Official Protocol Title:	A Phase 1 Open-label, Multicenter Study of MK-2118 Administered by Intratumoral Injection as Monotherapy and in Combination with Pembrolizumab or by Subcutaneous Injection in Combination with Pembrolizumab for Patients with Advanced/Metastatic Solid Tumors or Lymphomas
NCT number:	NCT03249792
Document Date:	22-September-2022

Title Page

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Protocol Title: A Phase 1 Open-label, Multicenter Study of MK-2118 Administered by Intratumoral Injection as Monotherapy and in Combination with Pembrolizumab or by Subcutaneous Injection in Combination with Pembrolizumab for Patients with Advanced/Metastatic Solid Tumors or Lymphomas

Protocol Number: 001-08

Compound Number: MK-2118

Sponsor Name and Legal Registered Address:

Merck Sharp & Dohme LLC
(hereafter called the Sponsor or MSD)

126 East Lincoln Avenue
P.O. Box 2000
Rahway, NJ 07065 USA

Regulatory Agency Identifying Number(s):

IND NUMBER: 133985

NCT NUMBER: NCT03249792

EudraCT NUMBER: Not applicable

Approval Date: 27 September 2022

Sponsor Signatory

Typed Name: Date
Title:

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

Investigator Signatory

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

Typed Name: Date
Title:

DOCUMENT HISTORY

Document	Date of Issue	Overall Rationale
Amendment 08	27-SEP-2022	Merck Sharp & Dohme Corp. underwent an entity name and address change to Merck Sharp & Dohme LLC, Rahway, NJ, USA. This conversion resulted only in an entity name change and update to the address.
Amendment 07	27-MAY-2021	To update the dose modification and toxicity management guidelines for irAEs.
Amendment 06	21-DEC-2020	To increase the potential maximum dose to CCI of MK-2118 administered subcutaneously in Arm 4 and to adjust the number of participants estimated for enrollment accordingly.
Amendment 05	04-AUG-2020	To update the timepoints for biomarker sample collection, the addition of the itRECIST response assessment guidelines, and to update the requirements for contraception to adopt the most stringent option..
Amendment 04	21-MAR-2019	Added inpatient observation periods following the second and third administrations of MK-2118 in order to provide additional safety monitoring and added intermediate dose levels for subcutaneous (SC) MK-2118 administration with corresponding volumes of administration.
Amendment 03	03-AUG-2018	To expand the top dose of MK-2118 beyond CCI ; additionally, Arm 3 was modified to begin with an accelerated titration design (ATD) at a starting dose of CCI MK-2118

Document	Date of Issue	Overall Rationale
Amendment 02	27-MAR-2018	To provide a response assessment for participants with cutaneous T-cell lymphoma, and for the addition of Arm 3 to evaluate intratumoral (IT) injection into liver metastasis/ lesions and Arm 4 to evaluate subcutaneous administration of MK-2118.
Amendment 01	19-JUN-2017	To implement clarifications requested by the United States (US) Food and Drug Administration (FDA) regarding the following: • timing of STING dosing relative to pembrolizumab administration, • communication of dosing and escalation decisions to sites, • wording of inclusion criterion #1 to ensure that participants with SOC options are not enrolled • wording of inclusion criterion #3 to clarify lymphoma lesion size
Original Protocol	21-APR-2017	Not appliable.

PROTOCOL AMENDMENT SUMMARY OF CHANGES

Amendment: 08

Overall Rationale for the Amendments:

Sponsor underwent an entity name change and update to the address

Summary of Changes Table:

Section # and Name	Description of Change	Brief Rationale
Title Page Section 12.3 Appendix 3: Study Governance Considerations Throughout	Sponsor entity name and address change.	Merck Sharp & Dohme Corp. underwent an entity name and address change to Merck Sharp & Dohme LLC, Rahway, NJ, USA. This conversion resulted only in an entity name change and update to the address.

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1 SYNOPSIS

Protocol Title:

A Phase 1 Open-label, Multicenter Study of MK-2118 Administered by Intratumoral Injection as Monotherapy and in Combination with Pembrolizumab or by Subcutaneous Injection in Combination with Pembrolizumab for Patients with Advanced/Metastatic Solid Tumors or Lymphomas

Short Title:

Phase 1b Open-label Study of MK-2118 by IT and SC Injection

Objectives/Hypotheses and Endpoints:

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

Objective/Hypothesis	Endpoint
Primary	
• Objective: To determine the safety and tolerability and to establish a preliminary RP2D and/or an MTD or an MAD of MK-2118 administered via IT) injection as monotherapy and in combination with pembrolizumab IV infusion or by SC injection in combination with pembrolizumab IV infusion.	• DLT • AE • Discontinuing study treatment due to an AE
Secondary	
• Objective: To evaluate the PK of MK-2118 administered via IT injection as monotherapy and in combination with pembrolizumab IV infusion, or administered via SC injection in combination with pembrolizumab IV infusion	• Pharmacokinetic parameters of MK-2118, including C_{min}, C_{max}, and AUC
• Objective: To evaluate the PK of pembrolizumab IV infusion in combination with MK-2118 administered via IT or SC injection	• Pharmacokinetic exposure of pembrolizumab

Overall Design:

Trial Phase	Phase 1b
Clinical Indication	Treatment of advanced/metastatic solid tumors or lymphomas
Population	Participants with any histologically or cytologically confirmed advanced/metastatic solid tumor or lymphoma by pathology report who have received, or have been intolerant to, all treatment known to confer clinical benefit.
Trial Type	Interventional
Type of Design	This is a first-in-human, dose escalation and confirmation, nonrandomized, 4-arm, multicenter, open-label trial of MK-2118 monotherapy and MK-2118 in combination with pembrolizumab.
Type of Control	No treatment control
Trial Blinding	Unblinded Open-label
Estimated Duration of Trial	The Sponsor estimates that the trial will require approximately 62 months from the time the first participant signs the informed consent until the last participant's last study-related phone call or visit.

Number of Participants:

Approximately 160 participants will be enrolled.

Treatment Groups and Duration:

Treatment Groups

Table 1 Summary of Study Treatment Arms 1, 2, 3, and 4

Treatment Arm	Arm 1 Monotherapy	Arm 2 Combination Therapy	Arm 3 Combination Therapy	Arm 4 Combination Therapy
Route of Administration of MK-2118	IT	IT	IT	SC
Potential Dose Range	CCI [redacted]			
MK-2118 Regimen	CCI [redacted] MK-2118 IT CCI [redacted] CCI [redacted] Q3W MK-2118 IT	CCI [redacted] MK-2118 IT CCI [redacted] CCI [redacted] Q3W MK-2118 IT	CCI [redacted] MK-2118 IT CCI [redacted] CCI [redacted] Q3W MK-2118 IT	CCI [redacted] MK-2118 SC (Monotherapy run in) CCI [redacted] MK-2118 SC CCI [redacted] MK-2118 SC
Pembrolizumab 200 mg IV Regimen	Not administered	Initiate at Cycle 1 Q3W	Initiate at Cycle 1 Q3W	Initiate at Cycle 2 Q3W

In Arm 1, Arm 2, and Arm 3, MK-2118 will be administered intratumorally (IT). In Arm 4, MK-2118 will be administered by subcutaneous injection. Pembrolizumab 200 mg IV will be administered Q3W in Arms 2, 3, and 4.

Arm 1 and Arm 2 will evaluate the IT administration of MK-2118 into cutaneous and subcutaneous lesions. In Arm 1 and Arm 2, IT MK-2118 dosing CCI [redacted]

Arm 3 will evaluate the IT administration of MK-2118 to liver metastasis/lesions in combination with pembrolizumab 200 mg IV. In Arm 3, MK-2118 will be administered IT CCI [redacted] after which MK-2118 will be administered IT CCI [redacted] Pembrolizumab will be administered IV Q3W at Cycle 1 and beyond.

	Arm 4 will evaluate the SC administration of MK-2118. In Arm 4, SC MK-2118 will be administered as monotherapy [redacted] Subsequently, SC MK-2118 will be administered [redacted] and beyond. In Arm 4, Pembrolizumab will be administered for Cycle 2 and beyond. For each dose level in each Arm, an assessment will be made of the safety and tolerability data prior to escalation to the next dose level. Arm 1 (Part A) will initiate with an ATD phase (see Section 7.2.1) at a starting dose of [redacted] of IT MK-2118. The trial will proceed in an ATD of single-participant cohorts up to a dose level that meets at least 1 of the following criteria: 1) a dose level of at least [redacted] is cleared by DLT evaluation OR 2) a ≥ Grade 2 toxicity as assessed by the Investigator to be related, probably related, or possibly related to the drug(s) at any dose level. Arm 1 will then proceed to mTPI (Arm 1 Part B) to determine the MTD and/or MAD of monotherapy MK-2118. Arm 2 (IT MK-2118 combination therapy with pembrolizumab) will initiate at least 2 dose levels behind the MK-2118 monotherapy dose, which has cleared by DLT evaluation. In Arm 2 Part C, dose escalation will proceed in an ATD up to a dose level that meets at least 1 of the following criteria: 1) A dose level of at least [redacted] MK-2118 in combination with pembrolizumab is cleared by DLT evaluation; OR 2) A ≥ Grade 2 toxicity as assessed by the Investigator to be related, probably related, or possibly related to the drug(s) at any dose level in combination. Arm 2 will then proceed to mTPI (Arm 2 Part D) to determine the MTD and/or MAD of combination therapy IT MK-2118 with pembrolizumab. The Arm 2 IT MK-2118 dose in combination with pembrolizumab will not exceed the MTD of IT MK-2118 monotherapy established in Arm 1. If the initiation of IT MK-2118 combination therapy arm with pembrolizumab (Arm 2 Part C) was triggered by a ≥ Grade 2 AE observed in the ATD phase of monotherapy (Arm 1 Part A), then dose escalation of MK-2118 in the combination therapy arm (Arm 2) should proceed from the ATD phase to the mTPI phase when that dose level of MK-2118 in the combination therapy arm has been reached. Arm 3 will include participants with liver metastases/lesions. MK-2118 will be administered IT into liver metastasis/lesions in combination with pembrolizumab 200 mg IV. This Arm (Part E) will initiate with an ATD (see Section 7.2.1) at a starting dose of [redacted] of IT MK-2118. The trial will proceed in an ATD of single-participant

	cohorts up to a dose level that meets at least 1 of the following criteria: 1) a dose level of at least [CCI] is cleared by DLT evaluation, OR 2) a ≥ Grade 2 toxicity as assessed by the Investigator to be related, probably related, or possibly related to the drug(s) at any dose level. Arm 3 will then proceed to mTPI (Arm 3 Part F) to determine the MTD and/or MAD of IT MK-2118 in visceral lesions in combination with pembrolizumab. Arm 4 will initiate once the [CCI] IT MK-2118 dose level in Arm 1 has completed DLT evaluation per mTPI design. The starting dose for Arm 4 will be up to, but not exceeding, [CCI] SC MK-2118. There will be a 2-week SC MK-2118 monotherapy treatment period in Cycle 1. Subsequent cycles will constitute treatment of SC MK-2118 with the addition of pembrolizumab (see Table 1). Arm 4 will utilize the mTPI design to determine a preliminary RP2D for SC MK-2118 in combination with pembrolizumab. A participant who has radiographic or clinical progression in Arm 1 (IT MK-2118 monotherapy) may cross over to Arm 2 (IT MK-2118 in combination with pembrolizumab) once they have completed the DLT evaluation period of 21 days in his/her assigned monotherapy dose level cohort. The crossover participant will initiate Arm 2 at screening.
Duration of Participation	Each participant will be enrolled in the trial for up to approximately 2 years from the time that the participant signs the ICF through the final contact. Following a screening period of up to 28 days, each participant may receive up to 35 cycles of treatment in Arm 1, Arm 2, or Arm 3. In Arm 4, treatment begins with a 2-week cycle of SC MK-2118 monotherapy (Cycle 1) followed by up to 35 cycles of treatment in combination with pembrolizumab. An Arm 1 crossover participant may receive up to 35 cycles of treatment in Arm 2 (IT MK-2118 with pembrolizumab combination therapy) regardless of the duration of treatment he/she received in Arm 1 (IT MK-2118 monotherapy). After the end of treatment, each participant will be followed up for safety at 30 days. Participants will be monitored for survival every 12 weeks thereafter. Participants with SAEs, events of clinical interest, or who become pregnant will be followed up for 120 days.

Abbreviations are not spelled out at first use. A list of abbreviations used in this document can be found in Appendix 1. Study governance considerations are outlined in Appendix 3.

2 SCHEDULE OF ACTIVITIES (SOA)

2.1 Schedule of Activities for Initial Screening for Arms 1 to 4 and for Crossover into Arm 2

Scheduled Day	Initial Screening	Crossover Screening	Notes Screening and Day 1 cannot be on the same day.
	-28 to -1	-28 to -1	
Administrative Procedures			
Informed Consent	X		Written consent must be obtained prior to performing any protocol-specific procedures. An ICF signed >28 days prior to C1D1 does not need to be replaced.
Informed Consent for Future Biomedical Research (FBR) (Optional)	X		
Participant Identification Card	X		
Inclusion/Exclusion Criteria	X	X	
Demographics and Medical History	X	X	For Crossover from Arm 1 into Arm 2, update only. Assessments obtained during Arm 1 may be eligible as a screening test for Arm 2 if they were obtained within 28 days of treatment initiation into Arm 2.
Prior Medication and Concomitant Medication Review	X	X	
Disease Details and Prior Oncology Treatment History	X	X	
Mutational Status / Tumor genetic alteration(s)	X		Tumor genetic alteration(s), by history if available, as determined by local testing results (eg, BRCA1, MSI-H).
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 or other polymerase chain reaction -based assays) should be recorded if available, as determined per institutional standard.
Efficacy Procedures			**See also: Imaging Manual**
Tumor Imaging, RECIST v.1.1, irRECIST, and/or itRECIST Response Assessment	X	X	Baseline tumor imaging (CT, PET/CT, or MRI, as indicated for tumor type) and/or medical photography of cutaneous lesions should be performed within 28 days of enrollment. Medical photography may be performed more often as medically warranted.
Medical Photography (Cutaneous Lesions)	X	X	
IWG Revised Response Criteria for Lymphoma	X	X	
CTCL Response Assessment (CTCL participants only)	X	X	The pretreatment evaluation and scoring of disease involvement (mSWAT) should be done at baseline (screening).

Scheduled Day	Initial Screening	Crossover Screening	Notes
			Screening and Day 1 cannot be on the same day.
	-28 to -1	**-28 to -1**	
Bone Marrow Biopsy/ Aspirate (Lymphoma Participants Only [excluding CTCL participants])	X	X	Must be performed if not previously done within 8 weeks prior to Screening with negative results. For a crossover participant, a repeat bone marrow biopsy at screening is required when the participant crosses over into Arm 2, if bone marrow biopsy results were negative at Screening in Arm 1.
Safety Assessments and Procedures			**See Procedures Manual for collection and management of tissue samples**
Full Physical Examination	X	X	
Height	X		
Weight	X	X	
12-lead ECG	X	X	ECG will be obtained within 7 days prior to MK-2118 administration on C1D1.
Vital Signs	X	X	Temperature, pulse, respiratory rate, blood pressure, and O_2 saturation
ECOG Performance Status	X	X	Additional ECOG assessments may be performed as clinically indicated
Tumor Markers	X	X	Perform all screening clinical laboratory tests within 7 days prior to treatment initiation. Tests performed prior to the participant signing consent as part of routine clinical management are acceptable in lieu of a screening test, if the test is performed within the specified time frame. Specific tumor markers (eg, CEA, CA-125, CA-19-9, and alpha fetoprotein) are to be obtained as clinically indicated.
CBC with Differential	X	X	
PT/INR and PTT or aPTT	X	X	
Chemistry Panel	X	X	
LDH, GGT	X	X	
Lipase and Amylase	X	X	
Urinalysis	X	X	
Pregnancy Test for WOCBP– Urine or Serum β-hCG	X	X	Perform within 7 days prior to treatment initiation. If a urine pregnancy test cannot be confirmed as negative, a serum pregnancy test is required. Perform pregnancy testing per local regulations.
Hepatitis B and C	X		Include HCV antibody or HCV RNA (qualitative) and HBsAg. HIV by history is acceptable for exclusion, unless testing is required by local regulations.
Pharmacokinetics (PK)/ Pharmacodynamics/ Future Biomedical Research/Biomarkers			**See Procedures Manual for collection and management of tissue samples.**
Blood for Genotyping	X		*CYP2C9* testing.
Tumor Tissue Biopsy [a]	X[a]	X[a]	

CBC = complete blood count; CT = computed tomography; CTCL = cutaneous T-cell lymphoma; CYP2C9 = Cytochrome P-450 family 2 subfamily C member 9; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; FBR = future biomedical research; GGT = Gamma glutamyl transpeptidase; HBsAg/HBV = Hepatitis B surface antigen/Hepatitis B virus; HCV = Hepatitis C virus; ICF = Informed Consent Form; irRECIST = immune-related RECIST; IT = intratumoral; IWG = International Working Group; MRI = magnetic resonance imaging; mSWAT = modified Severity Weighted Assessment Tool; O_2 = oxygen; PET = positron emission tomography; RECIST v1.1 = Response Evaluation Criteria In Solid Tumors, version 1.1; RNA = ribonucleic acid; WOCBP = women of childbearing potential.

a.) All participants in Arms 1, 2 and 3 will be required to provide a sample biopsy of the tumor to be injected with MK-2118 and a sample biopsy from a distant, discrete noninjected site (at least 2 biopsies at each site) at Screening, unless deemed medically unsafe by the Investigator. This predose tumor biopsy at Screening will be performed on both the tumor lesion that is intended for treatment with IT administration of MK-2118, as well as on the distant, discrete lesion that is not intended for IT administration with MK-2118. For the tumor lesion intended for treatment with IT administration of MK-2118, the sample will be obtained by either punch biopsy for cutaneous lesions, or ultrasound-guided biopsy for subcutaneous/visceral lesions, or cross-sectional image-guided biopsy for visceral lesions. For distant, discrete tumor lesions that are not intended for IT administration with MK-2118, the sample biopsy will be obtained by punch biopsy for cutaneous lesions, ultrasound guided biopsy for subcutaneous/visceral lesions, or cross-sectional image-guided biopsy, such as CT/MRI-guided biopsy, for additional lesions.

Participants in Arm 1 (monotherapy) who cross over to Arm 2 (combination therapy) are required to provide a fresh tumor biopsy at screening of both injected and noninjected sites, similar to participants who are newly enrolled into the study and assigned to Arm 2, unless one of the following 2 situations occur:
(1) The most recent Arm 1 biopsy occurred within 28 days of C1D1 of Arm 2, OR (2) The investigator deems the biopsy to be medically unsafe.

Participants in Arm 4 will be required to provide a sample biopsy of a discrete, noninjected tumor lesion prior to treatment (Screening), unless deemed medically unsafe by the Investigator. The sample biopsy will be obtained by punch biopsy for cutaneous lesions, ultrasound guided biopsy for subcutaneous/visceral lesions, or cross-sectional image-guided biopsy, such as CT/MRI-guided biopsy, for additional lesions. Method of biopsy will be per guidance of the Investigator as well as discussion with the Sponsor.

Biopsies obtained during this study will be submitted as formalin-fixed, paraffin-embedded samples. Leftover main study tissue will be stored for FBR if the participant consents to FBR. Samples of archival tumor tissue collected at Screening should be freshly cut, and the slides from this freshly cut archival tumor tissue should be submitted to the testing laboratory within 14 days of slide preparation. Instructions for tissue collection, processing, and shipment are provided in the Procedures Manual.

2.2 Schedule of Activities for the Treatment Period, IT Administration for Arm 1 (Monotherapy) and Arm 2 (Combination Therapy – Including Crossover to Arm 2)

Trial Period	Treatment Period MK-2118 Monotherapy Cycle = 21 days MK-2118 and Pembrolizumab Combination Therapy Cycle = 21 days										Notes
Cycle	Cycle 1			Cycle 2			Cycle 3			Cycle 4 and Beyond	
Scheduling Day	**1**	**8**	**15**	**1**	**8**	**15**	**1**	**8**	**15**	**1**	
Scheduled Window	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	
Administrative Procedures											
Prior Medication and Concomitant Medication Review	X	X	X	X	X	X	X	X	X	X	
CCI [redacted]											
Pembrolizumab Administration (Arm 2) (Table 3)	X			X			X			X	This is only for combination therapy in Arm 2. See Pembrolizumab Pharmacy Manual.
Efficacy Procedures											**See Imaging Manual - All imaging visits have a ± 7 day window**
Tumor Imaging, RECIST v.1.1, irRECIST, and/or itRECIST Response Assessment									X	X	For solid tumors, to be performed 9 weeks (± 7 days) after the first dose, and then every 9 weeks. For lymphoma, assess at 12 weeks (± 7 days), and then every 12 weeks. Tumor imaging (CT, PET/CT, or MRI, as indicated for tumor type), and medical photography should be performed on the same schedule, following **calendar days,** and should not be adjusted for delays in cycle starts. Medical photography can be performed more often as medically warranted.
Tumor Imaging, Lymphomas IWG Response Assessment (except for CTCL)										X	
Medical Photography (Cutaneous Lesions)									X	X	
IWG Revised Response Criteria for Lymphoma (excluding CTCL)										X	

Trial Period	Treatment Period MK-2118 Monotherapy Cycle = 21 days MK-2118 and Pembrolizumab Combination Therapy Cycle = 21 days										
Cycle	Cycle 1			Cycle 2			Cycle 3			Cycle 4 and Beyond	Notes
Scheduling Day	**1**	**8**	**15**	**1**	**8**	**15**	**1**	**8**	**15**	**1**	
Scheduled Window	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	
CTCL Clinical Response Assessment (ISCL/mSWAT) (CTCL patients only)	X			**X**			X			X	For CTCL, assess response and perform medical photography on Day 1 of every treatment cycle. All responses should be documented to be at least 4 weeks in duration. In cases where the definition of progressive disease or relapse is met, but the clinical impression is questionable, documentation for a period of at least 4 weeks is recommended.
Bone Marrow Biopsy/ Aspirate (Lymphoma Participants Only)		←								→	For participants with a negative bone marrow biopsy at screening, follow-up bone marrow biopsy need not be performed. Follow-up bone marrow biopsy may be performed to confirm a CR if the participant was initially positive or if it is clinically indicated.
Safety Assessments and Procedures											**See Procedures Manual for Collection And Management of Samples.**
Adverse Event Monitoring		←								→	
Full Physical Examination	X			X			X			X	
Directed Physical Examination		X	X		X	X					
Weight	X			X			X			X	
12-lead ECG	X			X			X				Obtain within 72 h prior to MK-2118 IT administration on C1D1, C2D1, and C3D1. A postdose ECG will be obtained on C1D1 within 30 min and at 3 to 4 h following MK-2118 IT administration
Vital Signs (temperature, pulse, respiratory rate, blood pressure, and O_2 saturation)	X	X	X	X	X	X	X	X	X	X	Collect VS **predose** within 1 h (± 30 min) of MK-2118 administration at each treatment visit. Collect VS **postdose** on C1D1 at 2, 4, 6, 8, and 12 h (± 30 min for each time point) after MK-2118 administration. At each subsequent treatment visit, collect VS at 1 h (±15 min) after MK-2118 administration. Additional VS monitoring may be obtained as clinically indicated.

Trial Period	Treatment Period MK-2118 Monotherapy Cycle = 21 days MK-2118 and Pembrolizumab Combination Therapy Cycle = 21 days										
Cycle	Cycle 1			Cycle 2			Cycle 3			Cycle 4 and Beyond	Notes
Scheduling Day	**1**	**8**	**15**	**1**	**8**	**15**	**1**	**8**	**15**	**1**	
Scheduled Window	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	
ECOG Performance Status	X			X			X			X	Additional ECOG can be performed as clinically indicated.
Tumor Markers	X			X			X			X	Specific tumor markers (eg, CEA, CA-125, CA-19-9, or alpha fetoprotein) to be obtained as clinically indicated
CBC with Differential	X	X	X	X	X	X	X	X	X	X	Required within 72 h of C1D1 and may be performed up to 72 h prior to dosing for subsequent cycles when scheduled.
PT/INR and PTT or aPTT	X			X			X			X	
Chemistry Panel	X	X	X	X	X	X	X	X	X	X	
LDH, GGT	X			X			X			X	
Urinalysis	X			X			X			X	
Lipase and Amylase	X			X			X			X	
Pregnancy Test for WOCBP – Urine or Serum β-hCG	X			X			X			X	Required within 24 h prior to first dose of study medication, and Day 1 of each cycle thereafter during treatment. Does not need to be repeated on C1D1 if screening test was done within 24 h of C1D1. If a urine pregnancy test cannot be confirmed as negative, a serum pregnancy test is required. Pregnancy testing must be done as required by local regulation.
Thyroid Function (TSH, T3, FT3, T4, FT4)	X						X			X	Required within 72 h prior to Day 1 of C1, C3, C5, C7, C9, C11, and at every other subsequent treatment cycle.
Pharmacokinetics (PK)/ Pharmacodynamics/ Future Biomedical Research/Biomarkers											**See Procedures Manual for Collection and Management of Samples.**
Serum for Cytokine Panel and CRP for MK-2118 Pharmacodynamics [b]	X[c]										Cytokine and CRP samples should be obtained **predose** on C1D1. **Postdose** serum samples for cytokine panels and CRP will be collected on C1D1, and if applicable, on Day 1 of the first cycle that the participant has undergone intraparticipant dose escalation of MK-2118. Postdose samples will be collected at 2 h (±15 min), 6 h (±15 min), 12 h (± 2 h), and 24 h (± 4 h) following MK-2118 administration. Collect samples at the same time as for MK-2118 PK when feasible.

Trial Period	Treatment Period MK-2118 Monotherapy Cycle = 21 days MK-2118 and Pembrolizumab Combination Therapy Cycle = 21 days										
Cycle	Cycle 1			Cycle 2			Cycle 3			Cycle 4 and Beyond	Notes
Scheduling Day	1	8	15	1	8	15	1	8	15	1	
Scheduled Window	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	
Plasma MK-2118 PK [b]	X			X						X[c]	Collect **predose** samples 1-8 h before MK-2118 administration on C1D1 and C2D1. Collect **postdose** samples on C1D1 and C2D1 at the following time points: end of MK-2118 administration (up to +15 min), and at 0.5 h (±15 min), 1 h (±15 min), 2 h (±15 min), 4 h (±15 min), 6 h (±15 min), and 8 h (±15 min) on C1D1 and C2D1. Additional postdose samples will be collected at 12 h (± 2 h) and at 24 h (± 4 h) following MK-2118 administration on C1D1 only. If applicable, collect on Day 1 of the first cycle that the participant has undergone intraparticipant dose escalation of MK-2118. Collect samples at the same time as for cytokines and CRP, and for pembrolizumab PK, when feasible.
Urine Sample for MK-2118	X										Collect **predose** (spot), and **postdose** 0-4 h, 4-8 h, and 8-24 h after MK-2118 administration.
Serum for Pembrolizumab PK	X			X						X	Pembrolizumab PK and ADA are for pembrolizumab-treated participants only. Collect samples **predose** 0 to 4 h before pembrolizumab IV infusion on C1D1, C2D1, C4D1, and on Day 1 of every 4 cycles thereafter (ie, C8, C12, etc.). Collect pembrolizumab and MK-2118 PK samples together, when feasible.
Serum for ADA	X			X						X	
Blood for RNA Analysis	X[c]										Collect **predose** 0 to 4 h before MK-2118 administration on C1D1 Collect **postdose** 6 to 8 h (±15 min) after MK-2118 administration on C1D1
Blood for Genetic Analysis [d]	X										Collect prior to treatment.

Trial Period	Treatment Period MK-2118 Monotherapy Cycle = 21 days MK-2118 and Pembrolizumab Combination Therapy Cycle = 21 days										
Cycle	Cycle 1			Cycle 2			Cycle 3			Cycle 4 and Beyond	Notes
Scheduling Day	1	8	15	1	8	15	1	8	15	1	
Scheduled Window	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	
Tumor Tissue Biopsy[e]					X			X			For the tumor lesion that is treated with IT administration of MK-2118, collect **postdose** tumor biopsy on the same day as treatment, 5 h (± 2 h) following IT administration of MK-2118 on C2D8, and optionally on C3D8 at 5 h (± 2 h) following IT administration of MK-2118. Biopsy of a distant, discrete, noninjected site is preferred on the same day as the IT administration of MK-2118, but may be performed up to 5 days after treatment of the injected lesion. The C3D8 biopsy time point is encouraged, but optional.

ADME = absorption, distribution, metabolism, and excretion; CRP = C-reactive protein; CR = complete response; CT = computed tomography; CTCL = cutaneous T-cell lymphoma; ECOG = Eastern Cooperative Oncology Group; FBR = future biomedical research; FT3 = free triiodothyronine; FT4 = free thyroxine; ISCL = International Society for Cutaneous Lymphomas ; irRECIST = immune-related RECIST; MRI = magnetic resonance imaging; mSWAT = modified Severity Weighted Assessment Tool; ; O_2 = oxygen; PET = positron emission tomography; RNA = ribonucleic acid; RECIST v1.1 = Response Evaluation Criteria In Solid Tumors, version 1.1; T3 = total triiodothyronine; T4 = total thyroxine; VS = vital signs; WOCBP = women of childbearing potential.

a) The inpatient observation periods may be extended up to 48 hours at the discretion of the Investigator, per local Institutional Review Board, Ethics Review Committee, and/or Health Authority mandate.
b) Up to 2 additional serum samples may be collected if deemed medically necessary (eg, in the setting of an AE).
c) In the event a participant has undergone intraparticipant dose escalation of MK-2118, these samples for biomarker analysis will be collected on Day 1 of the first cycle of the escalated new dose. Note: Blood for RNA testing will also be collected on Day 1 of the second cycle of the escalated new dose.
d) This sample will be drawn for genetic variations in ADME and planned analysis of the association between genetic variants in DNA and drug response. If the IRB/IEC does not approve of the planned analysis of the association between DNA variation and drug response, or if there is a local law or regulation prohibiting the same, then data analysis will be limited to investigate ADME genetic variations. If the sample is collected, leftover extracted DNA will be stored for FBR if the participant signs the FBR consent. If the planned genetic analysis is not approved, but FBR is approved and consent is given, then this sample will be collected for the purpose of FBR.
e) All participants will be required to provide a sample biopsy of the tumor to be injected with MK-2118 and a sample biopsy from a distant, discrete noninjected site (at least 2 biopsies at each site), unless deemed medically unsafe by the Investigator. For the tumor lesion intended for treatment with IT administration of MK-2118, the sample will be obtained by either punch biopsy for cutaneous lesions, or ultrasound-guided biopsy for subcutaneous lesions. For distant, discrete tumor lesions that are not intended for IT administration with MK-2118, the sample biopsy will be obtained by 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. Biopsies obtained during this study will be submitted as formalin-fixed, paraffin-embedded samples. Leftover main study tissue will be stored for FBR if the participant consents to FBR. Instructions for tissue collection, processing, and shipment are provided in the Procedures Manual.

2.3 Schedule of Activities for the Treatment Period of Arm 3 (Visceral IT Administration)

Trial Period	Treatment Period MK-2118 and Pembrolizumab Combination Therapy Cycle = 21 days								
Cycle	Cycle 1			Cycle 2			Cycle 3	Cycle 4 and Beyond	Notes
Scheduling Day	**1**	**8**	**15**	**1**	**8**	**15**	**1**	**1**	
Scheduled Window	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	
Administrative Procedures									
Prior Medication and Concomitant Medication Review	X	X	X	X	X	X	X	X	
CCI [redacted]									
Pembrolizumab Administration (Table 4)	X			X			X	X	See Pembrolizumab Pharmacy Manual for dose preparation.
Efficacy Procedures									**See Imaging Manual - All imaging visits have a ± 7 day window**
Tumor Imaging, Solid Tumors, RECIST, irRECIST, and/or itRECIST Response Assessment							X	X	For solid tumors, to be performed 9 weeks (± 7 days) after the first dose, and then every 9 weeks. For lymphoma, assess at 12 weeks (± 7 days), and then every 12 weeks. Tumor imaging (CT, PET/CT, or MRI, as indicated for tumor type), and medical photography should be performed on the same schedule, following **calendar days,** and should not be adjusted for delays in cycle starts. Medical photography can be performed more often as medically warranted.
Tumor Imaging, Lymphomas, IWG Response Criteria								X	
Medical Photography (Cutaneous Lesions)							X	X	
Bone Marrow Biopsy/ Aspirate (Lymphoma Participants Only)	←							→	For participants with a negative bone marrow biopsy at screening, follow-up bone marrow biopsy need not be performed. Follow-up bone marrow biopsy may be performed to confirm a CR if the participant was initially positive or if it is clinically indicated.

Trial Period	Treatment Period MK-2118 and Pembrolizumab Combination Therapy Cycle = 21 days								
Cycle	Cycle 1			Cycle 2			Cycle 3	Cycle 4 and Beyond	Notes
Scheduling Day	**1**	**8**	**15**	**1**	**8**	**15**	**1**	**1**	
Scheduled Window	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	
Safety Assessments and Procedures									**See Procedures Manual for Collection And Management of Samples.**
Adverse Event Monitoring	←							→	
Full Physical Examination	X			X			X	X	
Directed Physical Examination		X	X		X	X			
Weight	X			X			X	X	
12-lead ECG	X			X			X		Obtain within 72 h prior to MK-2118 IT administration on C1D1, C2D1, and C3D1. A postdose ECG will be obtained on C1D1 within 30 min and at 3 to 4 h following MK-2118 IT administration
Vital Signs (temperature, pulse, respiratory rate, blood pressure, and O_2 saturation)	X	X	X	X	X	X	X	X	Collect VS **predose** within 1 h (± 30 min) of MK-2118 administration at each treatment visit. Collect VS **postdose** on C1D1 at 2, 4, 6, 8, and 12 h (± 30 min for each time point) after MK-2118 administration. At each subsequent treatment visit, collect VS at 1 h (±15 min) after MK-2118 administration. Additional VS monitoring may be obtained as clinically indicated.
ECOG Performance Status	X			X			X	X	Additional ECOG can be performed as clinically indicated.
Tumor Markers	X			X			X	X	Specific tumor markers (eg, CEA, CA-125, CA-19-9, or alpha fetoprotein) to be obtained as clinically indicated
CBC with Differential	X	X	X	X	X	X	X	X	Required within 72 h of C1D1 and may be performed up to 72 h prior to dosing for subsequent cycles when scheduled.
PT/INR and PTT or aPTT	X			X			X	X	
Chemistry Panel	X	X	X	X	X	X	X X	X	
LDH, GGT	X			X			X	X	
Urinalysis	X			X			X	X	
Lipase and Amylase	X			X			X	X	

Trial Period	Treatment Period MK-2118 and Pembrolizumab Combination Therapy Cycle = 21 days								
Cycle	Cycle 1			Cycle 2			Cycle 3	Cycle 4 and Beyond	Notes
Scheduling Day	**1**	**8**	**15**	**1**	**8**	**15**	**1**	**1**	
Scheduled Window	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	
Pregnancy Test for WOCBP – Urine or Serum β-hCG	X			X			X	X	Required within 24 h prior to first dose of study medication, and Day 1 of each cycle thereafter during treatment. Does not need to be repeated on C1D1 if screening test was done within 24 h of C1D1. If a urine pregnancy test cannot be confirmed as negative, a serum pregnancy test is required. Pregnancy testing must be done as required by local regulation.
Thyroid Function (TSH, T3, FT3, T4, FT4)	X						X	X	Required within 72 h prior to dosing on Day 1 of C1, C3, C5, C7, C9, C11, and at every other subsequent treatment cycle.
Pharmacokinetics (PK)/ Pharmacodynamics/Future Biomedical Research/Biomarkers									**See Procedures Manual for Collection and Management of Samples.**
Serum for Cytokine Panel and CRP for MK-2118 Pharmacodynamics [b]	X								Cytokine and CRP samples should be obtained **predose** on C1D1. **Postdose** serum samples for cytokine panels and CRP will be collected on C1D1. Postdose samples will be collected at 2 h (±15 min), 6 h (±15 min), 12 h (± 2 h), and 24 h (± 4 h) following MK-2118 administration. Collect samples at the same time as for MK-2118 PK when feasible.
Plasma MK-2118 PK [b]	X			X					Collect **predose** samples 1-8 h before MK-2118 administration on C1D1 and C2D1. Collect **postdose** samples on C1D1 and C2D1 at the following time points: end of MK-2118 administration (up to +15 min), and at 0.5 h (±15 min), 1 h (±15 min), 2 h (±15 min), 4 h (±15 min), 6 h (±15 min), and 8 h (±15 min) on C1D1 and C2D1. Additional postdose samples will be collected at 12 h (± 2 h) and at 24 h (± 4 h) following MK-2118 administration on C1D1 only. Collect samples at the same time as for cytokines and CRP, and for pembrolizumab PK, when feasible.
Urine Sample for MK-2118	X								Collect **predose** (spot), and **postdose** 0-4 h, 4-8 h, and 8-24 h after MK-2118 administration.
Serum for Pembrolizumab PK	X			X				X	Collect samples **predose** 0 to 4 h before pembrolizumab IV infusion on C1D1, C2D1, C4D1, and on Day 1 of every 4

Trial Period	Treatment Period MK-2118 and Pembrolizumab Combination Therapy Cycle = 21 days								
Cycle	Cycle 1			Cycle 2			Cycle 3	Cycle 4 and Beyond	Notes
Scheduling Day	**1**	**8**	**15**	**1**	**8**	**15**	**1**	**1**	
Scheduled Window	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	
Serum for ADA	X			X				X	cycles thereafter (ie, C8, C12, etc.). Collect pembrolizumab and MK-2118 PK samples together, when feasible.
Blood for RNA Analysis	X								Collect **predose** 0 to 4 h before MK-2118 administration on C1D1 Collect **postdose** 6 to 8 h (±15 min) after MK-2118 administration on C1D1.
Blood for Genetic Analysis[c]	X								Collect prior to treatment.
Tumor Tissue Biopsy[d]					X		X		For the tumor lesion that is treated with IT administration of MK-2118, collect **predose** tumor biopsy on the same day as treatment, prior to IT administration of MK-2118 on C2D8, and optionally on C3D1. Biopsy of a distant, discrete, noninjected site is preferred on the same day as the IT administration of MK-2118, but may be performed up to 5 days after treatment of the injected lesion. The C3D1 biopsy time point is encouraged, but optional.

CRP = C-reactive protein; CT = computed tomography; ECOG = Eastern Cooperative Oncology Group; MRI = magnetic resonance imaging; FT3 = free triiodothyronine; FT4 = free thyroxine; PET = positron emission tomography; RNA = ribonucleic acid; RECIST v1.1 = Response Evaluation Criteria In Solid Tumors, version 1.1; irRECIST = immune-related RECIST; T3 = total triiodothyronine; T4 = total thyroxine; WOCBP = women of childbearing potential.

a) The inpatient observation periods may be extended up to 48 hours at the discretion of the Investigator, per local Institutional Review Board, Ethics Review Committee, and/or Health Authority mandate.
b) Up to 2 additional serum samples may be collected if deemed medically necessary (eg, in the setting of an AE).
c) This sample will be drawn for genetic variations in ADME and planned analysis of the association between genetic variants in DNA and drug response. If the IRB/IEC does not approve of the planned analysis of the association between DNA variation and drug response, or if there is a local law or regulation prohibiting the same, data analysis will be limited to investigate ADME genetic variations. If the sample is collected, leftover extracted DNA will be stored for FBR if the participant signs the FBR consent. If the planned genetic analysis is not approved, but FBR is approved and consent is given, this sample will be collected for the purpose of FBR.
d) All participants will be required to provide a sample biopsy of the tumor to be injected with MK-2118 and a sample biopsy from a distant, discrete noninjected site (at least 2 biopsies at each site), unless deemed medically unsafe by the Investigator. For the tumor lesion intended for treatment with IT administration of MK-2118, the sample will be obtained by either punch biopsy for cutaneous lesions, or ultrasound-guided biopsy for subcutaneous lesions. For distant, discrete tumor lesions that are not intended for IT administration with MK-2118, the sample biopsy will be obtained by 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. Biopsies obtained during this study will be submitted as formalin-fixed, paraffin-embedded samples. Leftover main study tissue will be stored for FBR if the participant consents to FBR. Instructions for tissue collection, processing, and shipment are provided in the Procedures Manual.

2.4 Schedule of Activities for the Treatment Period of Arm 4 (Subcutaneous Administration)

Trial Period	Treatment Period MK-2118 Run-in Monotherapy Cycle = 14 days MK-2118 and Pembrolizumab Combination Therapy Cycle = 21 days												
Cycle	**Cycle 1**		**Cycle 2**			**Cycle 3**			**Cycle 4**			**Cycle 5 and Beyond**	**Notes**
Scheduling Day	**1**	**8**	**1**	**8**	**15**	**1**	**8**	**15**	**1**	**8**	**15**	**1**	
Scheduled Window	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	
Administrative Procedures													
Prior Medication and Concomitant Medication Review	X	X	X	X	X	X	X	X	X	X	X	X	
CCI [redacted]													
Pembrolizumab Administration (Table 5)			X			X			X			X	See Pembrolizumab Pharmacy Manual.
Efficacy Procedures													**See Imaging Manual- All imaging visits have a ± 7 day window**
Tumor Imaging, solid tumors RECIST, irRECIST, and/or itRECIST Response Assessment									X			X	For solid tumors, to be performed 9 weeks (± 7 days) after the first dose of MK-2118, and then every 9 weeks. For lymphoma, assess at 12 weeks (± 7 days), and then every 12 weeks. Tumor imaging (CT, PET/CT, or MRI, as indicated for tumor type), and medical photography should be performed on the same schedule, following **calendar days,** and should
Tumor Imaging, Lymphomas IWG Revised Response Criteria for Lymphoma (excluding CTCL)											X	X	

Trial Period	Treatment Period MK-2118 Run-in Monotherapy Cycle = 14 days MK-2118 and Pembrolizumab Combination Therapy Cycle = 21 days												Notes
Cycle	**Cycle 1**		**Cycle 2**			**Cycle 3**			**Cycle 4**			**Cycle 5 and Beyond**	
Scheduling Day	**1**	**8**	**1**	**8**	**15**	**1**	**8**	**15**	**1**	**8**	**15**	**1**	
Scheduled Window	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	
Medical Photography (Cutaneous Lesions)									X			X	not be adjusted for delays in cycle starts. Medical photography can be performed more often as medically warranted.
CTCL Clinical Response Assessment (ISCL/mSWAT)	X		X			**X**			X			X	For CTCL, assess response and perform medical photography on Day 1 of every treatment cycle. All responses should be documented to be at least 4 weeks in duration. In cases where the definition of progressive disease or relapse is met, but the clinical impression is questionable, documentation for a period of at least 4 weeks is recommended.
Bone Marrow Biopsy/ Aspirate (Lymphoma Participants Only)			←								→		For participants with a negative bone marrow biopsy at screening, follow-up bone marrow biopsy need not be performed. Follow-up bone marrow biopsy may be performed to confirm a complete response (CR) if the participant was initially positive or if it is clinically indicated.
Safety Assessments and Procedures													**See Procedures Manual for Collection And Management of Samples.**
Adverse Event Monitoring	←							→					
Full Physical Examination	X		X			X			X			X	
Directed Physical Examination		X		X	X		X	X		X	X		
Weight	X		X			X			X			X	

Trial Period	Treatment Period MK-2118 Run-in Monotherapy Cycle = 14 days MK-2118 and Pembrolizumab Combination Therapy Cycle = 21 days												
Cycle	**Cycle 1**		**Cycle 2**			**Cycle 3**			**Cycle 4**			**Cycle 5 and Beyond**	**Notes**
Scheduling Day	**1**	**8**	**1**	**8**	**15**	**1**	**8**	**15**	**1**	**8**	**15**	**1**	
Scheduled Window	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	
12-lead ECG	X		X			X			X				Obtain within 72 h prior to MK-2118 SC administration on CID1, C2D1, C3D1, and C4D1. A postdose ECG will be obtained on C1D1 within 30 min and at 3 to 4 h following MK-2118 SC administration
Vital Signs (temperature, pulse, respiratory rate, blood pressure, and O_2 saturation)	X	X	X	X	X	X	X	X	X	X	X	X	Collect VS **predose** 1 h (± 30 min) of MK-2118 administration at each treatment visit. Collect VS **postdose** on C1D1 at 2, 4, 6, 8, and 12 h (± 30 min for each time point) after MK-2118 administration. At each subsequent treatment visit, collect VS at 1 h (±15 min) after MK-2118 administration. Additional VS monitoring may be obtained as clinically indicated.
ECOG Performance Status	X		X			X			X			X	Additional ECOG can be performed as clinically indicated.
Tumor Markers	X		X			X			X			X	Specific tumor markers (eg, CEA, CA-125, CA-19-9, or alpha fetoprotein) to be obtained as clinically indicated
CBC with Differential	X	X	X	X	X	X	X	X	X	X	X	X	Required within 72 h of C1D1 and may be performed up to 72 h prior to dosing for subsequent cycles when scheduled.
PT/INR and PTT or aPTT	X		X			X			X			X	
Chemistry Panel	X	X	X	X	X	X	X	X	X	X	X	X	
LDH, GGT	X		X			X			X			X	
Urinalysis	X		X			X			X			X	
Lipase and Amylase	X		X			X			X			X	

Trial Period	Treatment Period MK-2118 Run-in Monotherapy Cycle = 14 days MK-2118 and Pembrolizumab Combination Therapy Cycle = 21 days											
Cycle	**Cycle 1**		**Cycle 2**			**Cycle 3**			**Cycle 4**			**Cycle 5 and Beyond**	**Notes**
Scheduling Day	**1**	**8**	**1**	**8**	**15**	**1**	**8**	**15**	**1**	**8**	**15**	**1**	
Scheduled Window	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	
Pregnancy Test for WOCBP – Urine or Serum β-hCG	X		X			X			X			X	Required within 24 h prior to first dose of study medication, and Day 1 of each cycle thereafter during treatment. Does not need to be repeated on C1D1 if screening test was done within 24 h of C1D1.If a urine pregnancy test cannot be confirmed as negative, a serum pregnancy test is required. Pregnancy testing must be done as required by local regulation.
Thyroid Function (TSH, T3, FT3, T4, FT4)	X		X						X			X	Required within 72 h prior to dosing on Day 1 of C1, C2, C4, C6, C8, C10, C12, and at every other subsequent treatment cycle.

Trial Period	Treatment Period MK-2118 Run-in Monotherapy Cycle = 14 days MK-2118 and Pembrolizumab Combination Therapy Cycle = 21 days												Notes
Cycle	**Cycle 1**		**Cycle 2**			**Cycle 3**			**Cycle 4**			**Cycle 5 and Beyond**	
Scheduling Day	**1**	**8**	**1**	**8**	**15**	**1**	**8**	**15**	**1**	**8**	**15**	**1**	
Scheduled Window	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	
Pharmacokinetics (PK)/ Pharmacodynamics/ Future Biomedical Research/Biomarkers													**See Procedures Manual for Collection and Management of Samples.**
Serum for Cytokine Panel and CRP for MK-2118 Pharmacodynamics [b]	X												Cytokine and CRP samples should be obtained **predose** on C1D1). **Postdose** serum samples for cytokine panels and CRP will be collected on C1D1. Postdose samples will be collected at 2 h (±15 min), 6 h (±15 min), 12 h (± 2 h), and 24 h (± 4 h) following MK-2118 administration. On C1D1, an additional serum sample will be collected at 12 h (± 2 h) and at 24 h (± 4 h) following MK-2118 administration. Collect samples at the same time as for MK-2118 PK when feasible.

Trial Period	Treatment Period MK-2118 Run-in Monotherapy Cycle = 14 days MK-2118 and Pembrolizumab Combination Therapy Cycle = 21 days												Notes
Cycle	**Cycle 1**		**Cycle 2**			**Cycle 3**			**Cycle 4**			**Cycle 5 and Beyond**	
Scheduling Day	**1**	**8**	**1**	**8**	**15**	**1**	**8**	**15**	**1**	**8**	**15**	**1**	
Scheduled Window	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	
Plasma MK-2118 PK [b]	X		X			X							Collect **predose** samples 1-8 h before MK-2118 administration on C1D1, C2D1 and C3D1. Collect **postdose** samples at the following time points: end of MK-2118 SC administration (up to +15 min), and at 0.5 h (±15 min), 1 h (±15 min), 2 h (±15 min), 4 h (±15 min), 6 h (±15 min), and 8 h (±15 min) on C1D1, C2D1 and C3D1. Additional postdose samples will be collected at 12 h (± 2 h) and at 24 h (± 4 h) following MK-2118 SC administration on C1D1 only. Collect samples at the same time as for cytokines and CRP, and for pembrolizumab PK, when feasible.
Urine Sample for MK-2118	X												Collect **predose** (spot), and **postdose** 0-4 h, 4-8 h, and 8-24 h after MK-2118 administration.
Serum for Pembrolizumab PK			X			X						X	Collect samples **predose** 0 to 4 h before pembrolizumab IV infusion on C2D1, C3D1, C5D1, and on Day 1 of every 4 cycles thereafter (ie, C9, C13, C17, etc.). Collect with plasma samples for MK-2118 PK when feasible.
Serum for ADA			X			X						X	

Trial Period	Treatment Period MK-2118 Run-in Monotherapy Cycle = 14 days MK-2118 and Pembrolizumab Combination Therapy Cycle = 21 days												Notes
Cycle	**Cycle 1**		**Cycle 2**			**Cycle 3**			**Cycle 4**			**Cycle 5 and Beyond**	
Scheduling Day	**1**	**8**	**1**	**8**	**15**	**1**	**8**	**15**	**1**	**8**	**15**	**1**	
Scheduled Window	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	
Blood for RNA Analysis	X												Collect **predose** 0 to 4 h before MK-2118 administration on C1D1 Collect **postdose** 6 to 8 h (+ 15 min) after MK-2118 administration on C1D1.
Blood for Genetic Analysis [c]	X												Collect prior to treatment.
Tumor Tissue Biopsy[d]		X					X						Biopsy of a discrete, noninjected lesion at 5 h (± 2 h) following MK-2118 SC administration on Cycle 1 Day 8 and on Cycle 3 Day 8.

ADME = absorption, distribution, metabolism, and excretion; CT = computed tomography; CTCL = cutaneous T-cell lymphoma; ECOG = Eastern Cooperative Oncology Group; ISCL = International Society for Cutaneous Lymphomas ; FT3 = free triiodothyronine; FT4 = free thyroxine; MRI = magnetic resonance imaging; mSWAT = modified Severity Weighted Assessment Tool; PET = positron emission tomography; RNA = ribonucleic acid; RECIST v1.1 = Response Evaluation Criteria In Solid Tumors, version 1.1; irRECIST = immune-related RECIST; T3 = total triiodothyronine; T4 = total thyroxine; WOCBP = women of childbearing potential.

a) The inpatient observation periods may be extended up to 48 hours at the discretion of the Investigator, per local Institutional Review Board, Ethics Review Committee, and/or Health Authority mandate.
b) Up to 2 additional serum samples may be collected if deemed medically necessary (eg, in the setting of an AE).
c) This sample will be drawn for genetic variations in ADME and planned analysis of the association between genetic variants in DNA and drug response. If the IRB/IEC does not approve of the planned analysis of the association between DNA variation and drug response, or if there is a local law or regulation prohibiting the same, data analysis will be limited to investigate ADME genetic variations. If the sample is collected, leftover extracted DNA will be stored for FBR if the participant signs the FBR consent. If the planned genetic analysis is not approved, but FBR is approved and consent is given, this sample will be collected for the purpose of FBR.
d) All participants in Arm 4 will be required to provide a sample biopsy from a discrete tumor lesion, unless deemed medically unsafe by the Investigator. For Arm 4, three serial biopsies (screening, C1D8 and C3D8) from a single discrete tumor lesion will be required. The sample biopsy will be obtained by punch biopsy for cutaneous lesions, ultrasound guided biopsy for subcutaneous or visceral lesions, or image-guided biopsy, such as CT/MRI-guided biopsy, for additional lesions. Method of biopsy will be per guidance of the Investigator as well as discussion with the Sponsor. Biopsies obtained during this study will be submitted as formalin-fixed, paraffin-embedded samples. Leftover main study tissue will be stored for FBR if the participant consents to FBR. Instructions for tissue collection, processing, and shipment are provided in the Procedures Manual.

2.5 Discontinuation / End of Treatment and Post-treatment Follow-up for Arms 1 to 4

Trial Period	End of Treatment (EOT)/ Discontinuation	Post-treatment Period		Notes
		30-Day Safety Follow-up Visit	Survival Follow-up	
Scheduling Day		**30 days post last dose**	**Q12W**	
Scheduled Window	**±7**	**+7**	**±14**	
Administrative Procedures				
Prior Medication and Concomitant Medication Review	X	X		
Efficacy Procedures				**See Imaging Manual All imaging visits have a ± 7 -day window**
Tumor Imaging, RECIST, irRECIST, and itRECIST Response Assessment	X			
Medical Photography (Cutaneous Lesions)	X			
IWG Revised Response Criteria for Lymphoma (excluding CTCL)	X			
CTCL Response Criteria	X			
Survival Status Monitoring	←	—	→	Updated survival status may be requested by the Sponsor at any time during the course of the study. Upon Sponsor notification, all participants who do not/will not have a scheduled study visit or study contact during the Sponsor defined time period will be contacted for their survival status (excluding participants that have a death event previously recorded).
Safety Assessments and Procedures				**See Procedures Manual for collection and management of samples.**
Adverse Event Monitoring	X	X		
Full Physical Examination	X	X		
Weight	X	X		
12-lead ECG		X		
Vital Signs	X	X		Temperature, pulse, respiratory rate, blood pressure, and O_2 saturation

Trial Period	End of Treatment (EOT)/ Discontinuation	Post-treatment Period		Notes
		30-Day Safety Follow-up Visit	Survival Follow-up	
Scheduling Day		**30 days post last dose**	**Q12W**	
Scheduled Window	**±7**	**+7**	**±14**	
ECOG Performance Status	X	X		
CBC with Differential	X	X		
Chemistry Panel	X	X		
Lipase and Amylase	X	X		
Pregnancy Test for WOCBP – Urine or Serum β-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		
Pharmacokinetics (PK)/Pharmacodynamics/ Future Biomedical Research/Biomarkers				**See Procedures Manual for collection and management of samples.**
Serum for Pembrolizumab PK	X			Only for pembrolizumab-treated participants.
Serum for Antidrug Antibodies	X			

CT computed tomography; ECOG Eastern Cooperative Oncology Group; MRI magnetic resonance imaging; PET positron emission tomography; RECIST v1.1 Response Evaluation Criteria In Solid Tumors, version 1.1; irRECIST immune related RECIST; WOCBP women of childbearing potential.

3 INTRODUCTION

MK-2118 is a novel small molecule that is an agonist of the intracellular innate immune adaptor, STING. MK-2118 is under study for the treatment of solid tumors and lymphomas as monotherapy and as combination therapy with pembrolizumab. This is a FIH dose escalation, and dose finding trial to assess the safety and tolerability of IT injection of MK-2118, both as monotherapy and as combination therapy with pembrolizumab.

3.1 Study Rationale

Internal preclinical data demonstrate STING expression in multiple tumor types, supporting the study of a broad group of tumor types, including advanced/metastatic solid tumors and lymphomas. Endogenous STING pathway activation within the tumor induces spontaneous T-cell priming that is necessary for the generation of adaptive immunity. In mouse tumor models, STING activation in the tumor microenvironment leads to a potent antitumor response. IT injection of STING agonist in mice induces regression of established tumors and generates systemic immune responses, mediating rejection of distant metastases and providing immunologic (T cell) memory [Woo S. R., et al 2014] [Corrales, L., et al 2015]. The STING agonist MK-2118, therefore, has potential as a cancer therapeutic and will be evaluated in this FIH dose-finding trial.

The scientific rationale for combining MK-2118 with PD-1 blockade is based on the ability of STING agonists to induce type I IFNs and induce strong T-cell activation by promoting cross-presentation of tumor antigens. As strong T cell activation is accompanied by up-regulation of PD-1, which mediates T cell inhibition by tumors, combination therapy with anti-PD-1 will prevent the inhibition of T-cell activation.

The empirical rationale for combining MK-2118 with PD-1 blockade is based on the efficacy observed in anti-PD-1 nonresponsive syngeneic mouse tumor models in which sub-efficacious MK-2118 doses in combination with anti-PD-1 induced improved antitumor responses and complete tumor regression compared with either monotherapy treatment alone.

The rationale for the addition of a visceral IT arm of MK-2118 is to expand the tumor location for IT therapy to deeper and visceral organs such as the liver. In addition, the visceral IT arm will evaluate the safety, tolerability, PK, pharmacodynamics, and early efficacy of MK-2118 injected into visceral and deeper lesions.

Subcutaneous administration of MK-2118 is under investigation with the objective to expand treatment of tumor types beyond what is achievable with IT administration and to demonstrate that clinical efficacy can be achieved with systemic exposure of MK-2118. The rationale for studying systemic delivery of MK-2118 via SC administration is based on the observed therapeutic index in preclinical models. In mouse tumor models, SC dosing of MK-2118 as monotherapy and in combination with anti-PD-1 induces complete tumor regression. Subcutaneous administration in preclinical species produced toxic effects attributed to exaggerated pharmacology, which were observed in a dose-dependent manner. The rat and dog Highest Not Severely Toxic Dose Levels achieved exposures that were

greater than[CCI] respectively, of the projected efficacious exposure with SC MK-2118 administration in cancer patients. Continued clinical development of systemically administered SC MK-2118 is supported by evaluation of similar non cyclic dinucleotide STING agonist MSA-2 in syngeneic mouse tumor models[Pan, B. S., et al 2020]. In syngeneic mouse tumor models, subcutaneous and oral non cyclic dinucleotide MSA-2 regimens were well tolerated and stimulated interferon-β secretion in tumors, induced tumor regression with durable antitumor immunity, and synergized with anti PD-1 therapy. IT cytokine levels were demonstrated with this systemically administered regimen.

3.2 Background

Detailed background information on preclinical pharmacology, pharmacokinetics, pharmacodynamics, and metabolism of MK-2118 is available in the MK-2118 IB. This is an FIH trial.

3.2.1 Pharmaceutical and Therapeutic Background

MK-2118 is a small molecule that binds to STING and stimulates type I IFNs and proinflammatory cytokine production. STING agonism enhances the capacity of the innate immune system to present tumor-associated antigens to CD8+ T cells through antigen cross-presentation and is critical for immune-mediated tumor destruction. MK-2118 is being developed as monotherapy and in combination with pembrolizumab for the treatment of multiple human cancers.

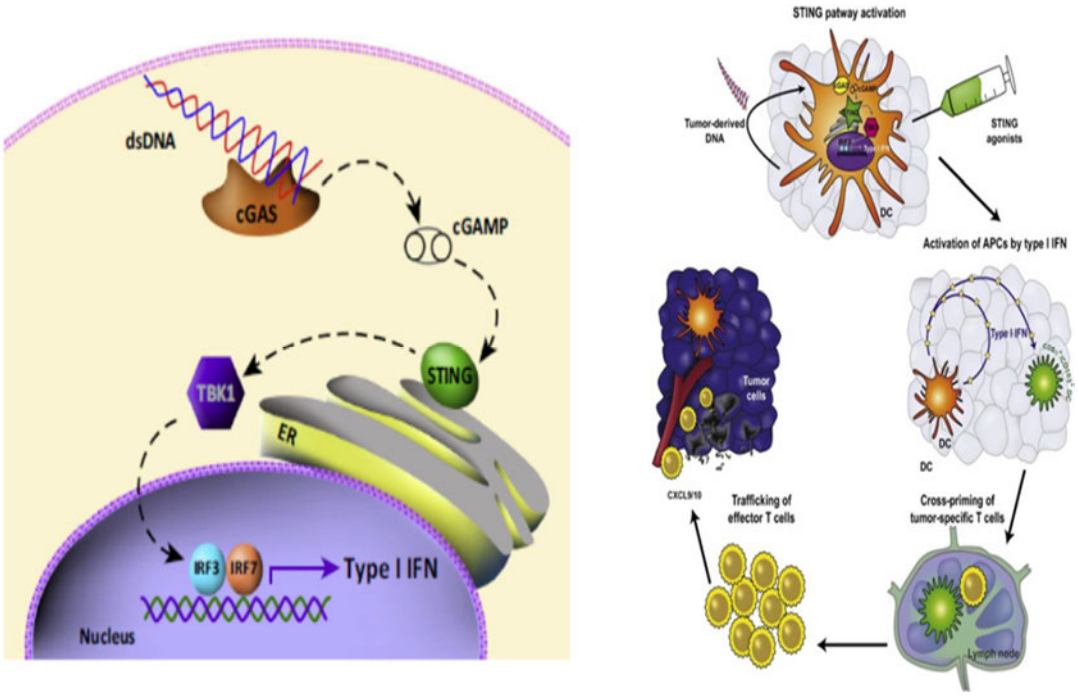
MK-2118 demonstrates cross-species activity, exhibits antitumor efficacy in preclinical mouse syngeneic tumor models in vivo, and induces significant responses in multiple primary human tumor types in situ. MK-2118 is a STING agonist that could induce antitumor responses in both injected and noninjected lesions with a reduced risk of inducing a harmful systemic elevation of cytokines.

Efficacy data obtained in syngeneic mouse tumor models that are partially responsive or non-responsive to anti-PD-1 monotherapy demonstrate that the combination of anti-PD-1 therapy with STING agonism can lead to improved induction of antitumor responses and tumor clearance.

3.2.2 Mechanism of Action

DNA in the cytoplasm of mammalian cells represents a cellular danger signal, and the cGAS/STING pathway is activated to respond to that potential threat (Figure 1). Free cytosolic DNA is recognized by cGAS, catalyzing the generation of the cyclic-dinucleotide 2'-3' cyclic GMP-AMP (cGAMP). cGAMP strongly binds to the endoplasmic reticulum-transmembrane adapter protein STING. This leads to a conformational change of the STING dimer, enabling the binding and activation of tumor necrosis factor receptor-associated factors -associated nuclear factor NF-κB activator, TBK1, and inducing downstream phosphorylation and activation of transcription factors IRF-3 and NF-κB. This ultimately leads to a strong induction of type I IFNs and proinflammatory cytokines such as IL-6 and TNF-α, which potentiate T-cell activation through multiple mechanisms.

Figure 1 Schematic Diagram Showing Mechanism of the Enhancement of T-cell Driven Antitumor Immunity Through the Action of STING Agonists



STING is expressed in numerous cell types, but functional responses (cytokine production in response to double-stranded DNA) were demonstrated only in a small subset of STING-expressing cells, mainly innate immune cells. Single nucleotide polymorphism analysis and sequencing studies have revealed the existence of 4 main STING variants in humans, with amino acid changes at positions 71, 230, 232, and 293. Although the most prevalent non- WT STING variants are present at allelic frequencies of up to 20% in the human population, the prevalence of homozygous non-WT STING carriers for any of the identified STING variants is estimated to be less than 5% [Yi, G., et al 2013].

Enhancing the capacity of the innate immune system to present tumor-associated antigens to CD8+ T cells, through antigen cross-presentation is critical for immune-mediated tumor destruction, and STING agonism enhances this response.

3.2.3 Preclinical Trials of MK-2118

Please refer to the MK-2118 IB for a description of preclinical evaluations of MK-2118.

3.2.4 Pembrolizumab Background

Please refer to the current pembrolizumab IB for a description of preclinical and clinical evaluations of pembrolizumab.

3.3 Benefit/Risk Assessment

Participants in clinical trials generally cannot expect to receive direct benefit from treatment during participation, as clinical trials are designed to provide information about the safety and effectiveness of an investigational medicine.

Additional details regarding specific benefits and risks for participants enrolled in this clinical trial may be found in the accompanying IB and Informed Consent documents.

4 OBJECTIVES/HYPOTHESES AND ENDPOINTS

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

Objective/Hypothesis	Endpoint
Primary	
• Objective: To determine the safety and tolerability and to establish a preliminary RP2D and/or an MTD or an MAD of MK-2118 administered via IT) injection as monotherapy and in combination with pembrolizumab IV infusion or by SC injection in combination with pembrolizumab IV infusion.	• DLT • AE • Discontinuing study treatment due to an AE
Secondary	
• Objective: To evaluate the PK of MK-2118 administered via IT injection as monotherapy and in combination with pembrolizumab IV infusion, or administered via SC injection in combination with pembrolizumab IV infusion	• PK parameters of MK-2118, including C_{min}, $C_{max,}$ and AUC
• Objective: To evaluate the PK of pembrolizumab IV infusion in combination with MK-2118 administered via IT or SC injection.	• PK exposure of pembrolizumab

Objective/Hypothesis	Endpoint
Tertiary/Exploratory	
• Objective: To evaluate the ORR and PFS of participants treated with MK-2118 as assessed by Investigator when used as monotherapy and in combination with pembrolizumab.	• Objective response is a confirmed CR or PR. PFS is time from the first dose of study medication to the first documented disease progression or death due to any cause, whichever occurs first. In solid tumors, assessment will be based on RECIST 1.1 and irRECIST. In lymphoma, assessment will be based on the IWG revised response criteria [Cheson, B. D., et al 2007].
• Objective: To evaluate OS of participants treated with MK-2118 both as monotherapy and in combination with pembrolizumab.	• OS is time from the first dose of study medication to death due to any cause.
• Objective: To evaluate the effect of MK-2118 on lesions not treated with IT injections, as assessed by the Investigator per itRECIST.	• Objective response of CR or PR for noninjected lesions as assessed by the investigator per itRECIST. • Maximal reduction in the sum of diameters of noninjected target lesions per itRECIST.

Objective/Hypothesis	Endpoint
• Objective: To identify molecular (genomic, metabolic and/or proteomic) biomarkers that may be indicative of clinical response/resistance, safety, pharmacodynamic activity, and/or the mechanism of action of MK-2118 as monotherapy and in combination with pembrolizumab and other treatments. a. To investigate TNF-α and other cytokines that may correlate with tumor response. b. To investigate other biomarkers in circulating blood cells or in tumor tissue that may correlate with tumor responses and to evaluate differences in tumor tissue characteristics in tumor biopsies taken prior to treatment with MK-2118 and following treatment with MK-2118. c. To investigate the relationship between CYP2C9 genetic variants and PK and pharmacodynamics of MK-2118 as monotherapy and in combination with pembrolizumab. d. To investigate the relationship between genetic variations in ADME genes and PK and pharmacodynamics of MK-2118 as monotherapy and in combination with pembrolizumab.	• Molecular (genomic, metabolic and/or proteomic) determinants of response or resistance to treatments, using blood and/or tumor tissue; pembrolizumab ADA.

5 STUDY DESIGN

5.1 Overall Design

This is a FIH, dose escalation, nonrandomized, 4-arm, multicenter, open-label trial of MK-2118 monotherapy and MK-2118 in combination with pembrolizumab in participants with advanced/metastatic solid tumors or lymphomas. MK-2118 will be administered IT in Arms 1, 2 and 3, and SC in Arm 4.

For Arm 1 and Arm 2, the study will enroll participants with cutaneous and subcutaneous lesions that are amenable to IT injection by visual inspection, palpation, or ultrasound guidance, including at least 1 measurable lesion that is amenable to IT injection and biopsy, as well as at least 1 measurable distant, discrete lesion that is amenable to biopsy. The distant, discrete lesion will not be injected with MK-2118. Both the injected lesion and the distant, discrete noninjected lesion will undergo biopsy prior to MK-2118 IT administration during Screening, as well as on Cycle 2 Day 8 following IT administration of MK-2118, unless deemed medically unsafe by the Investigator. Participants in Arms 1 and 2 with amenable lesions at both injected and noninjected sites may undergo an additional optional tumor biopsy on Cycle 3 Day 8 of both the injected lesion and the noninjected lesion (see Section 9.7.2).

For Arm 3, the study will enroll participants with liver metastasis/lesions that are amenable to IT injection via ultrasound or cross-sectional imaging (CT/MRI) guidance including at least 1 measurable lesion that is amenable to IT injection and biopsy, as well as at least 1 measurable distant, discrete lesion that is amenable to biopsy. The distant, discrete lesion will not be injected with MK-2118. Both the injected liver metastasis/lesion and the distant, discrete noninjected lesion will undergo biopsy during Screening, as well as on Cycle 2 Day 8, unless deemed medically unsafe by the Investigator. Participants in Arm 3 with amenable lesions at both injected and noninjected sites may undergo an additional optional tumor biopsy on Cycle 3 Day 1 of both the injected lesion and the noninjected lesion (see Section 9.7.2).

For Arm 4, the study will enroll participants with advanced solid tumors or lymphomas with at least 1 measurable, discrete lesion that is amenable to biopsy. MK-2118 will be administered by subcutaneous injection in Arm 4. There is no IT injection of MK-2118 in Arm 4. This discrete lesion will undergo biopsy prior to MK-2118 SC administration during Screening, as well as on Cycle 1 Day 8, and on Cycle 3 Day 8, unless deemed medically unsafe by the Investigator. Arm 4 will initiate once dose escalation in Arm 1 has proceeded beyond the CCI MK-2118 dose level. Once initiated, Arm 4 will dose escalate independently of Arms 1, 2 and 3.

In Arms 1 and 2, the interval for IT MK-2118 dosing CCI CCI. For Arm 2, pembrolizumab will be administered Q3W in Cycle 1 and beyond. Each cycle is 21 days.

In Arm 3, the interval for IT MK-2118 dosing CCI CCI. Pembrolizumab will be administered Q3W in Cycle 1 and beyond. Each cycle is 21 days.

In the Arm 4, the interval for SC MK-2118 is CCI CCI as combination therapy with pembrolizumab. Subcutaneously administered MK-2118 in CCI CCI in combination with pembrolizumab. Pembrolizumab will be administered Q3W in Cycle 2 and beyond. For Cycle 2 and beyond, each cycle is 21 days.

In Arms 1, 2, and 3, all participants will undergo at least a 24-hour inpatient observation period following dose administration on C1D1, C1D8, and C1D15. In Arm 4, a 24-hour inpatient observation period will follow MK-2118 administration on C1D1, C1D8, and C2D1. These inpatient observation periods may be extended to 48 hours at the discretion of the Investigator, per local Institutional Review Board, Ethics Review Committee, and/or Health Authority mandate. After discharge from the clinic, participants are to be counseled with post-discharge instructions.

In all 4 Arms, dose escalation of MK-2118 will proceed based on emerging safety and tolerability data. Each participant will be monitored for DLTs over the DLT evaluation period (21 days from initiation of study drug in Cycle 1 for Arm 1, Arm 2, and Arm 3; 35 days from initiation of study drug in Cycle 1 for Arm 4). For each dose level, an assessment will be made of the safety and tolerability data prior to escalating to the next dose level. The trial will proceed in an ATD up to a dose that meets at least 1 of the following criteria: 1) a dose level of at least CCI is cleared by DLT evaluation OR 2) a ≥ Grade 2 toxicity as assessed by the Investigator to be related, probably related, or possibly related to the drug(s) at any dose level.

The combination therapy arm (Arm 2 Part C) will initiate once 2 MK-2118 dose levels within Arm 1 have been cleared by DLT evaluation. Arm 2 combination therapy will initiate in ATD at an IT MK-2118 dose that is at least 2 dose levels behind the IT MK-2118 monotherapy dose. A fixed dose of IV pembrolizumab 200 mg will be administered Q3W in Arm 2. IT MK-2118 will be administered within CCI following completion of pembrolizumab IV infusion. If the initiation of IT MK-2118 combination therapy arm with pembrolizumab (Arm 2 Part C) was triggered by a ≥ Grade 2 AE observed in the ATD phase of monotherapy (Arm 1 Part A), then dose escalation of IT MK-2118 in the combination therapy arm (Arm 2) will proceed from the ATD phase to the mTPI phase up to that dose level of IT MK-2118 that triggered the ≥ Grade 2 AE in monotherapy (Arm 1).

As illustrated in Figure 2, Arm 1 (Part A), Arm 2 (Part C) and Arm 3 (Part E) treatment arms will start with an ATD, which will enroll single-participant- cohorts in order to limit participant exposure to subtherapeutic doses. During ATD, up to 3 participants may be enrolled per ATD cohort in the event of simultaneous enrollment, provided that there is at least a 7-day interval between the first dose of MK-2118 for each of the first 3 participants at each dose level evaluated. For Arm 1 (Part B), Arm 2 (Part D), and Arm 3 (Part F), the ATD phase will be followed by the mTPI method [Nie, L., et al 2016] [Yang, S., et al 2015], in which a minimum of 3 participants and up to 14 participants will be enrolled per cohort. There will be an observation period of at least 7 days between the first doses of MK-2118 for the first 3 participants treated at each dose level evaluated in the mTPI phase. Dose escalation in Arm 4 (Part G) will follow an mTPI design similar to that for Parts B, D and F in Arms 1, 2 and 3.

The number enrolled per cohort during dose escalation will be based on the occurrence of DLTs. Once a dose level cohort in the mTPI phase has been cleared for DLT evaluation, and a decision made to escalate to the next dose level, the cohort may be expanded to a total of 14 participants to obtain additional pharmacokinetic and pharmacodynamics data. Dose-

limiting toxicity information from these "back-filling" cohorts will not be formally included in the mTPI analysis for MTD determination, but will be taken into consideration for preliminary RP2D determination.

Intraparticipant dose escalation will be allowed once for qualified participants in Arm 1 monotherapy after a participant has completed at least 3 cycles of treatment with IT MK-2118 monotherapy without a ≥ Grade 2 drug-related toxicity, and provided that dose escalation has proceeded beyond the next dose level in Arm 1. Intraparticipant dose escalation is permitted once during Arm 1 for a qualifying participant. The participant may escalate to the highest dose level that has been cleared by DLT evaluation in Arm 1, as defined by the minimum number of DLT-evaluable participants within that cohort (for the ATD phase, 1 participant per cohort; for the mTPI phase, 3 participants per cohort). Intraparticipant dose escalation is not permitted in Arm 2 (Parts C and D), in Arm 3 (Parts E and F), nor in Arm 4.

In Arm 3, IT MK-2118 will be administered into liver metastasis/lesions in combination with pembrolizumab 200 mg IV. Arm 3 (Part E) will initiate at a dose of CCI of IT MK-2118 in ATD. The trial will proceed in an ATD up to a dose that meets at least 1 of the following criteria: 1) a dose level of at least CCI is cleared by DLT evaluation OR 2) a ≥ Grade 2 toxicity as assessed by the Investigator to be related, probably related, or possibly related to the drug(s) at any dose level.

Upon reaching at least 1 of the above triggering criteria, the visceral IT arm (Arm 3) of the study will proceed to a dose-finding phase (Part F), using an mTPI design.

Arm 4 (SC administration of MK-2118) will initiate with a dose up to, but not exceeding CCI of MK-2118, and dose escalate using the mTPI design. If the safety of IT MK-2118 as monotherapy in Arm 1 cannot be demonstrated at a dose of CCI then Arm 4 will initiate at the lower starting dose of CCI MK-2118.

The primary objectives are to identify the MTD/MAD of MK-2118 alone (Arm 1), and the MTD/MAD of MK-2118 in combination with pembrolizumab (Arms 2, 3, and 4), and to identify a preliminary RP2D of IT MK-2118 and SC MK-2118. The RP2D may be the same as the MTD/MAD, or the RP2D may be modified from the MTD/MAD based on overall exposure, emerging safety data, pharmacodynamic data, and clinical benefit data from this study.

Dose escalation of MK-2118 to determine the MTD/MAD will be guided by the mTPI design, targeting a DLT rate of 30%, with a tolerance interval of 3%. Doses of MK-2118 for IT administration used in combination with pembrolizumab will not exceed the MTD for monotherapy. If an MTD for the monotherapy arm is established, then the dose of IT MK-2118 in combination may continue escalation up to that established dose. For example, if the MTD for monotherapy (Arm 1 Part A) is CCI MK-2118, then the starting dose for combination therapy (Arm 2 Part C), if no DLTs occurred in monotherapy, would be CCI MK-2118, with a maximum dose escalation to CCI MK-2118. If the MTD for monotherapy (Arm 1, Part A) is CCI MK-2118, then the starting dose for combination

therapy will be CCI MK-2118. If in monotherapy (Arm 1, Part A), the dose level of CCI MK-2118 is completed and no DLTs occurred in monotherapy, then the starting dose in combination therapy (Arm 2 Part C) could be CCI MK-2118 (assuming sequential monotherapy dose cohorts of CCI MK-2118).

Dose escalation of SC MK-2118 in Arm 4 will be guided by clinical safety and tolerability. The dose of SC MK-2118 may be higher than the MAD achieved in IT MK-2118 administration in Arms 1, 2 and/or 3.

Participants may continue on their assigned treatment for up to 35 cycles for Arm 1, 2, and 3, and up to 36 cycles for Arm 4 (approximately 2 years) from the start of treatment. Treatment may continue until 1 of the following occurs: disease progression, unacceptable AEs, intercurrent illness that prevents further administration of treatment, Investigator decision to withdraw the participant, participant withdraws consent, pregnancy of the participant, noncompliance with trials treatment or procedure requirements, or administrative reasons requiring cessation of treatment.

Participants who progress by either clinical or radiographic evaluation on monotherapy with IT MK-2118 (Arm 1), may cross over into the combination therapy arm of IT MK-2118 and pembrolizumab (Arm 2), provided that they meet crossover eligibility criteria in Section 6.1.2 and Section 6.2.2. A participant may not cross over from Arm 1 (monotherapy) into Arm 2 (combination therapy with pembrolizumab) until that participant has completed the DLT evaluation period (21 days) in Arm 1. Participants who cross over from Arm 1 to Arm 2 will enter Arm 2 at Screening and will be allocated to a combination dose level cohort in Arm 2 through an IWRS. Participants who cross over from Arm 1 to Arm 2 are eligible for up to 35 cycles of treatment with MK-2118 in combination therapy with pembrolizumab, regardless of the duration of MK-2118 treatment they received in Arm 1. Crossover into Arm 3 (visceral IT administration) or Arm 4 (SC administration) is not allowed.

Treatment allocation will be accomplished by nonrandom assignment through an IWRS. When more than one treatment arm is open for enrollment, investigator assessment of eligibility, tumor accessibility to IT therapy, location of lesion, as well as presence of a distant discrete measurable lesion that can be biopsied, will determine allocation. See Section 7.3 for details on allocation to treatment arms.

The final number of participants enrolled in the study will depend on the empirical safety data (DLT observations, in particular, at which dose the mTPI design is triggered, and at which dose the preliminary RP2D is identified).

The total sample size across Parts A-G (Arms 1, 2, 3 and 4) will be approximately 160 participants. An interim analysis may be conducted to enable future trial planning at the Sponsor's discretion, and data will be examined on a continuous basis to allow for dose-finding decisions. The trial will be conducted in conformance with GCPs.

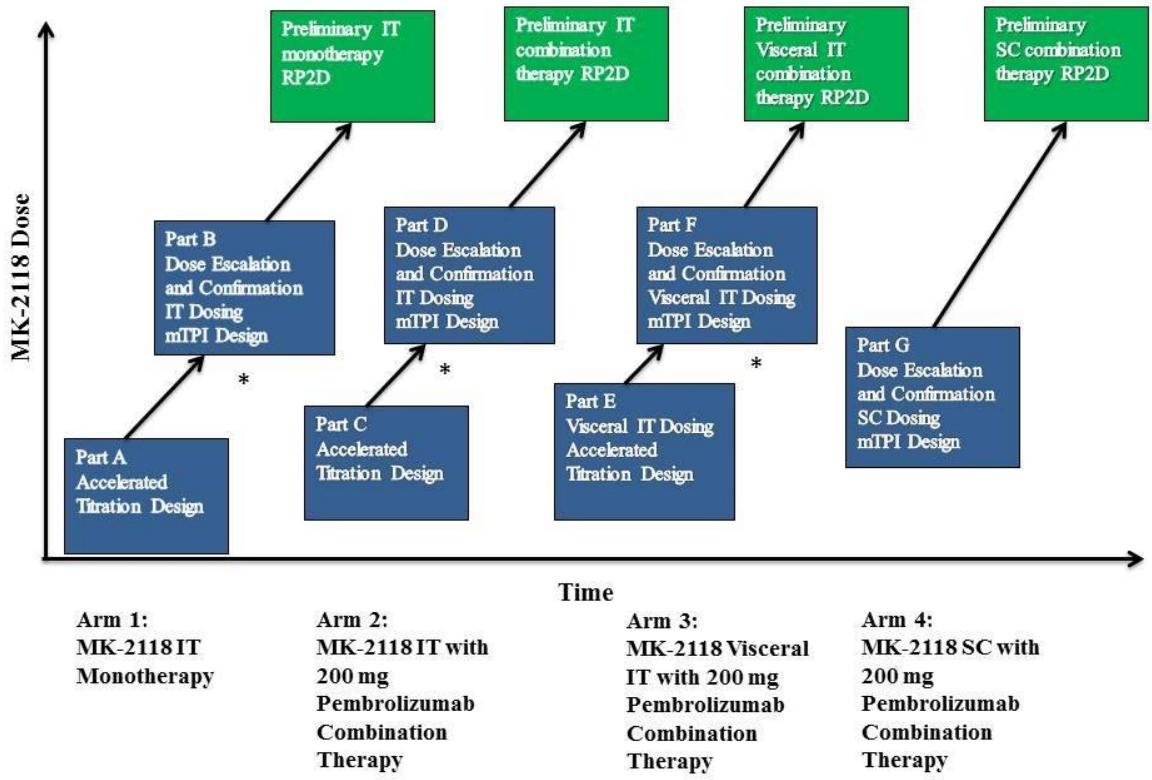
Adverse Experiences will be evaluated according to criteria outlined in the NCI CTCAE Version 4.0.

Specific procedures to be performed during the trial, as well as their prescribed times and associated visit windows, are outlined in the Trial SoA - Section 2. Details of each procedure are provided in Section 9 Study Assessments and Procedures.

5.1.1 Study Diagram

The trial design is depicted in Figure 2.

Figure 2 Trial Design Diagram



IT = intratumoral; mTPI = Modified Toxicity Probability Interval; RP2D = Recommended Phase 2 Dose; SC = subcutaneous

* Triggering criteria for the start of the mTPI design in Arm 1, Arm 2 and Arm 3: (1) a dose level of at least CCI is cleared by DLT evaluation OR (2) a ≥ Grade 2 toxicity as assessed by the Investigator to be related, y related, or possibly related to the drug(s) at any dose level.

Note: Arm 4 may initiate prior to the initiation of Arm 3.

5.2 Number of Participants

Approximately 200 participants will be allocated in screening through IWRS, such that approximately 160 evaluable participants complete the study as described in Section 10.9.

5.3 Beginning and End of Study Definition

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

5.3.1 Clinical Criteria for Early Trial Termination

The clinical trial may be terminated early if the extent (incidence and/or severity) of emerging effects/clinical endpoints is such that the risk/benefit ratio to the trial population as a whole is unacceptable. In addition, further recruitment in the trial or at (a) particular trial 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.

Ample notification will be provided in the event of Sponsor decision to no longer supply MK-2118 or pembrolizumab.

5.4 Scientific Rationale for Study Design

Internal data demonstrate STING expression in multiple tumor types, supporting the broad inclusion of such tumor types as advanced/metastatic solid tumors and lymphomas. Endogenous STING pathway activation within the tumor induces spontaneous T cell priming that is necessary for the generation of adaptive immunity. In mouse tumor models, STING activation in the tumor microenvironment leads to a potent antitumor response. IT injection of STING agonist induces regression of established tumors and generates systemic immune responses, mediating rejection of distant metastases and providing immunologic (T cell) memory in mice [Woo S. R., et al 2014], [Corrales, L., et al 2015]. MK-2118, therefore, has potential as a cancer therapeutic.

Preclinical efficacy data obtained in syngeneic mouse tumor models that are either partially responsive or nonresponsive to anti-PD-1 monotherapy, demonstrated that the combination of anti-PD-1 therapy with STING agonism can lead to improved induction of antitumor responses and tumor clearance. Robust antitumor efficacy in mouse tumor models was also seen with SC administration of MK-2118 in combination with anti-PD-1 therapy.

5.4.1 Efficacy Endpoints

An exploratory objective for this trial is to evaluate the antitumor activity of MK-2118 alone and MK-2118 in combination with pembrolizumab in participants with advanced or metastatic solid tumors and lymphomas. Tumor response in participants with solid tumors will be assessed using RECIST 1.1 and irRECIST (see Section 9.2.2.1). Tumor response in participants with lymphoma will be assessed using the IWG revised response criteria as assessed by Investigator review. A central imaging vendor will be used to collect, clean, and hold tumor imaging and medical photography. Images will be collected for possible analysis by blinded, independent central review.

Immunotherapeutic agents such as MK-2118 with 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 typical cytotoxic agents and can manifest a clinical response after an initial increase in tumor burden or even the appearance of new lesions. Standard response assessment criteria may not provide a comprehensive response assessment of immunotherapeutic agents such as MK-2118 with pembrolizumab. Therefore, the participant should not be discontinued from treatment unless the initial assessment of PD is confirmed at least 4 weeks later, provided the participant's clinical condition is stable, and irRECIST will thus be used to assess efficacy.

Sites are encouraged to have a multidisciplinary treatment and assessment plan to determine in advance which lesions will be treated, biopsied, and/or targeted for tumor assessment. Biopsied tumors should not be used for assessment by RECIST 1.1, irRECIST, or revised IWG criteria, except in cases with only target lesions available, after consultation with the Sponsor. See Section 7.1.1 on prioritization of lesion injection.

5.4.1.1 Immune-related RECIST (irRECIST)

RECIST 1.1 will be adapted to account for the unique tumor response characteristics seen with treatment immunotherapeutic agents. Immunotherapeutic agents 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 can manifest a clinical response after an initial increase in tumor burden or even the appearance of new lesions. Standard RECIST 1.1 may thus not provide an accurate response assessment of immunotherapeutic agents. With other immunotherapeutic agents, up to 7 % of evaluable participants experienced delayed or early tumor pseudoprogression. Of note, participants who had progressive disease by RECIST 1.1, but not by irRECIST, had longer OS than participants with progressive disease by both criteria. These findings support the need to apply a modification to RECIST 1.1 that takes into account the unique patterns of response in immunotherapy and enables treatment beyond initial radiographic progression.

Immune-related RECIST is RECIST 1.1 adapted to account for the unique tumor response seen with immunotherapeutic as described by Nishino, et al. [Nishino, M., et al 2013]. The assessment of unidimensional target lesions and response categories per irRECIST are identical to RECIST 1.1. However, the Sponsor has implemented an adaptation related to new lesions, nontarget and tumor burden assessment in order to confirm radiographic progression. Immune-related RECIST will be used by local site investigators to assess tumor response and progression, and to make treatment decisions for solid tumors. For lymphomas, a similar modification of the revised IWG criteria will be applied, so that investigators have the option to continue therapy after radiographic progression until a repeat scan confirms that progression has occurred.

5.4.1.2 IT Immunotherapy RECIST (itRECIST)

itRECIST, a response assessment tailored to IT immunotherapy, is aligned with RECIST 1.1 overall response assessment [Goldmacher, G. V., et al 2020], and is further described in Section 12.8.

itRECIST:

- provides a guidance on baseline categorization of target and nontarget lesions (Figure 3).
- provides guidance on recategorization of lesions during therapy (Figure 4).
- allows for separate response assessment in injected and noninjected lesions (Figure 5).
- for injected lesions, provides an iterative response assessment process that adapts to changes in lesion selection for IT immunotherapy (an example is provided in Figure 6).
- provides guidelines on prioritization of lesion injection during the course of IT immunotherapy (see Appendix 12.7).

itRECIST supports standardized collection of data from IT immunotherapy clinical trials to facilitate exploratory response analysis.

5.4.1.3 IWG Revised Response Criteria for Malignant Lymphomas

The antitumor activity of MK-2118 with pembrolizumab will be evaluated as part of the exploratory analyses using the IWG Revised Response Criteria for Malignant Lymphoma [Cheson, B. D., et al 2007] as detailed in Section 9.2.2.3.

The IWG response criteria include several components: 1) assessment of nodal and extranodal lesions by CT (for size) and FDG-PET (for viability) 2) physical examination assessment of liver, spleen, and other possible findings not included in imaging 3) evaluation of B-symptoms and 4) determination by biopsy of bone marrow involvement.

The response criteria will be applied by the site for assessment of disease response and as the basis for all protocol guidelines related to participant status (eg, discontinuation of study therapy).

Because of the possibility of immunotherapy-related flare, participants who show initial radiographic progression, if they are clinically stable, may be continued on therapy at the discretion of the investigator. A follow-up scan should be obtained at least 4 weeks later to confirm progression.

5.4.1.4 Response Assessment for Cutaneous T-cell Lymphoma

For participants with CTCL, determination of eligibility will be made in accordance with the modified ISCL/Cutaneous Lymphoma Task Force of the EORTC Revision of the TNMB Classification of mycosis fungoides/Sézary syndrome [Olsen, E., et al 2007]. The antitumor activity of MK-2118 and pembrolizumab will be evaluated using response criteria described by the ISCL, the United States Cutaneous Lymphoma Consortium, and the Cutaneous Lymphoma Task Force of the EORTC [Olsen, E. A., et al 2011].

The CTCL response criteria include a scoring system for assessing tumor burden in skin, lymph nodes, blood, and viscera, and a composite global response score, which are detailed in Section 9.2.2.4.

5.4.1.5 Overall Survival

Participants will be followed up by telephone contact every 12 weeks after the 30-day safety follow-up visit to assess OS.

5.4.2 Safety Endpoints

The primary objective of this trial is to characterize the safety and tolerability of MK-2118 as monotherapy and as combination therapy with pembrolizumab in participants with advanced/ metastatic solid tumors and lymphomas. The primary safety analysis will be based on participants who experience toxicities as defined by CTCAE criteria. Safety will be assessed by quantifying the toxicities and grades of toxicities experienced by participants who have received MK-2118 as monotherapy and in combination with pembrolizumab, including SAEs and AEs of special interest.

Safety will be assessed by reported adverse experiences using CTCAE, v 4.0. The attribution to drug, time of onset, duration of the event, its resolution, and any concomitant medications administered will be recorded. AEs that will be analyzed include, but are not limited to, all AEs, SAEs, fatal AEs, and laboratory changes.

Safety parameters commonly used for evaluating investigational systemic anticancer treatments are included as safety endpoints for the study including, but not limited to, the incidence of, causality, and outcome of AEs/SAEs; changes in vital signs and laboratory values. Adverse events will be assessed as defined by CTCAE, v 4.0.

5.4.3 Pharmacokinetic Endpoints

Secondary objectives of this trial are to characterize the PK profile of MK-2118 following administration as a single agent, and to characterize the pharmacokinetic profile of MK-2118 with pembrolizumab following administration as combination therapy. The serum concentrations of these agents will serve as the primary readout for the PK, and these data will be used to derive PK parameters of the agents alone and in combination. Furthermore, the results of these analyses will be used in conjunction with the pharmacodynamics, and the safety and exploratory endpoints in assessment of dosing strategies for MK-2118.

5.4.4 Systemic Cytokines

Because of the immune stimulation by a STING agonist and subsequent potential for cytokine release, systemic cytokines, including TNF-α, IL-6, IFNα, MIP-1α, MCP-2, IP-10, CXCL11, and CRP, will be monitored to provide supplementary information to assist in the evaluation of any safety events.

5.4.5 Pharmacodynamic Endpoints

As a required first step in pharmacologic activity, receptor engagement is fundamental to dosing strategies. To evaluate target engagement, a systemic cytokine/chemokine activation assay that compares a panel of cytokine/chemokine activation pre- and post administration of study drug at both mRNA and protein level is being developed. Additional exploratory analyses will be performed to assess the effect of study drug on immune cells in tumor tissues and in the circulation.

The immediate mediators of STING agonist activity are type I IFNs, proinflammatory cytokines and chemotactic factors. Thus, systemic cytokines will be monitored to provide information to assist in the evaluation of target engagement and safety events. The cytokines that will be assessed include, but are not limited to, TNF-α, IFNα, IL-6, MIP-1α, MCP-2, IP-10), and CXCL11.

5.4.6 Planned Exploratory Biomarker Research

5.4.6.1 Planned Genetic Analysis

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

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

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

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

5.4.6.2 Rationale for Planned Biomarker Research

Cancer immunotherapies represent an important and novel class of antitumor agents. However, the mechanism of action of these new immunotherapies, as well as the optimal leverage and combination of these immunotherapies in treating patients, is still under investigation. To further illuminate the benefits of immunotherapy and to aid clinical decisions, it is important to investigate the determinants of response or resistance to cancer immunotherapy, as well as the determinants of AEs in the course of our clinical trials. These efforts will identify novel predictive/pharmacodynamic biomarkers and generate information that will better guide single-agent therapy and combination therapy with immuno-oncology drugs. To identify novel biomarkers, we will collect biospecimens (blood components, tumor tissue specimen, etc.) 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 will evaluate whether genetic variation within a clinical trial 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. In addition to studying variation across the human genome, *CYP2C9* will be investigated. 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 (i.e., mutations, methylation status, MSI). Key molecular changes of interest to immune-oncology drug development include, for example, 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 (colorectal cancer).

This research contributes to understanding genetic determinants of efficacy and safety associated with the treatments in this study.

Tumor and blood RNA analyses: Both genome-wide and targeted mRNA expression profiling and sequencing in tumor tissue and in blood may be performed to define gene signatures that correlate clinical response to treatment with MK-2118 with pembrolizumab. Pembrolizumab induces a response in tumors that likely reflects an inflamed/immune phenotype. Specific immune-related gene set may be evaluated and new signatures may be

identified. Individual genes related to the immune system may also be evaluated (eg, IL-6). MicroRNA profiling may also be pursued.

Proteomics and immunohistochemistry (IHC) using blood or tumor: Tumor and blood samples from this study may undergo proteomic analyses (eg, PD-L1, CD8, CD4 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 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 cancer, and gastric cancer). 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 or liquid chromatography/mass spectrometry. This approach could identify novel protein biomarkers that could aid in participant selection for MK-2118 therapy.

Other Blood-derived Biomarkers: In addition to expression within the tumor tissue, tumor-derived proteins (eg, PD-L1) or tumor-derived DNA can be shed from tumor and released into the blood. In the case of proteins, enzyme-linked immunosorbent assay can measure such proteins in serum and plasma and correlate this expression with response to therapy, as well as levels of protein in the tumor. DNA can be analyzed using next generation sequencing or polymerase chain reaction-based technologies. An advantage to this method is that blood is a less invasive compartment from which tumor-derived protein or nucleic acid biomarkers may be measured.

5.4.6.3 Future Biomedical Research (FBR)

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

Such research is for biomarker testing to address emergent questions not described elsewhere in the protocol and will only be conducted on specimens from appropriately consented participants. The objective of collecting/retaining specimens for FBR 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 the FBR are presented in Appendix 6 Collection and Management of Specimens for Future Biomedical Research.

5.5 Justification for Dose

5.5.1 Starting Dose for This Trial

5.5.1.1 Starting Dose for Arm 1 and Arm 2

The human starting dose of MK-2118 for IT injection is based on an integration of nonclinical toxicological, pharmacological, and efficacy data (see the IB for detail). The FIH starting dose of CCI for MK-2118, based on tumor-bearing mouse models, is the dose that is associated with an insignificant change in systemic TNF-α concentration, while still being potentially efficacious, and have an acceptable safety profile in the advanced cancer patient population, in accordance with ICH S9 oncology guidance. CCI CCI CCI. Given the potential of MK-2118 to activate the immune system and the limitations of standard toxicology studies to model these effects in the preclinical setting, an FIH starting dose selection was also informed by modeling a minimally efficacious dose.

A summary of the approach used to select the FIH starting dose is presented here (see the IB for a detailed description and relevant data).

The readout of biological activity that has been used for translation from tumor-bearing mice to patients is antitumor efficacy. The dose-efficacy response relationship following at least 1 IT dose for multiple STING agonists was characterized in tumor-bearing mice implanted with MC38 cells. To leverage all the data that has been generated with multiple STING agonists, the IT dose for each STING agonist was normalized in mice on in vitro potency using mouse immune cells and on the tumor volume at the time of the first IT dose to mice. By taking this approach, the normalized dose at any level of efficacy could be scaled to patients after adjusting for differences in potency between mouse and human cells and initial tumor volume between tumor-bearing mice and patients.

Antitumor efficacy was expressed as a percent GRI and was modeled using an assumption that tumor growth dynamics are exponential [Yamazaki, S., et al 2008]. A dose-efficacy response relationship that relates the percent GRI versus the normalized dose was described by a maximum effect model and the variability of the model by a 95% confidence band.

The rationale for FIH dose selection is to choose a safe dose that is not associated with a significant change in systemic measures of pharmacology as measured by TNF-α. This dose corresponds to 135% GRI in mice suggesting signs of efficacy at this starting dose. In mice, 135% GRI corresponds to a level of inhibition that will result in tumor volume reduction from 80 mm^3 to a tumor volume below the limit of quantification within 5 days. The value of 135% GRI refers to an efficacy readout at which injection of a STING agonist resulted in complete regression of MC38 tumor in mice. Assuming that mouse data may be translated to humans, the starting dose selected is expected to cause complete regression of a relatively

small tumor (1 cm in diameter) in humans, without an associated significant elevation in TNF-α concentration.

The selected FIH starting dose is CCI for a total injectable tumor ≥ 0.5 cm^3 (1 cm in the longest dimension for a single lesion). Cytokine TNF-α was measured to corroborate the efficacy response expected at FIH starting dose with a pharmacological readout suggesting no remarkable pharmacological response at that dose. In tumor-bearing mice, the plasma concentration of cytokine TNF-α was measured at 4 hours after IT dose using 6 different small molecule STING agonists including MK-2118. No remarkable change in cytokine TNF-α concentration was observed at the normalized dose to mice (3.3 µg for 80 mm^3 tumor) that equates to the FIH starting dose of CCI for any total injectable tumor volume ≥0.5 cm^3.

The treatments to be used in this trial are described in Table 2 (Arm 1 monotherapy) and Table 3 (Arm 2 combination therapy).

Table 2 Trial Treatment for IT MK-2118 Monotherapy (Arm 1)

Drug	Dose/ Potency	Dose Frequency	Route of Administration	Regimen/ Treatment Period[a]	Use
MK-2118	Range: CCI	CCI CCI for subsequent 21-day cycles	IT via visual inspection for cutaneous lesions, and via ultrasound guidance for subcutaneous lesions, as needed	CCI	Experimental

Abbreviations: ATD = accelerated titration design; DLT = dose-limiting toxicity; IT = intratumoral; mTPI = modified toxicity probability interval ; CCI

[a] Arm 1 dose escalation will initiate in ATD (Part A) up to a dose that meets at least 1 of the following triggering criteria for a participant at any time during the first treatment cycle of MK-2118: (1) a dose level of at least CCI MK-2118 is cleared by DLT evaluation OR (2) a ≥ Grade 2 toxicity as assessed by the Investigator to be related, probably related, or possibly related to the drug(s) at any dose level. Dose escalation will then proceed to mTPI (Arm 1 Part B).

[b] Dose levels will be determined based on emerging safety data.

Table 3 Trial Treatment for IT MK-2118 Combination Therapy with Pembrolizumab (Arm 2)

Drug	Dose/ Potency	Dose Frequency	Route of Administration	Regimen/ Treatment Period[a]	Use
Pembrolizumab	200 mg	Q3W	IV infusion	Day 1 of each 21-day cycle	Experimental
MK-2118[b]	Range: CCI [c]	CCI for subsequent 21 day cycles	IT via visual inspection for cutaneous lesions, and via ultrasound guidance for subcutaneous lesions, as needed	CCI	Experimental

Abbreviations: ATD = accelerated titration design; DLT = dose-limiting toxicity; IT = intratumoral; mTPI = modified toxicity probability interval ; CCI

[a] Arm 2 will initiate at least 2 dose levels behind Arm 1, and proceed in ATD (Part C) up to a dose that meets at least 1 of the following triggering criteria for a participant at any time during the first treatment cycle of MK-2118: (1) a dose level of at least CCI MK-2118 is cleared by DLT evaluation OR (2) a ≥ Grade 2 toxicity as assessed by the Investigator to be related, probably related, or possibly related to the drug(s) at any dose level. Dose escalation will then proceed to mTPI (Arm 2 Part D).

[b] MK-2118 will be administered within CCI following completion of pembrolizumab IV infusion, as applicable.

[c] Dose levels will be determined based on emerging safety data.

This conservative approach is being taken to ensure an acceptable safety profile, while continued participant safety will be ensured through appropriate dose escalation design and monitoring in the clinic.

CCI. Dose escalation decisions will be made upon ongoing review of safety and PK/PD data at the current dose level. Weekly safety teleconferences will be held with the investigators from all sites. At these weekly safety teleconferences, safety data and PK/PD data will be reviewed for the current dose level, and dose escalation decisions will be made upon a consensus assessment. Subsequent dose levels will be communicated to all sites at the weekly safety teleconferences, and through written correspondence subsequent to the weekly safety teleconferences. Dose level escalations are sponsor-controlled through IWRS, which include the opening and closing of dose level cohorts upon dose escalation.

The injectate volume for Arm 1 and Arm 2 will be determined based on tumor size and number of lesions injected (see Section 7.1.1).

The planned dose of pembrolizumab for this study is 200 mg infusion Q3W. This dose is approved by the Food and Drug Administration (FDA) for treatment of melanoma.

5.5.1.2 Starting Dose for Arm 3

The starting dose for MK-2118 in Arm 3 (IT administration into visceral lesions) will be CCI (Table 4) based on the most conservative subcutaneous NOAEL observed in the GLP toxicology study conducted in dogs. Pembrolizumab 200 mg IV will be administered Q3W. As of Amendment 03, participants have been treated in Arm 2 (IT administration into cutaneous, subcutaneous, and/or nodal lesions that are visible, palpable, or detectable by ultrasound guidance) with doses of up to CCI with no DLTs and have tolerated treatment well. This is to allow for safety/tolerability assessment of IT MK-2118 in visceral lesions, while reducing redundancy of testing subtherapeutic doses of IT MK-2118 that have been evaluated in Arm 1 and in Arm 2.

Table 4 Trial Treatment for Visceral IT MK-2118 Combination Therapy with Pembrolizumab (Arm 3)

Drug, Vaccine, Biologic, Device, etc.	Dose/ Potency	Dose Frequency	Route of Administration	Regimen/ Treatment Period[a]	Use
Pembrolizumab	200 mg	Q3W	IV infusion	Day 1 of each 21-day cycle	Experimental
MK-2118[b]	Range: CCI CCI [c]	CCI	IT (Visceral) via ultrasound or cross-sectional imaging (CT/MRI) guidance for liver lesions, as needed	CCI	Experimental

Abbreviations: ATD = accelerated titration design; CT = computed tomography; DLT = dose-limiting toxicity; IT = intratumoral; mTPI = modified toxicity probability interval; MRI = magnetic resonance imaging; CCI

[a] Arm 3 dose escalation will initiate in ATD (Part E) up to a dose that meets at least 1 of the following triggering criteria for a participant at any time during the first treatment cycle of MK-2118: (1) a dose level of at least CCI MK-2118 is cleared by DLT evaluation OR (2) a ≥ Grade 2 toxicity as assessed by the Investigator to be related, probably related, or possibly related to the drug(s) at any dose level. Dose escalation will then proceed to mTPI (Arm 3 Part F).

[b] MK-2118 will be administered within CCI following completion of pembrolizumab infusion.

[c] Dose levels will be determined based on emerging safety data.

The injectate volume for Arm 3 will be determined based on tumor size and number of lesions injected (see Section 7.1.1).

5.5.1.3 Starting Dose for Arm 4

The human starting dose of MK-2118 for SC injection is based on an integration of nonclinical data (toxicological, pharmacological, and efficacy) as well as clinical data for IT administration (PK, efficacy and safety). CCI [redacted] In the safety and toxicology study in dogs, 1/6th highest nonseverely toxic dose was estimated to be CCI [redacted] in humans on a body surface area basis, providing additional support to a starting dose of CCI [redacted] as a safe dose that is not associated with significant changes in systemic measures of pharmacology including TNF-α.

The projected therapeutic dose range for subcutaneous administration of MK-2118 is CCI [redacted], a dose range higher than projected for IT therapy. Therefore, once Arm 1 dose escalation has proceeded beyond the CCI [redacted] dose level, Arm 4 SC MK-2118 will initiate at CCI [redacted] (Table 5). In case of DLTs in Arm 1 at doses lower than CCI [redacted] Arm 4 will initiate at CCI [redacted] The rationale for starting at a higher dose level in Arm 4 is to minimize exposure of participants to potentially subtherapeutic dose levels.

Table 5 Trial Treatment for MK-2118 Subcutaneous Administration in Combination with Pembrolizumab (Arm 4)

Drug	Dose/ Potency	Dose Frequency	Route of Administration	Regimen/ Treatment Period[a]	Use
Pembrolizumab	200 mg	Q3W	IV infusion	Day 1 of each 21-day cycle from Cycle 2 and beyond	Experimental
MK-2118[b]	Range: CCI [redacted][c]	CCI [redacted] for subsequent 21 day cycles	Subcutaneous	CCI [redacted]	Experimental

Abbreviations: DLT = dose-limiting toxicity; CCI [redacted]

[a] Arm 4 will initiate once Arm 1 dose escalation has proceeded beyond the CCI [redacted] dose level.

[b] MK-2118 will be administered within CCI [redacted] following completion of pembrolizumab IV infusion, as applicable.

[c] Dose levels will be determined based on emerging safety data.

The subcutaneous injectate volume for Arm 4 will be determined based on dose administered (see Section 7.1.2).

5.5.2 Maximum Dose/Exposure for This Trial

The determination of a preliminary RP2D (MTD/MAD) for MK-2118 is an objective of this trial.

5.5.2.1 Maximum Dose Exposure for IT Dosing

For IT dosing (Arms 1, 2, and 3), the proposed maximum dose/exposure for the trial is a dose of CCI or an exposure limit of CCI, whichever is lower.

The rationale for the upper dose limit and exposure limit was initially based on the maximum dose studied in dogs CCI and the exposure level observed at that dose, respectively. The therapeutic dose was initially expected to be less than CCI. As of Amendment 03, participants have been treated with doses of up to CCI with no DLTs and have tolerated treatment well. Therefore, the maximum dose of MK-2118 for IT dosing is now CCI This is based on the maximum dose/exposure for subcutaneous dosing (see Section 5.5.2.2), projected from systemic exposure attained in the GLP toxicology study and using standard approaches to scaling in vitro and in vivo preclinical disposition and pharmacology data. No remarkable differences in PK results are expected with IT versus subcutaneous administration.

5.5.2.2 Maximum Dose/Exposure for Subcutaneous Dosing

Arm 4 SC MK-2118 dose escalation is ongoing. Protocol amendment MK-2118-001-06 allows for a maximum SC MK-2118 dose of CCI in Arm 4. This maximum dose for Arm 4 has been increased from the previously proposed maximum SC MK-2118 dose of CCI The elevation of this maximum SC MK-2118 dose in Arm 4 is based on composite evaluation of clinical safety, preclinical safety, PK, pharmacodynamics, and early efficacy analysis. The highest nonseverely toxic dose studied in dogs in the GLP toxicology study was at an exposure of CCI. MK-2118 exposure-pharmacodynamic and -efficacy relationships were established in tumor-bearing mice and exposure levels were extrapolated to humans. A cumulative plasma exposure range of CCI was predicted to be efficacious. To consistently achieve efficacious exposures within this exposure range in patients, it is predicted that doses up to CCI SC MK-2118 may be required.

Emerging pharmacokinetic data in subjects from Arm 4 SC MK-2118 demonstrate a mean exposure of CCI at a SC MK-2118 CCI dose. To date, available data does not show clinically meaningful changes in explo harmacodynamic biomarkers for SC MK-2118. Dose escalation for SC MK-2118 to date demonstrates an acceptable safety profile. Rigorous safety monitoring will continue, including 24-hour inpatient safety monitoring for the first 3 injections. SC MK-2118 dose escalation will continue per mTPI design to determine the SC MK-2118 RP2D. Continued development of SC MK-2118 is supported by emerging clinical data.

Dose escalation of SC MK-2118 beyond the projected upper dose limit may be allowed if the systemic exposure achieved by SC dosing is significantly lower than expected and SC dosing of MK-2118 at the upper dose limit demonstrates sufficient safety and tolerability in patients.

5.5.3 Rationale for Dose Interval and Trial Design

The initial dose escalation will proceed following an ATD in order to minimize the number of participants treated at potentially subtherapeutic doses of MK-2118 before starting the mTPI design. In the ATD phase of dose escalation, dose escalation will occur in increments of 100% to 300%. For example, with a starting dose of CCI and in the absence of DLTs within this cohort, and the absence of 1 of the 2 triggering events, the next dose level will be CCI The exact dose of each cohort during dose escalation is not predetermined, which will allow for flexibility in dose escalation based on emerging safety data in the clinical trial.

A dose efficacy relationship in MC38 tumor-bearing mice was characterized for multiple STING agonists, including MK-2118. The projected efficacious human dose range for IT MK-2118 was CCI depending on the size of the injected tumor. The goal of the ATD with single-participant cohorts and dose escalation up to 300% is to minimize exposure to subtherapeutic dose levels in cancer patients.

The predicted efficacious dose is based on lesion volume. The CCI starting dose was selected based on the predicted efficacy of MK-2118 for a lesion volume of 0.5 cm^3, based on preclinical studies. The CCI dose level is near the predicted efficacious dose of MK-2118 for a lesion volume of 33.5 cm^3 (approximately 4 cm in diameter). Therefore, CCI was selected as a triggering dose for progression from the ATD phase to the mTPI phase in dose escalation.

Further dose finding (Parts B and D) will follow an mTPI design at a target DLT rate of 30%, with a tolerance interval of 3% [Nie, L., et al 2016] [Yang, S., et al 2015]. The model-based dose escalation mTPI approach will enroll 3 to 14 participants per cohort using dose increment increases of 30% to 100% of the prior dose.

5.5.3.1 Rationale for Design of Arm 3 (Visceral IT Injection)

The rationale for the addition of a visceral IT arm of MK-2118 is to expand the tumor location for IT therapy to deeper tumor lesions and to visceral organs such as the liver. In addition, the visceral IT arm will evaluate the safety, tolerability, PK, pharmacodynamics, and early efficacy of MK-2118 injected into visceral organs and deeper tumor lesions.

CCI . The trial will proceed in an ATD up to a dose that meets at least 1 of the 2 triggering criteria (Section 7.2.1). Upon reaching at least 1 of the triggering criteria, the visceral IT arm (Arm 3) of the study will proceed to a dose-finding phase (Part F), using an mTPI design. The MK-2118 starting dose in Arm 3 is based on the most conservative subcutaneous NOAEL observed in the GLP toxicology study conducted in dogs. To mitigate the potential safety risk of repeated

visceral and deeper lesion IT injections, the duration of weekly IT dosing in Arm 3 has been reduced from 9 weeks to 6 weeks.

5.5.3.2 Rationale for Design of Arm 4 (Subcutaneous/Systemic Administration)

The intent of the 2 week MK-2118 monotherapy lead-in period is to allow sufficient assessment of safety of MK-2118 SC as monotherapy prior to initiation of combination therapy of MK-2118 SC with pembrolizumab. As such, the DLT observation period will be extended in the SC administration Arm 4 to 5 weeks to encompass both the 2-week monotherapy lead-in and the first 3week cycle of combination therapy with pembrolizumab.

MK-2118 will proceed based on emerging safety and tolerability data using mTPI design with a target DLT rate of 30%, and a tolerance interval of 3%. Dose for each cohort will increase by 30% to 100% of prior dose.

6 STUDY POPULATION

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

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

6.1 Inclusion Criteria

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

6.1.1 Inclusion Criteria for Arm 1 and Arm 2

Type of Participant and Disease Characteristics

1. Have any histologically or cytologically confirmed advanced/metastatic solid tumor by pathology report and have received, or have been intolerant to, all treatment known to confer clinical benefit. Solid tumors and lymphomas of any type are eligible for enrollment. For CTCL, histopathological diagnosis should be confirmed in a skin biopsy representative of disease [Olsen, E., et al 2007].

2. Have Stage III or Stage IV disease that is not surgically resectable. Stage IIB ($T_3N_0M_0B_{0\ 1}$) CTCL participants are eligible [Olsen, E., et al 2007].

3. Have at least 1 injectable lesion that is amenable to injection and biopsy. Biopsy may be performed via visual inspection or ultrasound guidance. IT injection for cutaneous lesions may be performed via visual inspection. IT injection for subcutaneous lesions may be performed via ultrasound guidance or via palpation. This injectable lesion must be measurable and meet one of the following criteria:

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

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

    - For lymphoma, a nodal lesion ≥1.5 cm in short axis, or an extranodal lesion ≥1 cm in 2 dimensions. Nodal lesions ≥1.0 cm and <1.5 cm in the short axis may be injected, if involvement by lymphoma has been documented by pathology report. The longest diameter for an injectable lesion must be ≤10 cm.

4. Have at least 1 discrete and/or distant noninjected lesion that is amenable to biopsy via visual inspection or amenable to biopsy via image guidance. This lesion must be measurable as defined by the response criteria used to assess the participant (RECIST 1.1 for solid tumors or revised IWG criteria for lymphomas).

    - For RECIST 1.1, ≥1 cm in longest diameter for nonnodal lesions, or ≥1.5 cm in the short axis for nodal lesions.

    - For revised IWG, a nodal lesion >1.5 cm in longest diameter or >1.0 cm in short axis, or an extranodal lesion ≥1 cm in 2 dimensions.

5. Have an ECOG Performance Status of 0 or 1.

6. Demonstrate adequate organ function as defined by the following table (Table 6). All screening labs should be performed within 7 days prior to treatment initiation, unless otherwise specified.

Table 6 Adequate Organ Function Laboratory Values

System	Laboratory Value
Hematological	
Absolute neutrophil count	≥1500/mcL (>1,000/mcL for lymphoma participants)
Platelets	≥100000/mcL (≥75,000/mcL for lymphoma participants)
Hemoglobin	≥9 g/dL or ≥5.6 mmol/L[a] (≥8 g/dL or ≥5.0 mmol/L for lymphoma participants)
Renal	
Serum creatinine **or** 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 × institutional ULN
Hepatic	
Total bilirubin (serum)	≤1.5 × ULN **or** Direct bilirubin ≤ ULN for participants with total bilirubin levels >1.5 × ULN
AST and ALT	≤2.5 × ULN (≤5 × ULN for participants with liver metastases)
Coagulation	
INR or PT PTT or aPTT	≤1.5 × ULN unless participant is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants

Abbreviations: ALT = alanine aminotransferase; aPTT = activated partial thromboplastin time; AST = aspartate aminotransferase; CrCl = creatinine clearance; GFR = glomerular filtration rate; PT = prothrombin time; PTT = partial thromboplastin time; ULN = upper limit of normal.

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

[b] Creatinine clearance 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

7. Be ≥18 years of age on day of signing informed consent.

Male participants:

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

    - Refrain from donating sperm

PLUS either:

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

OR

- Must agree to use contraception unless confirmed to be azoospermic (vasectomized or secondary to medical cause [Appendix 5]) as detailed below:
  - Agree to use a male condom plus partner use of an additional contraceptive method when having penile-vaginal intercourse with a WOCBP who is not currently pregnant. Note: Men with a pregnant or breastfeeding partner must agree to remain abstinent from penile-vaginal intercourse or use a male condom during each episode of penile-vaginal penetration.
- Contraceptive use by men should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.

Female participants:

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

   - Is not a WOCBP

   OR

   - Is a WOCBP and using a contraceptive method that is highly effective (with a failure rate of <1% per year), with low user dependency, 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 and agrees not to donate eggs (ova, oocytes) to others or freeze/store for her own use for the purpose of reproduction during this period. 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 24 hours before the first dose of study intervention.
   - If a urine test cannot be confirmed as negative (eg, an ambiguous result), a serum pregnancy test is required. In such cases, the participant must be excluded from participation if the serum pregnancy result is positive.

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

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

Informed Consent

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

Additional Criteria

11. HIV-infected participants must meet these additional criteria:

    a) Have HIV-1 infection documented by any licensed rapid HIV test or HIV E/CIA test kit at any time prior to study entry (Day 1) and confirmed by a licensed Western blot or a second antibody test by a method other than the initial rapid HIV and/or E/CIA, or by HIV-1 p24 antigen, or plasma HIV-1 RNA VL.

    b) Have well-controlled HIV on antiretroviral therapy (ART), defined as:

        1) must have a CD4+ T-cell count >350 cells/mm^3 at time of screening;

        2) 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;

        3) 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).

    If temporary ART treatment interruptions are required, sponsor consultation is warranted to determine whether the patient can remain on the study or requires discontinuation. These interruptions should not result in poor disease control (eg, significant CD4 count decrease, uncontrolled viremia).

6.1.2 Inclusion Criteria for Crossover into Arm 2

Type of Participant and Disease Characteristics

In order to be eligible for crossover into Arm 2 of this trial, the participant must:

1. Have either clinical or radiographic disease progression, or progression by global response score for CTCL on Arm 1 MK-2118 monotherapy.

2. Have completed the DLT evaluation period (21 days of treatment within Cycle 1) in Arm 1 MK-2118 monotherapy.

3. Have at least 1 injectable lesion that is amenable to injection and biopsy via visual inspection for a cutaneous lesion, or via ultrasound guidance for a subcutaneous lesion. This injectable lesion must be measurable and meet one of the following criteria:

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

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

    - For lymphoma, a nodal lesion ≥1.5 cm in short axis, or an extranodal lesion ≥1 cm in 2 dimensions. Nodal lesions ≥1.0 cm and <1.5 cm in the short axis may be injected, if involvement by lymphoma has been documented by pathology report. The longest diameter for an injectable lesion must be ≤10 cm.

4. Have at least 1 discrete, distant noninjected lesion that is amenable to biopsy via visual inspection or amenable to biopsy via image guidance. This lesion must be measurable as defined by the response criteria used to assess the participant (RECIST 1.1 for solid tumors or IWG revised criteria for lymphomas).

    - For RECIST 1.1, ≥1 cm in longest diameter for nonnodal lesions, or ≥1.5 cm in the short axis for nodal lesions.

    - For revised IWG, a nodal lesion >1.5 cm in longest diameter or >1.0 cm in short axis, or an extranodal lesion ≥1 cm in 2 dimensions.

5. Have an ECOG Performance Status of 0 or 1.

6. Demonstrate adequate organ function as defined by Table 6. All screening labs should be performed within 7 days of treatment initiation.

Demographics

Male Participants:

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

    - Refrain from donating sperm

PLUS either:

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

OR

- Must agree to use contraception unless confirmed to be azoospermic (vasectomized or secondary to medical cause [Appendix 5]) as detailed below:
  - Agree to use a male condom plus partner use of an additional contraceptive method when having penile-vaginal intercourse with a WOCBP who is not currently pregnant. Note: Men with a pregnant or breastfeeding partner must agree to remain abstinent from penile-vaginal intercourse or use a male condom during each episode of penile-vaginal penetration.
- Contraceptive use by men should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.

Female Participants:

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

   - Is not a WOCBP

   OR

   - Is a WOCBP and using a contraceptive method that is highly effective (with a failure rate of <1% per year), with low user dependency, 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 and agrees not to donate eggs (ova, oocytes) to others or freeze/store for her own use for the purpose of reproduction during this period. 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 24 hours before the first dose of study intervention.
   - If a urine test cannot be confirmed as negative (eg, an ambiguous result), a serum pregnancy test is required. In such cases, the participant must be excluded from participation if the serum pregnancy result is positive.

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

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

6.1.3 Inclusion Criteria for Arm 3—Visceral IT Injection

Type of Participant and Disease Characteristics

1. Have any histologically or cytologically confirmed advanced/metastatic solid tumor by pathology report and have received, have been intolerant to all treatment known to confer clinical benefit. Solid tumors and lymphomas of any type are eligible for enrollment.

2. Have Stage III or Stage IV disease that is not surgically resectable.

3. Has metastatic liver and/or liver lesion involvement that does not exceed one third of the total liver volume in participants to be treated by liver IT injection. Hepatocellular carcinoma participants are excluded from eligibility for IT liver injection. In addition, has at least one injectable liver lesion with the following:

   - The injectable liver lesion is amenable to image-guided IT injection and biopsy via ultrasound guidance or cross-sectional imaging (CT/MRI) guidance.

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

4. Have at least 1 discrete and/or distant noninjected lesion that is amenable to biopsy via image guidance. This lesion must be measurable as defined by the response criteria used to assess the participant (RECIST 1.1 for solid tumors or revised IWG criteria for lymphomas).

   - For RECIST 1.1, ≥1 cm in longest diameter for nonnodal lesions, or ≥1.5 cm in the short axis for nodal lesions.

   - For revised IWG, a nodal lesion >1.5 cm in longest diameter or >1.0 cm in short axis, or an extranodal lesion ≥1 cm in 2 dimensions.

5. Have an ECOG Performance Status of 0 or 1.

6. Demonstrate adequate organ function as defined by Table 6.

   All screening labs should be performed within 7 days of treatment initiation, unless otherwise specified.

Demographics

7. Be ≥18 years of age on day of signing informed consent.

Male participants:

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

    - Refrain from donating sperm

    PLUS either:

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

    OR

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

        - Agree to use a male condom plus partner use of an additional contraceptive method when having penile-vaginal intercourse with a WOCBP who is not currently pregnant. Note: Men with a pregnant or breastfeeding partner must agree to remain abstinent from penile-vaginal intercourse or use a male condom during each episode of penile-vaginal penetration.

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

Female participants:

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

    - Is not a WOCBP

    OR

    - Is a WOCBP and using a contraceptive method that is highly effective (with a failure rate of <1% per year), with low user dependency, 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 and agrees not to donate eggs (ova, oocytes) to others or freeze/store for her own use for the purpose of reproduction during this period. 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 24 hours before the first dose of study intervention.

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

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

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

Informed Consent

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

Additional Criteria

11. HIV-infected participants must meet these additional criteria:

    a) Have HIV-1 infection documented by any licensed rapid HIV test or HIV E/CIA test kit at any time prior to study entry (Day 1) and confirmed by a licensed Western blot or a second antibody test by a method other than the initial rapid HIV and/or E/CIA, or by HIV-1 p24 antigen, or plasma HIV-1 RNA VL.

    b) Have well-controlled HIV on antiretroviral therapy (ART), defined as:

        1) must have a CD4+ T-cell count >350 cells/mm^3 at time of screening;

        2) 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;

        3) 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).

If temporary ART treatment interruptions are required, sponsor consultation is warranted to determine whether the patient can remain on the study or requires discontinuation. These interruptions should not result in poor disease control (eg, significant CD4 count decrease, uncontrolled viremia).

6.1.4 Inclusion Criteria for Arm 4 – Subcutaneous Injection

In order to be eligible for Arm 4 of this trial, the participant must:

1. Have any histologically or cytologically confirmed advanced/metastatic solid tumor by pathology report and have received, or have been intolerant to, all treatment known to confer clinical benefit. Solid tumors and lymphomas of any type are eligible for enrollment. For CTCL, histopathological diagnosis should be confirmed in a skin biopsy representative of disease [Olsen, E., et al 2007].

2. Have Stage III or Stage IV disease that is not surgically resectable. Stage IIB ($T_3N_0M_0B_{0\ 1}$) CTCL participants are eligible [Olsen, E., et al 2007].

3. Have measurable disease by RECIST 1.1 criteria for solid tumors or revised IWG revised criteria for lymphomas as assessed by the local site investigator/radiology. Lesions situated in a previously irradiated area are considered measurable if progression has been demonstrated in such lesions.

4. Have one or more discrete malignant lesions that are amenable to a minimum of three separate biopsies guided by one of the following modalities: visual inspection, ultrasound guidance, or cross-sectional image guidance (computed tomography/magnetic resonance imaging [CT/MRI]).

   Note: Participants should only be enrolled if during the screening assessment the investigator deems the biopsy of such lesions to be medically safe.

5. Have an ECOG Performance Status of 0 or 1.

6. Demonstrate adequate organ function as defined by Table 6.

   All screening labs should be performed within 7 days of treatment initiation, unless otherwise specified.

Demographics

7. Be ≥18 years of age on day of signing informed consent.

Male Participants:

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

    - Refrain from donating sperm

    PLUS either:

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

    OR

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

        - Agree to use a male condom plus partner use of an additional contraceptive method when having penile-vaginal intercourse with a WOCBP who is not currently pregnant. Note: Men with a pregnant or breastfeeding partner must agree to remain abstinent from penile-vaginal intercourse or use a male condom during each episode of penile-vaginal penetration.

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

Female Participants:

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

    - Is not a WOCBP

    OR

    - Is a WOCBP and using a contraceptive method that is highly effective (with a failure rate of <1% per year), with low user dependency, 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 and agrees not to donate eggs (ova, oocytes) to others or freeze/store for her own use for the purpose of reproduction during this period. 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 24 hours before the first dose of study intervention.

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

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

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

Additional Criteria

10. HIV-infected participants must meet these additional criteria:

    a) Have HIV-1 infection documented by any licensed rapid HIV test or HIV enzyme or chemiluminescence immunoassay (E/CIA) test kit at any time prior to study entry (Day 1) and confirmed by a licensed Western blot or a second antibody test by a method other than the initial rapid HIV and/or E/CIA, or by HIV-1 p24 antigen, or plasma HIV-1 RNA VL.

    b) Have well-controlled HIV on antiretroviral therapy (ART), defined as:

        1) must have a CD4+ T-cell count >350 cells/mm^3 at time of screening;

        2) 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;

        3) 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).

    If temporary ART treatment interruptions are required, sponsor consultation is warranted to determine whether the patient can remain on the study or requires discontinuation. These interruptions should not result in poor disease control (eg, significant CD4 count decrease, uncontrolled viremia).

6.2 Exclusion Criteria

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

6.2.1 Exclusion Criteria for Initial Treatment

Medical Conditions

1. 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.

2. 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 drug administration, and are off immunosuppressive doses of systemic steroids at least 2 weeks from enrollment.

3. Has had a severe hypersensitivity reaction to treatment with a monoclonal antibody.

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

5. Has a history of vasculitis.

6. Has an active infection requiring therapy.

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

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

   Note: Participants who have had a stem cell transplant greater than 5 years ago are eligible as long as there are no symptoms of GVHD.

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

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

11. Has known psychiatric or substance abuse disorders that would interfere in cooperation with the requirements of the trial.

12. Is pregnant or breastfeeding or expecting to conceive or father children within the projected duration of the study.

13. Has not fully recovered from any effects of major surgery and is free of significant detectable infection. Surgeries that required general anesthesia must be completed at least 2 weeks before first study drug administration. Surgery requiring regional/epidural anesthesia must be completed at least 72 hours before first study drug administration and participants should be recovered.

14. HIV-infected participants with history of Kaposi's sarcoma and/or multicentric Castleman's disease

15. HIV-infected participants who have had an HIV-related opportunistic infection within 6 months

16. Drug-drug interactions have to be taken into consideration and decisions whether a particular drug can be used as a concomitant medication in the study should be based on recommendations at the time of the study and depending on MOA of study drug. Patients on ART agents with a potentially significant overlapping toxicity profile should be excluded if the therapy cannot be switched to the regimen without overlapping toxicity.

Prior/Concomitant Therapy

17. Has had chemotherapy, definitive radiation, or biological cancer therapy within 4 weeks (2 weeks for palliative radiation) prior to the first dose of study therapy, or has not recovered to baseline or CTCAE Grade 1 (Grade 2 alopecia is allowed) from the AEs due to cancer therapeutics administered more than 4 weeks earlier.

18. Has been treated within 2 weeks of Cycle 1 Day1 with any of the following:

    - strong/moderate CYP2C9 inhibitors, such as: amiodarone, felbamate, fluconazole, miconazole, piperine, oxandrolone, fluorouracil and its derivatives (TS-1, UFT, tegafur, carmofur, doxifluridine, capecitabine), sulfaphenazole, cyclosporine, bucurol, and tienilic acid.

    - UGT1A3 inhibitors, which include ritonavir, quinidine, probenecid, and valproic acid.

    - strong CBR inhibitors, which include quercetin, menadione, glycyrrhetinic acid, and flufenamic acid.

19. Is currently participating and receiving study therapy or has participated in a study of an investigational agent and has received study therapy or has used an investigational device within 28 days of administration of MK-2118.

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

20. Is expected to require any other form of antineoplastic therapy while on study.

21. 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. For CTCL, continued use of either prednisone ≤ 10 mg/day or continued use of topical steroids is acceptable.

    Note: The use of physiologic replacement doses of corticosteroids may be approved after consultation with the Sponsor Medical Monitor or designee.

22. Has received a live vaccine within 28 days prior to first dose.

23. Has been treated with a STING agonist (eg, MK-1454, ADU-S100).

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

6.2.2 Exclusion Criteria for Crossover into Arm 2

The participant must be excluded from crossover into Arm 2 of the trial if the participant:

Medical Conditions

1. 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 drug administration, and are off immunosuppressive doses of systemic steroids at least 2 weeks from enrollment.

2. Has had a severe hypersensitivity reaction to treatment with a monoclonal antibody.

3. Has an active infection requiring therapy.

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

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

6. Is pregnant or breastfeeding or expecting to conceive or father children within the projected duration of the study.

7. Has not fully recovered from any effects of major surgery and is free of significant detectable infection. Surgeries that required general anesthesia must be completed at least 2 weeks before first study drug administration. Surgery requiring regional/epidural anesthesia must be completed at least 72 hours before first study drug administration and participants should be recovered.

8. 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.

Prior/Concomitant Therapy

9. Has had chemotherapy, definitive radiation, or biological cancer therapy within 4 weeks (2 weeks for palliative radiation) prior to the first dose of study therapy, or has not recovered to baseline or CTCAE Grade 1 (Grade 2 alopecia is allowed) from the AEs due to cancer therapeutics administered more than 4 weeks earlier.

10. Is currently participating and receiving study therapy or has participated in a study of an investigational agent and has received study therapy or has used an investigational device within 28 days of administration of MK-2118.

    Note: Prior exposure to MK-2118 is allowed, provided the participant has a washout period of at least 14 days and did not experience ≥ Grade 3 drug-related toxicity.

    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

11. Is expected to require any other form of antineoplastic therapy while on study.

12. 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.

    Note: The use of physiologic replacement doses of corticosteroids may be approved after consultation with the Sponsor Medical Monitor.

13. Has been treated within 2 weeks of Cycle 1 Day1 with any of the following:

    - strong/moderate CYP2C9 inhibitors, such as: amiodarone, felbamate, fluconazole, miconazole, piperine, oxandrolone, fluorouracil and its derivatives (TS-1, UFT, tegafur, carmofur, doxifluridine, capecitabine), sulfaphenazole, cyclosporine, bucurol, tienilic acid.

    - UGT1A3 inhibitors, which include ritonavir, quinidine, probenecid, and valproic acid

    - strong CBR inhibitors, which include quercetin, menadione, glycyrrhetinic acid, and flufenamic acid.

14. Has received a live vaccine within 28 days prior to first dose.

15. Has been treated with a STING agonist other than MK-2118 in Arm 1 (eg, MK-1454, ADU-S100).

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

6.3 Lifestyle Restrictions

6.3.1 Meals and Dietary Restrictions

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

6.3.2 Caffeine, Alcohol, and Tobacco

There are no restrictions on caffeine.

During each dosing session, participants will abstain from alcohol for 24 hours before the start of dosing until after collection of the final PK and/or pharmacodynamic sample.

Participants who use tobacco products will be instructed that use of nicotine-containing products (including nicotine patches) will not be permitted while they are in the clinical unit.

6.3.3 Activity

Sunscreen should be applied daily to exposed skin areas regardless of season. Participants should be encouraged to stay out of the sun. Protective clothing for sun protection and wearing a hat is recommended.

6.3.4 Contraception

Pembrolizumab may have adverse effects on a fetus in utero. Furthermore, it is not known if pembrolizumab has transient adverse effects on the composition of sperm.

MK-2118 should not be used by pregnant women.

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

Definitions of WOCBP and standards for adequate contraception are outlined in Appendix 5.

6.3.5 Pregnancy

If a participant inadvertently becomes pregnant while on treatment with pembrolizumab or MK-2118, the participant will be immediately discontinued from trial treatment. The site will contact the participant at least monthly and document the participant's status until the pregnancy has been completed or terminated. The outcome of the pregnancy will be reported to the Sponsor without delay and within 24 hours if the outcome is an SAE (eg, death, abortion, congenital anomaly, or other disabling or life-threatening complication to the mother or newborn). The trial investigator will make every effort to obtain permission to follow the outcome of the pregnancy and report the condition of the fetus or newborn to the Sponsor. If a male participant impregnates his female partner, the trial personnel at the site must be informed immediately and the pregnancy must be reported to the Sponsor and followed as described in Section 9.3.6.

6.3.6 Use in Nursing Women

It is unknown whether pembrolizumab or MK-2118 is excreted in human milk. Because many drugs are excreted in human milk, and because of the potential for serious adverse reactions in the nursing infant, participants who are breastfeeding are not eligible for enrollment.

6.4 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 entry guidelines.

6.5 Participant Replacement Strategy

Participants in Arms 1, 2, and 3 discontinuing within 21 days of the first dose due to reasons unrelated to study treatment will not be considered evaluable for DLTs and may be replaced. Participants in Arm 4 discontinuing within 35 days of the first dose due to reasons unrelated to study treatment will also not be considered evaluable for DLTs and may be replaced. Participants with a DLT within the DLT period should not be replaced. See Section 10.5.1 for description of safety analysis population.

7 TREATMENTS

Study treatment is defined as any investigational treatment(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 treatment(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.

7.1 Treatments Administered

The study treatments to be used in this trial are outlined below in Table 7.

Table 7 Study Treatment(s)

Study Treatment Name:	MK-2118[a]	Pembrolizumab, (MK-3475) Arms 2, 3, and 4	MK-2118 Diluent
Dosage Formulation:	Solution for injection	Solution for infusion	Solution for dosage preparation
Unit Dose Strength(s):	CCI [redacted]	100 mg/4 mL	CCI [redacted]
Dosage Level(s):		200 mg	
Route of Administration:	IT injection or SC injection	IV infusion	IT injection or SC injection
Sourcing:	Provided centrally by the Sponsor	Provided centrally by the Sponsor	Provided centrally by the Sponsor or locally by the study site, subsidiary, or designee

Abbreviations: IT = intratumoral; IV = intravenous; SC = subcutaneous.

[a] In Arm 2, 3, and 4, MK-2118 will be administered within CCI [redacted] following completion of pembrolizumab IV infusion.
[b] Dose levels will be determined based on emerging safety data.

All supplies indicated in Table 7 will be provided per the 'Sourcing' row depending upon local country operational requirements. Every attempt should be made to source these supplies from a single lot/batch number. The trial site is responsible for recording the lot number, manufacturer, and expiry date for any locally purchased product as per local guidelines unless otherwise instructed by the Sponsor.

Refer to section 9.1.8 for details regarding administration of the study treatment.

7.1.1 IT Injection (Arm 1, Arm 2, and Arm 3)

In Arms 1 and 2, MK-2118 will be administered by IT injection into cutaneous, subcutaneous, and/or nodal lesions that are visible, palpable, or detectable by ultrasound guidance.

In Arm 3, MK-2118 will be administered by injection into liver metastasis/lesions by ultrasound or cross-sectional imaging guidance (CT/MRI).

During dose escalation in both Arm 1 and Arm 2, each participant at a given dose level will receive a fixed dose of MK-2118 diluted in a volume of CCI [redacted] of diluent. See Table 2 and Table 3 for dose level ranges within Arm 1 and Arm 2, respectively. The volume of injectate delivered to each lesion will be based on the longest dimension of the target lesion as shown in Table 8, and on the number of lesions injected [Rehman, H., et al 2016]. Documentation of dose volume administered per lesion will be obtained.

During dose escalation in Arm 3, each participant at a given dose level will receive a fixed dose of MK-2118 diluted in a volume of [redacted] of diluent. See Table 4 for dose level ranges within Arm 3. The volume of injectate delivered to each lesion will be based on the longest dimension of the target lesion as shown in Table 9, and on the number of lesions injected.

Regarding prioritization of lesions to be injected at a treatment visit, any new or progressing lesion should be injected first, followed by injection of the largest lesion, with up to a total volume of injectate of 4 mL per treatment visit. Injection of more than one lesion, if feasible, is suggested. See Appendix 7 for further guidance.

For Arms 1 and 2, if there are multiple lesions, then up to a maximum of 8 lesions may be injected per treatment visit, with a minimum injectate volume of 0.5 mL per lesion, and a total injectate volume of 4 mL per treatment visit.

For Arm 3, if there are multiple lesions, then up to a maximum of 4 lesions may be injected per treatment visit, with a minimum injectate volume of 1 mL per lesion, and a total injectate volume of 4 mL per treatment visit.

For lesions that are no longer visible following treatment, discuss with Sponsor for continued injection. Distant lesion(s) assessed for "abscopal" response should not be injected, unless approved by the Sponsor Medical Monitor or designee. Deviation from the injectate volumes specified in Table 8 and in Table 9 for individual lesions may be permitted upon approval by the Sponsor Medical Monitor or designee under selected scenarios; eg, allocating the total injectate volume among multiple lesions rather than delivering the entire volume to the largest lesion.

Details on dose calculation, preparation, and administration of MK-2118 are provided in the Procedures Manual.

Table 8 Determination of MK-2118 Injection Volume for Cutaneous and Subcutaneous Injections Based on Lesion Size (Arms 1 and 2)

Lesion Size (longest dimension)	Injection Volume
>5.0 cm	≤ 4 mL
>2.5 cm to 5.0 cm	≤ 2 mL
>1.5 cm to 2.5 cm	≤ 1 mL
≥1.0 cm to 1.5 cm [a]	0.5 mL

[a] Doses [redacted] require a minimum of 1 mL of total injectate volume.

Table 9 Determination of MK-2118 Injection Volume for IT Injections Based on Visceral Lesion Size (Arm 3)

Lesion Size (longest dimension)	Injection Volume
>5.0 cm	≤ 4 mL
>2.5 cm to 5.0 cm	≤ 2 mL
>1.5 cm to 2.5 cm	≤ 1.5 mL
≥1.0 cm to 1.5 cm [a]	1.0 mL

[a] Doses CCI require a minimum of 1 mL of total injectate volume.

7.1.2 Subcutaneous Injection (Arm 4)

Sites will be supplied with CCI CCI for dosing SC MK-2118. Sites will determine the appropriate volume of subcutaneous injection based on the dose to be administered at each dose cohort. The Procedures Manual provides a guide to injection volume calculation for subcutaneous administration by dose. Note that lesion size does not impact the volume administered of MK-2118 in Arm 4. Administration will be via injection into the subcutaneous anterolateral abdominal tissue or into the subcutaneous anterolateral thigh tissue. Subcutaneous administration of MK-2118 is by the Investigator or qualified designee.

Dose escalation of subcutaneous MK-2118 beyond the projected upper dose limit may be allowed if the systemic exposure achieved by SC dosing is significantly lower than expected, or if the subcutaneous dosing of MK-2118 at the upper dose limit demonstrates sufficient safety and tolerability in humans.

7.2 Dose Modification (Escalation/Titration/Other)

7.2.1 Accelerated Titration Design

The initial dose escalation in Arms 1, 2, and 3 will proceed following an ATD.

Single participants will be enrolled into sequential dose levels with up to a 300% dose increment increases from the prior dose of MK-2118. Up to 3 participants per cohort may be allowed in the event of simultaneous enrollment. The first 2 participants in each cohort in the trial who receive MK-2118 treatment at a new dose level must be treated at least 7 days apart. The subsequent dose level to be tested in the next cohort of participants will be communicated to the investigators or designees following each dose escalation decision. Dose ranges for the ATD are outlined in Table 2, Table 3, and Table 4. Transition from ATD to mTPI will be triggered by the occurrence of at least 1 of the following events:

- A dose level of at least CCI is cleared by DLT evaluation OR

- A ≥ Grade 2 toxicity as assessed by the investigator to be related, probably related, or possibly related to the drug(s) at any dose level.

If a DLT occurs in the ATD phase, then the cohort in which the DLT occurred will be expanded at this dose, per mTPI guidelines. This dose expansion will include a minimum of 3 participants, and up to 14 participants per cohort (see Table 10 Dose Finding Rules). Therefore, dose escalation will have proceeded to the mTPI phase. If no DLT occurs in the ATD phase, then the ATD phase will proceed to the mTPI phase once 1 of the above triggers is met. In such a case, the starting dose for the mTPI phase will increase by a [redacted] increment from the last ATD dose.

To ensure safety, MK-2118 in Arm 2 (combination therapy with pembrolizumab) will initiate at least 2 dose levels behind the current Arm 1 monotherapy dose and will not exceed the MTD for monotherapy. If an MTD for the monotherapy arm is established, the dose of IT MK-2118 in combination with pembrolizumab may continue escalation up to that dose.

Intraparticipant dose escalation of IT MK-2118 is permitted once in Arm 1 (Parts A and B) for a qualifying participant at the discretion of the investigator, provided that the participant has completed at least 3 cycles of treatment with IT MK-2118 monotherapy without a ≥ Grade 2 drug-related toxicity, and that dose escalation has proceeded beyond the next dose level in Arm 1. Intraparticipant dose escalation is not permitted in Arm 2 (Parts C and D), in Arm 3 (Parts E and F), nor in Arm 4.

7.2.2 Dose Finding During Modified Toxicity Probability Interval Design

Dose escalation and de-escalation decisions based on the mTPI design depend on the number of participants enrolled and the number of DLTs observed at the current dose level. The dosing decisions for this study are outlined in Table 10 [Nie, L., et al 2016] [Yang, S., et al 2015].

A minimum of 3 participants are required at each dose. However, depending on the accrual rate, 3, 4, 5, or 6 participants may be enrolled at each new dose level. In Table 10, the columns indicate the number of participants treated at the current dose level, and the rows indicate the number of participants experiencing DLT. The entries of the table are the dose-finding decisions: E escalate to the next higher dose; S stay at the current dose; D de-escalate to the next lower dose; and DU the current dose is unacceptably toxic. For example, if 0 out of 3 participants at a given dose level develop a DLT, then the dose can escalate to the next level. If 2 participants out of 3 develop a DLT, the dose will be de-escalated to the next lower dose level. If 3 out of 3 participants develop a DLT, this indicates an unacceptable toxicity at this dose. The dose should be de-escalated, and the current dose will not be explored further. If 1 out of 3 participants at a given dose level develops a DLT, then additional participants should be enrolled at that dose level following the rules below.

When adding participants to a dose level in response to a “stay” decision in Table 10, the same principles will be applied whether 3, 4, 5 or 6 participants are initially enrolled at that dose level. First, 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 10). Secondly, to determine how many more participants can be enrolled at the dose level, 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 10).

A "D" or "DU" decision at the starting dose level of Arm 1 of the study will stop the trial. An E decision at the highest dose level will result in staying at that level. During dose finding, it may be acceptable to de-escalate to an intermediate dose that was not predefined and not previously studied if evaluation of toxicity at such a dose is desired. If this approach is taken, 3 to 6 new participants may be enrolled at the new intermediate dose, and the aforementioned rules should be used to determine further enrollment at this dose level.

After 14 participants have been enrolled at any of the tested doses (including intermediate doses), dose finding will stop if the mTPI table indicates "S" for staying at current dose. Otherwise, up to 14 new participants may be enrolled at a lower dose if "D" or "DU" is indicated, or at a higher dose if "E" is indicated.

The pool-adjacent-violators-algorithm [Ji, Y., et al 2007] 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 pharmacodynamic, PK, and safety data emerging throughout the trial. The preliminary RP2D of MK-2118 in the combination arm (Arm 2) will not exceed, but may equal, the preliminary RP2D in the MK-2118 monotherapy arm (Arm 1).

Note that although 30% was the target toxicity rate used to generate the guidelines in Table 10, the observed rates of participants with DLTs at the MTD may be slightly above or below 30%. The target DLT rate will be 30% with a tolerance interval of 3%.

Establishment of the MTD/MAD for the combination of IT MK-2118 with pembrolizumab (Arm 2) requires that at least half of the participants in that cohort have no prior exposure to MK-2118 (ie, noncrossover participants). Priority for enrollment in Arm 2 will be given to MK-2118-naïve participants. Enrollment into Arm 2 will be monitored through IWRS.

Once the triggering criterion is met in the ATD phase, Arm 3 will use the same dose escalation and confirmation rules as in the mTPI method with a minimum of 3 participants per dose level. Enrollment to Arm 3 will be monitored through IWRS.

The starting dose for Arm 4 will be up to, but not exceeding, CCI Arm 4 will use the same dose escalation and confirmation rules as in the mTPI method with a minimum of 3 participants per dose level. Enrollment to Arm 4 will be monitored through IWRS.

Table 10 Dose-finding Rules per mTPI Design

	Number of participants evaluable 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; DLT = dose-limiting toxicity; DU = current dose is unacceptably toxic; E = escalate to the next higher dose; mTPI = modified toxicity probability interval; S = stay at the current dose.
Target toxicity rate = 30%
Flat noninformative prior Beta (1,1) is used as a prior and ε1=ε2=0.0 [Ji, Y., et al 2007] [Ji, Y. and Wang, S.-J. 2013]

7.2.3 Definition of Dose-limiting Toxicity

Dose-limiting toxicities will be defined from toxicities observed during the DLT period, defined as the first cycle of treatment (21 days) for each dose level in Arms 1, 2, and 3; and during the monotherapy run-in and the first cycle of pembrolizumab (35 days) in Arm 4. See Section 6.5 for rules on replacement of participants in the DLT period.

Participants who experience a DLT in the DLT period will be discontinued from treatment. However, if in the opinion of the Investigator the participant is deriving clinical benefit from the study treatment (for example a marked reduction in tumor burden), then the participant may be allowed to continue on the study at a reduced dose level of MK-2118 upon resolution of the DLT to a ≤ Grade 1 adverse event or to baseline, and upon discussion with the Sponsor. Therefore, flexibility of rechallenge of MK-2118 at a lower dose per dose modification guidance below subsequent to a DLT may be considered. Exceptional circumstances to following the dose modification tables below may be considered after consultation with the Sponsor.

The occurrence of any of the following toxicities during the DLT period of each treatment arm, if assessed by the investigator to be related, probably related, or possibly related to the drug(s) will be considered a DLT, excluding toxicities clearly not related to the drug(s), such as disease progression, environmental factors, unrelated trauma, etc.:

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 is a DLT if associated with clinically significant bleeding

3. Any nonhematologic AE ≥ Grade 3 in severity should be considered a DLT, with the following exceptions: Grade 3 fatigue lasting ≤3 days; Grade 3 nausea, vomiting, or diarrhea lasting ≤3 days in the absence of antiemetics or antidiarrheals per standard of care; Grade 3 rash without use of corticosteroids or anti-inflammatory agents per standard of care; Grade 3 fever and Grade 3 flu-like symptoms lasting ≤24 hours with negative infectious disease workup (including negative blood and urine cultures)

4. Any Grade 3 or Grade 4 nonhematologic laboratory abnormality, if

    - Clinically significant medical intervention is required to treat the participant, or
    - the abnormality leads to hospitalization, or
    - the abnormality persists for >1 week.

5. Febrile neutropenia Grade 3 or Grade 4:

    - Grade 3 is defined as ANC <1000/mm3 with a single temperature of >38.3°C (101°F) or a sustained temperature of ≥38°C (100.4°F) for more than 1 hour.
    - Grade 4 is defined as ANC <1000/mm3 with a single temperature of >38.3°C (101°F) or a sustained temperature of ≥38°C (100.4°F) for more than 1 hour, with life-threatening consequences and urgent intervention indicated

6. Any toxicity that causes treatment discontinuation or causes the participant to miss at least 1 dose during the DLT period

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

8. Any elevated aspartate aminotransferase (AST) or alanine aminotransferase (ALT) lab value that is ≥3× ULN and an elevated total bilirubin lab value that is ≥2× ULN and an alkaline phosphatase lab value that is <2× ULN, in which no alternative reasons can be found to explain the combination of increased AST/ALT and total

bilirubin, such as viral hepatitis A, B or C, preexisting or acute liver diseases, or another drug capable of causing the observed injury

9. Any ≥ Grade 2 immune-mediated uveitis

10. Grade 5 toxicity

7.2.4 Dose Modification/Interruption Due to Adverse Events

The CTCAE v 4.0 must be used to grade the severity of AEs. The investigator may attribute each toxicity event to MK-2118 alone, or to pembrolizumab alone, or to combination therapy. Use dose modification according to Table 11 or Table 12. If a dose modification for toxicity occurs with MK-2118, the dose may not be re-escalated to the dose that preceded the dose modification. Dose modifications are always based on the previous cycle.

Participants may have up to 2 dose modifications of MK-2118 throughout the course of the study, as described in Section 7.2. If further toxicity occurs or the criteria for resuming treatment are not met, the participant must be discontinued from the study drug. If a participant experiences several toxicities and there are conflicting recommendations, follow the most conservative dose adjustment recommended (dose reduction appropriate to the most severe toxicity).

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 drugs. For example, in a combination therapy arm (Arm 2, Arm 3, or Arm 4) if MK-2118 is held due to an AE attributed to that drug, then pembrolizumab may continue to be administered. Appropriate documentation of which drug the investigator is attributing the AE to is required. If, in the opinion of the investigator, the toxicity is related to the combination of 2 study drugs, then both drugs should be held according to recommended dose modifications.

Adverse events (both nonserious and serious) associated with MK-2118 and pembrolizumab exposure may represent an immunological etiology. These AEs may occur shortly after the first dose or several months after the last dose of treatment.

Participants who experience a DLT in the DLT evaluation period will be discontinued from treatment. However, if in the opinion of the Investigator the participant is deriving clinical benefit from the study treatment (for example a marked reduction in tumor burden), the participant may be allowed to continue on the study at a reduced dose level of MK-2118 upon resolution of the DLT to a ≤ Grade 1 adverse event or to baseline, and upon discussion with the Sponsor. Therefore, flexibility for rechallenge with MK-2118 at a lower dose per dose modification guidance below subsequent to a DLT may be considered.

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

7.2.4.1 Dose Modification for MK-2118

Dose modification guidelines for drug-related AEs are presented in Table 11. See Table 14 for treatment guidelines for cytokine release syndrome.

Table 11 MK-2118 Dose Modification Guidelines for Drug-related Adverse Events in Monotherapy IT (Arm 1), Combination Therapy IT (Arm 2), Combination Therapy Visceral IT (Arm 3), and Combination Therapy Subcutaneous Administration (Arm 4)

Toxicity	Hold Treatment	Criteria for Restarting Treatment	Dose/Schedule for Restarting Treatment	Criteria for Discontinuation After Consultation with Sponsor
Hematological toxicities:				
• Any Grade 1 hematological toxicity	No	N/A	N/A	N/A
• Any Grade 2 hematological toxicity	Per medical assessment of the investigator	Per medical assessment of the investigator	Per medical assessment of the investigator: First, decrease dose by 1 dose level If AE persists, and upon discussion with Sponsor, then consider modification of dosing schedule per below: **Arm 1 and Arm 2:** **Cycle 1, 2, and 3:** Reduce dosing schedule to CCI [redacted] **Arm 3:** **Cycle 1 and 2:** Reduce dosing schedule to CCI [redacted] **Arm 4:** **Cycle 1, 2, 3, and 4:** Reduce dosing schedule to CCI [redacted] **Arm 1 and Arm 2:** **Cycle 4 and beyond**: Maintain dosing schedule at CCI [redacted] unless AE persists for 2 additional cycles, then reduce dosing schedule to CCI [redacted]	If AE persists for 12 weeks without resolution following the last dose of study drug administered

Toxicity	Hold Treatment	Criteria for Restarting Treatment	Dose/Schedule for Restarting Treatment	Criteria for Discontinuation After Consultation with Sponsor
			Arm 3: **Cycle 3 and beyond**: Maintain dosing schedule at CCI unless AE persists for 2 additional cycles, then reduce dosing schedule to CCI **Arm 4:** **Cycle 5 and beyond:** Maintain dosing schedule at CCI unless AE persists for 2 additional cycles, then reduce dosing schedule to CCI	
• Any Grade 3[a] hematological toxicity	Yes[a]	Treatment may be restarted when AE resolves back to baseline or to Grade 1	First, decrease dose by 1 dose level If AE persists, and upon discussion with Sponsor, then consider modification of dosing schedule per below: **Arm 1 and Arm 2:** **Cycle 1, 2, and 3**: Reduce dosing schedule to CCI **Arm 3:** **Cycle 1 and 2:** Reduce dosing schedule to CCI **Arm 4:** **Cycle 1, 2, 3, and 4:** Reduce dosing schedule to CCI **Arm 1 and Arm 2:** **Cycle 4 and beyond:** Maintain dosing schedule at CCI unless AE persists for 2 additional cycles, then reduce dosing schedule to CCI **Arm 3:** **Cycle 3 and beyond:** Maintain dosing schedule at CCI unless AE persists for 2 additional cycles, then reduce dosing schedule to CCI	If AE persists for 12 weeks without resolution following the last dose of study drug administered *Permanent discontinuation should be considered for any severe or life threatening event*

Toxicity	Hold Treatment	Criteria for Restarting Treatment	Dose/Schedule for Restarting Treatment	Criteria for Discontinuation After Consultation with Sponsor
			Arm 4: **Cycle 5 and beyond**: Maintain dosing schedule at CCI unless AE persists for 2 additional cycles, then reduce dosing schedule to CCI	
• Any Grade 4 hematological toxicity	Yes	Treatment may be restarted when AE resolves back to baseline or to Grade 1	First, decrease dose by 1 dose level If AE persists, and upon discussion with Sponsor, then consider modification of dosing schedule per below: **Arm 1 and Arm 2:** **Cycle 1, 2, and 3:** Reduce dosing schedule to CCI **Arm 3:** **Cycle 1 and 2,:** Reduce dosing schedule to CCI **Arm 4:** **Cycle 1, 2, 3, and 4:** Reduce dosing schedule to CCI **Arm 1 and Arm 2:** **Cycle 4 and beyond**: Maintain dosing schedule at CCI unless AE persists for 2 additional cycles, then reduce dosing schedule to CCI **Arm 3:** **Cycle 3 and beyond**: Maintain dosing schedule at CCI unless AE persists for 2 additional cycles, then reduce dosing schedule to CCI **Arm 4:** **Cycle 5 and beyond:** Maintain dosing schedule at CCI unless AE persists for 2 additional cycles, then reduce dosing schedule to CCI	If AE persists for 12 weeks without resolution following the last dose of study drug administered *Permanent discontinuation should be considered for any severe or life threatening event*

Toxicity	Hold Treatment	Criteria for Restarting Treatment	Dose/Schedule for Restarting Treatment	Criteria for Discontinuation After Consultation with Sponsor
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	Per medical assessment of the investigator	Per medical assessment of the investigator: First, decrease dose by 1 dose level If AE persists, and upon discussion with Sponsor, then consider modification of dosing schedule per below: **Arm 1 and Arm 2:** **Cycle 1, 2, and 3:** Reduce dosing schedule to CCI [redacted] **Arm 3:** **Cycle 1 and 2:** Reduce dosing schedule to CCI [redacted] **Arm 4:** **Cycle 1, 2, 3, and 4**: Reduce dosing schedule to CCI [redacted] **Arm 1 and Arm 2:** **Cycle 4 and beyond**: Maintain dosing schedule at CCI [redacted] unless AE persists for 2 additional cycles, then reduce dosing schedule to CCI [redacted] **Arm 3:** **Cycle 3 and beyond**: Maintain dosing schedule at CCI [redacted] unless AE persists for 2 additional cycles, then reduce dosing schedule to CCI [redacted]	If AE persists for 12 weeks without resolution after the last dose of study drug administered

Toxicity	Hold Treatment	Criteria for Restarting Treatment	Dose/Schedule for Restarting Treatment	Criteria for Discontinuation After Consultation with Sponsor
			Arm 4: **Cycle 5 and beyond**: Maintain dosing schedule at CCI unless AE persists for 2 additional c , then reduce dosing schedule to CCI	
• Any Grade 3 nonhematological toxicity	Yes	Treatment may be restarted when AE resolves back to baseline or to Grade 1	First, decrease dose by 1 dose level If AE persists, and upon discussion with Sponsor, then consider modification of dosing schedule per below: **Arm 1 and Arm 2:** **Cycle 1, 2, and 3:** Reduce dosing schedule to CCI **Arm 3:** **Cycle 1 and 2:** Reduce dosing schedule to CCI **Arm 4:** **Cycle 1, 2, 3, and 4:** Reduce dosing schedule to CCI **Arm 1 and Arm 2:** **Cycle 4 and beyond**: Maintain dosing schedule at CCI unless AE persists for 2 additional cycles, then reduce dosing schedule to CCI **Arm 3:** **Cycle 3 and beyond**: Maintain dosing schedule at CCI unless AE persists for 2 additional cycles, then reduce dosing schedule to CCI **Arm 4:** **Cycle 5 and beyond:** Maintain dosing schedule at CCI unless AE persists for 2 additional cycles, then reduce dosing schedule to CCI	If AE persists for 12 weeks without resolution following the last dose of study drug administered *Permanent discontinuation should be considered for any severe or life threatening event*

Toxicity	Hold Treatment	Criteria for Restarting Treatment	Dose/Schedule for Restarting Treatment	Criteria for Discontinuation After Consultation with Sponsor
• Any Grade 4 nonhematological toxicity	Yes	Treatment may be restarted when AE resolves back to baseline or to Grade 1	First, decrease dose by 1 dose level If AE persists, and upon discussion with Sponsor, then consider modification of dosing schedule per below: **Arm 1 and Arm 2:** **Cycle 1, 2, and 3:** Reduce dosing schedule to CCI [redacted] **Arm 3:** **Cycle 1 and 2:** Reduce dosing schedule to CCI [redacted] **Arm 4:** **Cycle 1, 2, 3, and 4:** Reduce dosing schedule to CCI [redacted] **Arm 1 and Arm 2:** **Cycle 4 and beyond**: Maintain dosing schedule at CCI [redacted] unless AE persists for 2 additional cycles, then reduce dosing schedule to CCI [redacted] **Arm 3:** **Cycle 3 and beyond**: Maintain dosing schedule at CCI [redacted] unless AE persists for 2 additional cycles, then reduce dosing schedule to CCI [redacted] **Arm 4:** **Cycle 5 and beyond:** Maintain dosing schedule at CCI [redacted] unless AE persists for 2 additional cycles, then reduce dosing schedule to CCI [redacted]	If AE persists for 12 weeks without resolution following the last dose of study drug administered *Permanent discontinuation should be considered for any severe or life threatening event*

[a] *For Lymphoma participants, the dose modification for Grade 3 hematological toxicities is to be determined per investigator medical assessment. Consideration should be given to underlying disease, disease progression, or prior cytotoxic therapy. Grade 1, Grade 2, and Grade 4 hematological toxicities, as well as all grades of nonhematological toxicities have the same dose modification guidelines for participants with solid tumors or lymphomas.*

In case toxicity does not resolve back to baseline or to Grade 1 within 12 weeks following dose modification, MK-2118 should be considered for discontinuation after consultation with the Sponsor.

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

In Arm 2, Arm 3, and Arm 4, pembrolizumab treatment will be modified for the AEs as described in Table 12.

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

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

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

Dose Modification and Toxicity Management Guidelines for irAEs associated with pembrolizumab monotherapy, coformulations, or IO combinations are provided in Table 12.

Table 12 Dose Modification and Toxicity Management Guidelines for Immune-related Adverse Events Associated with Pembrolizumab Monotherapy, Coformulations or IO Combinations

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

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

irAEs	Toxicity Grade (CTCAEv4.0)	Action With Pembrolizumab Monotherapy, Coformulations or IO Combinations	Corticosteroid and/or Other Therapies	Monitoring and Follow-up
AST / ALT Elevation or Increased Bilirubin	Grade 2	Withhold	• Administer corticosteroids (initial dose of 0.5-1 mg/kg prednisone or equivalent) followed by taper	• Monitor with liver function tests (consider weekly or more frequently until liver enzyme value returned to baseline or is stable)
	Grade 3 or 4	Permanently discontinue	• Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper	
T1DM or Hyperglycemia	New onset T1DM or Grade 3 or 4 hyperglycemia associated with evidence of β-cell failure	Withhold [a]	• Initiate insulin replacement therapy for participants with T1DM • Administer anti-hyperglycemic in participants with hyperglycemia	• Monitor participants for hyperglycemia or other signs and symptoms of diabetes
Hypophysitis	Grade 2	Withhold	• Administer corticosteroids and initiate hormonal replacements as clinically indicated	• Monitor for signs and symptoms of hypophysitis (including hypopituitarism and adrenal insufficiency)
	Grade 3 or 4	Withhold or permanently discontinue [a]		
Hyperthyroidism	Grade 2	Continue	• Treat with non-selective beta-blockers (eg, propranolol) or thionamides as appropriate	• Monitor for signs and symptoms of thyroid disorders
	Grade 3 or 4	Withhold or Permanently discontinue [a]		

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

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

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

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

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

7.2.4.3 Management of Infusion Reaction

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 within 24 hours of completion of infusion. Dose modification and toxicity management guidelines on pembrolizumab-associated infusion reaction are provided in Table 13.

Table 13 Infusion Reaction 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 infusion interruption, but responds promptly to symptomatic treatment (eg, antihistamines, nonsteroidal anti-inflammatories (NSAIDS), narcotics, IV fluids); prophylactic medications indicated for ≤ 24 hours	**Stop infusion and monitor symptoms.** Additional appropriate medical therapy may include, but is not limited to: IV fluids Antihistamines NSAIDS Acetaminophen Narcotics Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator. If symptoms resolve within 1 hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (eg, from 100 mL/h to 50 mL/h). Otherwise dosing will be held until symptoms resolve and the participant should be premedicated for the next scheduled dose. **Participants who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further study drug treatment**	Participant may be Premedicated 1.5 h (± 30 min) prior to infusion of pembrolizumab and/or MK-2118 if it can be determined which drug caused reaction (if suspect drug cannot be identified on Arm 2, premedicate prior to pembrolizumab) with: Diphenhydramine 50 mg po (or equivalent dose of antihistamine). Acetaminophen 500-1000 mg po (or equivalent dose of analgesic).

NCI CTCAE Grade	Treatment	Premedication at Subsequent Dosing
Grades 3 or 4 Grade 3: Prolonged (ie, not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (eg, renal impairment, pulmonary infiltrates) Grade 4: Life-threatening; pressor or ventilatory support indicated	**Stop infusion.** Additional appropriate medical therapy may include, but is not limited to: IV fluids Antihistamines NSAIDS Acetaminophen Narcotics Oxygen Pressors Corticosteroids Epinephrine 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. **Participant is permanently discontinued from further trial treatment administration.**	No subsequent dosing
Appropriate resuscitation equipment should be available in the room and a physician readily available during the period of drug administration. For further information, please refer to the CTCAE v 4.0 at http://ctep.cancer.gov		

7.2.4.4 Management of Cytokine Release Syndrome

CRS is defined in CTCAE v 4.0 as a disorder characterized by nausea, headache, tachycardia, hypotension, rash, and shortness of breath. CRS occurs when lymphocytes (B cells, T cells, and/or natural killer cells) and/or myeloid cells (macrophages, dendritic cells, and monocytes) become activated and release inflammatory cytokines [Lee, D. W., et al 2014]. In addition to the symptomatology defined under CTCAE, CRS may present with fever, chills, myalgias, and malaise. Table 14 shows treatment guidelines for participants who experience CRS.

Table 14 Cytokine Release Syndrome Treatment Guidelines

NCI CTCAE Grade	Treatment	Premedication at Subsequent Dosing
Grade 1 Mild reaction: Therapy interruption not indicated. Intervention not indicated.	Increase monitoring of vital signs and oxygen saturation, as medically indicated, until the participant is deemed medically stable in the opinion of the investigator	None
Grade 2 Therapy interruption indicated, but responds promptly to symptomatic treatment (eg, NSAIDS, narcotics, IV fluids). Prophylactic medications indicated for ≤24 hours	Increase monitoring of vital signs and oxygen saturation, as medically indicated, until the participant is deemed medically stable in the opinion of the investigator Additional appropriate medical therapy may include, but is not limited to: IV fluids NSAIDS Acetaminophen Narcotics Oxygen Perform fever work-up to exclude infectious etiologies; treat neutropenia if present	Participant may be premedicated 1.5 hours (± 30 minutes) prior to MK-2118 administration with acetaminophen 500 to 1000 mg po (or equivalent dose of antipyretic)
Grade 3 Prolonged (eg, not rapidly responsive to symptomatic medication); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae (eg, renal impairment, pulmonary infiltrates)	Additional appropriate medical therapy may include, but is not limited to: IV fluids NSAIDS Acetaminophen Narcotics Oxygen Pressors Corticosteroids Anti-IL6 (eg, tocilizumab) Empiric antibiotics Participants with ≥ Grade 3 CRS need to be monitored very closely, likely in an intensive care setting	For Grade 3 CRS, discuss with Sponsor prior to restart of MK-2118 treatment. Upon approval by Sponsor, MK-2118 may be restarted at a reduced dose when AE resolves back to baseline or to Grade 1 (see Table 11 – Dose Modification Guidelines). Participant may be premedicated 1.5 hours (± 30 minutes) prior to MK-2118 administration with acetaminophen 500 to 1000 mg po (or equivalent dose of antipyretic)
Grade 4 Life-threatening consequences; pressor or ventilatory support indicated	Additional appropriate medical therapy may include, but is not limited to: IV fluids NSAIDS Acetaminophen Narcotics Oxygen Pressors Corticosteroids Anti-IL6 (eg, tocilizumab) Empiric antibiotics Participants with ≥ Grade 3 CRS need to be monitored very closely, likely in an intensive care setting	Permanently discontinue MK-2118 in participants who develop Grade 4 CRS

7.2.4.5 Other Allowed Dose Interruption for MK-2118 or Pembrolizumab

Pembrolizumab or MK-2118 may be interrupted for situations other than treatment-related AEs such as medical or surgical events and/or unforeseen circumstances not related to study therapy. However, study therapy is to be restarted within 3 weeks of the originally scheduled dose and within 42 days of the previously administered dose, unless otherwise discussed with the Sponsor. The reason for interruption should be documented in the participant's study record.

7.2.5 Intraparticipant Dose Escalation

Intraparticipant dose escalation will be allowed once for qualified participants in Arm 1 monotherapy, after they have completed at least 3 cycles of treatment with MK-2118 monotherapy without a ≥ Grade 2 drug-related toxicity, and provided that dose escalation has proceeded beyond the next dose level in Arm 1. The participant may escalate to the highest dose level that has been cleared by DLT evaluation in Arm 1, as defined by the minimum number of DLT-evaluable participants within that cohort (for the ATD phase, 1 participant per cohort; for the mTPI phase, 3 participants per cohort). This dose will be communicated to the site via written communication from the Sponsor and administered by IWRS. De-escalation from this dose will be based on occurrence of DLTs per dose escalation guidelines for either the ATD or the mTPI phase (see Section 7.2.1), as appropriate. Dose modification will be based on CTCAEs per Dose Modification Guidelines (see Section 7.2.4). Intraparticipant dose escalation is not permitted in Arm 2 (Parts C and D), in Arm 3 (Parts E and F), nor in Arm 4 (Part G).

7.3 Method of Treatment Assignment

Treatment allocation will be accomplished by nonrandom assignment by IWRS.

When Arms 1 and 2 are open for enrollment, IWRS will alternate participant assignment between Arm 1 and Arm 2, starting with Arm 1. For example, if the CCI dose cohort of Arm 1 (MK-2118 monotherapy) and the CCI dose cohort of Arm 2 (MK-2118 combination therapy with pembrolizumab) are open for enrollment, then the first participant will be allocated to Arm 1, the second participant will be allocated to Arm 2, the third participant will be allocated to Arm 1, etc.

At least half of the participants in Arm 2 must have no prior exposure to IT MK-2118 (ie, noncrossover/ IT MK-2118-naïve participants) in order to establish the MTD/MAD dose level in the combination therapy arm of IT MK-2118 with pembrolizumab (Arm 2).

Investigator assessment of eligibility and lesion location will guide participant allocation to Arms 1/2, Arm 3, or Arm 4. The enrollment into Arm 3 and into Arm 4 is independent of enrollment into Arm 1 and into Arm 2, due to different inclusion/exclusion criteria. In the event that a participant qualifies for multiple arms, preference will be given to enrollment into the IT arms over the SC arm, based on presumed difficulty of identifying participants amenable to IT therapy.

7.3.1 Stratification

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

7.4 Blinding

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

7.5 Preparation/Handling/Storage/Accountability

7.5.1 Dose Preparation

MK-2118 will be administered as a sterile aqueous solution with a total volume of injectate for IT injection of [redacted] per treatment visit for all injected lesions combined as well as a sterile aqueous solution for SC injection. Details on the dose calculation, preparation, and administration of MK-2118 for IT injection and SC injection are provided in the Procedures Manual.

7.5.2 Handling, Storage and Accountability

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

Only participants enrolled in the study may receive study treatment and only authorized site staff may supply or administer study treatment. All study treatments 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 treatment accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).

For all trial 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 trial site is responsible for recording the lot number, manufacturer, and expiry date for any locally purchased product as per local guidelines unless otherwise instructed by the Sponsor.

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 treatments in accordance with the protocol and any applicable laws and regulations.

7.6 Treatment Compliance

All doses of MK-2118 with pembrolizumab will be administered under the supervision of a qualified physician and/or designee experienced in the use of anticancer agents.

7.7 Concomitant Therapy

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

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

All concomitant medications received within 28 days before the first dose of trial treatment through the Safety Follow-up Visit should be recorded. If participants experience an SAE or ECI, all concomitant medications administered 30 days after the last dose of study intervention are to be recorded as defined in in Section 9.3.1.

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

1. Immunotherapy not specified in this protocol.

2. Antineoplastic systemic chemotherapy or biological therapy not specified in this protocol.

3. Investigational agents not specified in this protocol.

4. Radiation therapy; radiotherapy for symptom management is allowed beyond Cycle 2 upon approval by the Sponsor Medical Monitor or designee.

5. Live vaccines within 28 days prior to the first dose of trial treatment and while participating in the trial. Examples of live vaccines include, but are not limited to, the

following: measles, mumps, rubella, chickenpox, yellow fever, rabies, Bacillus Chalmette Guerin, 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.

6. Systemic glucocorticoids for any purpose other than to modulate symptoms from an adverse event of suspected immunologic etiology. The use of physiologic doses of corticosteroids may be approved after consultation with the Sponsor.

7. Strong/moderate CYP2C9 inhibitors from 2 weeks of Cycle 1 Day 1 through the 30 day Safety Follow-up Visit. This includes, but is not limited to:

   Strong/moderate CYP2C9 inhibitors, such as amiodarone, felbamate, fluconazole, miconazole, piperine, oxandrolone, fluorouracil and its derivatives (TS-1, UFT, tegafur, carmofur, doxifluridine, capecitabine), sulfaphenazole, cyclosporine, bucurol, and tienilic acid.

8. Co-administered UGT1A3 inhibitors that include ritonavir, quinidine, probenecid, and valproic acid.

9. Strong CBR inhibitors that include quercetin, menadione, glycyrrhetinic acid, and flufenamic acid.

If the investigator determines that a participant requires any of the aforementioned treatments for any reason, study intervention (MK-2118 and pembrolizumab) must be discontinued.

Participants may receive other medications that the investigator deems to be medically necessary.

The Exclusion Criteria describe other medications which are prohibited in this trial.

There are no prohibited therapies during the Follow-up visits.

7.7.1 Rescue Medications & Supportive Care

Participants should receive appropriate supportive care measures as deemed necessary by the treating investigator. Suggested supportive care measures for the management of AEs with potential immunologic etiology are outlined along with the dose modification guidelines in Section 7.2.4. 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 11 and Table 12 in Section 7.2.4.1 and Section 7.2.4.2, respectively, for guidelines regarding dose modification and supportive care. Refer to Table 11 for treatment guidelines for AEs that are related to MK-2118 treatment and to Table 14 for guidelines regarding dose modification and supportive care for cytokine release syndrome.

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

7.8 Treatment After the End of the Study

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

7.9 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, phone 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 amount of missing data for the participant will be managed via the pre-specified data handling and analysis guidelines.

7.10 Clinical Supplies Disclosure

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

8 DISCONTINUATION/WITHDRAWAL CRITERIA

8.1 Discontinuation of Study Treatment

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

As certain data on clinical events beyond study treatment 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 treatment. Therefore, all participants who discontinue study treatment prior to completion of the protocol-specified treatment period

will still continue to participate in the study as specified in Section 2 - SoA and Section 9.10.3 Discontinued Participants Continuing to be Monitored in the Study.

Participants may discontinue study treatment at any time for any reason or be dropped from the study treatment at the discretion of the investigator should any untoward effect occur. In addition, a participant may be discontinued from study treatment by the investigator or the Sponsor if study treatment is inappropriate, the trial plan is violated, or for administrative and/or other safety reasons. Specific details regarding procedures to be performed at study treatment discontinuation are provided in Section 9.1.12 Discontinuation and Withdrawal.

A participant must be discontinued from study treatment 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 treatment.
- Confirmed radiographic disease progression outlined in Section 9.2.2 (exception if the Sponsor approves treatment continuation).
- The participant interrupts trial medication administration for more than 12 consecutive weeks.
- Any 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.
- Recurrent Grade 2 pneumonitis.
- The participant is noncompliant with the protocol.
- The participant has a medical condition or personal circumstance, which, in the opinion of the investigator and/or Sponsor, placed the participant at unnecessary risk from continued administration of study drug.
- The participant has a confirmed positive serum pregnancy test.
- Side effects of and/or concomitant medications required for treatment of HIV and/or its complications that are incompatible with continued study treatment.

For participants who are discontinued from treatment, but continue to be monitored in the trial, see the SoA in Section 2.5 Discontinuation / End of Treatment and Post-treatment Follow-up, and Section 9.10.3 Post-treatment Follow-up for those procedures to be completed at each specified visit.

For participants who progress by clinical or radiographic progression on monotherapy IT MK-2118 in Arm 1, crossover into Arm 2 will be allowed if the participant meets the crossover eligibility criteria stated in Section 6.1.2 and Section 6.2.2. Participants who cross over from Arm 1 into Arm 2 will enter Arm 2 at the start of Arm 2 (at screening).

8.2 Withdrawal from the Study

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

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

Specific details regarding procedures to be performed at the time of withdrawal from the study including 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, as well as specific details regarding withdrawal from Future Biomedical Research are outlined in Section 9.1.12 Discontinuation and Withdrawal.

9 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.
- 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.

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

9.1 Administrative and General Procedures

9.1.1 Informed Consent

The investigator or qualified designee must obtain documented consent from each potential participant or each participant's legally acceptable representative prior to participating in a clinical trial or Future Biomedical Research. If there are changes to the participant's status

during the trial (eg, health or age of majority requirements), the investigator or qualified designee must ensure the appropriate consent is in place.

9.1.1.1 General Informed Consent

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

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

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

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

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

9.1.1.2 Consent and Collection of Specimens for Future Biomedical Research

The investigator or medically qualified designee will explain the FBR 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 FBR. A copy of the informed consent will be given to the participant before performing any procedure related to FBR.

9.1.2 Inclusion/Exclusion Criteria

All inclusion and exclusion criteria (Section 6.1 and 6.2) will be reviewed by the investigator or qualified designee to ensure that the participant qualifies for the trial.

9.1.3 Participant Identification Card

All participants will be given a Participant Identification Card identifying them as participants in a research trial. The card will contain trial site contact information (including direct telephone numbers) to be utilized in the event of an emergency. The investigator or qualified designee will provide the participant with a Participant Identification Card immediately after the participant provides written informed consent. At the time of treatment

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 health care provider can obtain information about study treatment in emergency situations where the investigator is not available.

9.1.4 Medical History

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

9.1.5 Disease Details

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

9.1.6 Prior Oncology Treatment History

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

9.1.7 Eastern Cooperative Oncology Group Performance Status

The investigator or qualified designee will assess the ECOG performance status as the time points specified in the SoA (Section 2). Additional ECOG testing may be performed as clinically indicated.

9.1.8 Prior and Concomitant Medications Review

9.1.8.1 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 trial medication. Treatment for the disease for which the participant has been enrolled in this trial will be recorded separately and should not be listed in prior medications.

9.1.8.2 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 exception of those specifically excluded (see Section 6.2). 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 trial 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 trial treatment and up to 30 days after the last dose of trial treatment should be recorded. Concomitant medications administered 30 days after the last dose of trial treatment should be recorded for SAEs and events of clinical interest (ECIs) as defined in Section 9.3.7. The investigator or qualified designee will record medication, if any, taken by the participant during the trial.

9.1.9 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 treatment allocation. Each participant will be assigned only one 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 who crossed over from Arm 1 into Arm 2 will retain the original screening number assigned at the initial screening visit. Specific details on the screening visit requirements (screening/ rescreening) are provided in Section 9.10.1.

9.1.10 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.

9.1.11 Treatment Administration

Administration of trial medication will be witnessed by the investigator and/or trial staff.

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

See Section 7 for a description of treatment modifications. Instructions for preparing and administering study drugs will be provided in the Procedures Manual.

9.1.11.1 Timing of Dose Administration

In Arms 1 and 2 IT MK-2118 will be administered [redacted]. Beginning with [redacted] IT MK-2118 will be administered on Day 1 of each 21-day cycle.

In Arm 3, IT MK-2118 will be administered on [redacted]. Beginning with [redacted], IT MK-2118 will be administered on Day 1 of each 21-day cycle. In Arms 2 and 3 of the trial, IT MK-2118 will be administered within [redacted] following completion of pembrolizumab IV infusion.

In Arms 1, 2, and 3, pembrolizumab 200 mg will be administered as an IV infusion on Day 1 of each 21-day cycle. Participants may continue treatment with pembrolizumab for up to a total of 35 cycles (approximately 2 years). For participants who cross over from Arm 1 to Arm 2, combination treatment with IT MK-2118 and pembrolizumab, treatment may be continued for up to 35 cycles in Arm 2, regardless of duration of treatment in Arm 1.

In Arm 4, MK-2118 will be administered by subcutaneous injection into the anterolateral abdominal tissue or the anterolateral thigh tissue as monotherapy on [redacted]. Beginning with [redacted] SC MK-2118 will be administered [redacted] in Arm 4. Beginning with Cycle 2, SC MK-2118 will be administered within [redacted] following completion of pembrolizumab 200 mg IV infusion on Day 1 of each c

After Cycle 1 Day 1 in each treatment arm, trial treatments may be administered up to 3 days before, or up to 3 days after the scheduled treatment day within each cycle. 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.

9.1.12 Discontinuation and Withdrawal

Participants who discontinue study treatment 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 EOT 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 9.3 - Adverse Events, Serious Adverse Events and Other Reportable Safety Events, and Section 9.10.4 - 30-Day Safety Follow-up Visit.

9.1.12.1 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 trial. If medical records for the main trial 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 trial data and results. No new analyses would be generated after the request is received.

In the event that the medical records for the main trial are no longer available (eg, if the investigator is no longer required by regulatory authorities to retain the main trial 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.

9.1.13 Participant Blinding/Unblinding

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

9.1.14 Domiciling

Participants enrolled in Arms 1, 2, and 3 will report to the clinical research unit on C1D1. Participants will remain in the unit for an observation period of at least 24 hours, post study drug administration on C1D1, C1D8, and C1D15. For Arm 4, participants will remain in the unit for an observation period of at least 24 hours post study drug administration on C1D1, C1D8, and C2D1. At the discretion of the investigator, the inpatient observation periods may be extended beyond 24 hours and up to 48 hours post study drug administration. This requirement may be waived at the discretion of the Sponsor and will be communicated to sites via a memorandum.

After discharge from the clinic, participants are to be counseled with post-discharge instructions.

9.1.15 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 trial that provides information about inclusion/exclusion criteria and/or safety or efficacy parameters shall be suitably calibrated and maintained to ensure that the data obtained is reliable and/or reproducible. Documentation of equipment calibration must be retained as source documentation at the trial site.

9.2 Efficacy Assessments

9.2.1 Tumor Imaging and Medical Photography

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 version 1.1, IWG revised criteria, or ISCL criteria to confirm eligibility. In participants with CTCL, it is recommended that CT scans be performed at screening.

Solid tumor imaging should be acquired by CT. An MRI should be used when CT is contraindicated or for imaging of the brain. For subcutaneous lesions, imaging by either MRI or CT is to be obtained at screening and at the imaging time points outlined in Section 2 SoA for assessment of response.

For participants with CTCL, include medical photography with tumor imaging every 12 weeks. Medical photography may be done more frequently, if warranted.

For participants with solid tumors assessed by RECIST 1.1, PR and CR should be confirmed by a repeat imaging assessment. The imaging for confirmation of response may be performed at least 4 weeks after the first indication of response. Participants who receive additional imaging for confirmation may resume imaging at subsequent scheduled tumor imaging timepoint. If the additional confirmation imaging was within 4 weeks of subsequent scheduled tumor imaging timepoint, then tumor imaging does not need to be repeated.

The same imaging technique and the same imaging modality with/without the use of contrast for assessment of response should be performed in a participant throughout the trial to optimize visualization of existing and new tumor burden. Tumor imaging schedule for all indications being studied is based on **calendar days** from the first drug administration and will not be postponed due to delays in treatment cycles. Additional tumor imaging and/or medical photography may be performed as clinically indicated.

Please refer to the Site Imaging Manual for detailed instructions regarding tumor imaging and medical photography.

A central imaging vendor will be used to collect, clean, and hold tumor imaging and medical photography. Images will be collected for possible analysis by blinded, independent central review.

9.2.2 Response Assessments

9.2.2.1 Immune-related RECIST

Tumor imaging and/or medical photography for solid tumors should be repeated every 9 weeks (± 7 days) from the first dose of treatment.

RECIST 1.1 will be adapted to account for the unique tumor response characteristics seen in treatment with pembrolizumab and MK-2118. 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 can manifest a clinical response after an initial increase in tumor burden or even the appearance of new lesions. Standard RECIST may not provide an accurate response assessment of immunotherapeutic agents such as pembrolizumab and MK-2118. Immune-related RECIST (irRECIST) is RECIST 1.1 adapted as described below to account for the unique tumor response seen with immuno-therapeutics. irRECIST will be used by site investigators to assess tumor response and progression, and to make treatment decisions.

Therefore, RECIST 1.1 will be used with the following adaptations:

If radiologic imaging by local radiology shows initial PD, tumor assessment should be repeated at least 4 weeks later in order to confirm PD, with the option of continuing treatment while awaiting radiologic confirmation of progression, as described below.

If repeat imaging shows <20% increase in tumor burden compared to nadir, stable, or improved previous new lesion (that may have been identified as the cause for initial PD), and stable/improved nontarget disease (that may have been identified as the cause for initial PD), then PD is not confirmed. Treatment may be continued and will then follow the regular imaging schedule.

If repeat imaging confirms PD due to any of the scenarios listed below, then participants will be discontinued from study therapy. The initial date of progression will be recorded as the PD date.

In determining whether the tumor burden has increased or decreased, the investigator should consider all target lesions as well as nontarget lesions. For purposes of this protocol, biopsied tumors should not be used for assessment by RECIST 1.1 or irRECIST, except in cases with only target lesions available, after consultation with the Sponsor.

Scenarios where PD is confirmed at repeat imaging:

- Tumor burden increase remains ≥ 20% and at least 5 mm absolute increase compared to nadir
- Nontarget disease resulting in initial PD is worse (qualitative)
- New lesion resulting in initial PD is worse (qualitative)
- Additional new lesion(s) since last evaluation
- Additional new nontarget progression since last evaluation

In participants who have initial evidence of radiological PD, it is at the discretion of the investigator whether to continue a participant on study treatment until repeat imaging is obtained. This clinical judgment decision should be based on the participant's overall clinical condition, including performance status, clinical symptoms, and laboratory data. Participants may receive study treatment while waiting for confirmation of PD, if they are clinically stable as defined by the following criteria:

- Absence of symptoms and signs indicating clinically significant progression of disease, including worsening of laboratory values
- No decline in ECOG performance status
- Absence of rapid progression of disease
- Absence of progressive tumor at critical anatomical sites (eg, cord compression) requiring urgent alternative medical intervention

When feasible, participants should not be discontinued until progression is confirmed. This allowance to continue treatment despite initial radiologic progression 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 still have a subsequent disease response. Participants who are deemed clinically unstable are not required to have repeat imaging for confirmation of PD. In participants who discontinue trial treatment, tumor imaging should be performed at the time of treatment discontinuation (±4-week window). If a previous scan was obtained within 4 weeks prior to the date of discontinuation, then a scan at treatment discontinuation is not mandatory. In participants who discontinue trial treatment due to documented disease progression, this is the final required tumor imaging.

Confirmation of PR and CR is required at least 4 weeks after the initial response assessment of PR and CR.

9.2.2.2 IT Immunotherapy RECIST (itRECIST)

itRECIST, a response assessment tailored to IT immunotherapy, is aligned with RECIST 1.1 overall response assessment [Goldmacher, G. V., et al 2020] and is further described in Appendix 8, Section 12.8.

<u>itRECIST:</u>

- provides a guidance on baseline categorization of target and nontarget lesions (Figure 3).
- provides guidance on recategorization of lesions during therapy (Figure 4).
- allows for separate response assessment in injected and noninjected lesions (Figure 5).

- for injected lesions, provides an iterative response assessment process that adapts to changes in lesion selection for IT immunotherapy (an example is provided in Figure 6).

- provides guidelines on prioritization of lesion injection during the course of IT immunotherapy (see Appendix 12.7).

itRECIST supports standardized collection of data from IT immunotherapy clinical trials to facilitate exploratory response analysis.

9.2.2.3 IWG Revised Response Criteria for Malignant Lymphomas

Response to treatment for lymphomas will be assessed every 12 weeks (± 7 days) from the first dose of treatment.

Response to therapy will be assessed by CT, with or without PET, and bone marrow biopsy, and clinical information including physical examination and symptoms (fever, night sweats, weight loss), using the IWG revised response criteria for malignant lymphomas [Cheson, B. D., et al 2007]. Information collected for this assessment includes:

1. At a minimum, thoracic, abdominal, and pelvic CT scans will be performed even if those areas were not initially involved because of the unpredictable pattern of recurrence in malignant lymphoma. Neck CT should be performed at screening, at follow-up visits if there is nodal involvement in the neck at screening. FDG-PET scans may be obtained to supplement the anatomic imaging, and should always be collected at screening, 12 weeks, 24 weeks, and when CR is suspected.

2. Unilateral bone marrow biopsy and aspirates will be performed at Screening, if not previously performed within 8 weeks prior to Screening with negative results. The bone marrow biopsy will be performed to confirm a CR if the participant was initially positive or if it is clinically indicated by new abnormalities in the peripheral blood counts or blood smear.

Response of lesions will be recorded on the eCRF based on the definitions in Table 15 as appropriate. Suspected relapse or disease progression must be confirmed by physical examination, laboratory assessments, repeat bone marrow biopsy [Cheson, B. D., et al 2007], and CT scan. Participants with suspected relapse or disease progression should continue to follow study procedures until they need another therapy. If a participant requires another therapy, date of treatment and type of treatment will be recorded, and they will then be removed from the trial.

Tumor progression is defined as ≥50% increase from nadir in the SPD of target lesions, or by growth of a single nodal target lesion, or by growth of nontarget lesions, or the appearance of new lesions, as defined in the IWG revised response criteria for malignant lymphoma [Cheson, B. D., et al 2007]. For purposes of this protocol, biopsied tumors should not be used for assessment by revised IWG criteria, except in cases with only target lesions available, after consultation with the Sponsor.

Table 15 Response Criteria for Malignant Lymphoma

Response Category	Physical Examination	Nodal Masses	Spleen, Liver	Bone Marrow
Complete Response	Disappearance of all evidence of disease	(a) FDG-avid or PET positive prior to therapy; mass of any size permitted if PET negative (b) Variably FDG-avid or PET negative; regression to normal size on CT	Not palpable, nodules disappeared	Infiltrate cleared on repeat biopsy; if indeterminate by morphology, immunohistochemistry should be negative
Partial Response	No progression of palpable disease and no new sites	≥50% decrease in SPD of up to 6 largest dominant masses; no increase in size of other nodes (a) FDG-avid or PET positive prior to therapy; one or more PET positive at previously involved site (b) Variably FDG-avid or PET negative; regression on CT	≥50% decrease in SPD of nodules (for single nodule in greatest transverse diameter); no increase in size of liver or spleen	Irrelevant if positive prior to therapy; cell type should be specified
Stable Disease	Failure to attain CR/PR or PD	(a) FDG-avid or PET positive prior to therapy; PET positive at prior sites of disease and no new sites on CT or PET (b) Variably FDG-avid or PET negative; no change in size of previous lesions on CT		
Relapse/ Progression	Any new lesion or increase by ≥ 50% of previously involved sites from nadir	Appearance of a new lesion(s) 1.5 cm in any axis, ≥50% increase in SPD of more than one node, or ≥50% increase in longest diameter of a previously identified node >1 cm in short axis Lesions PET positive if FDG-avid lymphoma or PET positive prior to therapy	≥50% increase from nadir in the SPD of any previous lesions	New or recurrent involvement

Abbreviations: CR = complete response; CT = computed tomography; FDG = fluorodeoxyglucose; PD = progressive disease; PET = positron emission tomography; PR = partial response; SPD = Sum of the products of the greatest diameters.

9.2.2.4 Response Assessment for Cutaneous T-cell Lymphoma

The mSWAT (Table 16) will be used to evaluate the extent of disease in the CTCL participants prior to treatment at each cycle per the SoA. Imaging (CT scans and medical photography) will be performed at screening/baseline for all CTCL participants. In those patients with advanced disease at baseline (maximum/current stage greater than or equal to Stage IIB (T3N0M0B0)), repeat imaging studies should be performed at the time of PR and CR by assessment of the skin, and any time there is a question of new or PD in the lymph nodes or the viscera; and at the end of the study [Olsen, E. A., et al 2011].

Each scheduled response assessment will include evaluations of skin (Table 17), lymph nodes (Table 18), viscera (Table 19), and blood (Table 20); and will determine a global response score (Table 21) for CTCL participants. Medical photography will also be performed at the time of each response assessment (see SoA), or more often as warranted.

Table 16 Modified Severity Weighted Assessment Tool

Body Regions	**% BSA in Body Region**	**Assessment of Involvement in Patient's Skin**		
		Patch[a]	**Plaque[b]**	**Tumor[c]**
Head	7			
Neck	2			
Anterior trunk	13			
Arms	8			
Forearms	6			
Hands	5			
Posterior trunk	13			
Buttocks	5			
Thighs	19			
Legs	14			
Feet	7			
Groin	1			
Subtotal of lesion BSA Weighting factor		× 1	× 2	× 4
Subtotal lesion BSA × weighting factor				

Abbreviations: BSA = body surface area; mSWAT = modified Severity Weighted Assessment Tool
NOTE: mSWAT score equals summation of each column line
[a.] Any size lesion without induration of significant elevation above the surrounding uninvolved skin; poikiloderma may be present.
[b.] Any size lesion that is elevated or indurated, crusting, ulceration, or poikiloderma may be present.
[c.] Any solid or nodular lesion ≥ 1 cm in diameter with evidence of deep infiltration in the skin and/or vertical growth.

Table 17 Response in Skin (Cutaneous T-cell Lymphoma)

Response	**Definition**
CR	100% clearance of skin lesions
PR	50%-99% clearance of skin disease from baseline without new tumors (T_3) in patients with T_1, T_2 or T_4 only skin disease
SD	<25% increase to <50% clearance in skin disease from baseline without new tumors (T_3) in patients with T_1, T_2, or T_4 only skin disease
PD	Whichever criterion occurs first: ≥25% increase in skin disease from baseline OR New tumors (T_3) in patients with T_1, T_2 or T_4 only skin disease OR Loss of response: in those with complete or partial response, increase of skin score of greater than the sum of nadir plus 50% baseline score
Relapse	Any disease recurrence in those with complete response

Abbreviations: CR = complete response; PD – progressive disease; PR partial response; SD = stable disease.
NOTE. Based on modified Severity Weighted Assessment Tool (mSWAT) score. A biopsy of normal appearing skin is unnecessary to assign a complete response. However, a skin biopsy should be performed of a representative area of the skin if there is any question of residual disease (persistent erythema or pigmentary change) where otherwise a complete response would exist. If histologic features are suspicious or suggestive of mycosis fungoides/Sézary syndrome, the response should be considered a partial response only.

Table 18 Response in Lymph Nodes (Cutaneous T-cell Lymphoma)

Response	**Definition (peripheral and/or central lymph nodes)**
CR	All lymph nodes are now ≤1.5 cm in greatest transverse (long axis) diameter by method used to assess lymph nodes at baseline or biopsy negative for lymphoma; in addition, lymph nodes that were N_3 classification and ≤1.5 cm in their long axis and >1 cm in their short axis at baseline, must now be ≤1 cm in their short axis or biopsy negative for lymphoma
PR	Cumulative reduction ≥50% of the SPD of each abnormal lymph node at baseline and no new lymph node >1.5 cm in the diameter of the long axis or >1.0 cm in the diameter of the short axis if the long axis is 1-1.5 cm diameter
SD	Fails to attain the criteria for CR, PR, and PD
PD	Whichever criterion occurs first: ≥50% increase in SPD from baseline of lymph nodes OR Any new node >1.5 cm in the long axis or >1 cm in the short axis if 1-1.5 cm in the long axis that is proven to be N_3 histologically OR Loss of response: >50% increase from nadir in SPD of lymph nodes in those with PR
Relapse	Any new lymph node >1.5 cm in the long axis in those with CR proven to be N_3 histologically
Abbreviations: CR = complete response; PD – progressive disease; PR partial response; SD = stable disease.	

Table 19 Response in Viscera (Cutaneous T-cell Lymphoma)

Response	**Definition**
CR	Liver or spleen or any organ considered involved at baseline should not be enlarged on physical examination and should be considered normal by imaging; no nodules should be present on imaging of liver or spleen; any post treatment mass must be determined by biopsy to be negative for lymphoma
PR	≥50% regression in any splenic or liver nodules, or in measurable disease (SPD) in any organs abnormal at baseline; no increase in size of liver or spleen and no new sites of involvement
SD	Fails to attain the criteria for CR, PR, or PD
PD	Whichever criterion occurs first: >50% increase in size (SPD) of any organs involved at baseline OR New organ involvement OR Loss of response: >50% increase from nadir in the size (SPD) of any previous organ involvement in those with PR
Relapse	New organ involvement in those with CR
Abbreviations: CR = complete response; PD – progressive disease; PR partial response; SD = stable disease.	

Table 20 Response in Blood (Cutaneous T-cell Lymphoma)

Response[a]	**Definition**
CR[b]	B_0
PR[c]	>50% decrease in quantitative measurements of blood tumor burden from baseline in those with high tumor burden at baseline (B_2)
SD	Fails to attain criteria for CR, PR, or PD
PD	Whichever criterion occurs first: B_0 to B_2 OR >50% increase from baseline and at least 5,000 neoplastic cells/µL[Cheson, B. D., et al 1996] OR Loss of response: in those with PR who were originally B_2 at baseline, >50%increase from nadir and at least 5,000 neoplastic cells/µL
Relapse	Increase of neoplastic blood lymphocytes to ≥ B_1 in those with CR

Abbreviations: CR = complete response; PD – progressive disease; PR partial response; SD = stable disease.
a. As determined by absolute numbers of neoplastic cells/µL.
b. If a bone marrow biopsy was performed at baseline and determined to unequivocally be indicative of lymphomatous involvement, then to confirm a global CR where blood assessment now meets criteria for B_0, a repeat bone marrow biopsy must show no residual disease or the response should be considered a PR only.
c. There is no PR in those with B_1 disease at baseline as the difference within the range of neoplastic cells that define B_1 is not considered significant and should not affect determination of global objective response.

Table 21 Global Response Score for Cutaneous T-cell Lymphoma

Global Score	Definition	Skin	Nodes, Blood, Viscera
CR	Complete disappearance of all clinical evidence of disease	CR	All categories have CR/NI
PR	Regression of measurable disease	CR	All categories do not have a CR/NI and no category has a PD
		PR	No category has a PD and if any category involved at baseline, at least one has a CR or PR
SD	Failure to attain CR, PR, or PD representative of all disease	PR	No category has a PD and if any category involved at baseline, no CR or PR in any
		SD	CR/NI, PR, SD in any category and no category has a PD
PD	Progressive disease	PD in any category	
Relapse	Recurrence disease in prior CR	Relapse in any category	

Abbreviations: CR, complete response; NI, noninvolved; PR, partial response; PD, progressive disease; SD, stable disease.
*It is recommended that not only the proportion of patients who achieve a response or an unfavorable outcome be calculated, but a life table account for the length of the interval during which each patient is under observation also be generated.

9.2.3 Tumor Marker Assessments

Tumor markers alone cannot be used to assess response. However, some disease specific and validated tumor markers (eg, CEA, CA-125, CA-19-9, or alpha fetoprotein,) can be integrated as nontarget disease markers. If markers are initially above the upper-normal limit, they must normalize for a participant to be considered in complete clinical response when all lesions have disappeared.

Blood samples for tumor markers will be obtained at time points indicated in Section 2 - SoA, as clinically appropriate for the participant. Additional assessments may be done if clinically indicated, eg, progression.

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

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

Progression of the cancer under study is not considered an adverse event as described in Section 9.3.5 Disease-Related Events and/or Disease-Related Outcomes Not Qualifying as AEs or SAEs, and Appendix 4.

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

The investigator, who is a qualified physician, and any designees are responsible for detecting, assessing, documenting, and reporting events that meet the definition of an AE or SAE as well as other reportable safety events. Investigators remain responsible for following up AE, SAEs and other reportable safety events for outcome according to Section 9.3.3.

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

Progression of the cancer under study is not considered an AE unless it results in hospitalization or death.

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

- All AEs from the time of treatment allocation/randomization through 30 days following cessation of study treatment must be reported by the investigator.
- All AEs meeting serious criteria, from the time of treatment allocation/randomization through 120 days following cessation of study treatment, or 30 days following cessation of study treatment if the participant initiates new anticancer therapy, whichever is earlier must be reported by the investigator.
- All pregnancies and exposure during breastfeeding, from the time of treatment allocation/randomization through 120 days following cessation of study treatment, or 30 days following cessation of study treatment 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 to be drug-related.

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

considers the event to be reasonably related to the study treatment 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 timeframes as indicated Table 22.

Table 22 Reporting Time Periods and Timeframes for Adverse Events and Other Reportable Safety Events

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

9.3.2 Method of Detecting AE, SAE and Other Reportable Safety Events

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

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

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All AE, SAE and other reportable safety events including pregnancy and exposure during breastfeeding, ECI, Cancer and Overdose will be followed until resolution, stabilization, until the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 8.3). 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 4.

9.3.4 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 treatment 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 treatment under clinical investigation. All AEs will be reported to regulatory authorities, IRB/IECs and investigators in accordance with all applicable global laws and regulations, ie, per ICH Topic E6 (R1) Guidelines for Good Clinical Practice.

- Investigator safety reports must be prepared for SUSAR according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.

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

9.3.5 Disease-Related Events and/or Disease-Related Outcomes Not Qualifying as AEs or SAEs

Progression of the cancer under study is not considered a reportable event.

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

9.3.6 Pregnancy and Exposure During Breastfeeding

Although pregnancy and lactation are not considered AEs, it is the responsibility of investigators or their designees to report any pregnancy or lactation in a participant (spontaneously reported to them), including the pregnancy of a male participant's female partner that occurs during the trial. Pregnancies and lactations of participants and female partners of male participants from the time the consent form is signed, but before treatment

allocation/randomization, must be reported by the investigator if they cause the participant to be excluded from the trial, or are the result of a protocol-specified intervention, including, but not limited to, washout or discontinuation of usual therapy, diet, placebo treatment or a procedure. Pregnancies and lactations of participants and female partners of male participants that occur from the time of treatment allocation/randomization through 120 days following cessation of Sponsor's product, or 30 days following cessation of trial treatment if the participant initiates new anticancer therapy, whichever is earlier, must be reported. 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. Such events must be reported within 24 hours to the Sponsor either by electronic media or paper. Electronic reporting procedures can be found in the EDC data entry guidelines. Paper reporting procedures can be found in the investigator Trial File Binder (or equivalent).

9.3.7 Events of Clinical Interest (ECI)

Selected non-serious and SAEs are also known as ECIs and must be reported to the Sponsor.

Events of clinical interest for this trial include:

1. an overdose of Sponsor's product, as defined in Section 9.4 Treatment of Overdose, 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 trial site guidance for assessment and follow up of these criteria can be found in the Investigator Trial File Binder (or equivalent).

9.4 Treatment of Overdose

For this study, an overdose of pembrolizumab will be defined as any CCI or greater. No specific information is available on the treatment of overdose of pembrolizumab. In the event of overdose, the participant should be observed closely for signs of toxicity. Appropriate supportive treatment should be provided if clinically indicated.

For MK-2118, an overdose will be defined as any dose exceeding the prescribed dose by ≥20%. No specific information is available on the treatment of an overdose of MK-2118. In

the event of an overdose of MK-2118, the participant should be observed closely for signs of toxicity and provided appropriate supportive treatment, as clinically indicated.

9.5 Safety

Details regarding specific safety procedures/assessments to be performed in this trial are provided below. The total amount of blood/tissue to be drawn/collected over the course of the trial (from pretrial to post-trial visits), including approximate blood/tissue volumes drawn/collected by visit and by sample type per participant, can be found in the Procedures Manual.

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

9.5.1 Physical Examinations

The investigator or qualified designee will perform a complete physical examination during the Screening Period and at additional time points as defined in the SoA (Section 2). Height should be recorded only at Screening. Clinically significant findings from the screening examination should be recorded as medical history.

A directed physical examination should be repeated at the visits indicated in the SoA (Section 2). After the first dose of study treatment, new clinically significant abnormal findings should be recorded as AEs.

Weight should be recorded at Screening and at the visits indicated in the SoA (Section 2).

9.5.2 Vital Signs

Vital signs (VS) will include temperature, systolic and diastolic blood pressure, pulse, and O_2 saturation (pulse oximetry). Additional VS monitoring may be obtained as clinically indicated.

9.5.3 Electrocardiograms

A standard 12-lead ECG will be performed using local standard procedure at Screening, with any clinically significant abnormal findings recorded as medical history.

Additional time points for ECGs are according to the SoA (Section 2). Clinically significant abnormal findings seen on any ECGs performed after Screening should be recorded as AEs.

9.5.4 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 must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the

CRF. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those that are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.

- All protocol-required laboratory assessments, as defined in Appendix 2, must be conducted in accordance with the laboratory manual and the SoA.
- If laboratory values from nonprotocol specified laboratory assessments performed at the institution’s local laboratory require a change in study participant management or are considered clinically significant by the investigator (eg, SAE or AE or dose modification), then the results must be recorded in the appropriate CRF.
- 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 treatment, 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.

Laboratory samples, which cannot be processed locally, may be sent to the central laboratory.

9.6 Pharmacokinetics

To evaluate the immunogenicity (ADA) and exposure of pembrolizumab and exposure of MK-2118 in this indication, sample collections for analysis of ADA and PK are currently planned as shown in the Trial Flowchart. Blood samples for PK and ADA collected may be stored only at this time. Further analysis may be performed if required. If ongoing PK and/or ADA sampling is deemed to be unnecessary by the Sponsor, it may be reduced or discontinued.

9.6.1 Blood Collection for PK

Blood sample collection, processing, storage, and shipment instructions are provided in the Procedures Manual. PK samples should be drawn according to the PK collection schedule for all participants (Section 2).

Time points may be changed or eliminated based on emerging PK data. The MK-2118 PK plasma samples may also be used for MK-2118 metabolite measurements.

9.6.2 Blood Collection for Anti-pembrolizumab Antibodies

Sample collection, storage, and shipment instructions for serum samples are provided in the procedure manual. Anti-pembrolizumab antibody samples should be drawn according to the ADA collection schedule for all participants (Section 2). Simultaneous PK sampling is required for interpretation of ADA analysis. Time points may be changed or eliminated based on emerging ADA data.

9.6.3 Urine Collection for Urinary MK-2118

Urine samples for the evaluation of MK-2118 metabolites will be collected at the time points identified in Section 2 SoA. Sample collection, storage and shipment instructions for urine samples are provided in the Procedures Manual. The urine samples may also be used for MK-2118 metabolite measurements.

9.7 Pharmacodynamics

9.7.1 Blood for Pharmacodynamic Markers

Blood sample collection, storage, and shipment instructions for pharmacodynamic analysis are provided in the Procedures Manual.

The time points for pharmacodynamics sampling are described in Section 2 - SoA.

9.7.2 Tumor Biopsy

All participants in Arms 1, 2 and 3 will be required to provide a sample biopsy of the tumor to be injected with MK-2118 and a sample biopsy from a distant, discrete, noninjected site (at least 2 biopsies at each site) prior to or after IT administration of MK-2118, unless deemed medically unsafe by the investigator. Participants in Arm 4 will be required to provide a sample biopsy from a discrete lesion, irrespective of injection site. Tumor samples will be collected at the time points described in Section 2 SoA.

Tumor biopsies will only be performed at tumor sites that are deemed medically safe, in accordance with local guidelines. Sponsor selection criteria for the MK-2118 FIH study assured selection of sites that have investigative staff who are highly experienced in tumor biopsies.

For participants with lymphoma in Arms 1 or 2, only those participants that have superficial lesions amenable to IT injection will be eligible (cutaneous lesions injected via visual inspection, and subcutaneous lymph nodes injected via ultrasound guidance or palpation). No participants with lymphoma with exclusively deep lymph nodes will be included in this study. Participants with lymphoma who have both superficial and deep lymph nodes will be eligible for enrollment into this study, however only the superficial lymph nodes will be injected. In Arm 4, lymphoma patients are eligible regardless of the lesion location.

In Arms 1, 2, and 3, a predose tumor biopsy will be performed at Screening on both the tumor lesion which is intended for treatment with IT injection of MK-2118, as well as on the distant lesion which is not intended for IT injection of MK-2118. Participants in Arm 1 (monotherapy) who cross over to Arm 2 (combination therapy) are required to provide a fresh tumor biopsy at screening of both injected and noninjected sites, similar to participants who are newly enrolled into the study and assigned to Arm 2, unless one of the following 2 situations occur: 1) The most recent Arm 1 biopsy occurred within 28 days of C1D1 of Arm 2, OR 2) The investigator deems the biopsy to be medically unsafe. In Arm 4, a predose tumor biopsy will be performed at Screening on a single discrete, noninjected lesion.

For Arm 1 and 2, the tumor lesion intended for treatment with IT injection of MK-2118, the sample will be obtained by either punch biopsy for cutaneous lesions, or by ultrasound guided biopsy for subcutaneous lesions. For the tumor lesion that is treated with IT injection of MK-2118, the postdose tumor biopsy will be collected on the same day as treatment, at 5 hours (± 2 hours) following IT administration of MK-2118 on C2D8, and optionally on C3D8, at 5 hours (± 2 hours) following IT administration of MK-2118. On-treatment biopsy site location may vary from baseline biopsy site location based on lesion accessibility and participant tolerance.

For Arm 3, the liver metastasis/lesion intended for treatment with IT injection of MK-2118, the biopsy sample will be obtained by either ultrasound guidance or cross-sectional imaging guidance (CT/MRI). For the liver lesion that is treated with IT injection of MK-2118, the predose tumor biopsy will be collected prior to IT administration of MK-2118 on C2D8, and optionally on C3D1. Lesions which undergo biopsy during treatment may vary from lesions which undergo biopsy during screening, based on lesion accessibility and participant tolerance.

For Arm 1, 2, and 3 distant discrete tumor lesions that are not intended for IT injection with MK-2118, 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 day of MK-2118 treatment, however may be performed up to 3 days after treatment.

For Arm 4, biopsies from a single discrete tumor lesion will be required. The sample biopsy will be obtained by punch biopsy for cutaneous lesions, ultrasound guided biopsy for subcutaneous/visceral lesions, or image-guided biopsy, such as CT/MRI-guided biopsy, for additional lesions. The postdose tumor biopsies will be collected on the same day as treatment, at 5 hours (± 2 hours) following SC administration of MK-2118 on C1D8 and C3D8. Method of biopsy will be per guidance of the Investigator as well as discussion with the Sponsor.

Samples of archival tumor tissue collected at Screening should be freshly cut, and the slides from this freshly cut archival tumor tissue should be submitted to the testing laboratory within 14 days of slide preparation. Biopsies obtained during this study will be submitted as formalin-fixed, paraffin-embedded samples.

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

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

9.8 Future Biomedical Research Sample Collection

The following specimens are to be obtained as part of Future Biomedical Research:

- DNA for future research
- Leftover plasma and serum from biomarker analyses
- Leftover RNA
- Leftover main trial tumor tissue

9.9 Biomarkers

Collection of samples for other biomarker research is also part of this study. The following samples for biomarker research are required and will be collected from all participants in this study as specified in the SoA:

- Serum for Cytokine Panel and CRP for MK-2118 Pharmacodynamics Tumor tissue
- Blood for Genetic Analysis
- Blood for RNA Analysis

9.9.1 Planned Genetic Analysis Sample Collection

Sample collection, storage and shipment instructions for Planned Genetic Analysis samples will be provided in the Procedures Manual. The timing of collection of samples is provided in Section 2 SoA.

9.9.2 Blood for Genotyping

Blood sample collection, storage, and shipment instructions for the Screening blood sample for genotyping are provided in the Procedures Manual.

9.9.3 Immunogenicity Assessments

Blood sample collection, storage, and shipment instructions for anti-pembrolizumab drug antibodies analyses are provided in the Procedures Manual. The timing of collection of samples is provided in Section 2 SoA.

9.9.4 Blood for Serum Cytokine Analysis

Sample collection, processing, storage and shipment instructions for biomarker analysis samples are provided in the Procedures Manual. The timing of collection of samples is provided in Section 2 SoA.

9.9.5 Blood for RNA Analysis

Sample collection, processing, storage and shipment instructions for RNA analysis samples are provided in the Procedures Manual. The timing of collection of samples is provided in Section 2 SoA.

9.10 Visit Requirements

Visit requirements are outlined in Section 2 Schedule of Activities (SoA). Specific procedure-related details are provided above in Section 9 Study Assessments and Procedures.

9.10.1 Screening

Potential participants will be evaluated to determine that they fulfill the entry requirements as set forth in Section 6 within 28 days prior to Cycle 1 Day 1. Screening and Cycle 1 Day 1 cannot be on the same day.

Perform all screening clinical laboratory tests within 7 days of treatment initiation. Tests performed prior to the participant signing consent as part of routine clinical management are acceptable in lieu of a screening test, if the test is performed within the specified time frame. Perform pregnancy test for WOCBP within 7 days of treatment initiation. If a urine pregnancy test cannot be confirmed as negative, a serum pregnancy test is required.

Genotype testing must be completed prior to Cycle 1 Day 1. Baseline tumor imaging (CT, PET/CT, or MRI) and/or medical photography of cutaneous lesions should be performed within 28 days of enrollment. For lymphoma participants only, unilateral bone marrow biopsy and aspirates will be performed at Screening, if not previously performed within 8 weeks prior to Screening with negative results.

Participants may be rescreened after consultation with the Sponsor. Rescreening should include all screening procedures listed in the protocol SoA, including consent review. Results from assessments during the initial screening period are acceptable in lieu of a repeat screening test if performed within the specified time frame and the corresponding inclusion/exclusion criterion is met. A participant who is rescreened will retain their original screening number.

9.10.2 Treatment Period

The treatment period in each treatment arm begins with Cycle 1 and may continue for up to 35 cycles (approximately 2 years) for Arm 1, Arm 2, and Arm 3 and up to 36 cycles for Arm 4 (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 trials treatment or procedure requirements, or administrative reasons requiring cessation of treatment. For crossover participants, duration of treatment with MK-2118 with pembrolizumab combination therapy is up to 35 cycles in

Arm 2, regardless of the duration of treatment he/she received in Arm 1 (MK-2118 monotherapy). Each cycle includes study drug administration and all associated assessments as outlined in the SoA (see Section 2).

Specific procedure-related details are provided throughout Section 9.

9.10.2.1 Treatment Period beyond Disease Progression

See Section 9.2.2.1.

9.10.3 Post-treatment Follow-up

Discontinuation of treatment does not represent withdrawal from the trial. As certain data on clinical events beyond treatment discontinuation may be important to the trial, they must be collected through the participant's last scheduled follow-up, even if the participant has discontinued treatment.

9.10.3.1 30-Day Safety Follow-up Visit

The mandatory 30-day Safety Follow-up Visit should be conducted approximately 30 days (+7 days) after the last dose of trial treatment or before the initiation of a new anticancer treatment, whichever comes first. All AEs that occur prior to the 30-day Safety Follow-up Visit should be recorded. Participants with an AE of Grade >1 will be followed up until resolution of the AE to Grade 0-1 or until the beginning of a new antineoplastic therapy, whichever occurs first.

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

Participants who are eligible for crossover to combination therapy with IT MK-2118 and pembrolizumab may have up to 2 safety follow-up visits, 1 after monotherapy (Arm 1) and 1 after combination therapy (Arm 2).

9.10.3.2 Survival Follow-up

All participants, with the exception of those who withdraw consent or are lost to follow-up, will be followed up for survival and will be contacted every 12 weeks (±14 days) to monitor survival status. Participants who experience confirmed disease progression or start a new anticancer therapy, will move into the Survival Follow-Up Phase and should be contacted approximately every 12 weeks to assess for survival status until death, withdrawal of consent, or the end of the study, whichever occurs first.

To ensure current and complete survival data is available at the time of database locks, updated survival status may be requested during the course of the study by the Sponsor. For

example, updated survival status may be requested prior to, but not limited to, an eDMC safety review, interim and/or final analysis. Upon Sponsor notification, all participants who do not/will not have a scheduled study visit or study contact during the Sponsor-defined time period will be contacted for their survival status (excluding participants that have a previously recorded death event in the collection tool).

Every effort should be made to collect information regarding disease status until the start of new antineoplastic therapy, disease progression, death, or the end of the study.

10 STATISTICAL ANALYSIS PLAN

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

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

10.1 Statistical Analysis Plan Summary

This section contains a brief summary of the statistical analyses for this trial. Full details are in the Statistical Analysis Plan, Section 10.6 through Section 10.9.

Study Design Overview	Phase 1 trial in participants with advanced/metastatic solid tumors or lymphomas of IT MK-2118 monotherapy (Arm 1), IT MK-2118 in combination with pembrolizumab (Arm 2), IT MK-2118 in combination with pembrolizumab for liver metastasis/lesions (Arm 3), and SC administration of MK-2118 in combination with pembrolizumab (Arm 4). For Arm 1, Arm 2, and Arm 3, the study applies an ATD, followed by mTPI design to identify an MTD/MAD and a preliminary RP2D in each treatment arm. Arm 4 utilizes the mTPI design to identify an MTD/MAD and a preliminary RP2D.
Analysis Populations	Safety (Primary): All-Participants-as-Treated (APaT) and DLTe PK (Secondary): PP Efficacy (Exploratory): FAS
Primary Endpoint(s)	• DLT • AE • Discontinuing study treatment due to an AE

Key Secondary Endpoints	PK exposure of MK-2118 monotherapy and MK-2118 in combination with pembrolizumab; PK exposure of pembrolizumab in combination with MK-2118
Statistical Methods for Exploratory Efficacy/ Pharmacokinetic Analyses	Efficacy analyses are documented in the sSAP. Concentrations of MK-2118 will be summarized by planned visit and time for each dose separately.
Treatment Assignment	Participants will be allocated to receive single agent MK-2118 via IT injection (Arm 1), MK-2118 via IT injection co-administered with pembrolizumab (Arm 2), MK-2118 via visceral IT injection co-administered with pembrolizumab (Arm 3), or SC administration of MK-2118 in combination with pembrolizumab (Arm 4) centrally through an IWRS. Participants will be allocated by nonrandom assignment. Allocation will alternate between Arm 1 and Arm 2 when both arms are open for enrollment and alternating assignment begins with Arm 1. The trial is open-label.
Statistical Methods for Key Safety Analyses	Summary statistics (counts, percentages, means, standard deviations, etc.) will be provided for the safety endpoints as appropriate. The pool-adjacent-violators-algorithm [Ji, Y., et al 2007] will be used to estimate the DLT rates across doses. The estimates of the DLT rates among participants treated at MTD (or MAD) of MK-2118 and the 80% Bayesian credible intervals for the estimates will be provided.
Interim Analyses	An interim analysis may be conducted to enable future trial planning at the Sponsor's discretion and data will be examined on a continuous basis to allow for dose-finding decisions.
Multiplicity	No multiplicity adjustment is planned in this Phase 1 trial.
Sample Size and Power	The overall sample size for this study depends on the observed DLT profiles of MK-2118 monotherapy (Arm 1) and MK-2118 in combination with pembrolizumab (Arms 2, 3, 4). A target sample size of approximately 160 participants will be used for study planning purposes.
Abbreviations: AE = adverse event; APaT = all participants as treated; DLTe = dose-limiting toxicity evaluable; FAS = full analysis set; IT = intratumoral; MAD = maximum administered dose; MTD = maximum tolerated dose; PP = per protocol; RP2D = recommended Phase 2 dose; SC = subcutaneous	

10.2 Responsibility for Analyses/In-House Blinding

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

The trial is open-label, ie, participants, investigators, and Sponsor personnel will be aware of participant treatment assignment after each participant is enrolled and treatment is assigned. Allocation to treatment will not be randomized.

10.3 Hypotheses/Estimation

Objectives and hypotheses of the study are outlined in Section 4.0.

10.4 Analysis Endpoints

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

10.4.1 Efficacy/Pharmacokinetic Endpoints

Efficacy endpoints are exploratory endpoints in this study. Details of the statistical analysis plan will be documented in the sSAP. A description of efficacy measures is provided in Section 9.2.

Objective response rate is defined as the proportion of participants who have achieved confirmed CR or PR. Progression-free survival is defined as the time from the first dose of study treatment to the first documented disease progression or death due to any cause, whichever occurs first. Overall survival 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. Objective response rate for noninjected lesions is defined as the proportion of participants who have achieved at least 30% reduction in the sum of diameters of noninjected lesions, among participants with target noninjected lesions identified at baseline.

Pharmacokinetic endpoints include PK exposure of MK-2118 and pembrolizumab.

The exploratory evaluation of biomarkers to be measured in this trial is described in Section 9.9.

10.4.2 Safety Endpoints

The primary safety endpoint is the number/proportion of participants with DLT(s), AE(s), and who discontinue study treatment due to AE(s). A description of safety measures is provided in Section 9.3 - Adverse Events, Serious Adverse Events and Other Reportable Safety Events, and 9.5 - Safety.

10.5 Analysis Populations

10.5.1 Safety Analysis Population

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

of treatment administration errors, participants will be analyzed according to the treatment they actually received. The DLT-evaluable (DLTe) population for Arms 1, 2, and 3 includes APaT participants who were observed for safety for 21 days after the first dose of assigned treatment or experienced a DLT prior to 21 days after the first dose of assigned treatment will be used. For Arm 4, the DLTe population includes APaT participants who were observed for safety for 35 days after the first dose of treatment or experienced a DLT prior to 35 days after the first dose of treatment. The replacement participants will also be considered evaluable if the above specified criteria are met. Of note, both crossover participants and MK-2118-naïve participants enrolled in Arm 2 will be included for DLT evaluation of Arm 2. Safety data from crossover participants will also be presented separately.

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

10.5.2 Pharmacokinetic Analysis and Target Engagement Populations

The PP population will be used for 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 the data they generated will be likely to exhibit the effects of treatment, according to the underlying scientific model. Compliance covers such considerations as exposure to treatment, availability of measurements, and absence of major protocol violations. Major protocol violators will be identified, to the extent possible, by individuals responsible for data collection/compliance and its analysis and interpretation. Any participants or data values excluded from analysis 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 potentially will be included in the PP analysis dataset.

10.5.3 Efficacy Analysis Populations

The FAS population will be used for analysis of exploratory efficacy data in this study. It consists of all participants with a baseline scan that demonstrated measurable disease by investigator assessment, and who were administered a dose of study medicine. Efficacy data from crossover participants will be presented separately.

10.6 Statistical Methods

10.6.1 Statistical Methods for Efficacy Analyses

The statistical methods for efficacy analyses will be documented in the sSAP.

10.6.2 Statistical Methods for Safety Analyses

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

AEs will be summarized by counts and frequencies for each dose level and treatment arm. Laboratory tests, VS, and other safety endpoints will be summarized as appropriate.

DLTs will be listed, and further summarized by dose level and treatment arm. The pool adjacent-violators-algorithm [Ji, Y., et al 2007], which forces the DLT rate estimates to be nondecreasing with dose levels and pool adjacent violators for weighted estimates by sample size, will be used to estimate the DLT rates across doses in each treatment arm. The estimates of the DLT rates among participants treated at the MTDs (or MADs) and the 80% Bayesian credible intervals based on a prior distribution of Beta (1,1) for the estimates will be provided.

10.6.3 Summaries of Baseline Characteristics, Demographics, and Other Analyses

10.6.3.1 Demographic and Baseline Characteristics

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

10.6.3.2 Pharmacokinetics and Pharmacodynamics Modeling Analysis

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

10.7 Interim Analyses

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

10.8 Multiplicity

There will be no multiplicity control in this study.

10.9 Sample Size and Power Calculations

The overall sample size for this Phase 1 trial is expected to be up to approximately 160 participants (approximately 35 participants in each Arm 1, Arm 2, and Arm 3; 55 in Arm 4). The actual total will depend on the tolerability of the treatment and occurrence of DLTs.

Part A, Part C, and Part E (ATD phase) will be followed by Part B, Part D, and Part F (mTPI phase) of Arm 1, Arm 2, and Arm 3. The starting dose for Arm 4 will be up to, but not exceeding, CCI [redacted] Arm 4 will be based on the mTPI design. The ATD phase will have single-participant cohorts, but may allow up to 3 participants per cohort in the event of simultaneous enrollment. The mTPI phase will have up to 3 to 6 participants per cohort, however based on the occurrence of DLTs, up to 14 participants may enroll per dose level.

The actual sample size for Arm 1, Arm 2, Arm 3, and Arm 4 of this study is dependent on the number of dose levels tested and on the emerging safety data. The following scenario provides one example of the sample size.

In Arm 1 and Arm 2, in the absence of DLTs, and when using dose increments of up to 300% for ATD phase and of 30% to 100% for the mTPI phase, there would be 1 participant per dose level treated at CCI [redacted]; and 3 participants per dose level treated at CCI [redacted]; and 14 participants treated at dose level of CCI [redacted] The total sample size for both Arm 1 and Arm 2 would then be 33 participants.

In Arm 3, in the absence of DLTs, when using dose increments of up to 300% for ATD phase and of 30% to 100% for the mTPI phase, there would be 1 participant per dose level treated at CCI [redacted]; and 3 participants per dose level treated at CCI [redacted] and 14 participants treated at dose level of CCI [redacted] The total sample size would then be 31 for Arm 3.

In Arm 4, in the absence of DLTs for example, there would be 3 participants per dose level treated at CCI [redacted]; 6 participants per dose level treated at CCI [redacted] and 14 participants treated at dose level of CCI [redacted] In this scenario, the total sample size for Arm 4 would be 47 participants.

For dose escalation guidelines and specifications, see Section 5.5 and Section 7.

10.10 Subgroup Analyses

Subgroup analyses of efficacy endpoints will be documented in the sSAP.

10.11 Compliance (Medication Adherence)

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

10.12 Extent of Exposure

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

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12 APPENDICES

12.1 Appendix 1: Abbreviations and Trademarks

Abbreviation	Definition
Abscopal	A phenomenon in the treatment of metastatic cancer where localized treatment of a tumor causes not only a shrinking of the treated tumor, but also a shrinking of tumors outside the scope of the localized treatment.
ADA	Antidrug antibody
ADME	Absorption, Distribution, Metabolism, and Excretion
AE	Adverse event
ALT	Alanine aminotransferase
AMP	Adenosine monophosphate
ANC	Absolute neutrophil count
aPTT	Activated partial thromboplastin time
APaT	All-Participants-as-Treated
ART	Antiretroviral therapy
AST	Aspartate aminotransferase
ATD	Accelerated titration design
AUC	Area under the time-concentration curve
$AUC_{0\ 24hr}$	Area under the time-concentration curve from 0 to 24 hours
β-hCG	Beta-human chorionic gonadotropin
C1D1	Cycle 1 Day 1
CBC	Complete blood count
CBR	Carbonyl reductase
CD	Cluster of differentiation (eg, CD8, CD28)
CDN	Cyclic dinucleotide
cGAMP	Cyclic-dinucleotide 2'-3' cyclic GMP-AMP
cGAS	Cyclic (guanosine monophosphate-adenosine monophosphate) synthase
CI	Confidence interval
C_{max}	Maximum plasma concentration
C_{min}	Minimum plasma concentration
CONSORT	Consolidated Standards of Reporting Trials
CR	Complete response
CrCl	Creatinine clearance
CRF/eCRF	Case report form/electronic case report form
CRS	Cytokine release syndrome
CT	Computed tomography

Abbreviation	Definition
CTCL	Cutaneous T-cell lymphoma
CTCAE	Common Terminology Criteria for Adverse Events
CXCL11	C-X-C motif chemokine 11
DILI	Drug-induced liver injury
DLT	Dose-limiting toxicity
DNA	Deoxynucleic acid
E/CIA	Enzyme or chemiluminescence immunoassay
ECI	Event of clinical interest
ECOG	Eastern Cooperative Oncology Group
EDC	Electronic data capture
EMA	European Medicines Agency
EORTC	European Organisation for Research and Treatment of Cancer
EOT	End of treatment
FAS	Full Analysis Set
FBR	Future Biomedical Research
FDA	U.S. Food and Drug Administration
FDAA	Food and Drug Administration Amendments Act
FDG	Fluorodeoxyglucose
FIH	First in human
GCP	Good clinical practice
GGT	Gamma glutamyl transferase
GI	Gastrointestinal
GLP	Good Laboratory Practice
GMP	Guanosine monophosphate
GRI	Growth rate inhibition
GVHD	Graft-versus-host disease
HBsAg/HBV	Hepatitis B surface antigen/Hepatitis B virus
HBV	Hepatitis B virus
HCV	Hepatitis C virus
Hep C Ab	Hepatitis C antibody
HIV	Human immunodeficiency virus
HNSCC	Head and neck squamous cell carcinoma
IB	Investigator’s Brochure
ICF	Informed consent form

Abbreviation	Definition
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IFN	Interferon
IFNα	Interferon alpha
IHC	Immunohistochemistry
IL-6	Interleukin-6
INR	International normalized ratio
IP-10	Interferon gamma-induced protein 10
irAE	Immune-related adverse event
IRB/IEC	Institutional Review Board/Institutional Ethics Committee
IRF3	Interferon regulatory transcription factor-3
irRECIST	Immune-related Response Evaluation Criteria In Solid Tumors
ISCL	International Society for Cutaneous Lymphomas
IT	Intratumoral
itRECIST	Intratumoral Immunotherapy Response Evaluation Criteria In Solid Tumors
IV	Intravenous
IVD	In vitro diagnostic
IVRS/IWRS	Integrated web response system
IWG	International Working Group
LDH	Lactate dehydrogenase
LLOQ	Less than the limit of detection
MAD	Maximum administered dose
MCP-2	Monocyte chemoattractant protein-2
MIP-1α	Macrophage inflammatory protein-1 alpha
MOA	Mechanism of action
mRNA	Messenger ribonucleic acid
MRI	Magnetic resonance imaging
MSI	Microsatellite instability
mSWAT	modified Severity Weighted Assessment Tool
MTD	Maximum tolerated dose
mTPI	Modified toxicity probability interval
N/A	Not applicable
NCI	National Cancer Institute
NF-κB	Nuclear factor-κB

Abbreviation	Definition
NOAEL	No observed adverse effect level
NSAIDS	Nonsteroidal anti-inflammatory drugs
NSCLC	Non small cell lung cancer
NT-I	Nontarget injected
NT-NI	Nontarget noninjected
O_2	Oxygen
ORR	Objective response rate
OS	Overall survival
OTC	Over-the-counter
PD	Progressive disease
PD-1	Programmed cell death-1
PD-L1	Programmed cell death-1 ligand 1
PD-L2	Programmed cell death-1 ligand 2
PET	Positron emission tomography
PFS	Progression-free survival
PK	Pharmacokinetic
PO	Per os (by mouth)
PP	Per Protocol
PR	Partial response
PT	Prothrombin time
Q1W	Once a week
Q3W	Every three weeks
RECIST	Response Evaluation Criteria In Solid Tumors
RNA	Ribonucleic acid
RP2D	Recommended Phase 2 Dose
SAE	Serious adverse events
SC	Subcutaneous
SNP	Single nucleotide polymorphism
SoA	Schedule of Activities
SOD	Sum of diameters
SPD	Sum of the products of the greatest diameters
sSAP	Supplemental Statistical Analysis Plan
STING	Stimulator of Interferon Genes
SUSAR	Suspected unexpected serious adverse reactions
T1DM	Type 1 diabetes mellitus

Abbreviation	Definition
TBK1	Tumor necrosis factor receptor-associated factors (TRAF)-associated nuclear factor (NF)-κB activator
TNF-α	Tumor necrosis factor-alpha
T-I	Target injected
T-NI	Target noninjected
TS-1	tegafur/gimeracil/oteracil
TSH	Thyroid stimulating hormone
UFT	Ftorafur or tegafur/uracil
ULN	Upper limit of normal
VS	Vital signs
WOCBP	Women of childbearing potential
WT	Wild-type

12.2 Appendix 2: Clinical Laboratory Tests

- The tests detailed in Table 23 will be performed by the local laboratory. Laboratory samples, which cannot be processed locally, may be sent to the central laboratory.

- Laboratory safety tests for screening should be performed within 7 days prior to first dose of study medication. Starting with Cycle 1 Day 1, predose laboratory tests can be performed up to 72 hours prior to dosing. Results must be reviewed by the investigator or qualified designee and found to be acceptable prior to dosing.

- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 6 of the protocol.

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

Table 23 Protocol-required Safety Laboratory Assessments

Hematology	Chemistry	Urinalysis	Other
Hematocrit	Albumin	Blood	Follicle-stimulating hormone (FSH)[a]
Hemoglobin	Alkaline phosphatase	Glucose	Serum β-human chorionic gonadotropin (β-hCG)[b]
Platelet count	Alanine aminotransferase (ALT)	Protein	Hepatitis
WBC (total and differential)[c]	Aspartate aminotransferase (AST)	Specific gravity	Total triiodothyronine (T3) or Free T3 (FT3)
RBC	Carbon Dioxide or Bicarbonate	Microscopic examination, if abnormal results are noted	Total thyroxine (T4) or Free T4 (FT4)
PT or INR	Calcium	Urine pregnancy test[b]	Thyroid Stimulating Hormone (TSH)
aPTT or PTT	Chloride		
	Creatinine[d]		
	Gamma glutamyl transpeptidase (GGT)		
	Glucose		
	Phosphorus		
	Potassium		
	Sodium		
	Total Bilirubin		
	Direct Bilirubin, if total bilirubin is elevated above the upper limit of normal		
	Total protein		
	Blood Urea Nitrogen[e]		
	Lactic dehydrogenase		
	Uric acid		
	Lipase		
	Amylase		

[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 hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, confirmation with two FSH measurements in the postmenopausal range is required.
[b] Perform on women of childbearing potential only. If urine pregnancy results cannot be confirmed as negative, a serum pregnancy test will be required.
[c] Absolute or % acceptable per institutional standard
[d] For participants with a baseline calculated creatinine clearance that is below the normal institutional laboratory range, a baseline measured creatinine clearance should be performed.
[e] Blood Urea Nitrogen is preferred; if not available urea may be tested

Investigators must document their review of each laboratory safety report.

12.3 Appendix 3: Study Governance Considerations

Code of Conduct for Clinical Trials

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

Code of Conduct for Interventional Clinical Trials

I. Introduction

A. Purpose

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

B. Scope

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

II. Scientific Issues

A. Trial Conduct

1. Trial Design

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

The design (i.e., participant population, duration, statistical power) must be adequate to address the specific purpose of the trial and shall respect the data protection rights of all participants, trial site staff and, where applicable, third parties. All trial protocols are and will be assessed for the need and capability to enroll underrepresented groups. Participants must meet protocol entry criteria to be enrolled in the trial.

2. Site Selection

MSD's clinical trials are conducted globally in many different countries and in diverse populations, including people of varying age, race, ethnicity, gender, and accounting for other potential disease related factors. MSD selects investigative sites based on medical expertise, access to appropriate participants, adequacy of facilities and staff, previous performance in clinical trials, as well as budgetary considerations. Prior to trial initiation, sites are evaluated by MSD personnel (or individuals acting on behalf of MSD) to assess the ability to successfully conduct the trial.

Where appropriate, and in accordance with regulatory authority guidance, MSD will make concerted efforts to raise awareness of clinical trial opportunities in various communities. MSD will seek to engage underrepresented groups and those disproportionately impacted by the disease under study. MSD will support

clinical trial investigators to enroll underrepresented groups and expand access to those who will ultimately use the products under investigation.

3. Site Monitoring/Scientific Integrity

Investigative trial sites are monitored to assess compliance with the trial protocol and Good Clinical Practice (GCP). MSD reviews clinical data for accuracy, completeness, and consistency. Data are verified versus source documentation according to standard operating procedures. Per MSD policies and procedures, if potential fraud, scientific/research misconduct, privacy incidents/breaches or Clinical Trial related Significant Quality Issues are reported, such matters are investigated. When necessary, appropriate corrective and/or preventative actions are defined and regulatory authorities and/or ethics review committees are notified.

B. Publication and Authorship

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

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

III. Participant Protection

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

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

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

B. Safety

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

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

C. Confidentiality

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

D. Genomic Research

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

IV. Financial Considerations

A. Payments to Investigators

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

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

B. Clinical Research Funding

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

C. Funding for Travel and Other Requests

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

V. Investigator Commitment

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

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.

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 which 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.

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 institutional review board, ethics review committee (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 trial 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.

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 trial documents in order to verify worksheet/case report form data. By signing the consent form, the participant agrees to this process. If trial documents will be photocopied during the process of verifying worksheet/case report form 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 trial in accordance with all applicable privacy laws, rules and regulations.

Confidentiality of IRB/IEC Information

The Sponsor is required to record the name and address of each IRB/IEC that reviews and approves this trial. 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.

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.

Compliance with Trial 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 trial is solely responsible for determining whether the trial 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 trial, 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 trials for their disease conditions and pursue participation by calling a central contact number for further information on appropriate trial locations and trial 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 trial or its results to those registries.

Compliance with Law, Audit and Debarment

By signing this protocol, the investigator agrees to conduct the trial in an efficient and diligent manner and in conformance with this protocol; generally accepted standards of Good Clinical Practice (eg, International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use of Technical Requirements for Registration of Pharmaceuticals for Human Use Good Clinical Practice: Consolidated Guideline and other generally accepted standards of good clinical practice); and all applicable federal, state and local laws, rules and regulations relating to the conduct of the clinical trial.

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

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

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

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

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.

Trial documentation will be promptly and fully disclosed to the Sponsor by the investigator upon request and also shall be made available at the trial 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 regulatory authority as a result of an audit or inspection to cure deficiencies in the trial documentation and worksheets/case report forms.

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

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

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

Source Documents

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

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

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 trial site, the Sponsor will promptly notify that trial site's IRB/IEC.

12.4 Appendix 4: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

Definition of AE

AE Definition
• An AE is any untoward medical occurrence in a patient or clinical study participant, temporally associated with the use of study treatment, whether or not considered related to the study treatment. • 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 treatment. • NOTE: for purposes of AE definition, study treatment (also referred to as Sponsor's product) includes any pharmaceutical product, biological product, vaccine, device, diagnostic agent or protocol specified procedure whether investigational (including placebo or active comparator product) or marketed, manufactured by, licensed by, provided by or distributed by the sponsor for human use in this study.

Events Meeting the AE Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, or are considered clinically significant in the medical and scientific judgment of the investigator. • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. • New conditions detected or diagnosed after study treatment 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 treatment or a concomitant medication. • For all reports of overdose (whether accidental or intentional) with an associated adverse event, 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. • Any new cancer (that is not a condition of the study). Note: Progression of the cancer under study is not a reportable event. Refer to Section 9.3.5 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 9.3.5 for protocol specific exceptions

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

A 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 a serious adverse event. A pre-existing condition is a clinical condition that is diagnosed prior to the use of an MSD product and is documented in the patient'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) which 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 one 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 department or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

Additional Events reported in the same manner as SAE

Additional Events which require reporting in the same manner as SAE

• In addition to the above criteria, adverse events meeting either of the below criteria, although not serious per ICH definition, are reportable to the Sponsor in the same timeframe as SAEs to meet certain local requirements. Therefore, these events are considered serious by the Sponsor for collection purposes.
  ◦ Is a new cancer (that is not a condition of the study);
  ◦ Is associated with an overdose.

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 Adverse Event case report forms/worksheets at each examination. • It is **not** acceptable for the investigator to send photocopies of the participant's medical records to the Sponsor in lieu of completion of the AE CRF page. • There may be instances when copies of medical records for certain cases are requested by the Sponsor. In this case, all participant identifiers, with the exception of the participant number, will be blinded on the copies of the medical records before submission to the Sponsor. • The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.
Assessment of Intensity

• An event is defined as 'serious' when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.
• The investigator will make an assessment of intensity for each AE and SAE (and other reportable safety event) according to the NCI Common Terminology for Adverse Events (CTCAE), version 4.0. Any adverse event which changes CTCAE grade over the course of a given episode will have each change of grade recorded on the adverse event case report forms/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 adverse event?
  - The determination of the likelihood that the Sponsor's product caused the adverse event 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 adverse event 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 adverse event:
    - **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 trials 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 trial is a single-dose drug trial); or (4) Sponsor's product(s) is/are only used one time.)

- **Rechallenge:** Was the participant re-exposed to the Sponsor's product in this trial?
  - 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 trial is a single-dose drug trial); or (3) Sponsor's product(s) is/are used only one time.)

NOTE: IF A RECHALLENGE IS PLANNED FOR AN ADVERSE EVENT WHICH WAS SERIOUS AND WHICH 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 INSTITUTIONAL REVIEW BOARD/INDEPENDENT ETHICS COMMITTEE.

- **Consistency with Study treatment 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 one 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 adverse event causality to the combination regimen or to a single agent of the combination. In general, causality attribution should be assigned to the combination regimen (i.e., 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 adverse event 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.

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

AE, SAE, and Other Reportable Safety Event Reporting to Sponsor via Electronic Data Collection Tool

- The primary mechanism for reporting to the Sponsor will be the electronic data collection (EDC) tool.
  - Electronic reporting procedures can be found in the EDC data entry guidelines (or equivalent).
  - If the electronic system is unavailable for more than 24 hours, then the site will use the paper AE Reporting form.
    - Reference Section 9.3.1 Time Period and Frequency for Collecting AE and SAE and Other Reportable Safety Event Information 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 electronic data collection 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 electronic data collection 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 Trial File Binder (or equivalent).

SAE Reporting to the Sponsor via Paper CRF

- If the electronic data collection 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 Trial File Binder (or equivalent).

12.5 Appendix 5: Contraceptive Guidance and Pregnancy Testing

Woman of Childbearing Potential (WOCBP)

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

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

Women in the following categories are not considered WOCBP:

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

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

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

Contraception Requirements

Male Participants:

Male participants are eligible to participate if they agree to the following during the intervention period with MK-2118 and for at least 120 days after the last dose of MK-2118:

- Refrain from donating sperm

PLUS either:

- Be abstinent from heterosexual intercourse as their preferred and usual lifestyle (abstinent on a long term and persistent basis) and agree to remain abstinent
- Must agree to use contraception unless confirmed to be azoospermic (vasectomized or secondary to medical cause) 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:

Female participants of childbearing potential are eligible to participate if they agree to use a highly effective method of contraception consistently and correctly as described in Table 24 during the protocol-defined time frame in Section 6.1.

Table 24 Highly Effective Contraception Methods

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

Pregnancy Testing

WOCBP should only be included after a negative highly sensitive urine or serum pregnancy test and in accordance with local requirements. When applicable, this test should be repeated within 24 hours before the first dose.

Following initiation of treatment additional pregnancy testing will be performed per the SoA during the treatment period, at 30 days after the last dose of study treatment, and/or as required locally.

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

12.6 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

The specimens consented and/or collected in this trial as outlined in Section 9.8 Future Biomedical Research Sample Collection9.8 Future Biomedical Research Sample Collection 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

a. Participants for Enrollment

All participants enrolled in the clinical trial will be considered for enrollment in Future Biomedical Research.

b. Informed Consent

Informed consent for specimens (i.e., DNA, RNA, protein, etc.) will be obtained during screening for protocol enrollment from all participants or legal guardians, at a trial 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 trial flow chart. If delayed, present consent at next possible Participant Visit. Consent forms signed by the participant will be kept at the clinical trial site under secure storage for regulatory reasons.

A template of each trial 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 trial flow chart. 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 trial purposes.

4. Confidential Participant Information for Future Biomedical Research

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

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

At the clinical trial 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 trial site. No personal identifiers will appear on the specimen tube.

5. Biorepository Specimen Usage

Specimens obtained for the Sponsor will be used for analyses using good scientific practices. Analyses utilizing the Future Biomedical Research specimens may be performed by the Sponsor, or an additional third party (eg, a university investigator) designated by the Sponsor. The investigator conducting the analysis will follow the Sponsor's privacy and confidentiality requirements. Any contracted third-party analyses will conform to the specific scope of analysis outlined. 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

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 trial. If medical records for the main trial 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 trial data and results. No new analyses would be generated after the request is received.

In the event that the medical records for the main trial are no longer available (eg, if the investigator is no longer required by regulatory authorities to retain the main trial 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

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 trial 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 trial, the trial 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

Databases containing specimen information and test results are accessible only to the authorized Sponsor representatives and the designated trial 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

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

Every effort will be made to recruit all participants diagnosed and treated on Sponsor clinical trials for Future Biomedical Research.

11. Risks Versus Benefits of Future Biomedical Research

For future biomedical research, risks to the participant have been minimized.

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 e-mailed directly to clinical.specimen.management@MSD.com.

13. References

1. National Cancer Institute: http://www.cancer.gov/dictionary/?searchTxt biomarker

2. International Conference on Harmonisation: DEFINITIONS FOR GENOMIC BIOMARKERS, PHARMACOGENOMICS, PHARMACOGENETICS, GENOMIC DATA AND SAMPLE CODING CATEGORIES - E15; http://www.ich.org/LOB/media/MEDIA3383.pdf

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

12.7 Appendix 7: Prioritization of IT Lesion Injection

The selection and prioritization of lesions for IT injection is a complex set of decisions made by the clinician at each treatment visit. Ultimately, lesion prioritization is based on clinical judgment and patient tolerance; however, a set of guiding principles can be described.

Patient Safety

The first priority is patient safety. Lesions are to be selected that minimize the potential for procedural complications and maximize patient comfort. One important safety factor is vascularity within a lesion, and adjacent to a lesion. Injection into IT vessels should be avoided to minimize systemic administration. Vessels adjacent to a tumor should not be traversed to minimize bleeding risk, and areas of vascular encasement should be avoided in high risk locations (e.g. inferior vena cava encasement for liver lesions, or carotid artery encasement for head and neck tumors).

Lesion Accessibility

The next prioritization factor is accessibility. Preference should be given to cutaneous lesions which are visible, and superficial subcutaneous lesions and lymph nodes that are easily palpable. Deeper lesions, including nonpalpable lymph nodes and nonpalpable extranodal lesions in viscera or body cavities, may be more difficult to access. These deeper lesions typically require imaging guidance, which increases procedural complexity, and must be balanced against the clinical benefit that might result from their treatment, such as symptomatic relief.

Lesion Size, Tumor Necrosis, Amount of Viable Tumor Tissue, and Aggressive Tumors

At the initiation of therapy, the next factors that should guide lesion prioritization are the size of the lesion, and the amount of viable tumor tissue present in the lesion. Other factors being equal, larger lesions are preferred. Larger lesions may have a greater amount of tumor tissue, and are generally older in age than smaller lesions, and may have a greater breadth of tumor-specific antigens to stimulate a broader repertoire of antigen-specific T cells. Radiographically visible necrosis should be avoided. Direct IT immunotherapy into viable portions of a lesion. A larger lesion that is predominantly necrotic may be deprioritized compared to a smaller lesion with little or no radiographic necrosis. Another feature that should be considered is radiographic evidence of aggressiveness, such as local invasiveness. Aggressive lesions should be given higher priority.

New and/or Progressing Lesions

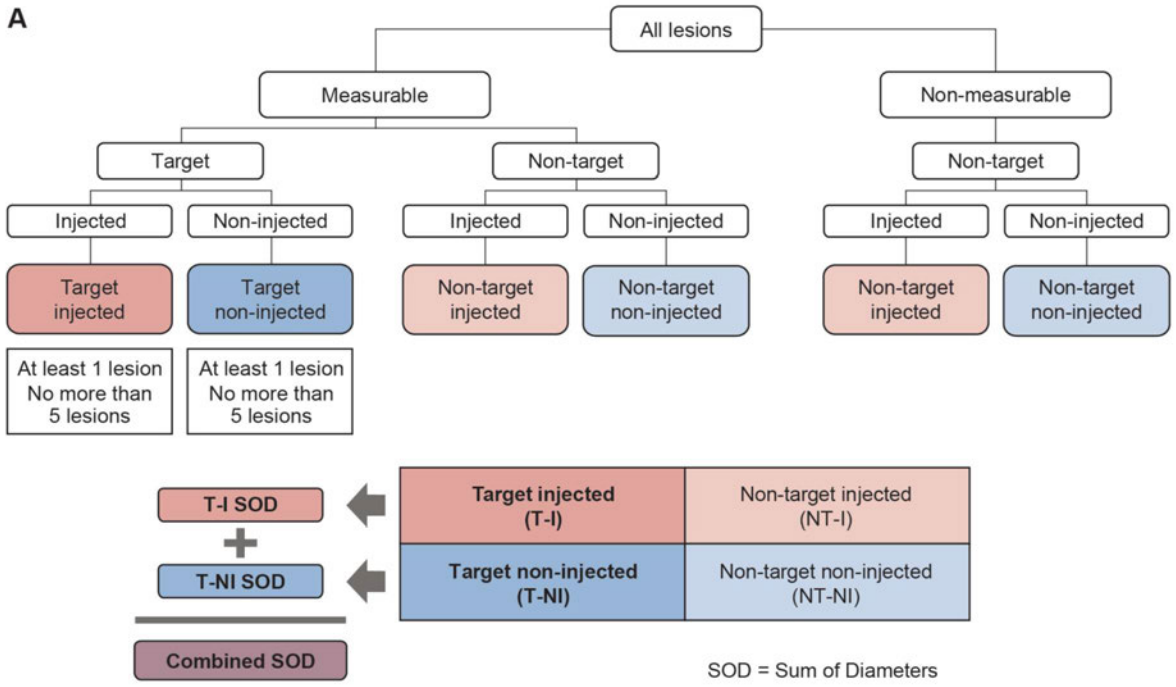
During therapy, lesions that are new or progressing should be given higher priority than lesions selected on the basis of size or on the basis of the imaging features described above. Safety and accessibility are of course still the primary considerations. New and progressing lesions contain actively dividing cells, which may be more responsive to injection with an IT

immunotherapeutic. Also, new or progressing lesions may contain newly mutated tumor cells, allowing for a broader spectrum of antigen-specific T cells in response to injection with an IT immunotherapeutic, and a subsequent improved systemic antitumor response. New lesions may contain novel tumor antigens compared to previously injected lesions.

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

12.8 Appendix 8: itRECIST Supplementary Figures

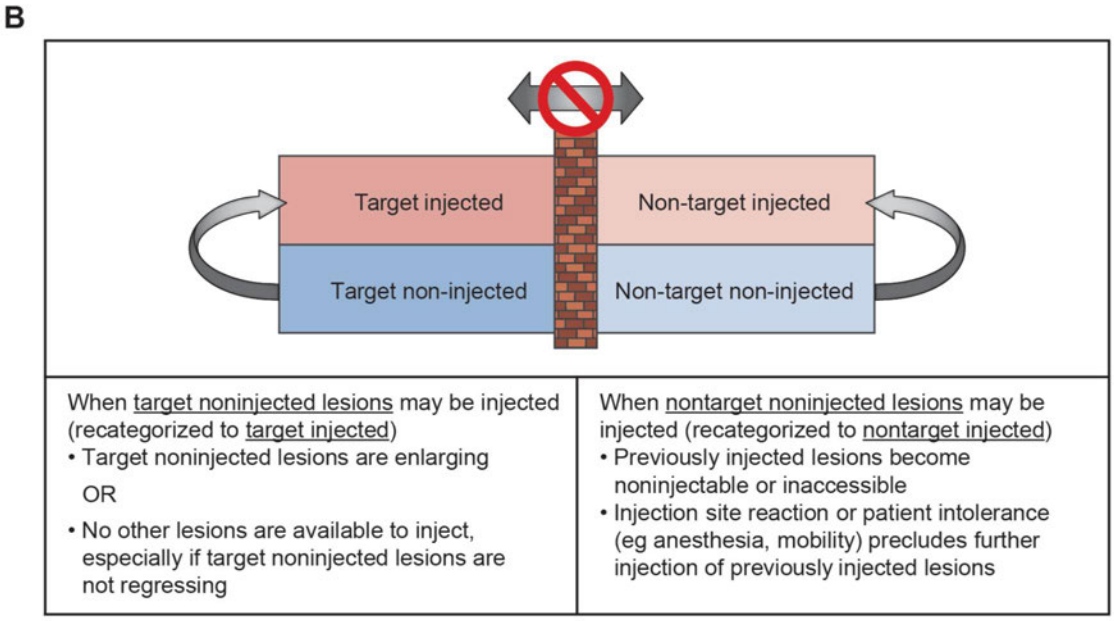
Figure 3 Algorithm for Classification of Lesions at Baseline



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 five lesions should be classified as target injected, and between one and five 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).

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

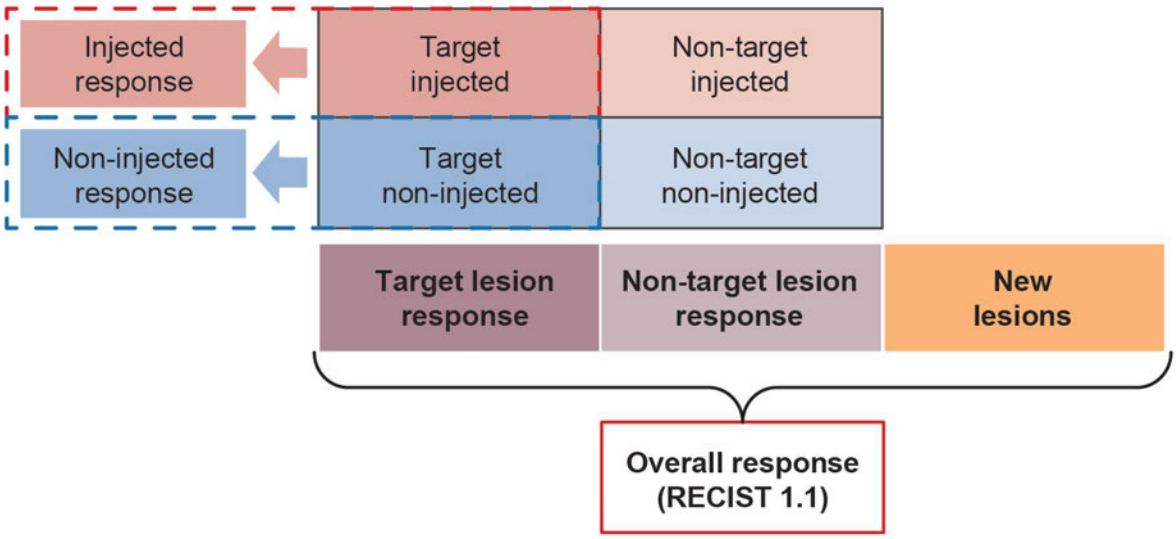
Figure 4 Reclassification of Noninjected Lesions



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 patient factor such as injection site reaction or patient 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.

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

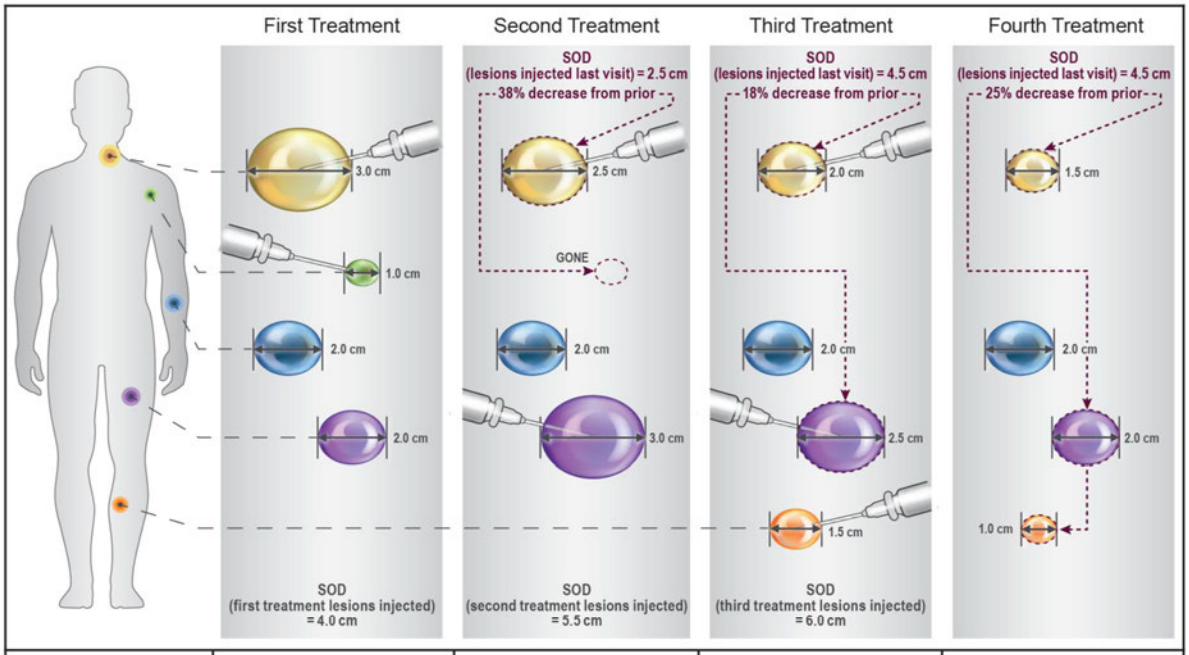
Figure 5 Overall Response Assessment Until Disease Progression



Overall response until disease progression per RECIST 1.1. The injected response at each visit is based on only the changes in the sum of diameters (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. RECIST 1.1, Response Evaluation Criteria in Solid Tumors, version 1.1; SOD, sum of diameters.

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

Figure 6 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.

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 patient 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.

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