Official Protocol Title:	A Phase 1/1b, Open-label Clinical Study of Intratumoral/Intralesional Administration of V938 in Combination with Pembrolizumab (MK-3475) in Participants with Advanced/ Metastatic or Recurrent Malignancies
NCT number:	NCT04135352
Document Date:	25-MAY-2022

Title Page

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Protocol Title: A Phase 1/1b, Open-label Clinical Study of Intratumoral/Intralesional Administration of V938 in Combination with Pembrolizumab (MK-3475) in Participants with Advanced/Metastatic or Recurrent Malignancies

Protocol Number: 001-08

Compound Number: V938

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	19161
EudraCT	2020-003431-25

Approval Date: 25 May 2022

Sponsor Signatory

Typed Name: Title:	Date

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

Investigator Signatory

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

Typed Name: Title:	Date

DOCUMENT HISTORY

Document	Date of Issue	Overall Rationale
Amendment 8	25-MAY-2022	V938-001 is going to be discontinued due to sponsor's development decision. The overall rationale for this amendment is to allow eligible participants who are still ongoing with the study treatment after Cycle 7 Day 1 to continue receiving pembrolizumab monotherapy for up to 35 cycles in a pembrolizumab extension study.
Amendment 7	22-JUN-2021	To clarify or update: collection times for shedding analysis; lesion requirements; and update the dose modification and toxicity management guidelines for irAEs for pembrolizumab.
Amendment 6	04-JAN-2021	The overall rationale for this amendment is to add a CRS grading system and to update the dose range for the ^{89}Zr Df-IAB22M2C tracer.
Amendment 5	22-OCT-2020	To add new cohorts under dose escalation to evaluate combination of V938 and pembrolizumab with pembrolizumab starting on C1D1. To modify dose toxicity criteria for V938 to allow dose reduction, and to provide general guidance on managing cytokine release syndrome.
Amendment 4	04-JUN-2020	The overall rationale for this amendment is to add Cohort 4 to dose escalation at a dose of V938 of 5×10^8 PFU.
Amendment 3	21-FEB-2020	To add a CD8 PET imaging study to be conducted at preapproved study sites
Amendment 2	27-AUG-2019	To implement revisions requested by the US FDA.
Amendment 1	26-JUN-2019	To remove an arm of the study in the Dose-confirmation Phase.
Original protocol	03-APR-2019	Not applicable.

PROTOCOL AMENDMENT SUMMARY OF CHANGES

Amendment: 08

Overall Rationale for the Amendments:

V938-001 is going to be discontinued due to sponsor's development decision. The overall rationale for this amendment is to allow eligible participants who are still ongoing with the study treatment after Cycle 7 Day 1 to continue receiving pembrolizumab monotherapy for up to 35 cycles in a pembrolizumab extension study.

Summary of Changes Table:

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

Section # and Name	Description of Change	Brief Rationale
1.3.2 Schedule of Activities for the Treatment Period 1.3.3 Schedule of Activities for the End-of-Treatment and Posttreatment Follow-up Periods	Removal of certain sample collections for V938 PK, neutralizing V938 antibodies, anti-IL-12 antibodies, pembrolizumab PK, anti-pembrolizumab antibodies, shedding analyses, blood for RNA biomarker analyses and ctDNA, and serum for cytokine/chemokine analyses. Removal of sample collections for pembrolizumab PK, anti-pembrolizumab antibodies, neutralizing V938 antibodies and anti-IL-12 antibodies, NDV RNA (V938 PK), shedding analyses, blood for RNA biomarker analyses and ctDNA analysis, and serum for cytokine/chemokine analyses.	Changes due to study closure.
1.3.2 Schedule of Activities for the Treatment Period	Changed the timeframe for injection of the PET tracer prior to tumor biopsy in the PET imaging study.	Change to the PET imaging study due to study closure.
8.1.9.1 Withdrawal from Future Biomedical Research Appendix 6: Collection and Management of Specimens for Future Biomedical Research	Updated e-mail address to clinical.specimen.management@MSD.com	Correction.

Section # and Name	Description of Change	Brief Rationale
8.6 Pharmacokinetics	Added that blood samples for PK and antidrug antibodies may be stored, collection reduced, or collection discontinued, and any changes will be communicated by an administrative memo.	To allow for flexibility for collection and analyses of these samples.
Title Page Section 10.1.1 Code of Conduct for Clinical Trials	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.
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 1/1b, Open-label Clinical Study of Intratumoral/Intralesional Administration of V938 in Combination with Pembrolizumab (MK-3475) in Participants with Advanced/Metastatic or Recurrent Malignancies

Short Title: Phase 1/1b Open-label Study of V938 plus pembrolizumab for advanced solid tumors

Acronym: Not applicable.

Hypotheses, Objectives, and Endpoints:

In male/female participants with advanced/metastatic solid tumors:

Primary Objectives	Primary Endpoints
- Objective: To determine the safety and tolerability and to identify a recommended Phase 2 dose (RP2D) of V938 administered in combination with pembrolizumab	- Dose-limiting toxicity (DLT) - Adverse events (AEs) - Discontinuing study intervention due to an AE
Secondary Objectives	Secondary Endpoints
- Objective: To evaluate the objective response rate (ORR), as assessed by the investigator, of V938 administered in combination with pembrolizumab. Assessment will be based on Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST 1.1) and modified RECIST 1.1 for immune-based therapeutics (iRECIST).	- Objective response is a confirmed complete response (CR) or partial response (PR)
- Objective: To evaluate the pharmacokinetics (PK) of V938 administered alone and in combination with pembrolizumab.	- PK parameters of V938, including area under the curve (AUC) and maximum concentration (Cmax) of Newcastle Disease Virus (NDV) RNA
- Objective: To assess environmental V938 shedding	- NDV in excretory tissue samples

Overall Design:

Study Phase	Phase 1
Primary Purpose	Treatment
Indication	The treatment of participants with advanced/metastatic or recurrent solid tumors.
Population	Participants with histologically or cytologically confirmed advanced/metastatic solid tumor.
Study Type	Interventional
Intervention Model	Sequential This is a multi-site study.
Type of Control	No treatment control
Study Blinding	Unblinded Open-label
Masking	No Masking
Estimated Duration of Study	The Sponsor estimates that the study will require approximately 5 years from the time the first participant (or their legally acceptable representative) provides documented informed consent until the last participant's last study-related contact.

Number of Participants:

Approximately 20 to 44 participants will be enrolled in the dose-escalation part of this study (3 to 6 participants/cohort [cap at 14]), and 40 participants in the initial dose-expansion part of the study (20 participants/cohort) with the potential for further expansion. The final number of participants enrolled in the study will depend on the empirical safety data (DLT observations and the dose at which the RP2D is identified) and the initial signal finding for efficacy.

Intervention Groups and Duration:

Intervention Groups

Intervention Group Name	Drug	Dose Strength	Dose Frequency	Route of Admin.	Regimen/ Treatment Period/ Vaccination Regimen	Use
Cohort 1	V938	1×10^7 PFU	Cycle 1 Days 1, 3, 5, and 8; then Q3W × 6 doses (Cycle 2 to Cycle 7)	Intratumoral injection of cutaneous, subcutaneous and nodal lesions	Total of 10 doses administered from Cycle 1 to Cycle 7	Experi-mental
Cohort 2		1×10^8 PFU				
Cohort 3		3×10^8 PFU				
Cohort 4		5×10^8 PFU				
Cohorts 1-4	Pembro-lizumab	200 mg	Q3W	IV infusion	w beginning at Cycle 2 Day 1 for a maximum of 35 cycles	Experi-mental
Cohort 2a	V938	1×10^8 PFU	Cycle 1 Days 1, 3, 5, and 8; then Q3W × 6 doses (Cycle 2 to Cycle 7)	Intratumoral injection of cutaneous, subcutaneous and nodal lesions	Total 10 doses administered from Cycle 1 to Cycle 7	Experi-mental
Cohort 3a		3×10^8 PFU				
Cohort 4a		5×10^8 PFU				
Cohorts 2a-4a	Pembro-lizumab	200 mg	Q3W	IV infusion	Q3W beginning at Cycle 1 Day 1 for a maximum of 35 cycles	Experi-mental
Dose Expansion Arms A and B	V938	RP2D	Cycle 1 Days 1, 3, 5, and 8; then Q3W × 6 doses	Intratumoral, injection of cutaneous, subcutaneous and nodal lesions	Total 10 doses administered from Cycle 1 Cycle 7	Experi-mental
	Pembro-lizumab	200 mg	Q3W	IV infusion	Q3W beginning at Cycle 1 Day 1 for a maximum of 35 cycles	Experi-mental

Note: Pembrolizumab will be administered within 8 hours after completion of intratumoral V938 when both drugs are administered on the same day. Every cycle = 21 days
Abbreviations: IV = intravenous; PFU = plaque-forming units; RP2D = Recommended Phase 2 Dose; Q3W = every 3 weeks.

Total Number	Approximately 6 or 7 cohorts in dose escalation and 2 arms in expansion
Duration of Participation	After a screening phase of up to 28 days, each eligible participant will be receive study treatments until disease progression is radiographically documented and, when clinically appropriate, confirmed by the site per iRECIST for treated participants, unacceptable AEs, intercurrent illness that prevents further administration of treatment, investigator's decision to withdraw the participant, noncompliance with study treatment or procedure requirements or administrative reasons requiring cessation of treatment, or until the participant has received 35 doses of pembrolizumab (approximately 2 years). After the end of treatment, each participant will be followed for the occurrence of AEs and spontaneously reported pregnancy. All participants will be followed by telephone for OS until death, withdrawal of consent, or end of the study, whichever occurs first. The duration of study from the first participant enrolled to the last participant's last visit is estimated to be approximately 5 years. Due to discontinuation of V938-001, all ongoing participants who have completed C7D1 V938 plus pembrolizumab treatment may be enrolled to an extension study to continue pembrolizumab monotherapy for total of 35 cycles since first dose in V938-001 and to be monitored per the extension study as appropriate.

Study Governance Committees:

Steering Committee	No
Executive Oversight Committee	No
Data Monitoring Committee	No
Clinical Adjudication Committee	No
There are no governance committees in this study. Regulatory, ethical, and study oversight considerations are presented in Appendix 1.	

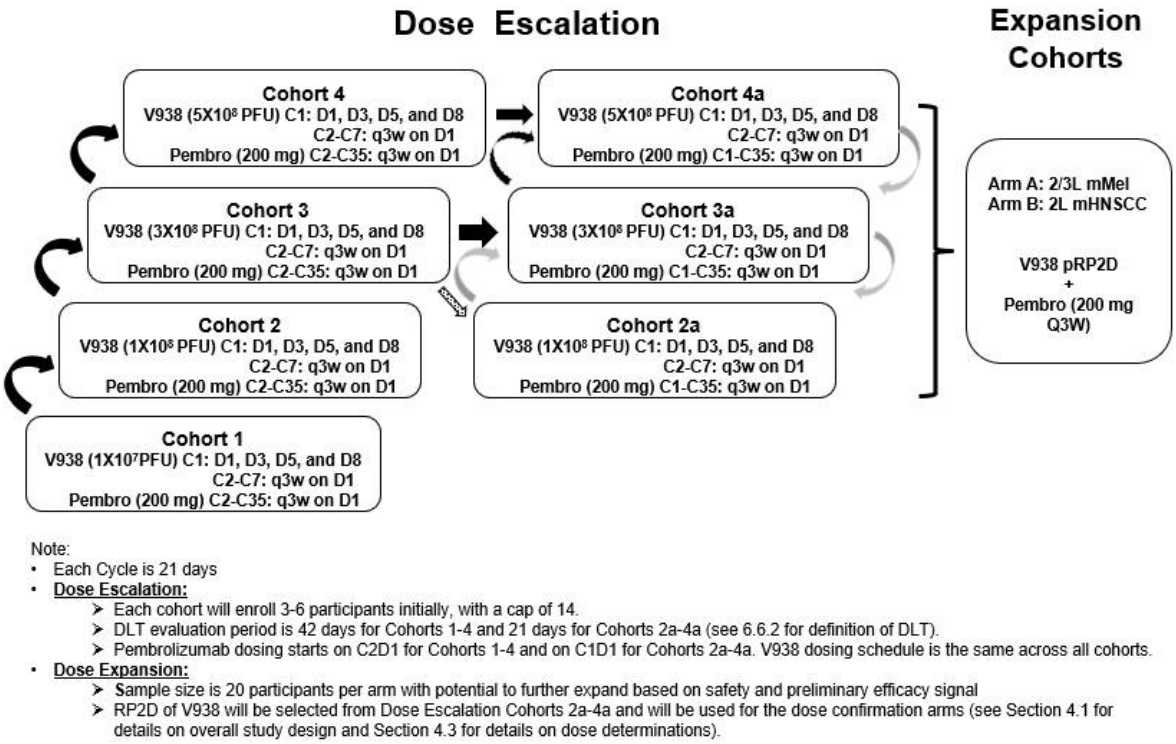
Study Accepts Healthy Volunteers: No

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

1.2 Schema

The study design is depicted in Figure 1.

Figure 1 Study Schema



Note:
- Each Cycle is 21 days
- Dose Escalation:
  - Each cohort will enroll 3-6 participants initially, with a cap of 14.
  - DLT evaluation period is 42 days for Cohorts 1-4 and 21 days for Cohorts 2a-4a (see 6.6.2 for definition of DLT).
  - Pembrolizumab dosing starts on C2D1 for Cohorts 1-4 and on C1D1 for Cohorts 2a-4a. V938 dosing schedule is the same across all cohorts.
- Dose Expansion:
  - Sample size is 20 participants per arm with potential to further expand based on safety and preliminary efficacy signal
  - RP2D of V938 will be selected from Dose Escalation Cohorts 2a-4a and will be used for the dose confirmation arms (see Section 4.1 for details on overall study design and Section 4.3 for details on dose determinations).

C=Cycle; D=Day; DLT=dose-limiting toxicity; mHNSCC=metastatic head and neck squamous cell carcinoma; mMEL=metastatic melanoma; pembro=pembrolizumab; PFU=plaque-forming units; RP2D=recommended Phase 2 dose; Q3W=every 3 weeks.
Note: Due to discontinuation of V938-001, all ongoing participants who have completed C7D1 V938 plus pembrolizumab treatment may be enrolled to an extension study to continue pembrolizumab monotherapy for total of 35 cycles since first dose in V938-001 and to be monitored per the extension study as appropriate.

1.3 Schedule of Activities (SoA)

1.3.1 Schedule of Activities for Screening

Study Period	Screening	Notes
Visit Days	-28 to -1	
Administrative Procedures		
Informed Consent	X	Documented informed consent must be obtained prior to performing any protocol-specific procedures. Tests performed prior to consent as part of routine clinical management are acceptable if performed within the specified timeframe.
Informed Consent for Future Biomedical Research (Optional)	X	Consent for future biomedical research is not required to participate in the study. Any leftover biomarker samples will be stored for future biomedical research if the participant (or their legally acceptable representative) provides documented informed consent for future biomedical research consent. Detailed instructions for the collection and management of future biomedical research specimens are provided in the Laboratory Procedure Manual.
Inclusion/Exclusion Criteria	X	
Participant Identification Card	X	Participant identification card to be updated with treatment number at the time of treatment allocation.
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), by history if available, as determined by local testing results (eg, BRCA1, BRCA2, MSI, TP53, MMR, PDL1, BRAF, KIT, KRAS, NRAS, PIK3CA)
HPV Status	X	HPV testing results by history in HNSCC and other squamous cell carcinoma tumors (eg, p16 IHC; multiplex nucleic acid sequence-based amplification [NASBA] or other polymerase chain reaction [PCR]-based assays) should be recorded if available, as determined per institutional standard.
Prior Medication	X	
Clinical Procedures/Assessments		
Tumor Imaging, RECIST 1.1	X	Baseline tumor imaging (CT or MRI as indicated for tumor type) and/or medical photography of cutaneous lesions should be performed within 28 days of enrollment. Please refer to Imaging Manual for detailed information.
Medical Photography (Cutaneous Lesions)	X	
Brain Imaging (Participants with Small Cell Lung Cancer, Thyroid Cancer, or Melanoma)	X	Participants with small cell lung, thyroid cancer, or melanoma must undergo brain imaging within 28 days prior to the first dose of study treatment, with local confirmation that no new or untreated brain metastases are present.
Physical Examination	X	A full physical examination to be performed within 72 hours prior to C1D1.
Height	X	
Weight	X	To be performed within 72 hours prior to C1D1
Vital Signs	X	To be performed within 72 hours prior to C1D1, including temperature, pulse, respiratory rate, and blood pressure.
ECOG Performance Status	X	To be performed within 72 hours prior to C1D1.
12-Lead Electrocardiogram	X	

Study Period Visit Days	Screening -28 to -1	Notes
Adverse Event Monitoring	X	All adverse events that occur after the consent form is signed, but before treatment allocation must be reported by the investigator if the event causes the participant to be excluded from the study or is the result of a protocol-specified intervention. There is to be continuous AE reporting from the time of treatment allocation.
Laboratory Procedures/Assessments – LOCAL		
CBC with Differential	X	Perform all screening clinical laboratory tests within 72 hours prior to C1D1 with exception of thyroid and hepatitis testing. Participants on anticoagulant therapy should be monitored throughout the study. Thyroid function: Total T4 and T3 are preferred over FT4 and FT3.
Chemistry Panel	X	
PT/INR and PTT or aPTT	X	
Thyroid Function Testing (T4 or FT4, T3 or FT3, TSH)	X	
Urinalysis	X	
Pregnancy Test for WOCBP Only (Urine or Serum hCG)	X	To be performed within 72 hours prior to C1D1. Urine pregnancy test to be performed as indicated; if test is positive or cannot be confirmed as negative, a serum pregnancy test is required. Additional pregnancy testing can be conducted if required by local regulations or if clinically indicated. See country-specific information in Appendix 7.
HIV, Hepatitis B and C Screen (per site SOP)	X	Acceptable to be based on history unless testing is required by local regulation. See country-specific requirements in Appendix 7.
Laboratory Procedures/Assessments -Central		
Tumor Tissue for Biomarker Analysis	X	Dose-escalation Cohorts 2a, 3a, 4a and expansion cohorts only. Must be performed for 1 planned injected lesion only after participant is deemed eligible for enrollment based on all other eligibility requirements. Optional biopsy from planned noninjected tumor lesion should also be collected if possible. Lesions for baseline biopsies should be clearly recorded so the on-treatment tumor biopsies could be taken from the same tumor lesion (respectively) if possible.
^{89}Zr-Df-IAB22M2C CD8 Tracer PET Imaging Evaluation (Expansion Cohorts Only)	X	For participants in the CD8 tracer PET imaging study in Part II ONLY at selected sites in the US. One to 4 days prior to tumor biopsy, participants will be injected with CD8 tracer and will return for CD8 tracer PET imaging 24 h (±3 h) and again (optional) 6 days (±1 day) later. This activity will only occur once the participant has been deemed eligible for enrollment based on all other criteria.
Optional 24-hour Observation Period for CD8 Tracer PET Imaging Evaluation (Expansion Cohorts Only)	X	A 24-hour observation period following PET tracer infusion is optional. The conduct of this observation will be at the discretion of the investigator.

Abbreviations: aPTT=activated partial thromboplastin time; BRAF=proto-oncogene B-rapidly accelerated fibrosarcoma; BRCA=breast cancer gene; C=Cycle; CBC=complete blood count; CD=cluster of differentiation; CT=computed tomography;; D=Day; ECOG=Eastern Cooperative Oncology Group; FT3=free triiodothyronine; FT4= free thyroxine; HBsAG=Hepatitis B surface antigen; HCV=hepatitis C virus; HNSCC=head and neck squamous cell carcinoma; hCG=human chorionic gonadotropin; ICF=Informed Consent Form; INR=International Normalized Ratio; iRECIST=modified RECIST 1.1 for immune-based therapeutics; IT=intratumoral; KIT=KIT proto-oncogene; KRAS=Kirsten ras oncogene homolog; MMR=mismatch repair; MRI=magnetic resonance imaging; MSI=microsatellite instable; NASBA = nucleic acid sequence based amplification; PCR = polymerase chain reaction; NRAS=neuroblastoma ras oncogene homolog; PD-L1=programmed cell death ligand 1; PIK3CA=phosphatidylinositol-4,5-bisphosphate 3-kinase cancer gene; 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; TP53=tumor protein p53; TSH=thyroid-stimulating hormone; WOCBP=women of childbearing potential.

1.3.2 Schedule of Activities for the Treatment Period

Study Period	**Treatment Period Cycle = 21 days**								**Notes**
Visit Timing	**Cycle 1**				**Cycle 2-7**			**Cycles ≥8**	**For all cycles:** Up to 35 cycles of pembrolizumab and up to 7 cycles (ie, 10 doses) of V938. All cycles are 21 days. For Cycle 2 and 3, D8 and D15 visits including safety assessments can be omitted if V938 is not dosed for that cycle due to interruption or discontinuation.
Visit Day (Days)	**1**	**3**	**5**	**8**	**1**	**8 (Cycles 2-3 only)**	**15 (Cycles 2-3 only)**	**1**	
Visit Window	**+1**	**±1**	**±1**	**±1**	**+3**	**±3**	**±3**	**±3**	**The visit window is +3 days for C2D1 and ±3 days for Day 1 of subsequent cycles.**
Pembrolizumab Administration Cohorts 1, 2, 3, and 4					X			X	For the first 3 doses of V938 (C1D1, C1D3, and C1D5), time of administration between 2 doses must be at least 24 hours apart. On visits when both V938 and pembrolizumab are administered, V938 IT injection will be administered prior to pembrolizumab IV infusion. See Pharmacy Manual for more details.
Pembrolizumab Administration Cohorts 2a, 3a, or 4a; and the Expansion Cohorts	X				X			X	
V938 Administration	X	X	X	X	X				
24-hour Observation Period	X	X							For **Dose-escalation Cohorts**, a 24-hour inpatient observation period following V938 administration on C1D1 and C1D3 is required for each participant. Observation for the remaining V938 doses will be at the discretion of the investigator, per local Institutional Review Board, Ethics Review Committee, and/or Health Authority mandate. For **Expansion Cohorts**, the requirement for 24-hour inpatient observation for the first 2 doses may be optional based on the updated safety profile.

Study Period	Treatment Period Cycle = 21 days								Notes
Visit Timing	**Cycle 1**				**Cycle 2-7**			**Cycles ≥8**	**For all cycles:** Up to 35 cycles of pembrolizumab and up to 7 cycles (ie, 10 doses) of V938. All cycles are 21 days. For Cycle 2 and 3, D8 and D15 visits including safety assessments can be omitted if V938 is not dosed for that cycle due to interruption or discontinuation.
Visit Day (Days)	**1**	**3**	**5**	**8**	**1**	**8 (Cycles 2-3 only)**	**15 (Cycles 2-3 only)**	**1**	
Visit Window	**+1**	**±1**	**±1**	**±1**	**+3**	**±3**	**±3**	**±3**	**The visit window is +3 days for C2D1 and ±3 days for Day 1 of subsequent cycles.**
Clinical Procedures/Assessments									
Tumor Imaging, RECIST 1.1, iRECIST, and/or itRECIST Response Assessment	←	—	—	—	—	—	—	→	Tumor imaging (CT or MRI) for solid tumors and medical photography of cutaneous lesions should be performed every 9 weeks (± 7 days) after the first dose for the first 54 weeks then every 12 weeks thereafter, **following calendar days**, and should not be adjusted for delays in cycle starts. Continue imaging schedule until disease progression, discontinuation, or the start of anticancer treatment Please refer to Imaging Manual for detailed information on medical photography.
Medical Photography (Cutaneous Lesions)	←	—	—	—	—	—	—	→	
Lesion Injection Scan	←	—	—	—	—	—	—	→	Obtain for all injected lesions for every IT injection performed. If imaging is used to guide injection (eg, CT, ultrasound, fluoroscopy), capture images to document injected lesions. If injection by visualization or palpation, it is recommended to capture photographs with skin markers to show injected lesions.
Physical Examination		X	X	X	X	X	X	X	Directed physical examinations to be performed unless a full examination is deemed necessary. To be performed on Days 3, 5, and 8 of Cycle 1; on Days 1, 8, and 15 of Cycle 2, and on Day 1 of every cycle thereafter.
Weight	X				X			X	Every other cycle (ie, Cycles 1, 3, 5, 7, 9, etc.).

Study Period	**Treatment Period Cycle = 21 days**								**Notes**
Visit Timing	**Cycle 1**				**Cycle 2-7**			**Cycles ≥8**	**For all cycles:** Up to 35 cycles of pembrolizumab and up to 7 cycles (ie, 10 doses) of V938. All cycles are 21 days. For Cycle 2 and 3, D8 and D15 visits including safety assessments can be omitted if V938 is not dosed for that cycle due to interruption or discontinuation.
Visit Day (Days)	**1**	**3**	**5**	**8**	**1**	**8 (Cycles 2-3 only)**	**15 (Cycles 2-3 only)**	**1**	
Visit Window	**+1**	**±1**	**±1**	**±1**	**+3**	**±3**	**±3**	**±3**	**The visit window is +3 days for C2D1 and ±3 days for Day 1 of subsequent cycles.**
Vital Signs * (temperature, pulse, respiratory rate, and blood pressure)	X	X	X	X	X	X	X	X	For Cycle 1, to be measured within 1 h prior to dosing, and 2, 4, and 6 hours (± 30 min for each timepoint) after V938 administration in Cycle 1. For Cycle 2 to Cycle 7, to be measured within 1 h prior to dosing, and 2 and 4 hours (± 30 min for each timepoint) after V938 administration. In addition, for Cycles 2 and 3, to be measured on Day 8 and Day 15. For Cycle 8 and beyond, to be measured within 1 h prior to each dosing with pembrolizumab. * For participants who interrupt or discontinue V938 but continue pembrolizumab, to be measured within 1 h prior to dosing with pembrolizumab.
ECOG Performance Status					X			X	ECOG PS may be performed up to 72 hours prior to dosing.
Concomitant Medication	X	X	X	X	X	X	X	X	
Adverse Events	⟷								Continuous AE reporting from the time of treatment allocation.
Survival Status	⟷								Upon Sponsor request, participants may be contacted for survival status at any time during the course of the study.

Study Period	Treatment Period Cycle = 21 days								Notes
Visit Timing	**Cycle 1**				**Cycle 2-7**			**Cycles ≥8**	**For all cycles:** Up to 35 cycles of pembrolizumab and up to 7 cycles (ie, 10 doses) of V938. All cycles are 21 days. For Cycle 2 and 3, D8 and D15 visits including safety assessments can be omitted if V938 is not dosed for that cycle due to interruption or discontinuation.
Visit Day (Days)	**1**	**3**	**5**	**8**	**1**	**8 (Cycles 2-3 only)**	**15 (Cycles 2-3 only)**	**1**	
Visit Window	**+1**	**±1**	**±1**	**±1**	**+3**	**±3**	**±3**	**±3**	**The visit window is +3 days for C2D1 and ±3 days for Day 1 of subsequent cycles.**
Laboratory Procedures/Assessments – LOCAL									
CBC with Differential				X	X	X	X	X	Perform all scheduled clinical laboratory tests (chemistry and hematology) within 72 hours prior to the start of each new cycle. For PT/INR/PTT/aPTT: Only as clinically indicated Participants on anticoagulant therapy should be monitored throughout the study. Thyroid function: After Cycle 1, samples are collected every other cycle (ie, Cycles 2, 4, 6, etc.). Total T4 and T3 are preferred over FT4 and FT3.
Chemistry Panel				X	X	X	X	X	
PT/INR and PTT or aPTT					X			X	
Thyroid Function Testing (T4 or FT4, T3 or FT3, TSH)					X			X	
Urinalysis					X			X	
Pregnancy test for WOCBP only (urine or serum hCG)	X								Perform within 72 hours prior to C1D1. Urine pregnancy test to be performed as indicated; if test is positive or cannot be confirmed as negative, a serum pregnancy test is required. Additional pregnancy testing can be conducted if required by local regulations or clinically indicated. See country-specific information in Appendix 7.

Study Period	Treatment Period Cycle = 21 days								Notes
Visit Timing	**Cycle 1**				**Cycle 2-7**			**Cycles ≥8**	**For all cycles:** Up to 35 cycles of pembrolizumab and up to 7 cycles (ie, 10 doses) of V938. All cycles are 21 days. For Cycle 2 and 3, D8 and D15 visits including safety assessments can be omitted if V938 is not dosed for that cycle due to interruption or discontinuation.
Visit Day (Days)	**1**	**3**	**5**	**8**	**1**	**8 (Cycles 2-3 only)**	**15 (Cycles 2-3 only)**	**1**	
Visit Window	**+1**	**±1**	**±1**	**±1**	**+3**	**±3**	**±3**	**±3**	**The visit window is +3 days for C2D1 and ±3 days for Day 1 of subsequent cycles.**
Laboratory Procedures/Assessments – CENTRAL									
NDV RNA (V938 PK)	X	X	X	X	X *			X	Collect blood for all required timepoints. Collect **predose** samples 0-24 h before V938 administration on C1D1, C1D3, C1D5, C1D8, C2D1, C3D1, C5D1, and predose samples 0-24 h before pembrolizumab administration on C8D1. Collect **postdose** samples C1D1, C1D8, C2D1 at 2, 4, and 6 h postdose. For C3D1, collect 1 sample between 2 to 4 h postdose. The sample window preference is ± 15 min. * For participants who discontinue V938 prematurely, collect sample an additional 30 days (±7 days) after the last dose of V938. This can be collected at the next cycle of pembrolizumab dosing if pembrolizumab continues or collected at termination/end-of-study and safety follow-up.
Pembrolizumab PK (Cohort 1-4)					X			X	Collect **predose** samples 0-24 h before pembrolizumab administration on C2D1, C3D1, C5D1, C8D1, and every 4 cycles thereafter. Additional **postdose** samples will be collected at termination/end-of-study and safety follow-up.
Pembrolizumab PK (Cohort 2a, 3a, or 4a; and Expansion Cohorts)	X				X			X	Collect **predose** samples 0-24 h before pembrolizumab administration on C1D1, C2D1, C3D1, C5D1, C8D1, and every 4 cycles thereafter. Additional **postdose** samples will be collected at termination/end-of-study and safety follow-up.

Study Period	Treatment Period Cycle = 21 days								Notes
Visit Timing	**Cycle 1**				**Cycle 2-7**			**Cycles ≥8**	**For all cycles:** Up to 35 cycles of pembrolizumab and up to 7 cycles (ie, 10 doses) of V938. All cycles are 21 days. For Cycle 2 and 3, D8 and D15 visits including safety assessments can be omitted if V938 is not dosed for that cycle due to interruption or discontinuation.
Visit Day (Days)	**1**	**3**	**5**	**8**	**1**	**8 (Cycles 2-3 only)**	**15 (Cycles 2-3 only)**	**1**	
Visit Window	**+1**	**±1**	**±1**	**±1**	**+3**	**±3**	**±3**	**±3**	**The visit window is +3 days for C2D1 and ±3 days for Day 1 of subsequent cycles.**
Neutralizing V938 antibodies	X			X	X *			X *	Collect **predose** samples for each time point: 0-24 h before V938 administration on C1D1, C1D8, C2D1, C3D1, C5D1, and predose samples 0 to 24 h before pembrolizumab administration on C8D1. * For participants who discontinue V938 prematurely, collect additional samples 30 days (±7 days) and 60 days (±7 days) after the last dose of V938. • If pembrolizumab is continued after the last dose of V938, neutralizing V938 antibody samples can be collected at the next 3 pembrolizumab treatment cycles (ie, approximately 21, 42, and 64 days after the last dose of V938).
Anti-IL-12 antibodies	X			X	X *			X *	Collect **predose** samples for each time point: 0-24 h before V938 administration on C1D1, C1D8, C2D1, C3D1, C5D1, and predose samples 0-24 h before pembrolizumab administration on C8D1. * For participants who discontinue V938 prematurely, collect additional samples 30 days (±7 days) and 60 days (±7 days) after the last dose of V938. • If pembrolizumab is continued after the last dose of V938, anti-IL-12 antibody samples can be collected at the next 3 pembrolizumab treatment cycles (ie, approximately 21, 42, and 64 days after the last dose of V938).

Study Period	**Treatment Period Cycle = 21 days**								**Notes**
Visit Timing	**Cycle 1**				**Cycle 2-7**			**Cycles ≥8**	**For all cycles:** Up to 35 cycles of pembrolizumab and up to 7 cycles (ie, 10 doses) of V938. All cycles are 21 days. For Cycle 2 and 3, D8 and D15 visits including safety assessments can be omitted if V938 is not dosed for that cycle due to interruption or discontinuation.
Visit Day (Days)	**1**	**3**	**5**	**8**	**1**	**8 (Cycles 2-3 only)**	**15 (Cycles 2-3 only)**	**1**	
Visit Window	**+1**	**±1**	**±1**	**±1**	**+3**	**±3**	**±3**	**±3**	**The visit window is +3 days for C2D1 and ±3 days for Day 1 of subsequent cycles.**
Anti-pembrolizumab antibodies (Cohort 1-4)					X			X	Collect **predose** samples 0-24 h before pembrolizumab administration C2D1, C3D1, C5D1, and C8D1. Additional **postdose** samples will be collected at termination/end-of-study and safety follow-up.
Anti-pembrolizumab antibodies (Cohort 2a, 3a, or 4a; and Expansion Cohort)	X				X			X	Collect **predose** samples 0-24 h before pembrolizumab administration C1D1, C2D1, C3D1, C5D1, and C8D1. Additional **postdose** samples will be collected at termination/end-of-study and safety follow-up.

Study Period	**Treatment Period Cycle = 21 days**								**Notes**
Visit Timing	**Cycle 1**				**Cycle 2-7**			**Cycles ≥8**	**For all cycles:** Up to 35 cycles of pembrolizumab and up to 7 cycles (ie, 10 doses) of V938. All cycles are 21 days. For Cycle 2 and 3, D8 and D15 visits including safety assessments can be omitted if V938 is not dosed for that cycle due to interruption or discontinuation.
Visit Day (Days)	**1**	**3**	**5**	**8**	**1**	**8 (Cycles 2-3 only)**	**15 (Cycles 2-3 only)**	**1**	
Visit Window	**+1**	**±1**	**±1**	**±1**	**+3**	**±3**	**±3**	**±3**	**The visit window is +3 days for C2D1 and ±3 days for Day 1 of subsequent cycles.**
Shedding Analysis 1 (NDV by PCR)	X	X		X	X *			X *	Collect samples from each: oral cavity/throat, urine, injection site, and anal swab. Collect **predose** samples 0-24 h prior to V938 on C1D1, C1D3, C1D8, C3D1, C5D1 and **predose** samples 0-24 h before pembrolizumab administration on C8D1. Collect **postdose** samples on C1D1 at 2 and 4-6 h post dose. The sample window preference is ± 15 min. * For participants who discontinue V938 prematurely, collect shedding samples 30 days (±7 days) and 60 days (±7 days) after the last dose of V938. • If pembrolizumab is continued after the last dose of V938, post V938 shedding samples can be collected at the next 3 pembrolizumab treatment cycles (ie, approximately 21, 42, and 64 days after the last dose of V938).

Study Period	**Treatment Period Cycle = 21 days**								**Notes**
Visit Timing	**Cycle 1**				**Cycle 2-7**			**Cycles ≥8**	**For all cycles:** Up to 35 cycles of pembrolizumab and up to 7 cycles (ie, 10 doses) of V938. All cycles are 21 days. For Cycle 2 and 3, D8 and D15 visits including safety assessments can be omitted if V938 is not dosed for that cycle due to interruption or discontinuation.
Visit Day (Days)	**1**	**3**	**5**	**8**	**1**	**8 (Cycles 2-3 only)**	**15 (Cycles 2-3 only)**	**1**	
Visit Window	**+1**	**±1**	**±1**	**±1**	**+3**	**±3**	**±3**	**±3**	**The visit window is +3 days for C2D1 and ±3 days for Day 1 of subsequent cycles.**
Shedding Analysis 2 (NDV Infectivity)	X	X		X	X*			X*	Collect samples from each: oral cavity/throat, urine, injection site, and anal swab. Collect **predose** samples at 0-24 h prior to V938 on C1D1, C1D3, C1D8, C3D1, C5D1 and **predose** samples 0-24 h before pembrolizumab administration on C8D1. * For participants who discontinue V938 prematurely, collect shedding samples 30 days (±7 days) and 60 days (±7 days) after the last dose of V938. • If pembrolizumab is continued after the last dose of V938, post V938 shedding samples can be collected at the next 3 pembrolizumab treatment cycles (ie, approximately 21, 42, and 64 days after the last dose of V938). Collect **postdose** samples on C1D1 at 2 and 4-6 h post dose. The sample window preference is ± 15 min.
Blood for RNA Biomarker Analyses	X	X		X	X				Collect **blood** for RNA biomarker analyses -4 to 0 h **predose**, and 4-8 h **postdose** of V938 administration on C1D1, C1D3, C1D8, C2D1, and C3D1.
Serum for Cytokine/Chemokine Analyses	X	X		X	X			X	For dose escalation phase, collect **blood** samples -4 to 0 h **predose** and at 2 h (±15 min), 4 h (±15 min), and 6 h (±15 min), **postdose** of V938 administration on C1D1, C1D3, C1D8, C2D1, and C3D1.Collect **blood** samples at predose and 2 h (±15 min) **postdose** of V938 administration on C4D1, C5D1, C6D1, and C7D1. If V938 is discontinued prematurely, samples will not be collected after V938 discontinuation.

Study Period	Treatment Period Cycle = 21 days								Notes
Visit Timing	**Cycle 1**				**Cycle 2-7**			**Cycles ≥8**	**For all cycles:** Up to 35 cycles of pembrolizumab and up to 7 cycles (ie, 10 doses) of V938. All cycles are 21 days. For Cycle 2 and 3, D8 and D15 visits including safety assessments can be omitted if V938 is not dosed for that cycle due to interruption or discontinuation.
Visit Day (Days)	**1**	**3**	**5**	**8**	**1**	**8 (Cycles 2-3 only)**	**15 (Cycles 2-3 only)**	**1**	
Visit Window	**+1**	**±1**	**±1**	**±1**	**+3**	**±3**	**±3**	**±3**	**The visit window is +3 days for C2D1 and ±3 days for Day 1 of subsequent cycles.**
Blood for Genetic Analyses	X								Collect prior to treatment on C1D1.
Tumor Tissue for Biomarker Analysis					X				Dose escalation 2a, 3a, 4a, and cohort expansion phases only. Required within 10 days prior to C3D1 in 1 planned injected lesion. Optional biopsy of 1 planned noninjected lesion 10 days prior to C3D1. Biopsy should be taken from the same tumor lesion(s) for baseline biopsies, respectively, if possible. Instructions for tissue collection, processing, and shipment are provided in the Laboratory Procedures Manual.
^{89}Zr-Df-IAB22M2C CD8 Tracer PET Imaging Evaluation (Cohort Expansion Phase Only)					X				For participants in the CD8 tracer PET imaging study conducted ONLY at selected sites in the US. One to 10 days prior to tumor biopsy, participants will be injected with PET tracer and return for CD8 tracer PET imaging 24 h (± 3 h) and (optional) 6 days (± 1 day) later.
Optional 24-hour Observation Period for CD8 Tracer PET Imaging Evaluation (Cohort Expansion Only)					X				A 24-hour observation period following CD8 tracer infusion is optional. The conduct of this observation will be at the discretion of the investigator.

Abbreviations: aPTT=activated partial thromboplastin time; C = Cycle; CBC = complete blood count; CT = computed tomography; D = Day; ECOG = Eastern Cooperative Oncology Group; FT3 = free triiodothyronine; FT4 = free thyroxine; hCG = human chorionic gonadotropin; IL-12 = interleukin 12; INR = International Normalized Ratio; iRECIST = modified RECIST 1.1 for immune-based therapeutics; IT = intratumoral; MRI = magnetic resonance imaging; NDV = Newcastle Disease Virus; PCR = polymerase chain reaction; PK = pharmacokinetic(s); PT = prothrombin time; PTT = partial thromboplastin time; RECIST 1.1 = Response Evaluation Criteria in Solid Tumors, version 1.1; RNA = ribonucleic acid; T3 = triiodothyronine; T4 = thyroxine; TSH = thyroid-stimulating hormone; WOCBP = women of childbearing potential.

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

Study Period	End of Treatment (EOT)/ Discontinuation	Posttreatment Period			Notes
		30-Day Safety Follow-up Visit	Imaging Follow-up	Survival Follow-up	
Visit Timing		**30 days after the last dose**	**Approxi-mately every 9 weeks**	**Approxi-mately every 12 weeks**	
Visit Window (Days)	**±7**	**+7**	**±7**	**±14**	
Administrative Procedures					
Concomitant Medication	X	X			
Efficacy Procedures					**See Imaging Manual – All imaging visits have a ± 7-day window**
Tumor Imaging, RECIST 1.1 and iRECIST Response Assessment	X		X		
Medical Photography (Cutaneous Lesions)	X		X		
New Anticancer Therapy Status	X	X	X		
Survival Status Monitoring	⟷				Upon Sponsor request, participants may be contacted for survival status at any time during the course of the study. After confirmed disease progression, each participant will be contacted by telephone for survival until participant withdrawal of consent, becoming lost to follow-up, death, or the end of the study.
Safety Assessments and Procedures					**See Laboratory Procedures Manual for collection and management of samples.**
Adverse Event Monitoring	X	X			
Full Physical Examination	X	X			
Weight	X	X			
Vital Signs	X	X			Temperature, pulse, respiratory rate, and blood pressure
ECOG Performance Status	X	X			
CBC with Differential	X	X			
Chemistry Panel	X	X			

Study Period	End of Treatment (EOT)/ Discontinuation	Posttreatment Period			Notes
		30-Day Safety Follow-up Visit	Imaging Follow-up	Survival Follow-up	
Visit Timing		**30 days after the last dose**	**Approxi-mately every 9 weeks**	**Approxi-mately every 12 weeks**	
Visit Window (Days)	**±7**	**+7**	**±7**	**±14**	
Pregnancy Test for WOCBP – Urine or Serum hCG		X			For WOCBP, perform every 30 days during a 120-day period following last dose, and as required locally. If a urine pregnancy test cannot be confirmed as negative, a serum pregnancy test is required.
Thyroid Function (TSH, T3, FT3, T4, FT4)		X			

Abbreviations: CBC = complete blood count; CT = computed tomography; ECOG = Eastern Cooperative Oncology Group; EOT = end of treatment; FT3 = free triiodothyronine; FT4 = free thyroxine; hCG = human chorionic gonadotropin; MRI = magnetic resonance imaging; NDV = Newcastle Disease Virus; PET = positron emission tomography; PK = pharmacokinetic(s); RNA = ribonucleic acid; RECIST v1.1 = Response Evaluation Criteria In Solid Tumors, version 1.1; iRECIST = immune-related RECIST; RNA = ribonucleic acid; T3 = triiodothyronine; T4 = thyroxine; TSH = thyroid-stimulating hormone; WOCBP = women of childbearing potential.

2 INTRODUCTION

Significant progress has been made in the field of immunotherapy to treat cancer. Antibodies targeting immune checkpoints have yielded impressive improvements in clinical outcomes for a range of tumor types. Despite this however, the majority of advanced cancer patients do not respond to immunotherapy alone, due to local immune tolerance at the tumor, absence of effector cells, and/or the development of resistance through a variety of adaptive mechanisms [Park, Y. J., et al 2018] [Sharma, P., et al 2017]. V938 is a novel oncolytic viral therapy that employs recombinant NDV engineered to encode human IL-12, being developed for IT/intralesional injection to treat advanced cancers.

This is a Phase 1 FIH study to assess the safety, tolerability, and PK/pharmacodynamics of V938 in combination with pembrolizumab for the treatment of advanced solid tumors.

2.1 Study Rationale

There is a great unmet medical need for therapeutic agents that can enhance the effect of immunotherapy. In preclinical studies, IT V938 was shown to overcome tumor resistance to immunotherapy via multiple mechanisms including activation of natural killer cells, cytotoxic CD8+ T cells, T cells that produce type 1 cytokines, and B cells [Trinchieri, G. 2003]. NDV is a potent inducer of immunogenic cell death [Cuadrado-Castano, S., et al 2015] and can induce type 1 IFN responses that trigger both innate and adaptive immune activations [Fournier, P., et al 2012] [Fernandez-Sesma, A., et al 2006]. The key potential advantage of NDV over other strategies that induce a type 1 IFN antitumor response is that in addition to induction of IFN-α by immune cells, NDV induces immune-cell death of infected tumor cells that results in release of cytokines, chemokines, and viral RNA that is recognized by immune cells. Finally, in preclinical studies in tumor-bearing mice, NDV armed with IL-12 in combination with muDX400 (mouse anti-programmed cell death ligand 1) resulted in the longest median OS compared with other treatment groups.

The empirical rationale for combining V938 with anti-PD-1 is based on the data from experiments in anti-PD-1-resistant syngeneic mouse tumor models that recapitulate many attributes of the proposed patient population. In these models, the combination of NDV-IL-12 with anti-PD-1 monotherapy resulted in significant reduction in tumor volumes in both injected and noninjected tumors, including complete regressions in 6 of 10 injected and 5 out of 10 noninjected tumors, demonstrating how NDV breaks resistance to immune checkpoint blockade. For further details, please refer to the V938 IB. The development plan is to evaluate V938 in combination with KEYTRUDA® (pembrolizumab) to improve efficacy over pembrolizumab alone. At the current time, as the preclinical studies most strongly support combination treatment, there are no plans to develop V938 as monotherapy treatment.

NDV possesses a number of potential immunological and safety advantages relative to other oncolytic agents. A summary of the immunological advantages of NDV relative to other DNA viruses (eg, adenovirus and herpesvirus) and other RNA viruses (eg, coxsackievirus) follows [Schirrmacher, V. 2016]:

- NDV is an avian pathogen and serology studies indicate that approximately 96% of the human population is seronegative. This circumvents the problem of pre-existing human immunity and pathogenicity [Miller, L. T. 1971] [Charan, S., et al 1981]. Both pre-existing immunity and pathogenicity are identified problems for vaccinia, herpes simplex virus (HSV)-1, adenovirus, and measles vectors.

- NDV possesses strong immune-stimulatory properties through induction of type 1 IFN and chemokines, upregulation of major histocompatibility complex and cell adhesion molecules, and facilitation of adhesion of lymphocytes and antigen-presenting cells through expression of viral glycoproteins on the surface of infected cells [Washburn, B. 2002]. These properties have been shown to generate effective antitumor immune responses, which may persist long after clearance of viral infection. In addition, by induction of secretion of proinflammatory cytokines and chemokines from tumor cells themselves, NDV potentially can convert a “cold” tumor to “hot” by recruitment of mediators of innate and immune responses such as NK cells, lymphocytes, and macrophages.

- The NDV genome allows for “arming” via the incorporation and stable expression of foreign genes of relatively large size. NDV, with a 15 kb genome and a diameter of 100 to 500 nm, has the capacity to encode one or more transgenes [DiNapoli, J. M., et al 2007]. This contrasts with other RNA viruses such as the picornaviruses Coxsackie, Seneca Valley, and Polio which are ~30 nm in diameter and do not have the capacity to stably encode a transgene.

- The ubiquitous nature of the NDV receptor allows for utilization of the virus against a wide variety of cancers. The specificity of the virus for cancer cells due to their defects or hyporesponsiveness in antiviral and apoptotic pathways ensures viral safety and may obviate the need for specific tumor targeting.

Several characteristics suggest that NDV will offer potential safety advantages relative to other oncolytic agents currently licensed or in development:

- Lack of integration with host cell DNA. NDV is an RNA virus that replicates in the cytoplasm. It lacks any form of a DNA intermediate; therefore, there is no possibility of integration of the virus in the host genome.

- Mild side effects in cancer patients. The reported side effects with NDV administration (nonsystemic formulations) in cancer patients in various studies were Grade 1 and 2.

- Replication of NDV is sensitive to IFN-based inhibition of replication; therefore, NDV is less likely to replicate permissively in nontumor cells/tissues in patients.

- The LaSota strain is nonpathogenic for its natural host (avian species) and humans; therefore, it exhibits enhanced safety over pathogenic strains by limiting the production of infectious virus progeny in treated patients. The replicative capacity of NDV is dependent on proteolytic conversion of the prefusion protein F0 to its active F form. This is governed by the sequence of amino acids that constitute the cleavage site. Virulent velogenic and mesogenic strains contain a double-basic (B) amino acid sequence of the general form BB-X-Q-X-BB, which permits cleavage of the F protein by intracellular proteases during F protein secretion/maturation in the infected cell as the protein traverses through the Golgi network. An enzyme in the trans Golgi, furin, cleaves and thereby activates the fusion property of the F protein. The amino acid sequence of the LaSota F protein at the cleavage activation site is not recognized as a furin substrate; therefore, virions are produced that are not infectious unless extracellular proteases activate them. Lentogenic viruses are propagated in embryonated eggs via activation of the F protein by a protease present in the allantoic fluid. Replication of lentogenic viruses will be self-limited in patients because although the viruses will replicate in tumor cells and produce viral progeny; the new virions will not be infectious due to the lack of cleavage of the F protein by cellular proteases [Panda, A., et al 2004].

The selection of IL-12 for the arming strategy may offer a potential advantage to improve on efficacy over T-VEC and MEDI5395, which both encode for GM-CSF. Emerging clinical data with Oncosec's ImmunoPulse® IL-12 show abscopal effects as monotherapy and in combination with pembrolizumab in patients with melanoma (EUROGIN 2016, ASCO-SITC 2017, and Keystone Symposium Conference "Cancer Immunology and Immunotherapy: Taking a Place in Mainstream Oncology" 2017). The effects of IL-12 include stimulation of CD8 and CD4 T cell proliferation and effector activity, differentiation of naïve T cells toward a TH1 phenotype, induction of IFN-γ, and potentiation of IL-2 signaling [Gately, M. K., et al 1998]. Preclinical studies showed that expression of IL-12, and not GM-CSF, enhanced the antitumor activity of a recombinant oncolytic HSV-1/2 virus in syngeneic mouse prostate tumor models [Varghese, S., et al 2006]. PD-1 blockade by pembrolizumab can show a protective effect on newly generated immune cell effectors in the tumor microenvironment and prevent inhibition of immune response (refer to the V938 IB). Therefore, a combination of the 2 treatment strategies can potentially enhance an antitumor response.

For preapproved study sites in the US only, a CD8 tracer PET imaging study will be performed to assess the CD8 tracer ^{89}Zr-Df-IAB22M2C. The ability to visualize CD8+ T cells in vivo before and after treatment would be highly valuable for the development of immuno-oncology treatments, and such a method has been unavailable. ^{89}Zr-Df-IAB22M2C has been developed by ImaginAb for imaging CD8+ T cells in humans. ImaginAb's initial clinical evaluation of ^{89}Zr-Df-IAB22M2C demonstrated favorable properties for clinical use and the potential targeting of CD8+ T cells [Pandit-Taskar, N., et al 2016]. The CD8 tracer PET imaging study will evaluate the quantitative accuracy of ^{89}Zr-Df-IAB22M2C for measuring CD8+ T cells in tumors by establishing the relationship of ^{89}Zr-Df-IAB22M2C accumulation in tumors with CD8+ TIL density measured by IHC following tumor biopsy. The goal of this study is to establish best practices for further development of ^{89}Zr-Df-IAB22M2C within the Sponsor's immuno-oncology studies.

This Phase 1/1b multicenter, open-label, study will evaluate the safety, tolerability, and preliminary antitumor activity of V938 via IT injection in combination with pembrolizumab IV in participants with advanced or recurrent solid tumors.

The study will be performed in compliance with the protocol, ICH, GCP, and local regulatory requirements. Aspects of the study concerned with manufacture and labeling of V938 will meet the requirements of GMP.

2.2 Background

Refer to the V938 IB for detailed background information on V938 and to the pembrolizumab IB for detailed background information on pembrolizumab. This is an FIH study.

2.2.1 Pharmaceutical and Therapeutic Background

2.2.1.1 V938 Pharmaceutical and Therapeutic Background

The virus was assembled in and rescued from baby hamster kidney cells and subsequently propagated in embryonated chicken eggs. A fit-for-purpose production and purification process suitable for GMP manufacture has been developed for Phase 1. Refer to the V938 IB for further information.

2.2.1.2 Mechanism of Action

NDV is an enveloped, nonsegmented, negative-sense single-stranded RNA avian virus of the Paramyxoviridae family [Lamb, R. A. 2013]. The NDV genome allows for “arming” via the incorporation and stable expression of foreign genes of relatively large size [DiNapoli, J. M., et al 2007], allowing for the selection of human IL-12 for our arming strategy. This arming strategy may offer a potential advantage to improve efficacy over other oncolytic virus strategies, such as those that encode GM-CSF, due to its enhanced antitumor activity [Varghese, S., et al 2006] [Choi, K. J., et al 2012]. Preclinical data support the combination of IT administration of V938 with an anti-PD 1 monoclonal antibody. This combination is hypothesized to have activity against a wide spectrum of malignancies in vivo, including the noninflamed cold tumors for which anti-PD-1 monotherapy has demonstrated limited efficacy. The key properties of NDV are tumor-selective replication and lysis and immunostimulatory activities. Induction of secretion of proinflammatory cytokines and chemokines from tumor cells potentially can convert a “cold” tumor to “hot” by recruiting NK cells, lymphocytes, and macrophages into the tumor.

2.2.1.3 Preclinical Studies of V938

Please refer to the V938 IB for a description of preclinical evaluations of V938.

2.2.1.4 Pembrolizumab Pharmaceutical and Therapeutic Background

The importance of intact immune surveillance function in controlling outgrowth of neoplastic transformations has been known for decades [Disis, M. L. 2010]. Accumulating evidence

shows a correlation between tumor infiltrating lymphocytes in cancer tissue and favorable prognosis in various malignancies. In particular, the presence of CD8+ T cells and the ratio of CD8+ effector T cells/FoxP3+ regulatory T cells correlates with improved prognosis and long-term survival in patients with solid malignancies, such as ovarian, colorectal, and pancreatic cancer; hepatocellular carcinoma; malignant melanoma; and renal cell carcinoma. Tumor-infiltrating lymphocytes can be expanded ex vivo and reinfused, inducing durable objective tumor responses in cancers such as melanoma [Dudley, M. E., et al 2005] [Hunder, N. N., et al 2008].

The PD-1 receptor-ligand interaction is a major pathway hijacked by tumors to suppress immune control. The normal function of PD-1, expressed on the cell surface of activated T cells under healthy conditions, is to down-modulate unwanted or excessive immune responses, including autoimmune reactions. PD-1 (encoded by the gene Pdcd1) is an immunoglobulin (Ig) superfamily member related to 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 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]. As a consequence, the PD-1/PD-L1 pathway is an attractive target for therapeutic intervention in solid tumors. Please refer to the current pembrolizumab IB for a description of preclinical and clinical evaluations of pembrolizumab.

2.2.2 Information on Other Study-related Therapy

Not applicable.

2.3 Benefit/Risk Assessment

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

Potential risks associated with the administration of V938 based on nonclinical data and mechanism of action may include the following:

- Local reactions at the injected tumor site (swelling, induration, erythema)
- Transient elevation of white blood cell count
- Fevers, chills, headache, flu-like symptoms

Additional details regarding specific benefits and risks for participants participating in this clinical study may be found in the accompanying V938 and pembrolizumab IBs and informed consent documents.

2.3.1 Ongoing Clinical Studies

2.3.1.1 V938 Clinical Studies

This is the first clinical study with V938.

2.3.1.2 Pembrolizumab Clinical Studies

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

3 HYPOTHESES, OBJECTIVES, AND ENDPOINTS

Throughout this protocol, the term RECIST 1.1 refers to modification to RECIST 1.1 to include a maximum of 10 target lesions and a maximum of 5 target lesions per organ. Refer to Section 4.2.1.1.1 for further details.

In male/female participants with advanced/metastatic solid tumors:

Objectives	Endpoints
Primary	
Objective: To determine the safety and tolerability and to identify a recommended Phase 2 dose (RP2D) of V938 administered in combination with pembrolizumab	Dose-limiting toxicity (DLT) Adverse events (AE) Discontinuing study intervention due to an AE
Secondary	
Objective: To evaluate the objective response rate (ORR), as assessed by the investigator, of V938 administered in combination with pembrolizumab. Assessment will be based on Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST 1.1) and modified RECIST 1.1 for immune-based therapeutics (iRECIST).	Objective response is a confirmed complete response (CR) or partial response (PR)
Objective: To evaluate the pharmacokinetics (PK) of V938 administered alone and in combination with pembrolizumab.	PK parameters of V938, including area under the curve (AUC) and maximum concentration (C_{max}) of Newcastle Disease Virus (NDV) RNA
Objective: To assess environmental V938 shedding	NDV in excretory tissue samples
Tertiary/Exploratory	
To evaluate overall survival (OS) and progression-free survival (PFS) of participants treated with V938 in combination with pembrolizumab. Assessment will be based on RECIST 1.1 and iRECIST.	OS is the time from the first dose of study treatment to death due to any cause PFS is the time from the first dose of study treatment to the first documented disease progression or death due to any cause, whichever occurs first
To identify molecular (genomic, metabolic and/or proteomic) biomarkers that may be indicative of clinical response/resistance, safety, pharmacodynamic activity, and/or the mechanism of action of V938 in combination with pembrolizumab.	Molecular (genomic, metabolic, and/or proteomic) determinants of response or resistance to treatments, using blood and/or tumor tissue.

Objectives	Endpoints
Objective: To evaluate the PK of pembrolizumab administered in combination with V938	PK parameters of pembrolizumab including minimum concentration (C_{min}) and C_{max}
To evaluate the development of antidrug and neutralizing antibodies, as appropriate, following administration of V938 and in combination with pembrolizumab	Neutralizing V938, anti-IL-12, and anti-pembrolizumab antibody levels
To evaluate performance of ^{89}Zr-Df-IAB22M2C (CD8) PET tracer in context of cancer immunotherapy	Standardized uptake value (SUV) from CD8 PET image CD8 immunohistochemistry (IHC) score

4 STUDY DESIGN

4.1 Overall Design

This is a FIH, multiarm, multicenter, global, open-label, Phase 1/1b study of V938 in combination with pembrolizumab in participants with a histologically confirmed diagnosis of an advanced solid tumor.

This study will evaluate the safety, tolerability, PK/pharmacodynamics, and preliminary efficacy of V938 in combination with pembrolizumab. Each candidate participant will have a screening period of up to 28 days for evaluation of eligibility and performing baseline assessments. Each participant must have a minimum of 1 lesion that is either cutaneous, subcutaneous, or nodal and is amenable to IT injection.

Eligible participants will start to receive study treatment on C1D1 and have required safety, efficacy, and other assessments per SoA (see Section 1.3).

The study includes a Dose-escalation Phase and a Cohort Expansion Phase. See Figure 1 for the study design schema and detailed description of Dose-escalation and Cohort Expansion in Section 4.1.1 and Section 4.1.2, respectively.

4.1.1 Dose-escalation Phase

The primary goal for the dose-escalation phase is to evaluate safety, tolerability, and PK/pharmacodynamics of V938 as monotherapy and in combination with pembrolizumab, with an ultimate goal of determining a RP2D of V938 in combination with pembrolizumab.

V938 IT will be evaluated at 4 dose levels: $1x10^7$ PFU (Dose Level 1, evaluated via Cohort 1), $1x10^8$ PFU (Dose Level 2, evaluated via Cohort 2 and possibly Cohort 2a), $3x10^8$ PFU (Dose Level 3, evaluated via Cohort 3 and Cohort 3a) and $5x10^8$ PFU (Dose Level 4, evaluated via Cohort 4 and Cohort 4a). The dosing schedule of V938 is the same across all

the cohorts with 4 doses during Cycle 1 on Days 1, Day 3, Day 5, Day 8 and 1 dose each on Day 1 of Cycle 2 to Cycle 7. Therefore, V938 will be dosed for a maximum of 10 doses.

Pembrolizumab will be dosed 200 mg IV Q3W for a maximum of 35 doses (in approximately 24 months) across all cohorts. Pembrolizumab dosing will start on C2D1 for Cohorts 1-4, which allows to evaluate safety and PK/pharmacodynamics of V938 as monotherapy for the first cycle. Pembrolizumab dosing for Cohorts 2a-4a will start on C1D1.

In general, dose escalation will progress using an mTPI design [Ji Y, Li Y, Bekele BN 2007] with the goal to identify the MTD and/or maximum administered dose of V938 administered as combination with pembrolizumab (Figure 1). Intermediate doses of V938 may also be explored with additional cohorts, depending on the combined safety, PK, and pharmacodynamics data available at each dose level.

During dose escalation, 3 to 6 participants will be initially enrolled to each dose level starting with Cohort 1. Treatment assignments will be nonrandom via an interactive voice response system/integrated web response system (IVRS/IWRS). Enrollment at the next dose level will begin once all participants in the current dose level complete DLT evaluation and a dose-escalation decision has been made. The DLT evaluation period for Cohorts 1-4 is 42 days (Cycle 1 + Cycle 2) to evaluate safety and PK/pharmacodynamics of 1 cycle of V938 as monotherapy and 1 cycle of V938 in combination with pembrolizumab; the DLT evaluation period for Cohorts 2a-4a is 21 days (Cycle 1 only) as pembrolizumab and V938 both start on C1D1.

For each participant enrolled to the dose-escalation cohorts, a minimum 24-hour inpatient observation period is required (may be longer based on institutional guidance) following administration of V938 for the first 2 doses (C1D1 and C1D3). For each new dose cohort, initiation of V938 treatment will be staggered by a 7-day period for the first 3 participants at that dose level (ie, between the first and the second, and between the second and the third enrolled participants).

For Cohorts 2a-4a, each enrolled participant must have at least 1 measurable lesion amenable to both IT injection and biopsy. One of the planned injected lesions will undergo (mandatory) biopsy during the screening period, once all other eligibility has been confirmed for the participant and within 10 days prior to C3D1 dosing. These biopsies (baseline and C3D1 biopsy for the same injected lesion) are mandatory unless deemed medically unsafe by the investigator or the lesion has completely resolved.

Dose escalation will end after up to 14 participants have been treated at any of the selected doses (which may include intermediate or higher dose levels) and the decision based on Table 1 is to stay. Dose-finding may also stop prior to enrolling 14 participants in a given dose. For example, if there were 0 out of 8 DLTs observed in the highest dose level, then even if the next 6 participants experienced a DLT, the decision would still be to stay at the highest dose. The pool adjacent violators algorithm [Ji, Y. 2013] will be used to estimate the DLT rates across doses. The totality of the data (including safety, PK, pharmacodynamics, and efficacy) will be considered before deciding on the RP2D.

The preferred V938 and pembrolizumab combination schedule is to have both V938 and pembrolizumab started on C1D1, hence selection of RP2D will be among Cohorts 2a, 3a, and 4a. See Section 4.3.3 for details on dosing finding using mTPI design and algorithm for dose escalation, stay, or de-escalation decisions for Cohorts 2a-4a.

4.1.2 Cohort Expansion Phase

Once a RP2D has been selected from Cohorts 2a-4a based on the totality of the data, including safety, efficacy, and manufacturing considerations (see Section 4.3), V938 and pembrolizumab combination will be further evaluated in the following tumor-specific arms for additional safety, preliminary efficacy, and additional PK/pharmacodynamics and biomarker data.

- Arm A will enroll participants with metastatic melanoma who have received and progressed from 1 or 2 prior lines of systemic treatment for metastatic melanoma, which must include 1 line of treatment with a PD1 or PD-L1 inhibitor either as monotherapy or in combination with other anticancer agents.

- Arm B will enroll participants with metastatic HNSCC who have received and progressed from 1 or 2 prior lines of systemic treatment for metastatic HNSCC, which must include 1 line of treatment with a PD1 or PD-L1 inhibitor either as monotherapy or in combination with other anticancer agents.

For each arm in the expansion cohorts, an interim analysis will be conducted once there are approximately 20 evaluable participants with at least 2 post-treatment tumor assessments (~18 weeks after start of treatment). For each arm, if there is ≤2 responder among the first 20 participants enrolled in that arm, the arm may be stopped early for futility. If 3 or more responders are observed from an arm, further expansion will be considered (see Section 9.7 for more details).

The assessments and schedules for the expansion cohorts (Arm A and Arm B) will follow that of dose-escalation Cohorts 2a-4a including the requirement for tumor biopsy (see Section 1.3 for SoA and Section 4.1.1 for detailed lesion requirement for baseline and on-treatment tumor biopsy).

A CD8 tracer PET imaging assessment will be performed at preapproved sites only in the US with 7-10 participants. These participants will undergo CD8 tracer PET imaging evaluation during the screening period and within 10 days prior to C3D1. At each time point, participants will be injected with a dose of 0.5-1.5 mg, or 0.8-1.2 mCi (26-48 MBq) of ^{89}Zr-Df-IAB22M2C tracer (CD8 tracer) as an IV infusion over 5-10 minutes using a syringe pump via a peripheral vein. Participants will return for PET imaging scans, one at 24 hours (±3 hours) and an optional second scan at 6 days (±1 day) after tracer infusion. The CD8 tracer infusion will occur 1 to 4 days prior to tumor biopsy.

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

V938 is an oncolytic virus armed with a human IL-12 transgene that offers potential immunological and safety advantages over other oncolytic viruses. V938 is being evaluated in a clinical study designed to assess the safety, tolerability, PK, and pharmacodynamics of escalating doses of V938 when used in combination with pembrolizumab in participants with advanced/refractory solid tumors.

This study exposes a small number of participants to each dose of V938 in combination with pembrolizumab and enrolls different participants for each cohort. A low starting dose is used to evaluate safety with minimal risk to participants.

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

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

4.2.1 Rationale for Endpoints

4.2.1.1 Efficacy Endpoints

Efficacy endpoints in this study include ORR (secondary endpoint, defined as the proportion of participants who have achieved confirmed CR or PR), PFS (exploratory), and OS (exploratory).

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

Tumor response in participants with solid tumors will be assessed using RECIST 1.1 and iRECIST (see Section 4.2.1.1.1 and Section 4.2.1.1.2) by investigator review. Antitumor activity will be measured through such endpoints as the ORR, PFS, and OS, which are described further in Section 9.4.1. A central imaging vendor will be used to collect, clean, and hold tumor imaging and medical photography from all patients enrolled in the study per the collection frequency outlined in the SoA. Images will be collected for possible analysis by blinded, independent central review. Instructions for collection and sending images from the site to the central vendor will be included in the imaging manual.

4.2.1.1.1 Response Rate Assessed by RECIST Version 1.1

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

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

iRECIST 1.1 will be adapted to account for the unique tumor response characteristics seen following treatment with pembrolizumab (Section 8.2.7). 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 OS 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.

iRECIST assessment has been developed and published by the RECIST Working Group, with input from leading experts from industry and academia, along with participation from the US Food and Drug Administration and the 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 as well as for secondary and tertiary/exploratory efficacy analyses.

For further information on iRECIST, see Section 8.2.7.

4.2.1.2 Safety Endpoints

The primary objective of this study is to characterize the safety and tolerability of V938 in combination with pembrolizumab in participants with advanced/ metastatic solid tumors. The primary safety analysis will be based on participants who experience toxicities as defined by CTCAE Version 4.0 criteria and DLTs further defined in Section 6.6.2. Safety will be assessed by quantifying the toxicities and grades of toxicities experienced by participants who have received V938 and in combination with pembrolizumab.

For AEs, attribution to drug, time-of-onset, duration of the event, its resolution, and any concomitant medications administered will be recorded. Adverse events that will be analyzed include, but are not limited to, all AEs, SAEs, fatal AEs, and laboratory changes. Viral shedding (including NDV PCR and infectivity) will be analyzed as an additional safety endpoint.

Assessment of safety will be monitored continuously throughout this Phase 1, open-label exploratory study. The approach to safety includes ongoing, frequent medical monitoring of AEs as they occur with timely and robust discussion around any safety events. SAEs will be followed until resolution, stabilization, until the event is otherwise explained, or the participant is lost to follow-up. Additional approaches to safety include: 1) a stepwise approach to enrollment with each new dose level requiring a minimum of 3 participants to be enrolled and complete the DLT evaluation period before enrollment of additional participants, and 2) utilization of a modified toxicity probability interval in the dose-escalation phase to determine requirements in dose adjustments and as a prerequisite to advance to the cohort expansion phase of the protocol. The totality of the data will be reviewed before deciding on the dose to carry forward to the cohort expansion phase and may be adjusted based on PK and emerging safety data. Additional details regarding medical monitoring can be found in Section 10.1.4.1.

4.2.1.3 Pharmacokinetic Endpoints

A secondary objective of this study is to characterize the PK profile of V938 following IT administration as a single agent, and to characterize the PK profile of V938 and pembrolizumab following administration as combination therapy. The RNA levels of V938 and the serum concentrations of pembrolizumab will serve as the primary readout for the PK, and these data will be used to derive PK parameters (AUC and C_{max} of NDV RNA) of the agents when administered in combination with pembrolizumab. 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 V938.

4.2.1.4 Pharmacodynamic Endpoints

4.2.1.4.1 Target Engagement

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

4.2.1.5 Anti-drug Antibodies (ADA)

Antibodies against V938 and pembrolizumab (eg, neutralizing antibodies and ADA) can potentially confound drug exposures at therapeutic doses and prime for subsequent infusion-related toxicity. Immunogenicity will be assessed at the beginning of each cycle. The incidence of immunogenicity will be evaluated and summarized over time by dose. Correlations between the presence/absence of positivity for immunogenicity and PK and pharmacodynamic markers, activity, and safety of V938 will be explored.

4.2.1.6 Serum Cytokines

Because treatment with V938 can result in immune stimulation and resulting potential for cytokine release, serum cytokines will be collected to provide supplementary information to assist in the evaluation of any safety events.

4.2.1.7 Planned Exploratory Biomarker Research

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

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

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

Genetic (DNA) analyses from tumor

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

Tumor and blood RNA analyses

Both genome-wide and targeted messenger RNA (mRNA) expression profiling and sequencing in tumor tissue and in blood may be performed to define gene signatures that correlate to clinical response to treatment with pembrolizumab or other immunotherapies. Pembrolizumab induces a response in tumors that likely reflects an inflamed/immune phenotype. Specific immune-related gene sets (ie, those capturing interferon-gamma

transcriptional pathways) may be evaluated and new signatures may be identified. Individual genes related to the immune system may also be evaluated (eg, IL-10). MicroRNA profiling may also be pursued as well as exosomal profiling.

Proteomics and immunohistochemistry (IHC) using blood or tumor

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

Other blood-derived biomarkers

In addition to expression on the tumor tissue, PD-L1 and other tumor derived proteins can be shed from tumor and released into the blood. Assays such as enzyme-linked immunoassay (ELISA) measure such proteins in serum. Correlation of expression with response to pembrolizumab therapy may identify new approaches for predictive biomarkers in blood, representing a major advance from today's reliance on assessing tumor biomarkers. This research would serve to develop such assays for future clinical use.

CD8 PET imaging

An experimental CD8 PET tracer (^{89}Zr-Df-IAB22M2C) will be used to assess levels of CD8 T cells within tumors in a sub-population of the study. The data collected from CD8 PET imaging with ^{89}Zr-Df-IAB22M2C will be compared with CD8 IHC in order to establish details pertaining to the sensitivity of the imaging agent within tumors.

4.2.1.8 Future Biomedical Research

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

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

participants receive the correct dose of the correct drug/vaccine at the correct time. The details of future biomedical research are presented in Appendix 6.

4.2.2 Rationale for Selection of Expansion Cohorts

PD-1 immune checkpoint inhibitors have demonstrated highly significant improvement in clinical efficacy for treating advanced cancers including advanced melanoma and HNSCC, either as single agent or in combination with chemotherapy or other immunotherapeutic agents and have become the new standard of care for these advanced cancers (NCCN guideline v4.2020 for cutaneous melanoma; NCCN guideline v2.2020). However, there are still a large proportion of patients who are refractory to the initial anti-PD-1 treatment, therefore an area with significant unmet medical need.

As elaborated in Section 2.1, NDV is a potent inducer of immunogenic cell death that can trigger both innate and adaptive immune activations via type I IFN responses. IL-12 is a cytokine can elicit strong proinflammatory reactions such as stimulation of CD4 and CD8 T-cell priming, proliferation, and their effector activity. In the preclinical in vivo studies, significant antitumor efficacy was observed with NDV-muIL-12 (murine surrogate of V938) in combination with muDX400, a murine anti-PD1, compared to either NDV-muIL-12 or muDX400 alone (see V938 IB Section 4). There is a potential that V938 can help overcome resistance to PD-1 inhibitor like pembrolizumab in these advanced cancers.

4.3 Justification for Dose

4.3.1 Starting and Maximum Dose of V938 and Rationale

The current projected safe starting clinical dose of V938 is 1×10^7 PFU, which is also expected to show clinical response. The dose projection is based on efficacy data from a B16F10 mouse bilateral tumor growth inhibition study, and cytokine data from 2 studies: an IV dose-ranging kinetic study in CD-1 mice and IT dosing study in tumor-bearing B16F10 mice. Please refer to V938 IB (Section 4) for details.

To determine the starting dose for the FIH study, the following approaches were used: (1) tumor volume normalization for the efficacious dose, and (2) serum cytokine predictions, (ie, projected serum levels of IL-12 and IFN-γ following V938 dosing in participants). Using both approaches, we predict a safe and efficacious starting dose for V938 to be 1×10^7 PFU in a 1 cm^3 human tumor.

The NOAEL dose in nonclinical rodent toxicity studies is 3×10^8 PFU given IV, which after normalizing to mouse body weight of 0.030 kg is 1×10^{10} PFU/kg. This NOAEL dose is 60,000-fold higher than the planned starting clinical dose of 1.67×10^5 PFU/kg (1×10^7 PFU normalized to 60-kg human).

A maximum clinical dose of 1×10^9 PFU is predicted to be safe and efficacious. The rodent NOAEL dose is 600-fold higher than the planned maximum clinical dose of 1.67×10^7 PFU/kg (1×10^9 PFU normalized to 60-kg human). This maximum dose is chosen based on modeling for safety and efficacy and on manufacturing complexities.

4.3.2 Rationale for Dose Interval and Escalation Increments

The human starting dose and dosing interval of V938 are based on an integration of nonclinical toxicological, pharmacological, and efficacy data. To ensure early and maximum treatment effect after IT dosing, V938 will initially have an accelerated every-2-days dosing frequency followed by a Q3W dosing frequency matching pembrolizumab dosing frequency. The10-fold increment between dose levels 1 and 2, during dose escalation, was chosen to ensure adequate dose differences based on in vitro activity. The development plan is to evaluate V938 in combination with pembrolizumab to improve efficacy over pembrolizumab alone. There are no plans to develop V938 as monotherapy treatment.

Cohorts 1-4 include Cycle 1 as a V938 monotherapy cycle for evaluation of safety, PK, and PD of V938 monotherapy before addition of pembrolizumab on C2D1. Cohorts 2a-4a have pembrolizumab dosing starts on C1D1 together with V938. This schedule will allow PD1/PD-L1 immune checkpoint inhibition to be unleashed within the tumor microenvironment and get the immune system ready to respond once immune activities are elicited by V938 via local tumor injection. It is expected that initiation of pembrolizumab on C1D1 may provide better clinical efficacy than delaying pembrolizumab by 1 cycle. In the preclinical in vivo studies using B16F10 mice bilateral tumor model, concurrent combination treatment with muDX400 (mice version of PD1 inhibitor) and NDV-muIL-12 showed significant survival benefit compared to treatment with either agent alone (see V938 IB Section 4).

4.3.3 Dose Finding Using a Modified Toxicity Probability Interval Design

Dose-finding will follow the mTPI design [Ji Y, Li Y, Bekele BN 2007] with a target DLT rate of 30%. Dose-escalation and de-escalation decisions are based on the mTPI design and depend on the number of participants enrolled and number of DLTs observed at the current dose level. The DLT analysis includes only the dose-escalation phase of the protocol.

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

When adding participants to a dose level in response to a "stay" decision, the number of additional participants to be enrolled is capped to minimize the exposure to a dose that may be unacceptably toxic (denoted as DU in Table 1). Second, to determine how many more participants can be enrolled at the dose level, one can count steps in diagonal direction (down and to the right) from the current cell to the first cell marked DU. For example, if 1 of 3 participants have experienced a DLT at a given dose level, no more than an additional 3 participants should be enrolled at this dose level until additional DLT data are available. This is because this dose level would be considered unacceptably toxic if all 3 of the additional participants experience a DLT (ie, 4/6 participants with DLT in Table 1). The same principles will be applied whether 3, 4, 5, or 6 participants are initially enrolled at that dose level.

A D or DU decision at the lowest dose level will stop the study. An E decision at the highest dose level will result in staying at that level. During dose-finding, it may be acceptable to de-escalate to an intermediate dose that was not predefined and not previously studied if evaluation of toxicity at such a dose is desired. If this approach is taken, 3 to 6 new participants may be enrolled at the new intermediate dose, and the aforementioned rules should be used to determine further enrollment at this dose level.

After 14 participants have been enrolled at any of the tested doses in the dose-escalation phase (including intermediate doses), dose-finding will stop if the mTPI table indicates "S" for staying at current dose. Otherwise, up to 14 new participants may be enrolled at a lower dose if "D" or "DU" is indicated, or at a higher dose if "E" is indicated. Dose-finding may also stop prior to enrolling 14 participants in a given dose. For example, if there were 0 out of 8 DLTs observed in the highest dose level, then even if the next 6 participants experienced a DLT, the decision would still be to stay at the highest dose. In this case, dose-finding is complete after observing the 0 out of 8 DLTs in the highest dose.

The pool adjacent violators algorithm [Ji, Y. 2013] will be used to estimate the DLT rates across doses. The dose with an estimated DLT rate closest to 30% will be treated as a preliminary MTD. However, the totality of the data will be considered before deciding on the dose(s) to carry forward to Phase 2, and the escalation schedule may be adjusted based on pharmacodynamics, PK, and safety data emerging throughout the study.

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

Table 1 Dose-finding Rules per mTPI Design

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

D=De-escalate to the next lower dose; DU=The current dose is unacceptably toxic; E=Escalate to the next higher dose; S=Stay at the current dose.

Target toxicity rate = 30%

Flat noninformative prior Beta (1,1) is used as a prior and ε1=ε2=0.03 [Ji Y, Li Y, Bekele BN 2007] [Ji, Y. 2013] [Ji, Y., et al 2010]

4.3.4 Dose Escalation, Stay or De-escalation Decision for Cohorts 2a, 3a and 4a

New cohorts for evaluation of dosing schedule with both V938 and pembrolizumab starting on C1D1 will be included via V938-001 Amendment 05 when the dose-finding decision has been made for Cohort 3, according to the rules described from the mTPI design (Section 4.3.3). When Cohort 3a, 4a, or 2a is open, 3 to 6 participants will be enrolled initially to each cohort, with potential to expand up to 14 participants. It is not necessary to have Cohort 3 or Cohort 4 expanding to 14 participants before transition to Cohort 3a, 4a, or 2a. The following algorithms are implemented for decision on dose-escalation, stay, or de-escalation for these new cohorts:

- Cohort 3:
  - If DLT evaluation indicates escalation, both Cohort 4 and Cohort 3a can be enrolled, with enrollment to Cohort 4 prioritized over Cohort 3a.
  - If DLT evaluation indicates stay, only Cohort 3a can be enrolled.
  - If DLT evaluation indicates de-escalation, only enroll Cohort 2a.

- Cohort 4:
  - If DLT evaluation indicates escalation or stay, Cohort 4a can be enrolled only if Cohort 3a also indicates dose escalation.
  - If DLT evaluation indicates de-escalation, wait for outcome from Cohort 3a.
- Cohort 3a:
  - If DLT evaluation indicates escalation, Cohort 4a can be enrolled only if Cohort 4 also indicates dose escalation.
  - If DLT evaluation indicates stay – expand cohort up to 14 participants.
  - If DLT evaluation indicates de-escalation, only enroll Cohort 2a.
- Cohort 4a:
  - If DLT evaluation indicates escalation or stay – cohort expand up to 14 participants
  - If DLT evaluation indicates de-escalation – expand Cohort 3a up to 14 participants
- Cohort 2a:
  - If DLT evaluation indicates escalation, may re-escalate to Cohort 3a.
  - If DLT evaluation indicates stay, cohort expand up to 14 participants.
  - If DLT evaluation indicates de-escalation, will end this dosing schedule.

The final selection of RP2D will be from Cohorts 2a, 3a, and 4a based on the totality of the available data.

4.4 Beginning and End of Study Definition

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

Due to discontinuation of V938-001, all ongoing participants who have completed C7D1 V938 plus pembrolizumab treatment may be enrolled to an extension study to continue pembrolizumab monotherapy for total of 35 cycles since first dose in V938-001 and to be monitored per the extension study as appropriate.

4.4.1 Clinical Criteria for Early Study Termination

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

Study recruitment/treatment will be paused if one of the following occurs:

- Any death (not due to disease progression) that is possibly, probably, or definitely related to V938 or V938 in combination with pembrolizumab.
- Two Grade 4 AEs that are possibly, probably, or definitely related to V938 or V938 in combination with pembrolizumab.

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

- Incidence or severity of adverse drug reactions in this or other studies suggest a potential health hazard to participants
- Plans to modify or discontinue the development of the study medication
- Quality or quantity of data recording is inaccurate or incomplete

Ample notification will be provided in the event of Sponsor decision to no longer supply V938 or pembrolizumab.

5 STUDY POPULATION

Male/female participants at least 18 years of age with advanced/metastatic solid tumors who have progressed on, been ineligible for, or refused other active therapies including targeted therapy based on mutation status (eg, MSI-H, BRAF) per standard of care, will be enrolled in this study.

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

5.1 Inclusion Criteria

To be eligible for inclusion in this study, the participant must:

Type of Participant and Disease Characteristics

1. **For Dose-escalation Cohorts:** Have a histologically confirmed advanced/metastatic solid tumor and have received, been intolerant to, or been ineligible for treatments known to confer clinical benefit. Solid tumors of any type are eligible for enrollment. Tumor types of greatest interest include, but are not limited to, malignant melanoma, HNSCC, and breast carcinoma.

For Arm A of Cohort Expansion: Have a histologically confirmed Stage III (unresectable) or Stage IV cutaneous melanoma and have received and progressed following 1 or 2 prior lines of systemic treatments for metastatic melanoma which must include 1 line of treatment with PD-1 or PD-L1 immune checkpoint inhibitor either as monotherapy or in combination with other therapy.

For Arm B of Cohort Expansion: Have a histologically confirmed advanced HNSCC and have received and progressed following 1 or 2 prior lines of systemic treatments for metastatic HNSCC which must include 1 line of treatment with PD-1 or PD-L1 immune checkpoint inhibitor either as monotherapy or in combination with other therapy.

For Arms A and B of Cohort Expansion: PD-1 treatment progression is defined by meeting all of the following criteria:

a. Has received at least 2 doses of an approved anti-PD-1/L1 mAb.

b. Has shown disease progression after anti-PD-1/L1 as defined by RECIST v1.1. The initial evidence of disease progression is to be confirmed by a second assessment no less than 4 weeks from the date of the first documented disease progression, in the absence of rapid clinical progression (as defined in 1.c).

c. Progressive disease has been documented within 12 weeks from the last dose of anti-PD-1/L1 mAb.

    i. Progressive disease is determined according to iRECIST.

    ii. This determination is made by the investigator. Once disease progression is confirmed, the initial date of disease progression documentation will be considered the date of disease progression.

2. Have a performance status of 0 or 1 on the ECOG Performance Scale.

3. Show adequate organ function as defined in Table 2. These samples must be collected within 72 hours prior to C1D1.

Table 2 Adequate Organ Function Laboratory Values

System	Laboratory Value
Hematological	
Absolute neutrophil count	≥1,500/mcL
Platelets	≥100,000/mcL
Hemoglobin	≥9 g/dL or >5.6 mmol/L[a])
Renal	
Serum creatinine or CrCl (measured or calculated)[b] or GFR 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	
INR or PT 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); 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) and platelet transfusion within the prior 2 weeks. Participants can be on stable dose of erythropoietin (≥ approximately 3 months).
[b] Creatinine clearance (CrCl) should be calculated per institutional standard.
Note: This table includes eligibility-defining laboratory value requirements for treatment; laboratory value requirements should be adapted according to local regulations and guidelines for the administration of specific chemotherapies.

Demographics

4. Are male or female, and must be at least 18 years of age 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.

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

- 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.

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

Female Participants

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

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

   - Is not a woman of childbearing potential (WOCBP)

     OR

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

   - A WOCBP must have a negative highly sensitive pregnancy test (urine or serum as required by local regulations) within 72 hours before C1D1.

   - 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.

Informed Consent

7. The participant (or legally acceptable representative) has provided documented informed consent/assent 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. See country-specific information in Appendix 7.

Additional Categories

8. Has well controlled HIV (for HIV-infected participants) on ART, defined as:

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

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

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

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

9. **Have lesions as defined below**:

    a. For All Participants: Have at least 1 cutaneous or subcutaneous lesion amenable to IT injection and must be measurable and meet 1 of the following criteria (per RECIST 1.1):

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

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

    b. For Expansion Cohorts (Arms A and B) ONLY: Have at least 1 distant and/or discrete noninjected lesion that is measurable per RECIST 1.1 criteria.

10. **For Dose-escalation Cohorts 2a, 3a, or 4a and Expansion Cohorts (Arms A and B) ONLY**: Have baseline biopsy performed from one of the injectable lesions that are planned for IT injection and with tumor tissue provided.

5.2 Exclusion Criteria

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

Medical Conditions

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

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

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

3. Has clinically active central nervous system metastases and/or carcinomatous meningitis. Participants with previously treated brain or meningeal metastases may participate and be eligible for treatment provided they are stable and asymptomatic (without evidence of progression by MRI scan of the brain separated by at least 4 weeks after treatment), have no evidence of new or enlarging brain metastases, are evaluated within 4 weeks prior to first study intervention administration, and are off immunosuppressive doses of systemic steroids at least 2 weeks prior to enrollment.

   Note: Participants with asymptomatic, previously untreated brain metastases may participate provided there are ≤3 total lesions in the brain and the longest diameter of each lesion is <1 cm. Stability of these lesions does not need to be confirmed by repeat imaging. Participants may not receive steroids to treat these lesions.

4. Has had a severe hypersensitivity reaction to treatment with the monoclonal antibody/components of the study intervention or has a history of any contraindication or has a severe hypersensitivity to any components of pembrolizumab (≥Grade 3).

5. Has an active infection requiring therapy.

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

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

8. Is on chronic systemic steroid therapy in excess of replacement doses (prednisone ≤10 mg/day is acceptable), or on any other form of immunosuppressive medication. Use of nonsystemic steroids is permitted.

9. Participants with known Hepatitis B or C infections or known to be positive for hepatitis B antigen/hepatitis B virus DNA or hepatitis C antibody or RNA. Active hepatitis C is defined by a known positive Hepatitis C antibody result and known quantitative hepatitis C virus RNA results greater than the lower limits of detection of the assay.

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

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

12. 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.

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

Prior/Concomitant Therapy

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

15. Has received prior treatment with either NDV or hIL-12.

Prior/Concurrent Clinical Study Experience

16. Is currently participating and receiving study intervention in a study of an investigational agent or has participated and received study intervention in a study of an investigational agent or has used an investigational device within 28 days of administration of V938.

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

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

Diagnostic Assessments

Other Exclusions

17. Has an active egg allergy.

18. Has a history of re-irradiation for HNSCC at the projected injection site.

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

20. Works on a farm or other profession if bird exposure is prominent.

21. For Expansion Cohorts ONLY: Has uveal or ocular melanoma.

22. For Expansion Cohorts ONLY: Has mucosal melanoma.

5.3 Lifestyle Considerations

5.3.1 Meals and Dietary Restrictions

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

5.3.2 Caffeine, Alcohol, and Tobacco Restrictions

None.

5.3.3 Activity Restrictions

None.

5.4 Screen Failures

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

5.5 Participant Replacement Strategy in Dose Escalation

In order to adequately evaluate the safety of the doses administered in this study, all participants enrolled must meet the criteria for evaluability for Cycle 1 and Cycle 2 for Cohorts 1-4 of dose escalation and must meet the criteria for evaluability for Cycle 1 for Cohorts 2a-4a. Participants are considered nonevaluable and will be replaced if:

They are allocated but not treated.

They discontinue from the study prior to completing all the safety evaluations for reasons other than treatment-related AEs.

They receive less than 75% of the total V938 PFU injection or pembrolizumab infusion in the DLT evaluation period (eg, if the infusion had to be discontinued due to an infusion reaction) and did not experience a DLT.

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

If a participant experiences a DLT in the DLT evaluation period, study intervention may be discontinued following discussion between the Sponsor and investigator. However, if the participant is deriving clinical benefit from the study intervention, the participant may be allowed to continue after discussion between the Sponsor and the investigator.

6 STUDY INTERVENTION

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

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

6.1 Study Intervention(s) Administered

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

Table 3 Study Interventions

Arm Name	Arm Type	Intervention Name	Type	Dose Formulation	Unit Dose Strength(s)	Dosage Level(s)	Route of Administration	Regimen/ Treatment Period/ Vaccination Regimen	Use	IMP/ NIMP	Sourcing
Dose Escalation (All Cohorts)	Experimental	V938	Biological/ Vaccine	Solution for Injection	Fixed dose; varies with injection volume	$1x10^7$ PFU, $1x10^8$ PFU, $3x10^8$ PFU $5x10^8$ PFU	Intratumoral	Cycle 1: Days 1, 3, 5, and 8 Cycle 2-7: Q3W beginning at Cycle 2, Day 1	Experimental	IMP	Provided centrally by Sponsor
Expansion Cohorts (Arms A-B)	Experimental	V938	Biological/ Vaccine	Solution for Injection	Fixed dose; varies with injection volume	RP2D	Intratumoral	Cycle 1: Days 1, 3, 5, and 8 Cycle 2-7: Q3W beginning at Cycle 2, Day 1	Experimental	IMP	Provided centrally by Sponsor
Dose Escalation (Cohorts 1-4)	Experimental	Pembrolizumab	Biological/ Vaccine	Solution for Infusion	25 mg/mL	200 mg	IV Infusion	Q3W, beginning at Cycle 2, Day 1	Experimental	IMP	Provided centrally by Sponsor
Dose Escalation (Cohorts 2a-4a)	Experimental	Pembrolizumab	Biological/ Vaccine	Solution for Infusion	25 mg/mL	200 mg	IV Infusion	Q3W, beginning at Cycle 1, Day 1	Experimental	IMP	Provided centrally by Sponsor
Tumor Immune Imaging and Tissue Collection Study (US only)	Other	^{89}Zr-Df-IAB22M2C tracer	Diagnostic Test	Solution for Infusion	0.8-1.2 mCi	0.5 mg-1.5 mg	IV Infusion	Once per CD8 PET imaging scan	Diagnostic	NIMP	Provided centrally by the Sponsor

Note: V938 will be administered up to 8 hours prior to pembrolizumab infusion (as appropriate).

Note: Anti-CD8 ^{89}Zr-Df-IAB22MC tracer (**US ONLY**)

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

All supplies indicated in Table 3 will be provided per the "Sourcing" column depending upon local country operational requirements. If local sourcing, every attempt should be made to source these supplies from a single lot/batch number.

Refer to Section 8.1.11 for details regarding administration of the study intervention.

6.1.1 Intratumoral Injection

V938 will be administered by IT injection into cutaneous, subcutaneous, and/or nodal lesions that are visible, palpable, or detectable by ultrasound guidance. At each dose level, a fixed V938 dose is administered to all participants enrolled to that dose level cohort (eg, Dose Level 3 = $3x10^8$ PFU) and at each visit for V938 dosing.

At each treatment, the required dose of V938 will be prepared in 0.5 to 4 mL of total volume of injectate based on the total lesion size and the nature of lesions, eg, cutaneous versus. subcutaneous or nodal lesions, or lesions with large narcotic areas, hence smaller injectable tissues (see Table 4 for estimation on total injected volume for each participant at each visit).

Prioritization of lesions to be injected should include consideration of the following order: if multiple lesions exist, a new or progressing lesion should be considered for injection first, followed by injection of the largest lesion, then injection of any additional lesions, up to a total volume of injectate of 4 mL and a maximum number of 5 lesions.

Selection of participants during screening should consider adequate lesion size for repeat lesion injection. Distant lesion(s) assessed for the “abscopal” response should not be injected, unless approved by the Sponsor.

Table 4 Estimation of Total Injected V938 Volume Based on Estimated Combined Lesion Size for Lesions to be Injected at Each V938 Treatment Visit

Estimation of Combined Lesion Size	Estimation of Total Injected Volume[a]
>5 cm	≤4 mL
>2.5 to 5 cm	≤3 mL
>1.5 to 2.5 cm	≤2 mL
≥1.0 to 1.5 cm	0.5 - 1 mL

[a] Volumes are estimates; minimum and maximum total volume injected per visit for all tumor lesions combined is 0.5 mL and 4 mL, respectively.

Details on dose calculation, preparation, and administration of V938 are provided in the Laboratory Procedures/Pharmacy Manual.

Injected tumor area should consist of vital tumor tissue (avoid injection into areas with significant necrosis, if feasible).

If at any time after treatment initiation a dose cannot be fully injected into the single injectable lesion identified at the start of treatment (eg, due to tissue induration or tumor shrinkage), the dose may be split and the remaining amount of V938 may be injected into another accessible lesion(s). Documentation of dose volume administered per injected lesion should be obtained. If no other lesion is accessible for injection or lesions are no longer visible, the remaining amount may alternatively be injected subcutaneously into the tissue immediately surrounding the previous injected lesion(s), if assessed feasible by the treating physician. Site and volume for each injection must be documented in the eCRF.

6.2 Preparation/Handling/Storage/Accountability

6.2.1 Dose Preparation

Details on preparation and administration of V938 and pembrolizumab are provided in the appropriate Pharmacy/Laboratory Procedures Manual.

6.2.2 Handling, Storage, and Accountability

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

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

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

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

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

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

6.3 Measures to Minimize Bias: Randomization and Blinding

6.3.1 Intervention Assignment

Intervention allocation will occur centrally using an IVRS/IWRS. Participants will be allocated to the following intervention arms: Cohorts 1-4 and 2a-4a in dose escalation, or Arms A and B in expansion cohorts.

Each new dose-escalation cohort will open for enrollment without delay once the DLT observation period of the previous dose cohort is completed and a dose-escalation decision is made.

Treatment allocation will be accomplished by nonrandom assignment by IVRS/IWRS.

6.3.2 Stratification

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

Interruptions from the protocol-specified treatment plan for >3 weeks between V938 or pembrolizumab doses for nondrug related or administrative reasons require consultation between the investigator and the Sponsor and written documentation of the collaborative decision on participant management.

6.5 Concomitant Therapy

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

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.

6.5.2 Prohibited Concomitant Medications

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

- Antineoplastic systemic chemotherapy or biological therapy
- Immunotherapy not specified in this protocol
- Chemotherapy not specified in this protocol
- Investigational agents other than those specified in this protocol
- Radiation therapy

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

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

Systemic glucocorticoids for any purpose other than to modulate symptoms from an AE of suspected immunologic etiology. The use of physiologic doses of corticosteroids may be approved after consultation with the Sponsor. Note: A maximum dose of 10 mg prednisone (or equivalent) per day is also allowed after consultation with Sponsor.

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

6.5.3 Supportive Care

6.5.3.1 V938 Supportive Care

Participants should receive appropriate supportive care measures as deemed necessary by the treating investigator. Refer to Table 5, Table 6, and Table 7 for guidelines regarding dose modification and supportive care.

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 Table 8. 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 8 for guidelines regarding dose modification and supportive care.

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

6.6 Dose Modification (Escalation/Titration/Other)

6.6.1 Dose Administration/Escalation

Details on preparation and administration of V938 and pembrolizumab are provided in the appropriate Pharmacy/Laboratory Procedures Manual.

6.6.2 Definition of Dose-limiting Toxicity

All toxicities will be graded using CTCAE Version 4.0, with exception of CRS, based on the investigator assessment. The CRS grading system used in this protocol is adapted from the ASTCT Consensus Grading for CRS [Lee, D. W., et al 2019].

The DLT observation period for Cohorts 1-4 will be 42 days during Cycles 1 and 2 (ie, the first monotherapy run-in cycle [Cycle 1] and the first combination therapy cycle [Cycle 2]). The DLT observation period for Cohorts 2a-4a will be 21 days during Cycle 1 only.

The occurrence of any of the following toxicities during the DLT observation period 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 thrombocytopenia:
    a. Grade 4 thrombocytopenia of any duration
    b. Grade 3 thrombocytopenia associated with clinically significant bleeding
3. Grade 3 nonhematologic AE with the following exceptions:
    a. Grade 3 fatigue lasting ≤72 hours
    b. Grade 3 diarrhea, nausea, or vomiting lasting ≤72 hours without use of antiemetics or antidiarrheals per standard of care
    c. Grade 3 rash without use of corticosteroids or anti-inflammatory agents per standard of care.
4. Any Grade 3 or Grade 4 nonhematologic laboratory value if:
    a. Clinically significant medical intervention is required to treat the participant, or
    b. The abnormality leads to hospitalization, or
    c. The abnormality persists for >1 week
    d. The abnormality results in a DILI (see Sections 8.4.1 and 8.4.7 for criteria)

    Exceptions: Clinically nonsignificant, treatable, or reversible laboratory abnormalities including liver function tests, uric acid, etc.
5. Febrile neutropenia Grade 3 or Grade 4:
    a. Grade 3 is defined as ANC <1000/mm^3 with a single temperature of >38.3°C (101°F) or a sustained temperature of ≥38°C (100.4°F) for more than 1 hour.
    b. Grade 4 is defined as ANC <1000/mm^3 with a single temperature of >38.3°C (101°F) or a sustained temperature of ≥38°C (100.4°F) for more than 1 hour, with life-threatening consequences and urgent intervention indicated.
6. Prolonged delay (>2 weeks) in initiating Cycle 3 (for Cohorts 1-4) or Cycle 2 (for Cohorts 2a-4a) due to study intervention-related toxicity.

7. Any study intervention-related toxicity that causes the participant to discontinue intervention during the DLT evaluation period.

8. Missing >1 injection of V938 as a result of drug-related AE(s) during the first 2 cycles (for Cohorts 1-4) or during the first cycle (for Cohort 2a-4a).

9. Grade 5 toxicity.

6.6.3 Timing of Dose Administration

Refer to Table 3 for dosing schedule of V938 and pembrolizumab for cohorts and arms in Dose-escalation and Cohort Expansion and allowed treatment windows in Section 1.3.

The reason for any variability in administration of V938 or pembrolizumab outside the protocol-specified window should be documented in the participant's chart and recorded on the eCRFs.

The Pharmacy/Laboratory Procedures Manual contains specific instructions (eg, dose calculation, reconstitution, preparation) for V938 and pembrolizumab administration.

6.6.4 Guidelines for Dose Modification due to Adverse Events

Adverse events (both nonserious and serious) associated with V938 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 4.0 must be used to grade the severity of AEs with exception of CRS. CRS is graded using the grading system adapted from the ASTCT Consensus Grading for CRS. The investigator may attribute each toxicity event to V938 alone, to pembrolizumab alone, or to the combination, and modify the dose according to Table 5 and/or Table 8.

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 V938 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.

6.6.4.1 Dose Modification and Management for V938

The dose of V938 may be interrupted or dose reduced by 1 dose level from Dose Level 3 ($3x10^8$ PFU) or Dose Level 4 ($5x10^8$ PFU) as described in Table 5. If dose cannot be resumed following dose interruption with the original or reduced or dose, then V938 treatment should be discontinued. If a participant experiences several toxicities, then the treating physician should adhere to the most conservative dose adjustment recommended (ie, adjustment based on the severest AE reported). Exceptional circumstances to following the dose modification tables below may be considered after consultation with the Sponsor.

Table 5 V938 Dose Modification and Treatment Discontinuation Guidelines for Drug-related Adverse Events

Toxicity	Hold Treatment	Criteria for Restarting Treatment	V938 Dose for Restarting Treatment	Criteria for Treatment 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.	Same dose level	If AE persists for 12 weeks without resolution
• Any Grade 3 hematological 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.	May decrease dose by 1 dose level.	If AE persists for 12 weeks without resolution 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.	Same dose level	If AE persists for 12 weeks without resolution

Toxicity	Hold Treatment	Criteria for Restarting Treatment	V938 Dose for Restarting Treatment	Criteria for Treatment Discontinuation After Consultation with Sponsor
• 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.	May decrease dose by 1 dose level.	If AE persists for 12 weeks without resolution Permanent discontinuation should be considered for any severe or life-threatening event
Note: For treatment-related CRS, refer to Table 6 for AE grading and Table 7 for V938 dose modification and AE management.				

6.6.4.1.1 Management of Cytokine Release Syndrome

CRS has been observed in participants who received V938 treatment. CRS toxicity will be graded per ASTCT CRS Consensus Grading system as shown in Table 6; the CRS management guideline is provided in Table 7.

Table 6 CRS Grading, Adapted From ASTCT CRS Consensus Grading

CRS Parameter	Grade 1	Grade 2	Grade 3	Grade 4
Fever [a]	Temperature ≥38°C	Temperature ≥38°C	Temperature ≥38°C	Temperature ≥38°C
			With	
Hypotension	None	Not requiring vasopressors	Requiring a vasopressor with or without vasopressin	Requiring multiple vasopressors (excluding vasopressin)
			And/or [b]	
Hypoxia	None	Requiring low-flow nasal canula [c] or blow-by	Requiring high-flow nasal canula [c], facemask, nonrebreather mask, or Venturi mask	Requiring positive pressure (eg, CPAP, BiPAP, intubation, and mechanical ventilation)

Abbreviations: ASTCT=American Society for Transplantation and Cellular Therapy; BiPAP= bilevel positive air pressure; CPAP=continuous positive air pressure ; CRS=cytokine release syndrome.
Note: Organ toxicities associated with CRS may be graded according to CTCAE v4.0, but they do not influence CRS grading.
Note: Grade 5 is death caused by CRS or its complications after excluding other causes.
[a] Fever is defined as temperature ≥38°C not attributable to any other cause. In participants who have CRS and then receive antipyretic or anticytokine therapy such as tocilizumab or steroids, fever is no longer required to grade subsequent CRS severity. In this case, CRS grading is driven by hypotension and/or hypoxia.
[b] CRS grade is determined by the more severe event: hypotension or hypoxia not attributable to any other cause. For example, a participant with temperature of 39.5°C, hypotension requiring 1 vasopressor, and hypoxia requiring low-flow nasal canula is classified as Grade 3 CRS.
[c] Low-flow nasal cannula is defined as oxygen delivered at ≤6 L/minute. Low flow also includes blow-by oxygen delivery, sometimes used in pediatrics. High-flow nasal cannula is defined as oxygen delivered at >6 L/minute.

Table 7 Dose Modification and Management Guideline for Treatment-related CRS

CRS Grade per ASTCT[a]	**V938 Dose Modification**	**CRS Management**	**Premedication for Subsequent Doses**
Grade 1	None	Increase monitoring of vital signs and oxygen saturation, as medically indicated, until the participant is deemed medically stable, in the opinion of the investigator.	Recommended. Participant may be premedicated with antipyretic, eg, acetaminophen 500 to 1000 mg po 1.5 h (±30 min), or with an antihistamine, prior to study intervention administration, or at the discretion of the investigator.
Grade 2	Delay next dose until AE is resolved, retreatment at the same dose level. For recurrent Grade 2, retreatment may be allowed at the same dose level or 1 dose level down upon discussion with the Sponsor	Increase monitoring of vital signs and oxygen saturation, as medically indicated, until the participant is deemed medically stable, in the opinion of the investigator. Additional appropriate medical therapy may include, but is not limited to: • IV fluids • NSAIDs • Acetaminophen • Narcotics • Oxygen Perform fever workup to exclude infectious etiologies; treat neutropenia if present.	

CRS Grade per ASTCT[a]	V938 Dose Modification	CRS Management	Premedication for Subsequent Doses
Grade 3 or Grade 4	Permanently discontinue V938	Additional appropriate medical therapy may include, but is not limited to: • IV fluids • NSAIDS • Acetaminophen • Narcotics • Oxygen • Vasopressors • Corticosteroids • Anti-IL6 (eg, tocilizumab) • Empiric antibiotics Participants with ≥ Grade 3 CRS need to be monitored very closely, likely in an intensive care setting.	NA

Abbreviations: ASTCT= American Society for Transplantation and Cellular Therapy ; CRS=cytokine release syndrome; IL=interleukin; IV=intravenous; NSAIDS=nonsteroidal anti-inflammatory drugs; PO=by mouth.

[a] CRS Grading adapted from ASTCT Consensus Grading (see Table 6).

If toxicity does not resolve to Grade 0 or 1 within 6 weeks after last intervention, V938 should be discontinued. With investigator and Sponsor agreement, participants with a laboratory AE still at Grade 2 after 6 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 or 1 or baseline prior to restarting.)

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

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

AEs associated with pembrolizumab monotherapy, coformulation, or IO combination exposure may represent an immune-related response. These irAEs may occur shortly after the first dose or several months after the last dose of pembrolizumab monotherapy, coformulation, or IO combination treatment and may affect more than one body system simultaneously. Therefore, early recognition and initiation of treatment is critical to reduce complications. Based on existing clinical study data, most irAEs were reversible and could be managed with interruptions of pembrolizumab monotherapy, coformulation, or IO combination administration of corticosteroids and/or other supportive care. For suspected irAEs, ensure adequate evaluation to confirm etiology or exclude other causes. Additional procedures or tests such as bronchoscopy, endoscopy, skin biopsy may be included as part of the evaluation.

Dose Modification and Toxicity Management Guidelines for irAEs associated with pembrolizumab monotherapy, coformulations, or IO combinations are provided in Table 8.

Table 8 Dose Modification and Toxicity Management Guidelines for Immune-related Adverse Events Associated with Pembrolizumab Monotherapy, Coformulations or IO Combinations

General instructions:

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

irAEs	**Toxicity Grade (CTCAEv4.0)**	**Action With Pembrolizumab Monotherapy, Coformulations or IO Combinations**	**Corticosteroid and/or Other Therapies**	**Monitoring and Follow-up**
Pneumonitis	Grade 2	Withhold	• Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper	• Monitor participants for signs and symptoms of pneumonitis • Evaluate participants with suspected pneumonitis with radiographic imaging and initiate corticosteroid treatment • Add prophylactic antibiotics for opportunistic infections
	Recurrent Grade 2 or Grade 3 or 4	Permanently discontinue		

irAEs	Toxicity Grade (CTCAEv4.0)	Action With Pembrolizumab Monotherapy, Coformulations or IO Combinations	Corticosteroid and/or Other Therapies	Monitoring and Follow-up
Diarrhea / Colitis	Grade 2 or 3	Withhold	• Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper	• Monitor participants for signs and symptoms of enterocolitis (ie, diarrhea, abdominal pain, blood or mucus in stool with or without fever) and of bowel perforation (ie, peritoneal signs and ileus) • Participants with ≥Grade 2 diarrhea suspecting colitis should consider GI consultation and performing endoscopy to rule out colitis • Participants with diarrhea/colitis should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion.
	Recurrent Grade 3 or Grade 4	Permanently discontinue		
AST / ALT Elevation or Increased Bilirubin	Grade 2[a]	Withhold	• Administer corticosteroids (initial dose of 0.5-1 mg/kg prednisone or equivalent) followed by taper	• Monitor with liver function tests (consider weekly or more frequently until liver enzyme value returned to baseline or is stable)
	Grade 3 [b] or 4[c]	Permanently discontinue	• Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper	
T1DM or Hyperglycemia	New onset T1DM or Grade 3 or 4 hyperglycemia associated with evidence of β-cell failure	Withhold[d]	• Initiate insulin replacement therapy for participants with T1DM • Administer anti-hyperglycemic in participants with hyperglycemia	• Monitor participants for hyperglycemia or other signs and symptoms of diabetes

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

irAEs	Toxicity Grade (CTCAEv4.0)	Action With Pembrolizumab Monotherapy, Coformulations or IO Combinations	Corticosteroid and/or Other Therapies	Monitoring and Follow-up
All Other irAEs	Persistent Grade 2	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology or exclude other causes
	Grade 3	Withhold or discontinue[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: Guillain-Barre Syndrome, encephalitis, myelitis, DRESS, SJS, TEN and other clinically important irAEs (eg, vasculitis and sclerosing cholangitis).

6.6.4.2.1 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 9.

Table 9 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 hrs	Stop Infusion Additional appropriate medical therapy may include, but is not limited to: IV fluids Antihistamines NSAIDs Acetaminophen Narcotics Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator. If symptoms resolve within 1 hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (eg, from 100 mL/hr to 50 mL/hr). Otherwise dosing will be held until symptoms resolve and the participant should be premedicated for the next scheduled dose. Participants who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further study drug intervention.	Participant may be premedicated 1.5 h (±30 minutes) prior to infusion of study intervention with: Diphenhydramine 50 mg po (or equivalent dose of antihistamine). Acetaminophen 500-1000 mg po (or equivalent dose of analgesic).
Grades 3 or 4 Grade 3: Prolonged (ie, not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (eg, renal impairment, pulmonary infiltrates) Grade 4: Life-threatening; pressor or ventilatory support indicated	Stop Infusion. Additional appropriate medical therapy may include, but is not limited to: Epinephrine** IV fluids Antihistamines NSAIDs Acetaminophen Narcotics Oxygen Pressors Corticosteroids Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator. Hospitalization may be indicated. **In cases of anaphylaxis, epinephrine should be used immediately. Participant is permanently discontinued from further study drug intervention.	No subsequent dosing
Appropriate resuscitation equipment should be available at the bedside and a physician readily available during the period of drug administration. For further information, please refer to the Common Terminology Criteria for Adverse Events v4.0 (CTCAE) at http://ctep.cancer.gov		

6.6.4.2.2 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.

6.7 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 8.1.12.

A participant must be discontinued from study intervention but continue to be monitored in the study for any of the following reasons:

- The participant or participant's legally acceptable representative requests to discontinue study intervention.
- The participant interrupts study intervention administration for more than 12 consecutive weeks.

- The participant has a medical condition or personal circumstance that, in the opinion of the investigator and/or Sponsor, 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 (exception if the Sponsor approves treatment continuation).

- Unacceptable adverse experiences as described in Section 6.6 and Section 8.4.3.

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

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

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

- Investigator's decision to discontinue treatment.

- Recurrent Grade 2 pneumonitis.

- Completion of 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).

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 8.1.12. The procedures to be performed should a participant repeatedly fail to return for scheduled visits and/or if the study site is unable to contact the participant are outlined in Section 7.3.

7.3 Lost to Follow-up

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

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

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

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

8 STUDY ASSESSMENTS AND PROCEDURES

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

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

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

- All study-related medical decisions must be made by an investigator who is a qualified physician.

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

- Procedures conducted as part of the participant's routine clinical management (eg, blood count) and obtained before signing of ICF may be utilized for screening or baseline purposes provided the procedure met the protocol-specified criteria and were performed within the time frame defined in the SoA.

- Additional evaluations/testing may be deemed necessary by the investigator and or the Sponsor for reasons related to participant safety. In some cases, such evaluation/testing may be potentially sensitive in nature (eg, HIV, Hepatitis C), and thus local regulations

may require that additional informed consent be obtained from the participant. In these cases, such evaluations/testing will be performed in accordance with those regulations.

The approximate amount of blood collected from each participant over the duration of the study for each participant for laboratory evaluations is provided in the Laboratory Procedures Manual.

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

8.1 Administrative and General Procedures

8.1.1 Informed Consent

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

8.1.1.1 General Informed Consent

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

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

The initial ICF, any subsequent revised ICF, and any information provided to the participant must receive the IRB/IEC's approval/favorable opinion in advance of use. The communication of this information will be provided and documented via a revised consent form or addendum to the original consent form that captures the participant's or the participant's legally acceptable representative's dated signature.

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

Specifics about the study and the study population are to be included in the study informed consent form template at the protocol level.

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

8.1.1.2 Consent and Collection of Specimens for Future Biomedical Research

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

8.1.2 Inclusion/Exclusion Criteria

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

8.1.3 Participant Identification Card

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

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

8.1.4 Medical History

A medical history will be obtained by the investigator or qualified designee. Medical history will include all active conditions, and any condition diagnosed within the prior 10 years that is 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. Smoking history will be obtained.

8.1.5 Disease Details

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

8.1.6 Prior Oncology Treatment History

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

8.1.7 Eastern Cooperative Oncology Group Performance Status

The investigator or qualified designee will assess the ECOG performance status at the time points specified in the SoA (Section 1.3). Additional ECOG testing may be performed as clinically indicated.

8.1.8 Prior and Concomitant Medications Review

8.1.8.1 Prior Medications

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

8.1.8.2 Concomitant Medications

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

All concomitant medications received within 28 days prior to the first dose of study treatment and up to 30 days after the last dose of study treatment should be recorded. Concomitant medications administered 30 days after the last dose of study treatment should be recorded for SAEs and ECIs as defined in Section 8.4.7.

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

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

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

8.1.9 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.

8.1.10 Assignment of Treatment/Randomization Number

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

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

8.1.11 Study Intervention Administration

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

Study treatment will begin on C1D1, once all predose assessments have been completed.

8.1.11.1 Timing of Dose Administration

See Sections 1.1, 1.3.2, 4.1.1, and 6.1 for timing of dose administration.

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

8.1.12 Discontinuation and Withdrawal

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

When a participant withdraws from participation in the study, all applicable activities scheduled for the End-of-Treatment Visit should be performed (at the time of withdrawal). Any AEs that are present at the time of withdrawal should be followed in accordance with the safety requirements outlined in Section 8.4 and Section 8.11.3.

8.1.12.1 Withdrawal From Future Biomedical Research

Participants may withdraw their consent for future biomedical research. Participants may withdraw consent at any time by contacting the principal investigator for the main study. If medical records for the main study are still available, the investigator will contact the Sponsor using the designated mailbox (clinical.specimen.management@MSD.com). Subsequently, the participant's consent for future biomedical research will be withdrawn. A letter will be sent from the Sponsor to the investigator confirming the withdrawal. It is the responsibility of the investigator to inform the participant of completion of withdrawal. Any analyses in progress at the time of request for withdrawal or already performed prior to the request being received by the Sponsor will continue to be used as part of the overall research study data and results. No new analyses would be generated after the request is received.

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.

8.1.13 Participant Blinding/Unblinding

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

8.1.14 Domiciling

On C1D1 and C1D3, the first 2 participants at each dose level will remain under observation for a minimum of a 24-hour period (may be longer based on guidance from the individual institution) following V938 administration. Observation for the remaining V938 doses for these participants and for any additional participants will be at the discretion of the investigator, per local IRB, Ethics Review Committee, and/or Health Authority mandate.

8.1.15 Calibration of Equipment

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

8.2 Efficacy/Immunogenicity Assessments

8.2.1 Tumor Imaging and Medical Photography

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

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

Sites will be required to send in anatomical images/medical photography of the injected lesions to a central imaging vendor, as indicated in the SIM.

Tumor imaging and medical photography should be repeated every 9 weeks from the first dose of treatment.

Solid tumor imaging should be acquired by CT (strongly preferred). Magnetic resonance imaging should be used when CT is contraindicated or for imaging in the brain. For subcutaneous lesions, imaging by either MRI or CT is to be obtained at screening and at the imaging timepoints outlined in Section 1.3 for assessment of response. Medical photography will be performed more frequently, if warranted.

The same imaging technique regarding modality and use of contrast should be used in a participant throughout the study to optimize the visualization of existing and new tumor burden. Tumor imaging schedule is based on calendar days from the first administration of study intervention and will not be postponed due to delays in treatment cycles. Additional tumor imaging and medical photography may be performed as clinically indicated.

Sites will be required to submit required anatomical images and medical photography to a central imaging vendor who will clean, collect, and hold the images. Images taken of lesions being injected (by medical photography and/or ultrasound) should also be submitted in the same manner. Images will be collected for possible analysis by blinded, independent central review. Required anatomical images as well as the process for image collection and transmission to the central imaging vendor can be found in the SIM.

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

8.2.2 Initial Tumor Imaging

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

Tumor imaging performed as part of routine clinical management is acceptable for use as screening tumor imaging if they are of diagnostic quality and performed within 42 days prior to the date of allocation.

8.2.3 Brain Imaging

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

For participants with stable brain metastases enrolled in the study, the baseline brain image must be submitted to the CIV to be held for possible future analysis. For any participant with known stable brain metastases at baseline and who achieves a CR during study treatment, follow-up brain imaging is required for confirmatory assessment of CR. This image may be submitted for independent central radiologic review.

Participants with small cell lung, thyroid cancer, and melanoma 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. For those participants with these tumor types subsequently enrolled in the study, this baseline brain scan should be submitted to the CIV, but independent central radiologic confirmation of a lack of brain metastases is not required.

Participants with small (<1 cm) asymptomatic brain metastases must be followed with regularly scheduled brain MRI scans throughout the study.

If a participant develops a new brain metastasis during treatment, the following steps will be taken:

- Participants with symptomatic brain metastases will be removed from study treatment.
- Participants with asymptomatic brain metastases (no need for steroids, no symptoms and signs indicating clinically significant progression of disease, no decline in ECOG performance status) can continue on study treatment under the following conditions:
    - If no immediate WBRT, both systemic lesions and brain lesions, can be followed by iRECIST.
    - If immediate WBRT is chosen, the brain lesions will be nonevaluable for iRECIST.
    - Brain MRI will be required at each subsequent image assessment.

8.2.4 Imaging for Bone Metastases

For any participant with clinical symptoms suggesting bone metastases, bone imaging (eg, bone scan or PET scan) should be performed to identify possible bone metastases. If bone metastases are identified that have not been imaged on the CT/MRI performed for Initial Tumor Imaging (Section 8.2.2), then additional baseline and all subsequent tumor imaging studies should include such lesions in the imaging field.

8.2.5 Tumor Imaging During the Study

Sites will be required to send in anatomical images/medical photography of the injected lesions to a central imaging vendor, as indicated in the SIM.

On-study imaging assessment for solid tumors should be performed at 9 weeks (±7 days) from the date of allocation. Subsequent tumor imaging should be performed every 9 weeks (±7 days) or more frequently if clinically indicated. After 54 weeks, participants who remain on treatment will have imaging performed every 12 weeks (±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, or death, whichever occurs first.

Partial response 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, whichever is clinically indicated. Participants will then return to regular scheduled imaging every 9 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. Note that response does not typically need to be verified in real time by the central imaging vendor.

Per iRECIST (Section 8.2.7.1), 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 8.2.7.1. 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 8.2.7.

8.2.6 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.

8.2.7 Response Assessment

8.2.7.1 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 10). 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. Images should continue to be sent in to the central imaging vendor for potential retrospective BICR.

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

- Increase in the sum of diameters of target lesion(s) identified at baseline to ≥20% and ≥5 mm from nadir
    - Note: the iRECIST publication uses the terminology "sum of measurements", but "sum of diameters" will be used in this protocol, consistent with the original RECIST 1.1 terminology.
- Unequivocal progression of 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 Section 1.3 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.

Table 10 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.

iCPD = immune confirmed progressive disease; iUPD = immune unconfirmed progressive disease; iCR = immune complete response; iRECIST = immune-related response evaluation criteria in solid tumors; PD = progressive disease; PFS = progression-free survival; iPR = immune partial response; iSD = immune stable disease

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.

8.2.7.2 itRECIST

itRECIST is a response assessment that is tailored to intratumoral immunotherapy, is aligned with RECIST 1.1 overall response assessment [Goldmacher, G. V., et al 2020], and is further described in Section 10.8.

itRECIST:

- Provides a guidance on baseline categorization of target and non-target lesions (Figure 2)
- Provides guidance on recategorization of lesions during therapy (Figure 3)
- Allows for separate response assessment in injected and noninjected lesions (Figure 4)
- For injected lesions, provides an iterative response assessment process that adapts to changes in lesion selection for intratumoral immunotherapy (an example is provided in Figure 5)
- Provides guidelines on prioritization of lesion injection during the course of intratumoral immunotherapy (see Appendix 8)

itRECIST supports standardized collection of data from intratumoral immunotherapy clinical studies to facilitate exploratory response analysis.

8.2.8 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 over the course of the study (from prestudy to poststudy visits), including approximate blood/tissue volumes drawn/collected by visit and by sample type per participant, can be found in the Laboratory Procedures Manual.

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

8.3.1 Physical Examinations

8.3.1.1 Full Physical Examination

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

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

8.3.1.2 Directed Physical Examination

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

8.3.2 Vital Signs

The investigator or qualified designee will take vital signs at screening, prior to the administration of each dose of study intervention and during the follow-up period as specified in the SoA. Vital signs include temperature, pulse, respiratory rate, weight and blood pressure. Height will be measured at Visit 1 only. Weight will be measured once a cycle.

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 Clinical Safety Laboratory Assessments

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

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

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

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

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

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

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

Laboratory tests for screening should be performed within 72 hours 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.

8.3.4.2 Pregnancy Test

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

8.3.5 Viral Shedding

Detailed information is provided in the Laboratory Procedures Manual.

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

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

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

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

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

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

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

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

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

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

All initial and follow-up AEs, SAEs, and other reportable safety events will be recorded and reported to the Sponsor or designee within the time frames as indicated in Table 11.

Table 11 Reporting Time Periods and Time Frames for Adverse Events and Other Reportable Safety Events

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

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

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

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

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

8.4.4 Regulatory Reporting Requirements for SAE

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

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

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

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

8.4.5 Pregnancy and Exposure During Breastfeeding

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

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

8.4.6 Disease-related Events and/or Disease-related Outcomes Not Qualifying as AEs or SAEs

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

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

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

8.4.7 Events of Clinical Interest (ECIs)

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

Events of clinical interest for this study include:

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

2. An elevated AST or ALT 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).

8.5 Treatment of Overdose

For purposes of this study, an overdose will be defined as any dose exceeding the prescribed dose for V938 by >40% 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 V938 or pembrolizumab. In the event of overdose, V938 or pembrolizumab should be discontinued and the participant should be observed closely for signs of toxicity. Appropriate supportive treatment should be provided if clinically indicated.

8.6 Pharmacokinetics

To further evaluate V938 and pembrolizumab immunogenicity and exposure in this indication, and to evaluate exposure of the proposed dosing regimen, sample collections for analysis of ADA and PK are currently planned as shown in Section 1.3. Blood samples will be obtained to measure PK of serum MK-3475 and NDV RNA. Pharmacokinetic parameters for pembrolizumab (eg, C_{max} and C_{trough}) at planned visits and times will be summarized.

Pharmacokinetic parameters for NDV RNA (eg, AUC and C_{max}) at planned visits and times will be summarized.

Blood samples for PK and antidrug antibodies for pembrolizumab and V938 may be decided to be stored, reduce further sample collection, or discontinue in this trial. Should this occur, it will be communicated by an administrative memo.

8.6.1 Blood Collection for Pembrolizumab and V938 PK

Pharmacokinetic samples should be drawn according to the PK collection schedule for all participants. Every effort should be taken to collect samples at 30 days after end-of-study intervention.

8.6.2 Viral Shedding

Sample collection, storage, and shipment instructions for oral cavity/throat, urine, injection site, and anal swab samples will be provided in the Laboratory Procedures Manual.

8.7 Pharmacodynamics

Sample collection, storage, and shipment instructions for pharmacodynamic samples will be provided in the Laboratory Procedures Manual.

8.7.1 Blood for Pharmacodynamic Markers

The time points for PD sampling are described in Section 1.3.

8.7.2 Tumor Biopsy

All participants in Cohorts 2a-4a and the Expansion Cohorts will be required to provide sample biopsies of the tumor to be injected with V938 unless deemed medically unsafe by the investigator. For the Expansion Cohorts ONLY, a sample biopsy from a distant, discrete, noninjected site after IT administration of V938 is optional. Tumor samples will be collected at the time points described in Section 1.3.

Tumor biopsies will only be performed at tumor sites that are deemed medically safe, in accordance with local guidelines. Sponsor selection criteria for the V938 FIH study ensured selection of sites that have investigative staff who are highly experienced in tumor biopsies.

A mandatory predose tumor biopsy will be performed at screening on the tumor lesion that is intended for treatment with IT injection of V938, and mandatory biopsy will also occur within 10 days prior to C3D1. For the tumor lesion intended for treatment with IT injection of V938, the sample will be obtained by either punch biopsy for cutaneous lesions, or by ultrasound-guided biopsy for subcutaneous lesions. On-treatment biopsy site location may vary from baseline biopsy site location based on lesion accessibility and participant tolerance.

For the optional biopsy of distant, discrete tumor lesions that are not intended for IT injection with V938 in the Expansion Cohorts, the sample biopsy will be obtained by 1 of the following: punch biopsy for cutaneous lesions, ultrasound-guided biopsy for subcutaneous lesions, or image-guided biopsy, such as CT guided biopsy for additional lesions. Method of biopsy will be per guidance of the investigator, as well as discussion with the Sponsor. The tumor biopsy of the noninjected distant, discrete lesion should, if feasible, be performed on the same day as the other biopsies are performed.

Leftover main study tissue will be stored for future biomedical research if the participant signs the future biomedical research consent.

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

8.8 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 biomarker specimens listed in Section 8.10

8.9 Planned Genetic Analysis Sample Collection

Sample collection, storage and shipment instructions for planned genetic analysis samples will be provided in the Laboratory Procedures Manual. Samples should be collected for planned analysis of associations between genetic variants in germline/tumor DNA and drug response. If a documented law or regulation prohibits (or local IRB/IEC does not approve) sample collection for these purposes, then such samples should not be collected at the corresponding sites. Leftover DNA extracted from planned genetic analysis samples will be stored for future biomedical research only if participant provides documented informed consent for future biomedical research.

8.10 Biomarkers

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

- Blood for genetic analysis
- Blood for RNA biomarker analyses
- Serum for cytokine/chemokine analyses
- Tumor tissue for biomarker analysis
- Blood for ctDNA analysis (for participants in the Cohort Expansion Phase only)

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

8.10.1 Blood Collection for Anti-drug Antibodies

Sample collection, storage and shipment instructions for serum samples will be provided in the Laboratory Procedures Manual. ADA and neutralizing antibodies samples should be drawn according to the ADA and neutralizing antibodies collection schedule for all participants (Section 1.3). Every effort should be taken to collect samples at 30 days after end-of-study intervention for ADA and neutralizing antibodies. Simultaneous PK sampling is required for interpretation of ADA and neutralizing antibodies analysis.

8.11 Visit Requirements

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

8.11.1 Screening

Within 28 days prior to treatment allocation, potential participants will be evaluated to determine that they fulfill the entry requirements as set forth in Sections 5.1 and 5.2. Screening procedures may be repeated after consultation with the Sponsor.

Documented 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. Exceptions are thyroid and hepatitis testing, which may be done up to 28 days prior to the first dose of study intervention.

- Evaluation of ECOG is to be performed within 72 hours prior to the first dose of study intervention.

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

8.11.2 Treatment Period/Vaccination Visit

The treatment period in each treatment arm begins with Cycle 1 and may continue for up to 35 cycles (approximately 2 years) from the start of treatment until disease progression, unacceptable AE(s), intercurrent illness that prevents further administration of treatment, investigator's decision to withdraw the participant, participant withdraws consent, pregnancy

of the participant, noncompliance with study treatment or procedure requirements, or administrative reasons requiring cessation of treatment. Each cycle includes study medication administration and all associated assessments as outlined in the SoA (see Section 1.3).

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

8.11.3 Discontinued Participants Continuing to be Monitored in the Study

Discontinuation of treatment does not represent withdrawal from the study.

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

8.11.4 Posttreatment Visits

8.11.4.1 Safety Follow-up Visit

The mandatory Safety Follow-up Visit should be conducted approximately 30 days (+7 days) after the last dose of study intervention or before the initiation of a new anticancer treatment, whichever comes first.

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

After the end of treatment, each participant will be followed up for at least 30 days for AE monitoring and 120 days for SAEs, ECIs, and spontaneously reported pregnancy. Serious adverse events, ECIs, and spontaneously reported pregnancy will be reported for 30 days after the end of treatment if the participant initiates new anticancer therapy. Progression of the cancer under study is not considered an AE.

8.11.4.2 Imaging Follow-up Visits

Participants who complete the protocol-required cycles of study intervention or who discontinue study intervention for reasons other than verified progressive disease should continue with imaging assessments per the protocol-defined schedule until: (1) progressive disease is verified or further confirmed by the investigator, (2) initiation of a new anticancer treatment, (3) death, (4) withdrawal of consent, or (5) study conclusion or early termination, whichever occurs first. Participants with an AE of Grade >1 will be followed up until resolution of the AE to Grade 0 or 1 or until the beginning of a new antineoplastic therapy, whichever occurs first. Participants who completed all imaging assessments and/or will not have further imaging assessments must enter the Survival Follow-up Phase.

8.11.4.3 Survival Follow-up Visits

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

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

- For participants who discontinue treatment intervention and who will not enter the Imaging Follow-up Phase, the first survival follow-up contact will be scheduled 12 weeks after the Discontinuation Visit and/or Safety Follow-up Visit (whichever is last).

- For participants who completed assessments in the Imaging Follow-up Phase, the first survival follow-up contact will be scheduled 12 weeks after the last efficacy assessment Follow-up Visit has been performed.

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

8.12 CD8 Tracer PET Imaging (ONLY at Preapproved Sites in the US)

At preapproved sites in the US only for CD8 tracer PET imaging, 7 to 10 participants will undergo CD8 tracer PET imaging evaluation during the screening period once the participant has been determined to be eligible for the study by all other criteria, and within 10 days prior to C3D1. At each time point, participants will be injected with a dose of 0.5 mg-1.5 mg, or 0.8-1.2 mCi of ^{89}Zr-Df-IAB22M2C tracer as an IV infusion over 5-10 minutes using a syringe pump via a peripheral vein and return for PET imaging scans, one at 24 hours (±3 hours) and an optional second scan at 6 days (±1 day) after tracer infusion. CD8 tracer infusion will occur 1 to 4 days prior to tumor biopsy. Details of CD8 tracer PET imaging and tissue collection will be provided in a separate manual (CD8 PET Imaging Manual). Details will be provided via a memo to the preapproved participating sites in the US regarding the storage conditions and timeframe for holding the samples collected on C3D1.

This study will assess and quantify any detectable changes in ^{89}Zr-Df-IAB22M2C uptake from baseline to posttreatment and establish the relationship of ^{89}Zr-Df-IAB22M2C accumulation in tumors with CD8+ TIL density. This will be achieved by comparing PET imaging data (SUV_{mean}) and CD8 immunofluorescence data collected from biopsied lesions (% CD8+ cells per mm^2). Further exploratory correlative analyses will also be performed using PET image data.

9 STATISTICAL ANALYSIS PLAN

9.1 Statistical Analysis Plan Summary

This section outlines the statistical analysis strategies and procedures for the study. Changes to analyses made after the protocol has been finalized, but prior to the conduct of any analyses, will be documented in a sSAP as needed and referenced in the CSR for the study. Post hoc exploratory analyses will be clearly identified in the CSR.

Key elements of the statistical analysis plan are summarized below: the comprehensive plan is provided in Sections 9.2 to 9.12.

Study Design Overview	Phase 1/1b study of V938 in combination with pembrolizumab in participants with histologically or cytologically confirmed diagnosis of an advanced solid tumor. In the dose-escalation phase, this study applies mTPI to identify a RP2D.
Intervention Assignment	Participants will be allocated centrally through IVRS/IWRS to V938 in combination with pembrolizumab based on cohort assigned.
Analysis Populations	Safety (Primary): ASaT and DLTe PK (Secondary): Per-Protocol (PP) Efficacy (Secondary): FAS
Primary Endpoint(s)	• Dose-limiting toxicity (DLT) • Adverse event (AE) • Discontinuing study treatment due to an AE
Secondary Endpoints	• Objective response (confirmed CR or PR)
Statistical Methods for Efficacy/Immunogenicity/ Pharmacokinetic Analyses	Objective response rate will be estimated using an exact method based on the binomial distribution (Clopper-Pearson interval) along with its 95% confidence interval. Methods for the exploratory efficacy analyses (PFS, OS) are documented in the sSAP. PK parameters of study medicines will be summarized by planned visit and time for each dose separately.
Statistical Methods for Safety Analyses	Summary statistics will be provided for the safety endpoints as appropriate. The pool adjacent violators algorithm [Ji Y, Li Y, Bekele BN 2007] will be used to estimate the DLT rates across doses. The estimate of the DLT rate among participants treated at RP2D of V938 in combination with pembrolizumab and the 80% Bayesian credible intervals for the estimate will be provided for each treatment arm.
Interim Analyses	An interim analysis may be conducted to enable future study planning at the Sponsor's discretion and data will be examined on a continuous basis to allow for dose-finding decisions. For Arm A and B of the Cohort Expansion Phase, if there are ≤2 responders among the initial 20 participants enrolled, the arm may be stopped early for futility.
Multiplicity	No multiplicity adjustment is planned in this Phase 1 study.
Sample Size and Power	The overall sample size for this study depends on the observed DLT profiles of V938 in combination with pembrolizumab. A target sample size of 69 to 124 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). Allocation to treatment will not be randomized in either phase of the study.

9.3 Hypotheses/Estimation

Objectives of the study are outlined in Section 3. There is no hypothesis testing in this study.

9.4 Analysis Endpoints

Efficacy and safety endpoints are listed below, followed by descriptions of selected endpoints.

9.4.1 Efficacy/Immunogenicity/Pharmacokinetics Endpoints

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

Other endpoints (eg, PFS or OS) are exploratory endpoints in this study and details of the analysis plan will be documented in the sSAP. Progression-free survival is defined as the time from the first dose of study treatment to the first documented disease progression, using RECIST 1.1 criteria as assessed by investigator review, or death due to any cause, whichever occurs first. OS is defined as the time from the first dose of study treatment to death due to any cause. Participants who do not die will be censored on the date of the last study assessment or contact. A description of efficacy measures is provided in Section 4.2.1.1.

Pharmacokinetic endpoints include serum concentrations of V938 and pembrolizumab, as well as derived PK parameters (AUC and C_{max} of NDV RNA).

9.4.2 Safety Endpoints

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

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

9.5 Analysis Populations

9.5.1 Safety Analysis Populations

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

The DLT-evaluable population includes ASaT participants that meet the criteria for DLT evaluability (see Section 6.6.2 for details).

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

The primary safety and DLT analysis will include participants in the dose-escalation cohorts. For the expansion cohorts, the safety and DLT analysis will pool participants with the same dose across arms.

9.5.2 Pharmacokinetic Analysis Populations

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

9.5.3 Efficacy Analysis Populations

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

There will be no formal efficacy analysis during the dose-escalation phase. Participants in the dose-escalation phase that meet the inclusion criteria for the respective cohort expansion arm and received the same dose level may be pooled as part of the FAS population.

9.6 Statistical Methods

This section describes the statistical methods that address the primary and secondary objectives. Methods related to exploratory endpoints will be described in the sSAP.

For the cohort expansion phase, safety and efficacy analyses for each cohort expansion arm (Arms A and B) will pool dose-escalation participants who meet the inclusion criteria for the

respective cohort expansion arm and received the same dose level of V938 in combination with pembrolizumab.

9.6.1 Statistical Methods for Efficacy Analysis

The statistical methods for efficacy analyses of exploratory nature (PFS, OS) will be documented in the sSAP. Additional details on efficacy analyses relating to abscopal responses (target injected lesions vs target noninjected lesions) are also included. ORR, along with the confidence interval, will be estimated using an exact method based on the binomial distribution (Clopper-Pearson Interval). For the cohort expansion phase, ORR will be assessed by arm and overall. For the dose-escalation phase, while safety is of primary interest, ORR will be assessed by dose level and overall.

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 cohort. Laboratory tests, vital signs, and other safety endpoints will be summarized as appropriate.

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

9.6.3 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. For the dose-escalation phase, these analyses will be performed by dose and overall. For the cohort expansion phase, these analyses will be performed by arm and overall.

9.6.3.2 Pharmacokinetic and Pharmacodynamic Modeling Analysis

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

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

9.7 Interim Analyses

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

For each of the arms in the cohort expansion phase (Arms A and B), a futility check will be performed once there are approximately 20 evaluable participants. An evaluable participant has at least 2 posttreatment tumor assessment that is evaluable.

For both Arm A and Arm B, if there are ≤2 responders, the arm may be stopped early for futility. If the true ORR is 30%, there is a 96% chance of continuing; if the true ORR is 20%, there is a 79% chance of continuing (Table 12). This bar may change depending on the number of treatment-naive participants enrolled.

The futility bar is not binding, and the totality of the data will be evaluated before making a decision to discontinue enrollment. The data will be analyzed on a continuous basis and enrollment will not be paused in the time between when the 20th participant in a particular arm is enrolled and when interim analyses are performed.

Table 12 Probability of Continuing Study (Interim at N=20), by True ORR and Futility Bar

Futility Bar (# of Confirmed Responses)	ORR = 15%	ORR = 20%	ORR = 25%	ORR = 30%
0	0.96	0.99	~1.00	~1.00
≤1	0.82	0.93	0.98	0.99
≤2	0.59	0.79	0.91	0.96
≤3	0.35	0.59	0.77	0.89
≤4	0.17	0.37	0.59	0.76
Abbreviations: ORR=objective response rate.				

9.8 Multiplicity

There will be no multiplicity control in this study.

9.9 Sample Size and Power Calculations

Dose-escalation Cohorts Sample Size:

The overall sample size for the dose-escalation phase is expected to be in a range of 20 to 44 participants. During mTPI, each dose level will enroll 3 to 6 participants initially. Based on the occurrence of DLTs, up to 14 participants may enroll per dose level.

The final sample size of the dose-escalation phase is dependent on the number of dose levels tested and emerging safety data.

Expansion Cohorts Sample Size:

The overall sample size for the cohort expansion phase is expected to be approximately 80 participants if both arms pass futility and will each enroll 40 participants.

The key efficacy endpoint will be ORR based on investigator assessment per RECIST 1.1. Table 13 and Table 14 show the ORR estimate and 95% CI (Clopper-Pearson) for N=20 (interim analysis sample size for Arms A and B) and N=40 (fully enrolled Arms A and B).

Table 13 Estimate and 95% CI of ORR (N=20)

Sample Size	Number of Responses (PR/CR)	Observed ORR	95% CI of ORR
20	1	5%	(0.1%, 24.9%)
	2	10%	(1.2%, 31.7%)
	3	15%	(3.2%, 37.9%)
	4	20%	(5.7%, 43.7%)
	5	25%	(8.7%, 49.1%)
	6	30%	(11.9%, 54.3%)
	8	40%	(19.1%, 63.9%)
	10	50%	(27.2%, 72.8%)
Abbreviations: CI = confidence interval; CR = complete response; ORR = objective response rate; PR = partial response.			

Table 14 Estimate and 95% CI of ORR (N=40)

Sample Size	Number of Responses (PR/CR)	Observed ORR	95% CI of ORR
40	4	10%	(2.8%, 23.7%)
	5	12.5%	(4.2%, 26.8%)
	6	15%	(5.7%, 29.8%)
	7	17.5%	(7.3%, 32.8%)
	8	20%	(9.1%, 35.6%)
	9	22.5%	(10.8%, 38.5%)
	10	25%	(12.7%, 41.2%)
	15	37.5%	(22.7%, 54.2%)
Abbreviations: CI = confidence interval; CR = complete response; ORR = objective response rate; PR = partial response.			

9.10 Subgroup Analyses

Subgroup analyses of efficacy endpoints will be documented in the sSAP. Subgroups of interest for this study may include PD-L1 status and lactate dehydrogenase (high versus normal).

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 of clinical trials. In all cases, MSD clinical trials will be conducted in compliance with local and/or national regulations (eg, International Council for Harmonisation Good Clinical Practice [ICH-GCP]) and in accordance with the ethical principles that have their origin in the Declaration of Helsinki.

B. Scope

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

II. Scientific Issues

A. Trial Conduct

1. Trial Design

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

The design (ie, participant population, duration, statistical power) must be adequate to address the specific purpose of the trial. Participants must meet protocol entry criteria to be enrolled in the trial.

2. Site Selection

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

3. Site Monitoring/Scientific Integrity

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

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

B. Publication and Authorship

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

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

III. Participant Protection

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

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

B. Safety

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

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

C. Confidentiality

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

D. Genomic Research

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

IV. Financial Considerations

A. Payments to Investigators

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

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

B. Clinical Research Funding

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

C. Funding for Travel and Other Requests

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

V. Investigator Commitment

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

10.1.2 Financial Disclosure

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

The investigator/subinvestigator(s) agree, if requested by the Sponsor in accordance with 21 CFR Part 54, to provide his/her financial interests in and/or arrangements with the Sponsor to allow for the submission of complete and accurate certification and disclosure statements. The investigator/subinvestigator(s) further agree to provide this information on a Certification/Disclosure Form, commonly known as a financial disclosure form, provided by the Sponsor. The investigator/subinvestigator(s) also consent to the transmission of this information to the Sponsor in the United States for these purposes. This may involve the transmission of information to countries that do not have laws protecting personal data.

10.1.3 Data Protection

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

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

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

10.1.3.1 Confidentiality of Data

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

10.1.3.2 Confidentiality of Participant Records

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

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

10.1.3.3 Confidentiality of IRB/IEC Information

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

10.1.4 Committees Structure

10.1.4.1 Internal Medical Monitoring Team

This study does not meet the FDA criteria for requiring an independent Study Safety Committee, as it is a Phase 1 open-label exploratory study, rather than a large, randomized/blinded study with OS as an endpoint.

Mechanisms have been put in place by the Sponsor to closely monitor participant safety. An MMT consisting of a core team of employees of the Sponsor has been formed to oversee the medical monitoring of this study. The roles and description of the members of the MMT are as follows:

Clinical Scientist: MMT Chair; identifies types of safety reports and topics for review to monitor participant safety

Clinical Director: Provides medical oversite as the Medical Monitor

Statistician: Analyzes trends and monitors participant safety

Statistical Programmer: Programs reports identified by the MMT

Data Manager: monitors participant safety, monitors SAEs and ECIs, and ensures AEs are properly encoded

Clinical Safety Scientist: Monitors participant safety

Formal monthly meetings will be scheduled during which the members of the MMT will review specific safety reports and any emerging participant safety themes.

During the MMT meetings, reports will be generated to review the following data points as well as any other findings relevant to participant safety; **the plan includes, but is not limited to, review of the following endpoints and deviations**:

Endpoint or Important Protocol Deviations	**Endpoint Category**	**Types of Data the MMT Will Monitor**
DILI	Event of Clinical Interest (Endpoint)	ECI (DILI): ALT or AST ≥3X ULN and TBili ≥2X ULN and AP <2X ULN
Overdose	Event of Clinical Interest (Endpoint)	V938: any dose exceeding the prescribed dose for V938 by >40% Pembro: ≥1000 mg (≥5 times the indicated dose)
DLT	Primary (Endpoint)	Refer to Section 6.6.2 of the protocol for definition.
AE	Primary (Endpoint)	Refer to Appendix 3 of the protocol.
Discontinuing study intervention due to AE	Primary (Endpoint)	Refer to Section 7.1 of the protocol.
IT RECIST	Tertiary/Exploratory (Endpoint)	Consistency in identification of injected/biopsied lesions and ensuring collection of injected lesion images
OS	Tertiary/Exploratory (Endpoint)	The time from randomization to death due to any cause
PFS	Tertiary/Exploratory (Endpoint)	The time from randomization to the first documented disease progression or death due to any cause, whichever occurs first
Pembro PK	Tertiary/Exploratory (Endpoint)	Ensure critical samples are being collected per protocol
Exploratory Molecular Biomarker	Tertiary/Exploratory (Endpoint)	Ensure critical samples are being collected per protocol
Pharmacokinetic Endpoints - V938 (RNA)	Secondary (Endpoint)	Ensure critical samples are being collected per protocol
Viral Shedding	Secondary (Endpoint)	Ensure critical samples are being collected per protocol

Endpoint or Important Protocol Deviations	Endpoint Category	Types of Data the MMT Will Monitor
ORR	Secondary (Endpoint)	Solid Tumor: Participants who have a confirmed complete response or partial response. Assessment will be based on RECIST 1.1 and iRECIST.
Antidrug Antibody Levels	Tertiary/Exploratory (Endpoint)	Ensure critical samples are being collected per protocol
Important Protocol Deviations	Informed Consent (LIPD)	Participant had no documented initial consent to enter the study.
Important Protocol Deviations	Safety Reporting (LIPD)	Participant had a reportable Safety Event and/or follow-up Safety Event information that was not reported per the timelines outlined in the protocol.
Abbreviations: AE=adverse event; ALT=alanine aminotransferase; AST=aspartate aminotransferase; DILI=drug-induced liver injury; DLT=dose-limiting toxicity; ECI=events of clinical interest; iRECIST=immune-related Response Evaluation Criteria in Solid Tumors; IT=intratumoral; LIPD=list of important protocol deviations; ORR=overall response rate; OS=overall survival; PFS=progression-free survival; PK=pharmacokinetics; RECIST= Response Evaluation Criteria in Solid Tumors; RNA=ribonucleic acid; ULN=upper limit of normal.		

10.1.5 Publication Policy

The results of this study may be published or presented at scientific meetings. The Sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.

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

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

10.1.6 Compliance with Study Registration and Results Posting Requirements

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

disease conditions and pursue participation by calling a central contact number for further information on appropriate study locations and study site contact information.

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

10.1.7 Compliance with Law, Audit, and Debarment

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

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

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

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

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

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

10.1.8 Data Quality Assurance

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

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

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

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

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

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

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

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

10.1.9 Source Documents

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

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

10.1.10 Study and Site Closure

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

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

10.2 Appendix 2: Clinical Laboratory Tests

The tests detailed in Table 15 below will be performed by the local laboratory.

Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5 of the protocol.

Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.

- Pregnancy testing:
  - Pregnancy testing requirements for study inclusion are described in Section 5.1.
  - 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 15 Protocol-required Safety Laboratory Assessments

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

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

[a] Perform on women of childbearing potential only 72 hours prior to Day 1 of Cycle 1. Pregnancy tests must be repeated prior to every cycle if required or as specified per local regulatory guidance.
[b] T3 is preferred; if not available, Free T3 may be tested.
[c] If the local laboratory is unable to perform these tests, the site should submit the sample to the central laboratory for testing. Details are provided in the Laboratory Procedures Manual.
[d] To be performed only if required by local regulatory agencies
[e] Report % or absolute results per standard of practice. Report the results in the same manner throughout the study.
[f] To be performed for HIV positive participants only.
[g] Direct bilirubin to be performed if total bilirubin is elevated above the upper limit of normal
[h] BUN is preferred. If BUN is not available, urea may be tested.

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 Definition of AE

AE definition

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

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

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

Events meeting the AE definition

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

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

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

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

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

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

Any new cancer (that is not a condition of the study). Progression of the cancer under study is not considered a reportable event unless it results in hospitalization or death. Refer to Section 8.4.6 for additional details.

Events NOT meeting the AE definition

- Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.
- Surgery planned prior to informed consent to treat a pre-existing condition that has not worsened.
- Refer to Section 8.4.6 for protocol-specific exceptions.

10.3.2 Definition of SAE

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

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

a. **Results in death**

b. **Is life-threatening**

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

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

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

d. **Results in persistent or significant disability/incapacity**

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.

- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) that may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. **Is a congenital anomaly/birth defect**

- In offspring of participant taking the product regardless of time to diagnosis.

f. **Other important medical events**

- Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent 1 of the other outcomes listed in the above definition. These events should usually be considered serious.

- Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

10.3.3 Additional Events Reported in the Same Manner as SAE

Additional events that require reporting in the same manner as SAE

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

10.3.4 Recording AE and SAE

AE and SAE recording

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

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

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

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

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

Assessment of intensity/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 4. Any AE that changes CTCAE grade over the course of a given episode will have each change of grade recorded on the AE CRFs/worksheets.

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

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

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

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

    - Grade 5: Death related to AE.

Assessment of causality

- Did the Sponsor's product cause the AE?

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

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

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

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

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

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

    - If yes, did the AE resolve or improve?

    - If yes, this is a positive dechallenge.

    - If no, this is a negative dechallenge.

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

- **Rechallenge:** Was the participant re-exposed to the Sponsor's product in this study?
    - If yes, did the AE recur or worsen?
    - If yes, this is a positive rechallenge.
    - If no, this is a negative rechallenge.

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

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

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

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

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

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

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

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

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

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

Follow-up of AE and SAE

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

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

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

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

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

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

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

- If the electronic system is unavailable for more than 24 hours, then the site will use the paper AE Reporting form.
    - Reference Section 8.4.1 for reporting time requirements.

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

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

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

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

SAE reporting to the Sponsor via paper CRF

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

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

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

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

10.4 Appendix 4: Device Events, Adverse Device Events, and Medical Device Incidents: Definitions, Collection, and Documentation

Not applicable.

10.5 Appendix 5: Contraceptive Guidance and Pregnancy Testing

10.5.1 Definitions

Women of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile (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 follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormone replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, confirmation with two FSH measurements in the postmenopausal range is required.
  - Females on HRT and whose menopausal status is in doubt will be required to use one of the nonhormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

10.5.2 Contraception Requirements

Contraceptives allowed during the study include[a]:
Highly Effective Contraceptive Methods That Have Low User Dependency[b] *Failure rate of <1% per year when used consistently and correctly.*
• Progestogen- only contraceptive implant[c,d] • Intrauterine hormone-releasing system (IUS)[c,e] • Intrauterine device (IUD) • Bilateral tubal occlusion
• Azoospermic partner (vasectomized or secondary to medical cause) This is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. A spermatogenesis cycle is approximately 90 days. Note: Documentation of azoospermia can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.
Highly Effective Contraceptive Methods That Are User Dependent[b] *Failure rate of <1% per year when used consistently and correctly.*
• Combined (estrogen- and progestogen- containing) hormonal contraception[c,d] - Oral - Intravaginal - Transdermal - Injectable
• Progestogen-only hormonal contraception[c,d] - Oral - Injectable
Sexual Abstinence • Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.
Acceptable Contraceptive Methods *Failure rate of >1% per year when used consistently and correctly.*
• Progesterone-only hormonal contraception where inhibition of ovulation is not the primary mode of action • Male or female condom with or without spermicide • Cervical cap, diaphragm, or sponge with spermicide • A combination of male condom with either cervical cap, diaphragm, or sponge with spermicide (double barrier methods)[f]
a. Contraceptive use by men or women should be consistent with local regulations regarding the use of contraceptive methods for participants of clinical studies. b. Typical use failure rates are higher than perfect-use failure rates (ie, when used consistently and correctly). c. Male condoms must be used in addition to the hormonal contraception. d. If locally required, in accordance with Clinical Trial Facilitation Group (CTFG) guidelines, acceptable contraceptive implants are limited to those which inhibit ovulation. e. IUS is a progestin releasing IUD. f. A combination of male condom with either cap, diaphragm, or sponge with spermicide are considered acceptable, but not highly effective, birth control methods. Note: The following are not acceptable methods of contraception: - Periodic abstinence (calendar, symptothermal, postovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea method (LAM). - 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 drugs/vaccines may interact with
- The biology of disease

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

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

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

a. Participants for Enrollment

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

b. Informed Consent

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

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

c. eCRF Documentation for Future Biomedical Research Specimens

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

d. Future Biomedical Research Specimen(s)

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

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

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

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

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

5. Biorepository Specimen Usage[3,4]

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

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

Participants may withdraw their consent for future biomedical research and ask that their biospecimens not be used for future biomedical research. Participants may withdraw consent at any time by contacting the principal investigator for the main study. If medical records for the main study are still available, the investigator will contact the Sponsor using the designated mailbox (clinical.specimen.management@MSD.com). Subsequently, the participant's 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.

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

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

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

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

10.7 Appendix 7: Country-specific Requirements

Germany

Section 1.3.1 Schedule of Activities for Screening

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

Section 1.3.2 Schedule of Activities for the Treatment Period

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

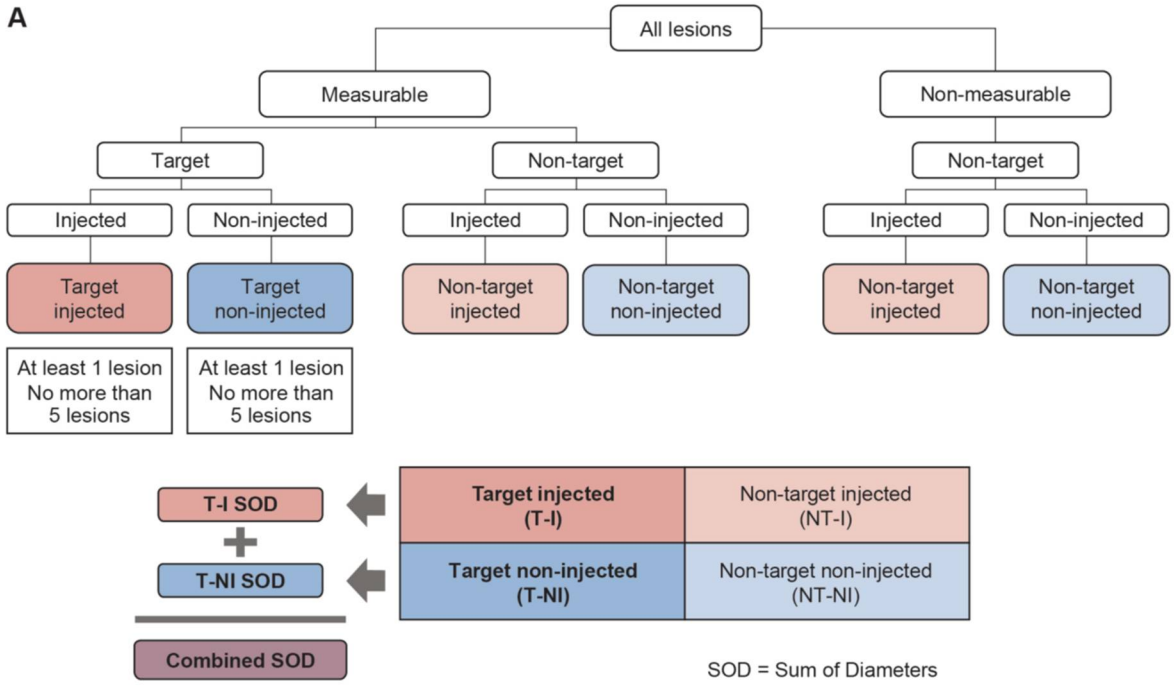
Section 5.1 Inclusion Criteria

Informed Consent

7. The participant has provided 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.

10.8 Appendix 8: itRECIST Supplementary Figures

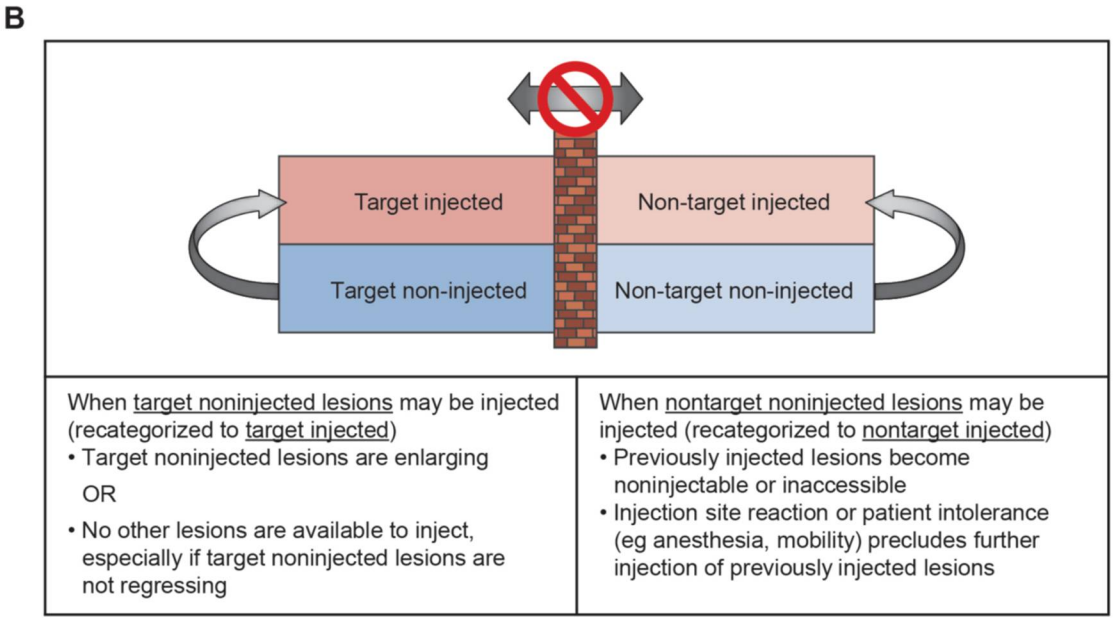
Figure 2 Algorithm for Classification of Lesions at Baseline



Source: Adapted from [Goldmacher, G. V., et al 2020]

Lesions are classified first as measurable or nonmeasurable using the standard RECIST 1.1 rules for measurability. Measurable lesions (those eligible for selection as target lesions) are then classified as target (selected to be followed quantitatively) or nontarget (selected to be followed qualitatively), and the decisions about which lesions are to be injected are made based on the prioritization rules discussed. Lesions selected for injection may be either target or nontarget in RECIST 1.1 terms. Between one and 5 lesions should be classified as target injected, and between one and 5 should be classified as target noninjected, for a maximum of 10 target lesions. All lesions not chosen as target are followed qualitatively as nontarget, and some of these may be selected for injection at baseline. T-I lesions and T-NI lesions each have their own distinct SOD. A combined SOD also includes all target lesions, injected and noninjected. NT-I and NT-NI lesions are followed qualitatively, exactly as in RECIST 1.1, classified in aggregate as showing complete response, unequivocal progression, or neither (called non-CR/non-PD in RECIST 1.1).

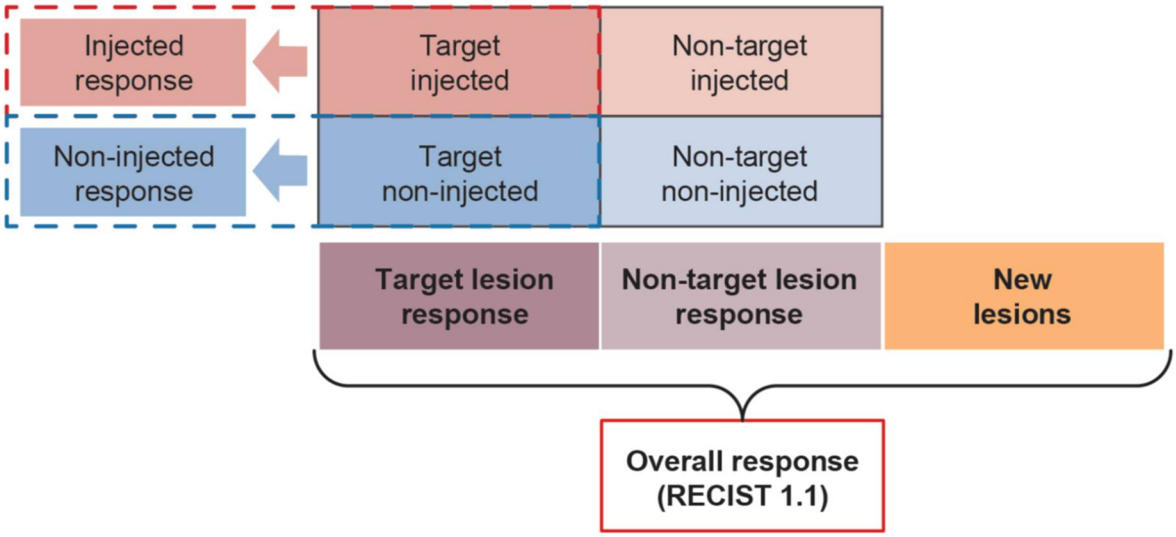
Figure 3 Reclassification of Noninjected Lesions



Source: Adapted from [Goldmacher, G. V., et al 2020].

Target or nontarget noninjected lesions can be recategorized as injected lesions if the decision is made to inject them after baseline assessment. Nontarget noninjected lesions may be injected if previously injected nontarget lesions regress completely or become inaccessible or if a participant factor such as injection site reaction or participant intolerance precludes further injection. Lesions initially selected as target noninjected should remain noninjected for as long as possible so the maximal noninjected effect can be evaluated, but they may be injected if they are enlarging, or if no other lesions are available for injection, especially if the lesions initially designated as target noninjected are not regressing. The barrier between target and nontarget categories means that all lesions remain target and nontarget in accordance with the initial designation, regardless of whether they are subsequently injected.

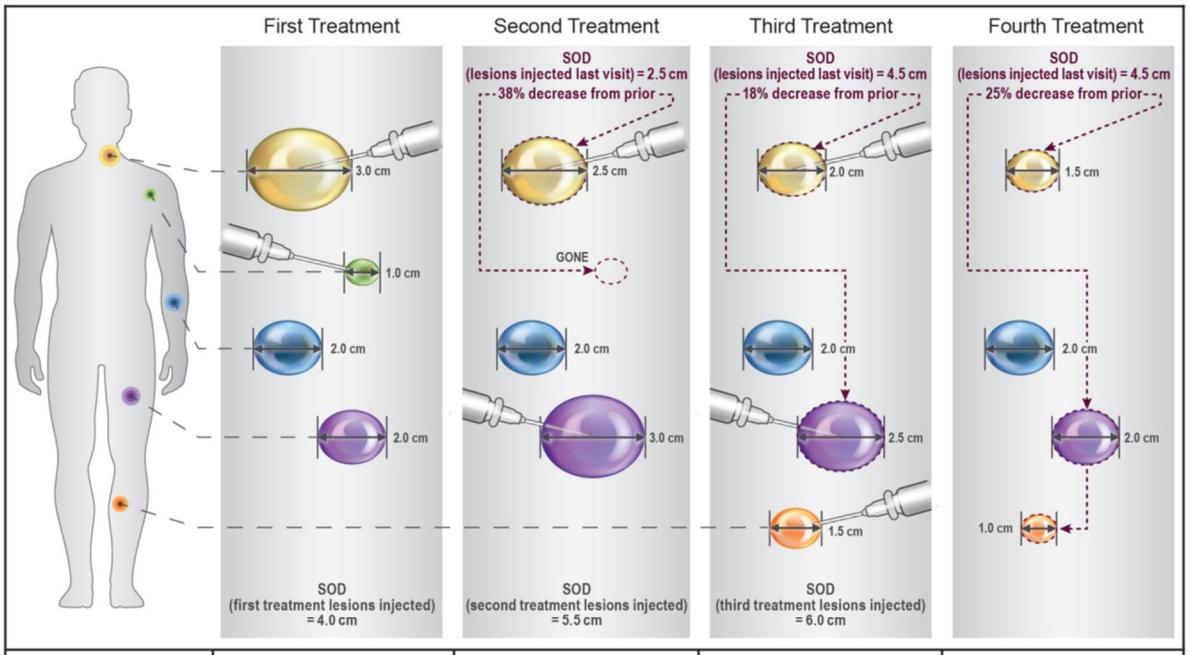
Figure 4 Overall Response Assessment Until Disease Progression



Abbreviations: RECIST 1.1=Response Evaluation Criteria in Solid Tumors, version 1.1.
Source: Adapted from [Goldmacher, G. V., et al 2020].

Overall response until disease progression per RECIST 1.1. The injected response at each visit is based on only the changes in the SODs of the lesions designated as target injected. The noninjected response at each visit is based on only the changes in the SODs of the target noninjected lesions. The overall response is based on the changes in the SODs of all target lesions together, the qualitative assessment of all nontarget lesions together, and the evaluation for possible new lesions and uses the same response categories and logical combination of these that RECIST 1.1 uses.

Figure 5 Example of Iterative Assessment of Injected Lesion Response During Treatment



	SOD for all lesions: 8.0 cm	Overall response SD (6% decrease from baseline)	Overall response PD (SD of target lesions, with new lesion)	Overall response iPR (PR of target lesions, no worsening of new lesion)
	SOD for injected lesions: 4.0 cm	Injected response PR (38% decrease)	Injected response SD (18% decrease)	Injected response PR (25% decrease)
	SOD for noninjected lesions: 4.0 cm	Noninjected response PD (25% increase)	Noninjected response NE	Noninjected response NE

Abbreviations: iPR = immunotherapeutic partial response; NE = not evaluable; NT-I = nontarget injected; NT-NI = nontarget noninjected; PD = progressive disease; PR = partial response; iRECIST 1.1 = immunotherapeutic Response Evaluation Criteria in Solid Tumors; SD = stable disease; SOD = sum of diameters (longest diameters for extranodal lesions, short axis for lymph nodes); T-I = target injected; T-NI = target noninjected.

Source: [Goldmacher, G. V., et al 2020]

This is an illustration of overall, injected, and noninjected response assessment, with a particular focus on the iterative assessment of injected lesions. All lesions from a single participant are displayed in simple schematic form and are not meant to be anatomically adjacent. For purposes of this illustration, the yellow and green lesions were selected at baseline as target injected, and the purple and blue lesions were selected as target noninjected; there are no nontarget lesions. In this simplified example, a full imaging assessment is performed at each treatment visit just before the decision about which lesions to inject at that visit. The overall response at each visit was based on the change in SODs for all the target lesions together (because there are no nontarget lesions in this example). Once progressive disease is observed (in this case, because of a new lesion), the overall response assessment thereafter is similar to that of iRECIST. The injected response is based on the change in SOD of the injected lesions from the assessment immediately before this one. The noninjected response is based on the changes in SOD from baseline and nadir and is

considered nonevaluable once any lesion that was initially selected as T-NI is subsequently injected, as happens in this case with the blue lesion. If this lesion were to grow later, it could contribute to an overall response of PD.

10.9 Appendix 9: Abbreviations

Abbreviation	Expanded Term
ADA	antidrug antibody
ADL	activities of daily living
AE	adverse event
ALT	alanine aminotransferase
ANC	absolute neutrophil count
ART	antiretroviral therapy
ASaT	All-Subjects-as-Treated
AST	aspartate aminotransferase
ASTCT	American Society for Transplantation and Cellular Therapy
AUC	area under the curve
BICR	blinded independent central review
BRAF	proto-oncogene B-rapidly accelerated fibrosarcoma
C	cycle
CD	cluster of differentiation
CD3ζ	cluster of differentiation 3 zeta
CIV	central imaging vendor
C_{max}	maximum concentration
C_{min}	minimum concentration
C_{trough}	lowest concentration of a drug just before the next dose
CR	complete response
CRF	case report form
CRS	cytokine release syndrome
CSR	clinical study report
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
ctDNA	circulating tumor deoxyribonucleic acid
CTLA-4	cytotoxic T lymphocyte associated protein 4
D	day
DILI	drug-induced liver injury
DLT	dose-limiting toxicity
DLTe	DLT-evaluable
DNA	deoxyribonucleic acid
ECG	electrocardiogram
ECI	event of clinical interest
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EDC	electronic data collection
EMA	European Medicines Agency
EORTC	European Organisation for Research and Treatment of Cancer
EOT	end of treatment
FAS	full analysis set
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act
FIH	first-in-human
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GM-CSF	granulocyte-macrophage colony-stimulating factor
GMP	Good Manufacturing Practice
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus

Abbreviation	Expanded Term
HCV	Hepatitis C virus
HIV	human immunodeficiency virus
HNSCC	head and neck squamous cell carcinoma
HRT	hormone replacement therapy
HSV	herpes simplex virus
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonisation
iCPD	immune confirmed progressive disease
iCR	immune complete response
IEC	Independent Ethics Committee
IFN	interferon
Ig	immunoglobulin
IHC	immunohistochemistry
IL	interleukin
iPR	immune partial response
irAE	immune-related adverse event
IRB	Institutional Review Board
iRECIST	immune-related Response Evaluation Criteria in Solid Tumors
iSD	immune stable disease
IT	intratumoral
iUPD	immune unconfirmed progressive disease
IV	intravenous
IVRS/IWRS	interactive voice response system/integrated web response system
LLOQ	lower limit of quantitation
MMT	Medical Monitoring Team
MRI	magnetic resonance imaging
MSI-H	Microsatellite instability-high
MTD	maximum tolerated dose
mTPI	modified toxicity probability interval
NDV	Newcastle Disease Virus
NK	natural killer
NOAEL	no observed adverse effect level
NSCLC	non-small-cell lung carcinoma
ORR	objective response rate
OS	overall survival
OTC	over-the-counter
PCR	polymerase chain reaction
PD	progressive disease
PD-1	programmed cell death protein 1
PD-L1	programmed cell death ligand 1
PD-L2	programmed cell death ligand 2
PET	positron emission tomography
PFS	progression-free survival
PFU	plaque-forming units
PK	pharmacokinetic(s)
PKCθ	protein kinase C theta
po	by mouth
PP	per-protocol
PR	partial response
Q3W	every 3 weeks
RECIST	Response Evaluation Criteria in Solid Tumors

Abbreviation	Expanded Term
RNA	ribonucleic acid
RP2D	recommended Phase 2 dose
SAE	serious adverse event
SIM	Site Imaging Manual
SoA	Schedule of Activities
SOD	sum of diameters
SPD	sum of the products of diameters
sSAP	supplementary SAP
SUSAR	suspected unexpected serious adverse reaction
SUV	standardized uptake value
TIL	T-cell infiltrating lymphocytes
WBRT	whole brain radiation treatment
WOCBP	woman/women of childbearing potential
ZAP70	zeta chain associated protein kinase

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