Official Protocol Title:	A Phase 1b/2 Clinical Study of Intratumoral Administration of V937 in Combination with Pembrolizumab (MK-3475) in Participants with Advanced/Metastatic Solid Tumors
NCT number:	NCT04521621
Document Date:	25-October-2022

Title Page

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Protocol Title: A Phase 1b/2 Clinical Study of Intratumoral Administration of V937 in Combination with Pembrolizumab (MK-3475) in Participants with Advanced/Metastatic Solid Tumors

Protocol Number: 013-04

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	2020-001908-42

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 04	25-OCT-2022	V937-013 is going to be discontinued due to the Sponsor's development decision. The overall rationale for this amendment is to allow ongoing patients to transfer to another sponsored protocol to continue receiving pembrolizumab, incorporates previously released Protocol Clarification Letters, and updates the Sponsor corporate name.
Amendment 03	19-APR-2021	This amendment provides clarification to address agency feedback and also provides updated language to the pembrolizumab dose modification portion of the study.
Amendment 02	01-DEC-2020	The overall rationale for the amendment is to clarify existing language, provide country-specific requirements, and to remove sections that are not applicable to this study.
Amendment 01	26-MAY-2020	The IND number was updated to address Agency feedback.
Original Protocol	14-MAY-2020	Not applicable.

PROTOCOL AMENDMENT SUMMARY OF CHANGES

Amendment: 04

Overall Rationale for the Amendments:

V937-013 is going to be discontinued due to the Sponsor's development decision. The overall rationale for this amendment is to allow ongoing patients to transfer to another sponsored protocol to continue receiving pembrolizumab; incorporate previously released Protocol Clarification Letters; and updates to the Sponsor corporate name.

Summary of Changes Table:

Section # and Name	Description of Change	Brief Rationale
1.2 Schema 1.3 Schedule of Activities 4.4.1 Clinical Criteria for Early Study Termination	Added language to allow participants to enroll in another study to continue receiving pembrolizumab.	Allows ongoing participants deriving benefit from pembrolizumab the opportunity to transfer to another active study upon study closure
1.1 Synopsis 1.2 Schema 4.1.1 Arm 1: Subcutaneous Tumors 4.1.3 Arm 2 Part II: Cohort Expansion in Metastatic Visceral Lesion Tumors 9.1 Statistical Analysis Plan Summary 9.9 Sample Size and Power Calculations	Added language indicating total planned enrollment number may not be met.	The study may not enroll the planned 185 participants due to early study termination

Section # and Name	Description of Change	Brief Rationale
1.3.2 Schedule of Activities for Treatment Phase: Arm 1 - Participants with Subcutaneous Tumors 1.3.3 Schedule of Activities for Treatment Phase: Arm 2 Part I - Dose Escalation in Participants with Visceral Tumors 1.3.4 Schedule of Activities for Treatment Phase: Arm 2 Part II - Cohort Expansion 1.3.5 Schedule of Activities for End of Treatment/Discontinuation and Posttreatment Phase: Arm 1, Arm 2 Part I Dose Escalation Phase, and Arm 2 Part II Expansion Phase	Removed sample collections for serum for V937 PK (RNA), neutralizing V937 antibodies, blood for ctDNA analysis, blood for RNA analyses, and blood for genetic analyses. Clarified that vital signs need not be collected post-dose of pembrolizumab when V937 is not administered.	Due to early study termination, collection of central laboratory samples is no longer required. Clarification of vital sign collection information and timing.
1.3.5 Schedule of Activities for End of Treatment/Discontinuation and Posttreatment Phase: Arm 1, Arm 2 Part I Dose Escalation Phase, and Arm 2 Part II Expansion Phase 8.11.3.1 Safety Follow-up Visit 8.11.3.2 Imaging Follow-up Visits 8.11.3.3 Survival Follow-up Contacts	Removed 'Posttreatment Phase' visits including Safety Follow-up, Imaging Follow-up, and Survival Follow-up visits.	Due to early study termination, completion of the 30-day Safety Follow-up visit, post-treatment 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 8.6.1 Blood Collection for Serum V937 8.6.2 Blood Collection for Neutralizing V937 Antibodies 8.7 Pharmacodynamics 8.8 Biomarkers	Added statement related to collection of samples if study is terminated early	Updated collection information, due to early study termination.
Title Page 10.1.1 Code of Conduct for Clinical Trials Throughout	Sponsor entity name and address change.	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.
1.1 Synopsis 6.1 Study Intervention(s) Administered	Updated the "Use" column to "Test Product" and updated the "IMP or NIMP/AxMP" column heading.	To align with EU CTR regulations.
8.4 Adverse Events, Serious Adverse Events, and Other Reportable Safety Events 10.3.1 Definitions of Medication Error, Misuse, and Abuse	Added investigator requirements for documenting SAEs related to medication error, misuse, abuse, and their definition	To align with EU CTR regulations.

Section # and Name	Description of Change	Brief Rationale
1.3.1 Schedule of Activities for Screening 8.1.1.2 Consent and Collection of Specimens for Future Biomedical Research 8.1.3 Participant Identification Card	Updated to "documented informed consent".	Adherence to COVID-19 requirements.
5.1.1 Overall Inclusion Criteria	Criterion #11: Updated to documented informed consent	Adherence to COVID-19 requirements.
5.2.1 Overall Exclusion Criteria	Criterion # 4 Clarified language related to timing of malignancy. Criterion #15 Added COVID-19 reference.	Clarification of curative treatment timing. Adherence to COVID-19 requirements.
6.5.2 Prohibited Concomitant Medications	Added COVID-19 vaccine information. Clarified acceptable uses of glucocorticoids.	Adherence to COVID-19 requirements. Clarification of information related to glucocorticoid use.
5.1.2.2 Specific Inclusion Criteria for Cohort B: Advanced/Metastatic Head and Neck Squamous Cell Carcinoma	Criterion #18: added note to clarify reporting of HPV status.	To clarify to obtain status for participants not previously tested.

Section # and Name	Description of Change	Brief Rationale
5.1.4.1 Specific Inclusion Criteria for Cohort D: Hepatocellular Carcinoma 8.1.1.1 General Informed Consent 8.1.1.2 Consent and Collection of Specimens for Future Biomedical Research 8.4.1 Time Period and Frequency for Collecting AE, SAE, and Other Reportable Safety Event Information 10.1.2 Financial Disclosure 10.1.3 Data Protection 10.3.5 Recording of AE and SAE	Change “he/she” to “the investigator” or “the participant” and “his/her” to “their”.	Adopt gender neutral language.
6.6.3 Guidance for Management of Hepatic Events of Clinical Interest 10.2 Appendix 2 Clinical Laboratory Tests	Added GGT testing as part of HECI workup.	Testing must be performed as part of HECI workup.
8.3.7 Pregnancy Test	Updated to clarify collection timing and procedures.	To clarify pregnancy testing requirements.
CCI [redacted]		

Section # and Name	Description of Change	Brief Rationale
9.10 Subgroup Analyses	Added subgroup analysis plan for participants whose lesions are injected versus noninjected.	Clarification of subgroup analysis information.
10.7.3 France-specific Requirements 10.7.4 Portugal-specific Requirements	Added information related to pregnancy testing and oocyte donation requirements. Added section with information related to pregnancy and HIV/Hep B/Hep C testing requirements.	Adherence to Health Authority requirements.
Throughout Document	Minor administrative, formatting, grammatical, and/or 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 1b/2 Clinical Study of Intratumoral Administration of V937 in Combination with Pembrolizumab (MK-3475) in Participants with Advanced/Metastatic Solid Tumors

Short Title: Phase 1b/2 Study of ITu V937 in Combination with Pembrolizumab

Acronym: Not applicable

Hypotheses, Objectives, and Endpoints:

There is no hypothesis testing in this study.

Throughout this protocol, the term RECIST 1.1 refers to a modification to RECIST 1.1 to allow a maximum of 10 target lesions in total and 5 per organ. Since ITu therapy is included by design in the study, RECIST 1.1 is also modified to specify that ITu injection by itself does not render a lesion non-evaluable. Refer to Section 4.2.1.1 for further details.

In male and female participants with advanced/metastatic solid tumors who are anti-PD-(L)1-treatment-naïve:

Arm 1: Subcutaneous Tumor Cohorts

Primary Objectives	Primary Endpoints
- To evaluate the objective response rate (ORR) of V937 administered in subcutaneous tumors in combination with pembrolizumab per Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST 1.1) as assessed by the investigator.	- Objective response is a confirmed complete response (CR) or partial response (PR).
Secondary Objectives	Secondary Endpoints
- To determine the safety and tolerability of V937 administered in subcutaneous tumors in combination with pembrolizumab.	- Adverse event (AE) - Discontinuing a study intervention due to an AE

- To evaluate progression-free survival (PFS) and duration of response (DOR) of participants treated with V937 in subcutaneous tumors in combination with pembrolizumab per RECIST 1.1 as assessed by the investigator.	- PFS is defined as the time from the first dose of study treatment to the first documented disease progression or death due to any cause, whichever occurs first. - DOR is defined as the time from the first documented evidence of CR or PR until progressive disease (PD) or death due to any cause, whichever occurs first, in participants demonstrating PR or CR.
- To evaluate the ORR, PFS, and DOR of V937 administered in subcutaneous tumors in combination with pembrolizumab per RECIST 1.1 for immune-based therapeutics (iRECIST) criteria as assessed by the investigator.	- ORR - PFS - DOR
- To evaluate OS (overall survival) of participants treated with V937 in subcutaneous tumors in combination with pembrolizumab.	- OS is defined as the time from the first dose of study treatment to the date of death from any cause.
Arm 2 Part I: Visceral Dose Escalation, and Arm 2 Part II: Visceral Tumor Expansion	
Primary Objectives	Primary Endpoints
- To determine the safety and tolerability and to establish a preliminary recommended Phase 2 dose (RP2D) of V937 administered in visceral tumors in combination with pembrolizumab.	- Dose-limiting toxicity DLT - AE - Discontinuing a study intervention due to an AE
Secondary Objectives	Secondary Endpoints
- To evaluate the ORR of V937 administered in visceral tumors at the preliminary RP2D with pembrolizumab per RECIST 1.1 and iRECIST criteria as assessed by the investigator.	- ORR

Overall Design:

Study Phase	Phase 1/Phase 2
Primary Purpose	Treatment
Indication	The treatment of participants with advanced/metastatic solid tumors
Population	Participants with histologically or cytologically-confirmed advanced/metastatic solid tumors by pathology report who have not received PD-(L)1 antibody treatment, talimogene laherparepvec (T-VEC) or other oncolytic viruses.
Study Type	Interventional
Intervention Model	Single Group This is a multi-site study.
Type of Control	No control
Study Blinding	Unblinded Open-label
Blinding Roles	No Blinding
Estimated Duration of Study	The Sponsor estimates that the study will require approximately 5 years from the time the first participant (or their legally acceptable representative) provides documented informed consent until the last participant's last study-related telephone call or visit.

Number of Participants:

Approximately 185 participants will be allocated to the following intervention arms:

- Arm 1: Subcutaneous tumors (ITu V937 + IV pembrolizumab)
- Arm 2 Part I: Visceral tumor dose escalation (ITu V937 + IV pembrolizumab)
- Arm 2 Part II: Visceral tumor cohort expansion (ITu V937 + IV pembrolizumab) with the RP2D defined in Arm 2 Part I.

Due to early study termination of this study, the total enrollment number may be less than 185 participants.

Intervention Groups and Duration:

Intervention Groups

Intervention Group Name	Drug	Dose Levels	Dose Frequency	Route of Administration	Regimen/ Treatment Period/ Vaccination Regimen	Use
Arm 1	V937	3 X 10^8 $TCID_{50}$	Cycle 1 Days 1, 3, 5 and 8 (4 doses); then every 3 weeks	ITu Injection	Days 1, 3, 5, and 8 of Cycle 1 (28-day cycle) Day 1 of Cycles 2 to 8 (21-day cycles)	Test Product
	Pembrolizumab	200 mg	Every 3 weeks	IV Infusion	Day 8 of Cycle 1 (28-day cycle) Day 1 of each subsequent 21-day cycle	Test Product
Arm 2 Part I	V937	DL1: 3 X 10^7, DL2: 1 X 10^8, DL3: 3 X 10^8 $TCID_{50}$	Cycle 1, Days 1 and 8 (2 doses); then every 3 weeks	ITu Injection	Days 1 and 8 of Cycle 1 (28-day cycle) Day 1 of Cycles 2 to 8 (21-day cycles)	Test Product
	Pembrolizumab	200 mg	Every 3 weeks	IV Infusion	Day 8 of Cycle 1 (28-day cycle) Day 1 of each subsequent 21-day cycle	Test Product
Arm 2 Part II	V937	RP2D DL1: 3 X 10^7, DL2: 1 X 10^8, or DL3: 3 X 10^8 $TCID_{50}$	Cycle 1, Days 1 and 8 (2 doses); then every 3 weeks	ITu Injection	Days 1 and 8 of Cycle 1 (28-day cycle) Day 1 of Cycles 2 to 8 (21-day cycles)	-Test Product
	Pembrolizumab	200 mg	Every 3 weeks	IV Infusion	Day 8 of Cycle 1 (28-day cycle) Day 1 of each subsequent 21-day cycle	Test Product

Abbreviations: ITu=intratumoral; IV=intravenous; RP2D = recommended Phase 2 dose; $TCID_{50}$=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); CAV21.

Total Number

Total Number of Intervention Groups/Arms: 2

Duration of Participation	Each participant will participate in the study from the time the participant provides documented informed consent through the final protocol-specified contact. After a screening phase of up to 28 days, each participant will be assigned to receive study intervention, as described above, for approximately 2 years until disease progression is radiographically documented, confirmed by the site per RECIST 1.1, 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 in Arm 1 will receive up to 11 administrations (in 8 cycles) of V937, and participants in Arm 2 will receive up to 9 administrations (in 8 cycles) V937 unless any of the above apply. After the end of treatment, each participant will be followed for the occurrence of adverse events and spontaneously reported pregnancy as described in Section 8.4. Participants who discontinue for reasons other than radiographic disease progression will have posttreatment 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, the start of a new anticancer 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.

Study Governance Committees:

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

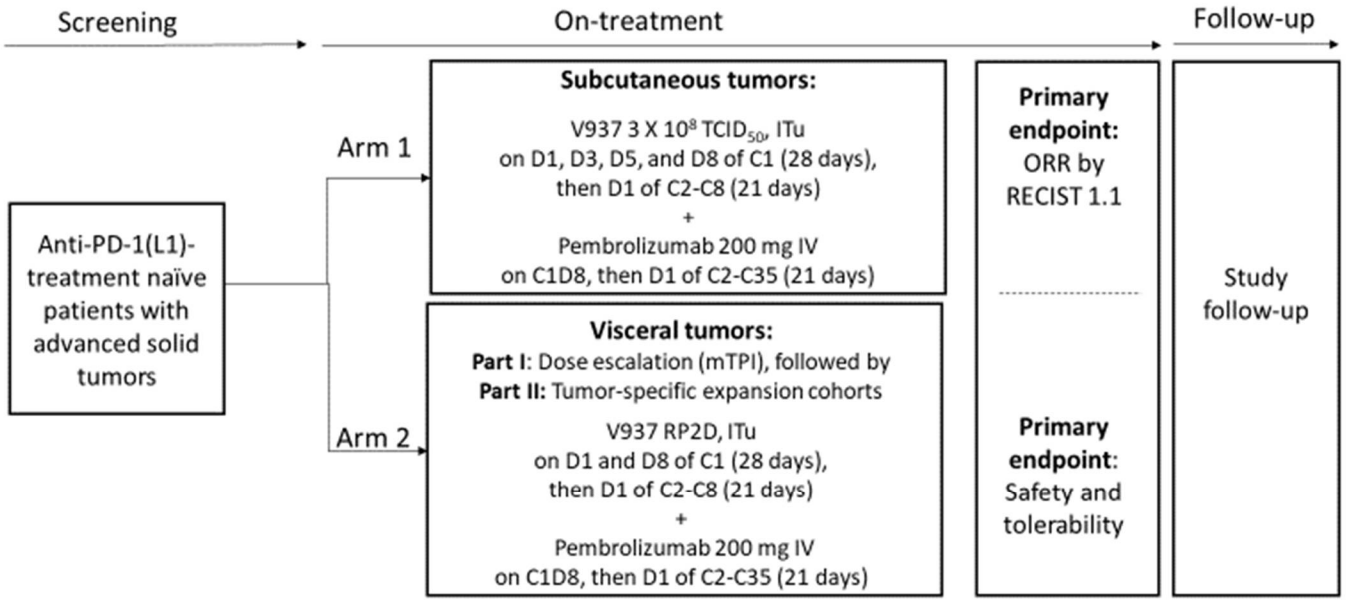
Study Accepts Healthy Volunteers: No

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

1.2 Schema

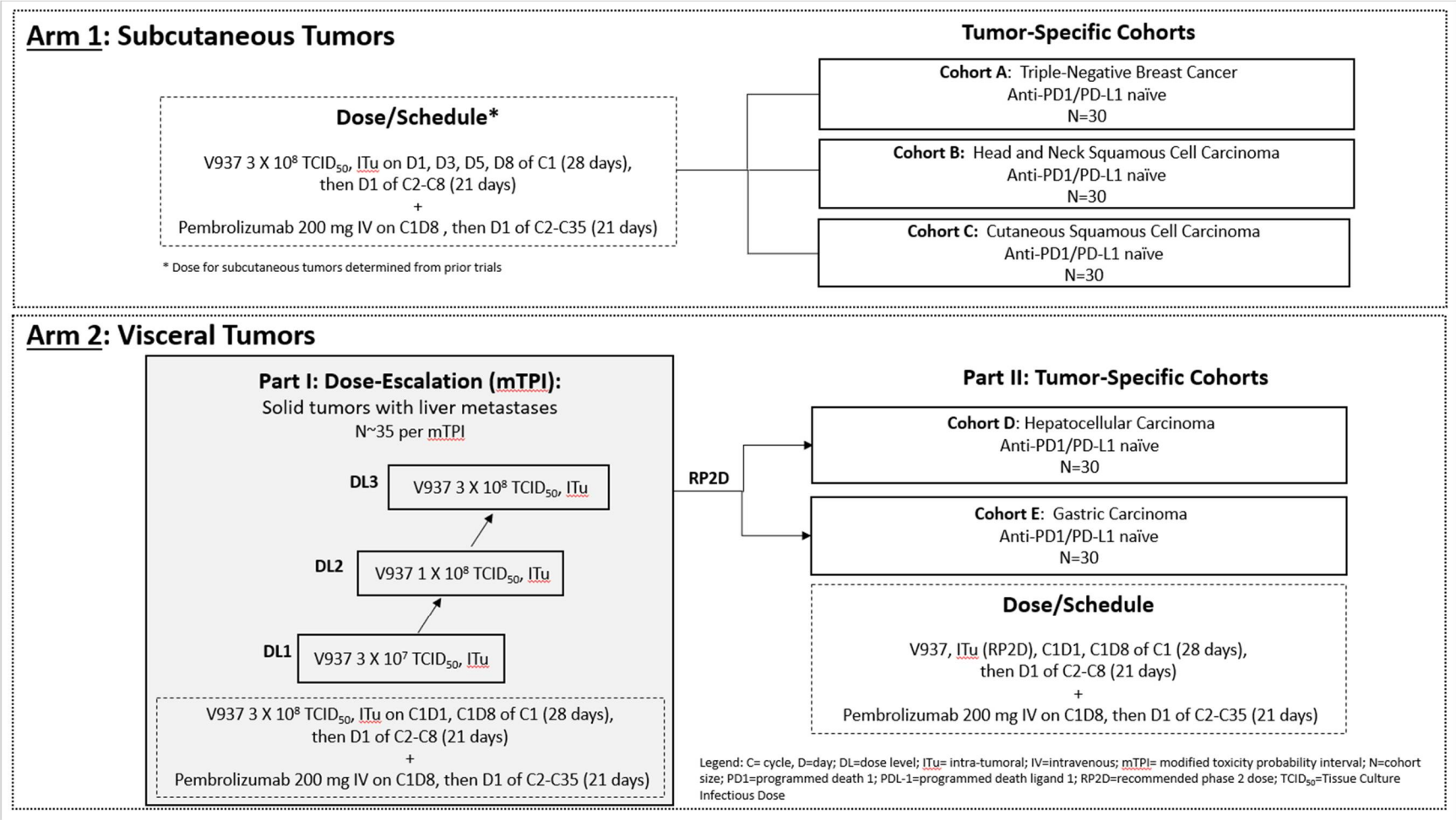
Study design is shown in the 2 figures below. Figure 1: high-level study design; Figure 2: detailed study design. Upon study completion or early study termination, participants who have completed or discontinued V937 treatment and are only receiving pembrolizumab may be enrolled in a pembrolizumab extension study, if available, to continue pembrolizumab monotherapy for up to 35 cycles from first pembrolizumab dose on V937-013. Due to early study termination of this study, the total enrollment number may be less than 185 participants.

Figure 1 High-level Study Design



Legend: C=cycle, D=day; DL=dose level; ITu= intra-tumoral; IV=intravenous; mTPI= modified toxicity probability interval; ORR=Objective Response Rate; PDL-1(L1)=programmed death ligand 1; RECIST 1.1= Response Evaluation Criteria in Solid Tumors, version 1.1; RP2D=recommended phase 2 dose; $TCID_{50}$=Tissue Culture Infectious Dose

Figure 2 Detailed Study Design



1.3 Schedule of Activities

See Appendix 7 for country-specific requirements.

Upon study completion or early study termination, 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 V937-013. Such participants will be monitored and follow the Schedule of Activities for the pembrolizumab extension study.

1.3.1 Schedule of Activities for Screening

Table 1 Schedule of Activities for Screening

Study Period:	**Screening**	**Notes**
Visit Day:	**-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.
Inclusion/Exclusion Criteria	X	
Participant Identification Card	X	Participant identification card to be updated with treatment number at the time of treatment assignment.
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	
Clinical Procedures/Assessments		
Tumor Imaging (CT or MRI as indicated) (RECIST 1.1, and iRECIST Response Assessment)	X	Baseline tumor imaging (CT or MRI as indicated) and/or medical photography of cutaneous lesions should be performed within 28 days prior to C1D1. Refer to Site Imaging Manual for detailed information.
Arm 1 only: Medical Photography (cutaneous lesions)	X	

Study Period:	Screening	Notes
Visit Day:	-28 to -1	
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.
Additional Imaging (PET/CT, bone scan, etc.)	X	May obtain additional scans if clinically indicated. Arm 1: HNSCC Cohort B: Include head and neck CT
Endoscopy	X	**Required for Arm 2 Part II, Cohort D only.** Participants should undergo screening for esophageal varices, unless such screening has been performed in the past 12 months before first dose of treatment.
Physical Examination	X	A full physical examination should be done at screening.
Child-Pugh Score	X	**Required for Arm 2 Part II, Cohort D only.** If any of the hepatic ECI criteria are met, document the Child-Pugh score with each visit until the hepatic ECIs resolve. Class A score required.
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	
Adverse Event (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 prior to C1D1 except for thyroid and hepatitis testing. Thyroid and hepatitis testing must be obtained within 28 days prior to C1D1. 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	
AST, ALT	X	
Thyroid Function Testing (T4 or FT4, T3 or FT3, TSH)	X	
Pregnancy test for WOCBP only (urine or serum β 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 Screen	X	Acceptable to be based on history unless testing is required by local regulation.

Study Period:	Screening	Notes
Visit Day:	-28 to -1	
Hepatitis B and C Screen	X	**Required for Arm 2 Part II, Cohort D only:** Hepatitis B and C Screen. **For Arm 2 Part II, Cohort D:** Include HCV antibody or HCV RNA (qualitative) and HBsAg. **For all other cohorts:** Acceptable to be based on history unless testing is required by local regulation.
HPV Status	X	**Required for Arm 1 Cohort B only.** HPV testing in oropharyngeal cancer (eg, p16 IHC; multiplex NASBA or other PCR-based assays) should be recorded, as determined per institutional standard.
PD-L1 tumor expression	X	**Required for Arm 1 Cohort B only.** HNSCC tumors must be PD-L1 positive (CPS ≥1); local testing and historical results are acceptable.
Laboratory Procedures/Assessments – CENTRAL		
Tumor Biopsy	X	An archival tissue sample is acceptable, otherwise a new biopsy will be obtained. Exception: Arm 2 Part I: If tissue block is not available, participant may be enrolled if all other inclusion criteria are satisfied. Instructions for tissue collection, processing, and shipment are provided in the Procedures Manual.

Abbreviations: AE=adverse event; ALT=alanine aminotransferase; aPTT=activated partial thromboplastin time; AST=aspartate aminotransferase; β hCG=β human chorionic gonadotropin; BRAF=proto-oncogene B-rapidly accelerated fibrosarcoma; C=Cycle; CBC=complete blood count; CPS=combined positive score; CT=computed tomography; D=Day; ECOG=Eastern Cooperative Oncology Group; F=free; FBR=future biomedical research; h=hour(s); HBsAg=Hepatitis B surface antigen; HCV=Hepatitis C virus; HIV=human immunodeficiency virus; HPV=human papillomavirus; IHC=immunohistochemistry; INR=International Normalized Ratio; MRI=magnetic resonance imaging; NASBA=nucleic acid sequence-based amplification; PCR=polymerase chain reaction; 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 Treatment Phase: Arm 1 - Participants with Subcutaneous Tumors

Table 2 Schedule of Activities for Treatment Phase: Arm 1 - Participants with Subcutaneous Tumors

Study Period:	Treatment Period						Notes
Treatment Cycle / Visit Title:	Cycle 1 (28 days)				Cycles 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.
Treatment Days per Cycle	1	3	5	8	1	1	
Scheduling/visit Window (Days)	± 0	± 1	± 1	± 1	+ 3	± 3	**C2D1:** The visit window is + 3 days. **C3D1 and subsequent cycles:** The visit window is ± 3 days. **All cycles:** These visit windows apply unless otherwise specified for individual process/procedure.
Treatment Assignment	X						Treatment assignment can occur up to 3 days prior to C1D1.
Participant ID Card	X						Participant identification card to be updated with treatment number at the time of treatment allocation.
Pembrolizumab Administration (Q3W)				X	X	X	**Cycle 2:** study treatment may be administered up to 3 days after the scheduled C2D1. **Cycle 3 and beyond:** study treatments may be administered up to 3 days before or after the scheduled Day 1.
V937 Administration for Subcutaneous Tumors	X	X	X	X	X		**Cycles 2-8:** V937 will be administered a maximum of 8 cycles; to be administered after a 200 mg dose of pembrolizumab infused over 30 min. For administration details, see Pharmacy Manual.
Clinical Procedures/Assessments							
Tumor Imaging (CT or MRI as indicated) (RECIST 1.1, and iRECIST Response Assessment)	←					→	Screening imaging should be performed within 28 days prior to C1D1. On-study imaging should be performed every 9 weeks (± 7 days) after C1D1 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 anticancer treatment. Refer to Site Imaging Manual for detailed information on medical photography.
Medical Photography (cutaneous lesions)	←					→	

Study Period:	Treatment Period						Notes
Treatment Cycle / Visit Title:	Cycle 1 (28 days)				Cycles 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.
Treatment Days per Cycle	1	3	5	8	1	1	
Scheduling/visit Window (Days)	± 0	± 1	± 1	± 1	+ 3	± 3	**C2D1:** The visit window is + 3 days. **C3D1 and subsequent cycles:** The visit window is ± 3 days. **All cycles:** These visit windows apply unless otherwise specified for individual process/procedure.
Brain imaging	←					→	Perform at screening ONLY for participants with previously documented brain metastases (to confirm stability) or as clinically indicated. On-study imaging to be performed if positive for brain metastases at screening and clinically indicated. Perform at CR for participants who were positive at baseline.
Additional Imaging (PET/CT, bone scan, etc.)	←					→	Obtain when clinically indicated. Arm 1: HNSCC Cohort B: Include head and neck CT
Lesion injection scan	←					→	Obtain for all injected lesions for every intratumoral injection performed. If imaging is used to guide injection (CT, ultrasound, fluoroscopy, etc.), capture images to document injected lesions. If injection by visualization or palpation, capture photographs with skin markers to show injected 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	**Cycle 1:** Measure within 1 h (± 30 min) prior to dosing, and 2, 4, and 6 h (± 30 min for each timepoint) after V937 administration. **Cycle 2 to Cycle 8:** Measure within 1 h (± 30 min) prior to dosing, and 2 and 4 h (± 30 min for each timepoint) after V937 administration. **Cycle 9 and beyond:** Measure within 1 h (± 30 min) prior to dosing with pembrolizumab on Day 1 of every cycle. If V937 is not administered at any cycle (eg, temporary withholding or discontinuation), vital signs are not required to be collected post-dose for that visit (ie, following administration of pembrolizumab).
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
Treatment Cycle / Visit Title:	Cycle 1 (28 days)				Cycles 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.
Treatment Days per Cycle	1	3	5	8	1	1	
Scheduling/visit Window (Days)	± 0	± 1	± 1	± 1	+ 3	± 3	**C2D1:** The visit window is + 3 days. **C3D1 and subsequent cycles:** The visit window is ± 3 days. **All cycles:** These visit windows apply unless otherwise specified for individual process/procedure.
Concomitant Medication	X	X	X	X	X	X	
AEs	◄———					———►	Continuous AE reporting from the time of treatment allocation.
Survival Status	◄———					———►	
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. Blood urea nitrogen is preferred; if not available, urea may be tested. Thyroid function: Samples are collected every other cycle (ie, Cycles 2, 4, 6, etc.). Total T4 and T3 are preferred over FT4 and FT3.
Chemistry Panel	X			X	X	X	
PT/INR and PTT or aPTT	X				X	X	
AST, ALT	X				X	X	
Thyroid Function Testing (T4 or FT4, T3 or FT3, TSH)					X	X	
Pregnancy test for WOCBP only (urine or serum β-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.

Abbreviations: AE=adverse event; AFP=alpha-fetoprotein; ALT=alanine aminotransferase; aPTT=activated partial thromboplastin time; AST=aspartate aminotransferase; β hCG=β human chorionic gonadotropin; C=cycle; CBC=complete blood count; CT=computed tomography; D=day; ECOG=Eastern Cooperative Oncology Group; F=free; h=hour(s); HbsAg=Hepatitis B surface antigen; HBV=Hepatitis B virus; INR=International Normalized Ratio; iRECIST=modified RECIST 1.1 for immune-based therapeutics; IT=intratumoral; IV=intravenous; MRI=magnetic resonance imaging; 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 Treatment Phase: Arm 2 Part I - Dose Escalation in Participants with Visceral Tumors

Table 3 Schedule of Activities for Treatment Phase: Arm 2 Part I - Dose Escalation in Participants with Visceral Tumors

Study Period:	Treatment Period				Notes
Treatment Cycle / Visit Title:	Cycle 1 (28 days)		Cycles 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, 9 doses) of treatment with V937.
Treatment Days per Cycle	1	8	1	1	
Scheduling/visit Window (Days)	± 0	± 1	± 5	± 5	
Treatment Assignment	X				Treatment assignment can occur up to 3 days prior to C1D1.
Participant ID Card	X				Participant identification card to be updated with treatment number at the time of treatment allocation.
Pembrolizumab Administration (Q3W)		X	X	X	**Cycle 1, Day 1:** Following the C1D1 dosing, participants must remain in the clinic for a minimum of 12 h for observation.
V937 Administration	X	X	X		**Cycle 2 and beyond:** Study treatments may be administered up to 5 days before or after the scheduled Day 1. **Cycles 2-8:** V937 will be administered after a 200 mg dose of pembrolizumab is infused over 30 min. For administration details, see Pharmacy Manual.
Clinical Procedures/Assessments					
Tumor Imaging (CT or MRI as indicated) (RECIST 1.1, and iRECIST Response Assessment)	←	—	—	→	Screening imaging should be performed -28 days prior to C1D1. On-study imaging should be performed every 9 weeks (± 7 days) after C1D1 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 anticancer treatment.
Additional Imaging (PET/CT, bone scan, etc.)	←	—	—	→	Obtain when clinically indicated.
Brain Imaging	←	—	—	→	Perform at screening ONLY for participants with previously documented brain metastases (to confirm stability) or who are clinically symptomatic. On-study imaging to be performed if positive for brain metastases at screening and clinically indicated. Perform at CR for participants who were positive at baseline.

Study Period:	Treatment Period				Notes
Treatment Cycle / Visit Title:	Cycle 1 (28 days)		Cycles 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, 9 doses) of treatment with V937.
Treatment Days per Cycle	1	8	1	1	
Scheduling/visit Window (Days)	± 0	± 1	± 5	± 5	
Lesion injection scan	←	———	———	→	Obtain for all injected lesions for every intratumoral injection performed. If imaging is used to guide injection (CT, ultrasound, fluoroscopy, etc.), capture images to document injected lesions. If injection by visualization or palpation, capture photographs with skin markers to show injected lesions.
Physical Examination	X	X	X	X	Directed physical examinations may be performed unless a full examination is deemed necessary. To be performed on Days 1and 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	Cycle 1: Measure within 1 h (± 30 min) prior to dosing, and 2, 4, and 6 h (± 30 min for each timepoint) after V937 administration. Cycle 2-8: Measure within 1 h (± 30 min) prior to dosing, and 2 and 4 h (± 30 min for each timepoint) after V937 administration. Cycle 9 and beyond: Measure within 1 h (± 30 min) prior to dosing with pembrolizumab on Day 1 of every cycle. If V937 is not administered at any cycle (eg, temporary withholding or discontinuation), vital signs are not required to be collected post-dose for that visit (ie, following administration of pembrolizumab).
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	
AEs	←	———	———	→	Continuous AE reporting from the time of treatment allocation.
Survival Status	←	———	———	→	

Study Period:	Treatment Period				Notes
Treatment Cycle / Visit Title:	Cycle 1 (28 days)		Cycles 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, 9 doses) of treatment with V937.
Treatment Days per Cycle	1	8	1	1	
Scheduling/visit Window (Days)	± 0	± 1	± 5	± 5	
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 C1D1 timepoint. For PT/INR/PTT/aPTT: PT/INR ≤6 h before every V937 ITu visceral administration. Blood urea nitrogen is preferred; if not available, urea may be tested. Thyroid function: Samples are collected every other cycle (ie, Cycles 2, 4, 6). Total T4 and T3 are preferred over FT4 and FT3.
Chemistry Panel	X	X	X	X	
PT/INR and PTT or aPTT	X	X	X	X[a]	
AST, ALT	X		X	X	
Thyroid Function Testing (T4 or FT4, T3 or FT3, TSH)			X	X	
Pregnancy test for WOCBP only (urine or serum β 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.

Abbreviations: AE=adverse event; ALT=alanine aminotransferase; aPTT=activated partial thromboplastin time; AST=aspartate aminotransferase; β hCG=β human chorionic gonadotropin; C=cycle; CBC=complete blood count; CT=computed tomography; D=day; ECOG=Eastern Cooperative Oncology Group; F=free; h=hour(s); INR=International Normalized Ratio; iRECIST=modified RECIST 1.1 for immune-based therapeutics; IT=intratumoral; IV=intravenous; min=minutes; MRI=magnetic resonance imaging; 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.

[a] Participants on anticoagulant therapy should be monitored throughout the study.

1.3.4 Schedule of Activities for Treatment Phase: Arm 2 Part II - Cohort Expansion

Table 4 Schedule of Activities for Treatment Phase: Arm 2 Part II - Cohort Expansion

Study Period:	Treatment Period				Notes
Treatment Cycle / Visit Title:	Cycle 1 (28 days)		Cycles 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, 9 doses) of treatment with V937.
Treatment Days per Cycle	1	8	1	1	
Scheduling Window (Days)	± 0	± 1	± 5	± 5	
Treatment Assignment	X				Treatment assignment can occur up to 3 days prior to C1D1.
Participant ID Card	X				Participant identification card to be updated with treatment number at the time of treatment allocation.
Pembrolizumab Administration (Q3W)		X	X	X	**Cycle 2 and beyond:** study treatments may be administered up to 5 days before or after the scheduled Day 1. Cycles 2-8: V937 will be administered after a 200 mg dose of pembrolizumab is infused over 30 min. For administration details, see Pharmacy Manual.
V937 Administration	X	X	X		
Clinical Procedures/Assessments					
Tumor Imaging (CT or MRI as indicated) (RECIST 1.1, and iRECIST Response Assessment)	⟷				Screening imaging should be performed 28 days prior to C1D1. On-study imaging should be performed every 9 weeks (± 7 days) after C1D1 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 anticancer treatment. HCC population: Imaging must include triphasic CT/MRI for liver evaluation. Details are provided in the SIM
Brain Imaging	⟷				Perform at screening ONLY for participants with previously documented brain metastases (to confirm stability) or who are clinically symptomatic. On-study imaging to be performed if positive for brain metastases at screening and clinically indicated. Perform at CR for participants who were positive at baseline.
Additional Imaging (PET/CT, bone scan, etc.)	⟷				Obtain when clinically indicated.

Study Period:	Treatment Period				Notes
Treatment Cycle / Visit Title:	Cycle 1 (28 days)		Cycles 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, 9 doses) of treatment with V937.
Treatment Days per Cycle	1	8	1	1	
Scheduling Window (Days)	± 0	± 1	± 5	± 5	
Lesion injection scan	←	———	———	→	Obtain for all injected lesions for every intratumoral injection performed. If imaging is used to guide injection (CT, ultrasound, fluoroscopy, etc.), capture images to document injected lesions. If injection by visualization or palpation, capture photographs with skin markers to show injected lesions.
Physical Examination	X	X	X	X	Directed physical examinations may be performed unless a full examination is deemed necessary. To be performed on Days 1 and 8 of Cycle 1; on Day 1 of every cycle thereafter
Weight	X		X	X	Every other cycle (ie, Cycles 1, 3, 5).
Vital Signs (temperature, pulse, respiratory rate, and blood pressure)	X	X	X	X	Cycle 1: Measure within 1 h (± 30 min) prior to dosing, and 2, 4, and 6 h (± 30 min for each timepoint) after V937 administration. Cycle 2 to Cycle 8: Measure within 1 h (± 30 min) prior to dosing, and 2 and 4 h (± 30 min for each timepoint) after V937 administration. Cycle 9 and beyond: Measure within 1 h (± 30 min) prior to dosing with pembrolizumab on Day 1 of every cycle. If V937 is not administered at any cycle (eg, temporary withholding or discontinuation), vital signs are not required to be collected post-dose for that visit (ie, following administration of pembrolizumab).
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	
AEs	←	———	———	→	Continuous AE reporting from the time of treatment allocation.
Survival Status	←	———	———	→	

Study Period:	Treatment Period				Notes
Treatment Cycle / Visit Title:	Cycle 1 (28 days)		Cycles 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, 9 doses) of treatment with V937.
Treatment Days per Cycle	1	8	1	1	
Scheduling Window (Days)	± 0	± 1	± 5	± 5	
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 C1D1 timepoint. For PT/INR/PTT/aPTT: PT/INR ≤6 h before every V937 ITu visceral administration. Blood urea nitrogen is preferred; if not available, urea may be tested. Thyroid function: Samples are collected every other cycle (ie, Cycles 2, 4, 6). Total T4 and T3 are preferred over FT4 and FT3.
Chemistry Panel	X	X	X	X	
PT/INR and PTT or aPTT	X	X	X	X[a]	
AST, ALT	X		X	X	
Thyroid Function Testing (T4 or FT4, T3 or FT3, TSH)			X	X	
Pregnancy test for WOCBP only (urine or serum β 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.
HCC (Cohort D) only: HBsAg and HBV titers			X	X	Applicable to participants with a known history of Hepatitis B infections/exposure or who have a diagnosis of HCC. Obtain **predose** to pembrolizumab, every 4th cycle (ie, Cycles 4, 8, 12).
HCC (Cohort D) only: AFP		X	X	X	Obtain **predose** to pembrolizumab infusion

Abbreviations: AE=adverse event; AFP=alpha-fetoprotein; ALT=alanine aminotransferase; aPTT=activated partial thromboplastin time; AST=aspartate aminotransferase; β hCG=β human chorionic gonadotropin; C=Cycle; CBC=complete blood count; CT=computed tomography; D=Day; ECOG=Eastern Cooperative Oncology Group; F=free; h=hour(s); HbsAg=Hepatitis B surface antigen; HBV=Hepatitis B virus; INR=International Normalized Ratio; iRECIST=modified RECIST 1.1 for immune-based therapeutics; IT=intratumoral; IV=intravenous; min=minutes; MRI=magnetic resonance imaging; 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.

[a] Participants on anticoagulant therapy should be monitored throughout the study.

1.3.5 Schedule of Activities for End of Treatment/Discontinuation and Posttreatment Phase: Arm 1, Arm 2 Part I Dose Escalation Phase, and Arm 2 Part II Expansion Phase

Table 5 Schedule of Activities for End of Treatment/Discontinuation and Posttreatment Phase: Arm 1, Arm 2 Part I Dose Escalation Phase, and Arm 2 Part II Expansion Phase

Study Period:	End of Treatment (EOT) / Discontinuation	Notes
Treatment Cycle / Visit Title:		
Treatment Days per Cycle:	At time of treatment discontinuation	
Scheduling Window (Days)	± 3	
Administrative Procedures		
Concomitant Medication	X	
Efficacy Procedures		
Tumor Imaging (CT or MRI as indicated) (RECIST 1.1, and iRECIST Response Assessment)	X	All imaging should be performed at the time of discontinuation. The evaluation window is ± 4 weeks.
Arm 1 only: Medical Photography (cutaneous lesions)	X	Perform brain imaging if positive for brain metastases at Screening and as clinically indicated. Perform at CR for participants who were positive for metastases at baseline.
Brain Imaging	X	
Additional Imaging (PET/CT, bone scan, etc.)	X	Obtain additional imaging as clinically indicated. HNSCC Cohort B: Include head and neck CT.
New Anticancer Therapy Status	X	
Safety Assessments and Procedures		
AE Monitoring	X	
Full Physical Examination	X	
Weight	X	
Vital Signs	X	Obtain temperature, pulse, respiratory rate, and blood pressure.
ECOG Performance Status	X	
CBC with Differential	X	See Procedures Manual for collection and management of laboratory samples.
Chemistry Panel	X	

Abbreviations: AE=adverse event; β hCG=β human chorionic gonadotropin; CBC=complete blood count; DNA=deoxynucleic acid; ECOG=Eastern Cooperative Oncology Group; iRECIST=immune-based RECIST; 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 results for the treatment of a variety of tumors. Despite such progress, many advanced cancer patients remain unresponsive to immunotherapy alone for reasons including, but not limited to: local immune tolerance at the tumor location, absence of effector T cells, and/or the development of resistance through a variety of adaptive mechanisms [Park, Y. J., et al 2018] [Sharma, P., et al 2017]. Efforts to combine preexisting and developmental therapies with anti-PD 1 agents such as conventional chemotherapy, dual CTLA-4, second-generation immunotherapy targets (TIGIT, LAG3, TIM-3, etc.), cancer vaccines, and oncolytic viruses are currently underway with the purpose of simultaneously targeting different hallmarks of tumor development/progression, which may have the potential to significantly enhance efficacy, response rates, and durability of clinical responses relative to single-agent first- and second-generation immunotherapies [Marshall, H. T. 2018].

V937 is a novel oncolytic viral therapy developed for ITu/intralesional administration to treat advanced cancers.

The use of oncolytic viruses to treat solid tumor malignancies has gained significant momentum over the last decade, with several oncolytic viruses active in Phase 2 and 3 clinical studies [Kaufman, H. L. 2010] [Rowan, K. 2010] [Senzer, N. N., et al 2009]. The antitumor activity of oncolytic viruses consists of 2 distinct mechanisms of action: first, selective replication within neoplastic cells that results in direct lysis of tumor cells; and second, the induction of a systemic antitumor immunity [Kaufman, H. L., et al 2015].

The first mechanism is achieved through the combination of viral receptor cell surface expression (ie, ICAM-1) followed by differential infectivity between normal cells and neoplastic cells. Although oncolytic viruses can enter both normal and cancer cells using cell surface receptors such as ICAM-1, abnormalities in a cancer cell's response to stress, cell signaling, and homeostasis provide a selective advantage for viral replication to occur. For example, a normal interferon response limits the ability of viruses to replicate within, and spread to, adjacent cells. However, cancer cells have defective interferon responses and toll-like receptor signaling due to pathologic alterations in metabolic pathways. Such deficiencies in interferon response enable oncolytic viruses to have a tumor-specific replication advantage [Krishnamurthy, S., et al 2006] [Stojdl, D. F., et al 2000]. Following viral replication, most oncolytic viruses induce cell death, which directly eliminates viable tumor cells, but also sets the stage for initiating a systemic immune response [Kaufman, H. L., et al 2015].

The second mechanism is achieved through the release of TAAs from tumor cells, which promotes an adaptive immune response leading to tumor regression at the injected site, as well as distant tumor sites unexposed to virus. Tumor cells can release PAMPs, which are common to both viruses and bacteria. The release of viral PAMPs and additional cellular DAMPs promote the maturation of APCs, which then activate antigen-specific CD4+ and CD8+ T-cell responses. Once activated, CD8+ T cells can expand into cytotoxic effector

cells, which can migrate into the tumor and mediate antitumor immunity upon antigen recognition [Kaufman, H. L., et al 2015].

V937 is being studied for the treatment of advanced/metastatic solid tumors in combination with pembrolizumab. This is a Phase 1B/2 study to assess the efficacy, safety, and tolerability of V937 administered ITu in combination with pembrolizumab IV.

2.1 Study Rationale

There is a great unmet medical need for therapeutic agents that may enhance the efficacy of immunotherapy. Non-clinical studies investigating the combination of ITu or IV V937 with two different immunomodulatory agents demonstrated that V937 in combination with anti-PD-1 and/or anti CTLA-4 blocking antibodies was generally well-tolerated in immunocompetent mouse models of melanoma and NSCLC. These studies showed that V937 has both antitumor activity and good tolerability in a monotherapy setting (CALM trial), as well as in combination with checkpoint inhibitors such as pembrolizumab and ipilimumab (CAPRA and MITCI trials, respectively).

In the CAPRA study, patients with advanced melanoma naïve to anti-PD-1/PD-L1 agents received the combination of ITu V937 and pembrolizumab. The study reported an overall response rate of 59% (16/27) in metastatic melanoma patients. Five Grade 3 or higher AEs were attributed to pembrolizumab in four participants. By contrast, few Grade 1 or 2 AEs were observed and attributable to V937 therapy. Thus, the combination of ITu V937 and pembrolizumab was generally well-tolerated among advanced melanoma patients.

In the MITCI study, patients with advanced melanoma who were naïve to checkpoint inhibitor therapy received the combination of ITu V937 and ipilimumab. The study reported an overall response rate of 50% (8/16) in metastatic melanoma patients. Additionally, a small number of PD-1 experienced patients were also enrolled on the trial and reported an overall response rate of 30% (3/10). As with the CAPRA study, patients reported AEs related to V937 which were largely limited to Grade 1 or 2 in severity.

The current study is intended to investigate whether ITu administration of V937 in combination with pembrolizumab in advanced/metastatic solid tumor malignancies can enhance the effectiveness of immunotherapy over immunotherapy monotherapy historical controls in different tumor types and metastatic lesion locations.

2.2 Background

V937 (Coxsackievirus A21; CVA21; CAVATAK®) is a non-genetically altered oncolytic virus derived from the *Kuykendall* strain of coxsackievirus A21 that has been propagated in cell culture. Coxsackievirus is a non-enveloped positive, single-stranded RNA virus with 4 capsid proteins which is a naturally-occurring human enterovirus. V937 has an acceptable preclinical safety profile and is in clinical development as an ITu/intralesional, intravesicular, and IV immunotherapy for advanced malignancies. For more specific details, refer to the V937 IB.

Pembrolizumab is a potent, humanized IgG4 mAb with high specificity of binding to the PD-1 receptor, thus inhibiting its interaction with PD-L1 and 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 several indications. For more details on specific indications refer to the pembrolizumab IB.

2.2.1 Pharmaceutical and Therapeutic Background

2.2.1.1 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 there is literature evidence for ICAM-1 receptor expression.

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 three major subclasses: polioviruses, echoviruses, and coxsackieviruses. The coxsackieviruses are further subdivided into Groups A (23 members) and B (6 members) [Zeichhardt, H. 2004].

Surface expression of ICAM-1 was identified as a necessary, but not entirely sufficient condition for successful lytic infection of 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 various other tissue types in the body.

Increased surface ICAM-1 expression levels is found on numerous malignant cells including, but not limited to: 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 demonstrated in metastatic human breast carcinoma cell lines [Rosette, C., et al 2005]. It is widely reported 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].

2.2.1.2 Pembrolizumab (MK-3475) Pharmaceutical and Therapeutic Background

The importance of intact immune surveillance function in controlling outgrowth of neoplastic transformations has been known for decades [Disis, M. L. 2010]. Accumulating evidence shows a correlation between TILs 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+ T-regs correlates with improved prognosis and long-term survival in solid malignancies, such as ovarian, colorectal, pancreatic, hepatocellular and renal cell carcinoma, and melanoma.

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

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

2.2.2 Preclinical and Clinical Studies

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

2.2.3 Ongoing Clinical Studies

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

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 investigational medicines.

Potential risks associated with the administration of V937 based on clinical data may include (but are not limited to) 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 IB and informed consent documents.

3 HYPOTHESES, OBJECTIVES, AND ENDPOINTS

There is no hypothesis testing in this study.

Throughout this protocol, the term RECIST 1.1 refers to a modification to RECIST 1.1 to allow a maximum of 10 target lesions in total and 5 per organ. Since ITu therapy is included by design in the study, RECIST 1.1 is also modified to specify that ITu injection by itself does not render a lesion non-evaluable. Refer to Section 4.2.1.1 for further details.

In male and female participants with advanced/metastatic solid tumors who are anti-PD-(L)1-treatment-naïve:

Arm 1: Subcutaneous Tumor Cohorts

Objectives	Endpoints
Primary	
• To evaluate the objective response rate (ORR) of V937 administered in subcutaneous tumors in combination with pembrolizumab per Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST 1.1) as assessed by the investigator.	• Objective response is a confirmed complete response (CR) or partial response (PR).

Objectives	Endpoints
Secondary	
• To determine the safety and tolerability of V937 administered in subcutaneous tumors in combination with pembrolizumab.	• Adverse event (AE) • Discontinuing a study intervention due to an AE
• To evaluate progression-free survival (PFS) and duration of response (DOR) of participants treated with V937 in subcutaneous tumors in combination with pembrolizumab per RECIST 1.1 as assessed by the investigator.	• PFS is defined as the time from the first dose of study treatment to the first documented disease progression or death due to any cause, whichever occurs first. • DOR is defined as the time from the first documented evidence of CR or PR until progressive disease (PD) or death due to any cause, whichever occurs first, in participants demonstrating PR or CR.
• To evaluate the ORR, PFS, and DOR of V937 administered in subcutaneous tumors in combination with pembrolizumab per RECIST 1.1 for immune-based therapeutics (iRECIST) criteria as assessed by the investigator.	• ORR • PFS • DOR
• To evaluate overall survival (OS) of participants treated with V937 in subcutaneous tumors in combination with pembrolizumab.	• OS is defined as the time from the first dose of study treatment to the date of death from any cause.

CCI

[redacted]

Objectives	Endpoints
CCI [redacted]	

Arm 2 Part I: Visceral Dose Escalation, and Arm 2 Part II: Visceral Tumor Expansion

Objectives	Endpoints
Primary	
• To determine the safety and tolerability and to establish a preliminary recommended Phase 2 dose (RP2D) of V937 administered in visceral tumors in combination with pembrolizumab.	• Dose limiting toxicity (DLT) • AE • Discontinuing a study intervention due to an AE
Secondary	
• To evaluate the ORR of V937 administered in visceral tumors at the preliminary RP2D with pembrolizumab per RECIST 1.1 and iRECIST criteria as assessed by the investigator.	• ORR
Tertiary/Exploratory	
CCI [redacted]	

Objectives	Endpoints
CCI	

4 STUDY DESIGN

4.1 Overall Design

This is a multicenter, worldwide, non-randomized, open-label, Phase 1b/2 study of V937 administered ITu in combination with pembrolizumab in participants with pathologically confirmed diagnosis of advanced/metastatic solid tumors where anti-PD1 therapy is recommended as first-line SOC, or for tumors unresponsive to standard treatments approved in the particular tumor subtype.

This study will evaluate the safety, tolerability, and preliminary efficacy of V937 administration in combination with pembrolizumab in 2 arms: Arm 1 includes subcutaneously-accessible tumors (Arm 1; Section 4.1.1), while Arm 2 includes tumors with visceral metastases. There are 2 parts to Arm 2. Arm 2 Part I consists of a dose escalation phase of V937 + pembrolizumab in solid tumors with metastatic lesions to the liver (Arm 2 Part I; Section 4.1.2). Following determination of a RP2D, we will proceed with Arm 2 Part II with 2 expansion cohorts in HCC and gastric carcinoma (Arm 2 Part II; Section 4.1.3).

Participants will enroll in Arm 1 and Arm 2 Part I simultaneously. In Arm 2 Part I, dose escalation will follow the mTPI design (Section 4.1.2). Per mTPI, the final number of participants enrolled in Arm 2 Part I will depend on empiric safety observations (DLTs) and final RP2D, which will have an upper boundary of 3×10^8 $TCID_{50}$ total dose per participant.

In Arm 1, preliminary efficacy will be evaluated using OR as assessed by the investigator using RECIST 1.1 as a primary endpoint. Safety and tolerability, PFS, and DOR will be evaluated using RECIST 1.1 as secondary endpoints. OR, PFS, and DOR will be evaluated using iRECIST 1.1 as additional secondary endpoints in addition to evaluation of OS. Finally, V937 PK/pharmacodynamic and exploratory biomarkers will be evaluated as tertiary/exploratory endpoints.

In Arm 2 Parts I and II, safety and tolerability and establishing RP2D of ITu administered V937 in combination with pembrolizumab in participants with visceral tumors will be assessed as a primary objective. The final RP2D for future studies will be confirmed using all available safety information (including early and late toxicities from Arm 1). OR will be evaluated using RECIST 1.1 and iRECIST criteria as a secondary endpoint. Finally, PFS and DOR will be evaluated using RECIST 1.1 and iRECIST criteria, in addition to OS, V937 PK/pharmacodynamic and exploratory biomarkers as tertiary/exploratory endpoints.

Participants will be monitored carefully for clinical and/or radiographic evidence of disease progression according to RECIST 1.1. However, iRECIST may be used by the investigator for treatment decisions. It will be at the discretion of the treating physician whether to continue a participant on study intervention until repeat imaging is obtained. Participants may continue to receive study intervention until tumor assessment is repeated ≥4 to 8 weeks later in order to confirm progressive disease by iRECIST per site assessment.

AEs will be evaluated by the investigator, according to criteria outlined in the NCI CTCAE v5.0, to establish safety and tolerability of V937 in combination with pembrolizumab as primary objectives in this study for all tumor cohorts.

The definition of DLTs and criteria for dose modification of V937 are outlined in Section 6.6.5 and 6.6.6.1. Pembrolizumab will be administered at a fixed dose of 200 mg every 3 weeks, which will not be modified.

Participants may receive study intervention (8 cycles of V937 in combination with up to 35 cycles of pembrolizumab) for approximately 2 years. Participants will be discontinued from the study treatment for any of the following reasons: progressive disease, unacceptable toxicity, cessation of treatment due to intercurrent illness, withdrawal of treatment by investigator, withdrawal of consent by participant, pregnancy of participant, noncompliance with study intervention or procedure requirements, completion of treatment, or cessation of treatment due to administrative reasons.

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

After confirmed progressive disease, each participant will be contacted every 12 weeks (84 ± 7 days) for survival until withdrawal of consent, loss to follow-up, death, or end of study, whichever comes first.

4.1.1 Arm 1: Subcutaneous Tumors

In Arm 1 of the study, approximately 30 participants (or less due to early study termination) will be enrolled into each of the following three tumor cohorts:

Cohort A: Triple negative breast cancer

Cohort B: Head and neck squamous cell carcinoma

Cohort C: Cutaneous squamous cell carcinoma

V937 will be administered at a maximum dose of 3×10^8 TCID50, administered ITu on Days 1, 3, 5, and 8 of Cycle 1 (28 days), then Day 1 of Cycle 2 through Cycle 8, for a maximum of 11 doses. V937 will be administered at a maximum dose of 3×10^8 TCID50. The administered dose is dependent on the volume of tumor injected (see Table 10 and Table 11). V937 is administered ITu on Days 1, 3, 5, and 8 of Cycle 1 (28 days), then Day 1 of Cycle 2 through Cycle 8, for a maximum of 11 doses. The dose of pembrolizumab in Arm 1 will remain constant at 200 mg IV every 3 weeks, for a maximum of 35 treatment cycles (approximately 2 years).

4.1.2 Arm 2 Part I: Dose Escalation in Metastatic Visceral Lesion Tumors

In Arm 2 Part I of the study, an mTPI design will be used to identify and confirm the RP2D of V937. Three predetermined dose levels of V937 will be evaluated:

Dose level 1: 3×10^7 (3E7) $TCID_{50}$

Dose level 2: 1×10^8 (1E8) $TCID_{50}$

Dose level 3: 3×10^8 (3E8) $TCID_{50}$

The number of participants enrolled per dose level during dose escalation will be based on the occurrence of DLTs per the mTPI design. The maximum RP2D will be capped at 3E8. The administered dose is dependent on the volume of tumor injected (see Table 10 and Table 11). V937 will be administered ITu on Days 1 and 8 of Cycle 1 (28 days), then Day 1 of Cycle 2 through Cycle 8, for a maximum of 9 doses. The dose of pembrolizumab will remain constant at 200 mg IV every 21 days for a maximum of 35 treatment cycles (approximately 2 years).

In Arm 2 Part I only, each of the first 3 participants in DL1 will undergo an observation period of 5 days before the next participant is dosed. Subsequent participants in all other dose levels will not undergo a staggered enrollment. Dose-finding and confirmation in Arm 2 Part I will end after 14 participants have been treated at any of the selected doses, per mTPI design. The pool-adjacent violators algorithm will be used to estimate the DLT rates across doses in each treatment arm under the assumption of monotonicity between DLT rates and dose levels [Ji, Y. and Wang, S.-J. 2013]. The dose with an estimated DLT rate closest to 30% may be treated as a preliminary RP2D. The totality of the data will be considered before deciding on the dose to carry forward to Arm 2 Part II.

4.1.3 Arm 2 Part II: Cohort Expansion in Metastatic Visceral Lesion Tumors

Arm 2 Part II supports the visceral cohort expansion phase, which will enroll 30 participants (or less due to early study termination) into each of the below cohorts:

Cohort D: Hepatocellular carcinoma

Cohort E: Gastric carcinoma

V937 will be administered at the RP2D (defined in Arm 2 Part I). V937 will remain at a constant dose administered ITu on Days 1 and 8 of Cycle 1 (28 days), then Day 1 of Cycle 2 through Cycle 8, for a maximum of 9 doses. The dose of pembrolizumab will remain constant at 200 mg IV every 21 days for a maximum of 35 treatment cycles (approximately 2 years).

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 two-arm, non-randomized, open-label study of ITu V937 + pembrolizumab IV in participants with advanced/metastatic solid tumors who have not received prior therapy with anti-PD-1/PD-L1 agents, T-VEC, or other oncolytic virus therapies.

V937 infects both normal and tumor cells by binding to ICAM-1, a viral cell surface receptor reported to be overexpressed in many different tumor types. Upon successful entry into a tumor cell, oncolytic viruses leverage a tumor cell's abnormal response to cell signaling, homeostasis, and stress in order to propagate an infection, which ultimately leads to cell lysis. Once lysis occurs, a cascade of events occurs involving the release of tumor-associated antigens as well as recruitment of antigen-presenting and cytotoxic T cells to the tumor site to affect an anti-tumor response [Krishnamurthy, S., et al 2006] [Stojdl, D. F., et al 2000].

4.2.1 Rationale for Endpoints

4.2.1.1 Efficacy Endpoints

Depending on the trial arm, the primary endpoints in this study include: OR (Arm 1) and DLT, AE and discontinuation of study intervention due to AE (Arm 2 Parts I and II). Secondary endpoints include PFS, DOR, OR by iRECIST and OS for Arm 1, and ORR by RECIST 1.1 and iRECIST for Arm 2 Part II. ORR is the proportion of participants with OR.

Tumor response will be assessed using RECIST 1.1 and iRECIST as assessed by investigator (see Section 8.2.1). Antitumor activity will be measured through such endpoints as the OR, 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 assess ORR based on RECIST 1.1 criteria as determined by the investigator. Objective response rate is an acceptable measure of clinical benefit that demonstrates superiority of a new antineoplastic therapy, especially if the magnitude of the effect is large and the therapy has an acceptable risk/benefit profile. The use of RECIST 1.1 to assess ORR is typically considered acceptable by regulatory authorities.

RECIST 1.1 will be used for efficacy measures as assessed by the investigator when determining eligibility (Section 8.2.1). 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 for a maximum of 10 target lesions in total and 5 per organ. Furthermore, because ITu therapy is included by design in this study, RECIST 1.1 is also modified to specify that ITu injection itself does not render a lesion non-evaluable.

RECIST 1.1 will be adapted to account for the unique tumor response characteristics seen following treatment with pembrolizumab (iRECIST, Section 8.2.5). 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 participants 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 PD by RECIST 1.1, but not by the immune-related response criteria [Wolchok, J. D., et al 2009] had longer overall survival than participants with PD by both criteria [Hodi, F. S., et al 2014]. Additionally, the data suggest that RECIST 1.1 may underestimate the benefit of pembrolizumab in approximately 15% of participants. These findings support the need to apply a modification to RECIST 1.1 that takes into account the unique patterns of atypical responses in immunotherapy and enables treatment beyond initial radiographic progression, if the participant is clinically stable.

Modified 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 FDA and the EMA [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.

For further information on iRECIST, see Section 8.2.5.

4.2.1.1.1 Response Rate Assessed by RECIST Version 1.1

RECIST 1.1 will be used to determine the objective response. Although traditional RECIST 1.1 references a maximum of 5 target lesions in total and 2 per organ, this protocol has implemented a modification to RECIST 1.1 to allow a maximum of 10 target lesions in total and 5 per organ. Furthermore, because ITu therapy is included by design in the study, RECIST 1.1 is also modified to specify that ITu injection itself does not render a lesion non-evaluable.

4.2.1.2 Safety Endpoints

In Arm 1, safety and tolerability of ITu V937 in combination with pembrolizumab is a secondary objective. In Arm 2, safety and tolerability of ITu V937 in combination with pembrolizumab is a primary objective. The primary safety analysis will be based on participants who experience toxicities as defined by NCI CTCAE v5.0 criteria. Safety will be assessed by quantifying the types and grades of toxicities experienced by participants who have received V937 in combination with pembrolizumab.

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

4.2.1.3 Pharmacokinetic Endpoints

A tertiary/exploratory objective of this study is to characterize the PK profile of V937 following ITu administration in combination with pembrolizumab. The serum concentrations of these agents will serve as the primary readout for the PK, and these data will be used to derive PK parameters of V937. Furthermore, the results of these analyses will be used in conjunction with the pharmacodynamics, and safety and exploratory endpoint data to help assess future dosing strategies for V937.

4.2.1.4 Pharmacodynamic Endpoints

4.2.1.4.1 Neutralizing V937 Antibodies

Neutralizing antibody responses at the beginning of each cycle will be determined to understand drug exposure and safety. The incidence of neutralizing antibodies will be evaluated and summarized over time. Correlations between the presence/absence of positivity for neutralizing antibodies, PK and pharmacodynamic markers, activity, and safety of V937 will be explored.

4.2.1.5 Planned Exploratory Biomarker Research

Cancer immunotherapies represent an important and novel class of antitumor agents. However, the mechanism of action of these exciting new therapies is not completely understood and much remains to be learned regarding how best to leverage these new drugs in treating patients. Thus, to aid future patients, it is important to investigate the determinants

of response or resistance to cancer immunotherapy and other treatments administered, as well as determinants of AEs in the course of our clinical studies. These efforts may identify novel predictive/PD biomarkers and generate information that may better guide single-agent and combination therapy with immuno-oncology drugs. To identify novel biomarkers, biospecimens (ie, blood components, tumor material) will be collected to support analyses of cellular components (eg, protein, DNA, RNA, metabolites) and other circulating molecules. Investigations may include but are not limited to:

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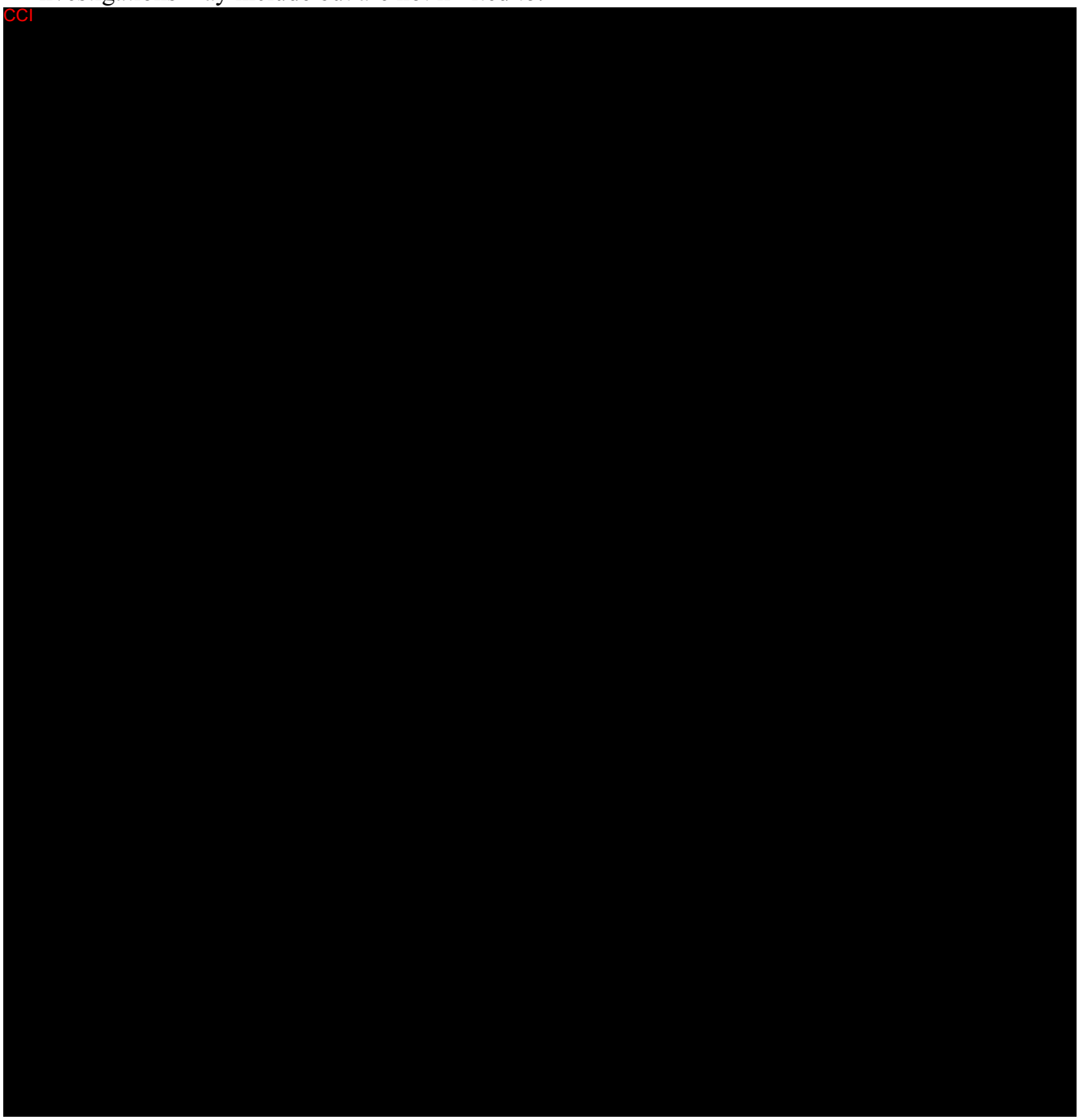

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4.2.1.6 Future Biomedical Research

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

Such research is for biomarker testing to address emergent questions not described elsewhere in the protocol (as part of the main study) and will only be conducted on specimens from appropriately consented participants. The objective of collecting/retaining specimens for future biomedical research is to explore and identify biomarkers that inform the scientific understanding of diseases and/or their therapeutic treatments. The overarching goal is to use such information to develop safer, more effective drugs/vaccines, and/or to ensure that participants receive the correct dose of the correct drug/vaccine at the correct time. The details of future biomedical research are presented in Appendix 6.

4.3 Justification for Dose

4.3.1 Starting Dose for This Study

4.3.1.1 Rationale for Starting and Maximum Dose of V937

Participants with Subcutaneous Tumors (V937 3 × 108 TCID50, ITu + Pembrolizumab 200 mg IV)

The clinical development of V937 has included safety and efficacy assessments using 3 different routes of administration: ITu, intravesical, and IV. CCI

The ITu dose for this study comes from Phase 2 studies conducted in participants with advanced melanoma (CALM and CAPRA). In the CALM study, late-stage melanoma participants were treated with V937 at a maximum dose of 3×10^8 $TCID_{50}$ and showed an ORR of 28%. Furthermore, in the CAPRA study, late-stage melanoma participants were treated with V937 at a dose of 3×10^8 $TCID_{50}$ in combination with pembrolizumab and showed an ORR of 59% [Pandha, H. S. 2018]. Evidence for biological activity and tolerability in the CALM and CAPRA studies supported moving forward with 3×10^8 $TCID_{50}$ RP2D in this study.

The dosing schedule in this study for ITu administration in Arm 1 is based on the CAPRA study. A maximum total dose of 3×10^8 $TCID_{50}$ will be administered on Days 1, 3, 5, 8, of Cycle 1, then every 3 weeks (Cycles 2-8) for a total of 11 doses.

The dose for pembrolizumab is 200 mg IV every 3 weeks. The pembrolizumab dose and schedule is identical to that used in the CAPRA study, which is based on the current SOC.

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

Participants with Visceral Tumors (V937 Dose Escalation and Cohort Expansion, ITu + Pembrolizumab 200 mg IV)

Injection into visceral tumors has not previously been tested with V937. Therefore, this regimen will employ dose escalation to determine the RP2D for visceral injections. Injection into visceral tumors is technically challenging compared to subcutaneous injections. Therefore, frequency of injections is limited to once-per-week.

V937 doses will be escalated at three different dose levels: 3×10^7 $TCID_{50}$; 1×10^8 $TCID_{50}$, and; 3×10^8 $TCID_{50}$. The total administered dose is dependent on the tumor size (see Table 11 and Table 13). The maximum injected doses for DL1, DL2 and DL3 of V937 will be 3×10^7 $TCID_{50}$, 1×10^8 $TCID_{50}$, and then 3×10^8 $TCID_{50}$. V937 is administered on

Day 1 and Day 8 of Cycle 1, and Day 1 of Cycles 2-8 for a total of 9 doses. The initial dose escalation will occur in all-comer tumors metastatic to liver. Note that injections will be direct into metastatic liver lesions, and NOT hepatic intraarterial injections. Multiple tumor histologies will be allowed in the visceral dose escalation cohort (including, but not limited to: NSCLC, CRC, and pancreatic carcinomas). After reaching a RP2D using the mTPI dose escalation scheme derived from Arm 2 Part I cohort, the trial will subsequently expand into 2 additional visceral tumor cohorts, HCC (Cohort D) and gastric carcinoma (Cohort E). These visceral cohorts will begin enrolling approximately 12 to 18 months following the completion of Arm 1 Part I dose escalation.

The dose for pembrolizumab is 200 mg IV every 3 weeks, which is based on the current SOC.

4.3.1.2 Rationale for Dose Interval and Escalation Increments

The starting dose and dose interval of V937 is based on integrating nonclinical toxicological, pharmacological, and efficacy data. Dose finding will proceed CCI

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[redacted]

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[redacted]

4.4 Beginning and End of Study Definition

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

4.4.1 Clinical Criteria for Early Study Termination

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

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

1. If the incidence and/or severity of adverse drug reactions or procedure-related complications suggest that the risk/benefit ratio is unfavorable to participant

2. If the incidence and/or severity of emerging effects/clinical endpoints suggest that the risk/benefit ratio to the study population is unacceptable

3. If there are plans to either modify or discontinue development of study drug

Ample notification will be provided if Sponsor decides to terminate the supply of V937 or pembrolizumab.

Upon study completion or early study termination, 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 V937-013.

5 STUDY POPULATION

Male and Female participants at least 18 years of age with advanced/metastatic solid tumors will be enrolled in this study. (See Appendix 7 for country-specific requirements.)

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:

5.1.1 Overall Inclusion Criteria

1. Has locally-advanced disease that is not amenable to surgery or radiation, or Stage IV advanced/metastatic solid tumor malignancies.

   Note: Tumor-specific criteria are provided in Section 5.1.2.1 (TNBC), Section 5.1.2.2 (HNSCC), Section 5.1.2.3 (cSCC), Section 5.1.3 (Visceral lesion dose escalation), Section 5.1.4.1. (HCC), and Section 5.1.4.2 (Gastric).

2. Has histologically- or cytologically-confirmed diagnosis of an advanced/metastatic solid tumor.

3. Has measurable disease by RECIST 1.1 criteria as assessed by investigator. Target lesions in a previously irradiated area will be considered measurable if progression has been demonstrated in such lesions.

4. Has submitted a baseline tumor sample for analysis (either *de novo* biopsy or an archival tumor block). For details on tumor tissue submission, see the Procedures Manual.

   Note: Arm 2 Part I: If tissue block is not available, participant may be enrolled if all other inclusion criteria are satisfied.

5. Has a performance status of 0 or 1 on the ECOG Performance Scale obtained within 72 hours prior to the first dose of study intervention.

6. If participants have known HIV-positive disease, participants must have well-controlled HIV on ART defined as:

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

   b. Must have achieved and maintained virologic suppression, defined as HIV RNA levels below 50, or LLOQ (below limits of detection), using a locally available assay at the time of screening.

   c. Must be on a stable regimen without any changes in drugs or dose modifications for a minimum of 4 weeks prior to study entry (Day 1) [Uldrick, T. S., et al 2019].

7. Demonstrate adequate organ function as defined in Table 7. These laboratory samples must be collected within 72 hours prior to the first dose of study intervention.

Table 7 Adequate Organ Function Laboratory Values for Non-HCC Population

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

Abbreviations: 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; PT=prothrombin time; ULN = upper limit of normal.

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

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

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.

Refer to Section 5.1.4.1 for laboratory value requirements for the HCC population.

Demographics

8. Is male or female, from ≥18 years of age inclusive, at the time of signing the 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.

9. Male participants are eligible to participate if they agree to the following during the intervention period for and for at least 120 days after the last dose of 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.

Note: For male participants on pembrolizumab only, no contraception measures are needed.

Female Participants

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

10. 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 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 located 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.

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

Informed Consent

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

5.1.2 Arm 1: Subcutaneously Accessible Tumors

12. Have at least 1 injectable lesion amenable to injection and/or biopsy. Biopsy may be performed via visual inspection, ultrasound guidance, or cross-sectional imaging. Injections for cutaneous and subcutaneous lesions may be done by visual inspection, ultrasound guidance and/or palpation. Lesion(s) must be measurable and meet one of the following criteria:

    - 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 solid tumor participants. The longest diameter for an injectable lesion must be ≤10 cm for both solid tumors and nodal lesions in solid tumor participants.

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

5.1.2.1 Specific Inclusion Criteria for Cohort A: Advanced/Metastatic Triple Negative Breast Cancer

13. Has locally-recurrent, inoperable OR metastatic breast cancer treated with or must have received at least 1 prior line of chemotherapy in the metastatic setting with skin involvement and/or subcutaneous lesions or accessible lymph nodes amenable to local injection.

    Note: An exception would be allowed for patients who are not eligible to receive chemotherapy.

    Chemotherapy ineligibility would be determined by a medical oncologist and may include reasons such as, but not limited to, comorbid medical conditions or lifetime chemotherapy dose. In such cases, a reasonable alternative would be consideration of participation in a clinical trial.

    Note: For participants with prior XRT, lesion(s) in a previously irradiated filed must have documented progression on scan to be considered amenable to injection.

14. Has diagnosis of triple-negative breast cancer (estrogen receptor, progesterone receptor, and HER2-receptor negative status).

15. Has been treated with (neo)adjuvant anthracycline (unless anthracycline was contraindicated based on treating physician's medical judgment).

Refer to Section 5.1.1 for additional inclusion criteria that apply to all tumor cohorts.

5.1.2.2 Specific Inclusion Criteria for Cohort B: Advanced/Metastatic Head and Neck Squamous Cell Carcinoma

16. Has histologically confirmed advanced or metastatic HNSCC of the oral cavity, oropharynx, hypopharynx, and/or larynx considered incurable and/or treated with no more than 1 previous line of therapy.

17. Tumors must be PD-L1+ (CPS ≥1).

18. Has documentation of HPV status for oropharyngeal cancers only.

    Note: Oral cavity, hypopharynx, and larynx cancers are exempt from requirement for HPV testing since these anatomical locations typically exhibit a low incidence of HPV positivity.

    Note: If a participant has not been previously tested, then status should be reported as "unavailable."

Refer to Section 5.1.1 for additional inclusion criteria that apply to all tumor cohorts.

5.1.2.3 Specific Inclusion Criteria for Cohort C: Locally-advanced/Metastatic Cutaneous Squamous Cell Carcinoma

19. Has histologically confirmed cSCC as the primary site of malignancy (metastatic skin involvement from another primary cancer or from cancers of unknown primary are not eligible).

    Note: Squamous cell carcinomas with primary tumor sites involving the anogenital region (eg, penis, scrotum, vulva, or perianal region) are not eligible.

20. Recurrent/metastatic disease only: Has metastatic disease defined as disseminated disease distant from the initial/primary site of diagnosis and/or with a history of locally-recurrent disease previously treated with surgery and/or radiotherapy, which is now incurable.

21. Locally-advanced disease only: Participants ineligible for surgical resection. Contraindications to surgery are defined as:

    - cSCC recurring in the same location following two or more surgical procedures, and not amenable to curative resection
    - cSCC with significant local invasion preventing total resection
    - cSCC in anatomically challenging locations where surgery is not feasible (ie, would cause severe dysfunction and disfigurement of structures such as the nose, ears, eyes, or limb amputation)

22. Locally-advanced disease only: Received prior XRT to the index site or deemed ineligible for XRT.

Refer to Section 5.1.1 for additional inclusion criteria that apply to all tumor cohorts.

5.1.3 Arm 2 Part I: Visceral Lesion Dose Escalation and Confirmation

23. Has a histologically-confirmed advanced/metastatic solid tumor that has progressed on all treatment known to confer clinical benefit. Solid tumors of any type are eligible for enrollment with exception noted below.

    Note: HCC tumors are excluded from the visceral dose escalation cohort.

24. Has metastatic liver lesion(s) not exceeding one-third of the total liver volume AND has a minimum of one injectable liver lesion with the following criteria:

    - Accessible for image-guided injection and biopsy via ultrasound guidance or cross-sectional imaging (CT/MRI)

      Note: If planning use of CT fluoroscopy for visceral lesion injections, must check that the participant has a CrCl ≥60 mL/min within 12 hours prior to procedure.

- lesion(s) must be ≥1 cm in longest diameter and ≤10 cm in longest diameter

Refer to Section 5.1.1 for additional inclusion criteria that apply to all tumor cohorts

5.1.4 Arm 2 Part II: Visceral Cohort Expansion

5.1.4.1 Specific Inclusion Criteria for Cohort D: Hepatocellular Carcinoma

25. Has advanced HCC following progression on, or intolerance to, sorafenib or lenvatinib with no curative options.

26. Has diagnosis of HCC confirmed by radiology, histology, or cytology (fibrolamellar and mixed hepatocellular/cholangiocarcinoma subtypes not eligible for enrollment).

    a. Radiologic diagnosis is defined as: evidence of liver cirrhosis and a liver mass measuring at least 1 cm with characteristic vascularization (intense enhancement in hepatic arterial-dominant phase and contrast washout in late portal venous phase) on triphasic CT or MRI scan.

27. Has Child-Pugh Class A score (see Appendix 9).

28. If a participant has a history of HCV infection, then the participant must have been successfully treated for this condition, which is defined as SVR12. Eligible participants must wait for a period of ≥4 weeks between achievement of SVR12 and start of study drug(s). (See Section 6.6.3)

29. If participant has a known history of chronic hepatitis B infection and/or exposure and has received treatment with anti-hepatitis B therapy. (See Section 6.6.3)

    a. Controlled (treated) hepatitis B participants will be allowed if they meet the following criteria: Antiviral therapy for HBV must have been given for a minimum of 12 weeks. HBV viral load must be less than 100 IU/mL prior to first dose of study intervention. **Participants on active HBV therapy with viral loads under 100 IU/mL should stay on the same therapy throughout study treatment**.

    b. Participants who are anti-HBc (+), negative for HBsAg, negative or positive for anti-HBs, and who have an HBV viral load under 100 IU/mL, do not require HBV anti-viral prophylaxis.

Refer to Section 5.1.3 for visceral lesion dose expansion inclusion criteria.

Refer to Section 5.1.1 for additional inclusion criteria that apply to all tumor cohorts.

30. Demonstrate adequate organ function as defined in Table 8. These laboratory samples must be collected within 72 hours prior to the first dose of study intervention.

Table 8 Adequate Organ Function Laboratory Values for HCC Population

System	Laboratory Value
Hematological	
Absolute neutrophil count	>1,200/mcL
Platelets	>60,000/mcL
Hemoglobin	≥8 g/dL without transfusion or EPO dependency within 7 days.
Renal	
Creatinine OR Measured or calculated[a] CrCl (GFR can also be used in place of CrCl)	≤1.5 × ULN or ≥30 mL/min for participants with creatinine levels >1.5 × ULN ≥60 mL/min required prior to CT fluoroscopy guided injections
Hepatic	
Total bilirubin	≤2 mg/dL or Direct bilirubin ≤ULN for participants with total bilirubin levels >2 mg/dL
AST (SGOT) and ALT (SGPT)	≤5 × ULN
Albumin	≥3.0 g/dL *Note: No albumin supplement (or BCAA) allowed within the last 14 days.*
Coagulation	
International Normalized Ratio (INR) or Prothrombin Time (PT) Activated Partial Thromboplastin Time (aPTT)	<1.5 × ULN (unless participant is receiving anticoagulant therapy, in which case PT/INR or aPTT should be within the therapeutic range of intended use of anticoagulants)

Abbreviations: ALT (SGPT) = alanine aminotransferase (serum glutamic pyruvic transaminase); aPTT=activated partial thromboplastin time; AST (SGOT) = aspartate aminotransferase (serum glutamic oxaloacetic transaminase); BCAA=branched-chain amino acids; CrCl=creatinine clearance; CT=computed tomography; EPO=erythropoietin; GFR = glomerular filtration rate; INR=International Normalized Ratio; PT=prothrombin time; ULN = upper limit of normal.

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

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

5.1.4.2 Specific Inclusion Criteria for Cohort E: Gastric Carcinoma

31. Has histologically- or cytologically-confirmed diagnosis of locally-advanced, unresectable or metastatic gastric or GEJ adenocarcinoma:

    a. must have received at least one prior line of therapy that includes a platinum/fluoropyrimidine doublet or triplet regimen. Progression can be confirmed by CT or PET/CT scan or clinical evidence (eg, cytology report from ascites and/or pleural fluid).

    b. must have proven clinical progression 6 months following (or during) last dose of adjuvant or neo-adjuvant therapy provided participant previously received a platinum/fluoropyrimidine doublet.

32. Participants with HER2 negative status; or, those with HER2 positive status AND documented disease progression on a prior regimen containing trastuzumab.

    Note: HER2 negative is defined as IHC (0, or 1+) or fluorescence in situ hybridization (FISH) negative (HER2:CEP17 ratio <2 with average HER2 copy number <4.0 signals/cell)

Refer to Section 5.1.3 for visceral expansion cohort inclusion criteria.

Refer to Section 5.1.1 for additional inclusion criteria that applies to all tumor cohorts.

5.2 Exclusion Criteria

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

5.2.1 Overall Exclusion Criteria

1. Has had chemotherapy, definitive radiation, or biological cancer therapy within 4 weeks (2 weeks for palliative radiation) prior to first dose of study intervention or has not recovered to CTCAE Grade 1 or better.

2. If major or minor surgery was performed at/near the area being considered for injection, participant must be recovered from toxicity and/or complications of intervention.

3. Has had injection, or radiation therapy of >30 Gy, participant must be recovered from toxicity and/or complications of intervention.

4. Has a history of second malignancy, unless potentially curative treatment has been completed with no further evidence of disease for ≥5 years.

    Note: Time requirement of ≥5 years without further evidence of disease does not apply to:

    - the tumor for which the participant is enrolled in the trial

- participants who underwent successful definitive resection of basal cell carcinoma of the skin; superficial bladder cancer; in situ cervical cancer, or other in situ cancers

5. Has known active CNS metastases and/or carcinomatous meningitis. Participants with treated brain metastases may participate if lesions are radiologically stable.

   Note: Repeat imaging should be done during screening with demonstration of stable lesions for a minimum of 4 weeks, and without need the for steroid therapy for at least 2 weeks prior to first dose of study intervention.

6. Has an active infection requiring therapy (exceptions: HIV criteria outlined in Section 5.1.1 and HBV and HCV criteria for HCC cohort as stated in Section 5.1.4.1).

7. Has a history of interstitial lung disease.

8. Has a history of noninfectious pneumonitis requiring active steroid therapy or ongoing pneumonitis.

9. Has an active autoimmune disease that required systemic treatment in the past 2 years (ie, necessitating 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 (steroid use ≤10 mg prednisone, or its equivalent, daily) is not considered a form of systemic treatment and is allowed. The use of non-systemic steroids is permitted.

10. Participants with known Hepatitis B or C infections or known to be positive for HBsAg/HBV DNA or Hepatitis C Antibody or RNA. Active Hepatitis C is defined by a known positive Hep C Ab result and known quantitative HCV RNA results greater than the lower limits of detection of the assay.

    Note: See Section 5.1.4.1 for hepatitis guidelines in HCC cohort only. (See Appendix 7 for country-specific requirements.)

11. Participants with a history of Kaposi's sarcoma and/or Multicentric Castleman's Disease.

12. Has known hypersensitivity to V937 and/or pembrolizumab or any of their excipients. (See Appendix 7 for country-specific requirements.)

13. Has known psychiatric or substance abuse disorder that significantly interferes with cooperation with requirements of the trial.

Prior/Concomitant Therapy

14. Has received prior therapy with anti-PD-1/PD-L1 agents, T-VEC or any other oncolytic virus therapies.

15. Has received a live or live-attenuated vaccine within 30 days prior to first dose of study intervention. Administration of killed vaccines is allowed.

    Refer to Section 6.5.2 for information on COVID-19 vaccines.

Prior/Concurrent Clinical Study Experience

16. 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 if it has been 4 weeks after the last dose of the previous investigational agent.

Other Exclusions

17. 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.

5.2.2 Arm 2 Part II: Visceral Cohort Expansion

5.2.2.1 Specific Exclusion Criteria for Cohort D: Hepatocellular Carcinoma

18. Has had esophageal or gastric variceal bleeding within the last 6 months. All participants should undergo screening for esophageal varices, unless such screening has been performed in the past 12 months before first dose of treatment. If varices are present, they should be treated according to institutional standards before receiving any study intervention.

19. Has Vp4, inferior vena cava, or cardia involvement from HCC based on imaging.

20. Has had clinically diagnosed hepatic encephalopathy in the 6 months prior to initiation of study intervention. Participants on standing rifaximin or lactulose to control hepatic encephalopathy are not eligible for the study.

Refer to Section 5.2.1 for additional exclusion criteria that apply to all tumor cohorts.

5.2.2.2 Specific Exclusion Criteria for Cohort E: Gastric Carcinoma

21. Has squamous cell or undifferentiated gastric cancer.

Refer to Section 5.2.1 for additional exclusion criteria that apply to all tumor cohorts.

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

No restrictions required.

5.3.3 Activity Restrictions

No restrictions required.

5.4 Screen Failures

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

Participants who fail screening may be re-screened for eligibility following consultation between the investigator and the Sponsor and written documentation of the collaborative decision on participant management.

5.5 Participant Replacement Strategy

A participant who discontinues from study intervention(s) 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 are 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 9.

Country-specific differences are noted in Appendix 7.

Table 9 Study Interventions

Arm Name	Arm Type	Inter-vention Name	Inter-vention Type	Dose Formu-lation	Unit Dose Strength(s)	Dosage Level(s)	Route of Adminis-tration	Regimen/ Treatment Period/ Vaccination Regimen	Use	IMP or NIMP/ AxMP	Sourcing
Arm 1	Experi mental	V937	Biological/ Vaccine	Solution for Infusion	7.5×10^7 $TCID_{50}$/ mL	3×10^8 $TCID_{50}$ (assume 4 mL injected)	ITu Injection	Day 1, 3, 5, and 8 of Cycle 1 (28-day cycle) Day 1 of Cycles 2 to 8 (21-day cycles)	Test Product	IMP	Provided centrally by Sponsor
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 2 Part I	Experi mental	V937	Biological/ Vaccine	Solution for Infusion	DL1, DL2, and DL3[a]: 7.5×10^7 $TCID_{50}$/ mL	DL1: 3×10^7 DL2: 1×10^8 DL3: 3×10^8 $TCID_{50}$ (assume 4 mL injected)	ITu Injection	Day 1 and 8 of Cycle 1 (28-day cycle) Day 1 of Cycles 2 to 8 (21-day cycles)	Test Product	IMP	Provided centrally by Sponsor
Arm 2 Part I	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	Inter-vention Name	Inter-vention Type	Dose Formu-lation	Unit Dose Strength(s)	Dosage Level(s)	Route of Adminis-tration	Regimen/ Treatment Period/ Vaccination Regimen	Use	IMP or NIMP/ AxMP	Sourcing
Arm 2 Part II	Experi mental	V937	Biological/ Vaccine	Solution for Infusion	DL1, DL2, and DL3: 7.5×10^7 $TCID_{50}$/ mL	RP2D DL1: 3×10^7, DL2: 1×10^8, or DL3: 3×10^8 $TCID_{50}$ (assume 4 mL injected)	ITu Injection	Days 1 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 Part II	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

Abbreviations: AxMP = Auxiliary Medicinal Product; IMP=Investigational Medicinal Product; ITu=intratumoral; IV=intravenous; NIMP=Non-Investigational Medicinal Product; RP2D=Recommended Phase 2 Dose; SoC=Standard of care; $TCID_{50}$= 50% tissue culture infectious dose.

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

Participants in Arm 2 Part I will be observed for 12 hours following the Cycle 1 Day 1 ITu administration of V937 (see Section 6.1.2.2 for additional details). All other study interventions will be administered on an outpatient basis. (See Appendix 7 for country-specific requirements.)

All products indicated in Table 9 will be provided centrally by the Sponsor.

Refer to Sections 6.1.1, 6.1.2, and 8.1.8, for details regarding administration of the study interventions.

6.1.1 Pembrolizumab Administration

Participants in Arms 1 and 2 will receive pembrolizumab on Day 8 of Cycle 1 (28-day cycle) and on Day 1 of Cycles 2-35 (21-day cycles). A 200 mg IV dose of pembrolizumab will be infused over 30 minutes. For administration details, see the Pharmacy Manual.

6.1.2 V937 Administration for Arm 1 and Arm 2

When selecting lesions for injection during the pre-treatment period, we recommend designating at least 1 lesion(s) to remain noninjected for the duration of study in order to determine maximal treatment effect (ie, abscopal effect). However, in the event such lesions enlarge and/or all other lesions cannot be injected, then such pre-designated lesions may be injected at a later date.

6.1.2.1 V937 Administration in Arm 1: Subcutaneous Tumors

In Arm 1, V937 will be administered into subcutaneous lesions that are visible, palpable, or visualizable by ultrasound guidance. Participants will receive V937 on Days 1, 3, 5, and 8 during Cycle 1 (28-day cycle), and Day 1 of Cycles 2-8 (21-day cycles). V937 administration will occur 0.5 to 12 hours after a 200 mg dose of pembrolizumab infused over 30 minutes. For administration details, see the Pharmacy Manual.

6.1.2.2 V937 Administration in Arm 2, Part I: Visceral Tumors

In Arm 2 Part I, V937 will administered into visceral tumors via image-guidance such as ultrasound or CT. Participants will receive V937 on Days 1 and 8 during Cycle 1 (28-day cycle) and Day 1 of Cycles 2-8 (21-day cycles). V937 administration will occur 0.5 to 12 hours after a 200 mg dose of pembrolizumab infused over 30 minutes. For administration details, see the Pharmacy Manual.

6.1.2.3 V937 Administration in Arm 2, Part II: Visceral Expansion Cohorts

In Arm 2 Part II, V937 will be administered into visceral lesions via image-guidance such as ultrasound or CT. Participants will receive V937 on Day 8 of Cycle 1 (28-day cycle) and Day 1 of Cycle 2-8 (21-day cycles). V937 administration will occur 0.5 to 12 hours after a 200 mg IV dose of pembrolizumab is infused over 30 minutes. For administration details, see the Pharmacy Manual.

6.1.2.4 V937 Administration in Arms 1 and 2: Target Lesion Size and Injection Volume

Each participant will receive V937 in a volume ranging from 0.5 to 4 mL of injectate for Arm 1 cohorts, and 1 to 4 mL in Arm 2 cohorts. The amount of V937 received will depend on both the number and size of lesions planned for actual injection of drug. See Table 10 and Table 11 for volume administration range. The amount of injectate volume delivered to each lesion will be determined by measuring the longest diameter of target lesion as shown in Table 10 and Table 11 (short axis for lymph nodes). V937 should be prepared in separate syringes for each individual lesion injection since the actual delivered dose will depend on target lesion size. Not all participants or lesions will receive the same total dose of drug. Documentation of dose volume administered per lesion will be recorded.

Prioritization of lesion(s) to be injected is as follows:

- first: new or progressing lesion(s)
- second: largest lesion(s)
- third: injection of any additional lesions (up to a total injectate volume of 4 mL spread across a maximum of 5 individual lesions)

Dose administration details:

- Table 10: describes the maximum total volume of V937 administered in Arm 1 (estimated maximum injectate volumes are scaled to lesion size).
- Table 11: describes the maximum total volume of V937 administered in Arm 2 Parts I and II (estimated maximum injectate volumes are scaled to lesion size).
- Table 12: describes the maximum total dose possible per participant in Arm 1 (ie, cohorts A, B, C), as well as total dose of V937 per mL of injectate.
- Table 13: describes the maximum total dose possible per participant in Arm 2 Part I (visceral dose escalation) in each of 3 predefined dose levels per mTPI design (DL1, DL2, DL3).

Table 10 Maximum Total Volume of V937 Administered in Arm 1 Scaled to Lesion Size

Lesion size (longest diameter in cm)[a]	Estimated max injection capacity (mL)
>5	4
>2.5 to 5	2
>1.5 to 2.5	1
≥0.5 to 1.5	0.5

a. Shortest axis should be used if lesion is a lymph node

Final dose administered for Arm 1, Cohorts A, B, and C depends on the designated lesion volume (see Table 10).

Table 11 Maximum Total Volume of V937 Administered in Arm 2 (Parts I and II) Scaled to Lesion Size

Lesion size (longest diameter in cm)[a]	Estimated max injection capacity (mL)
>5	4
>2.5 to 5	2
≥1.0 to 2.5	1

a. Shortest axis should be used if lesion is a lymph node

Final dose administered for Arm 2, Parts I and II depends on the designated lesion volume (see Table 11).

Table 12 Maximum Total Dose of V937 Possible per Participant as Well as Total Dose of V937 per mL of Injectate Given (Arm 1)

Dose level	Maximum dose per participant (assuming 4 mL volume limit)	Concentration of V937 administered per mL
Subcutaneous	3×10^8 $TCID_{50}$	7.5×10^7 $TCID_{50}$

Abbreviations: $TCID_{50}$= 50% tissue culture infectious dose.

Final administered dose is dependent on injected tumor volume (see Table 10 and Table 11).

Table 13 Maximum Total Dose of V937 Possible per Participant at Prespecified Dose Levels per mTPI Design (Arm 2 Part I)

Dose level	Maximum dose per participant (assuming 4 mL volume limit)	Concentration of V937 administered per mL
Visceral DL1	3×10^7 $TCID_{50}$	7.5×10^6 $TCID_{50}$
Visceral DL2	1×10^8 $TCID_{50}$	2.5×10^7 $TCID_{50}$
Visceral DL3	3×10^8 $TCID_{50}$	7.5×10^7 $TCID_{50}$

Abbreviations: $TCID_{50}$= 50% tissue culture infectious dose.

6.2 Preparation/Handling/Storage/Accountability

6.2.1 Dose Preparation

Details on the preparation and administration of V937 and pembrolizumab are provided in the respective 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 4.3.1.1.

6.2.2 Handling, Storage, and Accountability

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

Only participants enrolled in the study may receive study intervention, and only authorized site staff may supply or administer study intervention. All study interventions must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff.

The investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).

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

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

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

6.3 Measures to Minimize Bias: Randomization and Blinding

6.3.1 Intervention Assignment

Intervention allocation will occur centrally using an IVRS/IWRS. Participants will be assigned to 1 of 2 treatment arms.

Study intervention will be allocated by nonrandom assignment in both treatment arms. Arm 1 and Arm 2 Part I will undergo simultaneous enrollment. Investigator assessment of eligibility and tumor type will guide participant allocation to Arm1 or Arm 2 Part I. In Arm 2 Part I only, each of the first 3 participants in DL1 will undergo an observation period of 5 days before the next participant is dosed. All other participants enrolled (Arm 1; Arm 2 Part I participant 4 and greater; Arm 2 Part I dose levels 2 and 3; Arm 2 Part II) will not be staggered. Each new dose level will open for enrollment without delay once the 28-day DLT observation period of the previous dose level is completed and a dose escalation decision is made.

Arm 2 Part II will begin enrollment once the participants in Arm 2 Part I complete the DLT evaluation and a RP2D decision has been made; IVRS/IWRS will assign participants to 1 of 2 cohorts by tumor type.

6.3.2 Stratification

No stratification will be used in the study.

6.3.3 Blinding

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

6.4 Study Intervention Compliance

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

Interruptions from the protocol-specified treatment plan for >6 weeks between pembrolizumab doses for non-drug-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 >6 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 vaccines specifically prohibited in the exclusion criteria are not allowed during the ongoing study. If there is a clinical indication for any medication or vaccination specifically prohibited, discontinuation from study intervention may be required. The investigator should discuss any questions regarding this with the Sponsor's Clinical Director. The final decision on any supportive therapy rests with the investigator and/or the participant's primary physician. However, the decision to continue the participant on-study 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 CRF including all prescription, 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 30 days before the first dose of study intervention and 30 days after the last dose of study intervention should be recorded. Concomitant medications administered after 30 days after the last dose of study intervention should be recorded for SAEs and 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: (See Appendix 7 for country-specific requirements.)

- 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 after the DLT observation period for the participant to be considered evaluable for DLT.

  Note: Palliative radiation to non-target lesion(s) for symptomatic relief is permitted at the investigator's discretion. However, the participant must have clear, measurable disease outside the irradiated field. Palliative radiation to target lesion(s) will render those lesions as clinically progressed, and non-evaluable for the remainder of trial.

- Live or live-attenuated vaccines within 30 days prior to the first dose of study intervention and while participating in the study. Administration of killed vaccines are allowed.

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

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

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

6.5.3 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 14. 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 14 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) [Arm 1 and Arm 2 (Part I & II)]

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 v5.0 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 14.

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 are fatigue, chills, pyrexia and influenza-like illness. These events are mainly Grade 1 or 2 in severity, transient, and easily managed.

Treatment-related AEs specific to V937 ITu administration include injection site pain, erythema, pruritis, discharge and edema reactions. These AEs are largely risks associated with performing an intralesional injection procedure and have not been reported when V937 has been administered via IV or intravesicular routes. These symptoms have been largely mild in their severity (ie, Grade 1 or 2).

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 3 AEs reoccur in the same participants or are > Grade 3. For other instances in which dose interruption(s) may be required, discuss with Sponsor.

Within-participant dose escalation is not permitted.

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 14.(See Appendix 7 for country-specific requirements.)

Table 14 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		
Diarrhea/Colitis	Grade 2 or 3	Withhold	• Administer corticosteroids (initial dose of 1 to 2 mg/kg prednisone or equivalent) followed by taper	• Monitor participants for signs and symptoms of enterocolitis (ie, diarrhea, abdominal pain, blood or mucus in stool with or without fever) and of bowel perforation (ie, peritoneal signs and ileus) • Participants with ≥Grade 2 diarrhea suspecting colitis should consider GI consultation and performing endoscopy to rule out colitis • Participants with diarrhea/colitis should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion
	Recurrent Grade 3 or Grade 4	Permanently discontinue		

irAEs	Toxicity Grade (CTCAE v5.0)	Action With Pembrolizumab Monotherapy, Coformulations or IO Combinations	Corticosteroid and/or Other Therapies	Monitoring and Follow-up
AST or ALT Elevation or Increased Bilirubin	Grade 2 [a]	Withhold	• Administer corticosteroids (initial dose of 0.5 to 1 mg/kg prednisone or equivalent) followed by taper	• Monitor with liver function tests (consider weekly or more frequently until liver enzyme value returned to baseline or is stable)
	Grade 3 [b] or 4 [c]	Permanently discontinue	• Administer corticosteroids (initial dose of 1 to 2 mg/kg prednisone or equivalent) followed by taper	
T1DM or Hyperglycemia	New onset T1DM or Grade 3 or 4 hyperglycemia associated with evidence of β-cell failure	Withhold [d]	• Initiate insulin replacement therapy for participants with T1DM • Administer antihyperglycemic in participants with hyperglycemia	• Monitor participants for hyperglycemia or other signs and symptoms of diabetes
Hypophysitis	Grade 2	Withhold	• Administer corticosteroids and initiate hormonal replacements as clinically indicated	• Monitor for signs and symptoms of hypophysitis (including hypopituitarism and adrenal insufficiency)
	Grade 3 or 4	Withhold or permanently discontinue [d]		
Hyperthyroidism	Grade 2	Continue	• Treat with nonselective beta-blockers (eg, propranolol) or thionamides as appropriate	• Monitor for signs and symptoms of thyroid disorders
	Grade 3 or 4	Withhold or permanently discontinue [d]		

irAEs	Toxicity Grade (CTCAE v5.0)	Action With Pembrolizumab Monotherapy, Coformulations or IO Combinations	Corticosteroid and/or Other Therapies	Monitoring and Follow-up
Hypothyroidism	Grade 2, 3 or 4	Continue	• Initiate thyroid replacement hormones (eg, levothyroxine or liothyronine) per standard of care	• Monitor for signs and symptoms of thyroid disorders
Nephritis: grading according to increased creatinine or acute kidney injury	Grade 2	Withhold	• Administer corticosteroids (prednisone 1 to 2 mg/kg or equivalent) followed by taper	• Monitor changes of renal function
	Grade 3 or 4	Permanently discontinue		
Neurological Toxicities	Grade 2	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 3 or 4	Permanently discontinue		
Myocarditis	Grade 1	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 2, 3 or 4	Permanently discontinue		
Exfoliative Dermatologic Conditions	Suspected SJS, TEN, or DRESS	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology or exclude other causes
	Confirmed SJS, TEN, or DRESS	Permanently discontinue		

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

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

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

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

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

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

[d] The decision to withhold or permanently discontinue pembrolizumab monotherapy, 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 15.

Table 15 Pembrolizumab Infusion Reaction Dose Modification and Treatment Guidelines

NCI CTCAE Grade	Treatment	Premedication at Subsequent Dosing
Grade 1 Mild reaction; infusion interruption not indicated; intervention not indicated	Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator	None
Grade 2 Requires therapy or infusion interruption, but responds promptly to symptomatic treatment (eg, antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for ≤24 h	Stop Infusion Additional appropriate medical therapy may include, but is not limited to: IV fluids Antihistamines NSAIDs Acetaminophen Narcotics Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator. If symptoms resolve within 1 hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (eg, from 100 mL/h to 50 mL/h). Otherwise dosing will be held until symptoms resolve and the participant should be premedicated for the next scheduled dose. Participants who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further study drug 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
Abbreviations: IV=intravenous; NCI=National Cancer Institute; NSAID=nonsteroidal anti-inflammatory drugs; PO=taken orally, by mouth. 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		

6.6.2.1 Other Allowed Dose Interruption(s) for Pembrolizumab

Pembrolizumab may be interrupted for situations other than treatment-related AEs such as medical/surgical events or logistical reasons not related to study intervention. 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.

6.6.3 Guidance for Management of Hepatic Events of Clinical Interest

HECIs are described in Section 8.4.7. All of these HECIs will require holding study intervention and notification to the Sponsor within 24 hours. All cases of retreatment after interruption of study intervention for HECI must be reported to the Sponsor and recorded in the database. As per Section 8.4.7, HECIs are not the result of disease progression or ITu liver lesion injection complications; and therefore, the following evaluations are not required for these etiologies.

Immediate assessment in case of HECI:

<u>All Participants</u>

- All participants should be considered for evaluation according to the directions below within 72 hours of the alert for a non-overdose ECI.

- Procedures:
  - Consider obtaining a consultation with a hepatologist
  - Obtain a work-up for hepatitis if there is no underlying hepatitis, including hepatitis A, B, C, D, E, Epstein-Barr virus, and cytomegalovirus
  - Assess for ingestion of drugs/supplements with hepatotoxic potential
  - Assess for alcohol ingestion
  - Assess for potential bacterial infection, biliary obstruction, or occult gastrointestinal bleeding
  - Repeat ALT, AST, Tbil, Dbil, ALP, INR, and CBC with differential; GGT testing must be performed as part of the HECI workup
  - Measure HCV RNA viral load (applies only for participants who have current active HCV infection or had infection in the past)
  - HBV DNA, HBsAg, HBeAg, anti-HBc (total and IgM), anti-HBe, and anti-HBs regardless of prior HBV status (Note: participants should be questioned about compliance with the use of antiviral agents)
  - Other laboratories or imaging studies as clinically indicated
  - Consider liver biopsy if indicated

6.6.3.1 Diagnosis and Management of Non-overdose Hepatic ECIs

HCC participants are at risk for a range of complications that can cause hepatic laboratory abnormalities with or without clinical decompensation. Those with a history of chronic HCV or HBV infection also have the potential to experience virologic flares. Immune-related hepatitis has been observed in approximately 1% of participants who received pembrolizumab.

For dose interval modification, refer to Sections 6.6.1 and 6.6.2. Guidance related to the diagnosis and management of hepatic ECIs is located in Table 16.

Table 16 Management of Hepatic ECIs

Event	Diagnosis	Management
Hepatitis B consider flare or change in HBV immunologic status	Rapid elevation of ALT to >5 × ULN and/or >3 × baseline	Interrupt intervention for **up to 12** weeks. Start antiviral therapy or check for compliance if HBV is detectable. Measure safety labs for AST, ALT, ALP, Tbil, Dbil, and INR on **weekly** basis. Measure HBsAg and HBV DNA on **weekly** basis (if detected at the time of onset of ECI). Evaluate the following every 2 to 3 weeks: • anti-HBe, HBe antigen, anti-HBs, and HBV DNA levels (if not detected at the onset of ECI) Restart intervention only if ALT returns to normal or Grade 1 (if normal at baseline), or to baseline grade (if Grade 2 at baseline) within 12 weeks, and the participant is clinically stable; otherwise, the participant should be permanently discontinued.
Hepatitis C exacerbation in participants with HCV RNA positive	Rapid elevation of ALT to >5×ULN and/or >3x baseline	Interrupt intervention for **up to 12** weeks. Assess use of injection or inhalation drugs. Recheck HCV genotype at the time of relapse of HCV RNA to rule out new infection. Measure safety labs for AST, ALT, ALP, Tbil, Dbil, and INR on **weekly** basis. Measure HCV RNA levels **every 2 weeks**. Please discuss risk benefit with Sponsor prior to starting HCV antiviral therapy. Restart intervention only if ALT returns to normal or Grade 1 (if normal at baseline), or to baseline grade (if Grade 2 at baseline) within 12 weeks, and the participant is clinically stable; otherwise, the participant should be permanently discontinued.
Relapse of HCV infection for participants with successfully treated or new HCV infection	If HCV RNA was TND at baseline, and now has confirmed detectable HCV RNA (2 specimens, 1 week apart)	Interrupt intervention for **up to 12** weeks. Assess use of injection or inhalation drugs. Recheck HCV genotype at the time of relapse of HCV RNA to rule out new infection. Measure safety labs for AST, ALT, ALP, Tbil, Dbil, and INR on **weekly** basis. Measure HCV RNA levels **every 2 weeks**. Please discuss risk benefit with Sponsor prior to starting HCV antiviral therapy. Restart intervention only if ALT returns to normal or Grade 1 (if normal at baseline), or to baseline grade (if Grade 2 at baseline) within 12 weeks, and the participant is clinically stable; otherwise, the participant should be permanently discontinued.

Event	Diagnosis	Management
Immune-related Hepatitis	If any of the HECI criteria are met as defined in the protocol Section 8.4.7 Note: Immune-related hepatitis is a diagnosis made after excluding other possible etiologies such as viral flare, biliary or vascular obstruction, infection, medications, and alcohol use usually immune-related hepatitis response to dechallenge and/or steroids and re-occurs with rechallenge.	Interrupt intervention for **up to 12 weeks.** Start IV corticosteroid 60 mg/day of prednisone or equivalent followed by oral corticosteroid. Monitor with biweekly laboratory tests, including AST, ALT, Tbil, Dbil, ALP, and INR. **Restart intervention only if:** • Abnormal laboratory values resolve to Grade ≤1 or baseline (if abnormal at baseline) • Taper steroid over 28 days • Steroid treatment is tapered to prednisone <10 mg/day or equivalent **Permanently Discontinue intervention if:** ○ Laboratory abnormalities do not resolve within 3 weeks ○ Steroids cannot be lowered to ≤10 mg/day (or prednisone equivalent) within 12 weeks ○ Decompensation to CP-C status
Other Causes	Rule out infection with blood, urine, and ascites culture – antibiotics should be started if infection is found. If total bilirubin is elevated, imaging should be obtained to rule out vascular compromise, biliary obstruction, and/or tumor progression by imaging. Ruled out alcohol use and hepatotoxic drugs including herbal and alternative medications.	Restart intervention only if laboratory values have returned to Grade 1 or baseline (if normal or Grade 1 at start) or to baseline grade **within 3 weeks**. If biliary obstruction is present, consultation with a gastroenterologist and/or an interventional radiologist should be obtained to see if the obstruction may be relieved.
Abbreviations: ALP=alkaline phosphatase; ALT=alanine aminotransferase; AST=aspartate aminotransferase; CP-C=Child-Pugh Grade C; Dbil=direct bilirubin; DNA=deoxyribonucleic acid; HBs=hepatitis B surface; HBeAg=hepatitis B e antigen, HBV=hepatitis B virus; INR=international normalized ratio; IV=intravenous; Tbil=total bilirubin; TND=target not detected.		

6.6.4 Dose Administration/Escalation

6.6.4.1 Dose Administration (Preparation)

Details on preparation and administration of V937 (and pembrolizumab) are provided in the appropriate Pharmacy/Procedures Manual.

6.6.5 Definition of Dose‑limiting Toxicity for Arm 2 Part I (mTPI Escalation)

Dose-limiting toxicities are used in Arm 2 Part I to guide dose escalation and de-escalation decisions for the mTPI design (see Section 4.3.1.3). The DLT window of observation will be during Cycle 1.

All toxicities will be graded using NCI-CTCAE v5.0 based on the investigator assessment.

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

1. Grade 4 nonhematologic toxicity (not laboratory).

2. Grade 4 hematologic toxicity lasting ≥7 days except for thrombocytopenia or febrile neutropenia:

   - ≥Grade 3 thrombocytopenia associated with clinically significant bleeding of any duration, or

   - Any grade of febrile neutropenia

3. Any nonhematologic AE ≥Grade 3 in severity should be considered a DLT, with the following exceptions: Grade 3 fatigue lasting ≤3 days; Grade 3 diarrhea, nausea, or vomiting without use of anti-emetics or anti-diarrheals per SOC; clinically asymptomatic Grade 3 elevations of amylase or lipase without any imaging evidence suggestive of possible/probable etiology; Grade 3 rash without use of corticosteroids or anti-inflammatory agents per SOC.

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

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

   - The abnormality leads to hospitalization, or

   - The abnormality persists for >1 week, or

   - The abnormality results in a DILI (see Section 8.4.7 for criteria).

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

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

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

7. Missing the following number of ITu V937 doses as a result of drug-related AE(s) during the first cycle:

   - Visceral tumor, dose escalation: missing 1 dose of V937

8. Grade 5 toxicity.

6.6.6 Guidelines for Dose Modification due to Adverse Events

6.6.6.1 Dose Modification for V937 and/or Pembrolizumab due to Drug-related AEs in Arm 2 Part I

The CTCAE v5.0 must be used to grade the severity of AEs. The investigator may attribute toxicity events to the combination of V937 and pembrolizumab (since one may not be able to separate individual drug effects in every circumstance) and modify the dose according to Table 17. If a dose modification for toxicity occurs with V937, the dose may not be re-escalated to the dose that preceded the dose modification. Dose modifications are always based on the previous cycle.

Reduction or holding of 1 agent and not the other agent is appropriate if, in the opinion of the investigator, the toxicity is clearly related to 1 of the study interventions. For example, if V937 is held due to an AE attributed to that drug, then pembrolizumab may continue to be administered. Appropriate documentation is required regarding to which drug the investigator is attributing the adverse event. 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.

The dose of V937 may be decreased during Arm 2, Part I (as described in Table 17). Participants may receive up to 2 dose modifications of V937 during the dose escalation phase, provided this reduction is not lower than that specified in DL1 (Table 13). If a dose reduction is needed from DL1, then V937 treatment should be discontinued. If further toxicity occurs, or criteria for resuming treatment are not met, then the participant must also be discontinued from study. If a participant experiences several toxicities which result in conflicting therapeutic regimens, then the treating physician should adhere to the most conservative dose adjustment recommended (ie, adjustment based on the severest AE reported). There will be no V937 dose reductions in Arm 1 or Arm 2, Part II.

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

Table 17 V937 Dose Modification and Treatment Discontinuation Guidelines for Drug-related Adverse Events in Arm 2, Part I (mTPI)

Toxicity	Hold Treatment	Criteria for Restarting Treatment	V937 Dose for Restarting Treatment	Criteria for Discontinuation after Consultation with Sponsor
Hematological toxicities:				
• Any Grade 1 hematological toxicity	No	N/A	N/A	N/A
• Any Grade 2 hematological toxicity, or Grade 3 toxicity that persists for ≤5 days	Per medical assessment of the investigator	If treatment held, may be restarted when AE resolves back to baseline or to Grade 1.	Per medical assessment of the investigator: may decrease dose by 1 dose level.	If AE persists for 12 weeks without resolution following reduction in dose
• Any Grade 3 hematologic toxicity that persists for >5 days, or Grade 4 hematological toxicity • Febrile neutropenia • Grade 3 thrombocytopenia of any duration if associated with bleeding	Yes	Treatment may be restarted when AE resolves back to baseline or to Grade 1.	Decrease dose by 1 dose level.	If AE persists for 12 weeks without resolution following reduction in dosing schedule. Permanent discontinuation should be considered for any severe or life-threatening event
Nonhematological toxicities:				
• Any Grade 1 nonhematological toxicity • Grade 2 alopecia • Grade 2 fatigue	No	N/A	N/A	N/A
• Any Grade 2 nonhematological toxicity except Grade 2 alopecia and Grade 2 fatigue	Per medical assessment of the investigator	If treatment held, may be restarted when AE resolves back to baseline or to Grade 1.	Per medical assessment of the investigator: may decrease dose by 1 dose level.	If AE persists for 12 weeks without resolution following reduction in dose.
• Any Grade 3 or 4 nonhematological toxicity (not including laboratory, unless clinically significant medical intervention is required to treat the participant, or the abnormality leads to hospitalization, or the abnormality persists for >1 week)	Yes	Treatment may be restarted when AE resolves back to baseline or to Grade 1.	Decrease dose by 1 dose level.	If AE persists for 12 weeks without resolution following reduction in dose. Permanent discontinuation should be considered for any severe or life-threatening event

In case toxicity does not resolve to Grade 0-1 within 12 weeks after last intervention, V937 should be discontinued after consultation with the Sponsor.

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

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

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

6.7 Intervention After the End of the Study

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

6.8 Clinical Supplies Disclosure

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

7 DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT WITHDRAWAL

7.1 Discontinuation of Study Intervention

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

As certain data on clinical events beyond study intervention discontinuation may be important to the study, they must be collected through the participant's last scheduled follow-up, even if the participant has discontinued study intervention. Therefore, all participants who discontinue study intervention prior to completion of the protocol-specified treatment period will still continue to participate in the study as specified in Section 1.3 and Section 8.11.3.

Participants may discontinue study intervention at any time for any reason or be discontinued from the study intervention at the discretion of the investigator should any untoward effect occur. In addition, a participant may be discontinued from study intervention by the investigator or the Sponsor if study intervention is inappropriate, the study plan is violated, or for administrative and/or other safety reasons. Specific details regarding procedures to be performed at study intervention discontinuation are provided in Section 8.1.8.

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 6 consecutive weeks. Participants may continue on study upon consultation with Sponsor.

- The participant has a medical condition or personal circumstance which, in the opinion of the investigator and/or Sponsor, places the participant at unnecessary risk from continued administration of study intervention.

- The participant has a confirmed positive serum pregnancy test.

- Confirmed radiographic disease progression outlined in Section 8.2.3 (exception if the Sponsor approves treatment continuation).

- Unacceptable adverse experiences as described in Section 8.4.

- Progression or recurrence of any malignancy, or any occurrence of another malignancy that requires active treatment.

- Intercurrent illness other than another malignancy as noted above that prevents further administration of treatment.

- Investigator's decision to discontinue treatment.

- Use of prohibited concomitant medications as described in Section 6.5.2.

- 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.

- Completion of 35 treatments with pembrolizumab.

  Note: 35 cycles (approximately 2 years) are calculated from the first dose.

- 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)

- Participant has any of the following non-overdose HECIs:

  - ALT >20 × ULN

  - Child-Pugh score of ≥9 points

  - Gastrointestinal bleeding suggestive of portal hypertension (eg, esophageal or gastric varices)

  - New onset of clinically detectable ascites

  - Hepatic encephalopathy

- Recurrence of a severe or life-threatening event, or of any of the laboratory abnormalities listed above, that are presumed to be immune-related

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

7.2 Participant Withdrawal From the Study

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

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

Specific details regarding procedures to be performed at the time of withdrawal from the study, as well as specific details regarding withdrawal from future biomedical research, are outlined in Section 8.1.8.1. The procedures to be performed should a participant repeatedly fail to return for scheduled visits and/or if the study site is unable to contact the participant are outlined in Section 7.3.

7.3 Lost to Follow-up

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

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

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

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

8 STUDY ASSESSMENTS AND PROCEDURES

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

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

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

- All study-related medical (or dental) decisions must be made by an investigator who is a qualified physician (or dentist when appropriate).

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

- Procedures conducted as part of the participant's routine clinical management (eg, blood count) and obtained before signing of ICF may be 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.

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

8.1 Administrative and General Procedures

8.1.1 Informed Consent

The investigator or medically qualified designee (consistent with local requirements) must obtain documented consent from each potential participant or each participant's legally acceptable representative prior to participating in a clinical study or future biomedical research. If there are changes to the participant's status during the study (eg, health or age of majority requirements), the investigator or medically qualified designee must ensure the appropriate documented informed consent is in place.

8.1.1.1 General Informed Consent

Informed consent given by the participant or their legally acceptable representative must be documented on a consent form. The form must include the study protocol number, study protocol title, dated signature, and agreement of the participant (or their legally acceptable representative) and of the person conducting the consent discussion.

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

The initial ICF, any subsequent revised ICF, and any written information provided to the participant must receive the IRB/IEC's approval/favorable opinion in advance of use. The participant or 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.

The participant or their legally acceptable representative will be asked to sign consent at the point of initial radiographic disease progression.

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

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

8.1.1.2 Consent and Collection of Specimens for Future Biomedical Research

The investigator or medically qualified designee will explain the future biomedical research consent to the participant, or the participants's leagally acceptable representative, answer all of their 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 future biomedical research.

8.1.2 Inclusion/Exclusion Criteria

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

8.1.3 Participant Identification Card

All participants will be given a participant identification card identifying them as participants in a research study. The card will contain study site contact information (including direct telephone numbers) to be used in the event of an emergency. The investigator or qualified designee will provide the participant with a participant identification card immediately after the participant provides documented informed consent. At the time of intervention allocation, site personnel will add the treatment/randomization number to the participant identification card.

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

8.1.4 Medical History

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

8.1.5 Prior and Concomitant Medications Review

8.1.5.1 Prior Medications

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

8.1.5.2 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.

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

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

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

8.1.6 Assignment of Screening Number

All consented participants will be given a unique screening number that will be used to identify the participant for all procedures that occur prior to intervention allocation. 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 8.11.1.

8.1.7 Assignment of Treatment/Randomization Number

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

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

8.1.8 Study Intervention Administration

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

Study intervention for V937 should begin within 3 days of treatment allocation (for Arms 1 and 2).

See Section 6.1.1 for pembrolizumab and Section 6.1.2 for V937 ITu for details related to the timing of dose administration.

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 Sections 1.3 and 8.11.3.

Participants who withdraw from the study should be encouraged to complete all applicable activities scheduled for the final study visit at the time of withdrawal. Any AEs that are present at the time of withdrawal should be followed in accordance with the safety requirements outlined in Sections 8.4 and 8.11.3.

8.1.8.1 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.

8.1.9 Participant Blinding/Unblinding

This is an open-label study.

8.1.10 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

The process for image collection and transmission to the central imaging vendor can be found in the SIM. Tumor imaging is as follows:

- Chest, abdomen, and pelvis scans are required for all participants. CT with IV and oral contrast is preferred or non-contrast CT of the chest and MRI of the abdomen and pelvis with IV gadolinium for participants in whom iodinated contrast is contraindicated, or when mandated by local practice.

- Cohort B HNSCC: Include head and neck CT.

- Additional imaging acquired as per standard of care or as clinically indicated, used to support disease progression or efficacy assessments, should be sent to the imaging vendor.

- Brain imaging (MRI is preferred) is required at baseline and on-study for participants with a history of brain metastasis or when clinically indicated. Brain imaging is also required to confirm a CR in participants who have brain metastases at baseline.

- Bone imaging (eg, PET scan, bone scan) is required at baseline and on-study when clinically indicated for participants who are symptomatic (eg. new bone pain).

- Lesion injections (eg, CT, MRI, ultrasound, etc.) with the needle inserted into lesion(s) are required for all study drug injection procedures.

- Medical photography (including a scale/ruler) is required for assessment of cutaneous lesions at screening and on-study for Arm 1.

- Images to document which lesions were injected:

    - For lesions injected under CT, MRI, or fluoroscopic guidance, collect images from the procedure showing the tip of the needle in the lesion.

    - For lesions injected under ultrasound guidance, collect images from the procedure showing the tip of the needle in the lesion, with text overlays on the lesions indicating the location, with anatomic landmarks if available, and precise anatomic descriptors otherwise.

    - For lesions injected using direct visualization or palpation for guidance, collect photographs with a skin marker showing the location of the lesion. Photographs should include both close-up views and views distant enough to identify the location of the lesion.

Although RECIST 1.1 references to a maximum of 5 target lesions in total and 2 per organ, the Sponsor allows a maximum of 10 target lesions in total and 5 per organ, if clinically relevant to enable a broader sampling of tumor burden. Additionally, because intratumoral therapy is incorporated into this study, RECIST 1.1 will be modified to specify that intratumoral injection of a lesion does not render the lesion non-evaluable.

8.2.2 Initial Tumor Imaging

Initial tumor imaging at Screening must be performed within 28 days prior to the date of first dose (C1D1) of study intervention.

Tumor imaging performed as part of routine clinical management is acceptable for use as screening tumor imaging if they are of diagnostic quality and performed within 28 days prior to the date of first dose (C1D1).

Participants with previously treated brain metastases must undergo brain imaging within 28 days prior to the first dose (C1D1) of study intervention, with local confirmation that no new or untreated brain metastases are present.

8.2.3 Tumor Imaging During the Study

Sites will be required to send in anatomical images/medical photography of the needle into lesions during the study drug injection procedures to a central imaging vendor, as indicated in the SIM.

The first on-study imaging assessment should be performed at 9 weeks (63 days ± 7 days) from the date of first dose (C1D1). Subsequent tumor imaging should be performed every 9 weeks (63 days ± 7 days) or more frequently if clinically indicated. After 54 weeks, 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, the start of new anticancer treatment, withdrawal of consent, death, or notification by the Sponsor, whichever occurs first.

PR and CR should be confirmed by a repeat imaging assessment. The imaging for confirmation of response may be performed at the earliest 4 weeks after the first indication of response, or at the next scheduled scan (ie, 9 weeks or 12 weeks later), whichever is clinically indicated. Participants will then return to regular scheduled imaging every 9 weeks or 12 weeks, starting with the next scheduled imaging time point. Participants who receive additional imaging for confirmation do not need to undergo the next scheduled tumor imaging if it is less than 4 weeks later; tumor imaging may resume at the subsequent scheduled imaging time point.

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

8.2.4 End of Treatment and Follow-up Tumor Imaging

In participants who discontinue study intervention, tumor imaging should be performed at the time of intervention discontinuation (± 4-week window). If previous imaging was obtained within 4 weeks prior to the date of discontinuation, then imaging at intervention discontinuation is not mandatory. For participants who discontinue study intervention due to documented disease progression by RECIST 1.1, this is the final required tumor imaging if the investigator elects to not implement iRECIST.

8.2.5 iRECIST 1.1 Assessment of Disease

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

For participants who show evidence of radiological PD by RECIST 1.1 as determined by the investigator, the investigator will decide whether to continue a participant on study

intervention until repeat imaging is obtained (using iRECIST for participant management (see Table 18 and Figure 3). This decision by the investigator should be based on the participant's overall condition.

Clinical stability is defined as the following:

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

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

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

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

- Increase in the sum of diameters of target lesion(s) identified at baseline to ≥20% and ≥5 mm from nadir

Note: the iRECIST publication uses the terminology "sum of measurements", but "sum of diameters" will be used in this protocol, consistent with the original RECIST 1.1 terminology.

- Unequivocal progression of non-target 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 non-target 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 initial iUPD 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 non-target lesions
  - The appearance of additional new lesions

- Any new factor appears that would have triggered PD by RECIST 1.1

Persistent iUPD

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

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

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

Resolution of iUPD

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

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

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

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

Management Following the Confirmatory Imaging

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

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

Detection of Progression at Visits after Pseudoprogression Resolves

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

- Target lesions

Sum of diameters reaches the PD threshold (20% and 5 mm increase from nadir) either for the first time, or after resolution of previous pseudoprogression. The nadir is always the smallest SOD seen during the entire study, either before or after an instance of pseudoprogression.

- Non-target lesions

If non-target lesions have never shown unequivocal progression, their doing so for the first time results in iUPD

If non-target lesions had 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 factors above indicate iUPD, the iUPD evaluation process repeats, just as on the first occurrence of iUPD. iUPD must be confirmed before iCPD can occur.

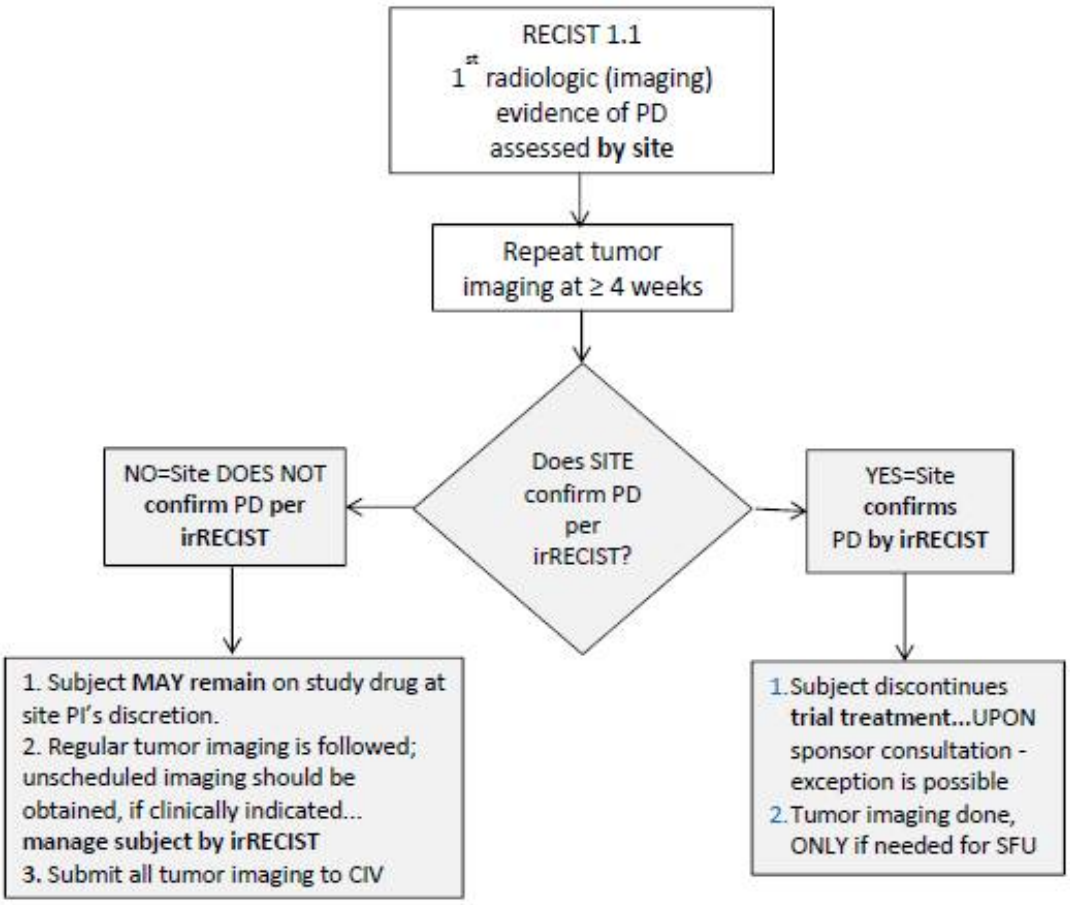
Additional details about iRECIST are provided in the iRECIST publication [Eisenhauer, E. A., et al 2009] [Seymour, L., et al 2017].

Table 18 Imaging and Treatment after First Radiologic Evidence of Progressive Disease

	Clinically Stable		Clinically Unstable	
	Imaging	**Treatment**	**Imaging**	**Treatment**
First radiologic evidence of PD by RECIST 1.1	Repeat imaging at 4 to 8 weeks to confirm PD	May continue study intervention at the local site investigator's discretion while awaiting confirmatory tumor imaging by site by iRECIST	Repeat imaging at 4 to 8 weeks to confirm PD per physician discretion only	Discontinue treatment
Repeat tumor imaging confirms PD (iCPD) by iRECIST per local assessment	No additional imaging required	Discontinue treatment (exception is possible upon consultation with Sponsor)	No additional imaging required	Not applicable
Repeat tumor imaging shows iUPD by iRECIST, per local assessment	Repeat imaging at 4 to 8 weeks to confirm PD. May occur at next regularly scheduled imaging visit.	Continue study intervention at the local site investigator's discretion	Repeat imaging at 4 to 8 weeks to confirm PD per physician discretion only	Discontinue treatment
Repeat tumor imaging shows iSD, iPR, or iCR by iRECIST per local assessment	Continue regularly scheduled imaging assessments	Continue study intervention at the local site 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 image should occur according to the regular imaging schedule.

Abbreviations: iCPD=immune confirmed progressive disease; iCR=immune complete response; iPR=immune partial response; iRECIST=immune-related response evaluation criteria in solid tumors; iSD=immune stable disease; iUPD=immune unconfirmed progressive disease; PD=progressive disease; PFS=progression-free survival.
If progression has been centrally verified, further management by the study site, based on iRECIST. Any further imaging should still be submitted to the vendor, but no rapid review will occur.

Figure 3 Imaging and Treatment for Clinically Stable Participants after First Radiologic Evidence of PD Assessed by the Investigator



iRECIST= 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.

8.2.6 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.

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 during of the study (from prestudy to poststudy visits), including approximate blood/tissue volumes drawn/collected by visit and by sample type per participant, can be found in Section 8.3.6.1.

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

8.3.1 Physical Examinations

8.3.1.1 Full Physical Examination

The investigator or qualified designee will perform a complete physical exam during the Screening period. Clinically significant abnormal findings should be recorded as medical history. The time points for full physical exams are described in the SoA. 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 exam as defined in the SoA, the investigator or qualified designee will perform a directed physical exam 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 and blood pressure. Weight will be obtained as specified in the SoA. Height will be measured at screening only.

8.3.3 Electrocardiograms

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

8.3.4 Endoscopy: Required for Arm 2 Part II, Cohort D only

An endoscopy will be performed using local standard procedures at screening for esophageal varices, unless such screening has been performed in the past 12 months prior to C1D1.

8.3.5 Child-Pugh Score: Required for Arm 2 Part II, Cohort D only

The Child-Pugh score will be assessed at screening only. If any of the hepatic ECI criteria are met, document the Child-Pugh score with each visit until the hepatic ECIs resolve. The Class A score is required for study eligibility. (See Section 10.9 for scoring guidelines.)

8.3.6 Clinical Safety Laboratory Assessments

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

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

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

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

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

8.3.6.1 Laboratory Safety Evaluations (Hematology and Chemistry)

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

The maximum amount of blood collected from each participant over the duration of the study will not exceed 950 mL (approximately 650 mL blood will be collected in Year 1 and 300 mL blood in Year 2). See Laboratory Manual for additional details.

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

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

8.3.7 Pregnancy Test

Pregnancy testing ([urine or serum] as required by local regulations) should be conducted according to Section 1.3 (SoA) and at the end of relevant systemic exposure for all arms.

- Pregnancy testing requirements for study inclusion are described in Section 5.1.
- Pregnancy testing (urine or serum) should be conducted at monthly intervals during intervention, according to local regulations or if clinically indicated.
- Pregnancy testing (urine or serum) should be conducted for the time it takes to eliminate systemic exposure after the last dose of study intervention(s) as noted in Section 5.1, ie, 120 days following cessation of pembrolizumab.

Additional serum or urine pregnancy tests may be performed as determined necessary by the investigator to establish the absence of pregnancy at any time during the participant's participation in the study. (See Appendix 7 for country-specific requirements.)

8.4 Adverse Events, Serious Adverse Events, and Other Reportable Safety Events

The definitions of an AE or SAE, as well as the method of recording, evaluating, and assessing causality of AE and SAE and the procedures for completing and transmitting AE, SAE, and other reportable safety event reports can be found in Appendix 3.

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

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

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

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

All AEs, SAEs, and other reportable safety events that occur after the participant provides documented informed consent but before intervention allocation must be reported by the investigator if the participant is receiving placebo run-in or other run-in treatment, if the event cause the participant to be excluded from the study, or is the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, or a procedure.

- All AEs from the time of intervention allocation through 30 days following cessation of study intervention must be reported by the investigator.

- All AEs meeting serious criteria, from the time of intervention allocation 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 allocation 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 the investigator considers the event to be reasonably related to the study intervention or study participation, the investigator must promptly notify the Sponsor.

All initial and follow-up AEs, SAEs, and other reportable safety events will be recorded and reported to the Sponsor or designee within the time frames as indicated in Table 19.

Table 19 Reporting Time Periods and Time Frames for Adverse Events and Other Reportable Safety Events

Type of Event	**Reporting Time Period:** Consent to Randomization/ Allocation	**Reporting Time Period:** Randomization/ Allocation through Protocol-specified Follow-up Period	**Reporting Time Period:** After the Protocol-specified Follow-up Period	Time Frame to Report Event and Follow-up Information to Sponsor:
NSAE	Report if: - due to protocol-specified intervention - causes exclusion - participant is receiving placebo run-in or other run-in treatment	Report all	Not required	Per data entry guidelines
SAE including Cancer and Overdose	Report if: - due to protocol-specified intervention - causes exclusion - participant is receiving placebo run-in or other run-in treatment	Report all	Report if: - drug/vaccine related. (Follow ongoing to outcome)	Within 24 hours of learning of event
Pregnancy/ Lactation Exposure	Report if: - participant has been exposed to any protocol-specified intervention (eg, procedure, washout or run-in treatment including placebo run-in)	Report all	Previously reported – Follow to completion/termination; report outcome	Within 24 hours of learning of event
ECI (require regulatory reporting)	Report if: - due to intervention - causes exclusion	Report - potential DILI - require regulatory reporting	Not required	Within 24 hours of learning of event
ECI (do not require regulatory reporting)	Report if: - due to intervention - causes exclusion	Report - non-DILI ECIs and those not requiring regulatory reporting	Not required	Within 5 calendar days of learning of event

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

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

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

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

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

8.4.4 Regulatory Reporting Requirements for SAE

Prompt notification (within 24 hours) by the investigator to the Sponsor of SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.

The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The Sponsor will comply with country-specific regulatory requirements and global laws and regulations relating to safety reporting to regulatory authorities, IRB/IECs, and investigators.

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

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

8.4.5 Pregnancy and Exposure During Breastfeeding

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

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

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

Events of clinical interest for this study include:

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

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

   *Note: These criteria are based upon available regulatory guidance documents. The purpose of the criteria is to specify a threshold of abnormal hepatic tests that 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).

3. HCC-specific expansion cohort, Arm 2 Part II:
   Hepatic ECIs include any of the following events if the events are considered not due to disease progression or TACE as judged by the investigator. All of these events (if not associated with disease progression under study) will require holding study treatment, notification of the event(s) to the Sponsor within 24 hours after awareness via electronic media or paper.

For dose interval modification, refer to Section 6.6.1 (V937) and 6.6.2 (pembrolizumab). For guidance related to the diagnosis and management of hepatic ECIs, refer to Section 6.6.3.

- ALT:
  - Among participants with Baseline ALT <2 × ULN: ALT ≥5 × ULN
  - Among participants with Baseline ALT ≥2 × ULN: ALT >3 × the Baseline level
  - ALT >500 U/L regardless of baseline level

- Total Bilirubin:
  - Total bilirubin >3.0 mg/dL
- Regardless of laboratory values, hepatic decompensation diagnosed clinically, including:
  - New onset clinically detectable ascites requiring intervention for >3 days
  - Hepatic encephalopathy
  - Gastrointestinal bleeding suggestive of portal hypertension (eg, esophageal or gastric varices)

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, V937 or pembrolizumab should be discontinued and the participant should be observed closely for signs of toxicity. Appropriate supportive treatment should be provided if clinically indicated.

8.6 Pharmacokinetics

PK supports evaluation of V937 immunogenicity and exposure in this indication, and evaluation of exposure of the proposed dosing regimen. Blood samples will be obtained to evaluate V937 exposures which are used to derive PK parameters (AUC and C_{max}) and immunogenicity.

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

PK sample collection is no longer required.

8.6.1 Blood Collection for Serum V937

PK sample collection is no longer required.

8.6.2 Blood Collection for Neutralizing V937 Antibodies

Neutralizing V937 antibodies sample collection is no longer required.

8.7 Pharmacodynamics

Pharmacodynamic sample collection is no longer required.

8.8 Biomarkers

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

- Blood for genetic analysis
- Blood for RNA analyses
- Blood for ctDNA analyses
- Tumor biopsy

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

- Leftover DNA for future research
- Leftover RNA from Blood RNA Analyses
- Leftover plasma from Blood for ctDNA analyses
- Leftover main study tumor biopsy

8.10 Health Economics Medical Resource Utilization and Health Economics

Not applicable to this study.

8.11 Visit Requirements

Visit requirements are outlined in Section 1.3, Table 1, Table 2, Table 3, Table 4, and Table 5. Specific procedure-related details are provided in Section 8.

8.11.1 Screening

Approximately 3 days prior to treatment allocation, potential participants will be evaluated to determine that they fulfill the entry requirements as set forth in the SoA. Screening procedures may be repeated after consultation with the Sponsor.

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

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

- Has a performance status of 0 or 1 on the ECOG Performance Scale.

- 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).

- Archival tumor sample collection is not required to be obtained within 28 days prior to the first dose of study intervention. Newly obtained tumor tissue may be obtained within 90 days of study intervention initiation.

8.11.2 Treatment Period/Vaccination Visit

The overall treatment period duration is 2 years. See Sections 4.1.1 (Arm 1), 4.1.2 (Arm 2 Part I), and 4.1.3 (Arm 2 Part II) for treatment details.

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

8.11.3 Discontinued Participants Continuing to be Monitored in the Study

The Discontinuation Visit should occur at the time study intervention is discontinued for any reason. Visit requirements are outlined in the SoA. Additional details regarding participant withdrawal and discontinuation are presented in Section 7.

8.11.3.1 Safety Follow-up Visit

All AEs that occur prior to the Discontinuation 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 visit will not be required after completion of the Discontinuation Visit.

8.11.3.2 Imaging Follow-up Visits

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

8.11.3.3 Survival Follow-up Contacts

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

9 STATISTICAL ANALYSIS PLAN

This section outlines the statistical analysis strategies and procedures for the primary and secondary analyses of the study. CCI [redacted]

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). CCI [redacted]

9.1 Statistical Analysis Plan Summary

This section contains a brief summary of statistical analyses for this trial. Full details are in the SAP, Sections 9.2 through 9.12.

Study Design Overview	Phase 1b/2 study of ITu administration of V937 in combination with pembrolizumab in participants with advanced/metastatic solid tumors. Arm 1 (Subcutaneous Tumors) will enroll participants with 3 tumor specific cohorts (Cohort A: TNBC; Cohort B: HNSCC; Cohort C: cSCC). Arm 2 (Visceral Tumors) Part I applies an mTPI design for dose escalation and confirmation of preliminary RP2Ds, followed by Part II expansion phase with 2 tumor-specific cohorts (Cohort D: HCC; Cohort E: Gastric)

Intervention Assignment	Participants will be allocated centrally through IRT by nonrandom assignment to receive V937 in combination with pembrolizumab. In Arm 1, participants will be allocated to one of the 3 cohorts (TNBC, HNSCC, cSCC) depending on their tumor types through IWRS. In Arm 2 Part I, participants will be allocated to solid tumors with liver metastases through IWRS. In Arm 2 Part II, participants will be allocated to one of the 2 cohorts (HCC, gastric) depending on their tumor types through IWRS. The trial is open-label.
Analysis Populations	Safety: APaT and DLTe CCI [redacted] Efficacy: FAS
Primary Endpoint(s)	Arm 1: • OR is a confirmed CR or PR by RECIST 1.1 assessed by the investigator Arm 2: • DLT • AE • Discontinuation of study intervention due to AE
Secondary Endpoints	Arm 1: • AE and discontinuation study intervention due to AE • PFS and DOR per RECIST 1.1 assessed by the investigator • OR, PFS, DOR per iRECIST assessed by the investigator • OS Arm 2 Parts I and II: • OR as evaluated by RECIST 1.1 and iRECIST criteria assessed by the investigator
Statistical Methods for Efficacy/ Immunogenicity/ Pharmacokinetic Analyses	ORR will be estimated using an exact method based on the binomial distribution (Clopper-Pearson interval) together with its 95% confidence interval. CCI [redacted]
Statistical Methods for Safety Analyses	Summary statistics (counts, percentages, means, standard deviations, etc.) will be provided for the safety endpoints as appropriate. CCI [redacted] The estimate of the DLT rate among participants treated at RP2D of V937 in combination with pembrolizumab and the 90% Bayesian credible intervals for the estimate will be provided.

CCI [redacted]	
Sample Size and Power	Arm 1 will enroll 90 participants (30 each for TNBC, HNSCC, and cSCC cohorts) or less due to early study termination. Arm 2 Part I will enroll approximately 35 participants for dose escalation and confirmation, and Arm 2 Part II will enroll 60 participants (30 each for HCC and gastric cohorts) or less due to early study termination. A target sample size of 185 participants will be used for study planning purposes.

9.2 Responsibility for Analyses/In-house Blinding

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

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

9.3 Hypotheses/Estimation

Objectives of the study are outlined in Section 3.

9.4 Analysis Endpoints

9.4.1 Efficacy/Immunogenicity/Pharmacokinetics Endpoints

OR is a confirmed CR or PR based on RECIST 1.1 by the investigator. OR is primary endpoint for the 3 cohorts in Arm 1 and is secondary endpoint for the 2 cohorts in Arm 2 Part II. ORR is the proportion of participants with OR.

PFS is defined as the time from the first dose of study treatment to the first documented PD based on RECIST1.1 by the investigator or death due to any cause, whichever occurs first. PFS is secondary endpoint for the 3 cohorts in Arm1.

DOR is defined as the time from the first documented evidence of CR or PR until PD based on RECIST1.1 by the investigator or death due to any cause, whichever occurs first, in participants demonstrating PR or CR. DOR is secondary endpoint for the 3 cohorts in Arm1.

OR, PFS and DOR are also evaluated based on iRECIST by the investigator.

OS is defined as the time from the first dose of study treatment to death due to any cause. Participants who do not die will be censored on the date of the last study assessment or contact. Overall survival is a secondary endpoint for Arm 1.

CCI

[redacted]

9.4.2 Safety Endpoints

The safety endpoints include DLTs, AEs, and discontinuation of study intervention due to AE. In addition, safety and tolerability will be assessed by clinical review of all relevant parameters including SAEs, laboratory tests, and vital signs.

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

9.5 Analysis Populations

9.5.1 Safety Analysis Populations

The APaT population will be used for the analysis of safety data in this study. The APaT population consists of all participants who received at least 1 dose of study intervention.

The DLT evaluable population includes APaT participants that meet the criteria for DLT evaluability (eg, finished Cycle 1 without a DLT or experienced a DLT in Cycle 1). See Section 6.6.5 for details.

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

CCI [redacted]

9.5.3 Efficacy Analysis Populations

The FAS population will be used for the analyses of efficacy data in this study. It consists of all participants with a baseline scan that demonstrated measurable disease by the investigator's assessment, and who were administered at least 1 dose of study intervention.

The efficacy analyses for Arm 2 Part II expansion cohort will pool Part I participants who meet the inclusion criteria for the respective Part II tumor type and received the same dose level of V937 in combination with pembrolizumab.

9.6 Statistical Methods

This section describes the statistical methods that address the primary and secondary objectives.CCI [redacted]

9.6.1 Statistical Methods for Efficacy Analysis

Objective response rate estimates in each treatment arm and cohort will be reported along with the 95% CI using the Clopper and Pearson method.

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. For PFS and OS, Kaplan-Meier curves and median estimates from the Kaplan-Meier curves will be provided as appropriate. Censoring rules for DOR and PFS will be provided in sSAP.

9.6.2 Statistical Methods for Safety Analysis

Safety and tolerability will be assessed by clinical review of all relevant parameters including AEs, SAEs, laboratory tests, vital signs, ECG measurements, and physical examinations.

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

For Arm 2 Part I, CCI [redacted] The estimate of the DLT rate among participants treated at the RP2D and the 90% Bayesian credible interval based on a prior distribution of Beta (1,1) for the estimate will be provided.

9.6.3 Summaries of Baseline Characteristics, Demographics, and Other Analyses

9.6.3.1 Demographic and Baseline Characteristics

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

CCI [redacted]

CCI [redacted]

9.9 Sample Size and Power Calculations

The overall sample size for this Phase 1b/2 trial is expected to be 185 participants or less due to early study termination. This is an estimation study and there is no formal hypothesis testing.

The planned sample size for Arm 1 is 90 participants (30 each for TNBC, HNSCC and cSCC cohorts) or less due to early study termination. The planned sample size for Arm 2 is 95 participants (35 for Part I and 60 for Part II) or less due to early study termination CCI [redacted]
Approximate 35 participants will be used for study planning purposes. Part II will have 60 participants (30 each for HCC and gastric cohorts) or less due to early study termination.

While there is no formal hypothesis testing in this study, CCI [redacted]

For each tumor-specific cohort, with total 30 participants and the presumable number of responders, response rate and estimated 95% CI are stated in Table 20.

Table 20 Estimate and 95% CI of ORR (N=30)

Sample Size	Number of Responses (PR/CR)	Observed ORR	95% CI of ORR
30	3	10.0%	(2.1%, 26.5%)
	4	13.3%	(3.8%, 30.7%)
	5	16.7%	(5.6%, 34. 7%)
	6	20.0%	(7.7%, 38.6%)
	7	23.3%	(9.9%,42.3%)
	8	26.7%	(12.3%,45.9%)
	9	30.0%	(14.7%,49.4%)
	10	33.3%	(17.3%,52.8%)

Abbreviations: CI = confidence interval; CR = complete response; ORR = objective response rate; PR = partial response

9.10 Subgroup Analyses

To determine whether the response rate is consistent across various subgroups, the estimate of ORR (with a nominal 90% CI) endpoint may be estimated within each category of the following classification variable:

- Participants having at least non-injected target lesion vs without having any non-injected target lesions.

If the number of participants in a category of a subgroup variable is less than 10% of the FAS population, the subgroup analysis may not be performed for this category of the subgroup variable. Details of other subgroup analyses, if any, will be documented in the sSAP.

9.11 Compliance (Medication Adherence)

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

9.12 Extent of Exposure

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

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

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

10.1.1 Code of Conduct for Clinical Trials

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

Code of Conduct for Interventional Clinical Trials

I. Introduction

A. Purpose

MSD, through its subsidiaries, conducts clinical trials worldwide to evaluate the safety and effectiveness of our products. As such, we are committed to designing, implementing, conducting, analyzing, and reporting these trials in compliance with the highest ethical and scientific standards. Protection of participants in clinical trials is the overriding concern in the design and conduct of clinical trials. In all cases, MSD clinical trials will be conducted in compliance with local and/or national regulations (including all applicable data protection 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 their financial interests in and/or arrangements with the Sponsor to allow for the submission of complete and accurate certification and disclosure statements. The investigator/subinvestigator(s) further agree to provide this information on a Certification/Disclosure Form, 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

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

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

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

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

10.1.3.1 Confidentiality of Data

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

10.1.3.2 Confidentiality of Participant Records

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

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

10.1.3.3 Confidentiality of IRB/IEC Information

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

10.1.4 Publication Policy

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

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

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

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

10.1.5 Compliance with Study Registration and Results Posting Requirements

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

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

10.1.6 Compliance with Law, Audit, and 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 Council on Harmonisation 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 Trials.

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

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

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

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

10.1.7 Data Quality Assurance

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

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

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

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

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

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

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

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

Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

10.1.8 Source Documents

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

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

10.1.9 Study and Site Closure

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

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

10.2 Appendix 2: Clinical Laboratory Tests

See Appendix 7 for country-specific requirements.

- The tests detailed in Table 21 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 and correspond with the time frame for female participant contraception in Section 5.1.
  - Additional serum or urine pregnancy tests may be performed, as determined necessary by the investigator or required by local regulation, to establish the absence of pregnancy at any time during the subject's participation in the study.

Table 21 Protocol-required Safety Laboratory Assessments

Hematology	**Comprehensive Chemistry Panel**	**Other**
Hematocrit	Albumin	Pregnancy test (serum or urine) [a]
Hemoglobin	Alkaline phosphatase	
Platelet count	Alanine aminotransferase	Total T3 (or Free T3 [FT3]), Total T4 (or Free T4 [FT4]), and TSH [b]
WBC (total and differential) [c]	Aspartate aminotransferase	
	Bicarbonate	
RBC	Calcium	Anti-HCV
Absolute lymphocyte Count [c]	Chloride	HCV viral load
	Creatinine	HCV genotype
Absolute neutrophil Count [c]	Glucose	anti-HBs
	Phosphorus	HBsAg
PT/INR	Potassium	anti-HBc (total and IgM)
aPTT or PTT	Sodium	HBeAg
	Total bilirubin	anti-HBe
	Direct bilirubin	HBV viral load
	Total protein	Anti-HDV
	Blood urea nitrogen (or Urea) [d]	AFP
		CD4+ T-cell count [e]
		GGT (for HECI assessment only)

Abbreviations: AFP=alpha-fetoprotein; aPTT=activated partial thromboplastin time; FT3= Free T3; FT4=Free T4; GGT=gamma glutamyl transpeptidase; HBc=hepatitis B core; HBeAg=hepatitis B e antigen; HBsAg=hepatitis B surface antigen; HBV=hepatitis B virus; HCV=hepatitis C virus; HDV= hepatitis delta virus; HECI= Hepatic Events of Clinical Interest; HIV=human immunodeficiency virus; IgM=immunoglobulin M; PTT=partial thromboplastin time; RBC=red blood cell; T3=triiodothyronine; T4=thyroxine; TSH=thyroid-stimulating hormone; WBC=white blood cell.

[a] Perform on women of childbearing potential only 72 hours 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. Total T4 is preferred; if not available, Free T4 may be tested.
[c] Report % or absolute results per standard of practice. Report the results in the same manner throughout the study.
[d] Blood urea nitrogen is preferred; if not available, urea may be tested.
[e] For HIV-positive participants only.

Investigators must document their review of each laboratory safety report.

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

10.3.1 Definitions of Medication Error, Misuse, and Abuse

Medication Error

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

Misuse

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

Abuse

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

10.3.2 Definition of AE

AE definition

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

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

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

Events meeting the AE definition

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

- Exacerbation of a chronic or intermittent 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.

  Note: Congenital disorders (eg, present from birth) not detected or diagnosed prior to study intervention administration do not qualify for reporting as AE.

- 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 their best clinical judgment, including consideration of the above elements.

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

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

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

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

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

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

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

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

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

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

Follow-up of AE and SAE

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

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

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

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

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

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

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

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

  - Reference Section 8.4.1 for reporting time requirements.

- The site will enter the SAE data into the electronic system as soon as it becomes available.

- After the study is completed at a given site, the EDC tool will be taken off-line to prevent the entry of new data or changes to existing data.

- If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the EDC tool has been taken off-line, then the site can report this information on a paper SAE form or by telephone (see next section).

- Contacts for SAE reporting can be found in the Investigator Study File Binder (or equivalent).

SAE reporting to the Sponsor via paper CRF

- If the EDC tool is not operational, facsimile transmission or secure e-mail of the SAE paper CRF is the preferred method to transmit this information to the Sponsor.

- In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the SAE data collection tool sent by overnight mail or courier service.

- Initial notification via telephone does not replace the need for the investigator to complete and sign the SAE CRF pages within the designated reporting time frames.

- Contacts and instructions for SAE reporting and paper reporting procedures can be found in the Investigator Study File Binder (or equivalent).

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

This section is not applicable to this study.

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

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

1. Definitions

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

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

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

d. DNA: Deoxyribonucleic acid.

e. RNA: Ribonucleic acid.

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

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

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

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

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

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

a. Participants for Enrollment

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

b. Informed Consent

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

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

c. eCRF Documentation for Future Biomedical Research Specimens

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

d. Future Biomedical Research Specimen(s)

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

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

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

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

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

5. Biorepository Specimen Usage[3,4]

Specimens obtained for the Sponsor will be used for analyses using good scientific practices. Analyses 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 Council on Harmonisation [Internet]: E15: Definitions for Genomic Biomarkers, Pharmacogenomics, Pharmacogenetics, Genomic Data and Sample Coding Categories. Available from http://www.ich.org/products/guidelines/efficacy/efficacy-single/article/definitions-for-genomic-biomarkers-pharmacogenomics-pharmacogenetics-genomic-data-and-sample-cod.html

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

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

10.7 Appendix 7: Country-specific Requirements

10.7.1 Japan-specific Requirements

1. *Additional procedures/assessments are included in the Schedule of Activities for Japan. See the corresponding tables in Section 1.3 (Schedule of Activities) for the comprehensive schedules: Section 1.3.1,* Table 1*; Section 1.3.3,* Table 3*; Section 1.3.4,* Table 4*; Section 1.3.5,* Table 5.

Table 1 Schedule of Activities for Screening

Study Period:	**Screen-ing**	**Notes**
Visit Day:	**-28 to -1**	
Clinical Procedures/Assessments		
Pulse Oximetry (SpO_2)	X	Assessments will be performed by the investigator or a qualified designee according to local standard procedures.
Laboratory Procedures/Assessments - LOCAL		
HBsAg, anti-HBc, and anti-HBs	X	

Table 3 Schedule of Activities for Treatment Phase: Arm 2 Part I - Dose Escalation in Participants with Visceral Tumors

Study Period:	Treatment Period				Notes
Treatment Cycle / Visit Title:	Cycle 1 (28 days)		Cycles 2-8 (21 days)	Cycles ≥9 (21 days)	
Treatment Days per Cycle	1	8	1	1	
Scheduling / visit Window (Days)	± 0	± 1	± 5	± 5	
Clinical Procedures/Assessments					
Pulse Oximetry (SpO_2)	X	X	X	X	Assessments will be performed by the investigator or a qualified designee according to local standard procedures.
Laboratory Procedures/Assessments - LOCAL					
AST and ALT		X			

Table 4 Schedule of Activities for Treatment Phase: Arm 2 Part II - Cohort Expansion

Study Period:	Treatment Period				Notes
Treatment Cycle / Visit Title:	Cycle 1 (28 days)		Cycles 2-8 (21 days)	Cycles ≥9 (21 days)	
Treatment Days per Cycle	1	8	1	1	
Scheduling / visit Window (Days)	± 0	± 1	± 5	± 5	
Clinical Procedures/Assessments					
Pulse Oximetry (SpO_2)	X	X	X	X	Assessments will be performed by the investigator or a qualified designee according to local standard procedures.

Table 5 Schedule of Activities for End of Treatment/Discontinuation and Posttreatment Phase: Arm 1, Arm 2 Part I Dose Escalation Phase, and Arm 2 Part II Expansion Phase

Study Period:	End of Treatment (EOT) / Discontinuation	Posttreatment Phase			Notes
Treatment Cycle / Visit Title:		Safety Follow-up	Imaging Follow-up	Survival Follow-up	
Treatment Days per Cycle:	At time of treatment discontinuation	30 days after the last dose	Every 9 or 12 weeks	Approximately every 12 weeks	
Scheduling Window (Days)	± 3	± 3	± 7	± 7	
Clinical Procedures/Assessments					
Pulse Oximetry (SpO_2)	X	X			Assessments will be performed by the investigator or a qualified designee according to local standard procedures.

2. Modified the language in Section 5 (Study Population) as shown by the underlined text.

Male and female, ≥20 years of age, with advanced/metastatic solid tumors will be enrolled in this study.

3. Modified the language for Criterion 8 in Section 5.1.1 (Overall Inclusion Criteria).

8. Male or female ≥20 years of age, at the time of signing the informed consent.

4. *Added language to Criteria 10 and 12 in Section 5.2 (Exclusion Criteria), as shown by the underlined text.*

    10. Participants with known Hepatitis B or C infections or known to be positive for HBsAg/HBV DNA or Hepatitis C Antibody or RNA. Active Hepatitis C is defined by a known positive Hep C Ab result and known quantitative HCV RNA results greater than the lower limits of detection of the assay.

        Note: See Section 5.1.4.1 for hepatitis guidelines in HCC cohort only.

        Participants who are positive for anti-HBc or anti-HBs are excluded from this study. If the participant is anti-HBs positive, anti-HBc negative, and has a history of HBV vaccination, the investigator can consider enrolling the patient in consultation with the Sponsor.

    12. Has known hypersensitivity to V937 and/or pembrolizumab or any of their excipients, and/or has known history of hypersensitivity to ingredients (derived from human, bovine, or porcine) used in the manufacturing process of the product.

5. *In Japan, V937 is designated as a Regenerative Medical Product, not 'IMP/NIMP' as shown in* Table 9.

6. *The language in the first paragraph following* Table 9 *in Section 6.1 (Study Interventions Administered) has been modified (see underlined text) to align with the requirement for participants to be hospitalization during Cycle 1, the DLT observation period.*

Participants in Arm 2 Part I will be hospitalized and monitored for the duration of Cycle 1 following the Cycle 1 Day 1 ITu administration of V937 (see Section 6.1.2.2 for additional details). All other study interventions will be administered on an outpatient basis.

7. *The following is an additional prohibited medication applicable to criteria listed in Section 6.5.2 (Prohibited Concomitant Medications).*

    - Transfusion therapy and hematopoietic factors such as granulocyte colony-stimulating factor (G-CSF) as primary prophylaxis during DLT assessment

8. *Section 8.3 (Safety Assessments) modifications were applied to address the collection of pulse oximetry assessments.*

In addition to the safety assessments outlined in Section 8.3, pulse oximetry assessments will be performed by the investigator or a qualified designee according to local standard procedures. Planned timepoints for these assessments are provided in supplements to Tables 1, 3, 4, and 5 provided at the beginning of Section 10.7.1.

9. *The following statement has been added to Section 10.3.6 (Reporting of AEs, SAEs, and Other Reportable Safety Events to the Sponsor):*

Other reporting items related to regenerative medical products:

Since V937 is categorized as a Regenerative Medical Product in Japan, AEs meeting below criteria should be reported to the Sponsor in addition to recording and reporting the AE as described in Section 10.3.

10. The following content has been added to Section 10.3.6 (Reporting of AEs, SAEs, and Other Reportable Safety Events to the Sponsor) to provide information specific to Regenerative Medical Product:

10.3.6.1 – Definition of Regenerative Medical Product

Regenerative Medical Products (Japan-specific regulation: Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices Article 2-9)

1. The following items intended for use in human or animal healthcare that are obtained after culturing or other processes using human or animal cells:

    - Reconstruction, repairing, or formation of the structure or function of the bodies of humans or animals

    - Treatment or prevention of disease in humans or animals

2. Items intended for use in the treatment of disease in humans or animals that are introduced into cells of humans or animals and contain genes to be expressed in their bodies.

The defect:

Any defect (or issue) of the regenerative medical products or generally poor conditions such as adverse reactions where the cells adversely affect the human body in any stages including manufacturing, delivery, storage or use.

Any defect (or issue) that is considered to have caused and/or may have caused SAEs.

Any defect (or issue) in the regenerative medical products concerned that cause or may cause death or SAEs. “The events concerned that may cause” means that there is the possibility that death or SAEs may occur in the participant, although these cases have not actually occurred.

10.3.6.2 - Regenerative Medical Products – Recording and Reporting

In order to fulfill Japan regulatory reporting obligations, the issue of regenerative medical products information that cause or may cause SAEs due to defect should be collected. The defect should be reported to the Sponsor via a Japan-specific paper reporting form. Information on Japan-specific paper reporting form will be reported only to Japan MSD.

- The SAEs that may occur due to defect should be reported within 5 calendar days to the Sponsor.
- The SAEs that occur due to defect should be reported within 24 hours to the Sponsor.

10.7.2 Norway-specific Requirements

1. Additional procedures/assessments are included in the Schedule of Activities for Norway. See the corresponding section and table for the comprehensive schedule: Section 1.3.5, Table 5.

Table 5 Schedule of Activities for End of Treatment/Discontinuation and Posttreatment Phase: Arm 1, Arm 2 Part I Dose Escalation Phase, and Arm 2 Part II Expansion Phase

Study Period:	End of Treatment (EOT) / Discontinuation	Posttreatment Phase			Notes
Treatment Cycle / Visit Title:		Safety Follow-up	Imaging Follow-up	Survival Follow-up	
Treatment Days per Cycle:	At time of treatment discontinuation	30 days after the last dose	Every 9 or 12 weeks	Approximately every 12 weeks	
Scheduling Window (Days)	± 3	± 3	± 7	± 7	
Laboratory Procedures/Assessments - LOCAL					
Pregnancy test for WOCBP only (urine or serum β hCG)	X				Pregnancy testing will be performed approximately every 30 days for 120 days following the last dose of study treatment.

2. This guidance supplements language in Section 8.3.7 (Pregnancy Test) requiring testing out to 120 days from last dose of study treatment (see underlined text).

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 each cycle of study intervention and 30 days posttreatment. If a urine test is positive or not evaluable, a serum test will be required. Participants must be excluded/discontinued from the study in the event of a positive or borderline-positive test result. Pregnancy testing will be performed approximately every 30 days for 120 days past the last dose of study treatment.

3. This guidance supplements the language provided in Section 10.2, Appendix 2 (Clinical Laboratory Tests), indicating additional pregnancy testing.

- Pregnancy Testing:
  - Pregnancy testing will be performed approximately every 30 days for 120 days past the last dose of study treatment.

10.7.3 France-specific Requirements

1. *Section 6.6.2 provides guidance for the management of immune-related AEs associated with pembrolizumab. In France, refer to the Keytruda European Summary of Product Characteristics available on the Public Drug Database for the guidelines regarding withholding or discontinuing pembrolizumab for Grades 2, 3, or 4 adrenal insufficiency as per investigator decision.*

2. *Pregnancy testing must be performed prior to study intervention administration at each cycle during the treatment period, and 120 days after the last dose at the end of study intervention.*

3. *Oocyte donation is prohibited during treatment and at least 120 days after last dose of study intervention.*

10.7.4 Portugal-specific Requirements

1. *HIV testing is required at screening.*

2. *Hepatitis B and Hepatitis C testing is required at screening.*

3. *Pregnancy testing must be performed for all WOCBP participants at screening, prior to study intervention administration at each cycle during the treatment period, as well as before the last dose of study intervention.*

10.8 Appendix 8: Abbreviations

Abbreviation	Expanded Term
ADA	anti-drug antibodies
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
APaT	All-Participants-as-Treated
AR	adverse reaction
ART	anti-retroviral therapy
AST	aspartate aminotransferase
ATD	accelerated titration design
ATP	adenosine triphosphate
AUC	areas under the curve
BCG	Bacillus Calmette–Guérin
BDS	blood drug screen
β-hCG	β-human chorionic gonadotropin
BID	twice daily
BMI	body mass index
BP	blood pressure
CBC	complete blood count
CD28	cluster of differentiation 28
CD3ζ	CD3 zeta
CI	confidence interval
C_{max}	maximum concentration
CNS	central nervous system
CONSORT	Consolidated Standards of Reporting Trials
CL	clearance
CPS	combined positive score
CrCl	creatinine clearance
CR	complete response
CRF	Case Report Form
cSCC	cutaneous Squamous Cell Carcinoma
CSR	Clinical Study Report
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTCAE v5.0	Common Terminology Criteria for Adverse Events, Version 5.0
ctDNA	circulating tumor DNA
CTFG	Clinical Trial Facilitation Group
CTLA-4	cytotoxic T-lymphocyte-associated protein 4
DAMP	danger-associated molecular pattern
Dbil	direct bilirubin
DILI	drug-induced liver injury
DL (1, 2, 3)	dose level (1, 2, 3)
DLT	dose-limiting toxicity
DLTe	dose-limiting toxicity-evaluable
DMC	data Monitoring Committee
DNA	deoxyribonucleic acid
DOR	duration of response
ECG	electrocardiogram
ECI	event of clinical interest
eCRF	electronic Case Report Form
eCTA	exploratory Clinical Trial Application

Abbreviation	Expanded Term
ECOG	Eastern Cooperative Oncology Group
EDC	electronic data collection
eGFR	estimated glomerular filtration rate
ELISA	enzyme-linked immunosorbent assay
EMA	European Medicines Agency
EudraCT	European Union Drug Regulating Authorities Clinical Trials
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act
FAS	Full Analysis Set
FFPE	formalin-fixed, paraffin embedded
FISH	fluorescence in situ hybridization
FSH	follicle stimulating hormone
GCP	Good Clinical Practice
GEJ	gastroesophageal junction
GGT	Gamma-glutamyl Transferase
HBc	hepatitis B core
HBeAg	hepatitis B e antigen
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCC	hepatocellular carcinoma
HCV	hepatitis C virus
HDV	hepatitis delta virus
HECI	Hepatic Events of Clinical Interest
Hep C Ab	hepatitis C antibody
HER2	human epiderma growth factor receptor 2
HIV	human immunodeficiency virus
HNSCC	head and neck squamous cell carcinoma
HPV	human papillomavirus
HR	heart rate
HRT	hormone replacement therapy
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council on Harmonisation
IEC	Independent Ethics Committee
iCPD	immune confirmed progressive disease
iCR	immune complete response
Ig	immunoglobulin
IgG4	immunoglobulin G4
IgM	immunoglobulin M
IgV	immunoglobulin-variable
IHC	immunohistochemistry
IND	Investigational New Drug
INR	International Normalize Ratio
IO	immuno-oncology
iPR	immune partial response
irAEs	immune-related AEs
IRB	Institutional Review Board
iRECIST	Response Evaluation Criteria in Solid Tumors 1.1 for immune-based therapeutics
IRT	interactive response technology
iSD	immune stable disease
ITP	idiopathic thrombocytopenic purpura
ITu	intratumoral

Abbreviation	Expanded Term
IUD	intrauterine device
iUPD	immune unconfirmed progressive disease
IUS	intrauterine hormone-releasing system
IV	intravenous
IVD	in vitro diagnostic
IVRS	interactive voice response system
IWRS	integrated web response system
LAM	lactational amenorrhoea method
LLOQ	lower limit of quantification
mAb	monoclonal antibody
MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging
mRNA	messenger RNA
MSI	microsatellite instability
MTD	maximum tolerated dose
mTPI	modified Toxicity Probability Interval
NCI	National Cancer Institute
NDA	New Drug Application
NSCLC	non-small cell lung cancer
OPV	oral poliovirus
OR	objective response
ORR	objective response rate
OS	overall survival
OTC	over-the-counter
PAMP	pathogen-associate molecular pattern
PBPK	physiologically-based PK
PD	progressive disease
PD-1	programmed cell death 1
PD-L1	programmed cell death ligand 1
PD-L2	programmed cell death ligand 2
PET	positron emission tomography
PFS	progression-free survival
PK	pharmacokinetic
PKCθ	protein kinase C-theta
PO	orally
PP	Per-protocol
PR	partial response
Q3W	every 3 weeks
RNA	ribonucleic acid
RP2D	Recommended Phase 2 Dose
SAE	serious adverse event
SAP	Statistical Analysis Plan
SIM	Site Imaging Manual
SoA	schedule of activities
sSAP	supplemental Statistical Analysis Plan
SUSAR	suspected unexpected serious adverse reaction
SVR12	sustained virologic response; no detectable amount of HCV in blood after 12 weeks of treatment
TAA	tumor-associated antigens
Tbil	total bilirubin
$TCID_{50}$	median tissue culture infectious dose
TILs	tumor-infiltrating lymphocytes

Abbreviation	Expanded Term
TMDD	target-mediated drug disposition
TNBC	triple negative breast cancer
T-regs	regulatory T cells
T-VEC	talimogene laherparepvec
WBC	white blood cell
WOCBP	woman/women of childbearing potential
XRT	radiotherapy

10.9 Appendix 9: Child-Pugh Score

The Child-Pugh score is used to assess the prognosis of chronic liver disease, mainly cirrhosis. Although it was originally used to predict mortality during surgery, it is now used to determine the prognosis, as well as the required strength of treatment and the necessity of liver transplantation.

Scoring

The score employs 5 clinical measures of liver disease. Each measure is scored from 1 to 3, with 3 indicating most severe derangement.

Measure	1 point	2 points	3 points
Total bilirubin[1] (mg/dL)	<2.0	2.0 to 3.0	>3.0
Serum albumin (g/dL)	>3.5	2.8 to 3.5	<2.8
INR[2] Or Prothrombin time, prolongation (seconds)	<1.7 <4.0	1.7 to 2.3 4.0-6.0	> 2.3 >6.0
Ascites	None	Mild (easily controlled by medication)	Moderate to Severe (poorly controlled)
Hepatic encephalopathy[3]	None	Grade I-II (mild or moderate)	Grade III-IV (severe or coma)

[1]In primary sclerosing cholangitis and primary biliary cirrhosis, the bilirubin references are changed to reflect the fact that these diseases feature high conjugated bilirubin levels. The upper limit for 1 point is 68 µmol/L (4 mg/dL) and the upper limit for 2 points is 170 µmol/L (10 mg/dL).
[2] Different textbooks and publications use different measures. Some older reference works substitute PT prolongation for INR
[3] Hepatic encephalopathy graded according to West Haven Criteria for Semi-quantitative Grading of Mental Status: *Adapted from: Conn H, Lieberthal M. The hepatic coma syndromes and lactulose. Baltimore: Williams & Wilkins; 1979.*

- Grade I: Trivial lack of awareness; euphoria or anxiety; shortened attention span; impaired performance of addition or subtraction

- Grade II: Lethargy or apathy; minimal disorientation for time or place; subtle personality change; inappropriate behavior

- Grade III: Somnolence to semi-stupor, but responsive to verbal stimuli

  Confusion; Gross disorientation

- Grade IV: Coma (unresponsive to verbal or noxious stimuli)

Interpretation

Chronic liver disease is classified into Child-Pugh class A to C, employing the added score from above.

Points	Class	One-year survival	Two-year survival
5–6	A	100%	85%
7–9	B	81%	57%
10–15	C	45%	35%

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