are otherwise structurally and morphologically indistinguishable. The enteroviruses are conventionally subdivided into 3 major subclasses: polioviruses, echoviruses, and coxsackieviruses. The coxsackieviruses are further subdivided into Groups A (23 members) and B (6 members) [Zeichhardt, H. 2004].

Surface-expressed ICAM-1 (CD54) was identified to be the virus uptake receptor for a number of human enteroviruses [Shafren, D.R., et al 1997] [Shafren, D. R. 1998] [Shafren, D. R., et al 2000]. The most exhaustively studied agents belong to the coxsackievirus A subgroup of the human enteroviruses, of which coxsackievirus A21 is a member.

For many years it has been known that moderate levels of ICAM-1 are expressed on nasal epithelium and can be used as a receptor by the major group of rhinoviruses, conferring susceptibility to common colds [Staunton, D. E., et al 1989]. ICAM-1 is also expressed on endothelium and used by leucocytes as a ligand by which they can transmigrate, particularly in response to local inflammatory mediators [Shaw, S. K., et al 2004].

High-level surface ICAM-1 expression is found on numerous malignant cells including breast cancer, head and neck cancer, prostate cancer, and melanoma [Anichini, A., et al 1990] [Berry, L.J., et al 2008] [Georgolios, A., et al 2006] [Kageshita, T., et al 1993] [Lang, S., et al 1999] [Si, Z. 1994] [Skelding KA, Barry RD, Shafren DR. 2009]. Several laboratories have shown that there is an association between the level of expression of ICAM-1 and the ability of melanoma cells to undergo metastasis [Anastassiou, G., et al 2000] [Anichini, A., et al 1990] [Bergelson, J. M., et al 1994] [Hakansson, A., et al 1999] [Johnson, J. P. 1991] [Pandolfi, F., et al 1992]. Upregulated ICAM-1 expression has also been implicated by study of metastatic human breast carcinoma cell lines [Rosette, C., et al 2005]. Surface-expressed ICAM-1 enables tumor cells to interact with circulating lymphocytes by way of integrin receptors including LFA-1 and Mac 1, thus potentially providing a means by which tumors undergo metastatic spread. It is widely accepted that ICAM-1 is expressed at much higher levels on melanoma metastases than on primary tumors or precancerous lesions, and this phenomenon can be used as an indicator of cancer progression [Kageshita, T., et al 1993].

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 (T-regs) correlates with improved prognosis and long-term survival in solid malignancies, such as ovarian, colorectal, and pancreatic cancer; hepatocellular carcinoma; malignant melanoma; and renal cell carcinoma. Tumor-infiltrating lymphocytes can be expanded ex vivo and reinfused, inducing durable objective tumor responses in cancers such as melanoma [Dudley, M. E., et al 2005] [Hunder, N. N., et al 2008].

The PD-1 receptor-ligand interaction is a major pathway hijacked by tumors to suppress immune control. The normal function of PD-1, expressed on the cell surface of activated T-cells under healthy conditions, is to down-modulate unwanted or excessive immune responses, including autoimmune reactions. PD-1 (encoded by the gene *Pdcd1*) is an immunoglobulin (Ig) superfamily member related to cluster of differentiation 28 (CD28) and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) that has been shown to negatively regulate antigen receptor signaling upon engagement of its ligands (PD-L1 and/or PD-L2) [Greenwald, R. J., et al 2005] [Okazaki, T., et al 2001].

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

2.2.3 Preclinical and Clinical Studies

Please refer to the pembrolizumab and V937 IBs for descriptions of the respective preclinical and clinical evaluations.

2.2.4 Ongoing Clinical Studies

Please refer to the pembrolizumab and V937 IBs for descriptions of ongoing clinical studies.

2.2.5 Information on Other Study-related Therapy

Not applicable.

2.3 Benefit/Risk Assessment

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

Potential risks associated with the administration of V937 based on clinical data may include the following:

- Fatigue

- Chills
- Injection site pain
- Pyrexia

Additional details regarding specific benefits and risks for participants participating in this clinical study may be found in the accompanying V937 and pembrolizumab IBs and informed consent documents.

3 HYPOTHESES, OBJECTIVES, AND ENDPOINTS

Hypotheses are aligned with objectives in the Objectives and Endpoints table.

Throughout this protocol, the term RECIST 1.1 refers to modification to RECIST 1.1 to include a maximum of 10 target lesions and a maximum of 5 target lesions per organ. Refer to Section 4.2.1.1 for further details.

In males and females with advanced/metastatic melanoma who are anti-PD-(L)1-treatment-naïve:

Objectives	Endpoints
Primary	
• Objective: To evaluate the objective response rate (ORR) of participants treated with IV V937 administered in combination with pembrolizumab, ITu V937 administered in combination with pembrolizumab, or pembrolizumab alone per Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST 1.1) by blinded independent central review (BICR). • Hypothesis: V937 administered either IV in combination with pembrolizumab or ITu in combination with pembrolizumab results in a superior ORR per RECIST 1.1 based on BICR, compared to pembrolizumab alone.	• Objective response is a confirmed complete response (CR) or partial response (PR)

Objectives	Endpoints
Secondary	
• To evaluate progression-free survival (PFS), and duration of response (DOR) of participants treated with IV V937 in combination with pembrolizumab, ITu V937 in combination with pembrolizumab, or pembrolizumab alone per RECIST 1.1 by blinded independent central review (BICR).	• PFS, defined as the time from randomization to the first documented progressive disease (PD) or death from any cause, whichever occurs first. • DOR, defined as the time from the first documented evidence of CR or PR until progressive disease (PD) or death due to any cause, whichever occurs first, in participants demonstrating CR or PR
• To evaluate ORR, PFS, and DOR of participants treated with IV V937 in combination with pembrolizumab, ITu V937 in combination with pembrolizumab, or pembrolizumab alone, per RECIST 1.1, as assessed by the investigator.	• Objective response • PFS • DOR
• To evaluate OS of participants treated with IV V937 in combination with pembrolizumab, ITu V937 in combination with pembrolizumab, or pembrolizumab alone.	• OS, defined as the time from randomization to the date of death from any cause
• Objective: To assess the safety and tolerability of participants treated with IV V937 in combination with pembrolizumab, ITu V937 in combination with pembrolizumab, or pembrolizumab alone.	• Adverse events (AEs) • Discontinuing study intervention due to an AE
Tertiary/Exploratory	
CCI [redacted]	

Objectives	Endpoints
CCI [redacted]	

4 STUDY DESIGN

4.1 Overall Design

This is a randomized, active-controlled, parallel-group, multisite, open-label, Phase 2 study of pembrolizumab in combination with V937 administered IV (Arm 1=IV pembro + IV V937) or ITu (Arm 2=IV pembro + ITu V937) versus pembrolizumab alone (Arm 3=IV pembro alone) in participants with a histologically or cytologically confirmed diagnosis of Stage III or IV melanoma. The study will enroll participants with advanced/metastatic melanoma with cutaneous, subcutaneous, or nodal lesions that are amenable to ITu injection by visual inspection, palpation, or ultrasound guidance. Participants need to have 1 measurable lesion that is amenable to ITu injection and biopsy, as well as 1 measurable discrete and/or distant lesion (bystander lesion) that is amenable to biopsy to evaluate any abscopal effect.

This study will evaluate the efficacy, safety, and tolerability, of V937 in combination with pembrolizumab versus pembrolizumab alone. Figure 1 depicts a summary of the study design.

After a screening period of up to 28 days, participants will be randomized to:
Arm 1: IV pembro + IV V937; Arm 2: IV pembro + ITu V937; or Arm 3: IV pembro alone. The first treatment cycle is 28 days, and each subsequent treatment cycle is 3 weeks. Participants will be treated for up to 35 cycles (approximately 2 years) after initiation of treatment with pembrolizumab alone or in combination with V937. V937 will be given for a total of 8 cycles. Discontinuation Follow-Up will be 30 days after the last dose.

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

This study design is a 3-arm randomized study in participants with PD-1-naïve melanoma, comparing: (1) IV pembro + IV V937 to IV pembro alone and (2) IV pembro + ITu V937 to IV pembro alone. The choice of melanoma is due to the observation of single-agent V937 activity when administered ITu, as well as evidence of viral replication in melanoma tumors when V937 is administered IV (Refer to the V937 IB).

Prior studies examining V937 combinations with pembrolizumab (eg, CAPRA for ITu and STORM [KN-200] for IV) were single-arm studies, and thus efficacy comparisons are limited to historic controls. The current study will be randomized to allow for a more rigorous evaluation of the impact of adding V937 to pembrolizumab, which is a standard of care treatment for advanced melanoma.

The current study is randomized but is not blinded due to the desire not to subject all participants to sham ITu injections or sham IV infusions. BICR will be used for primary endpoints to minimize bias in objective response rate (ORR) and PFS determinations. An

interim futility analysis, after 25 participants on each arm are enrolled and have at least 1 postbaseline scan, will be performed so as to limit the number of participants if the addition of V937 to pembrolizumab is deemed futile.

AJCC V8, divides metastatic melanoma is divided into 4 subsets, M1a, M1b, M1c, and M1d. These subgroups are characterized by their metastases: (M1a), nonvisceral (distant cutaneous, subcutaneous, nodal); (M1b), lung; (M1c), noncentral nervous system (CNS) visceral; and a new (M1d) designation for metastases involving the CNS. M1c no longer includes CNS metastasis. M1c and M1d have substantially different prognosis when compared to M1a and M1b, which provides a basis for stratification of this study [Dickson, P. V. 2011].

The current study combination dosing regimens are the same as that used in the nonrandomized CAPRA and STORM studies. Initial V937 dosing on Days 1, 3, 5, and 8 maximizes V937 exposure prior to the development of V937 neutralizing antibodies, which appear after Day 3 and peak ≥ Day 8. See the V937 IB for further information. An underlying hypothesis in these studies is that V937 given before (Days 1, 3, 5) administration of pembrolizumab (Day 8) would expand the T-cell repertoire for melanoma antigens and subsequent pembrolizumab may increase the lifespan and activity of these melanoma-specific T cells.

4.2.1 Rationale for Endpoints

4.2.1.1 Efficacy Endpoints

The primary efficacy endpoint in this study is ORR (defined as the proportion of participants who have achieved confirmed CR or PR). Secondary endpoints include PFS, OS, and DOR.

Tumor response will be assessed using RECIST 1.1 by BICR, RECIST 1.1 and iRECIST as assessed by investigator (see Section 8.2.1). Antitumor activity will be measured through such endpoints as the ORR, PFS, and OS, which are described further in Section 9.4.1. A planned interim futility analysis is described in Section 9.7.

This study will use ORR based on RECIST 1.1 criteria as assessed by BICR as the primary endpoint. Objective response rate is an acceptable measure of clinical benefit for a late -stage study that demonstrates superiority of a new antineoplastic therapy, especially if the magnitude of the effect is large and the therapy has an acceptable risk/benefit profile. The use of BICR and RECIST 1.1 to assess ORR is typically considered acceptable by regulatory authorities. Images will be submitted to an iCRO and read by an independent central review blinded to treatment assignment to minimize bias in the response assessments.

OS has been recognized as the gold standard for the demonstration of superiority of a new antineoplastic therapy in randomized clinical studies.

RECIST 1.1 will be used by the BICR when assessing images for efficacy measures and by the local site when determining eligibility (Section 8.2.1.4). 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.

RECIST 1.1 will be adapted to account for the unique tumor response characteristics seen following treatment with pembrolizumab (iRECIST, 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 10% 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.

4.2.1.2 Safety Endpoints

Safety parameters commonly used for evaluating investigational systemic anticancer treatments are included as safety endpoints including, but not limited to, the incidence of, causality, and outcome of adverse events (AEs)/serious adverse events (SAEs); and changes in vital signs and laboratory values. AEs will be assessed as defined by CTCAE, Version 5.0.

CCI

[redacted]

CCI

[redacted]

4.2.1.4 Pharmacodynamic Endpoints

There is no direct target engagement biomarker. Downstream exploratory pharmacodynamic biomarkers in tumor tissue and blood will be assessed for pathway activation.

4.2.1.5 Anti-drug Antibodies (ADA)

Antibodies against V937 and pembrolizumab (eg, neutralizing antibodies and ADA) can potentially confound drug exposures at therapeutic doses and prime for subsequent infusion-related toxicity. Neutralizing and ADA responses at the beginning of each cycle will be determined to understand drug exposure and safety. The incidence of neutralizing antibodies and ADA will be evaluated and summarized over time. Correlations between the presence/absence of positivity for neutralizing antibodies and ADA and PK and pharmacodynamic markers, activity, and safety of V937 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:

CCI

[redacted]

CCI

[redacted]

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 FBR.

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 FBR research are presented in Appendix 6.

4.2.2 Rationale for the Use of Comparator

Preclinical and clinical studies have shown that V937, when combined with checkpoint inhibitor such as pembrolizumab, may provide improved efficacy versus V937 monotherapy or pembrolizumab alone. Thus far, the combination studies have all been non-randomized single-arm studies. Pembrolizumab has been approved as a frontline treatment for patients with advanced/metastatic melanoma. To confirm that adding V937 to pembrolizumab provides clinical benefit, a pembrolizumab alone arm will be used as a comparator in this randomized study.

4.3 Justification for Dose

The clinical development of V937 has assessed safety and efficacy signals using 3 different routes of administration: ITu, intravesicular, and IV. CCI [redacted]

Previous ongoing/completed studies examined V937 monotherapy as well as pembrolizumab combinations in ITu and IV settings. The highest doses (1×10^9 $TCID_{50}$ in IV and 3×10^8 $TCID_{50}$ in ITu) were tested, alone and in combination with pembrolizumab. These doses were well tolerated, and the evidence of biological activity has been demonstrated at the proposed recommended Phase 2 dose (RP2D). In late-stage melanoma participants treated with monotherapy ITu V937 a 28% ORR was observed (CALM study). In the CAPRA study, V937 in combination with pembrolizumab (CAPRA study) a 59% ORR was observed (11^{th} International Oncolytic Virotherapy Conference held April 2018, in Oxford, UK). These responses were seen in lesions that had been injected with V937, but also in distant and noninjected lesions, both for surface melanoma lesions as well as visceral organs (lung and liver). In the STORM V937 IV study (KN200), viral RNA was detected in tumor biopsies obtained at Day 8 in subjects with advanced melanoma, bladder or NSCLC, indicating that

viral replication had occurred. Similarly, in the CALM monotherapy V937 ITu study, viral replication was observed in the tumor microenvironment from biopsies obtained at Day 8 in subjects with advanced melanoma. These samples also indicated upregulation of a number of interferon response and immune checkpoint inhibitory genes in injected melanoma lesions, including PD-L1.

The evidence of biological activity (antitumor and viral replication) as well as tolerability in the CALM, CAPRA, and STORM studies supports moving the previously determined RP2D forward into this study.

For V937 ITu administration, a total dose of 3 X 10^8 $TCID_{50}$ will be administered. In the cases of ITu administration, the dose may be divided among several lesions. Doses are administered on Days 1, 3, 5, 8, of Cycle 1, and then every 3 weeks (Cycles 2-8) for a total of 11 doses.

For V937 IV administration, the total dose is 1 X 10^9 $TCID_{50}$, administered on Days 1, 3, 5, 8 of Cycle 1, and then every 3 weeks (Cycles 2-8) for a total of 11 doses.

The dose for pembrolizumab is 200 mg every 3 weeks.

The dose of V937 and the dosing schedule in this study for the IV and ITu arms are based on the STORM and CAPRA studies, respectively. The IV dose being used in this study was found to be free of DLTs in the dose-escalation portion of the STORM study, when administered as monotherapy or in combination with pembrolizumab. The dosing schedule is the same. The ITu dose selected for this study is the same that has been used in several earlier studies in patients with advanced melanoma (CALM, MITCI, and CAPRA). The dosing schedule is the same, with the exception that the number of doses is limited to 11 doses, to be equivalent to that being used in the IV study arm.

The pembrolizumab dose and schedule used in this study is identical to that used in the CAPRA study, which is based on the current standard of care.

Please refer to the V937 IB for additional information regarding dose selection.

4.4 Beginning and End of Study Definition

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

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

If the study includes countries in the European Economic Area (EEA), the local start of the study in the EEA is defined as First Site Ready (FSR) in any Member State.

4.4.1 Clinical Criteria for Early Study Termination

The clinical study may be terminated early if the extent (incidence and/or severity) of emerging effects/clinical endpoints is such that the risk/benefit ratio to the study population as a whole is unacceptable. In addition, further recruitment in the study or at (a) particular study site(s) may be stopped due to insufficient compliance with the protocol, GCP, and/or other applicable regulatory requirements, procedure-related problems or the number of discontinuations for administrative reasons is too high.

5 STUDY POPULATION

Male/female participants ≥18 years of age with advanced/metastatic melanoma will be enrolled in this study.

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

5.1 Inclusion Criteria

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

1. Has histologically or cytologically confirmed diagnosis of advanced/metastatic melanoma

2. Has Stage III (unresectable) or Stage IV melanoma

3. Participants must be naive to anti-PD-(L)1 treatment, TVEC and other oncolytic viruses.

4. Has 2 lesions as defined below:

    1. Lesion 1: Has at least 1 cutaneous or subcutaneous lesion amenable to ITu injection and biopsy. The injectable lesion must be measurable and meet 1 of the following criteria (per RECIST 1.1 for solid tumors):

        - A cutaneous or subcutaneous lesion ≥ 1 cm in longest diameter for solid tumors, or ≥ 1.5 cm in short axis for a nodal lesion in participants with solid tumor. The longest diameter for an injectable lesion must be ≤ 10 cm for both solid tumors and nodal lesions in participants with solid tumor.

        - Multiple coalescing, superficial lesions that in aggregate have a longest diameter of ≥ 1 cm and ≤ 10 cm.

    2. Lesion 2: Have at least 1 measurable, distant and/or discrete noninjected lesion that is amenable to biopsy via visual inspection or amenable to biopsy via image guidance, such as ultrasound or computed tomography (CT)/magnetic resonance imaging (MRI). The lesion must be measurable and meet 1 of the above mentioned criteria per RECIST 1.1.

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

6. Demonstrates adequate organ function as defined in Table 6. These laboratory samples must be collected within 72 hours prior to the start of study treatment.

Table 6 Adequate Organ Function Laboratory Values

System	Laboratory Value
Hematological	
Absolute neutrophil count	>1,500/mcL (>1,000/mcL for lymphoma participants)
Platelets	>100,000/mcL (>75,000/mcL for lymphoma participants)
Hemoglobin	>9 g/dL or >5.6 mmol/L[a] (>8 g/dL or >5.0 mmol/L for lymphoma participants)
Renal	
Serum Creatinine or Creatinine Clearance (CrCl) (measured or calculated)[b] or Glomerular Filtration Rate (GFR) in place of CrCl	≤1.5 X ULN or >30 mL/min for participants with creatinine levels >1.5 X ULN
Hepatic	
Total bilirubin (serum)	≤1.5 X ULN or Direct bilirubin <ULN for participants with total bilirubin levels >1.5 X ULN
AST (SGOT) and ALT (SGPT)	<2.5 X ULN or ≤5 × ULN for participants with liver metastases
Lactate dehydrogenase (LDH)	≤2.5 X ULN
Coagulation	
International Normalized Ratio (INR) or Prothrombin Time (PT) Activated Partial Thromboplastin Time (aPTT)	<1.5 X ULN (unless participant is receiving anticoagulant therapy, in which case PT/INR or aPTT should be within the therapeutic range of intended use of anticoagulants)

System	Laboratory Value
aPTT=activated partial thromboplastin time; ALT (SGPT)=alanine aminotransferase (serum glutamic pyruvic transaminase); AST (SGOT)=aspartate aminotransferase (serum glutamic oxaloacetic transaminase); CrCl=creatinine clearance; GFR=glomerular filtration rate; INR=International Normalized Ratio; LDH=lactate dehydrogenase; PT=prothrombin time; ULN=upper limit of normal. [a] Criteria must be met without packed red blood cell (pRBC) and platelet transfusion within the prior 2 weeks. Participants can be on stable dose of erythropoietin (≥ approximately 3 months). [b] Creatinine clearance (CrCl) should be calculated per institutional standard. If no local guideline is available, CrCl should be calculated using the Cockcroft-Gault Method: CrCl=[(140-age)*weight(kg)*(0.85 for females only)]/(72*serum creatinine). 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.	

Demographics

7. Is male or female, from ≥18 years of age, at the time of providing documented informed consent.

Male Participants

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

8. Male participants are eligible to participate if they agree to the following during the intervention period and for at least 120 days:

    - Refrain from donating sperm

        PLUS either:

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

        OR

    - Must agree to use contraception unless confirmed to be azoospermic (vasectomized or secondary to medical cause [Appendix 5]) as detailed below:

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

Female Participants

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

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

    - Is not a woman of childbearing potential (WOCBP)

        OR

    - Is a WOCBP and using a contraceptive method that is highly effective (with a failure rate of <1% per year), or be abstinent from heterosexual intercourse as their preferred and usual lifestyle (abstinent on a long term and persistent basis), as described in Appendix 5 during the intervention period and for at least 120 days after the last dose of study intervention. The investigator should evaluate the potential for contraceptive method failure (ie, noncompliance, recently initiated) in relationship to the first dose of study intervention.

    - A WOCBP must have a negative highly sensitive pregnancy test (urine or serum as required by local regulations) within 72 hours before the first dose of study intervention.

    - If a urine test cannot be confirmed as negative (eg, an ambiguous result), a serum pregnancy test is required. In such cases, the participant must be excluded from participation if the serum pregnancy result is positive.

    - Additional requirements for pregnancy testing during and after study intervention are in Appendix 2.

    - The investigator is responsible for review of medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a woman with an early undetected pregnancy.

Informed Consent

10. The participant (or legally acceptable representative if applicable) provides documented informed consent for the study. The participant must consent to screening and on-treatment biopsies. The participant may also provide consent for future biomedical research (FBR). However, the participant may participate in the main study without participating in FBR.

Additional Categories

11. Has 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.

12. Is able to provide newly obtained core or excisional biopsy of a tumor lesion not previously irradiated. 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).

13. HIV-infected participants must have well controlled HIV on antiretroviral therapy (ART), defined as:

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

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

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

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

5.2 Exclusion Criteria

The participant must be excluded from the study if the participant:

Medical Conditions

1. Has had chemotherapy, definitive radiation, or biological cancer therapy or an investigational agent or investigational device within 4 weeks (2 weeks for palliative radiation) prior to the first dose of study intervention or has not recovered to Common Terminology Criteria for Adverse Events (CTCAE) Grade 1 or better (except alopecia) from any AEs that were due to cancer therapeutics administered more than 4 weeks earlier (this includes participants with previous immunomodulatory therapy with residual immune-related AEs). If the participant had major surgery or radiation therapy of >30 Gy, they must have recovered adequately from the procedure and/or any complications from the surgery prior to starting study intervention. Participants receiving ongoing replacement hormone therapy for endocrine immune-related AEs will not be excluded from participation in this study.

2. Has ocular melanoma.

3. Has radiographic evidence of major blood vessel invasion/infiltration. The degree of tumor invasion/infiltration of major blood vessels should be considered because of the potential risk of severe hemorrhage associated with tumor shrinkage/necrosis.

4. Has clinically significant hemoptysis or tumor bleeding within 2 weeks prior to the first dose of study drug.

5. 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.

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

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

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

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

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

10. Clinically significant (ie, active) cardiovascular disease: cerebral vascular accident/stroke (<6 months prior to enrollment), myocardial infarction (<6 months prior to enrollment), unstable angina, congestive heart failure (New York Heart Association Classification Class ≥ II), or serious cardiac arrhythmia requiring medication.

11. A woman of childbearing potential (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 intervention, another pregnancy test (urine or serum) must be performed and must be negative in order for participant to start receiving study medication.

Prior/Concomitant Therapy

12. Has received prior therapy with an anti-PD-1, anti-PD-L1, or anti-PD-L2 agent or with an agent directed to another stimulatory or coinhibitory T-cell receptor (eg, CTLA-4, OX-40, CD137).

13. Has received a live vaccine within 30 days prior to the first dose of study drug. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, varicella/zoster (chicken pox), yellow fever, rabies, Bacillus Calmette–Guérin (BCG),

and typhoid vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed; however, intranasal influenza vaccines (eg, FluMist®) are live attenuated vaccines and are not allowed.

Prior/Concurrent Clinical Study Experience

14. Is currently participating in or has participated in a study of an investigational agent or has used an investigational device within 4 weeks 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

15. Has a diagnosis of immunodeficiency or is receiving chronic systemic steroid therapy in excess of replacement doses (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. Use of nonsystemic steroids is permitted.

16. 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.

17. 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.

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

19. Has severe hypersensitivity (≥Grade 3) to V937 or any of its excipients.

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

21. Has an active infection requiring systemic therapy.

22. 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.

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

Other Exclusions

24. 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.

25. 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 Caffeine, Alcohol, and Tobacco Restrictions

None.

5.3.3 Activity Restrictions

None.

5.3.4 Contraception

Pembrolizumab may have adverse effects on a fetus in utero. Refer to Appendix 5 for approved methods of contraception.

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

5.3.5 Pregnancy

If a participant inadvertently becomes pregnant while on treatment with pembrolizumab, 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.

5.3.6 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 randomized in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any AEs or SAEs meeting reporting requirements as outlined in the data entry guidelines. Re-screening is allowed in the study (see Section 8.1.9).

5.5 Participant Replacement Strategy

A participant who discontinues from study intervention OR withdraws from the study will not be replaced.

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 of V937 and pembrolizumab provided by the Sponsor) will be packaged to support enrollment. Clinical supplies will be affixed with a clinical label in accordance with regulatory requirements.

6.1 Study Intervention(s) Administered

The study intervention(s) to be used in this study are outlined in Table 7.

Country-specific differences are noted in Appendix 7.

Table 7 Study Interventions

Arm Name	Arm Type	Interven-tion Name	Type	Dose Formu-lation	Unit Dose Strength(s)	Dosage Level(s)	Route of Admin-istration	Regimen/ Treatment Period/ Vaccination Regimen	Use	IMP or NIMP/ AxMP	Sourcing
Arm 1	Experi-mental	Pembro-lizumab	Biological/ Vaccine	Solution for Infusion	25 mg/mL	200 mg	IV Infusion	Day 8 of Cycle 1 (28-day cycle) Day 1 of each subsequent 21-day cycle	Test Product	IMP	Provided centrally by Sponsor
Arm 1	Experi-mental	V937	Biological/ Vaccine	Solution for Infusion	7.5 X 10^7 TCID50/ mL	1 X 10^9 TCID50	IV Infusion	Days 1, 3, 5, and 8 of Cycle 1 (28-day cycle) Day 1 of Cycles 2-8 (21-day cycles)	Test Product	IMP	Provided centrally by Sponsor
Arm 2	Experi-mental	Pembro-lizumab	Biological/ Vaccine	Solution for Infusion	25 mg/mL	200 mg	IV Infusion	Day 8 of Cycle 1 (28-day cycle) Day 1 of each subsequent 21-day cycle	Test Product	IMP	Provided centrally by Sponsor

Arm Name	Arm Type	Interven-tion Name	Type	Dose Formu-lation	Unit Dose Strength(s)	Dosage Level(s)	Route of Admin-istration	Regimen/ Treatment Period/ Vaccination Regimen	Use	IMP or NIMP/ AxMP	Sourcing
Arm 2	Experi-mental	V937	Biological/ Vaccine	Solution for Injection	7.5 X 10^7 TCID50/ mL	3 X 10^8 TCID50	Intra-tumoral	Days 1, 3, 5, and 8 of Cycle 1 (28-day cycle) Day 1 of Cycles 2-8 (21-day cycles)	Test Product	IMP	Provided centrally by Sponsor
Arm 3	Experi-mental	Pembro-lizumab	Biological/ Vaccine	Solution for Infusion	25 mg/mL	200 mg	IV Infusion	Day 8 of Cycle 1 (28-day cycle) Day 1 of each subsequent 21-day cycle	SoC	IMP	Provided centrally by Sponsor

Note: V937 will be administered 0.5 to 4 h after pembrolizumab infusion (as appropriate).

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

EEA=European Economic Area; IMP=Investigational Medicinal Product; IV=intravenous; NIMP/AxMP=Noninvestigational/Auxiliary Medicinal Product; SoC=standard of care; $TCID_{50}$=50% tissue culture infectious dose.

All study interventions will be administered on an outpatient basis.

All products indicated in Table 7 will be provided centrally by the Sponsor.

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 8.1.10 for details regarding administration of the study intervention.

6.1.1 Administration of Pembrolizumab

A 200-mg dose of pembrolizumab will be infused over 30 minutes. In Arms 1 and 2, pembrolizumab administration will be 0.5 to 4 hours prior to V937 administration. For administration details, see Pharmacy Manual.

6.1.2 Administration of V937 (Arms 1 and 2)

6.1.2.1 Administration of V937 in Arm 1

In Arm 1, V937 will be infused IV over 30 minutes. For Cycles 2-8, V937 administration will occur 0.5 to 4 hours after a 200-mg dose of pembrolizumab infused over 30 minutes. For administration details, see the Pharmacy Manual.

6.1.2.2 Administration of V937 in Arm 2

In Arm 2 of the study, V937 will be administered by ITu injection into cutaneous, subcutaneous, and/or nodal lesions that are visible, palpable, or detectable by ultrasound guidance. V937 will be administered with a total maximal volume of injectate of 4 mL per treatment visit for all injected lesions combined. **A maximum of 5 lesions can be injected per visit.**

V937 administration will occur 0.5 to 4 hours after a 200-mg dose of pembrolizumab infused over 30 minutes.

Each participant will receive V937 in a volume of 0.5 to 4 mL of injectate. The amount of V937 administered will depend on the number of lesions injected and the size of those lesions. See Table 8 for dose-level range. The volume of injectate delivered to each lesion will be based on the longest dimension of the target lesion as shown in Table 8 (short axis diameter in the case of lymph nodes), and on the number of lesions injected. Documentation of dose volume administered per lesion will be obtained.

Prioritization of lesions to be injected should include consideration of the following order:

First: New or progressing lesion(s)

Second: The largest lesion(s)

If multiple lesions exist, a new or progressing lesion should be considered for injection first, followed by injection of the largest lesion, then injection of any additional lesions, up to a total volume of injectate of 4 mL and a maximum number of 5 lesions.

The total volume administered to all lesions can range from 0.5 to 4 mL per participant, per visit. Distant lesion(s) assessed for the "abscopal" response should not be injected, unless approved by the Sponsor.

Table 8 Determination of Minimum Target Lesion Diameter at Treatment Initiation by Dose Level

Target Lesion Size (longest dimension)	**Injection Volume [a]**
>2.5 cm	2 mL
1.5 to 2.5 cm	1 mL
0.5 to <1.5 cm	0.5 mL

[a] Volumes are estimates; total volume injected per visit for all tumor lesions combined = 4 mL.

Details on dose calculation, preparation, and administration of V937 are provided in the Procedures Manual.

Injected tumor area should consist of vital tumor tissue (avoid injection into areas with significant necrosis, if feasible). The injected, single, sufficiently-sized target lesion at treatment initiation should be the same lesion that underwent pretreatment biopsy.

If at any time after treatment initiation a dose cannot be fully injected into the single target lesion identified at the start of treatment (eg, due to tissue induration or tumor shrinkage), the dose may be split and the remaining amount of V937 may be injected into another accessible target lesion(s). Documentation of dose volume administered per target lesion should be obtained. If no other target lesion is accessible for injection or lesions are no longer visible, the remaining amount may alternatively be injected subcutaneously into the tissue immediately surrounding the target lesion, if assessed feasible by the treating physician. Site and volume for each injection must be documented in the electronic case report form (eCRF).

6.2 Preparation/Handling/Storage/Accountability

6.2.1 Dose Preparation

Details on preparation and administration of V937 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

Participants will be randomized centrally using an interactive voice response system/integrated web response system (IVRS/IWRS). Participants will be randomly assigned in a 1:1:1 ratio to the following intervention arms: Arm 1 (IV pembro + IV V937); Arm 2 (IV pembro + ITu V937); Arm 3 (IV pembro alone).

6.3.2 Stratification

Intervention allocation/randomization will be stratified according to the following factor:

(M1c+M1d) versus others, according to AJCC Cancer Staging Manual, Eighth Edition

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

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

Interruptions from the protocol-specified treatment plan for >12 weeks between V937 doses 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

All treatments that the investigator considers necessary for a participant’s welfare may be administered at the discretion of the investigator in keeping with the community standards of medical care except for those that are prohibited as described in Section 6.5.2. All concomitant medication will be recorded on the eCRF including all prescription, over-the-counter (OTC), herbal supplements, and IV medications and fluids. If changes occur during the study period, documentation of drug dosage, frequency, route, and date may also be included on the eCRF.

All concomitant medications received within 28 days prior to the first dose of study intervention and 30 days after the last dose of study intervention should be recorded. If participants experience an SAE or ECI, all concomitant medications administered after 30 days after the last dose of study intervention are to be recorded for SAEs and events of clinical interest (ECIs) as defined in Section 8.4.7.

6.5.2 Prohibited Concomitant Medications

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

- Antineoplastic systemic chemotherapy or biological therapy

- Immunotherapy not specified in this protocol
- Chemotherapy not specified in this protocol
- Investigational agents other than pembrolizumab
- Radiation therapy
  Note: Radiation therapy to a symptomatic solitary lesion or to the brain may be allowed at the investigator's discretion.
- 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. (Refer local regulation in Appendix 7)
- Systemic glucocorticoids for any purpose other than to modulate symptoms from an AE that is suspected to have an immunologic etiology. The use of physiologic doses of corticosteroids may be approved after consultation with 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 treatment. Participants may receive other medications that the investigator deems to be medically necessary.

6.5.3 Rescue Medications and Supportive Care

6.5.3.1 V937 Supportive Care

Participants should receive appropriate supportive care measures as deemed necessary by the treating investigator.

6.5.3.2 Pembrolizumab Supportive Care

Participants should receive appropriate supportive care measures as deemed necessary by the treating investigator. Suggested supportive care measures for the management of AEs with potential immunologic etiology are outlined along with the dose modification guidelines in Section 6.6, Table 9. 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 9 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)

Adverse events (both nonserious and serious) associated with V937 and pembrolizumab exposure may represent an immunologic etiology. These AEs may occur shortly after the first dose or several months after the last dose of treatment.

The CTCAE Version 5.0 must be used to grade the severity of AEs. The investigator may attribute each toxicity event to V937 alone, to pembrolizumab alone, or to the combination, and modify the dose according to Table 9. Although the investigator may attribute an AE to V937 alone, pembrolizumab must be held for AEs as indicated in Table 9, regardless of attribution.

Reduction or holding of 1 agent and not the other agent is appropriate if, in the opinion of the investigator, the toxicity is clearly related to 1 of the study interventions. For example, in combination, if V937 is held due to an AE attributed to that drug, then pembrolizumab may continue to be administered, and vice versa. Appropriate documentation is required regarding to which drug the investigator is attributing the AE. If, in the opinion of the investigator, the toxicity is related to the combination of 2 agents, then both drugs should be held according to recommended dose modifications.

Pembrolizumab or V937 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.

6.6.1 Dose Modification for V937

The most common drug-related adverse reactions seen with V937 treatment continue to be fatigue, chills, pyrexia and influenza-like illness. These events are mainly Grade 1 or 2 in severity, transient, and easily managed.

In addition, a group of treatment-related AEs is specific to studies where V937 is delivered by ITu administration. This includes injection site pain, injection site erythema, injection site reaction, injection site pruritis, injection site discharge and injection site edema. These AEs are associated with the intralesional procedure, and have not been reported when V937 has been given by the IV or intravesicular route. These symptoms are limited to being mild (Grade 1) in severity.

As common practice, anti-inflammatory or anti-allergic agents, such as acetaminophen or ibuprofen, should be initiated if Grade 2 fever, chill, or site injection reaction occurs. Permanently discontinue V937 if these Grade 2 AEs reoccur in the same participants or are >Grade 2. For infusion reaction related to IV administered V937, please refer to Table 10 for guidance. For other instances in which dose interruption(s) may be required, discuss with Sponsor.

Pembrolizumab treatment will be modified for the AEs described in Section 6.6.2.

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

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

AEs associated with pembrolizumab 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 treatment and may affect more than one body system simultaneously. Therefore, early recognition and initiation of treatment is critical to reduce complications. Based on existing clinical study data, most irAEs were reversible and could be managed with interruptions of pembrolizumab, administration of corticosteroids and/or other supportive care. For suspected irAEs, ensure adequate evaluation to confirm etiology or exclude other causes. Additional procedures or tests such as bronchoscopy, endoscopy, skin biopsy may be included as part of the evaluation.

Dose Modification and Toxicity Management Guidelines for irAEs associated with pembrolizumab monotherapy, coformulations, or IO combinations are provided in Table 9.

Table 9 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 (CTCAE v5.0)	Action With Pembrolizumab Monotherapy, Coformulations or IO Combinations	Corticosteroid and/or Other Therapies	Monitoring and Follow-up
Pneumonitis	Grade 2	Withhold	• Administer corticosteroids (initial dose of 1 to 2 mg/kg prednisone or equivalent) followed by taper • Add prophylactic antibiotics for opportunistic infections	• Monitor participants for signs and symptoms of pneumonitis • Evaluate participants with suspected pneumonitis with radiographic imaging and initiate corticosteroid treatment
	Recurrent Grade 2, Grade 3 or 4	Permanently discontinue		

irAEs	Toxicity Grade (CTCAE v5.0)	Action With Pembrolizumab Monotherapy, Coformulations or IO Combinations	Corticosteroid and/or Other Therapies	Monitoring and Follow-up
Diarrhea/Colitis	Grade 2 or 3	Withhold	• Administer corticosteroids (initial dose of 1 to 2 mg/kg prednisone or equivalent) followed by taper	• Monitor participants for signs and symptoms of enterocolitis (ie, diarrhea, abdominal pain, blood or mucus in stool with or without fever) and of bowel perforation (ie, peritoneal signs and ileus) • Participants with ≥Grade 2 diarrhea suspecting colitis should consider GI consultation and performing endoscopy to rule out colitis • Participants with diarrhea/colitis should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion
	Recurrent Grade 3 or Grade 4	Permanently discontinue		
AST or ALT Elevation or Increased Bilirubin	Grade 2 [a]	Withhold	• Administer corticosteroids (initial dose of 0.5 to 1 mg/kg prednisone or equivalent) followed by taper	• Monitor with liver function tests (consider weekly or more frequently until liver enzyme value returned to baseline or is stable)
	Grade 3 [b] or 4 [c]	Permanently discontinue	• Administer corticosteroids (initial dose of 1 to 2 mg/kg prednisone or equivalent) followed by taper	
T1DM or Hyperglycemia	New onset T1DM or Grade 3 or 4 hyperglycemia associated with evidence of β-cell failure	Withhold [d]	• Initiate insulin replacement therapy for participants with T1DM • Administer antihyperglycemic in participants with hyperglycemia	• Monitor participants for hyperglycemia or other signs and symptoms of diabetes

irAEs	Toxicity Grade (CTCAE v5.0)	Action With Pembrolizumab Monotherapy, Coformulations or IO Combinations	Corticosteroid and/or Other Therapies	Monitoring and Follow-up
Hypophysitis	Grade 2	Withhold	• Administer corticosteroids and initiate hormonal replacements as clinically indicated	• Monitor for signs and symptoms of hypophysitis (including hypopituitarism and adrenal insufficiency)
	Grade 3 or 4	Withhold or permanently discontinue [d]		
Hyperthyroidism	Grade 2	Continue	• Treat with nonselective beta-blockers (eg, propranolol) or thionamides as appropriate	• Monitor for signs and symptoms of thyroid disorders
	Grade 3 or 4	Withhold or permanently discontinue [d]		
Hypothyroidism	Grade 2, 3 or 4	Continue	• Initiate thyroid replacement hormones (eg, levothyroxine or liothyronine) per standard of care	• Monitor for signs and symptoms of thyroid disorders
Nephritis: grading according to increased creatinine or acute kidney injury	Grade 2	Withhold	• Administer corticosteroids (prednisone 1 to 2 mg/kg or equivalent) followed by taper	• Monitor changes of renal function
	Grade 3 or 4	Permanently discontinue		
Neurological Toxicities	Grade 2	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 3 or 4	Permanently discontinue		

irAEs	Toxicity Grade (CTCAE v5.0)	Action With Pembrolizumab Monotherapy, Coformulations or IO Combinations	Corticosteroid and/or Other Therapies	Monitoring and Follow-up
Myocarditis	Grade 1	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 2, 3 or 4	Permanently discontinue		
Exfoliative Dermatologic Conditions	Suspected SJS, TEN, or DRESS	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology or exclude other causes
	Confirmed SJS, TEN, or DRESS	Permanently discontinue		
All Other irAEs	Persistent Grade 2	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology or exclude other causes
	Grade 3	Withhold or discontinue based on the event [e]		
	Recurrent Grade 3 or Grade 4	Permanently discontinue		

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

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

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

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

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

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

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

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

Dose Modification and Toxicity Management of Infusion Reactions Related to Pembrolizumab

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 10. Life-threatening infusion reactions have not been observed with V937.

Table 10 Pembrolizumab and V937 Infusion Reaction Dose Modification and Treatment Guidelines

NCI CTCAE Grade	Treatment	Premedication at Subsequent Dosing
Grade 1 Mild reaction; infusion interruption not indicated; intervention not indicated	Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator	None
Grade 2 Requires therapy or infusion interruption but responds promptly to symptomatic treatment (eg, antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for ≤24 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 intervention.	Participant may be premedicated 1.5 h (±30 minutes) prior to infusion of study intervention with: Diphenhydramine 50 mg PO (or equivalent dose of antihistamine). Acetaminophen 500-1000 mg PO (or equivalent dose of analgesic).

NCI CTCAE Grade	Treatment	Premedication at Subsequent Dosing
Grades 3 or 4 Grade 3: Prolonged (ie, not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (eg, renal impairment, pulmonary infiltrates) Grade 4: Life-threatening; pressor or ventilatory support indicated	Stop Infusion. Additional appropriate medical therapy may include but is not limited to: Epinephrine** IV fluids Antihistamines NSAIDs Acetaminophen Narcotics Oxygen Pressors Corticosteroids Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator. Hospitalization may be indicated. **In cases of anaphylaxis, epinephrine should be used immediately. Participant is permanently discontinued from further study drug intervention.	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 v5.0 (CTCAE) at http://ctep.cancer.gov		

6.7 Intervention After the End of the Study

Due to discontinuation of V937-011, participants who have completed or discontinued V937 treatment and are only receiving pembrolizumab may be enrolled in a pembrolizumab extension study, if available, to continue pembrolizumab monotherapy for up to 35 cycles from first pembrolizumab dose on V937-011 and to be monitored per the extension study as appropriate.

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 be monitored in this study and participate in the study visits and procedures as specified in Section 1.3 and Section 8.10.3 unless the participant has withdrawn from the study.

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 8.1.11.

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.
- The participant has a medical condition or personal circumstance that, in the opinion of the investigator and/or Sponsor, placed the participant at unnecessary risk from continued administration of study intervention.
- The participant has a confirmed positive serum pregnancy test.
- Unacceptable adverse experiences as described in Section 8.3.
- Use of prohibited concomitant medications as described in Section 6.5.2.
- Intercurrent illness other than another malignancy as noted above that prevents further administration of treatment.
- Investigator's decision to discontinue treatment.
- Side effects and/or concomitant medications required for treatment of HIV and/or its complications that are incompatible with continued study treatment (exceptions are permissible but should be discussed with the Sponsor).
- Confirmed radiographic disease progression outlined in Section 8.2 (exception if the Sponsor approves treatment continuation following confirmed PD per iRECIST)

- Any progression or recurrence of any malignancy, or any occurrence of another malignancy that requires active treatment

- Any study intervention-related toxicity specified as a reason for permanent discontinuation as defined in the guidelines for dose modification due to AEs in Section 6.6.

- Discontinuation of treatment may be considered for participants who have attained a confirmed complete response (CR) and have been treated for at least 8 cycles (at least 24 weeks), receiving at least 2 doses of pembrolizumab alone (Arm 3) or 2 cycles of the combination therapy (Arms 1 and 2) including 2 doses of pembrolizumab and at least 80% of the planned doses of V937 beyond the date when the initial CR was declared.

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

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

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

7.2 Participant Withdrawal From the Study

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

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

Specific details regarding procedures to be performed at the time of withdrawal from the study, as well as specific details regarding withdrawal from future biomedical research, are outlined in Section 8.1.11. The procedures to be performed should a participant repeatedly fail to return for scheduled visits and/or if the study site is unable to contact the participant are outlined in Section 7.3.

7.3 Lost to Follow-up

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

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

- The investigator or designee must make every effort to regain contact with the participant at each missed visit (eg, telephone calls and/or a certified letter to the participant’s last

known mailing address or locally equivalent methods). These contact attempts should be documented in the participant's medical record.

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

8 STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarized in the SoA.

- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.

- The investigator is responsible for ensuring that procedures are conducted by appropriately qualified (by education, training, and experience) staff. Delegation of study site personnel responsibilities will be documented in the Investigator Trial File Binder (or equivalent).

- All study-related medical 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 approximate amount of blood collected from each participant over the duration of the study is provided 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 trial protocol number, trial 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 template at the protocol level.

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

8.1.2 Inclusion/Exclusion Criteria

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

8.1.3 Participant Identification Card

All participants will be given a participant identification card identifying them as participants in a research study. The card will contain study site contact information (including direct telephone numbers) to be used in the event of an emergency. The investigator or qualified designee will provide the participant with a participant identification card immediately after the participant provides documented informed consent. At the time of intervention randomization, site personnel will add the treatment/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. The medical history will collect all active conditions and any condition diagnosed within the prior 10 years that the investigator considers to be clinically significant. Details regarding the disease for which the participant has enrolled in this study will be recorded separately and not listed as medical history.

8.1.5 Disease Details

The investigator or qualified designee will obtain prior and current details regarding disease status.

8.1.6 Prior Oncology Treatment History

The investigator or qualified designee will record all prior cancer treatments including systemic treatments, radiation, and surgeries.

8.1.7 Prior and Concomitant Medications Review

8.1.7.1 Prior Medications

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

8.1.7.2 Concomitant Medications

All treatments that the investigator considers necessary for a participant's welfare may be administered at the discretion of the investigator in keeping with the community standards of medical care, with the exceptions of those specifically excluded (see Section 6.5.2). All concomitant medication will be recorded on the eCRFs, including all prescription, OTC products, herbal supplements, and IV medications, and fluids. If changes occur during the study period, documentation of drug dosage, frequency, route, and date should also be included on the eCRF.

All concomitant medications received within 28 days 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 treatment should be recorded for SAEs and events of clinical interest (ECIs) as defined in Section 8.4.7.

The investigator or qualified designee will record medication, if any, taken by the participant during the study through the Safety Follow-up visit.

All medications related to reportable SAEs and ECIs should be recorded as defined in Section 8.4.7.

All new anticancer therapy initiated after the study start must be recorded in the eCRF. If a participant initiates another anticancer therapy other than the assigned study intervention(s), the study intervention(s) should be discontinued and the participant will move into the survival follow-up phase; if a participant initiates a new anticancer therapy within 30 days after the last dose of the study intervention, the 30-day Safety Follow-up Visit should occur before the first dose of the new therapy.

8.1.8 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 randomization. Each participant will be assigned only 1 screening number. Screening numbers must not be re-used for different participants.

Any participant who is screened multiple times will retain the original screening number assigned at the initial screening visit. Participants may be screened up to 2 times. Specific details on the screening/rescreening visit requirements are provided in Section 8.10.1.

8.1.9 Assignment of Treatment/Randomization Number

All eligible participants will be randomly allocated and will receive a treatment/randomization number. The treatment/randomization number identifies the participant for all procedures occurring after treatment 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.

8.1.10 Study Intervention Administration

Administration of study medication will be monitored by the investigator and/or study staff.

Study intervention(s) will be administered by the investigator and/or study staff according to the specifications within the pharmacy manual.

Study intervention should begin within 3 days of randomization (for Arms 1 and 2) or C1D8 ±1 day (for Arm 3).

8.1.10.1 Timing of Dose Administration

In all arms of the study, pembrolizumab will be administered on Day 8 of Cycle 1 (28-day cycle) and on Day 1 of all subsequent cycles. V937 will be administered either IV (Arm 1) or ITu (Arm 2) on Days 1, 3, 5, and 8 of Cycle 1 (28 days); on Day 8 of Cycle 1, V937 will be administered 0.5 to 4 hours after a 200-mg dose of pembrolizumab infused over 30 minutes. For Cycles 2-8, V937 will be administered IV (Arm 1) or ITu (Arm 2) on Day 1 of each 21-day cycle, 0.5 to 4 hours after a 200-mg dose of pembrolizumab infused over 30 minutes. Each participant may undergo up to 11 administrations of V937 and may continue treatment with pembrolizumab for up to a total of 35 cycles (approximately 2 years).

In Cycle 1, for the first 4 doses of V937 in Arms 1 and 2, a window of 24 hours for dosing will be allowed to accommodate weekends. In Cycle 2, study intervention may be administered up to 3 days after the scheduled Day 1. Beginning in Cycle 3, study intervention may be administered up to 3 days before or after the scheduled Day 1.

Dosing interruptions are permitted in the case of medical/surgical events or logistical reasons that are not related to study therapy (eg, elective surgery, unrelated medical events, participant vacation, and/or holidays). Participants should be placed back on study therapy within 3 weeks of the scheduled interruption, unless otherwise discussed with the Sponsor Medical Monitor or designee. The reason for interruption should be documented in the participant's study record.

8.1.11 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 as outlined in the SoA and Section 8.10.3.

When a participant withdraws from participation in the study, all applicable activities scheduled for the End-of-Treatment Visit should be performed (at the time of withdrawal). Any AEs that are present at the time of withdrawal should be followed in accordance with the safety requirements outlined in Section 8.4 and Section 8.10.3.

8.1.11.1 Withdrawal From Future Biomedical Research

Participants may withdraw their consent for future biomedical research. Participants may withdraw consent at any time by contacting the 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.

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

8.1.12 Participant Blinding/Unblinding

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

8.1.13 Calibration of Equipment

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

8.2 Efficacy/Immunogenicity Assessments

8.2.1 Tumor Imaging and Assessment of Disease

In addition to survival, efficacy will be assessed based on imaging evaluation of changes in tumor burden over time, until the participant is discontinued from the study or goes into survival follow-up. The process for image collection and transmission to the iCRO for BICR can be found in the Site Imaging Manual. Tumor imaging is strongly preferred to be acquired by CT. For the abdomen and pelvis, contrast-enhanced MRI may be used when CT with iodinated contrast is contraindicated, or when mandated by local practice. The same imaging technique should be used in a participant throughout the study to optimize the reproducibility of the assessment of existing and new tumor burden and improve the accuracy of the response assessment based on imaging. Note: for the purposes of assessing tumor imaging, the term “investigator” refers to the local investigator at the site and/or the radiological reviewer at the site or at an offsite facility. Tumor imaging schedule is based on calendar

days from the first administration of study intervention and will not be postponed due to delays in treatment cycles. Additional tumor imaging and medical photography may be performed as clinically indicated. Brain imaging is required for all participants with previously treated brain metastases at screening. Magnetic resonance imaging is preferred; however, CT imaging will be acceptable, if MRI is medically contraindicated.

Bone scans are also required for participants with a history of bone metastases and/or for those participants with new bone pain. Any supplemental imaging done to support a positive or negative bone scan, such as plain X-rays that may be acquired for correlation, should be submitted to the iCRO.

Other imaging modalities that may be collected, submitted to the iCRO, and included in response assessment include medical photography.

All scheduled imaging for all study participants will be submitted to the iCRO. In addition, imaging that is obtained at an unscheduled time point, for any reason (including suspicion of progression or other clinical reason), should also be submitted to the iCRO if it shows progression, or if it is used to support a response assessment. All imaging acquired within the protocol-specified window of time around a scheduled imaging visit can be classified as pertaining to that visit.

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

8.2.1.1 Initial Tumor Imaging

Initial tumor imaging at Screening must be performed within 28 days prior to the date of randomization, and the site study team must confirm that the participant has measurable disease as defined by RECIST 1.1 criteria to confirm eligibility. Tumor imaging performed as part of routine clinical management is acceptable for use as screening tumor imaging if they are of diagnostic quality and performed within 42 days prior to the date of randomization.

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 the first dose of pembrolizumab. Subsequent tumor imaging should be performed every 9 weeks (63 days ±7 days) or more frequently if clinically indicated. After 54 weeks (379 days ±7 days]), participants who remain on treatment will have imaging performed every 12 weeks (84 days ±7 days). 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 (unless the investigator elects to continue treatment and follow iRECIST), the start of new anticancer treatment, withdrawal of consent, or death, whichever occurs first. All supplemental imaging must be submitted to the iCRO.

Objective response should be confirmed by a repeat imaging assessment. Tumor imaging to confirm PR or CR should be performed at least 4 weeks after the first indication of a response is observed. Participants will then return to regular scheduled imaging, 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. Note: Response does not typically need to be verified in real time by the BICR.

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 by the site 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 study intervention. Exceptions are detailed in Section 8.2.1.5.

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 calculated from the date of first pembrolizumab administration (see Section 8.2.1.2) 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 BICR as the primary measure for assessment of tumor response, date of disease progression, and as a basis for all protocol guidelines related to disease status (eg, discontinuation of study 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. Images should continue to be sent in to the iCRO for potential retrospective BICR.

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.

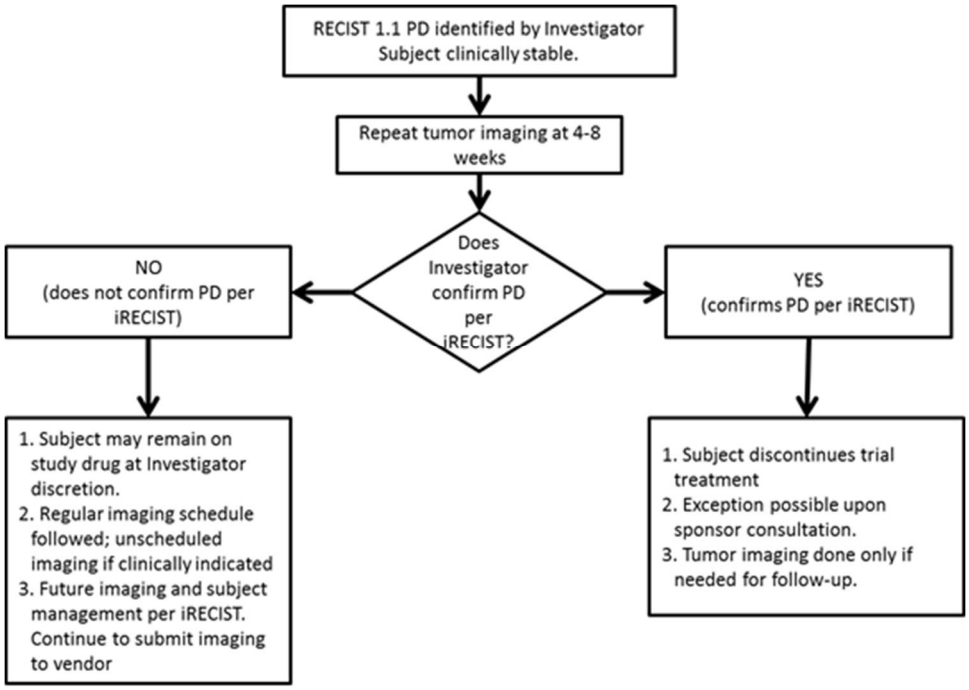
If a participant has confirmed radiographic progression (iCPD) as defined in Appendix 8, study intervention should be discontinued; however, if the participant is achieving a clinically meaningful benefit, an exception to continue study intervention may be considered following consultation with the Sponsor. 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 and submitted to the iCRO.

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 11 and illustrated as a flowchart in Figure 2.

Table 11 Imaging and Treatment After First Radiologic Evidence of Progressive Disease

	Clinically Stable		**Clinically Unstable**	
	Imaging	**Treatment**	**Imaging**	**Treatment**
First radiologic evidence of PD by RECIST 1.1 per investigator assessment	Repeat imaging at 4 to 8 weeks to confirm PD	May continue study treatment at the assessment of the investigator and after the participant's consent	Repeat imaging at 4 to 8 weeks to confirm PD per investigator's discretion only.	Discontinue 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; iRECIST=modified Response Evaluation Criteria in Solid Tumors 1.1 for immune-based therapeutics; iSD=iRECIST stable disease; iUPD=iRECIST unconfirmed progressive disease; PD=progressive disease; RECIST 1.1=Response Evaluation Criteria in Solid Tumors 1.1; VOP=verification of progression				

Figure 2 Imaging and Treatment for Clinically Stable Participants Treated With Pembrolizumab After First Radiologic Evidence of PD Assessed by the Investigator



iRECIST=modified Response Evaluation Criteria in Solid Tumors 1.1 for immune-based therapeutics; PD=progressive disease; RECIST 1.1=Response Evaluation Criteria in Solid Tumors 1.1.

8.2.2 Eastern Cooperative Oncology Group Performance Scale

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

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

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

8.3.1.2 Directed Physical Examination

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

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

8.3.2 Vital Signs

The investigator or qualified designee will take vital signs at screening, prior to the administration of each dose of study intervention and during the follow-up period as specified in the SoA. Vital signs include temperature, pulse, respiratory rate, weight, and blood pressure. Height will be measured at screening only. Weight will be measured at screening, at every other cycle, and in follow-up as specified in the SoA.

8.3.3 Electrocardiograms

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

8.3.4 Clinical Safety Laboratory Assessments

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

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

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

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

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 Study Flow Chart (Section 1.3) 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.

8.3.4.2 Pregnancy Test

All women who are being considered for participation in the study, and who are not surgically sterilized or postmenopausal, must be tested for pregnancy within 72 hours of 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 regulation.

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.

Progression of the cancer under study is not considered an AE as described in Section 8.4.6 and Appendix 3.

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

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

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

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

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

- All AEs meeting serious criteria, from the time of intervention randomization through 90 days following cessation of study intervention or 30 days following cessation of study intervention if the participant initiates new anticancer therapy, whichever is earlier, must be reported by the investigator.

- All pregnancies and exposure during breastfeeding, from the time of intervention randomization through 120 days following cessation of study intervention, or 30 days following cessation of study intervention if the participant initiates new anticancer therapy must be reported by the investigator.

- Additionally, any SAE brought to the attention of an investigator at any time outside of the time period specified above must be reported immediately to the Sponsor if the event is considered related to study intervention.

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

All initial and follow-up AEs, SAEs, and other reportable safety events will be recorded and reported to the Sponsor or designee within the time frames as indicated in Table 12.

Table 12 Reporting Time Periods and Time Frames for Adverse Events and Other Reportable Safety Events

Type of Event	**Reporting Time Period: Consent to Randomization/ Allocation**	**Reporting Time Period: Randomization/ Allocation through Protocol-specified Follow-up Period**	**Reporting Time Period: After the Protocol-specified Follow-up Period**	**Time Frame to Report Event and Follow-up Information to Sponsor:**
Nonserious Adverse Event (NSAE)	Report if: - due to protocol-specified intervention - causes exclusion - participant is receiving placebo run-in or other run-in treatment	Report all	Not required	Per data entry guidelines
Serious Adverse Event (SAE) including Cancer and Overdose	Report if: - due to protocol-specified intervention - causes exclusion - participant is receiving placebo run-in or other run-in treatment	Report all	Report if: - drug/vaccine related. (Follow ongoing to outcome)	Within 24 hours of learning of event
Pregnancy/ Lactation Exposure	Report if: - due to intervention - causes exclusion	Report all	Previously reported – Follow to completion/termination; report outcome	Within 24 hours of learning of event
Event of Clinical Interest (require regulatory reporting)	Report if: - due to intervention - causes exclusion	Report - potential drug-induced liver injury (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 AEs and/or SAEs and other reportable safety events. Open-ended and nonleading verbal questioning of the participant is the preferred method to inquire about AE occurrence.

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

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All AEs, SAEs, and other reportable safety events, including pregnancy and exposure during breastfeeding, events of clinical interest (ECIs), cancer, and overdose will be followed until resolution, stabilization, until the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3). In addition, the investigator will make every attempt to follow all nonserious AEs that occur in 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. The Sponsor will comply with country-specific regulatory requirements and global laws and regulations relating to safety reporting to regulatory authorities, IRB/IECs, and investigators.

Investigator safety reports must be prepared for 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 laboratory value that is greater than or equal to 3X the upper limit of normal and an elevated total bilirubin laboratory value that is greater than or equal to 2X the upper limit of normal and, at the same time, an alkaline phosphatase laboratory value that is less than 2X the upper limit of normal, as determined by way of protocol-specified laboratory testing or unscheduled laboratory testing.*

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

8.5 Treatment of Overdose

For purposes of this study, an overdose will be defined as any dose exceeding the prescribed dose for V937 by >50% of the indicated dose or a pembrolizumab dose of ≥1000 mg (≥5 times the indicated dose). No specific information is available on the treatment of overdose of V937 or pembrolizumab. In the event of overdose, the participant should be observed closely for signs of toxicity. Appropriate supportive treatment should be provided if clinically indicated.

8.6 Pharmacokinetics

PK supports evaluation of V937 and pembrolizumab immunogenicity and exposure of the proposed dosing regimen. Blood samples were obtained to evaluate V937 exposure which are used to derive PK of V937 RNA and serum pembrolizumab. PK parameters for pembrolizumab (eg, C_{trough}) at planned visits and times will be summarized. PK parameters for V937 RNA (eg, AUC and C_{max}) 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.

If ongoing PK, neutralizing V937 antibodies and anti-pembrolizumab antibody analysis is deemed to be unnecessary by the Sponsor, it may be reduced or discontinued.

PK collection is no longer required.

8.6.1 Blood Collection for V937 and Pembrolizumab

8.6.1.1 Blood Collection for PK

PK sample collection is no longer required.

8.6.1.2 Blood Collection for Neutralizing V937 Antibodies and Antipembrolizumab Antibodies

Neutralizing V937 antibodies and antipembrolizumab antibody sample collection is no longer required.

8.7 Pharmacodynamics

8.7.1 Blood for Pharmacodynamic Markers

Sample collection is no longer required.

8.7.2 Tumor Biopsy

Participants in Arms 1 and 2 will be required to provide mandatory tumor biopsies at C1D1 (predose) and C1D8 (predose) unless deemed medically unsafe by the investigator. A tumor biopsy on C2D1 (predose) is optional. Tumor samples will be collected at the time points described in Section 1.3 – SoA.

Predose biopsy collection on above visits can be performed within 48 hour prior to dosing.

Tumor biopsies will only be performed at tumor sites that are deemed medically safe, in accordance with local guidelines.

In Arm 2, for the tumor lesion intended for treatment with ITu injection of V937 and the distant/discrete lesion, the sample will be obtained by either punch biopsy for cutaneous lesions, or by ultrasound guided biopsy for subcutaneous lesions. These biopsies will be collected within 48 hours preceding ITu administration of V937. On-treatment biopsy site location may vary from baseline biopsy site location based on lesion accessibility and participant tolerance.

Leftover main study tissue will be stored for FBR if the participant signs the FBR consent.

Detailed instructions for tissue collection, processing, and shipment are provided in the Central Laboratory Manual.

8.8 Biomarkers

To identify novel biomarkers, the following biospecimens to support exploratory analyses of cellular components (eg, protein, RNA, DNA, metabolites) and other circulating molecules will be collected from all participants as specified in the SoA (collection no longer required):

- Blood for genetic analysis
- Blood for biomarker analyses
- Tumor biopsy
- Serum for biomarker analyses
- Blood for ctDNA analysis

8.8.1 Planned Genetic Analysis Sample Collection

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

8.9 Future Biomedical Research Sample Collection

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

- Leftover from specimens listed in Section 8.8, Biomarkers

8.10 Visit Requirements

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

8.10.1 Screening

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 72 hours 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 72 hours 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).

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.

8.10.2 Treatment Period/Vaccination Visit

The treatment period in each treatment arm begins with Cycle 1 (Arms 1 and 2: Cycle 1 Day 1 and Arm 3: Cycle 1 Day 8;) and may continue for up to 35 cycles (approximately 2 years) from the start of treatment until disease progression, unacceptable AE(s), intercurrent illness that prevents further administration of treatment, investigator's decision to withdraw the participant, participant withdraws consent, pregnancy of the participant, noncompliance with study treatment or procedure requirements, or administrative reasons requiring cessation of treatment. Each cycle includes study drug administration and all associated assessments as outlined in the SoA (Section 1.3).

Visit requirements are outlined in the SoA (Section 1.3). Specific procedure-related details are provided in Section 8.1.

8.10.3 Discontinued Participants Continuing to be Monitored in the Study

Discontinuation of treatment does not represent withdrawal from the study.

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

8.10.4 Posttreatment Visit

8.10.4.1 Safety Follow-up Visit

The mandatory Safety Follow-up Visit should be conducted approximately 30 days after the last dose of study intervention or before 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).

Due to early study discontinuation, participants may be enrolled in a pembrolizumab extension study, if available, to continue pembrolizumab monotherapy. The Safety Follow-up will not be required for such participants.

8.10.4.2 Follow-up Visits

Participants who complete the protocol-required cycles of study intervention or who discontinue study intervention for a reason other than disease progression will begin the Imaging Follow-up and should be assessed every 9 weeks to monitor disease status. Every effort should be made to collect information regarding disease status until the start of new anticancer therapy, disease progression, death, or the end of study, whichever occurs first. Information regarding poststudy anticancer treatment will be collected if new treatment is initiated. Participants who completed all imaging assessments and/or will not have further efficacy assessments must enter the Survival Follow-up Phase.

Due to early study discontinuation, participants may be enrolled in a pembrolizumab extension study, if available, to continue pembrolizumab monotherapy. The Imaging Follow-up will not be required for such participants.

8.10.4.3 Survival Follow-up Contacts

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

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

- For participants who discontinue treatment intervention and who will not enter the Efficacy Follow-up Phase, the first survival follow-up contact will be scheduled 12 weeks after the discontinuation visit and/or safety follow-up visit (whichever is last).
- For participants who completed assessments in the Efficacy Follow-up Phase, the first survival follow-up contact will be scheduled 12 weeks after the last efficacy assessment follow-up visit has been performed.

Due to early study discontinuation, participants may be enrolled in a pembrolizumab extension study, if available, to continue pembrolizumab monotherapy. The Survival Follow-up contact will not be required for such participants.

8.10.5 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 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. Separate analysis plans may be developed for PK/modeling analysis, biomarker analysis, and genetic data analysis. Post hoc exploratory analyses will be clearly identified in the CSR.

9.1 Statistical Analysis Plan Summary

Study Design Overview	A Phase 2, randomized study of IV or ITu administration of V937 in combination with pembrolizumab versus pembrolizumab alone in participants with advanced/metastatic melanoma
Treatment Assignment	Approximately 135 participants will be randomized in a 1:1:1 ratio to Arm 1 (IV pembro + IV V937), Arm 2 (IV pembro + ITu V937) and Arm 3 (IV pembro alone). The stratification factor is (M1c+M1d) versus others.
Analysis Populations	Efficacy (Primary and Secondary): Intention-to-Treat (ITT) Safety (Secondary): All-Participants-as-Treated (APaT)
Primary Endpoint(s)	Objective response (OR) is a confirmed complete response (CR) or partial response (PR) by RECIST 1.1 as assessed by BICR.
Secondary Endpoints	• Progression-free Survival (PFS) and Duration of response (DOR) by RECIST 1.1 as assessed by BICR. • OR, PFS and DOR per RECIST 1.1 as assessed by investigator. • Overall survival (OS) • Adverse events (AEs) • Discontinuing study intervention due to AE.
Statistical Methods for Key Efficacy	The primary hypothesis comparing Arm 1 to Arm 3, and Arm 2 to Arm 3 with regard to ORR will be evaluated using the stratified Miettinen and Nurminen method [Miettinen, O. and Nurminen, M. 1985]. The ORR between Arm 1 and Arm 2 will be compared without formal hypothesis testing. DOR will be summarized descriptively using Kaplan-Meier medians and quartiles if the sample size permits. The nonparametric Kaplan-Meier method will be used to estimate the PFS and OS curve in each treatment group. The hazard ratio for PFS and OS will be estimated using a stratified Cox regression model.
Statistical Methods for Key Safety Analyses	The analysis of safety results will follow a tiered approach for the comparison of Arm 1 vs Arm 3, Arm 2 vs Arm 3, and Arm 1 vs Arm 2. The tiers differ with respect to the analyses that will be performed. There is no Tier 1 safety endpoint for this study. Tier 2 parameters will be assessed via point estimates with 95% confidence intervals (CIs) provided for between-arm comparisons; only point estimates by treatment arm are provided for Tier 3 safety parameters. The 95% CIs for the between -treatment differences in percentages will be provided using the Miettinen and Nurminen method.
CCI [redacted]	

Sample Size and Power	The planned sample size for this study is approximately 135 participants or less due to early study termination.CCI [redacted]

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 Sponsor will generate a randomized allocation schedule for study treatment assignment for this protocol, and the randomization will be implemented in IRT.

Independent radiologists will perform the central imaging review without knowledge of treatment assignments.

9.3 Hypotheses/Estimation

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

9.4 Analysis Endpoints

9.4.1 Efficacy/Pharmacokinetics/Pharmacodynamic Endpoints

Primary Endpoint

- Objective Response (OR): a confirmed complete response (CR) or partial response (PR) per RECIST 1.1 based on BICR. ORR is the proportion of participants with objective response.

Secondary Endpoints

- PFS: time from randomization to the first documented PD per RECIST 1.1 based on BICR or death from any cause, whichever occurs first. See Section 9.6.1 for the definition of censoring.

- DOR**:** time from the first documented evidence of CR or PR until PD per RECIST 1.1 as assessed by BICR or death due to any cause, whichever occurs first, in participants demonstrating CR or PR.

- OS: time from randomization to the date of death due to any cause.

CCI

[redacted]

9.4.2 Safety Endpoints

Safety endpoint is the number/proportion of participants with AEs, and who discontinue study treatment due to AEs. In addition, safety and tolerability will be assessed by clinical review of all relevant parameters including adverse events (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 Efficacy Analysis Population

The analyses of efficacy endpoints (ORR, PFS, OS and DOR) are based on the intention-to-treat (ITT) population. All randomized participants will be included in this population. Participants will be analyzed in the treatment arm to which they are randomized.

CCI

[redacted]

9.5.3 Safety Analysis Population

The APaT population will be used for the analysis of safety data in this study. The APaT population consists of all randomized participants who receive at least 1 dose of study treatment. Participants will be analyzed in the treatment arm corresponding to the study treatment they actually receive. For most participants, this will be the treatment group to which they are randomized. Participants who receive incorrect study treatment for the entire treatment period will be included in the treatment arm corresponding to the study treatment actually received. Any participant who receives incorrect study medication for 1 cycle, but receives the correct treatment for all other cycles, will be analyzed according to the correct treatment group, and a narrative will be provided for any events that occur during the cycle for which the participant is incorrectly dosed.

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

9.6 Statistical Methods

9.6.1 Statistical Methods for Efficacy Analyses

This section describes the statistical methods that address the primary and secondary objectives. Methods related to exploratory objectives will be described in the sSAP. The final analyses will be performed using all data available.

9.6.1.1 Objective Response

The stratified Miettinen and Nurminen method [Miettinen, O. and Nurminen, M. 1985] will be used for the ORR comparison (Arm 1 vs Arm 3; Arm 2 vs Arm 3). The difference in ORR, 90% CI and p -values from the stratified Miettinen and Nurminen method with strata weighted by sample size will be reported. The stratification factor used for randomization (Section 6.3.2) will be applied to the analysis.

The ORR difference between Arm 1 and Arm 2 will also be evaluated via stratified Miettinen and Nurminen method [Miettinen, O. and Nurminen, M. 1985]. The difference in ORR and its 90% CI will be reported.

9.6.1.2 Progression-free Survival

The nonparametric Kaplan-Meier method will be used to estimate the PFS curve in each treatment group. The treatment difference in PFS will be assessed by the stratified log-rank test. A stratified Cox proportional hazard model with Efron's method of tie handling will be used to assess the magnitude of the treatment difference (ie, the HR) between the treatment arms. The HR and its 95% CI from the stratified Cox model with Efron's method of tie handling and with a single treatment covariate will be reported. The stratification factor used for randomization (Section 6.3.2) will be applied to both the stratified log-rank test and the stratified Cox model.

Because disease progression is assessed periodically, PD can occur any time in the interval between the last assessment when PD is not documented and the assessment when PD is documented. For the primary analysis, for participants with PD, the true date of disease progression will be approximated by the date of the first assessment at which PD is objectively documented per RECIST 1.1, based on BICR. Death is always considered as a confirmed PD event. Participants who do not experience a PFS event will be censored at the last disease assessment. Sensitivity analyses will be performed for comparison of PFS based on the investigator's assessment.

9.6.1.3 Overall Survival

The nonparametric Kaplan-Meier method will be used to estimate the survival curves. The treatment difference in survival will be assessed by the stratified log-rank test. A Cox proportional hazard model with Efron's method of tie handling will be used to assess the magnitude of the treatment difference (ie, the HR). The HR and its 95% CI from the Cox model with a single treatment covariate will be reported. The stratification factors used for randomization (Section 6.3.2) will be applied to both the stratified log-rank test and the stratified Cox model. Participants without documented death at the time of analysis will be censored at the date of last known contact.

9.6.1.4 Duration of Response

For participants with a CR or PR, whichever occurs first; censoring rules for DOR are summarized in Table 13. DOR will be assessed using RECIST 1.1 by BICR, RECIST 1.1 by investigator, and iRECIST by investigator.

For each DOR analysis, a corresponding summary of the reasons for which responding participants are censored will also be provided. Responses in participants who are alive, have not progressed, have not initiated new anticancer treatment, and have not been determined to be lost to follow-up, and who have had a disease assessment within approximately 5 months of the data cutoff date, are considered ongoing at the time of analysis. If a participant meets multiple criteria for censoring, the censoring criterion that occurs earliest will be applied.

If the sample size permits, DOR will be summarized descriptively using Kaplan-Meier medians and quartiles. Only the subset of participants with a confirmed CR or PR will be included in this analysis.

Table 13 Censoring Rules for Duration of Response

Situation	Date of Progression or Censoring	Outcome
No progression nor death, no new anticancer therapy initiated	Last adequate disease assessment	Censor (non-event)
No progression nor death, new anticancer therapy initiated	Last adequate disease assessment before new anticancer therapy was initiated	Censor (non-event)
Death or progression immediately after ≥2 consecutive missed disease assessments or after new anticancer therapy, if any	Earlier date of last adequate disease assessment prior to ≥2 missed adequate disease assessments and new anticancer therapy, if any	Censor (non-event)
Death or progression after ≤1 missed disease assessments and before new anticancer therapy, if any	Progressive disease or death	End of response (Event)
A missed disease assessment includes any assessment that is not obtained, or is considered inadequate for evaluation of response.		

9.6.1.5 Analysis Strategy for Key Efficacy Endpoints

Table 14 summarizes the analysis strategy for the primary and secondary efficacy endpoints.

Table 14 Analysis Strategy for Key Efficacy Variables

Endpoint/Variable	Statistical Method	Analysis Population	Missing Data Approach
Primary Analyses			
Objective Response (RECIST 1.1 by BICR)	Test and estimation: Stratified Miettinen and Nurminen method.	ITT	Participants with missing data are considered nonresponders
Secondary Analyses			
Objective Response (RECIST 1.1 by Investigator)	Estimation: Stratified Miettinen and Nurminen method.	ITT	Participants with missing data are considered nonresponders
PFS (RECIST 1.1 by BICR and RECIST 1.1 by investigator)	Summary statistics using Kaplan-Meier method Estimation: stratified Cox model with Efron's tie-handling method	ITT	See section 9.6.1.2
DOR (RECIST 1.1 by BICR and RECIST 1.1 by investigator)	Summary statistics using Kaplan-Meier method	All responders in ITT	Censored according to rules in Table 13

Endpoint/Variable	Statistical Method	Analysis Population	Missing Data Approach
OS	Summary statistics using Kaplan-Meier method Estimation: stratified Cox model with Efron's tie-handling method	ITT	Censored at last known alive date
BICR=blinded independent central review; DOR=duration of response; ITT=intention-to-treat; ORR=objective response rate; OS=overall survival; PFS=progression-free survival; RECIST 1.1=Response Evaluation Criteria in Solid Tumors Version 1. Note: Sensitivity analyses will be performed for PFS, ORR, and DOR based on investigator's assessment.			

9.6.2 Statistical Methods for Safety Analyses

There are no safety hypotheses for this study. Safety and tolerability will be assessed by clinical review of all relevant parameters, including AEs, laboratory tests, and vital signs.

The analysis of safety results will follow a tiered approach (Table 15). The tiered approach will be used for the comparisons of Arm 1 vs Arm 3, Arm 2 vs Arm 3, and Arm 1 vs Arm 2. The tiers differ with respect to the analyses that will be performed. Adverse Events (specific terms as well as system organ class terms) and events that meet pre-defined limits of change (PDLCs) in laboratory, vital sign, and ECG parameters are either pre-specified as Tier 1 events, or will be classified as belonging to Tier 2 or Tier 3 based on the number of events observed.

Tier 1 Events

Safety parameters or adverse events of special interest (AEOSIs) that are identified a priori constitute Tier 1 safety events that will be subject to inferential testing for statistical significance.

AEOSIs that are immune mediated or potentially immune mediated are well documented and will be evaluated separately; however, these events have been characterized consistently throughout the pembrolizumab clinical development program and determination of statistical significance is not expected to add value to the safety evaluation. The combination of pembrolizumab and V937 has not been associated with any new safety signals. Finally, based on review of historic data from ongoing V937 and pembrolizumab clinical studies, there are no known AEs associated with participants with melanoma for which determination of a p -value is expected to impact the safety assessment. Therefore, there are no Tier 1 events for this protocol.

Tier 2 Events

Tier 2 events will be assessed via point estimates with 95% confidence intervals provided for differences in the proportion of participants with events using the Miettinen and Nurminen method, an unconditional, asymptotic method [Miettinen, O. and Nurminen, M. 1985].

Membership in Tier 2 requires that at least 4 participants (~10%) in any treatment arm exhibit the event. The threshold of at least 4 events was chosen because the 95% CI for the between-group difference in percent incidence will always include zero when treatment groups of equal size each have less than 4 events and thus would add little to the interpretation of potentially meaningful differences. In addition, Grades 3 to 5 AEs and SAEs with at least 2 participants (~5%) in 1 of the treatment arms will be considered Tier 2 events. Because many 95% CIs may be provided without adjustment for multiplicity, the CIs should be regarded as a helpful descriptive measure to be used in safety review, not a formal method for assessing the statistical significance of the between treatment differences.

In addition to individual events that occur in 4 or more participants in any treatment group, the broad AE categories consisting of the proportion of participants with any AE, a drug-related AE, a Grade 3 to 5 AE, an AE that is both Grade 3 to 5 and drug-related, a serious AE, an AE that is both serious and drug-related, a dose interruption(s) due to an AE, and a discontinuation due to an AE will be considered Tier 2 endpoints.

Tier 3 Events

Safety events that are not Tier 1 or Tier 2 events will be considered Tier 3 events. Only point estimates by treatment arm will be provided for Tier 3 safety parameters.

Continuous Safety Measures

For continuous measures such as changes from baseline in laboratory, vital sign, and ECG parameters, summary statistics for baseline, on -treatment, and change from baseline values will be provided by treatment arm in table format.

Table 15 Analysis Strategy for Safety Parameters

Safety Tier	Safety Endpoint	95% CI for Treatment Comparison	Descriptive Statistics
Tier 2	Any AE	X	X
	Any serious AE	X	X
	Any Grade 3 to 5 AE	X	X
	Any drug-related AE	X	X
	Any serious and drug-related AE	X	X
	Any Grade 3 to 5 and drug-related AE	X	X
	Dose interruption(s) due to AE	X	X
	Discontinuation due to AE	X	X
	Specific AEs, SOCs (incidence ≥4 participants in one of the treatment groups)	X	X

Safety Tier	Safety Endpoint	95% CI for Treatment Comparison	Descriptive Statistics
Tier 3	Specific AEs, SOCs (incidence <4 participants in both treatment groups) or PDLCs		X
	Change from baseline results (laboratory, vital signs)		X

AE=adverse events; CI=confidence interval; SOC=system organ class; PDLC=predefined limit of change.
Note: X = results will be provided.

9.6.3 Summaries of Baseline Characteristics, Demographics, and Other Analysis

9.6.3.1 Demographic and Baseline Characteristics

The comparability of the treatment groups for each relevant demographic and baseline characteristic will be presented in tables and/or graphs. No statistical hypothesis tests will be performed on these characteristics. The number and percentage of participants randomized and the primary reason for discontinuation will be displayed. Demographic variables (such as age) and baseline characteristics will be summarized by treatment either by descriptive statistics or categorical tables.

CCI

CCI

[redacted]

9.9 Sample Size and Power Calculations

The study will randomize approximately 135 participants or less due to early study termination in a 1:1:1 ratio to Arm 1 (IV pembro + IV V937), Arm 2 (IV pembro + ITu V937), and Arm 3 (IV pembro alone).

CCI

[redacted]

CCI

[redacted]

CCI

[redacted]

9.11 Compliance (Medication Adherence)

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

9.12 Extent of Exposure

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

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

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

10.1.1 Code of Conduct for Clinical Trials

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

Code of Conduct for Interventional Clinical Trials

I. Introduction

A. Purpose

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

B. Scope

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

II. Scientific Issues

A. Trial Conduct

1. Trial Design

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

The design (i.e., participant population, duration, statistical power) must be adequate to address the specific purpose of the trial. 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 (or individuals acting on behalf of MSD) 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 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-non-compliance 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 the primary and secondary results of its registered trials of marketed products in which treatment is assigned, according to the pre-specified plans for data analysis. To the extent scientifically appropriate, MSD seeks to publish the results of other analyses it conducts that are important to patients, physicians, and payers. Some early phase or pilot trials are intended to be hypothesis-generating rather than hypothesis testing; in such cases, publication of results may not be appropriate since the trial may be underpowered and the analyses complicated by statistical issues such as multiplicity.

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

III. Participant Protection

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

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

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

B. Safety

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

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

C. Confidentiality

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

D. Genomic Research

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

IV. Financial Considerations

A. Payments to Investigators

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

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

B. Clinical Research Funding

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

C. Funding for Travel and Other Requests

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

V. Investigator Commitment

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

10.1.2 Financial Disclosure

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

The investigator/subinvestigator(s) agree, if requested by the Sponsor in accordance with 21 CFR Part 54, to provide 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 data. By signing the consent form, the participant agrees to this process. If study documents will be photocopied during the process of verifying worksheet/CRF information, the participant will be identified by unique code only; full names/initials will be masked prior to transmission to the Sponsor.

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

10.1.3.3 Confidentiality of IRB/IEC Information

The Sponsor is required to record the name and address of each IRB/IEC that reviews and approves this study. The Sponsor is also required to document that each IRB/IEC meets regulatory and ICH GCP requirements by requesting and maintaining records of the names and qualifications of the IRB/IEC members and to make these records available for regulatory agency review upon request by those agencies.

10.1.4 Committees Structure

Not applicable.

10.1.5 Publication Policy

The results of this study may be published or presented at scientific meetings. The Sponsor will comply with the requirements for publication of study results. In accordance with

standard editorial and ethical practice, the Sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.

If publication activity is not directed by the Sponsor, the investigator agrees to submit all manuscripts or abstracts to the Sponsor before submission. This allows the Sponsor to protect proprietary information and to provide comments.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

10.1.6 Compliance with Study Registration and Results Posting Requirements

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

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

10.1.7 Compliance with Law, Audit, and Debarment

By signing this protocol, the investigator agrees to conduct the study in an efficient and diligent manner and in conformance with this protocol; generally accepted standards of GCP (eg, International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use GCP: Consolidated Guideline and other generally accepted standards of GCP); and all applicable federal, state and local laws, rules and regulations relating to the conduct of the clinical study.

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

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

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

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

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

10.1.8 Data Quality Assurance

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

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

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

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

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

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

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

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

10.1.9 Source Documents

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

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

10.1.10 Study and Site Closure

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

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

10.2 Appendix 2: Clinical Laboratory Tests

- The tests detailed in the table below will be performed by the local laboratory.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5 of the protocol.
- Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.
- Pregnancy testing:
  - Pregnancy testing requirements for study inclusion are described in Section 5.1.
  - Pregnancy testing (urine or serum as required by local regulations) should be conducted at the end of relevant systemic exposure.
  - Additional serum or urine pregnancy tests may be performed, as determined necessary by the investigator or required by local regulation, to establish the absence of pregnancy at any time during the subject's participation in the study.

Protocol-required Safety Laboratory Assessments

Hematology	Comprehensive Chemistry Panel	Urinalysis	Other
Hematocrit	Albumin	Blood	Pregnancy test (serum or urine)[a]
Hemoglobin	Alkaline phosphatase	Glucose	Total T3 (or Free T3 [FT3]), Total T4 (or Free T4 [FT4]), and TSH[b,c]
Platelet count	Alanine aminotransferase	Protein	Anti-HCV [e]
WBC (total and differential)[d]	Aspartate aminotransferase	Specific gravity	HCV viral load[c, e]
RBC	Carbon dioxide or bicarbonate	Microscopic examination, if abnormal results are noted	HIV Viral Load, HIV 1,2 Antibody [e, f]
Absolute lymphocyte count[d]	Calcium		anti-HBs[c, e]
	Chloride		HbsAg
Absolute neutrophil count[d]	Creatinine		anti-HBc (total and IgM)[c, e]
PT/INR	Glucose		HbeAg[c, e]
PTT or aPTT	Phosphorus		anti-Hbe[c, e]
Basophil	Potassium		HBV viral load[c, e]
Eosinophil	Sodium		CD4+ T-cell count [f]

Hematology	Comprehensive Chemistry Panel	Urinalysis	Other
Monocyte	Total bilirubin		
	Direct bilirubin		
	Total protein		
	Blood urea nitrogen		
	Urea		
	Lactate dehydrogenase		

aPTT=activated partial thromboplastin time; HBc=hepatitis B core; HBeAg=hepatitis B e-antigen; HBsAg=hepatitis B surface antigen; HBV=hepatitis B virus; HCV=hepatitis C virus; HIV=human immunodeficiency virus; INR=International Normalized Ratio; PT=prothrombin time; PTT=partial thromboplastin time; RBC=red blood count; T3=triiodothyronine; T4=thyroxine; TSH=thyroid-stimulating hormone; WBC=white blood count.

[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] If the local laboratory is unable to perform these tests, the site should submit the sample to the central laboratory for testing. Details are provided in the Laboratory Manual.

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

[e] Only collect if consistent with local requirements.

[f] For HIV-positive participants only

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 Definitions of Medication Error, Misuse, and Abuse

Medication error

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

Misuse

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

Abuse

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

10.3.2 Definition of AE

AE definition

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

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

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

Events meeting the AE definition

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

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

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

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

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

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

- Any new cancer (that is not a condition of the study). Progression of the cancer under study is not considered a reportable event unless it results in hospitalization or death.

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 8.4.6 for protocol-specific exceptions.

10.3.3 Definition of SAE

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

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

a. **Results in death**

b. **Is life-threatening**

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

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

- Hospitalization is defined as an inpatient admission, regardless of length of stay, even if the hospitalization is a precautionary measure for continued observation. (Note: Hospitalization for an elective procedure to treat a 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.

10.3.4 Additional Events Reported in the Same Manner as SAE

Additional events that require reporting in the same manner as SAE

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

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

- Is associated with an overdose

10.3.5 Recording AE and SAE

AE and SAE recording

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

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

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

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

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

Assessment of intensity/toxicity

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

- The investigator will make an assessment of intensity for each AE and SAE (and other reportable safety event) according to the NCI CTCAE, version 5.0. Any AE that changes CTCAE grade over the course of a given episode will have each change of grade recorded on the AE CRFs/worksheets.

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

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

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

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

    - Grade 5: Death related to AE.

Assessment of causality

- Did the Sponsor's product cause the AE?

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

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

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

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

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

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

    - If yes, did the AE resolve or improve?

    - If yes, this is a positive dechallenge.

    - If no, this is a negative dechallenge.

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

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

    - If yes, did the AE recur or worsen?

- If yes, this is a positive rechallenge.
- If no, this is a negative rechallenge.

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

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

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

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

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

  - Yes, there is a reasonable possibility of Sponsor's product relationship:
    - There is evidence of exposure to the Sponsor's product. The temporal sequence of the AE onset relative to the administration of the Sponsor's product is reasonable. The AE is more likely explained by the Sponsor's product than by another cause.
  - No, there is not a reasonable possibility of Sponsor's product relationship:
    - Participant did not receive the Sponsor's product OR temporal sequence of the AE onset relative to administration of the Sponsor's product is not reasonable OR the AE is more likely explained by another cause than the Sponsor's product. (Also entered for a participant with overdose without an associated AE.)

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

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

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

- The causality assessment is 1 of the criteria used when determining regulatory reporting requirements.

- For studies in which multiple agents are administered as part of a combination regimen, the investigator may attribute each AE causality to the combination regimen or to a single agent of the combination. In general, causality attribution should be assigned to the combination regimen (ie, to all agents in the regimen). However, causality attribution may be assigned to a single agent if in the investigator's opinion, there is sufficient data to support full attribution of the AE to the single agent.

Follow-up of AE and SAE

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by Sponsor to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.

- New or updated information will be recorded in the CRF.

- The investigator will submit any updated SAE data to the Sponsor within 24 hours of receipt of the information.

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

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

- The primary mechanism for reporting to the Sponsor will be the 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: Device Events, Adverse Device Events, and Medical Device Incidents: Definitions, Collection, and Documentation

Not applicable.

10.5 Appendix 5: Contraceptive Guidance

10.5.1 Definitions

Women of Childbearing Potential (WOCBP)

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

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

Women in the following categories are not considered WOCBP:

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

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

  Note: Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.
- Postmenopausal female
  - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
    - A high FSH level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or HRT. However, in the absence of 12 months of amenorrhea, confirmation with two FSH measurements in the postmenopausal range is required.
  - Females on HRT and whose menopausal status is in doubt will be required to use one of the nonhormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

10.5.2 Contraception Requirements

Contraceptives allowed during the study include[a]:
Highly Effective Contraceptive Methods That Have Low User Dependency[b] *Failure rate of <1% per year when used consistently and correctly.*
• Progestogen-only subdermal contraceptive implant[c,d] • IUS[d,e] • IUD • Bilateral tubal occlusion
• Azoospermic partner (vasectomized or secondary to medical cause) This is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. A spermatogenesis cycle is approximately 90 days. • Note: Documentation of azoospermia can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.
Highly Effective Contraceptive Methods That Are User Dependent[b] *Failure rate of <1% per year when used consistently and correctly***.**
• Combined (estrogen- and progestogen- containing) hormonal contraception[c,d] - Oral - Intravaginal - Transdermal - Injectable
• Progestogen-only hormonal contraception[c,d] - Oral - Injectable
Sexual Abstinence • Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.
a. Contraceptive use by men or women should be consistent with local regulations regarding the use of contraceptive methods for participants of clinical studies. b. Typical use failure rates are higher than perfect-use failure rates (ie, when used consistently and correctly). c. If locally required, in accordance with CTFG guidelines, acceptable contraceptive implants are limited to those which inhibit ovulation. d. Male condoms must be used in addition to female participants hormonal contraception. e. IUS is a progestin releasing IUD. Note: The following are not acceptable methods of contraception: - Periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and LAM. - Male condom with cap, diaphragm, or sponge with spermicide. - Male and female condom should not be used together (due to risk of failure with friction).

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

1. Definitions

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

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

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

d. DNA: Deoxyribonucleic acid.

e. RNA: Ribonucleic acid.

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

The specimens consented and/or collected in this study as outlined in Section 8.9 will be used in various experiments to understand:

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

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

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

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

a. Participants for Enrollment

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

b. Informed Consent

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

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

c. eCRF Documentation for Future Biomedical Research Specimens

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

d. Future Biomedical Research Specimen(s)

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

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

In order to optimize the research that can be conducted with future biomedical research specimens, it is critical to link participant' clinical information with future test results. In fact little or no research can be conducted without connecting the clinical study data to the specimen. The clinical data allow specific analyses to be conducted. Knowing participant characteristics like gender, age, medical history and 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 utilizing the future biomedical research specimens may be performed by the Sponsor, or an additional third party (eg, a university investigator) designated by the Sponsor. The investigator conducting the analysis will follow the Sponsor's privacy and confidentiality requirements. Any contracted third party analyses will conform to the specific scope of analysis outlined in 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 future biomedical research and ask that their biospecimens not be used for future biomedical research. Participants may withdraw consent at any time by contacting the 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 specimens will be flagged in the biorepository and restricted to main study use only. If specimens were collected from study participants specifically for future biomedical research, these specimens will be removed from the biorepository and destroyed. Documentation will be sent to the investigator confirming withdrawal and/or destruction, if applicable. It is the responsibility of the investigator to inform the participant of completion of the withdrawal and/or destruction, if applicable. Any analyses in progress at the time of request for withdrawal/destruction or already performed prior to the request being received by the Sponsor will continue to be used as part of the overall research study data and results. No new analyses would be generated after the request is received.

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

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 main study. Specimens may be stored for longer if a regulatory or governmental authority has active questions that are being answered. In this special circumstance, specimens will be stored until these questions have been adequately addressed.

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

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

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

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

United Kingdom

Sections 1.3.2 (Table 2), 1.3.3 (Table 3), and 1.3.4 (Table 4) - Schedule of Activities for the Treatment Period

This language replaces what is documented in the corresponding section of the referenced tables.

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

Section 5.1 – Inclusion Criteria

This language replaces what is documented in the corresponding section of the protocol.

8. Male participants are eligible to participate if they agree to the following during the intervention period and for at least 120 days:

- Refrain from donating sperm (from screening to 120 days after the last study intervention)

PLUS either:

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

OR

- Must agree to use contraception unless confirmed to be azoospermic (vasectomized or secondary to medical cause [Appendix 5]) as detailed below:

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

Section 6.5.2 – Prohibited Concomitant Medications

This language replaces what is documented in the corresponding bullet of the protocol.

- Live vaccines within 30 days prior to the first dose of study intervention, while participating in the study, and for 90 days after the end of study intervention. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, varicella/zoster, yellow fever, rabies, Bacillus Calmette–Guérin (BCG), and typhoid vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed; however, intranasal influenza vaccines (eg, FluMist®) are live attenuated vaccines and are not allowed.

Section 8.3.4.2 – Pregnancy Testing

This language replaces what is documented in the corresponding section of the protocol.

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 of 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. During study treatment, pregnancy testing should be repeated approximately monthly and then again 30 days after the last study dose of study treatment.

Appendix 2 Clinical Laboratory Tests

This language replaces what is documented in corresponding table footnote.

Footnote to the table reads:

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

Norway

Sections 1.3.5 (Table 1)- Schedule of Activities for the End of Treatment and Posttreatment Follow-up Periods

This language replaces what is documented in the corresponding section of the referenced tables.

Assessment	Notes
Pregnancy Test for WOCBP – Urine or Serum hCG	For WOCBP, perform as required locally. If a urine pregnancy test cannot be confirmed as negative, a serum pregnancy test is required. Monthly pregnancy testing should be conducted up to 120 days after the last administration of pembrolizumab.

5.2 Exclusion Criteria

This language replaces what is documented in the corresponding section of the protocol.

Exclusion criterion 21 “Has an active infection requiring systemic therapy, with the exception of HIV infection.”

Section 8.8.1 Planned Genetic Analysis Sample Collection

In this study, genetic analyses will be performed.

In cases where comprehensive mapping of the participant’s genomes are conducted, the Norwegian legislation will be adhered to.

If a significant health finding is observed in a participant during the trial, the finding will be assessed and the participant informed, if required, in accordance with the Norwegian legislation.

France

6.6.2 Dose Modification for Pembrolizumab

The following information provides additional irAEs and related details to what is stated in Table 9.

irAEs	Toxicity grade (CTCAE v5.0)	Action with pembrolizumab
Endocrinopathies	Grade 2 adrenal insufficiency and hypophysitis	Withhold treatment until controlled by hormone replacement
	Grades 3 or 4 adrenal insufficiency or symptomatic hypophysitis Type 1 diabetes associated with Grade ≥3 hyperglycemia (glucose >250 mg/dL or >13.9 mmol/L) or associated with ketoacidosis Hyperthyroidism Grade ≥3	Withhold until adverse reactions recover to Grades 0-1[a] For patients with Grade 3 or Grade 4 endocrinopathies that improved to Grade 2 or lower and are controlled with hormone replacement, if indicated, continuation of pembrolizumab may be considered after corticosteroid taper, if needed. Otherwise treatment should be discontinued.
	Hypothyroidism	Hypothyroidism may be managed with replacement therapy without treatment interruption.

irAEs	Toxicity grade (CTCAE v5.0)	Action with pembrolizumab
Hepatitis	Grade 2 with aspartate aminotransferase (AST) or alanine aminotransferase (ALT) >3 to 5 times ULN or total bilirubin >1.5 to 3 times ULN	Withhold until adverse reactions recover to Grades 0-1[a]
	Grade ≥3 with AST or ALT >5 times ULN or total bilirubin >3 times ULN	Permanently discontinue
	In case of liver metastasis with baseline Grade 2 elevation of AST or ALT, hepatitis with AST or ALT increases ≥50% and lasts ≥1week	Permanently discontinue
Skin reactions	Grade 3 or suspected Stevens-Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN)	Withhold until adverse reactions recover to Grades 0-1[a]
	Grade 4 or confirmed SJS or TEN	Permanently discontinue
[a] If treatment-related toxicity does not resolve to Grades 0-1 within 12 weeks after last dose of pembrolizumab, or if corticosteroid dosing cannot be reduced to ≤10 mg prednisone or equivalent per day within 12 weeks, pembrolizumab should be permanently discontinued.		

Italy

6.6.2 Dose Modification for Pembrolizumab

The following information provides additional irAEs and related details to what is stated in Table 9.

irAEs	Toxicity grade (CTCAE v5.0)	Action with pembrolizumab
Skin reactions	Grade 3 or suspected Stevens-Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN)	Withhold until adverse reactions recover to Grades 0-1[a]
	Grade 4 or confirmed SJS or TEN	Permanently discontinue
[a] If treatment-related toxicity does not resolve to Grades 0-1 within 12 weeks after last dose of pembrolizumab, or if corticosteroid dosing cannot be reduced to ≤10 mg prednisone or equivalent per day within 12 weeks, pembrolizumab should be permanently discontinued.		

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 4 to 8 weeks later is obtained (using iRECIST for participant management (see Table 11 and Figure 2). 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. Images should continue to be sent in to the iCRO for potential retrospective BICR.

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

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

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	Expanded Term
ADA	antidrug antibodies
ADL	activities of daily living
AE	adverse event
ALT (SGPT)	alanine aminotransferase (serum glutamic pyruvic transaminase)
aPTT	activated partial thromboplastin time
AST (SGOT)	aspartate aminotransferase (serum glutamic oxaloacetic transaminase)
AUC	area under the curve
C	Cycle
CBC	complete blood count
C_{max}	maximum plasma concentration
CNS	central nervous system
CrCl	creatinine clearance
CRF	Case Report Form
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
ctDNA	circulating tumor deoxyribonucleic acid;
CTFG	Clinical Trial Facilitation Group
C_{trough}	trough concentration
D	Day
DILI	drug-induced liver injury
DNA	deoxyribonucleic acid
ECG	electrocardiogram
ECI	event of clinical interest
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic Case Report Form
EDC	electronic data collection
EEA	European Economic Area
EMA	European Medicines Agency
F	free
FBR	future biomedical research
FDAAA	Food and Drug Administration Amendments Act
FSH	follicle-stimulating hormone
FSR	first site ready
GCP	Good Clinical Practice
GFR	glomerular filtration rate
HBc	hepatitis B core
HBeAg	hepatitis B e antigen
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
hCG	human chorionic gonadotropin
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HRT	hormone replacement therapy
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
INR	International Normalized Ratio
IRB	Institutional Review Board

Abbreviation	Expanded Term
iRECIST	modified RECIST 1.1 for immune-based therapeutics
ITu	intratumoral(ly)
IUD	intrauterine device
IUS	intrauterine hormone-releasing system
IV	intravenous(ly)
LDH	lactate dehydrogenase
LLOQ	lower limit of quantitation
M1a	nonvisceral (distant cutaneous, subcutaneous, nodal) metastasis
M1b	lung metastasis
M1c	non-CNS viscera metastasis
M1d	CNS metastasis
MRI	magnetic resonance imaging
NCI	National Cancer Institute
ORR	objective response rate
PBMC	peripheral blood mononuclear cells
PD	progressive disease
PD-1	programmed cell death 1
PD-L1	programmed cell death ligand 1
PD-L2	programmed cell death ligand 2
PD-(L)1	programmed cell death (ligand) 1
pembro	pembrolizumab
PK	pharmacokinetic(s)
PT	prothrombin time
PTT	partial thromboplastin time
RECIST 1.1	Response Evaluation Criteria in Solid Tumors, version 1.1
RNA	ribonucleic acid
RP2D	recommended Phase 2 dose
SAE	serious adverse event
SoA	Schedule of Activities
SUSAR	suspected unexpected serious adverse reaction
T3	triiodothyronine
T4	thyroxine
$TCID_{50}$	50% tissue culture infectious dose
TSH	thyroid-stimulating hormone
ULN	upper limit of normal
WOCBP	woman/women of childbearing potential

11 REFERENCES

[American Cancer Society 2012]	American Cancer Society. Cancer Facts & Figures 2012.	[00VNYG]
[Anastassiou, G., et al 2000]	Anastassiou G, Schilling H, Stang A, Djakovic S, Heiligenhaus A, Bornfeld N. Expression of the cell adhesion molecules ICAM-1, VCAM-1 and NCAM in uveal melanoma: a clinicopathological study. Oncology. 2000;58:83-8.	[05759R]
[Anderson, B. D., et al 2004]	Anderson BD, Nakamura T, Russell SJ, Peng KW. High CD46 receptor density determines preferential killing of tumor cells by oncolytic measles virus. Cancer Res. 2004 Jul 15;64:4919-26.	[0577KD]
[Anichini, A., et al 1990]	Anichini A, Mortarini R, Supino R, Parmiani G. Human melanoma cells with high susceptibility to cell-mediated lysis can be identified on the basis of ICAM-1 phenotype, VLA profile and invasive ability. Int J Cancer. 1990;46:508-15.	[0577KG]
[Bergelson, J. M., et al 1994]	Bergelson JM, Chan M, Solomon KR, St John NF, Lin H, Finberg RW. Decay-accelerating factor (CD55), a glycosylphosphatidylinositol-anchored complement regulatory protein, is a receptor for several echoviruses. Proc Natl Acad Sci USA. 1994 Jun;91:6245-8.	[0577M4]
[Berry, L.J., et al 2008]	Berry, L.J.;Au, G.G.;Barry, R.D.;Shafren, D.R. Potent oncolytic activity of human enteroviruses against human prostate cancer. Prostate. 2008 May 1;68(6):577-87. doi: 10.1002/pros.20741.	[0565BZ]
[Chemnitz, J. M., et al 2004]	Chemnitz JM, Parry RV, Nichols KE, June CH, Riley JL. SHP-1 and SHP-2 associate with immunoreceptor tyrosine-based switch motif of programmed death 1 upon primary human T cell stimulation, but only receptor ligation prevents T cell activation. J Immunol 2004;173:945-54.	[00VMPN]
[Clopper, C. J. and Pearson, E. S. 1934]	Clopper CJ, Pearson ES. The use of confidence or fiducial limits illustrated in the case of binomial. Biometrika 1934;26(4):404-13.	[03RMKM]

[Dickson, P. V. 2011]	Dickson PV, Gershenwald JE. Staging and prognosis of cutaneous melanoma [manuscript]. 2011. 20 p.	[057SC6]
[Disis, M. L. 2010]	Disis ML. Immune regulation of cancer. J Clin Oncol 2010;28(29):4531-8.	[058SQL]
[Dudley, M. E., et al 2005]	Dudley ME, Wunderlich JR, Yang JC, Sherry RM, Topalian SL, Restifo NP, et al. Adoptive cell transfer therapy following non-myeloablative but lymphodepleting chemotherapy for the treatment of patients with refractory metastatic melanoma. J Clin Oncol 2005;23(10):2346-57.	[00VMPR]
[Farrington, C. P. 1990]	Farrington CP, Manning G. Test Statistics and Sample Size Formulae for Comparative Binomial Trials with Null Hypothesis of Non-Zero Risk Difference or Non-Unity Relative Risk. Stat Med Vol. 9,1447-1454 (1990)	[04FS6L]
[Ferlay, J., et al 2010]	Ferlay J, Shin HR, Bray F, Forman D, Mathers C, Parkin DM. Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008. Int J Cancer 2010;127:2893-917.	[023Y69]
[Forsyth, P., et al 2008]	Forsyth P, Roldan G, George D, Wallace C, Palmer CA, Morris D, et al. A phase I trial of intratumoral administration of reovirus in patients with histologically confirmed recurrent malignant gliomas. Mol Ther. 2008 Mar;16(3):627-32.	[057B5H]
[Francisco, L. M., et al 2010]	Francisco LM, Sage PT, Sharpe AH. The PD-1 pathway in tolerance and autoimmunity. Immunol Rev 2010;236:219-42.	[058SQP]
[Georgolios, A., et al 2006]	Georgolios A, Batistatou A, Bonitsis N, Stagikas D, Manolopoulos L, Charalabopoulos K. The role of intercellular adhesion molecule-1 in head and neck cancer. Exp Oncol. 2006 Dec;28(4):270-4.	[057B5X]
[Greenwald, R. J., et al 2005]	Greenwald RJ, Freeman GJ, Sharpe AH. The B7 family revisited. Annu Rev Immunol 2005;23:515-48.	[00VMQL]

[Hakansson, A., et al 1999]	Hakansson A, Gustafsson B, Krysander L, Hjelmqvist B, Rettrup B, Hakansson L. Expression of ICAM-1 during IFN-alpha-based treatment of metastatic malignant melanoma: relation to tumor-infiltrating mononuclear cells and regressive tumor changes. J Interferon Cytokine Res. 1999;19:171-7.	[05788M]
[Harrington, K. J., et al 2010]	Harrington KJ, Vile RG, Melcher A, Chester J, Pandha HS. Clinical trials with oncolytic reovirus: moving beyond phase I into combinations with standard therapeutics. Cytokine Growth Factor Rev. 2010;21:91-8.	[05788T]
[Hodi, F. S., et al 2014]	Hodi FS, Ribas A, Daud A, Hamid O, Robert C, Kefford R, et al. Patterns of response in patients with advanced melanoma treated with Pembrolizumab (MK-3475) and evaluation of immune-related response criteria (irRC). J Immunother Cancer. 2014;2(Suppl 3):P103.	[0465RW]
[Hunder, N. N., et al 2008]	Hunder NN, Wallen H, Cao J, Hendricks DW, Reilly JZ, Rodmyre R, et al. Treatment of metastatic melanoma with autologous CD4+ T cells against NY-ESO-1. N Engl J Med 2008;358(25):2698-703.	[00VMPX]
[Johnson, J. P. 1991]	Johnson JP. Cell adhesion molecules of the immunoglobulin supergene family and their role in malignant transformation and progression to metastatic disease. Cancer Metastasis Rev. 1991;10:11-22.	[05788Z]
[Kageshita, T., et al 1993]	Kageshita T, Yoshii A, Kimura T, Kuriya N, Ono T, Tsujisaki M, et al. Clinical relevance of ICAM-1 expression in primary lesions and serum of patients with malignant melanoma. Cancer Res. 1993 Oct 15;53:4927-32.	[057897]
[Kaufman, H. L. 2010]	Kaufman HL, Bines SD. OPTIM trial: a phase III trial of an oncolytic herpes virus encoding GM-CSF for unresectable stage III or IV melanoma. Future Oncol. 2010;6(6):941-9.	[05789Z]

[Krishnamurthy, S., et al 2006]	Krishnamurthy S, Takimoto T, Scroggs RA, Portner A. Differentially regulated interferon response determines the outcome of Newcastle disease virus infection in normal and tumor cell lines. J Virol. 2006 Jun;80(11):5145-55.	[0578MH]
[Lang, S., et al 1999]	Lang S, Whiteside TL, Lebeau A, Zeidler R, Mack B, Wollenberg B. Impairment of T-cell activation in head and neck cancer in situ and in vitro: strategies for an immune restoration. Arch Otolaryngol Head Neck Surg. 1999 Jan;125:82-8.	[0578MJ]
[Liu, T. C., et al 2008]	Liu TC, Hwang T, Park BH, Bell J, Kirn DH. The targeted oncolytic poxvirus JX-594 demonstrates antitumoral, antivascular, and anti-HBV activities in patients with hepatocellular carcinoma. Mol Ther. 2008 Sep;16(9):1637-42.	[0578ML]
[Merrick, A. E., et al 2009]	Merrick AE, Ilett EJ, Melcher AA. JX-594, a targeted oncolytic poxvirus for the treatment of cancer. Curr Opin Investig Drugs. 2009;10(12):1372-82.	[0578MR]
[Miettinen, O. and Nurminen, M. 1985]	Miettinen O, Nurminen M. Comparative analysis of two rates. Stat Med 1985;4:213-26.	[00VMQY]
[Okazaki, T., et al 2001]	Okazaki T, Maeda A, Nishimura H, Kurosaki T, Honjo T. PD-1 immunoreceptor inhibits B cell receptor-mediated signaling by recruiting src homology 2-domain-containing tyrosine phosphatase 2 to phosphotyrosine. Proc Natl Acad Sci U S A 2001;98(24):13866-71.	[00VMQ6]
[Pandolfi, F., et al 1992]	Pandolfi F, Trentin L, Boyle LA, Stamenkovic I, Byers HR, Colvin RB, et al. Expression of cell adhesion molecules in human melanoma cell lines and their role in cytotoxicity mediated by tumor-infiltrating lymphocytes. Cancer. 1992 Mar 1;69(5):1165-73.	[05790Z]
[Park, Y. J., et al 2018]	Park YJ, Kuen DS, Chung Y. Future prospects of immune checkpoint blockade in cancer: from response prediction to overcoming resistance. Exp Mol Med. 2018;50:109.	[056G69]

[Parry, R. V., et al 2005]	Parry RV, Chemnitz JM, Frauwirth KA, Lanfranco AR, Braunstein I, Kobayashi SV, et al. CTLA-4 and PD-1 receptors inhibit T-cell activation by distinct mechanisms. Mol Cell Biol 2005;25(21):9543-53.	[00VMQ7]
[Riley, J. L. 2009]	Riley JL. PD-1 signaling in primary T cells. Immunol Rev 2009;229:114-25.	[00VMQ9]
[Rosette, C., et al 2005]	Rosette C, Roth RB, Oeth P, Braun A, Kammerer S, Ekblom J, et al. Role of ICAM1 in invasion of human breast cancer cells. Carcinogenesis. 2005;26(5):943-50.	[05792C]
[Rowan, K. 2010]	Rowan K. Oncolytic viruses move forward in clinical trials. J Natl Cancer Inst. 2010 May 5;102(9):590-5.	[05792D]
[Senzer, N. N., et al 2009]	Senzer NN, Kaufman HL, Amatruda T, Nemunaitis M, Reid T, Daniels G, et al. Phase II clinical trial of a granulocyte-macrophage colony-stimulating factor-encoding, second-generation oncolytic herpesvirus in patients with unresectable metastatic melanoma. J Clin Oncol. 2009 Dec 1;27(34):5763-71.	[05792H]
[Seymour, L., et al 2017]	Seymour L, Bogaerts J, Perrone A, Ford R, Schwartz LH, Mandrekar S, et al. iRECIST: guidelines for response criteria for use in trials testing immunotherapeutics. Lancet Oncol. 2017 Mar;18(3):e143-52.	[04P9RV]
[Shafren, D. R. 1998]	Shafren DR. Viral cell entry induced by cross-linked decay-accelerating factor. J Virol. 1998 Nov;72(11):9407-12.	[0578YF]
[Shafren, D. R., et al 2000]	Shafren DR, Dorahy DJ, Thorne RF, Barry RD. Cytoplasmic interactions between decay-accelerating factor and intercellular adhesion molecule-1 are not required for coxsackievirus A21 cell infection. J Gen Virol. 2000;81:889-94.	[0578YG]

[Shafren, D.R., et al 1997]	Shafren, D.R.;Dorahy, D.J.;Ingham, R.A.;Burns, G.F.;Barry, R.D. Coxsackievirus A21 binds to decay-accelerating factor but requires intercellular adhesion molecule 1 for cell entry. J Virol. 1997 Jun;71(6):4736-43.	[0566DY]
[Sharma, P., et al 2017]	Sharma P, Hu-Lieskovan S, Wargo JA, Ribas A. Primary, adaptive, and acquired resistance to cancer immunotherapy. Cell. 2017 Feb 9;168:707-23	[056H7T]
[Shaw, S. K., et al 2004]	Shaw SK, Ma S, Kim MB, Rao RM, Hartman CU, Froio RM, et al. Coordinated redistribution of leukocyte LFA-1 and endothelial cell ICAM-1 accompany neutrophil transmigration. J Exp Med. 2004 Dec 20;200(12):1571-80.	[0578YH]
[Sheppard, K-A, et al 2004]	Sheppard K-A, Fitz LJ, Lee JM, Benander C, George JA, Wooters J, et al. PD-1 inhibits T-cell receptor induced phosphorylation of the ZAP70/CD3zeta signalosome and downstream signaling to PKCtheta. FEBS Lett. 2004;574:37-41.	[00VMQC]
[Si, Z. 1994]	Si Z, Hersey P. Immunohistological examination of the relationship between metastatic potential and expression of adhesion molecules and 'selectins' on melanoma cells. Pathology. 1994 Jan;26:6-15.	[0578YM]
[Siegel, R., et al 2012]	Siegel R, Naishadham D, Jemal A. Cancer statistics, 2012. CA Cancer J Clin. 2012 Jan-Feb;62(1):10-29.	[03ZND3]
[Skelding KA, Barry RD, Shafren DR. 2009]	Skelding KA, Barry RD, Shafren DR. Systemic targeting of metastatic human breast tumor xenografts by Coxsackievirus A21. Breast Cancer Res Treat. 2009 Jan;113(1):21-30. doi: 10.1007/s10549-008-9899-2. Epub 2008 Feb 7.	[0566F8]
[Staunton, D. E., et al 1989]	Staunton DE, Merluzzi VJ, Rothlein R, Barton R, Marlin SD, Springer TA. A cell adhesion molecule, ICAM-1, is the major surface receptor for rhinoviruses. Cell. 1989 Mar 10;56:849-53.	[0578YN]

[Stojdl, D. F., et al 2000]	Stojdl DF, Lichty B, Knowles S, Marius R, Atkins H, Sonenberg N, et al. Exploiting tumor-specific defects in the interferon pathway with a previously unknown oncolytic virus. Nat Med. 2000 Jul;6(7):821-5.	[0578YP]
[Wolchok, J. D., et al 2009]	Wolchok JD, Hoos A, O'Day S, Weber JS, Hamid O, LebbéC, et al. Guidelines for the evaluation of immune therapy activity in solid tumors: immune-related response criteria. Clin Cancer Res 2009;15(23):7412-20.	[00VMNZ]
[Zeichhardt, H. 2004]	Zeichhardt H, Grunert HP. Infectious diseases. 2nd ed. Cohen J, Powderly WG, editors. London (United Kingdom): Elsevier Limited, c2004. Section 8 clinical microbiology: viruses. Chapter 213, Enteroviruses: polioviruses, Coxsackie viruses, echoviruses and enteroviruses 68-71; p. 1993-2005.	[0579CH]
[Zhang, X., et al 2004]	Zhang X, Schwartz J-CD, Guo X, Bhatia S, Cao E, Chen L, et al. Structural and functional analysis of the costimulatory receptor programmed death-1. Immunity 2004;20:337-47.	[00VMQJ]