Official Protocol Title:	Phase 1 Open-label, Multicenter Study of MK-1454 Administered by Intratumoral Injection as Monotherapy and in Combination with Pembrolizumab for Patients with Advanced/Metastatic Solid Tumors or Lymphomas
NCT number:	
Document Date:	

THIS PROTOCOL AMENDMENT AND ALL OF THE INFORMATION RELATING TO IT ARE CONFIDENTIAL AND PROPRIETARY PROPERTY OF MERCK SHARP & DOHME CORP., A SUBSIDIARY OF MERCK & CO., INC., WHITEHOUSE STATION, NJ, U.S.A.

SPONSOR:
Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc.
(hereafter referred to as the Sponsor or Merck)
One Merck Drive
P.O. Box 100
Whitehouse Station, New Jersey, 08889-0100, U.S.A.

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

TITLE:

Phase 1 Open-label, Multicenter Study of MK-1454 Administered by Intratumoral Injection as Monotherapy and in Combination with Pembrolizumab for Patients with Advanced/Metastatic Solid Tumors or Lymphomas

IND NUMBER: 129450
EudraCT NUMBER: 2016-003160-40

NCT: NCT03010176

TABLE OF CONTENTS

DOCUMENT HISTORY **12**

SUMMARY OF CHANGES **14**

1.0 TRIAL SUMMARY **18**

2.0 TRIAL DESIGN **20**

2.1 Trial Design **20**

2.1.1 Part I – Dose Escalation and Confirmation Phase 20

2.1.2 Part II –Expansion Phase 23

2.2 Trial Diagram **24**

2.2.1 Trial Diagram for Part I - Dose Escalation and Confirmation 24

2.2.2 Trial Diagram for Part II – Expansion Cohorts 26

3.0 OBJECTIVE(S) & HYPOTHESIS(ES) **26**

3.1 Primary Objective(s) & Hypothesis(es) **26**

3.2 Secondary Objective(s) & Hypothesis(es) **27**

3.3 Exploratory Objectives **27**

4.0 BACKGROUND & RATIONALE **28**

4.1 Background **28**

4.1.1 Pharmaceutical and Therapeutic Background 30

4.1.1.1 MK-1454 Background 30

4.1.1.2 Pembrolizumab Background 30

4.2 Rationale **31**

4.2.1 Rationale for the Trial and Selected Subject Population 31

4.2.1.1 Rationale for Part I - Dose Escalation and Confirmation 31

4.2.1.2 Rationale for Part II - Expansion Cohorts 32

4.2.1.2.1 Microsatellite Instability Testing 33

4.2.2 Rationale for Dose Selection/Regimen 34

4.2.2.1 Starting Dose for This Trial 34

4.2.2.2 Maximum Dose/Exposure for This Trial 35

4.2.2.3 Rationale for Dose Interval and Trial Design 35

4.2.2.4 Rationale for Visceral Intratumoral Injection 36

4.2.2.5 Rationale for Dose of MK-1454 Expansion Cohorts A and B (Part II)..... 36
4.2.2.6 Rationale for Dose Schedule Expansion Cohorts A and B (Part II)..... 37
4.2.3 Rationale for Endpoints..... 37
4.2.3.1 Efficacy Endpoints..... 37
4.2.3.1.1 Immune-related RECIST (irRECIST)..... 38
4.2.3.1.2 IWG Revised Response Criteria for Malignant Lymphomas..... 38
4.2.3.1.3 Response Assessment for CTCL..... 39
4.2.3.2 Safety Endpoints..... 39
4.2.3.3 Pharmacokinetic Endpoints..... 39
4.2.3.4 Pharmacodynamic Endpoints..... 39
4.2.3.5 Planned Exploratory Biomarker Research..... 40
4.2.3.5.1 Planned Genetic Analysis..... 40
4.2.3.6 Future Biomedical Research..... 41
4.3 Benefit/Risk..... 42

5.0 METHODOLOGY..... 42
5.1 Entry Criteria..... 42
5.1.1 Diagnosis/Condition for Entry into the Trial..... 42
5.1.2 Subject Inclusion Criteria for Part I - Dose Escalation and Confirmation..... 42
5.1.2.1 Subject Inclusion Criteria for Arms 1 and 2..... 42
5.1.2.2 Subject Inclusion Criteria for Crossover Into Arm 2..... 45
5.1.2.3 Subject Inclusion Criteria for Arm 3..... 48
5.1.3 Subject Inclusion Criteria for Part II - Expansion Cohorts..... 50
5.1.4 Subject Exclusion Criteria for Part I - Dose Escalation and Confirmation..... 54
5.1.4.1 Exclusion Criteria for Arms 1, 2, and 3..... 54
5.1.4.2 Exclusion Criteria for Crossover Into Arm 2..... 56
5.1.5 Exclusion Criteria for Part II - Expansion Cohorts..... 57
5.2 Trial Treatment(s)..... 60
5.2.1 Dose Selection/Modification..... 63
5.2.1.1 Dose Selection (Preparation)..... 63
5.2.1.1.1 Dose Selection in Part I - Dose Escalation and Confirmation (Arm 1, Arm 2, and Arm 3)..... 63
5.2.1.1.2 Dose Selection in Part II - Expansion Cohorts (Cohorts A and B)..... 64

5.2.1.2 Accelerated Titration Design in Arms 1, 2, and 3 65
5.2.1.3 Dose Escalation and Confirmation During Modified Toxicity Probability Interval Design 66
5.2.2 Definition of Dose-Limiting Toxicity 68
5.2.3 Dose Modification Due to Adverse Events 69
5.2.3.1 Dose Modification for MK-1454 Drug-related AEs in Part I - Arm 1, Arm 2, and Arm 3 70
5.2.3.2 Dose Modification for MK-1454 in Part II - Expansion Cohorts 77
5.2.3.3 Immune-Related Events and Dose Modification (Withhold, Treat, Discontinue) 78
5.2.3.4 Treatment for Cytokine Release Syndrome 84
5.2.4 Intrasubject Dose Escalation 85
5.2.5 Timing of Dose Administration 86
5.2.5.1 Timing of MK-1454 Dose Administration in Part I - Dose Escalation and Confirmation 86
5.2.5.2 Timing of MK-1454 Dose Administration in Part II - Expansion Cohorts 86
5.2.5.3 Timing of Pembrolizumab Administration 86
5.2.6 Trial Blinding 87
5.2.7 Replacement of Subjects During the DLT Evaluation Period 87
5.3 Randomization or Treatment Allocation 87
5.4 Stratification 87
5.5 Concomitant Medications/Vaccinations (Allowed and Prohibited) 87
5.6 Rescue Medications & Supportive Care 89
5.6.1 Supportive Care Guidelines 89
5.7 Diet/Activity/Other Considerations 89
5.7.1 Diet 89
5.7.2 Contraception 89
5.7.2.1 Definitions 89
5.7.2.2 Acceptable Contraception Methods 90
5.7.3 Use in Pregnancy 92
5.7.4 Use in Nursing Women 92
5.8 Subject Withdrawal/Discontinuation Criteria 92
5.8.1 Discontinuation of Treatment 92

5.8.2 Withdrawal From the Trial 93
5.8.2.1 Participants Who Withdraw Consent During the Study 93
5.9 Subject Replacement Strategy 94
5.10 Beginning and End of the Trial 94
5.11 Clinical Criteria for Early Trial Termination 94
6.0 SCHEDULE OF ACTIVITIES 95
6.1 Schedule of Activities for Part I - Dose Escalation and Confirmation (Arms 1, 2, and 3) 95
6.1.1 Schedule of Activities for Initial Screening for Arms 1 Through 3 and for Crossover Into Arm 2 95
6.1.2 Schedule of Activities for the Treatment Period, Intratumoral Administration for Arm 1 (Monotherapy) and Arm 2 (Combination Therapy – Including Crossover to Arm 2) 98
6.1.3 Schedule of Activities for the Treatment Period of Arm 3 (Visceral IT Administration) 103
6.1.4 Discontinuation / End of Treatment and Posttreatment Follow-up for Arms 1 to 3 107
6.2 Schedule of Activities for Part II- Expansion Cohorts 109
6.2.1 Schedule of Activities for Part II - Expansion Cohorts Screening and Treatment Period, MK-1454 Intratumoral Administration With Pembrolizumab Combination Therapy 109
6.2.2 Discontinuation / End of Treatment and Posttreatment Follow-up for Part II – Expansion Cohorts 115
7.0 TRIAL PROCEDURES 117
7.1 Trial Procedures 117
7.1.1 Administrative Procedures 117
7.1.1.1 Informed Consent 117
7.1.1.1.1 General Informed Consent 117
7.1.1.1.2 Consent and Collection of Specimens for Future Biomedical Research 118
7.1.1.2 Inclusion/Exclusion Criteria 118
7.1.1.3 Subject Identification Card 118
7.1.1.4 Medical History 118
7.1.1.5 Disease Details 118
7.1.1.6 Prior Oncology Treatment History 118

7.1.1.7 Prior and Concomitant Medications Review 119
7.1.1.7.1 Prior Medications 119
7.1.1.7.2 Concomitant Medications 119
7.1.1.8 Assignment of Screening Number 119
7.1.1.9 Assignment of Treatment/Randomization Number 119
7.1.1.10 Trial Compliance (Medication/Diet/Activity/Other) 120
7.1.1.11 Trial Communication Plan Summary 120
7.1.2 Clinical Procedures/Assessments 120
7.1.2.1 Adverse Event Monitoring 120
7.1.2.2 Full Physical Examination 121
7.1.2.3 Vital Signs and Weight 121
7.1.2.4 Electrocardiogram 121
7.1.2.5 Eastern Cooperative Oncology Group Performance Status 121
7.1.2.6 Tumor Imaging and Medical Photography 122
7.1.2.7 Response Assessment 122
7.1.2.7.1 Immune-related RECIST 122
7.1.2.7.2 Intratumoral Immunotherapy RECIST (itRECIST) 124
7.1.2.7.3 IWG Revised Response Criteria for Malignant Lymphomas 124
7.1.2.7.4 Response Assessment Criteria for CTCL 126
7.1.3 Laboratory Procedures/Assessments 132
7.1.3.1 Laboratory Safety Evaluations (Hematology, Chemistry, and Urinalysis) 132
7.1.3.2 Pharmacokinetic/Pharmacodynamic Evaluations 133
7.1.3.2.1 Blood Collection for MK-1454 and Pembrolizumab PK 133
7.1.3.2.2 Blood Collection for Anti-Pembrolizumab Antibodies (ADA) 133
7.1.3.2.3 Blood for Pharmacodynamic Markers 133
7.1.3.2.4 Tumor Biopsy 133
7.1.3.3 Planned Genetic Analysis Sample Collection 135
7.1.3.4 Future Biomedical Research Samples 135
7.1.4 Other Procedures 135
7.1.4.1 Withdrawal/Discontinuation 135
7.1.4.1.1 Withdrawal From Future Biomedical Research 136
7.1.4.1.2 Lost to Follow-up 136

7.1.4.2 Subject Blinding/Unblinding 136
7.1.4.3 Domiciling 137
7.1.4.4 Calibration of Equipment 137
7.1.5 Visit Requirements 137
7.1.5.1 Screening 137
7.1.5.2 Treatment Period 137
7.1.5.3 Treatment Period Beyond Disease Progression 138
7.1.5.4 Discontinued Subjects Continuing to be Monitored in the Trial 138
7.1.5.5 30-Day Safety Follow-up Visit 138
7.1.5.6 Survival Status Monitoring 138
7.2 Assessing and Recording Adverse Events 139
7.2.1 Definition of an Overdose for This Protocol and Reporting of Overdose to the Sponsor 140
7.2.2 Reporting of Pregnancy and Lactation to the Sponsor 140
7.2.3 Immediate Reporting of Adverse Events to the Sponsor 141
7.2.3.1 Serious Adverse Events 141
7.2.3.2 Events of Clinical Interest 142
7.2.3.3 Protocol-Specific Exceptions to Serious Adverse Event Reporting 142
7.2.4 Evaluating Adverse Events 143
7.2.5 Sponsor Responsibility for Reporting Adverse EventsSAEs 146
8.0 STATISTICAL ANALYSIS PLAN 146
8.1 Statistical Analysis Plan Summary 146
8.2 Responsibility for Analyses/In-house Blinding 148
8.3 Hypotheses/Estimation 148
8.4 Analysis Endpoints 148
8.4.1 Efficacy/Pharmacokinetic Endpoints 148
8.4.2 Safety Endpoints 148
8.5 Analysis Populations 148
8.5.1 Safety Analysis Population 148
8.5.2 Pharmacokinetic Analysis and Target Engagement Populations 149
8.5.3 Efficacy Analysis Populations 149
8.6 Statistical Methods 149

8.6.1 Statistical Methods for Efficacy Analyses 149
8.6.2 Statistical Methods for Safety Analyses 149
8.6.3 Summaries of Baseline Characteristics, Demographics, and Other Analyses .. 150
8.6.3.1 Demographic and Baseline Characteristics 150
8.6.3.2 Pharmacokinetics and Pharmacodynamics Modeling Analysis 150
8.7 Interim Analyses 150
8.8 Multiplicity 150
8.9 Sample Size and Power Calculations 151
8.9.1 Part I Sample Size 151
8.9.2 Part II Sample Size 151
8.10 Subgroup Analyses and Effect of Baseline Factors 152
8.11 Compliance (Medication Adherence) 152
8.12 Extent of Exposure 152
9.0 LABELING, PACKAGING, STORAGE AND RETURN OF CLINICAL SUPPLIES 153
9.1 Investigational Product 153
9.2 Packaging and Labeling Information 153
9.3 Clinical Supplies Disclosure 154
9.4 Storage and Handling Requirements 154
9.5 Discard/Destruction/Returns and Reconciliation 154
9.6 Standard Policies 154
10.0 ADMINISTRATIVE AND REGULATORY DETAILS 154
10.1 Confidentiality 154
10.1.1 Confidentiality of Data 154
10.1.2 Confidentiality of Subject Records 155
10.1.3 Confidentiality of Investigator Information 155
10.1.4 Confidentiality of IRB/IEC Information 155
10.2 Compliance With Financial Disclosure Requirements 155
10.3 Compliance With Law, Audit and Debarment 156
10.4 Compliance With Trial Registration and Results Posting Requirements 158
10.5 Quality Management System 158
10.6 Data Management 158

10.7 Publications 158

11.0 LIST OF REFERENCES 160

12.0 APPENDICES 164

12.1 Merck Code of Conduct for Clinical Trials 164

12.2 Collection and Management of Specimens for Future Biomedical Research 166

12.3 Prioritization of Intratumoral Lesion Injection 170

12.4 itRECIST Supplementary Figures 172

12.5 Country-specific Requirements 177

12.6 List of Abbreviations and Definitions 180

13.0 SIGNATURES 185

13.1 Sponsor's Representative 185

13.2 Investigator 185

LIST OF TABLES

Table 1 Adequate Organ Function Laboratory Values 43
Table 2 Anti-PD-1/PD-L1 Antibody Refractory Definition 52
Table 3 Trial Treatment for MK-1454 IT Monotherapy (Arm 1) 60
Table 4 Trial Treatment for MK-1454 IT in Combination with Pembrolizumab (Arm 2) 61
Table 5 Trial Treatment for MK-1454 Visceral IT in Combination with Pembrolizumab (Arm 3) 62
Table 6 Determination of MK-1454 Injection Volume for Intratumoral Injection of Cutaneous Lesions Based on Lesion Size (Part I - Arm 1 and Arm 2) 64
Table 7 Determination of MK-1454 Injection Volume for Intratumoral Injection into Subcutaneous Lesions Based on Lesion Size (Part I Arm 1 and Arm 2) 64
Table 8 Trial Treatment for MK-1454 IT in Combination with Pembrolizumab Part II (Expansion Cohorts A, B, and C) 65
Table 9 Injectate Volume for Arm 3 Visceral IT (Part I) and Expansion Cohorts (Part II) 65
Table 10 Dose-finding Rules per mTPI Design 68
Table 11 MK-1454 Dose Modification Guidelines for Drug-related AEs in Monotherapy (Arm 1), Combination Therapy (Arm 2), and Combination Therapy Visceral IT (Arm 3) 71
Table 12 Guidelines for Management of MK-1454 Intratumoral Injection Site Reactions 77
Table 13 Dose Modification and Toxicity Management Guidelines for Immune-related Adverse Events Associated with Pembrolizumab Monotherapy, Coformulations or IO Combinations 79
Table 14 Pembrolizumab Infusion Reaction Dose Modification and Treatment Guidelines 82
Table 15 Cytokine Release Syndrome Treatment Guidelines 84
Table 16 Response Criteria for Malignant Lymphoma 125
Table 17 Modified Severity Weighted Assessment Tool 127
Table 18 Response in Skin (CTCL) 128
Table 19 Response in Lymph Nodes (CTCL) 129
Table 20 Response in Viscera (CTCL) 130
Table 21 Response in Blood (CTCL) 131
Table 22 Global Response Score for CTCL 131
Table 23 Laboratory Tests 132
Table 24 Evaluating Adverse Events 144
Table 25 Estimate and 95% CI of ORR (N=30) 152
Table 26 Estimate and 95% CI of ORR (N=60) 152
Table 27 Product Descriptions 153

LIST OF FIGURES

Figure 1 Part I - Dose Escalation and Confirmation Phase 24
Figure 2 Arm 3 Dose and Frequency Escalation 25
Figure 3 Part II - Expansion Cohorts 26
Figure 4 Schematic Diagram Showing Mechanism of the Enhancement of T Cell Driven Antitumor Immunity through the Action of Cyclic-Dinucleotide STING Agonists 29
Figure 5 Algorithm for Classification of Lesions at Baseline 172
Figure 6 Reclassification of Noninjected Lesions 173
Figure 7 Overall Response Assessment Until Disease Progression 174
Figure 8 Example of Iterative Assessment of Injected Lesion Response During Treatment 175

DOCUMENT HISTORY

Document	Date of Issue	Overall Rationale
MK-1454-001-08	27-JUL-2021	Updated the dose modification and toxicity management guidelines for irAEs.
MK-1454-001-07	11-AUG-2020	Updated the inclusion criteria for Triple-negative Breast Cancer Expansion Cohort to include anti-PD-1/PD-L1 refractory subjects and to add an upper limit for LDH for this cohort, removed the requirement for having a second lesion for biopsy in the Expansion Cohorts, added itRECIST as an exploratory objective, and updated the contraception requirements.
MK-1454-001-06	23-AUG-2019	Documented the Recommended Phase 2 Dose (RP2D) to be used in Expansion Cohorts A and B.
MK-1454-001-05	03-JAN-2019	Updated inclusion criteria for Cohort A at the request of the United States (US) Food and Drug Administration (FDA), to allow the inclusion of subjects with head and neck squamous cell carcinoma (HNSCC) Stage III, IVa, IVb, and IVc disease per TNM Staging AJCC Eighth Edition.
MK-1454-001-04	04-OCT-2018	Designated Dose Escalation and Confirmation phase (Arms 1, 2, and 3) as Part I and updated sections accordingly. Added Expansion phase with 3 Expansion Cohorts (Cohorts A to C) as Part II of the study and added new subsections to describe design, entry criteria, dosing schedule, flow chart, and statistical analysis for the Expansion Cohorts in order to evaluate the safety and tolerability of MK-1454 intratumoral (IT) in combination with pembrolizumab in specific cancer tumor types. Updated sample size, secondary/exploratory objectives, treatments, and schedule of activities to reflect addition of the Expansion Cohorts. Revised the dose escalation and confirmation rules for Arm 3 to include an accelerated titration design (ATD) phase starting at [redacted] of MK-1454. Visceral IT dosing will increase in frequency and escalate dose b subject tolerance per modified toxicity probability interval (mTPI) design. This change was based on an FDA request to start visceral IT dosing in combination with pembrolizumab at the No observed adverse effect level (NOAEL) dose of [redacted]

Document	Date of Issue	Overall Rationale
MK-1454-001-03	09-MAR-2018	Updated protocol sections to add rationale, background, entry criteria, schedule of activities, and procedures for Arm 3 for intratumoral (IT) injection of MK-1454 into visceral lesions in combination with pembrolizumab treatment in order to allow inclusion of subjects with visceral lesions to be treated by IT injection. Updated the objectives, inclusion criteria, schedule of activities, and response assessment criteria for subjects with cutaneous T-cell lymphoma (CTCL).
MK-1454-001-02	03-JAN-2017	Added detailed guidelines for the management of cytokine release syndrome in response to UK Medicines and Healthcare products Regulatory Agency request to add detailed supportive care guidelines for potential cytokine release syndrome (CRS).
MK-1454-001-01	07-DEC-2016	Entry criterion #3 text was revised from "for which there is no standard available therapy..." to "and who have received, or been intolerant to, all treatment known to confer clinical benefit." Definition of a DLT was revised so that causality assessment by the investigator was whether the AE was "related, probably related, or possibly related to the drug, excluding toxicities clearly not related to the drug, such as disease progression, environmental factors, unrelated trauma, etc.," rather than "unrelated to the underlying disease." Additionally, Item #3 in the definition of a DLT was revised to clarify that exceptions to Grade 3 nonhematologic toxicity (not laboratory) lasting >3 days as include: Grade 3 fatigue lasting ≤3 days; Grade 3 diarrhea, nausea, or vomiting without use 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).
MK-1454-001-00	17-OCT-2016	Original Protocol

SUMMARY OF CHANGES

PRIMARY REASON(S) FOR THIS AMENDMENT:

Section Number (s)	Section Title(s)	Description of Change (s)	Rationale
5.2.3.3	Immune-Related Events and Dose Modification (Withhold, Treat, Discontinue)	The dose modification and toxicity management guidelines for irAEs and table were updated.	Requested by the US FDA in an effort to harmonize the presentation of safety information across all FDA-approved PD-1/L1 antibody prescribing information.
6.1.2	Schedule of Activities for the Treatment Period, Intratumoral Administration for Arm 1 (Monotherapy) and Arm 2 (Combination Therapy – Including Crossover to Arm 2)	Removed the requirement for a urine sample to be obtained for metabolite and renal clearance analysis.	Analysis of MK-1454 plasma metabolites showed low risk, so MK-1454 urine metabolite analysis is not needed. Analysis of renal excretion not needed at this time, based on current phase of clinical development.
6.1.3	Schedule of Activities for the Treatment Period of Arm 3 (Visceral IT Administration)		
6.2.1	Schedule of Activities for Part II - Expansion Cohorts Screening and Treatment Period, MK-1454 Intratumoral Administration With Pembrolizumab Combination Therapy		
7.1.3.2.4	Urine Collection for MK-1454 Metabolites		Section 7.1.3.2.4 Urine Collection for MK-1454 Metabolites removed; this section number is now used for Tumor Biopsy.

Section Number (s)	Section Title(s)	Description of Change (s)	Rationale
9.1	Investigational Product	Added MK-1454 CCI formulation and removed the CCI formulations.	CCI MK-1454 formulation is available. The CCI formulations are no longer supplied.

ADDITIONAL CHANGE(S) FOR THIS AMENDMENT:

Section Number (s)	Section Title (s)	Description of Change (s)	Rationale
5.7.2.2	Acceptable Contraception Methods	Deleted instructional text regarding hormonal contraception that was inadvertently left from the template.	Correction.
2.2.2	Trial Diagram for Part II – Expansion Cohorts	Updated the trial schema to add "locally advanced metastatic" to the Cohort B indication description	Corrected an error of omission
2.2.2	Trial Diagram for Part II – Expansion Cohorts	Corrected figure legend from CCI to CCI	Correction of typographical error.
5.1.2.1	Subject Inclusion Criteria for Arms 1 and 2	Corrected the renal function criterion for serum creatinine or creatinine clearance from "≥1.5 × upper limit of normal (ULN)" to "≤1.5 × ULN." Added "GFR in place of CrCl." Corrected the hepatic function criterion for total bilirubin from "≥1.5 × ULN" to "≤1.5 × ULN."	Correction of typographical errors and omission of GFR.
6.1.3	Schedule of Activities for the Treatment Period of Arm 3 (Visceral IT Administration)	Deleted the "X" for "Plasma MK-1454 PK" in Cycle 3	Correction – no samples are to be collected in Cycle 3.

Section Number (s)	Section Title (s)	Description of Change (s)	Rationale
6.2.1	Schedule of Activities for Part II - Expansion Cohorts Screening and Treatment Period, MK-1454 Intratumoral Administration With Pembrolizumab Combination Therapy	Removed extraneous language regarding ECOG performance status "Obtain within 72 h prior to MK 1454 IT administration. Does not need to be repeated on C1D1 if screening ECG was done within 72 hours of C1D1."	Sentence was included in error.
7.1.3.1	Laboratory Safety Evaluations (Hematology, Chemistry, and Urinalysis)	Updated footnote c in Table 23 to allow for GFR in place of creatinine clearance.	Correction of omission.
12.4	itRECIST Supplementary Figures – Figure 8	Corrected word in figure legend describing responses in noninjected lesions from "blue" to "purple"	Correction of typographical error
Throughout	NA	Updated the document style to remove spelled out abbreviations from the text, and corrected format and grammar.	To adhere to current Merck template style for future content reuse.

1.0 TRIAL SUMMARY

Abbreviated Title	Phase 1 Study of MK-1454 Administered by Intratumoral Injection
Sponsor Product Identifiers	MK-1454 Pembrolizumab (MK-3475)
Trial Phase	Phase 1/1b
Clinical Indication	The treatment of subjects with advanced/metastatic solid tumors or lymphomas.
Trial Type	Interventional
Type of control	None
Route of administration	Intratumoral (MK-1454) Intravenous Infusion (pembrolizumab)
Trial Blinding	Unblinded Open-label
Treatment Groups	Subjects will be allocated by IWRS assignment to one of the following treatment arms: **Part I: Dose Escalation and Confirmation** Arm 1: MK-1454 IT as monotherapy CCI in cutaneous or subcutaneous lesions Arm 2: MK-1454 IT CCI in combination with pembrolizumab CCI in cutaneous or subcutaneous lesions Arm 3: MK-1454 IT (at escalating frequencies starting with CCI in combination with pembrolizumab (Q3W) in visceral lesions **Part II: Expansion Cohorts** Eligible subjects with advanced/metastatic solid tumors will be allocated by IWRS for treatment with a combination of MK-1454 IT and pembrolizumab IV: Cohort A: HNSCC, anti-PD-1/PD-L1 refractory; Cohort B: Anti-PD-1/PD-L1 treatment-naïve or refractory unresectable locally advanced or metastatic TNBC Cohort C: Anti-PD-1/PD-L1 treatment-naïve solid tumors with liver metastases/lesions
Number of trial subjects	Approximately 235 subjects will be enrolled.
Estimated duration of trial	The Sponsor estimates that the study will require approximately 4.5 to 5 years from the time the first participant (or their legally acceptable representative) provides documented informed consent until the last participant's last study-related contact.

Duration of Participation	Each subject will participate in the trial from the time the participant provides documented consent through the final contact. After a screening phase of up to 28 days, eligible subjects will be allocated by IWRS assignment into an open treatment arm. During Part I (Dose Escalation and Confirmation), subjects will receive treatment with MK-1454 as monotherapy (Arm 1) or as combination therapy with pembrolizumab (Arm 2 or Arm 3). Study treatment will begin on Day 1 of each 21-day cycle. Subjects enrolled in Arm 1 (treatment with MK-1454 as monotherapy) and in Arm 2 or Arm 3 (treatment with MK-1454 and pembrolizumab combination therapy) may continue treatment for up to 35 cycles (approximately 2 years) from the start of treatment. Subjects who progress by either clinical or radiographic evaluation on monotherapy with MK-1454 (Arm 1), may cross over into the combination therapy arm of MK-1454 and pembrolizumab (Arm 2), provided they meet eligibility criteria. A crossover subject may receive up to 35 cycles of treatment in Arm 2 (MK-1454 with pembrolizumab combination therapy) regardless of the duration of treatment received in Arm 1 (MK 1454 monotherapy). Subjects treated with monotherapy MK-1454 (Arm 1) may participate in intrasubject dose escalation after the completion of Cycle 3. A subject may undergo dose escalation once during monotherapy with MK-1454. Subjects in Arm 2 may not participate in intrasubject dose escalation. Subjects in Arm 3, an ATD phase, may undergo intrasubject dose escalation one time after receiving 3 cycles of treatment without a ≥ Grade 2 drug-related toxicity. Subjects may continue treatment until one of the following occurs: disease progression, unacceptable AE(s), intercurrent illness that prevents further administration of treatment, investigator's decision to withdraw the subject, subject withdraws consent, pregnancy of the subject, noncompliance with trials treatment or procedure requirements, or administrative reasons requiring cessation of treatment. After the EOT, each subject will be followed up for 30 days for monitoring all AEs. SAEs and ECI will be collected for 130 days after the EOT or for 30 days after the EOT if the subject initiates new anticancer therapy, whichever is earlier. The Expansion phase (Part II) will open to enroll subjects in Cohorts A to C to evaluate the safety and efficacy of MK-1454 IT in combination with pembrolizumab 200 mg IV. Cohort A will evaluate MK-1454 in 30 subjects with anti-PD-1/PD-L1 refractory HNSCC: Cohort B will include 30 subjects with anti-PD-1/PD-L1 treatment-naïve or refractory TNBC, and Cohort C will include 60 subjects with anti-PD-1/PD-L1 treatment-naïve solid tumors with liver metastases, with a cap at 15 subjects each with colorectal cancer (CRC) or pancreatic cancer. The starting dose for expansion Cohorts A and B will be the preliminary RP2D established in Arm 2. The starting dose and frequency for Cohort C will be the RP2D established for visceral IT administration in Arm 3. All subjects, except for those who withdraw consent or are lost to follow-up, will be followed up for survival. Subjects who experience confirmed disease progression or start a new anticancer therapy, will move into the Survival Follow-Up Phase and should be contacted every 12 weeks to assess for survival status until death, withdrawal of consent, or the end of the study, whichever occurs first.

Randomization Ratio	Subjects will be allocated without randomization. Allocation will be guided by lesion histology and arm completion. In the expansion phase, subjects will be allocated to a cohort corresponding to the histology and pathology of their lesions and will receive MK-1454 in combination with a fixed dose of pembrolizumab.

Abbreviations are not spelled out at first use. A list of abbreviations used in this document can be found in Appendix 12.6. Note: Both "subject" or "participant" may be used to refer to individuals enrolled in clinical trials.

2.0 TRIAL DESIGN

2.1 Trial Design

This is a nonrandomized, multisite, open-label trial of MK-1454 monotherapy and MK-1454 combination therapy with a fixed dose of pembrolizumab 200 mg IV in subjects with advanced/metastatic solid tumors or lymphomas. MK-1454 will be administered IT. Each cycle within the trial is a 21-day cycle. The trial will begin with the Dose Escalation and Confirmation phase (Part I) comprising Arms 1, 2, and 3. Subsequently, an expansion phase will initiate to further examine safety and efficacy of MK-1454 IT in combination with pembrolizumab.

2.1.1 Part I – Dose Escalation and Confirmation Phase

Unless deemed medically unsafe by the investigator, all subjects will be required to undergo a biopsy of the lesion to be injected with MK-1454, and a biopsy of a noninjected distant, discrete lesion, during the screening period (prior to MK-1454 administration). Also, in Arm 1 and Arm 2 on Cycle 3 Day 15, biopsy of an injected lesion treated with MK-1454, and biopsy of a distant, discrete noninjected lesion are to be obtained. In Arm 3, this biopsy will occur on Cycle 3 Day 1. On Cycle 6 Day 1, subjects with amenable lesions at both an injected and a noninjected site may undergo additional optional tumor biopsies. The optional biopsies on Cycle 6 Day 1 will be performed on both an injected lesion treated with MK-1454, and a noninjected distant, discrete lesion.

All subjects will undergo at least a 24-hour observation period following the first dose administration of MK-1454 on C1D1. The inpatient observation period on C1D1 may be extended up to 48 hours at the discretion of the investigator, and/or per local IRB/IEC, and/or Health Authority mandate.

In the Part I, MK-1454 dosing in the first 3 cycles of Arm 1 and Arm 2 is[CCI] and dosing in Cycles 4 and beyond is[CCI] MK-1454 dosing frequency in Arm 3 to visceral lesions will begin at[CCI] and is intended to escalate to a maximum frequency of[CCI] thereafter.

Dose escalation will proceed based on emerging safety and tolerability data of MK-1454 as monotherapy and as combination therapy with pembrolizumab. For each dose level, an assessment will be made of the safety and tolerability data in order to define the next dose level to be tested (see Section 5.2 and Table 3 and Table 4). Arm 1, Arm 2, and Arm 3 will start with an ATD phase followed by an mTPI phase to identify an MTD and/or MAD of MK-1454 monotherapy (Arm 1) or MK-1454 combination therapy with pembrolizumab

(Arm 2 and Arm 3). The Dose Escalation and Confirmation phase in Arms 1 and 2 of this study will aim to identify a preliminary RP2D of intratumorally administered MK-1454 in monotherapy and in combination with pembrolizumab IV infusion. In Arm 3, the aim will be to identify the RP2D of MK-1454 IT administered to visceral lesions in combination with pembrolizumab IV infusion. 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.

Starting with a dose of CCI of MK-1454 in single-subject cohorts (Arm 1, Part A), the trial will proceed in an ATD up to a dose that meets at least 1 of the following 3 triggering criteria: 1) The CCI cohort is completed, 2) ≥ Grade 2 toxicity as assessed by the investigator to be related, probably related, or possibly related to the drug at any dose level, or 3) Elevation of systemic TNF-α in blood above baseline levels by ≥3-fold for a given subject at any time during the first cycle of MK-1454.

Upon completion of the ATD phase by reaching at least 1 of the above triggering criteria, the monotherapy arm (Arm 1) of the study will proceed to dose escalation and confirmation using an mTPI design (Part B). In addition, Arm 2 (Part C), the combination therapy arm, will initiate once 2 dose levels have been cleared by DLT evaluation in Arm 1.

Arm 2 (Part C), MK-1454 combination therapy with pembrolizumab, will begin in single-subject cohorts starting with a dose that is at least 2 dose levels behind MK-1454 monotherapy dose, and will proceed in an ATD up to a dose level, which meets at least 1 of the 3 triggering criteria. Arm 2 will then proceed to mTPI phase (Arm 2, Part D) to determine the MTD/MAD of the combination of MK-1454 with pembrolizumab.

Intrasubject dose escalation of MK-1454 to a higher dose level is permitted in Arm 1, including Parts A and B. Intrasubject dose escalation will be at the discretion of the investigator, provided that the subject remains on study drug after receiving 3 cycles of treatment without ≥ Grade 2 drug-related toxicity, and provided that the dose escalation has proceeded beyond the next dose level. The subject's dose may be escalated to the highest dose level that has been cleared by DLT evaluation. Intrasubject dose escalation is not permitted in Arm 2 (Parts C and D).

Arm 3 will assess the safety and tolerability of MK-1454 administered intratumorally to visceral lesions in combination with pembrolizumab infusion. Dose escalation in Arm 3 will begin in an ATD at CCI and proceed to an mTPI when at least 1 of the following 2 criteria is met: 1) The CCI cohort in combination is completed, 2) ≥ Grade 2 toxicity as assessed by the investigator to be related, probably related, or possibly related to the drug at any dose level in combination. Arm 3 will use the same dose escalation and confirmation rules as in the mTPI method with a minimum of 3 subjects per dose level in order to establish an MTD/MAD in visceral lesions for the combination of MK-1454 IT and pembrolizumab IV. In mTPI phase, visceral IT dosing of MK-1454 will increase in frequency up to CCI thereafter. Once safety and tolerability of dosing frequency of MK-1454 visceral IT is established, dose escalation will continue per mTPI. See Section 5.2.1.3 for the Arm 3 dosing schedule. Intrasubject dose escalation may be permitted in Arm 3 subjects allotted to doses evaluated in the ATD (Part E) part once they have completed 3 cycles of treatment without a ≥ Grade 2 drug-related toxicity. Intrasubject dose escalation may proceed to the highest dose that has cleared DLT evaluation.

The ATD phase in Arm 1, Arm 2, and Arm 3 will have single-subject cohorts, but may allow up to 3 subjects per cohort to account for simultaneous enrollment. During MK-1454 dose escalation in Arm 1 (Parts A and B), Arm 2 (Parts C and D), and Arm 3 (Parts E and F), there will be at least 7 days of observation between each of the first 2 subjects at each dose level. Dose escalation of MK-1454 to determine the MTD/MAD for all 3 treatment arms will be guided by the mTPI design, targeting a DLT rate of 30%. Doses of MK-1454 used in combination with pembrolizumab will be at least 2 dose levels behind the monotherapy MK-1454 dose and will not exceed the MTD for monotherapy. If an MTD for the monotherapy arm is established, then the dose of MK-1454 in combination may continue escalation up to that dose. For example, if the MTD for monotherapy (Arm 1, Part A) is CCI, then the starting dose for combination therapy (Arm 2, Part C), if no DLTs occurred in monotherapy, may be CCI with a maximum dose escalation to CCI. If the MTD for monotherapy (Arm 1, Part A) is CCI then the starting dose for combination therapy will be CCI In monotherapy (Arm 1, Part A), if the CCI dose level is completed, then the starting dose in combination therapy (Arm 2, Part C) will be CCI

Once a dose level in the mTPI phase has been cleared for DLT, and a decision made to escalate to the next dose level, the cohort may be expanded to a total of 14 subjects 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. For each new dose level in the mTPI phase, there may be a minimum of 3 subjects and up to 6 subjects per cohort. Based on the occurrence of DLTs, up to 14 subjects may enroll per dose level. Therefore, during mTPI, up to 14 subjects may be enrolled per dose level, depending on the occurrence of a DLT. Subjects may continue their assigned treatment for up to 35 cycles (approximately 2 years) from the start of treatment.

Treatment may continue until one of the following occurs: disease progression, unacceptable AEs, intercurrent illness that prevents further administration of treatment, investigator decision to withdraw the subject, subject withdraws consent, pregnancy of the subject, noncompliance with trials treatment or procedure requirements, or administrative reasons requiring cessation of treatment.

Subjects who progress by either clinical or radiographic evaluation on monotherapy with MK-1454 (Arm 1), may cross over into the combination therapy arm of MK-1454 and pembrolizumab (Arm 2), provided they meet crossover eligibility criteria in Section 5.1.4 and Section 5.1.5. Subjects who cross over from Arm 1 to Arm 2 are eligible for up to 35 cycles of treatment within Arm 2, regardless of the number of cycles of MK-1454 treatment received in Arm 1. Subjects who cross over will enter Arm 2 at the start of Arm 2, which will be at screening.

Treatment allocation will be accomplished by nonrandom assignment through an IWRS. When both Arm 1 and Arm 2 are open for enrollment, IWRS will alternate subject assignment between arms, starting with Arm 1. Establishment of the MTD/MAD in combination therapy of MK-1454 and pembrolizumab (Arm 2) requires that at least half of the 14 subjects in Arm 2 have no prior exposure to MK-1454 (ie, non-crossover subjects). When Arm 3 is opened, eligible subjects will be allocated in a nonrandomized fashion by IWRS.

The final number of subjects enrolled in the Dose Escalation and Confirmation parts of the study will depend on the empirical safety data (DLT observations, the dose that triggers the mTPI phase, and the preliminary recommended Phase 2 dose). For example, in a scenario where MK-1454 monotherapy starts at CCI and continues to the highest dose, the sample size across Parts A and B may be approximately 40 subjects. For combination therapy of MK-1454 with pembrolizumab, in a scenario where Arm 2 starts at CCI of MK-1454 with 200 mg of pembrolizumab, and continues to the highest dose, the sample size across Parts C and D may be approximately 40 subjects. For combination therapy of MK-1454 IT in visceral lesions with pembrolizumab 200 mg IV (Arm 3), if dosing starts at CCI of MK-1454 and continues to the highest dose, the sample size across Parts E and F may be approximately 35 subjects. In this scenario, the total sample size across Parts A-F will be approximately 115 subjects. An administrative analysis may be conducted to enable future trial planning at the Sponsor's discretion. The data will be examined on a continuous basis to allow for dose escalation and confirmation decisions.

2.1.2 Part II –Expansion Phase

Initiation of Expansion Cohorts will be staggered based on emerging safety and tolerability data from Part I. Unless deemed medically unsafe by the investigator, all subjects will be required to undergo a biopsy of the lesion to be injected with MK-1454 during the screening period (prior to MK-1454 administration). Subjects with an amenable lesion at the injected site will also undergo tumor biopsies on Cycle 2 Day 1 and optionally on Cycle 3 Day 1, unless deemed medically unsafe by the investigator. The expansion phase of the trial (Figure 3) will evaluate MK-1454 in combination with pembrolizumab 200 mg IV in the following populations:

- Cohort A: Subjects with HNSCC who are anti-PD-1/PD-L1 refractory
- Cohort B: Subjects with either anti-PD-1/PD-L1 treatment-naïve or refractory unresectable locally advanced or metastatic TNBC
- Cohort C: Subjects with other anti-PD-1/PD-L1 treatment-naïve solid tumors with liver metastases

Cohorts A and B will begin at the preliminary RP2D from Arm 2. MK-1454 IT will be administered CCI from Cycle 3 and beyond, in combination with pembrolizumab 200 mg IV Q3W beginning on C1D1). The RP2D dose and the dose for expansion is confirmed to be CCI MK-1454, administered intratumorally to a minimum of 1 lesion per subject per treatment day and a maximum of 3 lesions per subject per treatment day, in combination with pembrolizumab IV.

Cohorts A and B will initiate prior to initiation of Cohort C.

Cohort C will begin at the preliminary RP2D and frequency established from Arm 3.

Treatment duration in each cohort in Part II will be up 35 cycles (approximately 2 years).

Cohorts A and B will each enroll a maximum of 30 subjects, while Cohort C will enroll up to 60 subjects, for a total of up to 120 subjects in the expansion phase. The 60 Cohort C subjects will be enrolled with approximately 15 non-MSI-H CRC subjects, 15 pancreatic ductal adenocarcinoma subjects, and 30 subjects without these specific diagnoses.

The trial will be conducted in conformance with GCP.

AEs will be evaluated according to criteria outlined in the NCI CTCAE v4.

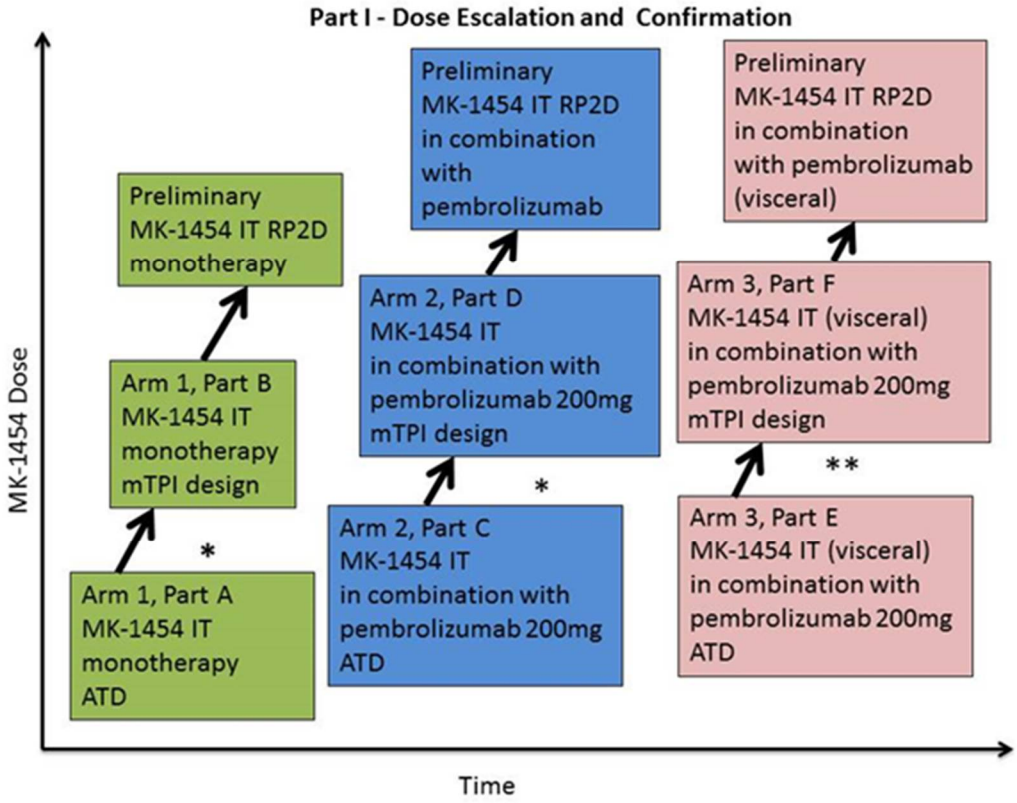
Specific procedures to be performed during the trial, as well as their prescribed times and associated visit windows, are outlined in the Schedule of Activities - Section 6.0. Details of each procedure are provided in Section 7.0 – Trial Procedures.

2.2 Trial Diagram

2.2.1 Trial Diagram for Part I - Dose Escalation and Confirmation

The trial design for the dose escalation and confirmation phase is depicted in Figure 1.

Figure 1 Part I - Dose Escalation and Confirmation Phase



ATD = accelerated titration design; IT = intratumoral; MTD = maximum tolerated dose; mTPI = Modified Toxicity Probability Interval; Q3W = once every 3 weeks; RP2D = Recommended Phase 2 Dose.

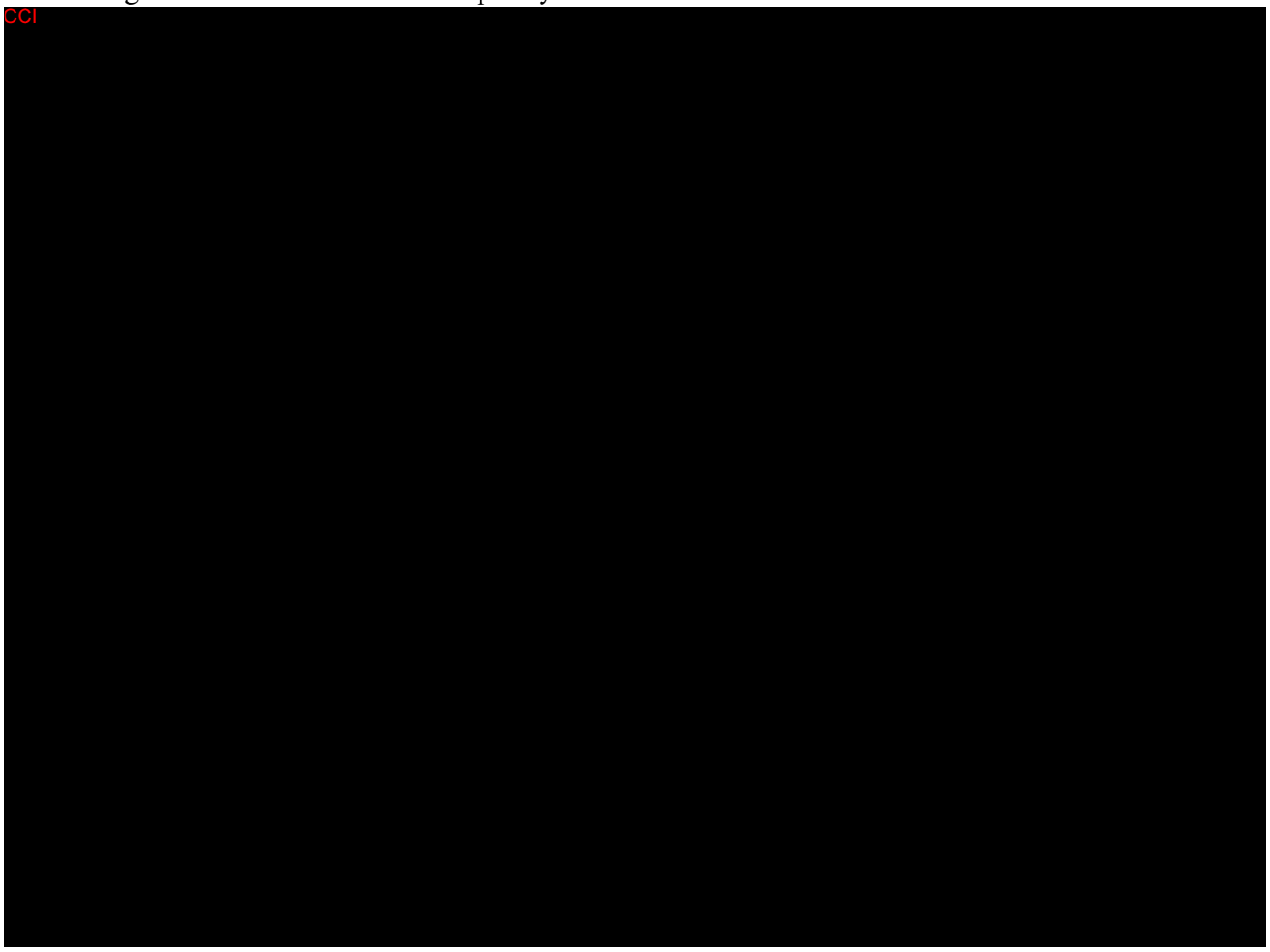
* Triggering criteria for the start of the mTPI design for Arms 1 and 2: 1) The CCI cohort is completed, 2) ≥ Grade 2 toxicity as assessed by the investigator to be related, probably related, or possibly related to the drug at any dose level, or 3) Elevation of systemic TNF-α in blood above baseline by ≥ 3-fold at any time during the first cycle. For example, baseline TNF-α value of 20 pg/mL increases to 60 pg/mL during the first cycle.

** Triggering criterion for the start of the mTPI design for Arm 3: 1) The CCI cohort is completed, 2) ≥ Grade 2 toxicity as assessed by the investigator to be related, probably related, or possibly related to the drug at any dose level.

Treatment in Arm 1, Part A, MK-1454 dose escalation will begin with a CCI dose and will proceed based on safety events to a maximum dose of CCI. The doses of MK-1454 used in combination with pembrolizumab will not exceed the MTD for monotherapy. Once an MTD for monotherapy is established, the dose of MK-1454 administered in Arm 2 combination with pembrolizumab may continue escalation up to that defined dose. At least 7 days of observation will occur between the first and second subject treated at each dose level. Arm 3 (visceral IT) will begin at CCI Arm 3, Part F mTPI design will initiate at a dosing frequency of CCI followed by increasing frequency and dose escalation by mTPI design.

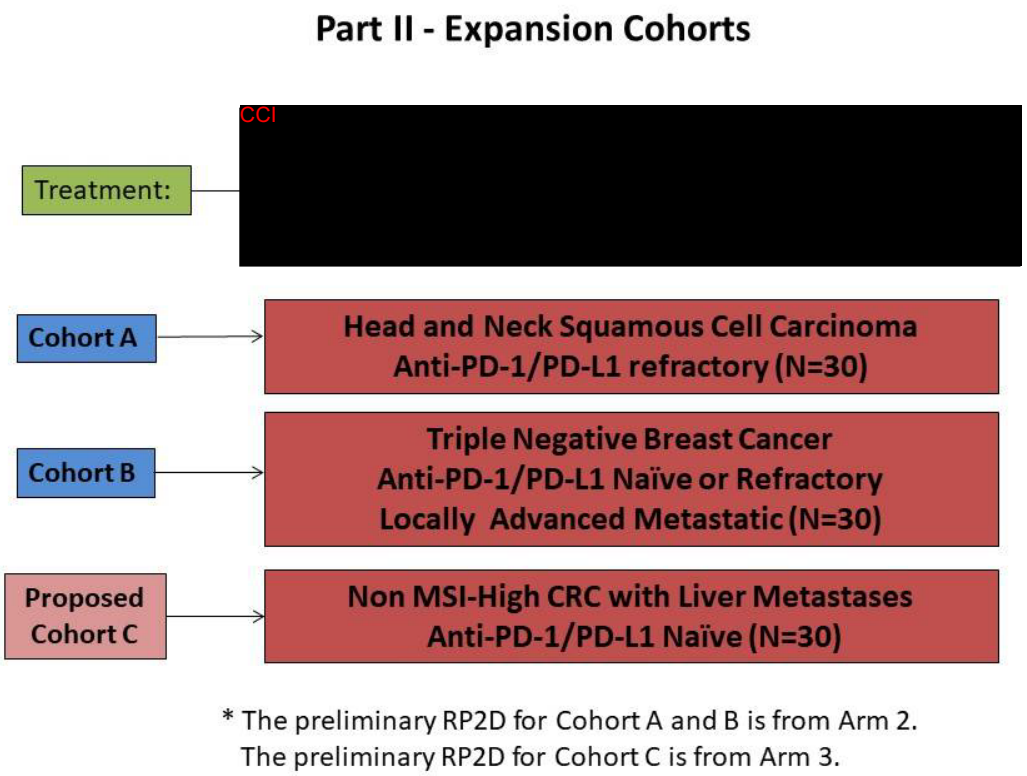
Figure 2 Arm 3 Dose and Frequency Escalation

CCI



2.2.2 Trial Diagram for Part II – Expansion Cohorts

Figure 3 Part II - Expansion Cohorts



IT – intratumoral; IV = intravenous; PD-1 = Programmed death-1 PD-L1 = programmed death ligand 1; CCI Q3W = every 3 weeks; RP2D = recommended Phase 2 dose.

3.0 OBJECTIVE(S) & HYPOTHESIS(ES)

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

3.1 Primary Objective(s) & Hypothesis(es)

(1) **Objective:** For Parts I and II, to determine the safety and tolerability and to establish a preliminary recommended Phase 2 dose of MK-1454 administered via IT injection as monotherapy and in combination with pembrolizumab IV infusion.

3.2 Secondary Objective(s) & Hypothesis(es)

(1) **Objective:** For Parts I and II, to evaluate the pharmacokinetics of MK-1454 administered via IT injection as monotherapy and to evaluate the pharmacokinetics of MK-1454 administered via IT injection as combination therapy with pembrolizumab IV infusion.

(2) **Objective:** For Parts I and II, to evaluate the pharmacokinetics of pembrolizumab IV infusion in combination with MK-1454 administered via IT injection.

(3) **Objective:** Separately for each tumor type in Part II*, to evaluate the ORR of MK-1454 at the preliminary RP2D in combination with pembrolizumab as assessed by the investigator by Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST 1.1) modified to follow a maximum of 10 total target lesions with a maximum of 5 target lesion per organ.

3.3 Exploratory Objectives

(1) **Objective:** For Part I, to evaluate the ORR and PFS of MK-1454 as assessed by investigator when used as monotherapy and as combination therapy with pembrolizumab. In solid tumors, assessment will be based on RECIST 1.1 and irRECIST. ORR and PFS as assessed according to RECIST v1.1 modified to follow a maximum of 10 total target lesions with a maximum of 5 target lesions per organ. In lymphomas, assessment will be based on the IWG revised response criteria [1]. For subjects with CTCL, response assessment will be based on the Global Response Score (see Table 22) [2].

(2) **Objective**: Separately for each tumor type in Part II*, evaluate PFS of MK-1454 at the preliminary RP2D in combination with pembrolizumab as assessed by the investigator by RECIST 1.1 modified to follow a maximum of 10 total target lesions and a maximum of 5 target lesions per organ.

(3) **Objective**: In Parts I and II, to evaluate the effect of the study intervention on lesions not treated with IT injections, as assessed by investigator. The measurements of effect will include the ORR for noninjected lesions and the maximal reduction in the sum of diameters of noninjected target lesions, as described in itRECIST [3].

(4) **Objective**: In Part I, to evaluate overall survival (OS) of subjects treated with MK-1454 both as monotherapy and as combination therapy with pembrolizumab.

* Note: Efficacy analyses for each Part II expansion cohort will pool Part I subjects who meet the inclusion criteria for the respective Part II tumor type and received the same dose level of MK-1454 in combination with pembrolizumab.

(5) **Objective**: Separately for each tumor type in Part II*, to evaluate OS of MK-1454 at the preliminary RP2D in combination with pembrolizumab.
*Note: Efficacy analyses for each Part II expansion cohort will pool Part I subjects who meet the inclusion criteria for the respective Part II tumor type and received the same dose level of MK-1454 in combination with pembrolizumab.

(6) **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-1454 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 biopsies taken prior to treatment and following treatment with MK-1454.

c. To investigate the relationship between the SNP of the STING gene, and to investigate the toxicity/efficacy of MK-1454 as monotherapy and as combination therapy with pembrolizumab.

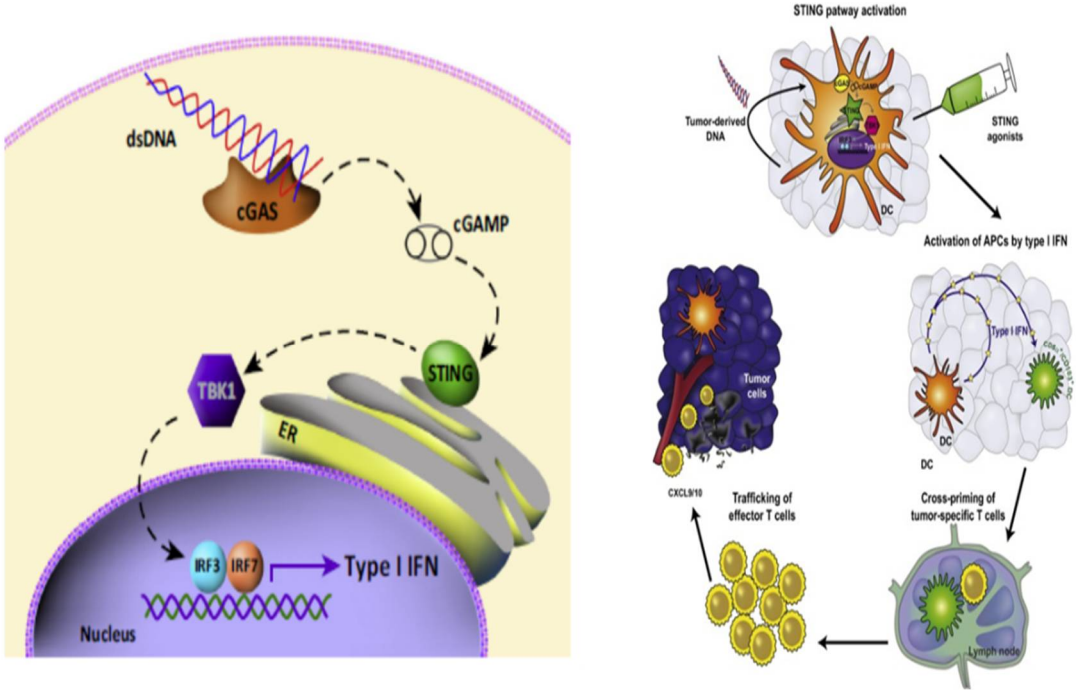
4.0 BACKGROUND & RATIONALE

4.1 Background

Detailed background information on preclinical pharmacology, pharmacokinetics, pharmacodynamics, and metabolism of MK-1454 is available in the MK-1454 IB.

The Sponsor is developing MK-1454, a CDN STING agonist with activity across species. DNA in the cytoplasm of mammalian cells represents a cellular danger signal, and the cGAS-AMP/STING pathway is activated to respond to that potential threat (Figure 4). Free cytosolic DNA is recognized by cGAS, catalyzing the generation of the cyclic-dinucleotide 2'-3' cGAMP. Cyclic-dinucleotide 2'-3' 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 TBK1 and inducing downstream phosphorylation and activation of transcription factors IRF-3 and NF-kB. 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 4 Schematic Diagram Showing Mechanism of the Enhancement of T Cell Driven Antitumor Immunity through the Action of Cyclic-Dinucleotide STING Agonists



Abbreviations: APC = antigen-presenting cells; cGAMP = cyclic guanosine monophosphate-adenosine monophosphate; cGAS = cyclic (guanosine monophosphate-adenosine monophosphate) synthase; CXCL9/10 = chemokine C-X-C motif ligand 9/10; DC = dendritic cell; dsDNA = double-stranded deoxyribonucleic acid; ER = endoplasmic reticulum; IFN = interferon; IRF7 = interferon regulatory factor 7; STING = stimulator of interferon genes; TBK1 = tank-binding kinase 1.

STING is expressed in numerous cell types, but functional responses (cytokine production in response to dsDNA) 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. While 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%.

Recent studies showed that all tested STING variants demonstrated comparable response to synthetic CDN-derivative STING agonist.

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.

4.1.1 Pharmaceutical and Therapeutic Background

4.1.1.1 MK-1454 Background

Published and internal data demonstrate that IT delivery of STING agonists leads to complete tumor regression or significant tumor growth inhibition in both anti-programmed cell death-1 (PD-1)-responsive and nonresponsive mouse syngeneic tumor models, and can also induce immune-mediated clearance of noninjected tumors [4] [5] [6].

Importantly, tumor-bearing mice whose tumors completely regress through the action of a CDN STING agonist become protected against subsequent challenges with the same tumor, indicating that induction of tumor-specific T cell memory has occurred [4]. Recently presented external [7] and in-house data demonstrated a discrepancy between the CDN doses associated with full eradication of the injected tumor and with maximal protection against tumor re-growth in rechallenge studies. These findings suggest that a "bell-shaped" relationship may exist between CDN STING agonist doses and the potential for abscopal action of intratumorally-dosed CDN STING agonist. It is hypothesized that these preclinical findings are driven, at higher CDN doses, by innate immune cell activation, cytokine production and function in such a robust manner that it hampers the ability of the adaptive immune system to develop antitumor adaptive immune memory.

With the success of checkpoint inhibitors in the clinic, combination therapies focused on boosting the ability of the host's innate immune system to activate adaptive immune antitumor responses are increasingly being advanced in preclinical studies and clinical trials [8].

With this in mind, the Sponsor is developing a CDN STING agonist that demonstrates antitumor efficacy in multiple syngeneic mouse models, with an acceptable safety profile. Attributes of MK-1454 include induction of T cell memory, as evidenced by protection in tumor rechallenge models, and enhanced antitumor efficacy in combination with anti-PD-1 mAb.

The mechanism of action (Figure 4) suggests that a CDN STING agonist could provide efficacy either as a stand-alone agent or in combination with the anti-PD-1 mAb pembrolizumab. Based on preclinical data, combination therapy with MK-1454 and pembrolizumab may demonstrate efficacy in patients who either did not respond to pembrolizumab or who progressed on pembrolizumab therapy, as well as those patients who are predicted to be poor responders based on PD-L1 expression in the tumor. MK-1454 will be presented in the clinic as a sterile liquid in a single use vial for IT injection. The active formulation will be available in low and high concentrations, along with diluent to enable customization of the dosing concentration per tumor size/ administered volume.

4.1.1.2 Pembrolizumab Background

The importance of intact immune surveillance function in controlling outgrowth of neoplastic transformations has been known for decades [9]. Accumulating evidence shows a correlation between tumor-infiltrating lymphocytes in cancer tissue and favorable prognosis in various

malignancies. In particular, the presence of CD8+ T cells and the ratio of CD8+ effector T cells/FoxP3+ regulatory T cells correlates with improved prognosis and long-term survival in solid malignancies, such as ovarian, colorectal, and pancreatic cancer; hepatocellular carcinoma; malignant melanoma; and renal cell carcinoma. Tumor-infiltrating lymphocytes can be expanded ex vivo and reinfused, inducing durable objective tumor responses in cancers such as melanoma [10] [11].

The PD-1 receptor-ligand interaction is a major pathway hijacked by tumors to suppress immune control. The normal function of PD-1, expressed on the cell surface of activated T cells under healthy conditions, is to down-modulate unwanted or excessive immune responses, including autoimmune reactions. PD-1 (encoded by the gene Pdcd1) is an Ig superfamily member related to CD28 and CTLA-4 that has been shown to negatively regulate antigen receptor signaling upon engagement of its ligands (PD-L1 and/or programmed cell death-1 ligand 2 [PD-L2]) [12] [13].

The structure of murine PD-1 has been resolved [14]. PD-1 and family members are type I transmembrane glycoproteins containing an Ig Variable–type domain responsible for ligand binding and a cytoplasmic tail responsible for the binding of signaling molecules. The cytoplasmic tail of PD-1 contains 2 tyrosine-based signaling motifs, an immunoreceptor tyrosine-based inhibition motif, and an immunoreceptor tyrosine-based switch motif. Following T cell stimulation, PD-1 recruits the tyrosine phosphatases, SHP-1 and SHP-2, to the immunoreceptor tyrosine-based switch motif within its cytoplasmic tail, leading to the dephosphorylation of effector molecules such as CD3ζ, protein kinase C-θ, and ZAP70, which are involved in the CD3 T cell signaling cascade [15] [16], [17]. The mechanism by which PD-1 down modulates T cell responses is similar to, but distinct from, that of CTLA-4, because both molecules regulate an overlapping set of signaling proteins [18] [19]. As a consequence, the PD-1/PD-L1 pathway is an attractive target for therapeutic intervention in solid tumors and lymphomas (see the IB).

Pembrolizumab is a potent and highly selective humanized monoclonal antibody (mAb) of the IgG4/kappa isotype designed to directly block the interaction between PD-1 and its ligands, PD-L1, and PD-L2. Pembrolizumab has shown clinical activity in multiple tumor types [20]. Please refer to the current label.

Pembrolizumab will be presented in the clinic as a sterile lyophilized powder for reconstitution in a single use vial for dilution to be administered as an IV infusion.

4.2 Rationale

4.2.1 Rationale for the Trial and Selected Subject Population

4.2.1.1 Rationale for Part I - Dose Escalation and Confirmation

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. Intratumoral injection of CDN 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 [21] [4]. Therefore, a synthetic CDN, such as MK-1454, has potential as a cancer therapeutic.

Tumor treatment site selection initially will be based on accessibility of the tumor site to IT injection. The FIH Phase I study of MK-1454 will enroll subjects with refractory solid tumors and lymphomas with cutaneous, subcutaneous, and/or nodal lesions that are visible, palpable, or detectable by ultrasound guidance for IT injection, as well as subjects with metastatic liver lesions amenable to injection via ultrasound or cross-sectional imaging (CT/MRI) guidance. Subjects must have at least one lesion that is amenable to IT injection. For solid tumor subjects, this lesion must be ≥1 cm for solid tumors or ≥1.5 cm for nodal lesions, and ≤10 cm in longest diameter for both solid tumors and nodal lesions in solid tumor subjects. For lymphoma subjects, 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 for both solid tumor subjects and lymphoma subjects.

The injectable lesion must be accessible for biopsy at screening and after IT injection with MK-1454. See Section 5.1.2 for Inclusion Criteria. In addition, a distant, discrete noninjected lesion, which is separate from the injected lesion, will undergo biopsy at screening and after the subject has received treatment with MK-1454. This distant, discrete lesion is not injected with MK-1454.

4.2.1.2 Rationale for Part II - Expansion Cohorts

STING has been reported to be expressed in many human tissues and broadly across multiple human tumor subsets, including pancreatic adenocarcinoma, head and neck cancer, melanoma, colorectal cancer, TNBC, and other solid tumors. In addition, tumor type selection was based on projected accessibility for IT injection into cutaneous lesions, subcutaneous solid tumors, subcutaneous lymph nodes, and liver lesions. The selected subject populations for Expansion Cohorts represent an unmet medical need.

In preclinical studies intratumoral delivery of STING agonists leads to complete tumor regression or significant tumor growth inhibition in both anti-PD-1 -responsive and nonresponsive mouse syngeneic tumor models and can also induce immune-mediated clearance of noninjected tumors. In addition, tumor-bearing mice whose tumors completely regress through the action of a STING agonist become protected against subsequent challenges with the same tumor, indicating that induction of a durable tumor-specific T cell memory has occurred [4] [5] [6].

Existing and emerging, external and internal data suggest that the observed antitumor efficacy of STING agonism is primarily obtained through enhancing the capacity of the innate immune system to present tumor-associated antigens to $CD8^+$ T cells as well as through a direct anti-proliferative effect on tumor cells.

Based on preclinical data and mechanism of action of STING agonism, combination therapy of MK-1454 with the anti-PD-1 mAb pembrolizumab may demonstrate efficacy in patients who did not respond to pembrolizumab or are predicted to be poor responders based on gene expression profiling [22], PD-L1 expression and/or low tumor mutational burden. In these patients, a two-step process is hypothesized to occur, STING agonism-driven priming and initial expansion of antitumor $CD8^+$ T cells and pembrolizumab-driven expansion of relevant tumor-specific T cells with prevention of T cell exhaustion.

Therefore, MK-1454 in combination with pembrolizumab may be beneficial for subjects with tumor types selected in the Expansion Cohorts, who have received or been intolerant to standard of care regimen(s).

4.2.1.2.1 Microsatellite Instability Testing

Pembrolizumab is approved for the treatment of patients with MSI-H or dMMR cancer, agnostic of tumor type. This accelerated approval was based on an ORR of 39.6% in a population of 149 subjects with 15 different cancer types. This high response rate necessitates accounting for MSI-H/dMMR status in any study evaluating the efficacy of pembrolizumab therapy, either alone or in combination with additional agents. Additionally, in patients with tumors that are not MSI-H/dMMR, where a higher unmet medical need exists, agents in combination might enhance responses to pembrolizumab treatment. As such, in any expansion cohort in this trial, only subjects with tumors that are not MSI-H/dMMR by local testing will be eligible for enrollment.

Prior to this tumor type-agnostic approval of pembrolizumab in MSI-H/dMMR cancer, tumor MSI/dMMR local testing was already in clinical use and recommended for management of patients with a number of different malignancies. Subsequent to this approval, testing for MSI-H/dMMR is now recommended for the management of multiple additional malignancies. As such, local testing of tumors for MSI/dMMR is now regularly performed and therefore widely available.

For this trial, MSI/dMMR testing must have been performed on any patient being considered for expansion cohort enrollment, using either an archival or a newly obtained tumor sample. MSI/dMMR status must be determined by examining either (1) 5 tumor microsatellite loci using PCR-based assay, or (2) protein expression by IHC of 4 MMR enzymes (MLH1/MSH2/MSH6/PMS2), respectively. MSI testing methods based on DNA sequencing are also being developed and may be utilized for eligibility testing for this study, provided details of such a test are provided to and approved by the Sponsor.

Tumors are classified as MSI-H when at least 2 allelic shifts among the 5 analyzed microsatellite markers are detected by PCR and are classified as dMMR when expression of at least 1 of 4 MMR proteins is not detected by IHC. In situations where multiple tests have been performed, a subject will be considered to have an MSI-H/dMMR tumor if any of these tests yields an MSI-H/dMMR result.

4.2.2 Rationale for Dose Selection/Regimen

4.2.2.1 Starting Dose for This Trial

The FIH starting dose of MK-1454 is targeted to be a minimally efficacious dose, corroborated by an insignificant change in systemic TNF-α concentration, and to have an acceptable safety profile in the advanced cancer patient population, in accordance with ICH S9 oncology guidance. Based on projected doses evaluated in rat and dog toxicity studies, an FIH starting dose that is selected based on a fraction of the highest non-severely toxic dose or the severely toxic dose to 10% of animals would be above the dose predicted to demonstrate efficacy in patients with tumors of certain volumes. Given the potential of MK-1454 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 one IT dose for multiple CDN STING agonists including MK-1454 was characterized in tumor-bearing mice implanted with MC38 cells. To leverage all the data that has been generated with multiple CDN STING agonists, the IT dose for each CDN 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 [23]. A dose-efficacy response relationship that relates the percent GRI versus the normalized dose was described by a maximum effect model (E_{max} 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 mm3 to a tumor volume below the limit of quantification within 5 days. A value of 135% GRI in mice was assumed to be a percent GRI that will result in clinical response in patients. The selected FIH starting dose is [redacted] for a total injectable tumor ≥0.5 cm3 (1 cm in the longest dimension for a single lesion). The injectate volume will be determined based on tumor size (see Table 6 and Table 7).

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 CDN STING agonists including MK-1454. No remarkable change in cytokine TNF-α concentration was observed at the normalized dose to mice (3.3 µg for 80 mm3 tumor) that equates to the FIH starting dose of [CCI] for any total injectable tumor volume ≥0.5 cm3. The rationale for the upper dose limit of [CCI] is based on the maximum dose studied in dogs (3 mg). The therapeutic dose is expected to be less than [CCI] The [CCI] dose level is near the predicted efficacious dose of MK-1454 for a lesion volume of 33.5 cm3 (approximately 4 cm in diameter). Therefore, [CCI] was selected as a triggering dose for progression from the ATD phase to the mTPI phase.

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

The planned dose of pembrolizumab for this trial is 200 mg Q3W. Based on the totality of data generated in the Keytruda development program, 200 mg Q3W is the appropriate dose of pembrolizumab across all indications and regardless of tumor type. Please refer to the IB for details on the clinical development of pembrolizumab.

4.2.2.2 Maximum Dose/Exposure for This Trial

The determination of a preliminary RP2D for MK-1454 is an objective of Part I of this trial, which may evaluate dose levels up to [CCI]

4.2.2.3 Rationale for Dose Interval and Trial Design

The human starting dose of MK-1454 is based on an integration of nonclinical toxicological, pharmacological, and efficacy data. Initial dose escalation in Part I will proceed following an ATD in order to minimize the number of subjects treated at potentially subtherapeutic doses of MK-1454. The ATD will utilize 1-3 subjects per cohort with up to a 300% dose increment increase from the prior dose of MK-1454, followed by a model-based dose escalation mTPI approach with 3-14 subjects per cohort using dose increment increases of 30% to 100% of the prior dose. Transition from ATD to mTPI will be triggered by the occurrence of at least 1 of the following 3 events: 1) The [CCI] cohort is completed, 2) ≥ Grade 2 toxicity as assessed by the investigator to be related, probably related, or possibly related to the drug at any dose level, or 3) Elevation of systemic TNF-α in blood above baseline levels by ≥3-fold for a given subject at any time during the first cycle of MK-1454.

Dose escalation decisions will be made upon ongoing review of safety and available PK/pharmacodynamic 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/pharmacodynamic 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 safety teleconference. Dose level escalations are Sponsor-controlled through IWRS, which include the opening and closing of dose level cohorts upon dose escalation.

To ensure safety, doses of MK-1454 used in combination with pembrolizumab in Arm 2 will be at least 2 dose levels behind the monotherapy dose, even if combination therapy was triggered to start earlier, and will not exceed the MTD/MAD for monotherapy. If an MTD/MAD for monotherapy is established, the dose of MK-1454 in combination with pembrolizumab may continue escalation up to that dose. Intrasubject dose escalation of MK-1454 to the next dose level is permitted in Arm 1 (Parts A and B) at the discretion of the investigator provided that the subject remains on study after receiving 3 cycles of treatment without a ≥ Grade 2 drug-related toxicity, and provided that dose escalation has proceeded beyond the next dose level. Intrasubject dose escalation is permitted once during Arm 1 for a qualifying subject. Intrasubject dose escalation is not permitted in Arm 2 (Parts C and D) or in Arm 3 (Parts E and F).

The starting dose for Arm 3 will be CCI in combination with pembrolizumab 200 mg IV. MK-1454 will initially be administered to visceral lesions CCI. Pembrolizumab will be administered Q3W. Arm 3 will proceed in an ATD, then transition to mTPI when at least one of the following 2 triggers are met: 1) The CCI cohort in combination is completed, 2) ≥ Grade 2 toxicity as assessed by the investigator to be related, probably related, or possibly related to the drug at any dose level in combination. Dose escalation and increasing dosing frequency of MK-1454 visceral IT injection (see Table 5 and Figure 2) will be based on subject tolerance per mTPI rules. The starting dose of CCI MK-1454 in Arm 3 is based on the preclinical NOAEL dose level, and the rationale is to reduce redundancy of evaluating dose levels in Arm 3 for which safety evaluation of MK-1454 in combination with pembrolizumab had already occurred in Arm 2.

4.2.2.4 Rationale for Visceral Intratumoral Injection

The rationale for the addition of a visceral intratumoral arm of MK-1454 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/PD, and early efficacy of MK-1454 injected into visceral organs and deeper tumor lesions. To mitigate the potential safety risk of repeated visceral and deeper lesion IT injections, the IT dosing will begin at Q3W. Increased frequency and/or dosage of visceral IT administration as shown in Figure 2 will be based on subject tolerance and clinical assessment of safety.

4.2.2.5 Rationale for Dose of MK-1454 Expansion Cohorts A and B (Part II)

The recommended Phase 2 dose for MK-1454 was based on analysis of the safety, pharmacodynamic, and early efficacy data from Part I of this Phase 1 study. In Part I dose escalation, responses were observed at doses of CCI Preclinical data in mice suggested a bell-shaped dose response for immunologic memory induced by STING agonism. In combination therapy with pembrolizumab, greater reduction in injected and noninjected target lesions was seen at MK-1454 doses of CCI MK-1454 doses of CCI, suggesting improved efficacy at the lower MK-1454 doses evaluated in Part I (dose escalation) of this Phase 1 study. Pharmacodynamic analysis demonstrated nanostring gene signature and IP-10 dose-dependent increases, which peaked at CCI followed by plateau. Overall safety profile of MK-1454 was tolerable. Based on composite evaluation of safety, pharmacodynamic, and

efficacy data, CCI was selected as the recommended Phase 2 dose and dose for Expansion Cohorts A and B. To assure that the dose per lesion remained in the efficacious dose range when more than one lesion was injected per treatment visit, the total MK-1454 CCI dose may be administered in a minimum of 1 lesion and a maximum of 3 lesions per visit, with a minimum volume of 1 mL to be injected in a single lesion, and a maximum volume of 3 mL to be injected per subject per treatment visit.

4.2.2.6 Rationale for Dose Schedule Expansion Cohorts A and B (Part II)

The starting dose for expansion Cohorts A and B will be the preliminary RP2D established in Arm 2, based on emerging safety, tolerability, and PK/pharmacodynamic data. The rationale for weekly dosing for the first 6 weeks (Cycle 1 and Cycle 2), followed by dosing every 3 weeks thereafter, is to allow for congruence of the dosing schedule of visceral intratumoral administration (Part I: Dose Escalation and Confirmation Arm 3) to the dosing schedule for cutaneous and subcutaneous intratumoral administration.

The starting dose and frequency for Cohort C will be the preliminary RP2D established in Arm 3.

4.2.3 Rationale for Endpoints

4.2.3.1 Efficacy Endpoints

An exploratory objective for this trial is to evaluate the antitumor activity of MK-1454 monotherapy and MK-1454 combination therapy with pembrolizumab in subjects with advanced or metastatic solid tumors and lymphomas. Tumor response in subjects with solid tumors will be assessed using RECIST 1.1 and irRECIST. International Working Group revised response criteria will be applied to lymphoma subjects 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-1454 and 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-1454 and pembrolizumab. Therefore, the subject should not be discontinued from treatment unless the initial assessment of PD is confirmed at least 4 weeks later, provided the subject's clinical condition is stable. Immune-related RECIST will be used to assess efficacy.

Sites are encouraged to have a multidisciplinary treatment and assessment plan to determine in advance that lesions will be treated, biopsied, and/or targeted for tumor assessment. A lesion that is designated as target for assessment by RECIST 1.1, irRECIST, or revised IWG criteria should ideally not undergo core or punch biopsy.

4.2.3.1.1 Immune-related RECIST (irRECIST)

RECIST 1.1 will be adapted to account for the unique tumor response characteristics seen with treatment with 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 patients experienced delayed or early tumor pseudoprogression. Of note, patients who had PD by RECIST 1.1 but not by irRECIST had longer OS than patients with PD 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 (irRECIST) is RECIST 1.1 adapted to account for the unique tumor response seen with immunotherapeutics as described by Nishino, et al. [24]. The assessment of unidimensional target lesions and response categories per irRECIST are identical to RECIST 1.1. However, Merck 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.

4.2.3.1.2 IWG Revised Response Criteria for Malignant Lymphomas

For subjects with malignant lymphoma, the antitumor activity of MK-1454 and pembrolizumab will be evaluated as part of the primary and secondary analyses using the IWG Revised Response Criteria for Malignant Lymphomas [25] as detailed in Section 7.1.2.7.2.

The revised response criteria include several components: 1) assessment of nodal and extranodal lesions by CT (for size) and FDG-PET (for viability), 2) physical exam 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 subject status (eg, discontinuation of study therapy).

Because of the possibility of immunotherapy-related flare, subjects 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.

4.2.3.1.3 Response Assessment for CTCL

For subjects with CTCL, determination of eligibility will be made in accordance with the modified ISCL/Cutaneous Lymphoma Task Force of the EORTC revision of the classification of mycosis fungoides/Sézary syndrome [26]. The antitumor activity of MK-1454 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 [2].

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 7.1.2.7.3.

4.2.3.2 Safety Endpoints

The primary objective of this trial is to characterize the safety and tolerability of MK-1454 as monotherapy and as combination therapy with pembrolizumab in subjects with advanced/ metastatic solid tumors and lymphomas. The primary safety analysis will be based on subjects who experience toxicities as defined by CTCAE criteria. Safety will be assessed by quantifying the toxicities and grades of toxicities experienced by subjects who have received MK-1454 as monotherapy and in combination with pembrolizumab, including SAEs and AEs of special interest.

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

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 to, and outcome of AEs/SAEs; changes in vital signs and laboratory values. AEs will be assessed as defined by CTCAE, Version 4.0.

4.2.3.3 Pharmacokinetic Endpoints

Secondary objectives of this trial are to characterize the PK profile of MK-1454 following administration as a single agent, and to characterize the PK profile of MK-1454 and pembrolizumab following administration as combination therapy. The 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, safety and exploratory endpoints to help assess future dosing strategies for MK-1454.

4.2.3.4 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 has been 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 CDN 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 potential safety events associated with immune stimulation and cytokine release. The cytokines that will be assessed include but are not be limited to TNF-α, IFNβ, IL-6, MIP-1α, MCP-2, IP-10, and CXCL11.

4.2.3.5 Planned Exploratory Biomarker Research

Introduction: Cancer immunotherapies represent an important and novel class of antitumor agents. However, the mechanism of action of these exciting new therapies is not completely understood and much remains to be learned regarding how best to leverage these new drugs in treating patients. Thus, to aid future patients, it is important to investigate the determinants of response or resistance to cancer immunotherapy, as well as 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 and combination therapy with immuno-oncology drugs. To identify novel biomarkers, biospecimens (ie, blood components, tumor material) will be collected to support analyses of cellular components (eg, protein, DNA, RNA, metabolites) and other circulating molecules. Investigations may include but are not limited to planned genetic analysis, as outlined in Section 4.2.3.5.1.

4.2.3.5.1 Planned Genetic Analysis

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. Finally, microsatellite instability (MSI) may be evaluated as this is an important biomarker for some cancers (ie, colorectal cancer).

Genetic (DNA) analyses from tumor: The application of new technologies, such as next generation sequencing, has provided scientists the opportunity to identify tumor-specific DNA changes (ie, mutations, methylation status, 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 (ie, 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-1454 and 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-10). 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 in vitro diagnostic 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, TNBC, 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, liquid chromatography/mass spectrometry. This approach could identify novel protein biomarkers that could aid in patient selection for MK-1454 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 pembrolizumab therapy, as well as levels of protein in the tumor. Deoxynucleic acid can be analyzed using next generation sequencing or polymerase chain reaction-based technologies. Advantages to this method are that blood is a less invasive compartment from which tumor-derived protein or nucleic acid biomarkers may be measured.

4.2.3.6 Future Biomedical Research

The Sponsor will conduct Future Biomedical Research on specimens consented for future biomedical research 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 future biomedical research.

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 subjects. The objective of collecting/retaining specimens for Future Biomedical Research is to explore and identify biomarkers that inform the scientific understanding of diseases and/or their therapeutic treatments. The overarching goal is to use such information to develop safer, more effective drugs/vaccines, and/or to ensure that subjects receive the correct dose of the correct drug/vaccine at the correct time. The details of this Future Biomedical Research are

presented in Section 12.2 – Collection and Management of Specimens for Future Biomedical Research.

4.3 Benefit/Risk

It cannot be guaranteed that subjects in clinical trials will directly 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 subjects participating in this clinical trial may be found in the accompanying IB and Informed Consent documents.

5.0 METHODOLOGY

5.1 Entry Criteria

5.1.1 Diagnosis/Condition for Entry into the Trial

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

5.1.2 Subject Inclusion Criteria for Part I - Dose Escalation and Confirmation

5.1.2.1 Subject Inclusion Criteria for Arms 1 and 2

In order to be eligible for participation in Arm 1 or Arm 2 of this trial, the subject must:

1. Be ≥18 years of age on day of signing informed consent.
2. Voluntarily agreed to participate by providing documented informed consent. The subject may also provide consent for Future Biomedical Research. However, the subject may participate in the main trial without participating in Future Biomedical Research.
3. Have a histologically or cytologically confirmed advanced/metastatic solid tumor or lymphoma by pathology report and who 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. Tumor types of greatest interest include, but are not limited to, malignant melanoma, HNSCC, breast adenocarcinoma, and lymphomas.
4. Have Stage III or Stage IV disease that is not surgically resectable. Stage IIB ($T_3N_0M_0B_{0-1}$) CTCL subjects are eligible [26].
5. Have at least 1 injectable lesion which is amenable to injection and biopsy. Biopsy may be performed via visual inspection, ultrasound guidance, or cross-sectional imaging. Intratumoral injection for cutaneous lesions may be performed via visual inspection. Intratumoral 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 solid tumor subjects. The longest

diameter for an injectable lesion must be ≤10 cm for both solid tumors and nodal lesions in solid tumor subjects.

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

6. Have at least 1 distant and/or discrete noninjected lesion that is amenable to biopsy via visual inspection or amenable to biopsy via image guidance, such as ultrasound or CT/MRI. This lesion must be measurable as defined by the response criteria used to assess the subject (RECIST 1.1 for solid tumors or revised IWG criteria for lymphomas).
   - For RECIST 1.1, ≥1 cm in longest diameter for non-nodal lesions, or ≥1.5 cm in 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.
7. Have an ECOG Performance Status of 0 or 1.
8. Demonstrate adequate organ function as defined by Table 1.

   All screening labs should be performed within 7 days prior to treatment initiation.

Table 1 Adequate Organ Function Laboratory Values

System	Laboratory Value
Hematological	
Absolute neutrophil count	≥1,500/mcL(>1,000/mcL for lymphoma subjects)
Platelets	≥100,000/mcL (≥75,000/mcL for lymphoma subjects)
Hemoglobin	≥9 g/dL or ≥5.6 mmol/L[a] (≥8 g/dL or ≥5.0 mmol/L for lymphoma subjects)
Renal	
Serum Creatinine **or** CrCl (measured or calculated[b]) **or** GFR in place of CrCl	≤1.5 × ULN **or** ≥60 mL/min for subject with creatinine levels >1.5 X ULN
Hepatic	
Total bilirubin (serum)	≤1.5 × ULN **or** Direct bilirubin ≤ ULN for subjects with total bilirubin levels >1.5 X ULN
AST and ALT	≤2.5 × ULN ≤5 × ULN for subjects with liver metastases

System	Laboratory Value
Coagulation	
INR or PT	≤1.5 × ULN
PTT or aPTT	≤1.5 × ULN

Abbreviations: ALT = Alanine aminotransferase; aPTT = activated partial thromboplastin time; AST = aspartate aminotransferase INR = International Normalized Ratio; 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. Subjects can be on stable dose of erythropoietin (≥ approximately 3 months).

[b] CrCl should be calculated per institutional standard.

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 Section 5.7.2 during the intervention period and for at least 130 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) 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.
    - Additional requirements for pregnancy testing during and after study intervention are located in Section 5.7.2.
    - The investigator is responsible for review of medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a woman with an early undetected pregnancy.
    - Contraceptive use by women should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.

10. Male subjects are eligible to participate if they agree to the following during the intervention period and for at least 130 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 [Section 5.7.2]) 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.

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

    - 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.
    - Have well-controlled HIV on ART, defined as:
        - must have a CD4+ T cell count >350 cells/mm^3 at time of screening;
        - must have achieved and maintained virologic suppression defined as confirmed HIV RNA level below 50 or the LLOQ (below the limit of quantification) using the locally available assay at the time of screening and for at least 12 weeks prior to screening;
        - 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).

5.1.2.2 Subject Inclusion Criteria for Crossover Into Arm 2

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

1. Have either clinical or radiographic disease progression, or progression by global response score for CTCL on Arm 1 MK-1454 monotherapy.
2. Have at least one injectable lesion which is amenable to injection and biopsy. Biopsy may be performed via visual inspection, ultrasound guidance, or cross-sectional imaging guidance. Intratumoral injection for a cutaneous lesion may be performed via visual inspection. Intratumoral 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 solid tumor subjects. The longest diameter for an injectable lesion must be ≤10 cm for both solid tumors and nodal lesions in solid tumor subjects.
- Multiple coalescing, superficial lesions which in aggregate have a longest diameter of ≥1 cm and ≤10 cm.
- For lymphoma subjects, 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.

3. Have at least one distant and/or discrete noninjected lesion that is amenable to biopsy via visual inspection or amenable to biopsy via image guidance. Biopsy may be performed via visual inspection, ultrasound guidance, or cross-sectional imaging guidance. This lesion must be measurable as defined by the response criteria used to assess the subject (RECIST 1.1 for solid tumors or IWG revised criteria for lymphomas).
    - For RECIST 1.1, ≥1 cm in longest diameter for non-nodal lesions, or ≥1.5 cm in 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.
4. Have an ECOG Performance Status of 0 or 1.
5. Demonstrate adequate organ function as defined by Table 1 within 7 days prior to treatment initiation. All screening labs should be performed within 7 days prior to treatment initiation.
6. A female participant is eligible to participate if she is not pregnant or breastfeeding, and at least one of the following conditions applies:
    - Is not a 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 Section 5.7.2 during the intervention period and for at least 130 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) 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.

- Additional requirements for pregnancy testing during and after study intervention are located in Section 5.7.2.
- The investigator is responsible for review of medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a woman with an early undetected pregnancy.
- Contraceptive use by women should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.

7. Male subjects are eligible to participate if they agree to the following during the intervention period and for at least 130 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 [Section 5.7.2]) 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.

8. HIV-infected subjects must meet these additional criteria:

    - 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.
    - Have well-controlled HIV on ART, defined as:
        - must have a CD4+ T cell count >350 cells/mm3 at time of screening;
        - must have achieved and maintained virologic suppression defined as confirmed HIV RNA level below 50 or the LLOQ (below the limit of quantification) using the locally available assay at the time of screening and for at least 12 weeks prior to screening;

- 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).

5.1.2.3 Subject Inclusion Criteria for Arm 3

In order to be eligible for participation in Arm 3 of this trial, the subject must meet the following inclusion criteria:

1. Be ≥18 years of age on day of signing informed consent.
2. Voluntarily agreed to participate by providing documented informed consent. The subject may also provide consent for Future Biomedical Research. However, the subject may participate in the main trial without participating in Future Biomedical Research.
3. Have a histologically- or cytologically confirmed advanced/metastatic solid tumor or lymphoma by pathology report and who 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. Tumor types of greatest interest include, but are not limited to, malignant melanoma, HNSCC, breast adenocarcinoma, and lymphomas.
4. Have Stage III or Stage IV disease that is not surgically resectable.
5. Has metastatic liver involvement that does not exceed one-third of the total liver volume in subjects to be treated by liver IT injection. Hepatocellular carcinoma subjects are excluded from eligibility of intratumoral liver injection. In addition, has at least one injectable liver lesion with the following:
    - The injectable liver lesion is amenable to image-guided intratumoral injection and biopsy via ultrasound guidance or cross-sectional imaging (CT/MRI).
    - Injectable lesion(s) must be ≥1 cm in longest diameter and ≤10 cm in longest diameter.
6. Have at least 1 distant and/or discrete noninjected lesion that is amenable to biopsy via visual inspection or amenable to biopsy via image guidance, such as ultrasound or CT/MRI. This lesion must be measurable as defined by the response criteria used to assess the subject (RECIST 1.1 for solid tumors or revised IWG criteria for lymphomas).
    - For RECIST 1.1, ≥1 cm in longest diameter for non-nodal lesions, or ≥1.5 cm in 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.
7. Have an ECOG Performance Status of 0 or 1.
8. Demonstrate adequate organ function as defined by Table 1.

    All screening labs should be performed within 7 days prior to treatment initiation.

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 Section 5.7.2 during the intervention period and for at least 130 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) 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.
    - Additional requirements for pregnancy testing during and after study intervention are located in Section 5.7.2.
    - The investigator is responsible for review of medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a woman with an early undetected pregnancy.
    - Contraceptive use by women should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.

10. Male subjects are eligible to participate if they agree to the following during the intervention period and for at least 130 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 [Section 5.7.2]) 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.

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

    - 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.
    - Have well-controlled HIV on ART, defined as:
        - must have a CD4+ T cell count >350 cells/mm3 at time of screening;
        - must have achieved and maintained virologic suppression defined as confirmed HIV RNA level below 50 or the LLOQ (below the limit of quantification) using the locally available assay at the time of screening and for at least 12 weeks prior to screening;
        - 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).

5.1.3 Subject Inclusion Criteria for Part II - Expansion Cohorts

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

2. Voluntarily agreed to participate by providing documented informed consent. The subject may also provide consent for Future Biomedical Research. However, the subject may participate in the main trial without participating in Future Biomedical Research.

3. Have at least one measurable lesion which is amenable to injection. Tumor lesions situated in a previously irradiated area are considered measurable if progression has been demonstrated in such lesions. Intratumoral injection for cutaneous lesions may be performed via visual inspection. Intratumoral injection for subcutaneous lesions may be performed via ultrasound guidance or via palpation. This injectable lesion must 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 subjects. The longest diameter for an injectable lesion must be ≤10 cm for both solid tumors and nodal lesions in solid tumor subjects.
      OR
    - Multiple coalescing, superficial lesions which in aggregate have a longest diameter of ≥1 cm and ≤10 cm.

4. In subjects to be treated by liver IT injection, has metastatic liver involvement that does not exceed one-third of the total liver volume. Hepatocellular carcinoma subjects are excluded from eligibility for intratumoral liver injection. In addition, has at least one injectable liver lesion that meets both the following conditions:
    - The injectable liver lesion is amenable to image-guided intratumoral injection and biopsy via ultrasound guidance or cross-sectional imaging (CT/MRI). AND
    - Injectable lesion(s) must be ≥1 cm in longest diameter and ≤10 cm in longest diameter.
5. Subjects with any one of the following solid malignancies who meet all listed conditions of eligibility for an expansion cohort:
    - Cohort A: HNSCC of the oral cavity, oropharynx, hypopharynx, or larynx; anti-PD-1/PD-L1 refractory (see Table 2) metastatic or recurrent. Subjects may not have a primary tumor site of the nasopharynx (any histology).
        - Have histologically confirmed Stage III, IVa, or IVb disease per TNM staging, AJCC Eighth edition, with recurrent or persistent disease after definitive chemoradiation, deemed unresectable and considered refractory to both platinum-based combination chemotherapy and anti-PD-1/PD-L1 antibody therapy.

          OR
        - Have histologically confirmed Stage IVc disease per TNM staging, AJCC Eighth edition, considered refractory to platinum-based combination chemotherapy and anti-PD-1/PD-L1 antibody therapy.
    - Cohort B: Either anti-PD-1/PD-L1 treatment-naïve or refractory (see Table 2) TNBC
        - Have confirmed unresectable locally advanced or metastatic TNBC as locally determined according to the ASCO-CAP guidelines [27] on a newly obtained core or excisional biopsy from a not previously irradiated, tumor lesion.
        - Have received at least one prior systemic treatment for breast cancer and have documented disease progression on or after their most recent therapy.
        - Have been previously treated with an anthracycline and/or taxane in the (neo)adjuvant or metastatic setting unless there was a medical contraindication to this treatment regimen.
        - Have LDH <2.5 × ULN [28] [29] [30].
    - Cohort C: Other anti-PD-1/PD-L1 treatment-naïve solid tumors with liver metastases (including pancreatic cancer, non-MSI-H CRC, and other solid tumors. MSI-H status is to be determined by local testing).
        - Have histologically or cytologically confirmed Stage IV solid tumor that is not surgically resectable.

Table 2 Anti-PD-1/PD-L1 Antibody Refractory Definition

Patients must have progressed on treatment with an anti-PD-1/PD-L1 monoclonal antibody (mAb) administered either as monotherapy, or in combination with other checkpoint inhibitors or other therapies. anti-PD-1/PD-L1 treatment progression is defined by meeting all of the following criteria: a) Has received at least 2 doses of an approved anti-PD-1/PD-L1 mAb. b) Has demonstrated disease progression after anti-PD-1/PD-L1 as defined by RECIST v1.1. The initial evidence of disease progression (PD) is to be confirmed by a second assessment no less than 4 weeks from the date of the first documented PD, in the absence of rapid clinical progression.[1,2.] c) Progressive disease has been documented within 12 weeks from the last dose of anti-PD-1/PD-L1 mAb. 1. Seymour et al; iRECIST: Guidelines for response criteria for use in trials testing immunotherapeutics. Lancet Oncol 18: e143-52 2. This determination is made by the investigator. Once PD is confirmed, the initial date of PD documentation will be considered the date of disease progression.

6. Complete resolution of toxic effect(s) of the most recent prior chemotherapy to Grade 1 or baseline (except alopecia). If the subject received major surgery or radiation therapy of >30 Gy, they must have recovered from the toxicity and/or complications from the intervention.
7. Have an ECOG Performance Status of 0 or 1.
8. Demonstrate adequate organ function as defined by Table 1. All screening labs should be performed within 7 days prior to treatment initiation.
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 Section 5.7.2 during the intervention period and for at least 130 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) 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.
- Additional requirements for pregnancy testing during and after study intervention are located in Section 5.7.2.
- The investigator is responsible for review of medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a woman with an early undetected pregnancy.
- Contraceptive use by women should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.

10. Male subjects are eligible to participate if they agree to the following during the intervention period and for at least 130 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 [Section 5.7.2]) 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.

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

    - 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.
    - Have well-controlled HIV on ART, defined as:
        - must have a CD4+ T cell count >350 cells/mm3 at time of screening;
        - must have achieved and maintained virologic suppression defined as confirmed HIV RNA level below 50 or the LLOQ (below the limit of quantification) using the locally available assay at the time of screening and for at least 12 weeks prior to screening;

- 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).

5.1.4 Subject Exclusion Criteria for Part I - Dose Escalation and Confirmation

The subject must be excluded from participating in any arm of the trial if the subject:

5.1.4.1 Exclusion Criteria for Arms 1, 2, and 3

1. Has had chemotherapy, definitive radiation, or biological cancer therapy within 4 weeks (2 weeks for palliative radiation) prior to the first dose of study 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.
2. 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-1454.

   Note: Prior exposure to immunotherapeutics is allowed, including PD-1 and PD-L1 inhibitors, provided patient did not experience a ≥ Grade 3 drug-related toxicity on monotherapy with a PD-1 or PD-L1 inhibitor.
3. Is expected to require any other form of antineoplastic therapy while on study.
4. 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.
5. 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 subjects who underwent successful definitive resection of basal cell carcinoma of the skin, superficial bladder cancer or in situ cervical cancer.
6. Has clinically active central nervous system metastases and/or carcinomatous meningitis. Subjects 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.
7. Has had a severe hypersensitivity reaction to treatment with a monoclonal antibody.
8. 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.

9. Has a history of vasculitis.
10. Has an active infection requiring therapy.
11. Has a history of (non-infectious) pneumonitis that required steroids or current pneumonitis.
12. Has undergone prior allogeneic hematopoietic stem cell transplantation within the last 5 years.

    Note: Subjects who have had a transplant greater than 5 years ago are eligible as long as there are no symptoms of GVHD.
13. Has Hepatitis B or C infections, or is known to be positive for Hepatitis B surface antigen/Hepatitis B virus (HBsAg/HBV) DNA or Hepatitis C Antibody (Hep C Ab) or ribonucleic acid (RNA). Active Hepatitis C virus (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.
14. Has a history or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the study, interfere with the subject's participation 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 subject to participate, in the opinion of the treating investigator.
15. Has known psychiatric or substance abuse disorders that would interfere in cooperation with the requirements of the trial.
16. Is pregnant or breastfeeding, or expecting to conceive or father children within the projected duration of the study.
17. 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 subjects should be recovered.
18. Has received a live vaccine within 30 days prior to first dose.
19. Has a history of re-irradiation for HNSCC at the projected injection site.
20. 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.
21. HIV-infected subjects with history of Kaposi's sarcoma and/or multicentric Castleman's disease.
22. HIV-infected subjects who have had an HIV-related opportunistic infection within 6 months.

23. 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 the MOA of the 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.

5.1.4.2 Exclusion Criteria for Crossover Into Arm 2

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

1. Has had chemotherapy, definitive radiation, or biological cancer therapy within 4 weeks (2 weeks for palliative radiation) prior to the first dose of study 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.
2. 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-1454.

   Note: Prior exposure to MK-1454 is allowed, provided the patient has a washout period of at least 14 days and did not experience Grade 3 or higher drug-related toxicity.

   Note: Prior exposure to immunotherapeutics is allowed, including PD-1 and PD-L1 inhibitors, provided patient did not experience a ≥ Grade 3 drug-related toxicity on monotherapy with a PD-1 or PD-L1 inhibitor
3. Is expected to require any other form of antineoplastic therapy while on study.
4. 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.
5. Has clinically active central nervous system metastases and/or carcinomatous meningitis. Subjects 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.
6. Has had a severe hypersensitivity reaction to treatment with a monoclonal antibody.
7. Has an active infection requiring therapy.
8. Has a history of (non-infectious) pneumonitis that required steroids or current pneumonitis.

9. Has a history or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the study, interfere with the subject's participation 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 subject to participate, in the opinion of the treating investigator.
10. Is pregnant or breastfeeding, or expecting to conceive or father children within the projected duration of the study.
11. Has not fully recovered from any effects of major surgery, and be 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 subjects should be recovered.
12. Has received a live vaccine within 30 days prior to first dose.
13. Has a history of re-irradiation for SCCHN at the projected injection site.
14. 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.

5.1.5 Exclusion Criteria for Part II - Expansion Cohorts

1. Has had chemotherapy, definitive radiation, or biological cancer therapy within 4 weeks (2 weeks for palliative radiation) prior to the first dose of study 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 (this includes subjects with previous immunomodulatory therapy with residual immune-related AEs). Subjects receiving ongoing replacement hormone therapy for endocrine immune-related AEs will not be excluded from participation in this study.
2. 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-1454.

   Note: Where prior exposure to immunotherapeutics is allowed, including PD-1 and PD-L1 inhibitors, patient has experienced a Grade 3 or higher drug-related toxicity on monotherapy with a PD-1 or PD-L1 inhibitor requiring steroid treatment (>10 mg/day prednisone or equivalent) for >12 weeks or CTCAE Grade 2 or higher pneumonitis regardless of steroid treatment.
3. Is expected to require any other form of antineoplastic therapy while on study.
4. 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 or designee.

5. 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 subjects who underwent successful definitive resection of basal cell carcinoma of the skin, superficial bladder cancer, in situ cervical cancer, or other in situ cancers.

6. Has clinically active central nervous system metastases and/or carcinomatous meningitis. Subjects 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.

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

8. 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.

9. Has a history of vasculitis.

10. Has a history of interstitial lung disease.

11. Has an active infection requiring therapy.

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

13. Has a history or current evidence of a gastrointestinal (GI) condition (eg, inflammatory bowel disease, Crohn's disease, ulcerative colitis) or impaired liver function or diseases that in the opinion of the investigator may significantly alter the absorption or metabolism of oral medications; any condition, therapy, or laboratory abnormality that might confound the results of the study, interfere with the subject's participation for the full duration of the study, make administration of the study drugs hazardous, or make it difficult to monitor adverse effects such that it is not in the best interest of the subject to participate, in the opinion of the treating investigator.

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

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

15. Has Hepatitis B or C infections, or is 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.

16. HIV-infected subjects with history of Kaposi's sarcoma and/or multicentric Castleman's disease.
17. HIV-infected subjects who have had an HIV-related opportunistic infection within 6 months.
18. 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 the MOA of the 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.
19. Has been treated with a STING agonist (eg, MK-1454, ADU-S100).
20. Has a history or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the study, interfere with the subject's participation 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 subject to participate, in the opinion of the treating investigator.
21. Has known psychiatric or substance abuse disorders that would interfere in cooperation with the requirements of the trial.
22. Is pregnant or breastfeeding or expecting to conceive or father children within the projected duration of the study.
23. Has not fully recovered from any effects of major surgery and be 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 subjects should be recovered.
24. Has received a live vaccine within 30 days prior to first dose.
25. Has a history of re-irradiation for SCCHN at the projected injection site in the head and neck.
26. 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 in the head or neck.
27. Has experienced weight loss >10% over 2 months prior to first dose of study therapy.
28. Has clinically relevant ascites at baseline (defined as requiring paracentesis) or with moderate radiographic ascites. A minimal amount of radiographic ascites is allowed.

29. For Cohort C, subjects with MSI-H CRC are excluded.

5.2 Trial Treatment(s)

The human starting dose of MK-1454 for IT injection is based on an integration of nonclinical toxicological, pharmacological, and efficacy data (see Section 4.2.2). The treatments to be used in Arm 1 and Arm 2 of this trial are outlined below in Table 3 and Table 4, respectively, and for Arm 3 are provided in Table 5.

Dose escalation will proceed based on emerging safety and tolerability data of MK-1454 as monotherapy and in combination with pembrolizumab. For each dose level, an assessment will be made of the safety and tolerability data in order to define the next dose level to be tested. For the ATD phase, in both Arm 1 and Arm 2, dose escalation may proceed in increments of up to 300%. For example, during ATD, in the absence of DLTs and toxicity, dose escalation may proceed from CCI [redacted] For the mTPI phase, in both Arm 1 and Arm 2, dose escalation may proceed in increments of 30% to 100%. For example, during mTPI, in the absence of DLTs and toxicity, dose escalation may proceed from CCI [redacted] Intermediate doses between CCI [redacted] ments are within a 300% increase from prior dose for the ATD phase and within a 30% to 100% increase from prior dose for the mTPI phase. For example, in the ATD phase with toxicity findings, dose escalation may proceed from CCI [redacted] See Section 5.2.2 for dose delays fulfilling DLT criteria during for directions on how to proceed in the case of an AE.

Arm 3 will initiate in an ATD at CCI [redacted] and escalate as shown in Figure 2 and Table 5.

Table 3 Trial Treatment for MK-1454 IT Monotherapy (Arm 1)

Drug, Vaccine, Biologic, Device, etc.	Dose/ Potency	Dose Frequency	Route of Administration	Regimen/ Treatment Period	Use
MK-1454	Range: CCI [redacted]	CCI [redacted]	Intratumoral Via visual inspection for cutaneous lesions, and via ultrasound guidance or palpation for subcutaneous lesions, as needed	CCI [redacted]	Experimental

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

Table 4 Trial Treatment for MK-1454 IT in Combination with Pembrolizumab (Arm 2)

Drug, Vaccine, Biologic, Device, etc.	Dose/ Potency	Dose Frequency	Route of Administration	Regimen/ Treatment Period[a]	Use
Pembrolizumab	200 mg	CCI	IV infusion	Day 1 of each 21-day cycle	Experimental
MK-1454[b]	Range: CCI	CCI	Intratumoral Via visual inspection for cutaneous lesions, and via ultrasound guidance or palpation for subcutaneous lesions, as needed	CCI	Experimental

[a] Cohorts staggered at least 2 dose levels behind Arm 1, triggered by at least 1 of the following: 1) The CCI MK-1454 cohort is completed, 2) ≥ Grade 2 toxicity as assessed by the investigator to be related, probably related, or possibly related to the drug at any dose level, or 3) Elevation of systemic TNF-α in blood above baseline levels by ≥3-fold for a given subject at any time during the first cycle of MK-1454 (eg, increase from 20 pg/mL to 60 pg/mL).

[b] MK-1454 will be administered within 0.5 to 4 hours following completion of pembrolizumab infusion, as applicable.

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

Table 5 Trial Treatment for MK-1454 Visceral IT in Combination 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-1454	CCI	ATD phase – Q3W mTPI[b]: Dose frequency to escalate as follows: CCI	Intratumoral (Visceral) Via ultrasound or cross-sectional imaging (CT/MRI) guidance for liver lesions, as needed	CCI	Experimental

ATD = Accelerated titration design; mTPI = modified toxicity probability interval

[a] MK-1454 will be administered within 0.5 to 4 hours following completion of pembrolizumab infusion.

[b] Dose frequency of visceral IT injections may increase with each cohort based on subject tolerance and clinical assessment of safety. Once a dose level is administered at the highest frequency and cleared by mTPI design, the next dose level may begin.

Trial treatment should begin on the day of treatment allocation/randomization or as close as possible to the date on which the subject is allocated/assigned.

All supplies indicated in Table 3 through Table 5 above will be provided centrally by the Sponsor or locally by the trial site, subsidiary or designee, depending on local country operational or regulatory requirements.

For any commercially available product that is provided by the trial site, subsidiary or designee every attempt will 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.

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

5.2.1 Dose Selection/Modification

5.2.1.1 Dose Selection (Preparation)

5.2.1.1.1 Dose Selection in Part I - Dose Escalation and Confirmation (Arm 1, Arm 2, and Arm 3)

MK-1454 will be administered as a sterile aqueous solution with a total volume of injectate of up to 4 mL per treatment visit for all injected lesions combined for Arm 1 and Arm 2. For Arm 3, the maximum injectate volume will be 3 mL. MK-1454 will be administered by injection into cutaneous, subcutaneous, and/or nodal lesions that are visible, palpable, or detectable by ultrasound guidance or cross-sectional imaging guidance as clinically appropriate. As well as into liver lesions that are detectable by ultrasound guidance or cross-sectional imaging guidance as clinically appropriate.

During dose escalation in both Arm 1 and Arm 2 (Parts A-D), each subject at a given dose level will receive a fixed dose of MK-1454 diluted in a volume of 0.5 mL to 4 mL of injectate. For Arm 3, each subject at a given dose level will receive a fixed dose of MK-1454 diluted in a volume of 1.0 mL to 3 mL of injectate. See Table 3 and Table 4 and Table 5 for dose level range within Arm 1, Arm 2, and Arm 3 respectively. The volume of injectate delivered to each lesion will be based on the longest dimension of the target lesion as shown in Table 6 and Table 7, 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 for Arm 1 and Arm 2, and 3 mL per treatment visit for Arm 3. As clinically feasible, injection of more than one lesion may be performed. Injectate volume per lesion based on lesion size is specified in Table 6 for cutaneous lesions and in Table 7 for subcutaneous lesions. See Appendix 12.3 for further guidance on lesion injection prioritization.

For cutaneous lesions, up to a maximum of 8 lesions may be injected per treatment visit, with a minimum injectate volume of 0.5 mL per lesion. For subcutaneous tumor lesions, a maximum of 4 lesions may be injected per treatment visit, with a minimum injectate volume of 1.0 mL. For visceral lesions, a maximum of 3 lesions may be injected per treatment visit, with a minimum injectate volume of 1.0 mL. The total injectate volume per treatment visit per subject is of 4 mL for subjects in Arm 1 and Arm 2, and 3 mL for subjects in Arm 3. Documentation of dose volume administered per lesion will be obtained.

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 6 for individual lesions may be permitted upon approval by the Sponsor Medical Monitor or designee under selected scenarios.

Table 6 Determination of MK-1454 Injection Volume for Intratumoral Injection of Cutaneous Lesions Based on Lesion Size (Part I - Arm 1 and Arm 2)

Lesion Size (longest dimension)	Injection Volume
>5 cm	≤4 mL
>2.5 cm to 5 cm	≤2 mL
>1.5 cm to 2.5 cm	≤1 mL
≥1.0 cm to 1.5 cm	0.5 mL

Details on dose calculation, preparation, and administration of MK-1454 are provided in the Procedures Manual.

Table 7 Determination of MK-1454 Injection Volume for Intratumoral Injection into Subcutaneous Lesions Based on Lesion Size (Part I Arm 1 and Arm 2)

Lesion Size (longest dimension)	Injection Volume
>5 cm	≤4 mL
>2.5 cm to 5 cm	≤2 mL
>1.5 cm to 2.5 cm	≤1.5 mL
≥1.0 cm to 1.5 cm	1.0 mL

5.2.1.1.2 Dose Selection in Part II - Expansion Cohorts (Cohorts A and B)

The starting dose for Cohorts A and B is confirmed to be [redacted] based on the safety, PK, and PD data from dose escalation and confirmation of MK-1454 IT in combination with pembrolizumab in Arm 2 (Table 8). The minimum number of lesions per subject per treatment visit to be injected is 1 lesion, and the maximum number of lesions to be injected per subject per treatment visit is 3 lesions. Each subject at this [redacted] dose level will receive a fixed dose of intratumoral MK-1454 prepared in a volume of 1 mL to 3 mL of injectate, based on lesion size (see Table 9).

The starting dose for Cohort C will be the preliminary RP2D (both dose level and frequency) from the dose escalation and confirmation of MK-1454 visceral IT established in combination with pembrolizumab in Arm 3.

Dose volume for Expansion Cohorts will be determined by lesion size, as detailed in Table 9.

Table 8 Trial Treatment for MK-1454 IT in Combination with Pembrolizumab Part II (Expansion Cohorts A, B, and C)

Drug, Vaccine, Biologic, Device, etc.	Dose/ Potency	Dose Frequency	Route of Administration	Regimen/ Treatment Period	Use
Pembrolizumab	200 mg	Q3W	IV infusion	Day 1 of each 21-day cycle	Experimental
MK-1454[a]	Cohorts A and B: CCI Cohort C: Preliminary RP2D established in Arm 3	Cohorts A and B: CCI Cohort C: TBD[b]	Intratumoral Via visual inspection for cutaneous lesions, or via ultrasound or cross-sectional imaging (CT/MRI) guidance, as needed	Cohorts A and B: CCI Cohort C: TBD[b]	Experimental

CT = computed tomography; MTD/MAD = maximum tolerated dose/maximum administered dose; MRI = magnetic resonance imaging; QW = once each week; Q3W = once every 3 weeks; RP2D = Recommended Phase 2 Dose; TBD = to be determined.

[a] MK-1454 will be administered within 0.5 to 4 hours following completion of pembrolizumab infusion.

[b] Dose frequency will be determined in Arm 3.

Table 9 Injectate Volume for Arm 3 Visceral IT (Part I) and Expansion Cohorts (Part II)

Lesion Size (longest dimension)	Injection Volume
>5 cm	3 mL
>2.5 cm to 5 cm	2 mL
≥1.0 cm to 2.5 cm	1 mL

5.2.1.2 Accelerated Titration Design in Arms 1, 2, and 3

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

Single subjects will be enrolled into sequential dose levels with up to 300% dose increment increases from the previous dose, eg CCI Dose ranges are outlined in Table 3, Table 4, and Table 5. Up to 3 subjects per cohort may be allowed in the event of simultaneous enrollment. The first 2 subjects who will receive MK-1454 treatment at a new dose level must be at least 7 days apart. The subsequent dose level to be tested in the next cohort of subjects will be communicated to the investigator or designee following each dose escalation decision meeting.

The dose for ending ATD will be the dose level at which one of the following occurs:

- The CCI cohort is completed.
- ≥ Grade 2 toxicity as assessed by the investigator to be related, probably related, or possibly related to the drug according to NCI CTCAE v4.

- Elevation of systemic TNF-α in blood above baseline levels by ≥3-fold in a given subject during the first cycle of MK-1454 (Arm 1 and 2 only).

5.2.1.3 Dose Escalation and Confirmation During Modified Toxicity Probability Interval Design

Dose escalation and confirmation of MK-1454 will proceed from ATD phase (Part A, Part C, or Part E) to mTPI phase (Part B, Part D, or Part F) once at least 1 of the 3 triggering criteria is met (see Section 2.1) [31]. Subjects will be enrolled via IWRS according to the dose escalation and confirmation guidelines outlined in Section 5.2. The target DLT rate is 30%, with a tolerance interval of 3%. The specific dose levels for the ATD and mTPI phases will be determined through emerging safety and toxicity data. For the mTPI phase, dose escalation will proceed at dose increments between 30% and 100% of the prior dose level. The dose to be tested in the next cohort of subjects will be communicated to the investigator or designee following each dose escalation decision meeting. Depending on the accrual rate, there may be a minimum of 3 and up to 6 subjects enrolled within 21 days of initiation at each new dose level. The first 2 subjects in each new dose level will receive MK-1454 treatment at least 7 days apart. Based on the occurrence of DLTs, up to 14 subjects may enroll per dose level. Enrollment will be monitored through IWRS.

Dose escalation based on the mTPI design will be conducted according to Table 10, which provides the rules for determining the next dose [32] [33]. In Table 10, the columns show the number of patients treated at a dose level, and the rows correspond to the number of subjects who experience a DLT. The entries of the table are dose-finding decisions: E, S, D, and DU, which represent the following parameters: Escalating the dose, Staying at the same dose, De-escalating the dose, and excluding the Dose from the trial due to Unacceptable toxicity. For example, if 0 out of the first 3 subjects in a given dose level develop a DLT, then the dose can escalate to the next level without further expansion. If 2 subjects out of the first 3 subjects develop a DLT, then the dose will be de-escalated to the next lower dose level. If 3 out of the first 3 subjects develop a DLT, then this indicates an unacceptable toxicity. If 1 out of the first 3 subjects of a given dose level develops a DLT, then the current dose level cohort will be expanded by continuing enrollment according to Table 10. The same principle will be applied whether 3, 4, 5 or 6 subjects are initially enrolled in the same dose cohort according to Table 10.

The number of subjects who are enrolled at each dose is capped to minimize the exposure to a dose that may be unacceptably toxic (denoted as DU in Table 10). To find out how many more subjects may be enrolled, count steps in a diagonal direction (down and to the right) from the cell (3 subjects, 1 DLT) to the first cell marked DU. For example, if 1/3 of the subjects have experienced a DLT at a given dose level, then no more than an additional 3 subjects 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 subjects experience a DLT (ie, 4/6 subjects with DLT in Table 10).

De-escalation (D) or excluding the dose from the trial due to unacceptable toxicity (DU) at the starting dose level of Arm 1 of the study indicates stopping of the trial. Escalation (E) at the highest dose level indicates staying at that level. During dose escalation and confirmation, it may be acceptable to de-escalate to an intermediate, not predefined and not

previously-studied dose if evaluation of toxicity at such a dose is desired. If this approach is taken, 3-6 new subjects 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 subjects 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 subjects may be enrolled at a lower dose if "D" or "DU" is indicated, or at a higher dose if "E" is indicated. Establishment of the MTD/MAD for the combination of MK-1454 and pembrolizumab in Arm 2 requires that at least half of the 14 subjects in the MTD/MAD cohort have had no prior exposure to MK-1454 (ie, non-crossover subjects). Priority for enrollment in the MTD/MAD confirmation cohort of Arm 2 will be given to MK-1454-naïve subjects.

While the mTPI design is applied separately to Arm 1 and Arm 2, doses of MK-1454 used in combination with pembrolizumab via cutaneous or subcutaneous IT injection will be at least 2 dose levels behind the MK-1454 monotherapy dose, and will not exceed the MTD for monotherapy. If an MTD for monotherapy (Arm 1) is established, then the dose of MK-1454 in Arm 2 may continue escalation up to that established dose.

For Arm 3, dose escalation will proceed by incrementing dose frequency then dosage level. The initial dose frequency of visceral IT will be CCI. Per mTPI design, frequency will increase in the next cohort to CCI, then to CCI thereafter. Further increase in visceral IT injection frequency to CCI for 2 cycles, followed by CCI thereafter in a subsequent cohort will be based on mTPI design. After Cycle 3, the frequency of visceral IT administration may be modified based on clinical assessment of safety by the investigator in consultation with Sponsor. Dose decisions will be made jointly with the investigators. Enrollment into Arm 3 will be monitored through IWRS.

Table 10 Dose-finding Rules per mTPI Design

	Number of subjects evaluable for DLT at current dose											
Number of subjects with at least 1 DLT	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**
0	E	E	E	E	E	E	E	E	E	E	E	E
1	S	S	S	E	E	E	E	E	E	E	E	E
2	D	S	S	S	S	S	S	S	E	E	E	E
3	DU	DU	D	S	S	S	S	S	S	S	S	S
4		DU	DU	DU	D	D	S	S	S	S	S	S
5			DU	DU	DU	DU	DU	D	S	S	S	S
6				DU	DU	DU	DU	DU	DU	D	S	S
7					DU	DU	DU	DU	DU	DU	DU	D
8						DU	DU	DU	DU	DU	DU	DU
9							DU	DU	DU	DU	DU	DU
10								DU	DU	DU	DU	DU
11									DU	DU	DU	DU
12										DU	DU	DU
13											DU	DU
14												DU

D = De-escalate to the next lower dose
DU = The current dose is unacceptably toxic
E = Escalate to the next higher dose
S = Stay at the current dose
Target toxicity rate = 30%
Flat non-informative prior Beta (1,1) is used as a prior and $\varepsilon1=\varepsilon2=0.03$ [31] [34]

5.2.2 Definition of Dose-Limiting Toxicity

Dose-limiting toxicities will be defined from toxicities observed during the first cycle of treatment (21 days) for each dose level. See Section 5.9 for rules on replacement of subjects in the DLT period.

Subjects who experience a DLT in Cycle 1 will be discontinued from treatment. However, if in the opinion of the investigator the subject is deriving clinical benefit from the study treatment (for example a marked reduction in tumor burden), the subject may be allowed to continue on the study at a reduced dose level of MK-1454 upon resolution of the DLT to a ≤ Grade 1 AEs or to baseline, and upon discussion with the Sponsor Therefore, flexibility of rechallenge of MK-1454 at a lower dose per dose modification guidance below subsequent to a DLT may be considered.

The occurrence of any of the following toxicities during Cycle 1, if assessed by the investigator to be related, probably related, or possibly related to the drug will be considered a DLT, excluding toxicities clearly not related to the drug, 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
    - medical intervention is required, or
    - the abnormality leads to hospitalization, or
    - the abnormality persists for >1 week
5. Febrile neutropenia Grade 3 or Grade 4
6. Any drug-related toxicity that causes treatment discontinuation or dose delay >7 days between consecutive doses during Cycle 1
7. Any drug-related toxicity that causes a greater than 2-week delay in initiation of Cycle 2
8. Any elevated AST or 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

5.2.3 Dose Modification Due to Adverse Events

The Common Terminology Criteria for Adverse Events, version 4.0 (CTCAE 4.0) must be used to grade the severity of AEs. The investigator may attribute each toxicity event to MK-1454 alone, or to pembrolizumab alone, or to combination therapy. Use dose modification according to Table 11, Table 12, , Table 14, or Table 15. If a dose modification for toxicity occurs with MK-1454, the dose may not be re-escalated to the dose that preceded the dose modification. Dose modifications are always based on the previous cycle.

Subjects may have a maximum of 2 dose modifications of MK-1454 throughout the course of the study for toxicities, as described in Section 5.2.3.1. If further toxicity occurs or the criteria for resuming treatment are not met, the subject must be discontinued from the agent. If a subject 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 one agent and not the other agent is appropriate if, in the opinion of the investigator, the toxicity is clearly related to one of the study drugs. For example, in the combination arms (Arm 2 and Arm 3), if MK-1454 is held due to an AE attributed to that drug, then pembrolizumab may continue to be administered. Appropriate documentation is required regarding which drug the investigator is attributing the AE to. If, in the opinion of the investigator, the toxicity is related to the combination of 2 agents, then both drugs should be held according to recommended dose modifications.

AEs (both nonserious and serious) associated with MK-1454 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.

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

5.2.3.1 Dose Modification for MK-1454 Drug-related AEs in Part I - Arm 1, Arm 2, and Arm 3

Dose modification guidelines for MK-1454 drug-related AEs are presented in Table 11. In Arm 2, pembrolizumab treatment will be modified for the AEs as described below in . See Table 15 for treatment guidelines for cytokine release syndrome.

Table 11 MK-1454 Dose Modification Guidelines for Drug-related AEs in Monotherapy (Arm 1), Combination Therapy (Arm 2), and Combination Therapy Visceral IT (Arm 3)

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 one 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 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 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
• Any Grade 3[a] hematological toxicity	Yes[a]	Treatment may be restarted when AE resolves back to baseline or to Grade 1[b]	First, decrease dose by one dose level If AE persists, and upon discussion with Sponsor, then consider modification of dosing schedule per below: **<u>Arm 1 and Arm 2</u>:** **Cycle 1, 2, and 3**: Reduce dosing schedule to CCI [redacted] **<u>Arm 3:</u>** **Cycle 1 and 2:** Reduce dosing schedule to CCI [redacted] **<u>Arm 1 and Arm 2</u>:** **Cycle 4 and beyond:** Maintain dosing schedule at CCI [redacted] unless AE persists for 2 additional cycles, then reduce dosing schedule to CCI [redacted] **<u>Arm 3:</u>** **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 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 hematological toxicity	Yes	Treatment may be restarted when AE resolves back to baseline or to Grade 1[b]	First, decrease dose by one dose level If AE persists, and upon discussion with Sponsor, then consider modification of dosing schedule per below: **<u>Arm 1 and Arm 2</u>:** **Cycle 1, 2, and 3:** Reduce dosing schedule to CCI **<u>Arm 3:</u>** **Cycle 1 and 2:** Reduce dosing schedule to CCI **<u>Arm 1 and Arm 2:</u>** **Cycle 4 and beyond**: Maintain dosing schedule at CCI s unless AE persists for 2 additional cycles, then reduce dosing schedule to CCI **<u>Arm 3:</u>** **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*
Nonhematological toxicities:				
• Any Grade 1 nonhematological toxicity • Grade 2 alopecia • Grade 2 fatigue	No	N/A	N/A	N/A

Toxicity	Hold Treatment	Criteria for Restarting Treatment	Dose/Schedule for Restarting Treatment	Criteria for Discontinuation after Consultation with Sponsor
• 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 one 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 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
• Any Grade 3 nonhematological toxicity	Yes	Treatment may be restarted when AE resolves back to baseline or to Grade 1[b]	First, decrease dose by one 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 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 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**[c]	First, decrease dose by one 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 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*
AE = adverse event; Q3W = every 3 weeks; CCI				

[a] For Lymphoma subjects, 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 both solid tumor and lymphoma subjects.

[b] In case toxicity does not resolve back to baseline or to Grade 1 within 12 weeks following dose modification, MK-1454 should be considered for discontinuation after consultation with the Sponsor.

[c] After any Grade 4 drug-related AE, subjects 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)

5.2.3.2 Dose Modification for MK-1454 in Part II - Expansion Cohorts

Guidelines for dose modification and/or treatment discontinuation for treatment-related injection site reactions and for CRS AEs are provided in Table 12.

Table 12 Guidelines for Management of MK-1454 Intratumoral Injection Site Reactions

NCI CTCAE Grade	MK-1454 Dose Modification	Treatment
Grade 1 Tenderness with or without associated symptoms (eg, warmth, erythema, itching)	No dose reduction warranted.	Observe. Dose to be held per medical assessment of the investigator. Analgesia as needed.
Grade 2 Pain; lipodystrophy; edema; phlebitis	Per medical assessment of the investigator: • Consider holding dose until resolution to Grade 1 or baseline. • Consider decreasing dose of IT MK-1454 to 450 µg and limit injections to a maximum of 2 lesions per study visit. • If AE persists, discuss continuation with Sponsor.	Observe. Local care to injection site. Analgesia as needed. Consider injection into a different lesion, if available.
Grade 3 Ulceration or necrosis; severe tissue damage; operative intervention indicated	• Hold dose until resolution to Grade 1 or Baseline. • Decrease dose of IT MK-1454 to 450 µg and limit injections to a maximum of 2 lesions per study visit. • If AE persists, discuss continuation with Sponsor.	Wound care with consultation from institutional wound care specialist. Analgesia as needed. Consider injection into a different lesion, if available.
Grade 4 Life-threatening consequences; urgent intervention indicated	• Permanently discontinue IT MK-1454 treatment.	Aggressive wound care with surgical consultation. Analgesia as needed.

NCI CTCAE ver. 5

5.2.3.3 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 13.

Table 13 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).

Dose modification and toxicity management of infusion-reactions related to pembrolizumab

Pembrolizumab may cause severe or life-threatening infusion-reactions including severe hypersensitivity or anaphylaxis. Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion. Dose modification and toxicity management guidelines on pembrolizumab associated infusion reaction are provided in Table 14.

Table 14 Pembrolizumab Infusion Reaction Dose Modification and Treatment Guidelines

NCI CTCAE Grade	Treatment	Premedication at Subsequent Dosing
Grade 1 Mild reaction; infusion interruption not indicated; intervention not indicated	Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator.	None
Grade 2 Requires therapy or infusion interruption but responds promptly to symptomatic treatment (eg, antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for ≤24 hrs.	**Stop Infusion.** Additional appropriate medical therapy may include but is not limited to: IV fluids Antihistamines NSAIDs Acetaminophen Narcotics Increase monitoring of vital signs as medically indicated until the subject 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 (e.g. from 100 mL/hr to 50 mL/hr). Otherwise dosing will be held until symptoms resolve and the subject should be premedicated for the next scheduled dose. Subjects who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further study drug treatment	Subject may be premedicated 1.5h (± 30 minutes) prior to infusion of 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: Epinephrine** IV fluids Antihistamines NSAIDs Acetaminophen Narcotics Oxygen Pressors Corticosteroids Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator. Hospitalization may be indicated. **In cases of anaphylaxis, epinephrine should be used immediately. **Subject is permanently discontinued from further study drug treatment.**	No subsequent dosing
Appropriate resuscitation equipment should be available at the bedside and a physician readily available during the period of drug administration. For further information, please refer to the Common Terminology Criteria for Adverse Events v4.0 (CTCAE) at http://ctep.cancer.gov		

Other allowed dose interruption for pembrolizumab

Pembrolizumab may be interrupted for situations other than treatment-related AEs such as medical 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, unless otherwise discussed with the Sponsor. The reason for interruption is to be documented in the subject's study record.

5.2.3.4 Treatment for Cytokine Release Syndrome

Table 15 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 subject 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 subject is deemed medically stable in the opinion of the investigator Additional appropriate medical therapy may include, but is not limited to: IV fluids NSAIDS Acetaminophen Narcotics Oxygen Perform fever workup to exclude infectious etiologies; treat neutropenia if present	Subject may be premedicated 1.5 hours (± 30 minutes) prior to MK-1454 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 Subjects 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-1454 treatment. Upon approval by Sponsor, MK-1454 may be restarted at a reduced dose when AE resolves back to baseline or to Grade 1 (see Table 11). Subject may be premedicated 1.5 hours (± 30 minutes) prior to MK-1454 administration with acetaminophen 500 to 1000 mg po (or equivalent dose of antipyretic)

NCI CTCAE Grade	Treatment	Premedication at subsequent dosing
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 Subjects with ≥ Grade 3 CRS need to be monitored very closely, likely in an intensive care setting	Permanently discontinue MK-1454 in subjects who develop Grade 4 CRS

Treatment by local surgery and/or radiation therapy of isolated or symptomatic progressing lesions in the setting of improving baseline disease may be permitted for palliative or potentially curative management following completion of Cycle 2. Subsequently, all interventions, including continuation of study drug, should be discussed with the Sponsor Medical Monitor or designee.

5.2.4 Intrasubject Dose Escalation

Intrasubject dose escalation will be allowed for subjects in Arm 1 (Parts A and B) monotherapy at the discretion of the investigator provided that the subject remains on study after receiving 3 cycles of treatment with MK-1454 monotherapy without a ≥ Grade 2 drug-related toxicity, and provided that dose escalation has proceeded beyond the next dose level. The subject may undergo intrasubject dose escalation one time while enrolled in this treatment arm.

Subjects enrolled in the ATD phase of Arm 3 may undergo dose escalation one time after receiving 3 cycles of treatment without a ≥ Grade 2 drug-related toxicity.

Intrasubject dose escalation is not permitted during the DLT evaluation period.

The subject may escalate to the highest dose level (and frequency for Arm 3) that has been cleared by DLT evaluation. This dose will be communicated to the site via written consent 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 5.2.1), as appropriate. Dose modification will be based on CTCAEs per Dose Modification Guidelines (see Section 5.2.3).

5.2.5 Timing of Dose Administration

Each subject may undergo up to 35 cycles (approximately 2 years) of MK-1454 treatment in both the monotherapy arm (Arm 1) and the combination therapy arms (Arm 2 and Arm 3), as well as the Expansion Cohorts (Cohort A to C).

After C1D1, trial treatment 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, patient vacation, and/or holidays). Subjects 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 subject's study record.

5.2.5.1 Timing of MK-1454 Dose Administration in Part I - Dose Escalation and Confirmation

MK-1454 will be administered on Day 1, Day 8, and Day 15 in each 21-day cycle for Cycles 1, 2, and 3 for Arms 1 and 2. Beginning with Cycle 4, MK-1454 will be administered on Day 1 of each 21-day cycle.

For Arm 3, MK-1454 will be administered IT to visceral lesions at escalating frequencies. In the ATD phase, MK-1454 will be administered [redacted] In the mTPI phase, frequency of administration will begin with [redacted] Escalation of frequency may proceed first to a [redacted] on Day 1 of Cycle 3 and beyond. Escalation of frequency may then proceed to [redacted] After Cycle 3, frequency of visceral IT administration may be modified by the investigator based on clinical assessment of the investigator and discussion with the Sponsor.

In Arm 2 and Arm 3 of the trial, MK-1454 will be administered within 0.5 to 4 hours following completion of pembrolizumab infusion.

5.2.5.2 Timing of MK-1454 Dose Administration in Part II - Expansion Cohorts

In Cohorts A and B, MK-1454 IT will be administered on Day 1, Day 8, and Day 15 in each 21-day cycle for Cycles 1 and 2. Beginning with Cycle 3, MK-1454 will be administered on Day 1 of each 21-day cycle.

Cohort C will initiate MK-1454 visceral IT treatment at the dose and frequency established as the RP2D from Arm 3.

5.2.5.3 Timing of Pembrolizumab Administration

Pembrolizumab 200 mg will be administered as an IV infusion on Day 1 of each 21-day cycle, in all combination treatment arms in Part I and Part II.

5.2.6 Trial Blinding

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

5.2.7 Replacement of Subjects During the DLT Evaluation Period

Subjects 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. Subjects with a DLT within 21 days of the first dose should not be replaced. See Section 8.5.1 for description of safety analysis population.

5.3 Randomization or Treatment Allocation

Treatment allocation in the dose escalation and confirmation phase (Arms 1, 2, and 3) will be accomplished by nonrandom assignment. Enrollment into Arm 2 (MK-1454 with pembrolizumab combination therapy) will begin once:

1. At least 1 of the 3 triggering criteria are met in Arm 1 (MK-1454 monotherapy)
2. A dose escalation decision has been made
3. 2 dose levels within Arm 1 have been cleared by DLT evaluation

When Arm 1 and Arm 2 are open for enrollment, alternating subject assignment between Arm 1 and Arm 2, starting with Arm 1, will be via IWRS. For example, once the CCI dose cohort of Arm 1 (MK-1454 monotherapy) and the CCI dose cohort of Arm 2 (MK-1454 combination therapy with pembrolizumab) are open for enrollment, then the first subject will be allocated to Arm 1, the second subject will be allocated to Arm 2, the third subject will be allocated to Arm 1, etc. Subjects will be allocated to Arm 3 by nonrandom assignment via IWRS.

In the expansion phase, eligible subjects will be allocated to an appropriate open treatment arm by IWRS. For Cohorts A and B, 30 subjects will be allocated to each cohort. For Cohort C, 60 subjects will be allocated to treatment in total. There will be a cap at 15 subjects each for non MSI-H CRC and pancreatic cancer.

5.4 Stratification

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

5.5 Concomitant Medications/Vaccinations (Allowed and Prohibited)

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 subject's primary physician. However, the decision to continue the

subject on trial therapy or vaccination schedule requires the mutual agreement of the investigator, the Sponsor and the subject.

All treatments that the investigator considers necessary for a subject's welfare may be administered at the discretion of the investigator and 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 IV fluids. If changes occur during the trial period, then documentation of drug dosage, frequency, route, and date will also be included in the CRF.

All concomitant medications received within 30 days before the first dose of trial treatment through the 30-day Safety Follow-up Visit should be recorded. If subjects 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 Section 7.2.

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

- Immunotherapy not specified in this protocol.
- Antineoplastic systemic chemotherapy or biological therapy not specified in this protocol.
- Investigational agents not specified in this protocol.
- Radiation therapy; radiotherapy for symptom management is allowed beyond Cycle 2 upon approval by the Sponsor Medical Monitor or designee.
- Live vaccines within 30 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.
- Systemic glucocorticoids for any purpose other than to modulate symptoms from an AE of suspected immunologic etiology. The use of physiologic doses of corticosteroids may be approved after consultation with the Sponsor.

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

5.6 Rescue Medications & Supportive Care

5.6.1 Supportive Care Guidelines

Subjects 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 5.2.3.2 (and Table 14). Where appropriate, these guidelines include the use of oral or IV treatment with corticosteroids, as well as additional anti-inflammatory agents if symptoms do not improve with administration of corticosteroids. Note that several courses of steroid tapering may be necessary as symptoms may worsen when the steroid dose is decreased. For each disorder, attempts should be made to rule out other causes such as metastatic disease or bacterial or viral infection, which might require additional supportive care. The treatment guidelines are intended to be applied when the investigator determines the events to be related to pembrolizumab.

Note: If after the evaluation of the event, it is determined not to be related to pembrolizumab, the investigator does not need to follow the treatment guidance. Refer to Table 11 for treatment guidelines for AEs that are related to MK-1454 treatment and to Table 15 for guidelines regarding dose modification and supportive care for CRS.

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

5.7 Diet/Activity/Other Considerations

5.7.1 Diet

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

5.7.2 Contraception

MK-1454 and pembrolizumab may have adverse effects on a fetus in utero. Furthermore, it is not known if either drug has transient adverse effects on the composition of sperm. Consequently, subjects should be informed that taking either MK-1454 or pembrolizumab may involve unknown risks to the fetus if pregnancy were to occur during the study, and should be advised not to conceive or father children during treatment and for up to 130 days after the last dose. If there is any question that a subject of childbearing potential will not reliably comply with the requirements for contraception, that subject should not be entered into the study.

5.7.2.1 Definitions

Women of Childbearing Potential (WOCBP)

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

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

Women in the following categories are not considered WOCBP:

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

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

Note: Documentation can come from the site personnel's review of the subject'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 2 FSH measurements in the postmenopausal range is required.
  - Females on HRT and whose menopausal status is in doubt will be required to use one of the nonhormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

Male subjects receiving MK-1454 or pembrolizumab should be advised to have sperm samples frozen and stored before treatment.

5.7.2.2 Acceptable Contraception Methods

Acceptable methods of contraception are as follows[a]:

Single method (one of the following is acceptable):

- Progestogen-only subdermal contraceptive implant [b,c]

- IUS[c,d]
- Nonhormonal IUD
- Bilateral tubal occlusion
- Azoospermic partner (vasectomized or secondary to medical cause) This is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. A spermatogenesis cycle is approximately 90 days.

  Note: Documentation of azoospermia can come from the site personnel's review of the subject's medical records, medical examination, or medical history interview.

Sexual Abstinence

- Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the subject.

a Contraceptive use by men or women should be consistent with local regulations regarding the use of contraceptive methods for subjects of clinical studies. Where local regulations require monthly pregnancy testing, see Appendix 12.5.

b If locally required, in accordance with CTFG guidelines, acceptable contraceptive implants are limited to those that 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, postovulation 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).

‡If a contraceptive method listed above is restricted by local regulations/guidelines, then it does not qualify as an acceptable method of contraception for subjects participating at sites in this country/region.

Please see Appendix 12.5 for country-specific pregnancy testing.

5.7.3 Use in Pregnancy

If a subject inadvertently becomes pregnant while on treatment with MK-1454 or pembrolizumab, the subject will immediately be removed from treatment. The site will contact the subject at least monthly and document the subject's status until the pregnancy has been completed or terminated. The outcome of the pregnancy will be reported to the Sponsor without delay and within 24 hours if the outcome is a serious adverse experience (eg, death, abortion, congenital anomaly, or other disabling or life-threatening complication to the mother or newborn). The study investigator will make every effort to obtain permission to follow the outcome of the pregnancy and report the condition of the fetus or newborn to the Sponsor. If a male subject impregnates his female partner the study personnel at the site must be informed immediately and the pregnancy reported to the Sponsor and followed as described above and in Section 7.2.2.

5.7.4 Use in Nursing Women

It is unknown whether MK-1454 or pembrolizumab is excreted in human milk. Since many drugs are excreted in human milk, and due to the potential for serious adverse reactions in the nursing infant, subjects who are breastfeeding are not eligible for enrollment.

5.8 Subject Withdrawal/Discontinuation Criteria

5.8.1 Discontinuation of Treatment

Discontinuation of treatment does not represent withdrawal from the trial.

As certain data on clinical events beyond treatment discontinuation may be important to the study, they must be collected through the subject's last scheduled follow-up, even if the subject has discontinued treatment. Therefore, all subjects who discontinue trial treatment prior to completion of the treatment will still continue to participate in the trial as specified in Section 6.0 - Schedule of Activities and Section 7.1.5.4 – Discontinued Subjects Continuing to be Monitored in the Trial.

Subjects may discontinue treatment at any time for any reason or be dropped from treatment at the discretion of the investigator should any untoward effect occur. In addition, a subject may be discontinued from treatment by the investigator or the Sponsor if treatment is inappropriate, the trial plan is violated, or for administrative and/or other safety reasons. Specific details regarding procedures to be performed at treatment discontinuation are provided in Section 7.1.4 – Other Procedures.

A subject must be discontinued from treatment but continue to be monitored in the trial for any of the following reasons:

- The subject or subject's legally acceptable representative requests to discontinue treatment.
- Confirmed radiographic disease progression outlined in Section 7.1.2.7 (exception if the Sponsor approves treatment continuation).

- The subject 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 subject is noncompliant with the protocol.
- The subject has a medical condition or personal circumstance which, in the opinion of the investigator and/or Sponsor, placed the subject at unnecessary risk from continued administration of study drug.
- The subject has a confirmed positive serum pregnancy test.
- Side effects and/or concomitant medications required for treatment of HIV and/or its complications that are incompatible with continued study treatment (exceptions are permissible but should be discussed with the Sponsor).

For subjects who are discontinued from treatment but continue to be monitored in the trial, see Section 6.0 – Schedule of Activities and Section 7.1.5.4 – Discontinued Subjects Continuing to be Monitored in the Trial for those procedures to be completed at each specified visit.

For subjects who progress on monotherapy MK-1454 in Arm 1, crossover into Arm 2 will be allowed if the subject meets the crossover eligibility criteria stated in Section 5.1.4 and Section 5.1.5. Subjects who cross over from Arm 1 into Arm 2 will enter Arm 2 at the start of Arm 2 (at screening).

5.8.2 Withdrawal From the Trial

If a subject fails to return for scheduled visits and/or if the study site is unable to contact the subject after multiple attempts (ie, is lost to follow-up), the procedures to be performed are outlined in Section 7.1.4.1.

If a subject decides not to continue receiving study medication, the subject is to be encouraged to continue visits in the study for follow-up, imaging, and vital status assessment.

5.8.2.1 Participants Who Withdraw Consent During the Study

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

Section 7.4.1 delineates the specific procedures performed at the time of withdrawal and withdrawal from future biomedical research.

Any AEs that are present at the time of withdrawal should be followed in accordance with the safety requirements outlined in Section 7.1.5.4 and Section 7.2.

5.9 Subject Replacement Strategy

A subject who discontinues from the trial will not be replaced except as described in Section 5.2.7 Replacement of Subjects During the DLT Evaluation Period.

5.10 Beginning and End of the Trial

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

5.11 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.

6.0 SCHEDULE OF ACTIVITIES

6.1 Schedule of Activities for Part I - Dose Escalation and Confirmation (Arms 1, 2, and 3)

6.1.1 Schedule of Activities for Initial Screening for Arms 1 Through 3 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		Documented informed 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 FBR (Optional)	X		
Subject Identification Card	X		
Inclusion/Exclusion Criteria	X	X	
Demographics and Medical History	X	X	For Crossover 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	
HPV status	X		HPV testing results by history in HNSCC and other squamous cell carcinoma tumors (eg, p16 IHC; multiplex NASBA or other PCR-based assays) should be recorded if available, as determined per institutional standard.
Tumor genetic alteration(s)	X		Tumor genetic alteration(s), if available, as determined by local testing results (eg, BRCA1, MSI-H).
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	X	X	The pretreatment evaluation and scoring of response parameters 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 Subjects Only [excluding CTCL subjects])	X	X	Must be performed if not previously done within 8 weeks prior to Screening with negative results. For a crossover subject, a repeat bone marrow biopsy at screening is required when the subject 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 Electrocardiogram (ECG)	X	X	ECG will be obtained within 7 days prior to MK-1454 IT administration on C1D1.
Vital Signs	X	X	Temperature, pulse, respiratory rate, blood pressure, and oxygen (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 subject 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	
Thyroid Function (TSH, T3, FT3, T4, FT4)	X	X	
Pregnancy Test for WOCBP– Urine or Serum 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.
Laboratory Procedures/Assessments: Analysis performed by CENTRAL laboratory			**See Procedures Manual for collection and management of tissue samples.**
Serum for Cytokine Panel and C-Reactive Protein (CRP) for MK-1454 Pharmacodynamics	X	X	Blood samples for serum cytokine panels and CRP taken at Screening should be obtained either both in the morning (8 AM to 12 PM) or both in the afternoon (1 PM to 5 PM). Collect with the samples for MK-1454 PK, when feasible.
Blood for Plasma Biomarker Analysis	X	X	
Blood for Serum Biomarker Analysis	X	X	
Tumor Tissue Biopsy [a]	X[a]	X[a]	

Scheduled Day	Initial Screening	Crossover Screening	Notes
			Screening and Day 1 cannot be on the same day.
	-28 to -1	-28 to -1	

aPTT = activated partial thromboplastin time; CBC = complete blood count; hCG = Beta-human chorionic gonadotropin; CRP = C-reactive protein; CT = computed tomography; CTCL = cutaneous T-cell lymphoma; ECOG = Eastern Cooperative Oncology Group; FBR = future biomedical research; GGT = gamma glutamyl transferase; HIV = human immunodeficiency virus; HNSCC = Head and Neck Squamous Cell Carcinoma; HPV = human papillomavirus; INR = international normalized ratio; IT = intratumoral; IWG = International Working Group; LDH = lactate dehydrogenase; MRI = magnetic resonance imaging; NASBA = nucleic acid sequence-based amplification; PET = positron emission tomography; PT = prothrombin time; PTT = partial thromboplastin time; RNA = ribonucleic acid; RECIST v1.1 = Response Evaluation Criteria In Solid Tumors, version 1.1; irRECIST = immune-related RECIST; (F)T3 = (free) triiodothyronine; (F)T4 = (free) thyroxine; TSH = thyroid-stimulating hormone; WOCBP = women of childbearing potential.

a.) All subjects will be required to provide a sample biopsy of the tumor to be injected with MK-1454 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-1454, as well as on the distant lesion that is not intended for IT administration with MK-1454. For the tumor lesion intended for treatment with IT administration of MK-1454, the sample will be obtained by either punch biopsy for cutaneous lesions, or ultrasound guided biopsy for subcutaneous lesions, or cross-sectional image-guided biopsy for visceral and deeper tumor lesions. For distant, discrete tumor lesions that are not intended for IT administration with MK-1454, the sample biopsy will be obtained by punch biopsy for cutaneous lesions, ultrasound guided biopsy for subcutaneous lesions/visceral lesions, or cross-sectional image-guided biopsy, such as CT-guided biopsy, for visceral and deeper tumor lesions. Method of biopsy will be per guidance of the investigator as well as discussion with the Sponsor.

Instructions for tissue collection, processing, and shipment are provided in the Procedures Manual. Leftover main study tissue will be stored for FBR if the subject 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.

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

Trial Period	Treatment Phase MK-1454 Monotherapy Cycle = 21 Days MK-1454 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**	
Administrative Procedures											
Informed Consent					X						Additional consent is required for treatment beyond disease progression.
Prior Medication and Concomitant Medication Review	X	X	X	X	X	X	X	X	X	X	
MK-1454 Administration (Arm 1 and Arm 2) (Table 3)	CCI										There will be an at least a 24-hour inpatient observation period following MK-1454 administration on C1D1. In Arm 2, MK-1454 will be administered within 0.5 to 4 h after completion of pembrolizumab IV infusion. See Procedures Manual for dose preparation.
Pembrolizumab Administration (Arm 2) (Table 4)	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, irRECIST, and/or itRECIST Response Assessment									X	X	For solid tumors, perform at 9 weeks (± 7 days) after first dose, and then Q9W. For lymphoma, assess at 12 weeks (± 7 days), and then Q12W. 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. Continue imaging schedule until disease progression, discontinuation, or EOT. Medical photography can be performed more often as medically warranted.
Medical Photography (Cutaneous Lesions)									X	X	
IWG Revised Response Criteria for Lymphoma (excluding CTCL)										X	

Trial Period	Treatment Phase MK-1454 Monotherapy Cycle = 21 Days MK-1454 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/Modified Severity Weighted Assessment Tool – [mSWAT])	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 Subjects Only)	←==========→										For subjects 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 subject was initially positive or if it is clinically indicated.
Safety Assessments and Procedures											**See Procedures Manual for Collection And Management of Samples.**
AE 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-1454 IT administration on C1D1, C2D1, and C3D1. Does not need to be repeated on C1D1 if screening ECG was done within 72 hours prior to C1D1. A postdose ECG will be obtained on C1D1 within 30 min and at 3 to 4 h following MK-1454 IT administration.
Vital Signs (temperature, pulse, respiratory rate, blood pressure, and oxygen (O_2) saturation)	X	X	X	X	X	X	X	X	X	X	Collect VS **predose** within 1 h (± 30 min) of MK-1454 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-1454 administration. At each subsequent treatment visit, collect VS at 1 h (±15 min) after MK-1454 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.

Trial Period	Treatment Phase MK-1454 Monotherapy Cycle = 21 Days MK-1454 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**	
CBC with Differential	X	X	X	X	X	X	X	X	X	X	Required within 72 h of C1D1. Does not need to be repeated if screening labs were done within 72 hours of C1D1. 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 hCG	X										Required within 24 h prior to first dose of study medication. Does not need to be repeated if screening test was done within 24 hours 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. Where local regulations require monthly pregnancy testing per CTFG guidelines, see Appendix 12.5.
Thyroid Function (TSH, T3, FT3, T4, FT4)	X						X			X	Required within 72 hours prior to Day 1 of C1, C3, C5, C7, C9, C11, and at every other subsequent treatment cycle. Does not need to be repeated if screening labs were done within 72 hours of C1D1.
Pharmacokinetics (PK)/ Pharmacodynamics/ Future Biomedical Research/Biomarkers											**See Procedures Manual for Collection and Management of Samples.**
Serum for Cytokine Panel and CRP for MK-1454 Pharmacodynamics [b]	X			X						X[c]	Cytokine and CRP samples should be obtained **predose** on C1D1, C2D1 and C5D1, either both in the morning (8 AM to 12 PM) or both in the afternoon (1 PM to 5 PM). **Postdose** serum samples for cytokine panels and CRP will be collected on C1D1, C2D1, and C5D1, and if applicable, on Day 1 of the first cycle that the subject has undergone intrasubject dose escalation of MK-1454. Postdose samples will be collected at 4 h (±15 min) and 6 h (±15 min) after MK-1454 administration. On C1D1, an additional serum sample will be collected at 12 h (± 2 h) and 24 h (± 4 h) following MK-1454 administration. Collect samples at the same time as for MK-1454 PK when feasible.

Trial Period	Treatment Phase MK-1454 Monotherapy Cycle = 21 Days MK-1454 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-1454 PK [b,c]	X			X						X[c]	Collect **predose** samples 1-8 h before MK-1454 administration on C1D1 and C2D1. Collect **postdose** samples on C1D1 and C2D1 at the following time points: end of IT injection (up to +15 min), 0.5 h (±15 min), 1 h (±15 min), 1.5 h (±15 min), 4 h (±15 min), and 6 h (±15 min). Additional postdose samples will be collected at 12 h (±2 h) and 24 h (±4 h) following MK-1454 IT administration on C1D1 only. If applicable, collect on Day 1 of the first cycle that the subject has undergone intrasubject dose escalation of MK-1454. Collect samples at the same time as for cytokines and CRP, and for pembrolizumab PK, when feasible.
Serum for Pembrolizumab PK	X			X						X	Pembrolizumab PK and ADA are for pembrolizumab-treated subjects 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-1454 PK samples together, when feasible.
Serum for ADA	X			X						X	
Blood for Plasma Biomarker Analysis				X						X	Collect prior to MK-1454 administration (Arm 1) and prior to pembrolizumab administration (Arm 2) on C2D1 and C5D1.
Blood for Serum Biomarker Analysis				X						X	
Blood for RNA Analysis	X									[c]	Collect **predose** 0-4 h before MK-1454 administration on C1D1. Collect **postdose** 6 h (±15 min) after MK-1454 administration on C1D1.
Blood for Genetic Analysis [d]	X										Collect prior to treatment.

Trial Period	Treatment Phase MK-1454 Monotherapy Cycle = 21 Days MK-1454 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-1454, collect postdose tumor biopsy on the same day as treatment, 5 h (± 2 h) following IT administration of MK-1454 on C3D15, and optionally on C6D1 at 5 h (± 2 h) following IT administration of MK-1454. Biopsy of a distant, discrete, noninjected site is preferred on the same day as the IT administration of MK-1454, but may be performed up to 3 days after treatment of the injected lesion. The C6D1 biopsy time point is encouraged, but optional.

ADA = antidrug antibodies; AE = adverse event; aPTT = activated partial thromboplastin time; CBC = complete blood count; CRP = C-reactive protein; CT = computed tomography; CTCL = cutaneous T-cell lymphoma; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; FBR = future biomedical research; GGT = gamma glutamyl transferase; hCG = human chorionic gonadotropin; HIV = human immunodeficiency virus; HNSCC = Head and Neck Squamous Cell Carcinoma; HPV = human papillomavirus; IEC = Institutional Ethics Committee; INR = international normalized ratio; IRB= Institutional Review Board; ISCL = International Society for Cutaneous Lymphomas; IT = intratumoral; LDH = lactate dehydrogenase; MRI = magnetic resonance imaging; PET = positron emission tomography; PT = prothrombin time; PTT = partial thromboplastin time; RNA = ribonucleic acid; RECIST v1.1 = Response Evaluation Criteria In Solid Tumors, version 1.1; irRECIST = immune-related RECIST; (F)T3 = (free) triiodothyronine; (F)T4 = (free) thyroxine; TSH = thyroid-stimulating hormone; WOCBP = women of childbearing potential.

a) The inpatient observation period may be extended up to 48 hours at the discretion of the investigator, per local IRB/IEC, 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 subject has undergone intrasubject dose escalation of MK-1454, these samples for biomarker analysis will be collected on Day 1 of the first cycle of the escalated new dose.
d) This sample will be drawn for genetic variations in absorption, distribution, metabolism, and excretion (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 (or their legally acceptable representative) provides documented informed consent for FBR. 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.

All subjects will be required to provide a sample biopsy of the tumor to be injected with MK-1454 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-1454, 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-1454, 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-guided biopsy, for visceral and deeper tumor lesions. Method of biopsy will be per guidance of the investigator as well as discussion with the Sponsor. Instructions for tissue collection, processing, and shipment are provided in the Procedures Manual. Leftover main study tissue will be stored for FBR if the subject consents to FBR. Instructions for tissue collection, processing, and shipment are provided in the Procedures Manual.

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

Trial Period	Treatment Phase MK-1454 Monotherapy Cycle = CCI then Q3W MK-1454 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**	
Informed Consent	X								Additional consent is required for treatment beyond disease progression.
Prior Medication and Concomitant Medication Review	X	X	X	X	X	X	X	X	
MK-1454 Administration (Arm 3) (Table 5)	C [redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	There will be an at least a 24-hour inpatient observation period following MK-1454 administration on C1D1. MK-1454 will be administered within 0.5 to 4 h after completion of pembrolizumab IV infusion. Frequency of visceral IT administration may be modified by Investigator in consultation with Sponsor based on subject tolerance and clinical assessment of safety. *Administration on Day 8 and Day 15 of Cycles 1 and 2 will be based on cohort designation in Arm 3. See Procedures Manual for dose preparation.
Pembrolizumab Administration (Table 5)	X			X			X	X	See Procedures Manual for dose preparation.
Efficacy Procedures									**See Imaging Manual – All imaging visits have a ± 7 day window**
Tumor Imaging, RECIST, irRECIST, and/or itRECIST Response Assessment								X	For solid tumors, to be performed at 9 weeks after the first dose, and then every 9 weeks. For lymphoma, assess at 12 weeks, 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. Continue imaging schedule until disease progression, discontinuation, or EOT. Medical photography can be performed more often as medically warranted.
Medical Photography (Cutaneous Lesions)								X	
IWG Revised Response Criteria for Lymphoma								X	
Bone Marrow Biopsy/ Aspirate (Lymphoma Subjects Only)	←═══════════════════════════════════→								For subjects 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 subject was initially positive or if it is clinically indicated.

Trial Period	Treatment Phase MK-1454 Monotherapy Cycle = [redacted], then Q3W MK-1454 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.**
AE 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-1454 IT administration on C1D1, C2D1, and C3D1. Does not need to be repeated on C1D1 if screening ECG was done within 72 hours of C1D1. A postdose ECG will be obtained on C1D1 within 30 min and at 3 to 4 h following MK-1454 IT administration.
Vital Signs (temperature, pulse, respiratory rate, blood pressure, and oxygen (O_2) saturation)	X	X	X	X	X	X	X	X	Collect VS **predose** within 1 h (± 30 min) MK-1454 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-1454 administration. At each subsequent treatment visit, collect VS at 1 h (±15 min) after MK-1454 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. Does not need to be repeated if screening labs were done within 72 hours of C1D1. 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	
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 hCG	X								Required within 24 h prior to first dose of study medication. Does not need to be repeated if screening test was done within 24 hours 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. Where local regulations require monthly pregnancy testing per CTFG guidelines, see Appendix 12.5.

Trial Period	Treatment Phase MK-1454 Monotherapy Cycle = CCI , then Q3W MK-1454 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**	
Thyroid Function (T4, FT4, T3, FT3, TSH)	X						X	X	To be performed within 72 hours prior to Day 1 of C1, C3, C5, C7, C9, C11, and at every other subsequent treatment cycle. Does not need to be repeated if screening labs were done within 72 hours of C1D1.
Pharmacokinetics (PK)/ Pharmacodynamics/ Future Biomedical Research/Biomarkers									**See Procedures Manual for Collection and Management of Samples.**
Serum for Cytokine Panel and CRP for MK-1454 Pharmacodynamics [b]	X			X				X[b]	Cytokine and CRP samples should be obtained **predose** on C1D1 and C2D1 either both in the morning (8 AM to 12 PM) or both in the afternoon (1 PM to 5 PM). **Postdose** serum samples for cytokine panels and CRP will be collected on C1D1, C2D1, and C5D1. Postdose samples will be collected at 4 h (±15 min) and 6 h (±15 min) after MK-1454 administration. On C1D1, an additional serum sample will be collected at 12 h (± 2 h) and 24 h (± 4 h) following MK-1454 administration. Collect samples at the same time as for MK-1454 PK when feasible.
Plasma MK-1454 PK	X			X				X[b]	Collect **predose** samples 1-8 h before MK-1454 administration on C1D1 and C2D1. Collect **postdose** samples on C1D1 and C2D1 at the following time points: end of IT injection (up to +15 min), 0.5 h (±15 min), 1.0 h (±15 min), 1.5 h (±15 min), 4 h (±15 min), and 6 h (±15 min). Additional postdose samples will be collected at 12 h (± 4 h) and 24 h (± 4 h) following MK-1454 IT administration on C1D1 only. Collect samples at the same time as for cytokines and CRP, and for pembrolizumab PK, when feasible.
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 cycles thereafter (ie, C8, C12, etc.). Collect with plasma samples for MK-1454 PK when feasible.
Serum for ADA	X			X				X	
Blood for Plasma Biomarker Analysis				X				X	Collect prior to MK-1454 administration (Arm 1) and prior to pembrolizumab administration (Arm 2 and Arm 3) on C2D1 and C5D1.
Blood for Serum Biomarker Analysis				X				X	

Trial Period	Treatment Phase MK-1454 Monotherapy Cycle = CCI then Q3W MK-1454 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	
Blood for RNA Analysis	X								Collect **predose** 0-4 h before MK-1454 administration on C1D1 Collect **postdose** 6 h (±15 min) after MK-1454 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-1454, collect **predose** tumor biopsy on the same day as treatment prior to IT administration of MK-1454 on C3D1, or up to 3 days prior to treatment on C3D1, and optionally on C6D1 prior to IT administration of MK-1454, or up to 3 days prior to treatment on C6D1. If available, biopsy of a distant, discrete, noninjected site is preferred on the same day as the IT administration of MK-1454 but may be performed up to 3 days after treatment of the injected lesion. The C6D1 biopsy time point is encouraged, but optional.

ADA = antidrug antibodies; AE = adverse event; aPTT = activated partial thromboplastin time; CBC = complete blood count; CRP = C-reactive protein; CT = computed tomography; CTCL = cutaneous T-cell lymphoma; DNA = deoxyribonucleic acid; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; FBR = future biomedical research; GGT = gamma glutamyl transferase; hCG = human chorionic gonadotropin; HIV = human immunodeficiency virus; HNSCC = Head and Neck Squamous Cell Carcinoma; HPV = human papillomavirus; IEC = Institutional Ethics Committee; INR = international normalized ratio; IRB = Institutional Review Board; irRECIST = immune-related RECIST; ISCL = International Society for Cutaneous Lymphomas; IT = intratumoral; LDH = lactate dehydrogenase; MRI = magnetic resonance imaging; PET = positron emission tomography; PT = prothrombin time; PTT = partial thromboplastin time; RECIST v1.1 = Response Evaluation Criteria In Solid Tumors, version 1.1; RNA = ribonucleic acid; (F)T3 = (free) triiodothyronine; (F)T4 = (free) thyroxine; TSH = thyroid-stimulating hormone; WOCBP = women of childbearing potential.

a) The inpatient observation period may be extended up to 48 hours at the discretion of the investigator, per local IRB/IEC, 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 (or their legally acceptable representative) provides documented informed consent for FBR. 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 subjects will be required to provide a sample biopsy of the tumor to be injected with MK-1454 and a sample biopsy from a distant, discrete noninjected site (at least 2 biopsies at each site), unless deemed medically unsafe by the investigator. The sample will be obtained by ultrasound guidance or cross-sectional imaging (CT/MRI) guidance. Method of biopsy will be per guidance of the investigator as well as discussion with the Sponsor. Instructions for tissue collection, processing, and shipment are provided in the Procedures Manual. Leftover main study tissue will be stored for FBR if the subject consents to FBR. Instructions for tissue collection, processing, and shipment are provided in the Procedures Manual.

6.1.4 Discontinuation / End of Treatment and Posttreatment Follow-up for Arms 1 to 3

Trial Period	EOT/ Discontinuation	Posttreatment 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				
Tumor Imaging, RECIST, irRECIST, and/or 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 subjects 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 subjects that have a death event previously recorded).
Safety Assessments and Procedures				**See Procedures Manual for collection and management of samples.**
AEs 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
ECOG Performance Status	X	X		
CBC with Differential	X	X		
Chemistry Panel	X	X		
Lipase and Amylase	X	X		

Trial Period	EOT/ Discontinuation	Posttreatment Period		Notes
		30-Day Safety Follow-up Visit	Survival Follow-up	
Scheduling Day		**30 days post last dose**	**Q12W**	
Scheduled Window	**±7**	**+7**	**±14**	
Pregnancy Test for WOCBP – Urine or Serum hCG		X		For WOCBP, perform 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		
PK/Pharmacodynamics/ Future Biomedical Research/Biomarkers				**See Procedures Manual for collection and management of samples.**
Serum for Pembrolizumab PK	X			Only for pembrolizumab-treated subjects.
Serum for ADA	X			
Blood for Plasma Biomarker Analysis	X			
Blood for Serum Biomarker Analysis	X			

ADA = antidrug antibodies; AE = adverse event; CBC = complete blood count; CTCL = cutaneous T-cell lymphoma; DNA = deoxyribonucleic acid; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; EOT = end of treatment; (F)T3 = (free) triiodothyronine; (F)T4 = (free) thyroxine; hCG = human chorionic gonadotropin; irRECIST = immune-related RECIST; PK = pharmacokinetic; RECIST = Response Evaluation Criteria In Solid Tumors; RNA = ribonucleic acid; TSH = thyroid-stimulating hormone; WOCBP = women of childbearing potential.

6.2 Schedule of Activities for Part II- Expansion Cohorts

6.2.1 Schedule of Activities for Part II - Expansion Cohorts Screening and Treatment Period, MK-1454 Intratumoral Administration With Pembrolizumab Combination Therapy

Trial Period	Screening	Treatment Phase MK-1454 Cycle = [redacted], then Q3W; or Q3W Pembrolizumab Cycle = 21 Days										Notes
Cycle		Cycle 1			Cycle 2			Cycle 3			Cycle 4 and Beyond	
Scheduling Day	**-28 to -1**	**1**	**8**	**15**	**1**	**8**	**15**	**1**	**8**	**15**	**1**	
Scheduled Window		**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	
	Administrative Procedures											
Informed Consent	X											Documented informed 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. Additional informed consent is required for treatment beyond progression.
Informed Consent for FBR (Optional)	X											
Subject Identification Card	X											
Inclusion/Exclusion Criteria	X											
Demographics and Medical History	X											
Prior Medication and Concomitant Medication Review	X	X	X	X	X	X	X	X	X	X	X	
HPV status	X											HPV testing results of HNSCC and other squamous cell carcinoma tumors (eg, p16 IHC; multiplex NASBA or other PCR-based assays) should be collected if available, as determined per institutional standard.
Tumor genetic alteration(s)	X											Tumor genetic alteration(s), if available, as determined by the local testing results (eg, BCRA1, MSI-H.).

Trial Period	Screening	Treatment Phase MK-1454 Cycle = CCI then Q3W; or Q3W Pembrolizumab Cycle = 21 Days										Notes
Cycle		Cycle 1			Cycle 2			Cycle 3			Cycle 4 and Beyond	
Scheduling Day	**-28 to -1**	**1**	**8**	**15**	**1**	**8**	**15**	**1**	**8**	**15**	**1**	
Scheduled Window		**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	
MK-1454 Administration (Table 8)		CCI										There will be an at least an 8-hour observation period following MK-1454 administration on C1D1. MK-1454 will be administered within 0.5 to 4 h after completion of pembrolizumab IV infusion. See Procedures Manual for dose preparation.
Pembrolizumab Administration (Table 8)		X			X			X			X	See Pembrolizumab Pharmacy Manual.
	Efficacy Procedures											**See Imaging Manual – All imaging visits have a ± 7 day window**
Tumor Imaging, RECIST, irRECIST, and/or itRECIST Response Assessment Cohort B	X									X	X	To be performed at 9 weeks (± 7 days) after the first dose, and then every 9 weeks thereafter. 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. Continue imaging schedule until disease progression, discontinuation, or EOT. Medical photography can be performed more often as medically warranted.
Medical Photography (Cutaneous Lesions)	X									X	X	
	Safety Assessments and Procedures											**See Procedures Manual for Collection And Management of Samples.**
AE Monitoring		←==========→										
Full Physical Examination	X	X			X			X			X	
Directed Physical Examination			X	X		X	X					
Weight	X	X			X			X			X	
Height	X											
12-lead ECG	X											

Trial Period	Screening	Treatment Phase MK-1454 Cycle = [redacted] then Q3W; or Q3W Pembrolizumab Cycle = 21 Days										Notes
Cycle		Cycle 1			Cycle 2			Cycle 3			Cycle 4 and Beyond	
Scheduling Day	**-28 to -1**	**1**	**8**	**15**	**1**	**8**	**15**	**1**	**8**	**15**	**1**	
Scheduled Window		**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	
Vital Signs (temperature, pulse, respiratory rate, blood pressure, and oxygen (O_2) saturation)	X	X	X	X	X	X	X	X	X	X	X	Collect VS **predose** within 1 h (± 30 min) of MK-1454 administration at each treatment visit. Collect VS **postdose** on C1D1 at 2, 4, 6, and 8h (± 30 min for each time point) after MK-1454 administration. At each subsequent treatment visit, collect VS at 1 h (±15 min) after MK-1454 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	Perform all screening clinical laboratory tests within 7 days prior to C1D1. Tests performed prior to the subject 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. For C1D1 and subsequent cycles testing must be performed within 72 h prior to dosing when scheduled. Does not need to be repeated on C1D1 if screening labs were done within 72 hours of C1D1.
PT/INR and PTT or aPTT	X	X			X			X			X	
Chemistry Panel	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	
Pregnancy Test for WOCBP – Urine or Serum hCG	X	X										Required within 24 h prior to first dose of study medication. Does not need to be repeated if screening test was done within 24 hours 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. Where local regulations require monthly pregnancy testing per CTFG guidelines, see Appendix 12.5.
Thyroid Function (TSH, T3, FT3, T4, FT4)	X	X						X			X	Required within 72 hours prior to Day 1 of C1, C3, C5, C7, C9, C11, and at every other subsequent treatment cycle. Does not need to be repeated on C1D1 if screening labs were done within 72 hours of C1D1.
HIV, Hepatitis B and C screen (per site SOP)	X											Include HCV antibody or HCV RNA (qualitative) and HBsAg.

Trial Period	Screening	Treatment Phase MK-1454 Cycle = [CCI] then Q3W; or Q3W Pembrolizumab Cycle = 21 Days										Notes
Cycle		Cycle 1			Cycle 2			Cycle 3			Cycle 4 and Beyond	
Scheduling Day	**-28 to -1**	**1**	**8**	**15**	**1**	**8**	**15**	**1**	**8**	**15**	**1**	
Scheduled Window		**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	
	Laboratory Procedures/Assessments: Analysis performed by CENTRAL laboratory											**See Procedures Manual for Collection and Management of Samples.**
Serum for Cytokine Panel and CRP for MK-1454 Pharmacodynamics [b]	X	X			X						X,	Cytokine and CRP samples should be obtained at Screening, and **predose** on C1D1, C2D1 and C5D1, either both in the morning (8 AM to 12 PM) or both in the afternoon (1 PM to 5 PM). **Postdose** serum samples for cytokine panels and CRP will be collected on C1D1, C2D1, and C5D1. Postdose samples will be collected at 4 h (±15 min) and 6 h (±15 min) after MK-1454 administration. Collect samples at the same time as for MK-1454 PK when feasible.
Plasma MK-1454 PK [b]		X			X						X	Collect **predose** samples 1-8 h before MK-1454 administration on C1D1 and C2D1. Collect **postdose** samples on C1D1 and C2D1 at the following time points: end of IT injection (up to +15 min), 0.5 h (±15 min), 1 h (±15 min), 1.5 h (±15 min), 4 h (±15 min), and 6 h (±15 min). Collect samples at the same time as for cytokines and CRP, and for pembrolizumab PK, when feasible.

Trial Period	Screening	Treatment Phase MK-1454 Cycle = CCI then Q3W; or Q3W Pembrolizumab Cycle = 21 Days										Notes
Cycle		Cycle 1			Cycle 2			Cycle 3			Cycle 4 and Beyond	
Scheduling Day	**-28 to -1**	**1**	**8**	**15**	**1**	**8**	**15**	**1**	**8**	**15**	**1**	
Scheduled Window		**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	
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 cycles thereafter (ie, C8, C12, etc.). Collect pembrolizumab and MK-1454 PK samples together, when feasible.
Serum for ADA		X			X						X	
Blood for Plasma Biomarker Analysis					X						X	Collect prior to MK-1454 administration (Arm 1) and prior to pembrolizumab administration (Arm 2) on C2D1 and C5D1.
Blood for Serum Biomarker Analysis					X						X	
Blood for RNA Analysis		X										Collect **predose** 0-4 h before MK-1454 administration on C1D1 Collect **postdose** 6 h (±15 min) after MK-1454 administration on C1D1.
Blood for Genetic Analysis [c]		X										Collect prior to treatment.
Tumor Tissue Biopsy[d]	X				X			X				For the tumor lesion that is treated with IT administration of MK-1454, collect **predose** tumor biopsy on the same day as treatment prior to IT administration of MK-1454, or up to 5 days prior to treatment on C2D1 and on C3D1 (optional). If available, biopsy of a distant, discrete, noninjected site may be performed up to 5 days before treatment of the injected lesion.

AE = adverse event; aPTT = activated partial thromboplastin time; CBC = complete blood count; CRP = C-reactive protein; CT = computed tomography; CTCL = cutaneous T-cell lymphoma; ECOG = Eastern Cooperative Oncology Group; EOT = end of treatment; FBR = future biomedical research; (F)T3 = (free) triiodothyronine; (F)T4 = (free) thyroxine; GGT = gamma glutamyl transferase; hCG = human chorionic gonadotropin; HCV = hepatitis C virus; HIV = human immunodeficiency virus; HNSCC = Head and Neck Squamous Cell Carcinoma; HPV = human papillomavirus; INR = international normalized ratio; irRECIST = immune-related RECIST; ISCL = International Society for Cutaneous Lymphomas; IT = intratumoral; LDH = lactate dehydrogenase; MRI = magnetic resonance imaging; NASBA = nucleic acid sequence-based amplification; PET = positron emission tomography; PK = pharmacokinetics; PT = prothrombin time; PTT = partial thromboplastin time; RECIST v1.1 = Response Evaluation Criteria In Solid Tumors, version 1.1; RNA = ribonucleic acid; TSH = thyroid-stimulating hormone; WOCBP = women of childbearing potential.

Trial Period	Screening	Treatment Phase MK-1454 Cycle = CCI then Q3W; or Q3W Pembrolizumab Cycle = 21 Days										
Cycle		Cycle 1			Cycle 2			Cycle 3			Cycle 4 and Beyond	Notes
Scheduling Day	-28 to -1	1	8	15	1	8	15	1	8	15	1	
Scheduled Window		±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	

a) The observation period may be extended at the discretion of the investigator, per local IRB/IEC, 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, 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 (or their legally acceptable representative) provides documented informed consent for FBR. 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.
d) All subjects will be required to provide a sample biopsy of the tumor to be injected with MK-1454 and, if available, 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-1454, the sample will be obtained by either punch biopsy for cutaneous lesions, or ultrasound guided biopsy for subcutaneous lesions. If available, for distant, discrete tumor lesions that are not intended for IT administration with MK-1454, 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-guided biopsy, for visceral and deeper tumor lesions. Method of biopsy will be per guidance of the investigator as well as discussion with the Sponsor. Instructions for tissue collection, processing, and shipment are provided in the Procedures Manual. Leftover main study tissue will be stored for FBR if the subject consents to FBR. Instructions for tissue collection, processing, and shipment are provided in the Procedures Manual.

6.2.2 Discontinuation / End of Treatment and Posttreatment Follow-up for Part II – Expansion Cohorts

Trial Period	End of Treatment (EOT)/ Discontinuation	Posttreatment 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				
Tumor Imaging, RECIST, irRECIST, and/or itRECIST Response Assessment	X			
Medical Photography (Cutaneous Lesions)	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 subjects 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 subjects that have a death event previously recorded).
Safety Assessments and Procedures				**See Procedures Manual for collection and management of samples.**
AE 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
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 hCG		X		For WOCBP, perform as required locally. If a urine pregnancy test cannot be confirmed as negative, a serum pregnancy test is required.

Trial Period	End of Treatment (EOT)/ Discontinuation	Posttreatment Period		Notes
		30-Day Safety Follow-up Visit	Survival Follow-up	
Scheduling Day		**30 days post last dose**	**Q12W**	
Scheduled Window	**±7**	**+7**	**±14**	
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 subjects.
Serum for ADA	X			
Blood for Plasma Biomarker Analysis	X			
Blood for Serum Biomarker Analysis	X			

ADA = antidrug antibodies; AE = adverse event; CT = computed tomography; DNA = deoxyribonucleic acid; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; (F)T3 = (free) triiodothyronine; (F)T4 = (free) thyroxine; hCG = human chorionic gonadotropin; irRECIST = immune-related RECIST; MRI = magnetic resonance imaging; PET = positron emission tomography; RECIST v1.1 = Response Evaluation Criteria In Solid Tumors, version 1.1; RNA = ribonucleic acid; TSH = thyroid-stimulating hormone; WOCBP = women of childbearing potential.

7.0 TRIAL PROCEDURES

7.1 Trial Procedures

The Schedule of Activities - Section 6.0 summarizes the trial procedures to be performed at each visit. Individual trial procedures are described in detail below. It may be necessary to perform these procedures at unscheduled time points if deemed clinically necessary by the investigator.

Furthermore, additional evaluations/testing may be deemed necessary by the investigator and or the Sponsor for reasons related to subject safety. In some cases, such evaluation/testing may be potentially sensitive in nature (e.g., HIV, Hepatitis C, etc.), and thus local regulations may require that additional informed consent be obtained from the subject. In these cases, such evaluations/testing will be performed in accordance with those regulations.

7.1.1 Administrative Procedures

7.1.1.1 Informed Consent

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

7.1.1.1.1 General Informed Consent

Consent must be documented by the subject's dated signature or by the subject'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 subject before participation in the trial.

The initial informed consent form, any subsequent revised informed consent form and any written information provided to the subject must receive the IRB/ERC's approval/favorable opinion in advance of use. The subject or his/her legally acceptable representative should be informed in a timely manner if new information becomes available that may be relevant to the subject'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 subject's dated signature or by the subject'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/ERC requirements, applicable laws and regulations and Sponsor requirements.

7.1.1.1.2 Consent and Collection of Specimens for Future Biomedical Research

The investigator or qualified designee will explain the FBR consent to the subject, or the subject'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 subject before performing any procedure related to FBR.

7.1.1.2 Inclusion/Exclusion Criteria

All inclusion and exclusion criteria will be reviewed by the investigator or qualified designee to ensure that the subject qualifies for the trial.

7.1.1.3 Subject Identification Card

All subjects will be given a Subject 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 subject with a Subject Identification Card immediately after the subject provides documented informed consent. At the time of treatment allocation/randomization, site personnel will add the treatment/randomization number to the Subject Identification Card.

The subject identification card also contains contact information for the emergency unblinding call center so that a health care provider can obtain information about trial medication/vaccination in emergency situations where the investigator is not available.

7.1.1.4 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 subject has been enrolled in the trial will be recorded separately and should not be listed in the medical history. Smoking history will be obtained.

7.1.1.5 Disease Details

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

7.1.1.6 Prior Oncology Treatment History

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

7.1.1.7 Prior and Concomitant Medications Review

7.1.1.7.1 Prior Medications

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

7.1.1.7.2 Concomitant Medications

The investigator or qualified designee will record medication, if any, taken by the subject during the trial and through the 30-day Safety Follow-up Visit. After the Safety Visit, record all medications related to reportable SAEs and ECIs.

All medications related to reportable SAEs and ECIs should be recorded as defined in Section 7.2 – Assessing and Recording Adverse Events.

7.1.1.8 Assignment of Screening Number

All consented subjects will be given a unique screening number that will be used to identify the subject for all procedures that occur prior to randomization or treatment allocation. Each subject will be assigned only one screening number. Screening numbers must not be re-used for different subjects.

Any subject who is screened multiple times will retain the original screening number assigned at the initial screening visit.

Subjects who crossed over 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 7.1.5.1.

7.1.1.9 Assignment of Treatment/Randomization Number

Part I

All eligible subjects will be allocated, by IWRS assignment, and will receive a treatment number. The treatment number identifies the subject for all procedures occurring after treatment allocation. The assigned screening number will become the subjects' treatment number. Once a treatment number is assigned to a subject, it can never be reassigned to another subject.

A single subject cannot be assigned more than 1 treatment number.

This treatment number will be used throughout the protocol for operational purposes. The treatment number will be assigned by IWRS at the time of enrollment. Treatment allocation will be accomplished by nonrandom assignment by 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.

Part II

Treatment allocation will be accomplished by nonrandom assignment by IWRS. When more than one cohort is open for enrollment, investigator assessment of tumor histology, eligibility, and lesion accessibility to IT therapy will determine allocation.

7.1.1.10 Trial Compliance (Medication/Diet/Activity/Other)

Interruptions from the protocol specified treatment plan for ≥3 weeks require consultation between the investigator and the Sponsor and written documentation of the collaborative decision on subject management.

All doses of MK-1454 and pembrolizumab will be administered under the supervision of a qualified physician and/or designee experienced in the use of anticancer agents.

Instructions for preparing and administering study drugs will be provided in the Procedures Manual.

7.1.1.11 Trial Communication Plan Summary

Safety data from individual subjects will be closely followed by the Principal Investigator and the Sponsor on an ongoing basis and shared at regular safety teleconferences (typically once per week). The safety and tolerability of all subjects, including those undergoing DLT evaluation as well as those who have completed DLT evaluation, will be reviewed prior to the start of the next cohort. The Sponsor and principal investigators will assess the appropriateness of dose escalation and assess safety and tolerability at the completion of each cohort, and prior to the opening of enrollment for the next cohort. The subsequent dose level to be tested in the next cohort of subjects will be communicated to the investigator or designee following each dose escalation decision meeting. A memorandum will be sent to each site to communicate the specified next dose level. Subjects will be enrolled and allocated via IWRS according to the dose escalation and confirmation guidelines outlined in Section 5.2. The dose at each cohort will be specified via IWRS. Cohorts will be opened or closed through IWRS to assure correct dosing in each cohort.

7.1.2 Clinical Procedures/Assessments

7.1.2.1 Adverse Event Monitoring

The investigator or qualified designee will assess each subject to evaluate for potential new or worsening AEs as specified in the Schedule of Activities and more frequently if clinically indicated. AEs will be graded according to NCI CTCAE Version 4. Toxicities will be characterized in terms of seriousness, causality, toxicity grade, and action taken with regard to trial treatment.

All AEs of unknown etiology associated with MK-1454 and pembrolizumab exposure should be evaluated to determine if it is an ECI of a potential immunological etiology (irAE). See Section 7.2.3.2 regarding the identification, evaluation, and management of AEs of a potential immunological etiology.

This is a dose escalation trial to establish the MTD of MK-1454 alone and MK-1454 in combination with pembrolizumab. Therefore, each dose escalation will be based on the safety and tolerability experienced by subjects at each dose level. The safety and tolerability of each cohort for the DLT evaluation period will be reviewed prior to the start of the next cohort. The Sponsor and the principal investigators or subinvestigators will review the safety and tolerability of each trial treatment, assess the appropriateness of dose escalation, decide the completion of each cohort, and decide the opening of enrollment for the next cohort. Frequency of these communications will depend on the enrollment of each cohort, as well as any potential new information regarding a safety concern in this trial or other relevant trials.

As a Phase 1 trial, there is no plan for an external safety reviewer. Data from individual subjects will be closely followed on an ongoing basis by the Principal Investigator and the Sponsor.

7.1.2.2 Full Physical Examination

The investigator or qualified designee will perform a complete physical exam during the screening period and at additional time points as defined in the Schedule of Activities (Section 6.0). Clinically significant findings from the screening exam should be recorded as medical history.

A directed physical exam should be repeated according to the frequency defined in the Schedule of Activities (Section 6.0). After the first dose of study treatment, new clinically significant abnormal findings should be recorded as AEs.

7.1.2.3 Vital Signs and Weight

Vital signs include temperature, pulse, respiratory rate, blood pressure, and oxygen saturation (pulse oximetry) at the frequency defined in the Schedule of Activities (Section 6.0).

Weight will be obtained at Screening, at C1D1 of each treatment cycle, at EOT, and at the 30-day Safety Follow-up Visit. Height will be obtained at Screening only.

7.1.2.4 Electrocardiogram

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 Schedule of Activities (Section 6.0). Clinically significant abnormal findings seen on all ECGs performed after Screening should be recorded as AEs.

7.1.2.5 Eastern Cooperative Oncology Group Performance Status

The investigator or qualified designee will assess the ECOG performance status as the time points specified in the Schedule of Activities (Section 6.0). Additional ECOG testing may be performed as clinically indicated.

7.1.2.6 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 subject has measurable disease as defined by RECIST version 1.1, IWG revised criteria, or ISCL criteria to confirm eligibility. In subjects with CTCL, it is recommended that CT and PET scans be performed at screening.

Part I – Dose Escalation and Confirmation

For Arms 1, 2, and 3 (Part I), tumor imaging and/or medical photography should be repeated every 9 weeks for solid tumors or every 12 weeks for lymphomas from the first dose of treatment. For subjects with CTCL, medical photography will be performed at each treatment cycle, however, tumor imaging will be repeated only to document and confirm PR, CR, or PD.

Part II – Expansion Cohorts

For Cohort A (HNSCC) and Cohort B (TNBC), imaging will begin at 9 weeks and occur every 9 weeks thereafter. Imaging for HNSCC should include the head, neck, chest, and abdomen at all timepoints. Imaging of the pelvis is optional.

Solid tumor imaging should be acquired by CT (with PET for CTCL, as clinically indicated). 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. MRI should be used when CT is contraindicated or for imaging of the brain. The same imaging technique and the same imaging modality with/without the use of contrast should be performed for assessment of response in a subject throughout the trial to optimize visualization of existing and new tumor burden. Tumor imaging schedule 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 made available for possible future independent review.

7.1.2.7 Response Assessment

7.1.2.7.1 Immune-related RECIST

RECIST 1.1 will be adapted to account for the unique tumor response characteristics seen in treatment with pembrolizumab and MK-1454. 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-1454. Immune-related RECIST (irRECIST) is RECIST 1.1 adapted as described below to account for the unique tumor response seen with

immunotherapeutics. 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 subjects 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 lesions will not be target lesions for RECIST 1.1 or irRECIST.

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 subjects who have initial evidence of radiological PD, it is at the discretion of the investigator whether to continue a subject on study treatment until repeat imaging is obtained. This clinical judgment decision should be based on the subject's overall clinical condition, including performance status, clinical symptoms, and laboratory data. Subjects 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, subjects should not be discontinued until progression is confirmed. This allowance to continue treatment despite initial radiologic progression takes into account the

observation that some subjects can have a transient tumor flare in the first few months after the start of immunotherapy, and still have a subsequent disease response. Subjects who are deemed clinically unstable are not required to have repeat imaging for confirmation of PD.

NOTE: In subjects who discontinue study therapy without documented disease progression, every effort should be made to continue monitoring of their disease status by radiologic imaging every 9 weeks (± 7 days) until: (1) the start of new anticancer treatment, (2) disease progression (3) death, or (4) the end of the study, whichever occurs first.

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

7.1.2.7.2 Intratumoral Immunotherapy RECIST (itRECIST)

itRECIST is a response assessment that is tailored to IT immunotherapy, is aligned with RECIST 1.1 overall response assessment [3] and is further described in Appendix 12.4.

itRECIST:

- provides a guidance on baseline categorization of target and nontarget lesions (Figure 5);
- provides guidance on recategorization of lesions during therapy (Figure 6);
- allows for separate response assessment in injected and noninjected lesions (Figure 7);
- 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 8); and
- provides guidelines on prioritization of lesion injection during the course of intratumoral immunotherapy (see Appendix 12.3)

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

7.1.2.7.3 IWG Revised Response Criteria for Malignant Lymphomas

Response to treatment for lymphomas will continue to be assessed every 12 weeks that a subject remains in the trial.

Response to therapy will be assessed by CT or CT/PET, bone marrow biopsy, and clinical information including physical exam and symptoms, using the IWG Revised Response Criteria for Malignant Lymphomas [25]. Information collected 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, and at follow-up visits if there is nodal involvement in the neck at screening. Fluorodeoxyglucose-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 subject 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 16 as appropriate. Suspected relapse or disease progression must be confirmed by physical exam, laboratory assessments, repeat bone marrow biopsy [25], and CT scan. Subjects with suspected relapse or disease progression should continue to follow study procedures until they need another therapy. If a subject 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 sum of the products of diameters (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 malignancy lymphoma [25].

Table 16 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

Response Category	Physical Examination	Nodal Masses	Spleen, Liver	Bone Marrow
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: CT = computed tomography; FDG = fluorodeoxyglucose; PET = positron-emission tomography; SPD = sum of the product of the longest bidimensional diameters

7.1.2.7.4 Response Assessment Criteria for CTCL

The Modified Severity Weighted Assessment Tool (mSWAT - Table 17) will be used to evaluate the extent of disease in the CTCL subjects prior to treatment at each cycle per the SoA. Imaging (CT scans and medical photography) will be performed at screening/baseline for all CTCL subjects. 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 [2].

Each scheduled response assessment will include evaluations of skin (Table 18), lymph nodes (Table 19), viscera (Table 20), and blood (Table 21); and will determine a global response score (Table 22) for CTCL subjects. Medical photography will also be performed at the time of each response assessment (see SoA), or more often as warranted.

Table 17 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 18 Response in Skin (CTCL)

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 19 Response in Lymph Nodes (CTCL)

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; SPD = sum of the product of the longest bidimensional diameters	

Table 20 Response in Viscera (CTCL)

Response	Definition
CR	Liver or spleen or any organ considered involved at baseline should not be enlarged on physical exam and should be considered normal by imaging; no nodules should be present on imaging of liver or spleen; any posttreatment 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; SPD = sum of the product of the longest bidimensional diameters	

Table 21 Response in Blood (CTCL)

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 [35] 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 22 Global Response Score for CTCL

Global Score[a]	**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	

Global Score[a]	Definition	Skin	Nodes, Blood, Viscera
Abbreviations: CR = complete response; NI = noninvolved; PD, progressive disease; PR = partial response; SD = stable disease. [a] 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.			

7.1.3 Laboratory Procedures/Assessments

Details regarding specific laboratory 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 pre-trial to post-trial visits), including approximate blood/tissue volumes drawn/collected by visit and by sample type per subject can be found in the Procedures Manual.

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

Laboratory tests for hematology, chemistry, and urinalysis are specified in Table 23.

Table 23 Laboratory Tests

Hematology	Chemistry	Urinalysis	Other
Hematocrit	Albumin	Blood	FSH[a]
Hemoglobin	Alkaline phosphatase	Glucose	Serum hCG
Platelet count	ALT	Protein	Hepatitis
WBC (total and differential)[b]	AST	Specific gravity	HIV
RBC	Carbon Dioxide or Bicarbonate	Microscopic exam, if abnormal results are noted	T3 or FT3
PT or INR	Calcium	Urine pregnancy test[a]	T4 or FT4
PTT or aPTT	Chloride		TSH
	Creatinine[d]		HPV[e]
	GGT		
	Glucose		
	Phosphorus		
	Potassium		
	Sodium		
	Total Bilirubin		
	Direct Bilirubin, if total bilirubin is elevated above the ULN		
	Total protein		
	BUN[e]		
	LDH		
	Uric acid		

Hematology	Chemistry	Urinalysis	Other
ALT=alanine aminotransferase; aPTT=activated partial thromboplastin time; AST=aspartate aminotransferase; BUN=blood urea nitrogen; FT3=free triiodothyronine; FT4=free thyroxine; FSH=follicle stimulating hormone; GGT=gamma glutamyl transpeptidase; HCG=human chorionic gonadotropin; HNSCC = head and neck squamous cell carcinoma; HPV=human papilloma virus; INR=International Normalized Ratio; LDH=lactic dehydrogenase; PT=prothrombin time; PTT=partial thromboplastin time; RBC=red blood count; SCC = squamous cell carcinoma; T3=total triiodothyronine; T4=total thyroxine; TSH=thyroid stimulating hormone; ULN=upper limit of normal; WBC=white blood count; WOCBP = women of childbearing potential..			
[a] Perform on WOCBP only. If urine pregnancy results cannot be confirmed as negative, a serum pregnancy test will be required. [b] Absolute or % acceptable per institutional standard [c] For subjects with a baseline calculated creatinine clearance that is below the normal institutional laboratory range, a baseline measured creatinine clearance should be performed. GFR can be used in place of creatinine clearance. [d] HNSCC or other SCC subjects only [e] BUN is preferred; if not available urea may be tested			

Laboratory safety tests for screening should be performed within 28 days prior to first dose of study medication, unless otherwise specified in the SoA. After Cycle 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.

7.1.3.2 Pharmacokinetic/Pharmacodynamic Evaluations

7.1.3.2.1 Blood Collection for MK-1454 and Pembrolizumab PK

Blood sample collection, storage, and shipment instructions will be provided in the Procedures Manual. MK-1454 PK samples can be used for metabolite analysis. Pembrolizumab PK and ADA samples can be discontinued based on early data.

7.1.3.2.2 Blood Collection for Anti-Pembrolizumab Antibodies (ADA)

Blood sample collection, storage, and shipment instructions for ADA analysis will be provided in the Procedures Manual.

7.1.3.2.3 Blood for Pharmacodynamic Markers

Blood sample collection, storage, and shipment instructions for PD analysis will be provided in the Procedures Manual.

The time points for PD sampling are described in Section 6.0-Schedule of Activities.

7.1.3.2.4 Tumor Biopsy

Tumor samples will be collected at the time points described in Section 6.0 – Schedule of Activities.

All subjects will be required to provide a sample biopsy of the tumor to be injected with MK-1454 and a sample biopsy from a distant, discrete noninjected site (if feasible) (at least 2 biopsies at each site) after IT administration of MK-1454, unless deemed medically unsafe by the investigator. For Part II Expansion Cohort, only the injected tumor biopsy is required,

unless deemed medically unsafe by the investigator. The noninjected lesion should be measurable as defined by RECIST 1.1. Tumor dimensions must be ≥1 cm in longest diameter for non-nodal lesions, or ≥1.5 cm in short axis for nodal lesions.

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-1454 FIH study assured selection of sites that had investigative staff that were highly experienced in tumor biopsies.

For subjects with lymphoma, only those subjects that have superficial lesions amendable to intratumoral injection will be eligible (cutaneous lesions injected via visual inspection, and subcutaneous lymph nodes injected via ultrasound guidance or palpation). No lymphoma subjects with exclusively deep lymph nodes will be included in this study. Lymphoma subjects 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.

A predose tumor biopsy will be performed at screening on both the tumor lesion which is intended for treatment with IT injection of MK-1454, as well as on the distant lesion which is not intended for IT injection with MK-1454. For Part II Expansion Cohort, only the injected tumor biopsy is required, unless deemed medically unsafe by the investigator.

For the tumor lesion intended for treatment with IT injection of MK-1454, the sample will be obtained by either punch biopsy for cutaneous lesions, by ultrasound guided biopsy for subcutaneous/visceral lesions, or by cross-sectional imaging guidance for visceral lesions.

For distant discrete tumor lesions which are not intended for IT injection with MK-1454, the sample biopsy will be obtained by one of the following: punch biopsy for cutaneous lesions, ultrasound guided biopsy for subcutaneous/visceral lesions, or image-guided biopsy, such as CT-guided biopsy for visceral lesions and deeper tumor lesions. On-treatment biopsy site location may vary from baseline biopsy site location based on lesion accessibility and subject tolerance. Method of biopsy will be per guidance of the investigator, as well as discussion with the Sponsor.

For visceral lesions, the sample biopsy will be obtained via ultrasound guidance or cross-sectional imaging (CT/MRI) guidance.

Leftover main study tissue will be stored for FBR if the subject 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.

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

7.1.3.3 Planned Genetic Analysis Sample Collection

Sample collection, storage and shipment instructions for Planned Genetic Analysis samples will be provided in the Procedures Manual. This sample should be drawn for planned analysis of the association between genetic variants in DNA and drug response. If there is either a documented law or regulation prohibiting collection, or if the IRB/IEC does not approve the collection of the sample for these purposes, then this sample will not be collected at that site. If the sample is collected, leftover extracted DNA will be stored for FBR if the subject provides documented informed consent for FBR. 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.

7.1.3.4 Future Biomedical Research Samples

The following specimens are to be obtained as part of FBR:

- DNA for future research

In addition, any tissue obtained for protocol-specified assessments that is remaining after the assessment is completed will be stored for future research, including:

- RNA
- Serum
- Plasma
- Tumor tissue
- Bone marrow biopsy/aspirate

Instructions for the collection and management of FBR specimens are provided in the Procedures Manual and Appendix 12.2.

7.1.4 Other Procedures

7.1.4.1 Withdrawal/Discontinuation

It has been well documented that a higher rate of withdrawal can render a study uninterpretable; therefore, unnecessary withdrawal of subjects should be avoided. As clinical event data are important to study endpoints, subjects who discontinue/withdraw from treatment prior to completion of the treatment regimen should be encouraged to continue to be followed for all remaining study visits for follow-up and vital status assessments as outlined in the SoA.

When a subject discontinues/withdraws from participation in the trial, all applicable activities scheduled for the final trial visit should be performed at the time of discontinuation. Any AEs which are present at the time of discontinuation/withdrawal should be followed in accordance with the safety requirements outlined in Section 7.2 - Assessing and Recording Adverse Events.

The Investigator is to inform the subjects that

- they may discontinue from study medication at any time during the study, and

- they are encouraged to continue visits in the study for follow-up, imaging, and vital status assessment.

If participants elect to stop study procedures, they are encouraged to continue to be followed, which allows periodic survival follow-up and vital status data to be collected.

7.1.4.1.1 Withdrawal From Future Biomedical Research

Subjects may withdraw their consent for FBR. Subjects 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@merck.com). Subsequently, the subject's consent for FBR 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 subject 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 (e.g., 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 subject’s personal information and their specimens. In this situation, the request for specimen withdrawal cannot be processed.

7.1.4.1.2 Lost to Follow-up

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

- The site must attempt to contact the subject and reschedule the missed visit. If the subject is contacted, the subject 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 subject at each missed visit (eg, phone calls and/or a certified letter to the subject’s last known mailing address or locally equivalent methods). These contact attempts should be documented in the subject’s medical record.
- Note: A subject is not considered lost to follow-up until the last scheduled visit for the individual subject. The amount of missing data for the subject will be managed via the prespecified data handling and analysis guidelines.

7.1.4.2 Subject Blinding/Unblinding

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

7.1.4.3 Domiciling

Subjects in Part I (Arms 1 2, and 3) will report to the CRU on C1D1 and will remain for inpatient observation for at least 24 hours post MK-1454 administration on C1D1. The inpatient observation period post MK-1454 administration on C1D1 may be extended to 48 hours, based on the discretion of the investigator, and/or local IRB/IEC, and/or Health Authority mandate.

This requirement may be waived at the discretion of the Sponsor and will be communicated to sites via a memorandum.

Subjects in Part II (Expansion Cohorts A, B, and C) will report to the CRU on C1D1 and will remain in the clinic for at least 8 hours post MK-1454 administration on C1D1. The observation period post MK-1454 administration on C1D1 may be extended based on the discretion of the investigator and/or local IRB/IEC, and/or Health Authority mandate.

7.1.4.4 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/or maintained to ensure that the data obtained is reliable and/or reproducible. Documentation of equipment calibration must be retained as source documentation at the trial site.

7.1.5 Visit Requirements

Visit requirements are outlined in Section 6.0 – Schedule of Activites. Specific procedure-related details are provided above in Section 7.1 - Trial Procedures.

7.1.5.1 Screening

Up to 28 days prior to treatment allocation/randomization, potential subjects will be evaluated to determine if they fulfill the entry requirements as set forth in Section 5.1. Tests performed as part of routine clinical management prior to the subject signing consent are acceptable in lieu of a screening test, if these tests are performed within the specified time frame of 28 days prior to treatment allocation/randomization. Bone marrow biopsy results for lymphoma subjects are permissible up to 8 weeks prior to screening.

Screening procedures may be repeated after consultation with the Sponsor.

7.1.5.2 Treatment Period

The treatment period in each treatment arm or expansion cohort (Arm 1, Arm 2, and Arm 3; Cohorts A, B, and C) begins with Cycle 1 and may continue for up to 35 cycles (approximately 2 years) from the start of treatment until disease progression, unacceptable AE(s), intercurrent illness that prevents further administration of treatment, investigator's decision to withdraw the subject, subject withdraws consent, pregnancy of the subject, noncompliance with trials treatment or procedure requirements, or administrative reasons requiring cessation of treatment. Subjects who cross over from Arm 1 to Arm 2 are eligible

for up to 35 cycles of treatment within Arm 2, regardless of the number of cycles of MK-1454 treatment received in Arm 1. Each cycle includes study drug administration and all associated assessments as outlined in the Schedule of Activities (see Section 6.0).

Specific procedure-related details are provided throughout Section 7.0.

7.1.5.3 Treatment Period Beyond Disease Progression

See Section 7.1.2.7.

7.1.5.4 Discontinued Subjects Continuing to be Monitored in the Trial

The Discontinuation Visit should occur at the time study treatment is discontinued for any reason. If the Discontinuation Visit occurs 30 days from the last dose of study treatment, at the time of the mandatory Safety Follow-up Visit, the Discontinuation Visit procedures and any additional Safety Follow-up procedures should be performed. Visit requirements are outlined in Section 6 - Schedule of Activities. Additional details regarding subject withdrawal and discontinuation are presented in Section 5.8 –Subject Withdrawal/Discontinuation Criteria.

7.1.5.5 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 antineoplastic treatment, whichever comes first. All AEs that occur prior to the 30-day Safety Follow-up Visit should be recorded. Subjects with an AE of Grade >1 will be followed until the resolution of the AE to Grade 0-1 or until the beginning of a new antineoplastic therapy, whichever occurs first.

After the EOT, each subject will be followed for 30 days for AE monitoring and 130 days for SAEs, ECI, and spontaneously reported pregnancy. SAEs, ECI, and spontaneously reported pregnancy will be reported for 30 days after the EOT if the subject initiates new anticancer therapy. Progression of the cancer under study is not considered an AE.

7.1.5.6 Survival Status Monitoring

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

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 interim and/or final analysis. Upon Sponsor notification, all subjects 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 subjects who have withdrawn consent or 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.

7.2 Assessing and Recording Adverse Events

An AE is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product or protocol-specified procedure, whether or not considered related to the medicinal product or protocol-specified procedure. Any worsening (i.e., any clinically significant adverse change in frequency and/or intensity) of a preexisting condition that is temporally associated with the use of the Sponsor's product, is also an AE.

Changes resulting from normal growth and development that do not vary significantly in frequency or severity from expected levels are not to be considered AEs. Examples of this may include, but are not limited to, teething, typical crying in infants and children and onset of menses or menopause occurring at a physiologically appropriate time.

Sponsor's product includes any pharmaceutical product, biological product, device, diagnostic agent or protocol-specified procedure, whether investigational (including placebo or active comparator medication) or marketed, manufactured by, licensed by, provided by or distributed by the Sponsor for human use.

AEs may occur during clinical trials, or as prescribed in clinical practice, from overdose (whether accidental or intentional), from abuse and from withdrawal.

Progression of the cancer under study is not considered an AE.

All AEs that occur after consent is documented but before treatment allocation/randomization must be reported by the investigator if they cause the subject 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. From the time of treatment allocation/randomization through 30 days following cessation of treatment, all AEs must be reported by the investigator. Such events will be recorded at each examination on the AE CRFs/worksheets. The reporting timeframe for AEs meeting any serious criteria is described in section 7.2.3.1. The investigator will make every attempt to follow all subjects with nonserious adverse events for outcome.

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).

AEs will not be collected for subjects during the pre-screening period (for determination of archival tissue status) as long as that subject has not undergone any protocol-specified procedure or intervention. If the subject requires a blood draw, fresh tumor biopsy etc., the subject is first required to provide consent to the main study and AEs will be captured according to guidelines for standard AE reporting.

7.2.1 Definition of an Overdose for This Protocol and Reporting of Overdose to the Sponsor

For purposes of this trial, an overdose will be defined as any dose exceeding the prescribed dose for MK-1454 by 20% of the indicated dose or a pembrolizumab dose of ≥1000 mg (≥5 times the indicated dose). No specific information is available on the treatment of overdose of MK-1454 or pembrolizumab. In the event of overdose, treatment with MK-1454 and/or pembrolizumab should be discontinued and the subject should be observed closely for signs of toxicity. Appropriate supportive treatment should be provided if clinically indicated.

If an AE(s) is associated with ("results from") the overdose of Sponsor's product or vaccine, the AE(s) is/are reported as an SAE, even if no other seriousness criteria are met.

If a dose of Sponsor's product or vaccine meeting the protocol definition of overdose is taken without any associated clinical symptoms or abnormal laboratory results, the overdose is reported as a non-serious ECI, using the terminology "accidental or intentional overdose without adverse effect."

All reports of overdose with and without an AE must be reported by the investigator 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).

7.2.2 Reporting of Pregnancy and Lactation to the Sponsor

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 subject (spontaneously reported to them) that occurs during the trial.

Pregnancies and lactations that occur after the consent form is signed but before treatment allocation/randomization must be reported by the investigator if they cause the subject 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 that occur from the time of treatment allocation/randomization through 130 days following cessation of Sponsor's product, or 30 days following cessation of trial treatment if the subject initiates new anticancer therapy, whichever is earlier, must be reported by the investigator. 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 by either 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).

7.2.3 Immediate Reporting of Adverse Events to the Sponsor

7.2.3.1 Serious Adverse Events

An SAE is any AE occurring at any dose or during any use of Sponsor's product that:

- Results in death;
- Is life threatening;
- Results in persistent or significant disability/incapacity;
- Results in or prolongs an existing inpatient hospitalization;
- Is a congenital anomaly/birth defect;
- Is another important medical event.

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

- Is a new cancer (that is not a condition of the study);
- Is associated with an overdose.

Refer to Table 24 for additional details regarding each of the above criteria.

For the time period beginning when the consent form is signed until treatment allocation/randomization, any SAE, or follow up to a SAE, including death due to any cause, that occurs to any subject must be reported within 24 hours to the Sponsor if it causes the subject 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, placebo treatment or a procedure.

For the time period beginning at treatment allocation/randomization through 130 days following cessation of trial treatment, or 30 days following cessation of trial treatment if the subject initiates new anticancer therapy, whichever is earlier, any SAE, or follow up to an SAE, including death due to any cause, whether or not related to the Sponsor's product, 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).

Additionally, any SAE, considered by an investigator who is a qualified physician to be related to the Sponsor's product that is brought to the attention of the investigator at any time following consent through the end of the specified safety follow-up period specified in the paragraph above, or at any time outside of the time period specified in the previous paragraph also must be reported immediately to the Sponsor.

All subjects with SAEs must be followed up for outcome.

7.2.3.2 Events of Clinical Interest

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

For the time period beginning when consent is documented until treatment allocation/randomization, any ECI, or follow up to an ECI, that occurs to any subject must be reported within 24 hours to the Sponsor if it causes the subject 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, placebo treatment or a procedure.

For the time period beginning at treatment allocation/randomization through 130 days following cessation of treatment, or 30 days following cessation of trial treatment if the subject initiates new anticancer therapy, whichever is earlier, any ECI, or follow up to an ECI, whether or not related to the Sponsor's product, 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).

Events of clinical interest for this trial include:

1. an overdose of Sponsor's product, as defined in Section 7.2.1 - Definition of an Overdose for This Protocol and Reporting of Overdose to the Sponsor, 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 ULN and an elevated total bilirubin lab value that is greater than or equal to 2X the ULN and, at the same time, an alkaline phosphatase lab value that is less than 2X the ULN, 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).

7.2.3.3 Protocol-Specific Exceptions to Serious Adverse Event Reporting

Efficacy endpoints as outlined in this section will not be reported to the Sponsor as described in Section 7.2.3. Any such event will be submitted to the Sponsor within 24 hours either by electronic or paper media.

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

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

7.2.4 Evaluating Adverse Events

An investigator who is a qualified physician will evaluate all AEs according to the NCI CTCAE, version 4.0 (Table 24). Any AE which changes CTCAE grade over the course of a given episode will have each change of grade recorded on the AE CRF/worksheets.

All AEs regardless of CTCAE grade must also be evaluated for seriousness.

For studies in which multiple agents are administered as part of a combination regimen, the investigator may attribute each AE causality to the combination regimen or to a single agent of the combination. In general, causality attribution should be assigned to the combination regimen (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 AE to the single agent.

Table 24 Evaluating Adverse Events

An investigator who is a qualified physician, will evaluate all AEs as to:

V4.0 CTCAE Grading	**Grade 1**	**Mild; asymptomatic or mid 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 or hospitalization indicated; disabling; limiting self-care ADL.**
	Grade 4	**Life threatening consequences; urgent intervention indicated.**
	Grade 5	**Death related to AE**
Seriousness	An SAE is any AE occurring at any dose or during any use of Sponsor's product that:	
	†**Results in death**; or	
	†**Is life threatening; or** places the subject, in the view of the investigator, at immediate risk of death from the event as it occurred (Note: This does not include an AE that, had it occurred in a more severe form, might have caused death.); or	
	†**Results in a persistent or significant disability/incapacity** (substantial disruption of one's ability to conduct normal life functions); or	
	†**Results in or prolongs an existing inpatient hospitalization** (hospitalization is defined as an inpatient admission, regardless of length of stay, even if the hospitalization is a precautionary measure for continued observation. (Note: Hospitalization for an elective procedure to treat a pre-existing condition that has not worsened is not an SAE. A pre-existing condition is a clinical condition that is diagnosed prior to the use of a Merck product and is documented in the patient's medical history.); or	
	†**Is a congenital anomaly/birth defect** (in offspring of subject taking the product regardless of time to diagnosis);or	
	Is a new cancer (that is not a condition of the study) **(**although not serious per ICH definition, is reportable to the Sponsor within 24 hours to meet certain local requirements); **or**	
	Is an overdose (whether accidental or intentional). Any AE associated with an overdose is considered an SAE for collection purposes. An overdose that is not associated with an AE is considered a nonserious ECI and must be reported within 24 hours.	
	Other important medical events that may not result in death, not be life threatening, or not require hospitalization may be considered an SAE when, based upon appropriate medical judgment, the event may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed previously (designated above by a †).	
Duration	Record the start and stop dates of the adverse event. If less than 1 day, indicate the appropriate length of time and units	
Action taken	Did the AE cause the Sponsor's product to be discontinued?	
Relationship to Sponsor's Product	Did the Sponsor's product cause the AE? The determination of the likelihood that the Sponsor's product caused the AE will be provided by an investigator who is a qualified physician. The investigator's signed/dated initials on the source document or worksheet that supports the causality noted on the AE form, ensures that a medically qualified assessment of causality was done. This initialed document must be retained for the required regulatory time frame. The criteria below are intended as reference guidelines to assist the investigator in assessing the likelihood of a relationship between the test drug and the AE based upon the available information. **The following components are to be used to assess the relationship between the Sponsor's product and the AE**; the greater the correlation with the components and their respective elements (in number and/or intensity), the more likely the Sponsor's product caused the AE:	
	Exposure	Is there evidence that the subject 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

Relationship to Sponsor's Product (continued)	**The following components are to be used to assess the relationship between the test drug and the AE: (continued)**	
	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; or (3) the trial is a single-dose drug trial); or (4) Sponsor's product(s) is/are only used one time.)
	Rechallenge	• Was the subject re-exposed to the Sponsor's product in this study? - If yes, did the AE recur or worsen? ◦ If yes, this is a positive rechallenge. If no, this is a negative rechallenge. (Note: This criterion is not applicable if: (1) the initial AE resulted in death or permanent disability, or (2) the 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 AE WHICH WAS SERIOUS AND WHICH MAY HAVE BEEN CAUSED BY THE SPONSOR'S PRODUCT, OR IF REEXPOSURE TO THE SPONSOR'S PRODUCT POSES ADDITIONAL POTENTIAL SIGNIFICANT RISK TO THE SUBJECT, THEN THE RECHALLENGE MUST BE APPROVED IN ADVANCE BY THE SPONSOR CLINICAL DIRECTOR AS PER DOSE MODIFICATION GUIDELINES IN THE PROTOCOL.
	Consistency with Trial 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.		
Record one of the following	**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	Subject 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 subject with overdose without an associated AE.)	

7.2.5 Sponsor Responsibility for Reporting Adverse EventsSAEs

All Adverse EventsSAEs will be reported to regulatory authorities, IRB/IECs and investigators in accordance with all applicable global laws and regulations, i.e., per ICH Topic E6 (R1) Guidelines for Good Clinical Practice.

8.0 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 non-confirmatory analyses will be outlined in a separate 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 non-confirmatory 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.

8.1 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, Sections 8.2 through 8.12.

Study Design Overview	Phase 1 trial of MK-1454 IT as monotherapy and in combination with pembrolizumab in subjects with advanced/metastatic solid tumors or lymphomas. Part I, dose escalation and confirmation, includes monotherapy (cutaneous or subcutaneous lesions) (Arm 1), MK-1454 IT in combination with pembrolizumab (cutaneous or subcutaneous lesions) (Arm 2), and MK-1454 IT in combination with pembrolizumab (visceral lesions) (Arm 3) in subjects with advanced/metastatic solid tumors or lymphomas. For Arms 1, 2, and 3, the study applies an ATD followed by a modified TPI design for dose escalation and confirmation to establish an MTD/MAD and to identify a preliminary RP2D in each treatment arm. In the expansion phase of this trial, Part II, Cohort A and B will begin enrolling after the preliminary RP2D is established from Arm 2 and will evaluate MK-1454 in combination with pembrolizumab. Expansion Cohort C will begin enrolling after the preliminary RP2D is established from Arm 3 and will evaluate MK-1454 in combination with pembrolizumab.
Analysis Populations	Safety (Primary): ASa and DLTe PK (Secondary): PP Efficacy (Secondary and Exploratory): Full Analysis Set (FAS)
Primary Endpoint(s)	• DLT • AE • Discontinuing study treatment due to an AE

Key Secondary Endpoints	• PK parameters of MK-1454 monotherapy, PK parameters for MK-1454 in combination with pembrolizumab, and PK parameters for pembrolizumab in combination with MK-1454. • ORR
Statistical Methods for Key Efficacy/Immunogenicity/ Pharmacokinetic Analyses	Plasma concentrations of MK-1454 will be summarized by planned visit and time for each dose separately; PK parameters will be summarized by dose. For pembrolizumab, serum concentrations will be compared to the historical monotherapy pembrolizumab data. ORR will be estimated using an exact method based on the binomial distribution (Clopper-Pearson interval) together with its 95% confidence interval
Treatment Assignment	In Part I, subjects will be allocated to receive single-agent MK-1454 (Arm 1), MK 1454 co-administered with pembrolizumab via cutaneous or subcutaneous IT injection (Arm 2), or MK 1454 co-administered with pembrolizumab via visceral IT injection (Arm 3) centrally through an IWRS. Subjects 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. In Part II, subjects will be allocated to one of 3 cohorts depending on their tumor type and other characteristics through IWRS. 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 [31] will be used to estimate the DLT rates across doses. The estimates of the DLT rates among subjects treated at MTD (or MAD) of MK-1454 and the 80% Bayesian credible intervals for the estimates will be provided.
Interim Analyses	An administrative 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 escalation and confirmation decisions. For each expansion cohort (Cohorts A-C) in Part II, if there are no responders among approximately the first 15 evaluable subjects, the cohort may be stopped early. For Cohort C, an additional futility check may be performed if applicable for the first 30 evaluable subjects. If there are 1 or less responders in Cohort C, the Cohort may be stopped early for futility.
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-1454 monotherapy and MK-1454 in combination with pembrolizumab for Part I and the number of Expansion Cohorts to be enrolled for Part II. A target sample size of approximately 235 subjects will be used for study planning purposes.

8.2 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, subjects, investigators, and Sponsor personnel will be aware of subject treatment assignment after each subject is enrolled and treatment is assigned. Allocation to treatment will not be randomized.

8.3 Hypotheses/Estimation

Objectives and hypotheses of the study are outlined in Section 3.0.

8.4 Analysis Endpoints

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

8.4.1 Efficacy/Pharmacokinetic Endpoints

ORR in subjects treated with MK-1454 in combination with pembrolizumab as assessed by investigator using RECIST 1.1 criteria is a secondary endpoint for Part II of the trial. PFS and OS are exploratory endpoints in this study. Details of the statistical analysis plan for exploratory endpoints will be documented in the sSAP. A description of efficacy measures is provided in Section 4.2.3.

ORR is defined as the proportion of subjects 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.

OS is defined as the time from the first dose of study treatment to death due to any cause. Subjects who do not die will be censored on the date of the last study assessment or contact.

ORR 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.

PK endpoints include concentrations of MK-1454 and pembrolizumab, as well as any derived PK parameters.

8.4.2 Safety Endpoints

The primary safety endpoint is the number/proportion of subjects with DLT(s), AE(s), and who discontinue study treatment due to AE(s). A description of safety measures is provided in Section 4.2.3.2.

8.5 Analysis Populations

8.5.1 Safety Analysis Population

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

of treatment administration errors, subjects will be analyzed according to the treatment they actually received. The DLTe population includes ASaT subjects that 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. The replacement subjects will also be considered evaluable if the above specified criteria are met.

At least one 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.

8.5.2 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 subjects 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 subjects 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 subjects who were compliant with the study procedures and have available data from at least one treatment will be potentially included in the PP analysis dataset.

8.5.3 Efficacy Analysis Populations

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

A supportive approach using modified FAS population may be performed for the efficacy endpoints. The modified FAS population includes FAS subjects without substantial dose interruption as defined in the sSAP.

8.6 Statistical Methods

8.6.1 Statistical Methods for Efficacy Analyses

For the secondary endpoint of ORR, the point estimate and 95% CI will be evaluated in Part II subjects treated with MK-1454 in combination with pembrolizumab at the RP2D for each tumor cohort separately, using an exact method based on the binomial distribution (Clopper-Pearson Interval). Other exploratory endpoints (eg, PFS) may also be examined within each expansion cohort. Of note, efficacy analyses for each Part II expansion cohort will pool Part I subjects who meet the inclusion criteria for the respective Part II tumor type and received the same dose level of MK-1454 in combination with pembrolizumab.

8.6.2 Statistical Methods for Safety Analyses

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

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

Dose-limiting toxicities will be listed, and further summarized by dose level and arm. The pool adjacent-violators-algorithm [31], which forces the DLT rate estimates to be nondecreasing with dose levels and pools adjacent violators for weighted estimates by sample size, will be used to estimate the DLT rates across doses in each treatment arm. The estimates of the DLT rates among subjects 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.

8.6.3 Summaries of Baseline Characteristics, Demographics, and Other Analyses

8.6.3.1 Demographic and Baseline Characteristics

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

8.6.3.2 Pharmacokinetics and Pharmacodynamics Modeling Analysis

Plasma concentrations of MK-1454 will be summarized by planned visit and time for each dose separately; PK parameters will be summarized by dose. For pembrolizumab, serum concentrations will be compared to the historical monotherapy pembrolizumab data. Details of statistical analysis of pharmacokinetics-pharmacodynamics analyses will be documented in the sSAP.

8.7 Interim Analyses

An administrative 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 escalation and confirmation decisions.

An interim futility check will be performed for each of the selected solid tumor cohorts in Part II (Cohorts A through C). For Cohorts A, B, and C, if there are no responders among approximately the first 15 evaluable subjects, the cohort may be stopped early for futility. For Cohort C, an additional futility check may be performed if applicable for the first 30 evaluable subjects. If there is one or less responder among the first 30 evaluable subjects in Cohort C, the Cohort may be stopped early for futility. An evaluable subject has at least one postbaseline imaging assessment. If the true response rate is 10%, there is an 80% chance to observe at least 1 responder among 15 subjects, and an 82% chance to observe at least 2 responders among 30 subjects.

The futility bar is not binding, and the totality of the data will be evaluated before making a decision to discontinue enrollment. The data will be analyzed on a continuous basis and enrollment will not be paused when interim analyses are performed.

8.8 Multiplicity

There will be no multiplicity control in this study.

8.9 Sample Size and Power Calculations

The overall sample size for this Phase 1 trial is expected to be approximately 235 subjects.

8.9.1 Part I Sample Size

The overall sample size for Part I is expected to be approximately 115 subjects (approximately 40 subjects each in Arm 1 and Arm 2, and 35 in Arm 3). Part A, Part C, and Part E (ATD phase) will be followed by Part B, Part D and Part F (mTPI phase) of all 3 Arms. The ATD phase will have single-subject cohorts that may enroll up to 3 subjects to account for simultaneous enrollment. The mTPI phase will have 3 to 6 subjects per cohort, based on the occurrence of DLTs; up to 14 subjects may enroll per dose level.

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

In Arm 1 and Arm 2, in the absence of DLTs, utilizing dose increments of up to 300% for the ATD phase, and dose increments of 30% to 100% for the mTPI phase, there would be 1 subject per dose level treated at [redacted] and 3 subjects per dose level treated at [redacted] and 14 subjects treated at a dose level of [redacted] The total sample size for both Arm 1 and Arm 2 would then be 30.

In Arm 3, in the absence of DLTs and with 2 possible dose cohorts for the ATD phase and dose increments of 30% to 100% for the mTPI phase, there would be 1 subject per dose level treated at [redacted] and 14 subjects treated at a dose level of [redacted] The total sample size would then be 34 for Arm 3.

For dose escalation guidelines and specifications, see Section 5.2 and Table 3, Table 4, and Table 5.

8.9.2 Part II Sample Size

The overall sample size for Part II is expected to be approximately 120 subjects. For Cohort A (anti-PD-1/PD-L1 refractory HNSCC) and Cohort B (anti-PD-1/PD-L1 treatment-naïve or refractory unresectable locally advanced or metastatic TNBC), 30 subjects will be enrolled in each tumor cohort. For Cohort C (other anti-PD-1/PD-L1 treatment-naïve solid tumors with liver metastases), 60 subjects will be enrolled with approximately 15 non-MSI-H CRC patients, 15 pancreatic ductal adenocarcinoma patients, and 30 patients without these specific diagnoses.

The key efficacy endpoint will be ORR based on investigator assessment per RECIST 1.1. Table 25 and Table 26 show the ORR estimate and the 95% CI (Clopper-Pearson) for N=30 (Cohorts A and B, and Cohort C subgroup of Non-CRC/pancreatic tumors) and N=60 (Cohort C) respectively.

Table 25 Estimate and 95% CI of ORR (N=30)

Sample Size	Number of Responses (PR/CR)	Observed ORR	95% CI of ORR
CCI			

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

Table 26 Estimate and 95% CI of ORR (N=60)

Sample Size	Number of Responses (PR/CR)	Observed ORR	95% CI of ORR
CCI			

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

8.10 Subgroup Analyses and Effect of Baseline Factors

For Cohort C, other solid tumors with liver metastases, subgroup analysis of the efficacy endpoint ORR will be conducted between non-MSI-H CRC patients, pancreatic ductal adenocarcinoma patients, and the remaining Cohort C patients.

Other subgroup analyses for the Part II Expansion Cohorts A-C may be conducted as needed, for example by age or race.

8.11 Compliance (Medication Adherence)

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

8.12 Extent of Exposure

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

9.0 LABELING, PACKAGING, STORAGE AND RETURN OF CLINICAL SUPPLIES

9.1 Investigational Product

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 investigational product in accordance with the protocol and any applicable laws and regulations.

Clinical Supplies will be provided by the Sponsor as summarized in Table 27.

Clinical supplies will be packaged to support enrollment and replacement subjects as required. When a replacement subject is required, the Sponsor or designee needs to be contacted prior to dosing the replacement supplies.

Table 27 Product Descriptions

Product Name & Potency	Dosage Form	Source/Additional Information
MK-1454, CCI [redacted]	Solution for Injection	Provided centrally by the Sponsor.
MK-1454, CCI [redacted]	Solution for Injection	Provided centrally by the Sponsor.
MK-1454, Diluent	Solution for dosage preparation	Provided centrally by the Sponsor or locally by the study site, subsidiary, or designee.
Pembrolizumab (MK-3475) 100 mg/4 mL	Solution for Infusion	Provided centrally by the Sponsor.

All supplies indicated in Table 27 will be provided per the "Source/Additional Information" column depending on local country operational requirements.

Any commercially available product not included in Table 27 will be provided by the trial site, subsidiary or designee. 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.

9.2 Packaging and Labeling Information

Clinical supplies will be affixed with a clinical label in accordance with regulatory requirements.

In addition, 10 mL, sterile empty vials will be provided for on-site dosage preparation.

Subjects will receive open-label study drug at each treatment visit.

9.3 Clinical Supplies Disclosure

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

9.4 Storage and Handling Requirements

Clinical supplies must be stored in a secure, limited-access location under the storage conditions specified on the label.

Receipt and dispensing of trial medication must be recorded by an authorized person at the trial site.

Clinical supplies may not be used for any purpose other than that stated in the protocol.

9.5 Discard/Destruction/Returns and Reconciliation

The investigator is responsible for keeping accurate records of the clinical supplies received from the Sponsor or designee, the amount dispensed to and returned by the subjects and the amount remaining at the conclusion of the trial. 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.

9.6 Standard Policies

Trial site personnel will have access to a central electronic treatment allocation/randomization system (IWRS system) to allocate subjects, to assign treatment to subjects and to manage the distribution of clinical supplies. Each person accessing the IWRS system must be assigned an individual unique PIN. They must use only their assigned PIN to access the system, and they must not share their assigned PIN with anyone.

10.0 ADMINISTRATIVE AND REGULATORY DETAILS

10.1 Confidentiality

10.1.1 Confidentiality of Data

By signing this protocol, the investigator affirms to the Sponsor that information furnished to the investigator by the Sponsor will be maintained in confidence, and such information will be divulged to the institutional review board, ethics review committee (IRB/ERC) 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.

10.1.2 Confidentiality of Subject Records

By signing this protocol, the investigator agrees that the Sponsor (or Sponsor representative), IRB/ERC, 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 subject agrees to this process. If trial documents will be photocopied during the process of verifying worksheet/case report form information, the subject 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 subject data used and disclosed in connection with this trial in accordance with all applicable privacy laws, rules and regulations.

10.1.3 Confidentiality of Investigator Information

By signing this protocol, the investigator recognizes that certain personal identifying information with respect to the investigator, and all subinvestigators and trial site personnel, may be used and disclosed for trial management purposes, as part of a regulatory submissions, and as required by law. This information may include:

1. name, address, telephone number and e-mail address;
2. hospital or clinic address and telephone number;
3. curriculum vitae or other summary of qualifications and credentials; and
4. other professional documentation.

Consistent with the purposes described above, this information may be transmitted to the Sponsor, and subsidiaries, affiliates and agents of the Sponsor, in your country and other countries, including countries that do not have laws protecting such information. Additionally, the investigator's name and business contact information may be included when reporting certain serious adverse events to regulatory authorities or to other investigators. By signing this protocol, the investigator expressly consents to these uses and disclosures.

If this is a multicenter trial, in order to facilitate contact between investigators, the Sponsor may share an investigator's name and contact information with other participating investigators upon request.

10.1.4 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.

10.2 Compliance With Financial Disclosure Requirements

Financial Disclosure requirements are outlined in the US Food and Drug Administration Regulations, Financial Disclosure by Clinical Investigators (21 CFR Part 54). It is the

Sponsor's responsibility to determine, based on these regulations, whether a request for Financial Disclosure information is required. It is the investigator's/subinvestigator's responsibility to comply with any such request.

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

10.3 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 (e.g., International Conference on Harmonization 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 Merck, is provided in Section 12.1 - Merck Code of Conduct for Clinical Trials.

The investigator also agrees to allow monitoring, audits, IRB/ERC review and regulatory authority inspection of trial-related documents and procedures and provide for direct access to all trial-related source data and documents.

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

The investigator shall prepare and maintain complete and accurate trial documentation in compliance with Good Clinical Practice standards and applicable federal, state and local laws, rules and regulations; and, for each subject participating in the trial, provide all data, and, upon completion or termination of the clinical trial, submit any other reports to the Sponsor as required by this protocol or as otherwise required pursuant to any agreement with the Sponsor.

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 as a result of an audit to cure deficiencies in the trial documentation and worksheets/case report forms.

The investigator must maintain copies of all documentation and records relating to the conduct of the trial in compliance with all applicable legal and regulatory requirements. This

documentation includes, but is not limited to, the protocol, worksheets/case report forms, advertising for subject participation, adverse event reports, subject source data, correspondence with regulatory authorities and IRBs/ERCs, consent forms, investigator's curricula vitae, monitor visit logs, laboratory reference ranges, laboratory certification or quality control procedures and laboratory director curriculum vitae. By signing this protocol, the investigator agrees that documentation shall be retained until at least 2 years after the last approval of a marketing application in an ICH region or until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. Because the clinical development and marketing application process is variable, it is anticipated that the retention period can be up to 15 years or longer after protocol database lock. The Sponsor will determine the minimum retention period and notify the investigator when documents may be destroyed. The Sponsor will determine the minimum retention period and upon request, will provide guidance to the investigator when documents no longer need to be retained. The sponsor also recognizes that documents may need to be retained for a longer period if required by local regulatory requirements. All trial documents shall be made available if required by relevant regulatory authorities. The investigator must consult with and obtain written approval by the Sponsor prior to destroying trial and/or subject files.

ICH Good Clinical Practice guidelines recommend that the investigator inform the subject's primary physician about the subject's participation in the trial if the subject has a primary physician and if the subject agrees to the primary physician being informed.

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

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.

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

According to European legislation, a Sponsor must designate an overall coordinating investigator for a multi-center trial (including multinational). When more than one trial site is open in an EU country, Merck, as the Sponsor, will designate, per country, a national principal coordinator (Protocol CI), responsible for coordinating the work of the principal investigators at the different trial sites in that Member State, according to national regulations. For a single-center trial, the Protocol CI is the principal investigator. In addition, the Sponsor must designate a principal or coordinating investigator to review the trial report that summarizes the trial results and confirm that, to the best of his/her knowledge, the report accurately describes the conduct and results of the trial [Clinical Study Report (CSR) CI]. The Sponsor may consider one or more factors in the selection of the individual to serve as the Protocol CI and or CSR CI (e.g., availability of the Protocol/CSR CI during the anticipated review process, thorough understanding of clinical trial methods, appropriate enrollment of subject cohort, timely achievement of trial milestones). The Protocol CI must be a participating trial investigator.

10.4 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. Merck, as Sponsor of this trial, will review this protocol and submit the information necessary to fulfill these requirements. Merck entries are not limited to FDAAA or the EMA clinical trial directive mandated trials. Information posted will allow subjects 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.

10.5 Quality Management System

By signing this protocol, the Sponsor agrees to be responsible for implementing and maintaining a quality management system with written development procedures and functional area standard operating procedures (SOPs) to ensure that trials are conducted and data are generated, documented, and reported in compliance with the protocol, 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.

10.6 Data Management

The investigator or qualified designee is responsible for recording and verifying the accuracy of subject data. By signing this protocol, the investigator acknowledges that his/her electronic signature is the legally binding equivalent of a written signature. By entering his/her electronic signature, the investigator confirms that all recorded data have been verified as accurate.

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

10.7 Publications

This trial is intended for publication, even if terminated prematurely. Publication may include any or all of the following: posting of a synopsis online, abstract and/or presentation at a scientific conference, or publication of a full manuscript. The Sponsor will work with the authors to submit a manuscript describing trial results within 12 months after the last data become available, which may take up to several months after the last subject visit in some cases such as vaccine trials. However, manuscript submission timelines may be extended on OTC trials. For trials intended for pediatric-related regulatory filings, the investigator agrees to delay publication of the trial results until the Sponsor notifies the investigator that all relevant regulatory authority decisions on the trial drug have been made with regard to pediatric-related regulatory filings. Merck will post a synopsis of trial results for approved

products on www.clinicaltrials.gov by 12 months after the last subject's last visit for the primary outcome, 12 months after the decision to discontinue development, or product marketing (dispensed, administered, delivered or promoted), whichever is later.

These timelines may be extended for products that are not yet marketed, if additional time is needed for analysis, to protect intellectual property, or to comply with confidentiality agreements with other parties. Authors of the primary results manuscript will be provided the complete results from the Clinical Study Report, subject to the confidentiality agreement. When a manuscript is submitted to a biomedical journal, the Sponsor's policy is to also include the protocol and statistical analysis plan to facilitate the peer and editorial review of the manuscript. If the manuscript is subsequently accepted for publication, the Sponsor will allow the journal, if it so desires, to post on its website the key sections of the protocol that are relevant to evaluating the trial, specifically those sections describing the trial objectives and hypotheses, the subject inclusion and exclusion criteria, the trial design and procedures, the efficacy and safety measures, the statistical analysis plan, and any amendments relating to those sections. The Sponsor reserves the right to redact proprietary information.

For multicenter trials, subsequent to the multicenter publication (or after public disclosure of the results online at www.clinicaltrials.gov if a multicenter manuscript is not planned), an investigator and his/her colleagues may publish their data independently. In most cases, publication of individual trial site data does not add value to complete multicenter results, due to statistical concerns. In rare cases, publication of single trial site data prior to the main paper may be of value. Limitations of single trial site observations in a multicenter trial should always be described in such a manuscript.

Authorship credit should be based on 1) substantial contributions to conception and design, or acquisition of data, or analysis and interpretation of data; 2) drafting the article or revising it critically for important intellectual content; and 3) final approval of the version to be published. Authors must meet conditions 1, 2 and 3. Significant contributions to trial execution may also be taken into account to determine authorship, provided that contributions have also been made to all three of the preceding authorship criteria. Although publication planning may begin before conducting the trial, final decisions on authorship and the order of authors' names will be made based on participation and actual contributions to the trial and writing, as discussed above. The first author is responsible for defending the integrity of the data, method(s) of data analysis and the scientific content of the manuscript.

The Sponsor must have the opportunity to review all proposed abstracts, manuscripts or presentations regarding this trial 45 days prior to submission for publication/presentation. Any information identified by the Sponsor as confidential must be deleted prior to submission; this confidentiality does not include efficacy and safety results. Sponsor review can be expedited to meet publication timelines.

11.0 LIST OF REFERENCES

[1] Cheson BD, Pfistner B, Juweid ME, Gascoyne RD, Specht L, Horning SJ, et al. Revised response criteria for malignant lymphoma. J Clin Oncol 2007;25(6):579-86.

[2] Olsen EA, Whittaker S, Kim YH, Duvic M, Prince HM, Lessin SR, et al. Clinical end points and response criteria in mycosis fungoides and Sezary syndrome: a consensus statement of the International Society for Cutaneous Lymphomas, the United States Cutaneous Lymphoma Consortium, and the Cutaneous Lymphoma Task Force of the European Organisation for Research and Treatment of Cancer. J Clin Oncol. 2011 Jun 20;29(18):2598-607.

[3] Goldmacher GV, Khilnani AD, Andtbacka RHI, Luke JJ, Hodi FS, Marabelle A, et al. Response criteria for intratumoral immunotherapy in solid tumors: itRECIST. J Clin Oncol. In press 2020.

[4] Corrales L, Glickman LH, McWhirter SM, Kanne DB, et al. Direct Activation of STING in the Tumor Microenvironment Leads to Potent and Systemic Tumor Regression and Immunity. Cell Rep. 2015 May 19;11(7):1018-30.

[5] Fu J, Kanne DB, Leong M, Glickman LH, McWhirter SM, et al. STING agonist formulated cancer vaccines can cure established tumors resistant to PD-1 blockade. Sci Transl Med. 2015 Apr 15;7(283):283ra52.

[6] Baird JR, Friedman D, Cottam B, Dubensky TW Jr, Kanne DB, et al. Radiotherapy Combined with Novel STING-Targeting Oligonucleotides Results in Regression of Established Tumors. Cancer Res. 2016 Jan 1;76(1):50-61.

[7] Glickman LH, Kanne DB, Kasibhatla S, Li J, Pferdekamper AC, Gauthier KS, et al. Activation in the tumor microenvironment with a synthetic human STING-activating cyclic dinucleotide leads to potent anti-tumor immunity. Poster session presented at: 2016 AACR Annual Meeting; 2016 Apr 16-20; New Orleans, LA.

[8] Woo SR, Corrales L, Gajewski TF. The STING pathway and the T cell-inflamed tumor microenvironment. Trends Immunol. 2015 Apr;36(4):250-6.

[9] Disis ML. Immune regulation of cancer. J Clin Oncol 2010;28(29):4531-8.

[10] Dudley ME, Wunderlich JR, Yang JC, Sherry RM, Topalian SL, Restifo NP, et al. Adoptive cell transfer therapy following non-myeloablative but lymphodepleting chemotherapy for the treatment of patients with refractory metastatic melanoma. J Clin Oncol 2005;23(10):2346-57.

[11] Hunder NN, Wallen H, Cao J, Hendricks DW, Reilly JZ, Rodmyre R, et al. Treatment of metastatic melanoma with autologous CD4+ T cells against NY-ESO-1. N Engl J Med 2008;358(25):2698-703.

[12] Greenwald RJ, Freeman GJ, Sharpe AH. The B7 family revisited. Annu Rev Immunol 2005;23:515-48.

[13] Okazaki T, Maeda A, Nishimura H, Kurosaki T, Honjo T. PD-1 immunoreceptor inhibits B cell receptor-mediated signaling by recruiting src homology 2-domain-containing tyrosine phosphatase 2 to phosphotyrosine. Proc Natl Acad Sci U S A 2001;98(24):13866-71.

[14] Zhang X, Schwartz J-CD, Guo X, Bhatia S, Cao E, Chen L, et al. Structural and functional analysis of the costimulatory receptor programmed death-1. Immunity 2004;20:337-47.

[15] Chemnitz JM, Parry RV, Nichols KE, June CH, Riley JL. SHP-1 and SHP-2 associate with immunoreceptor tyrosine-based switch motif of programmed death 1 upon primary human T cell stimulation, but only receptor ligation prevents T cell activation. J Immunol 2004;173:945-54.

[16] Sheppard K-A, Fitz LJ, Lee JM, Benander C, George JA, Wooters J, et al. PD-1 inhibits T-cell receptor induced phosphorylation of the ZAP70/CD3zeta signalosome and downstream signaling to PKCtheta. FEBS Lett. 2004;574:37-41.

[17] Riley JL. PD-1 signaling in primary T cells. Immunol Rev 2009;229:114-25.

[18] Parry RV, Chemnitz JM, Frauwirth KA, Lanfranco AR, Braunstein I, Kobayashi SV, et al. CTLA-4 and PD-1 receptors inhibit T-cell activation by distinct mechanisms. Mol Cell Biol 2005;25(21):9543-53.

[19] Francisco LM, Sage PT, Sharpe AH. The PD-1 pathway in tolerance and autoimmunity. Immunol Rev 2010;236:219-42.

[20] Le DT, Uram JN, Wang H, Bartlett BR, Kemberling H, Eyring AD, et al. PD-1 Blockade in tumors with mismatch repair deficiency. N Engl J Med. Forthcoming 2015.

[21] Woo SR, Fuertes MB, Corrales L, Spranger S, Furdyna MJ, Leung MY, et al. STING-dependent cytosolic DNA sensing mediates innate immune recognition of immunogenic tumors. Immunity. 2014 Nov 20;41(5):830-42.

[22] Ayers M, Lunceford J, Nebozhyn M, Murphy E, Loboda A, Kaufman DR, et al. IFN-gamma-related mRNA profile predicts clinical response to PD-1 blockade. J Clin Invest. 2017 Aug;127(8):2930-40.

[23] Yamazaki S, Skaptason J, Romero D, Lee JH, Zou HY, Christensen JG, et al. Pharmacokinetic-pharmacodynamic modeling of biomarker response and tumor growth inhibition to an orally available cMet kinase inhibitor in human tumor xenograft mouse models. Drug Metab Dispos. 2008 Jul;36(7):1267-74.

[24] Nishino M, Giobbie-Hurder A, Gargano M, Suda M, Ramaiya NH, Hodi FS. Developing a common language for tumor response to immunotherapy: immune-related response criteria using unidimensional measurements. Clin Cancer Res. 2013 Jul 15;19(14):3936-43.

[25] Cheson BD, Pfistner B, Juweid ME, Gascoyne RD, Specht L, Horning SJ. Revised response criteria for malignant lymphoma. J Clin Oncol 2007;25(5):579-86.

[26] Olsen E, Vonderheid E, Pimpinelli N, Willemze R, Kim Y, Knobler R, et al. Revisions to the staging and classification of mycosis fungoides and Sezary syndrome: a proposal of the International Society for Cutaneous Lymphomas (ISCL) and the cutaneous lymphoma task force of the European Organization of Research and Treatment of Cancer (EORTC). Blood 2007;110(6):1713-22.

[27] Hammond ME, Hayes DF, Dowsett M, Allred DC, Hagerty KL, Badve S, et al. American Society of Clinical Oncology/College Of American Pathologists guideline recommendations for immunohistochemical testing of estrogen and progesterone receptors in breast cancer. J Clin Oncol. 2010 Jun 1;28(16):2784-95.

[28] Nanda R, Chow LQ, Dees EC, Berger R, Gupta S, Geva R, et al. Pembrolizumab in patients With Advanced Triple-Negative Breast Cancer: Phase Ib KEYNOTE-012 study. J Clin Oncol. 2016 Jul 20;34(21):2460-7.

[29] Adams S, Loi S, Toppmeyer D, Cescon DW, De Laurentiis M, Nanda R, et al. Pembrolizumab monotherapy for previously untreated, PD-L1-positive, metastatic triple-negative breast cancer: cohort B of the phase II KEYNOTE-086 study. Ann Oncol. 2019;30(3):405-11.

[30] Adams S, Schmid P, Rugo HS, Winer EP, Loirat D, Awada A, et al. Pembrolizumab monotherapy for previously treated metastatic triple-negative breast cancer: cohort A of the phase II KEYNOTE-086 study. Ann Oncol. 2019;30(3):397-404.

[31] Ji Y, Li Y, Bekele BN. Dose-finding in phase l clinical trials based on toxicity probability intervals. Clin Trials 2007;4:235-44.

[32] Nie L, Rubin EH, Mehrotra N, Pinheiro J, Fernandes LL, Roy A, et al. Rendering the 3 + 3 design to rest: more efficient approaches to oncology dose-finding trials in the era of targeted therapy. Clin Cancer Res. 2016 Jun 1;22(11):2623-9.

[33] Yang S, Wang SJ, Ji Y. An integrated dose-finding tool for phase I trials in oncology. Contemp Clin Trials. 2015 Nov;45(Pt B):426-34.

[34] Ji Y, Wang S-J. Modified toxicity probability interval design: a safer and more reliable method than the 3 + 3 design for practical phase I trials. J Clin Oncol 2013;31:1-12.

[35] Cheson BD, Bennett JM, Grever M, Kay N, Keating MJ, O'Brien S, et al. National Cancer Institute-Sponsored working group guidelines for chronic lymphocytic leukemia: Revised guidelines for diagnosis and treatment. Blood 1996;87(12):4990-7.

12.0 APPENDICES

12.1 Merck Code of Conduct for Clinical Trials

Merck*
Code of Conduct for Clinical Trials

I. Introduction

A. Purpose

Merck, 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 subject safety is the overriding concern in the design of clinical trials. In all cases, Merck clinical trials will be conducted in compliance with local and/or national regulations and in accordance with the ethical principles that have their origin in the Declaration of Helsinki.

B. Scope

Such standards shall be endorsed for all clinical interventional investigations sponsored by Merck 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 which are observational in nature, or which are retrospective. Further, this Code does not apply to investigator-initiated trials which are not under the control of Merck.

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 Merck or comparator products. Alternatively, Merck may conduct outcomes research trials, trials to assess or validate various endpoint measures, or trials to determine subject preferences, etc.

The design (i.e., subject population, duration, statistical power) must be adequate to address the specific purpose of the trial. Research subjects must meet protocol entry criteria to be enrolled in the trial.

2. Site Selection

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

3. Site Monitoring/Scientific Integrity

Trial sites are monitored to assess compliance with the trial protocol and general principles of Good Clinical Practice. Merck reviews clinical data for accuracy, completeness and consistency. Data are verified versus source documentation according to standard operating procedures. Per Merck policies and procedures, if fraud, misconduct or serious GCP-non-Compliance are suspected, the issues are promptly investigated. When necessary, the clinical site will be closed, the responsible regulatory authorities and ethics review committees notified and data disclosed accordingly.

B. Publication and Authorship

To the extent scientifically appropriate, Merck seeks to publish the results of trials it conducts. 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 of multiplicity.

Merck's policy on authorship is consistent with the requirements outlined in the ICH-Good Clinical Practice guidelines. 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. Merck funding of a trial will be acknowledged in publications.

III. Subject Protection

A. IRB/ERC review

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

B. Safety

The guiding principle in decision-making in clinical trials is that subject welfare is of primary importance. Potential subjects 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. Subjects are never denied access to appropriate medical care based on participation in a Merck clinical trial.

All participation in Merck clinical trials is voluntary. Subjects are enrolled only after providing informed consent for participation. Subjects may withdraw from a Merck 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

Merck is committed to safeguarding subject confidentiality, to the greatest extent possible. Unless required by law, only the investigator, sponsor (or representative) and/or regulatory authorities will have access to confidential medical records that might identify the research subject by name.

D. Genomic Research

Genomic Research will only be conducted in accordance with informed consent and/or as specifically authorized by an Ethics Committee.

IV. Financial Considerations

A. Payments to Investigators

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

Merck does not pay for subject referrals. However, Merck may compensate referring physicians for time spent on chart review to identify potentially eligible subjects.

B. Clinical Research Funding

Informed consent forms will disclose that the trial is sponsored by Merck, and that the investigator or sponsoring institution is being paid or provided a grant for performing the trial. However, the local IRB/ERC may wish to alter the wording of the disclosure statement to be consistent with financial practices at that institution. As noted above, publications resulting from Merck trials will indicate Merck 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 including, in the U.S., those established by the American Medical Association (AMA).

V. Investigator Commitment

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

* In this document, "Merck" refers to Merck Sharp & Dohme Corp. and Schering Corporation, each of which is a subsidiary of Merck & Co., Inc. Merck is known as MSD outside of the United States and Canada. As warranted by context, Merck also includes affiliates and subsidiaries of Merck & Co., Inc."

12.2 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 7.1.3.4 – Future Biomedical Research Samples 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. Subjects for Enrollment

All subjects 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 subjects 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 subjects on the visit designated in the trial flow chart. If delayed, present consent at next possible Subject Visit. Consent forms signed by the subject 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 subject consent for Future Biomedical Research will be captured in the electronic Case Report Forms (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 subject is having blood drawn for other trial purposes.

4. Confidential Subject 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 subject' 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 subject 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 subject 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 (e.g., a university investigator) designated by the Sponsor. The investigator conducting the analysis will follow the Sponsor's privacy and confidentiality requirements. Any contracted third party analyses will conform to the specific scope of analysis outlined in future biomedical research protocol and consent. Future Biomedical Research specimens remaining with the third party after specific analysis is performed will be reported to the Sponsor.

6. Withdrawal From Future Biomedical Research

Subjects may withdraw their consent for Future Biomedical Research and ask that their biospecimens not be used for Future Biomedical Research. Subjects 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@merck.com).

Subsequently, the subject'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 subject 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 (e.g., 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 subject'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 Subjects

No information obtained from exploratory laboratory studies will be reported to the subject, family, or physicians. Principle reasons not to inform or return results to the subject include: Lack of relevance to subject 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 subjects. Subjects 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 subjects 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 subject have been minimized. No additional risks to the subject have been identified as no additional specimens are being collected for Future Biomedical Research (i.e., only leftover samples are being retained).

The Sponsor has developed strict security, policies and procedures to address subject 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@merck.com.

13. References

1. National Cancer Institute: http://www.cancer.gov/dictionary/?searchTxt=biomarker
2. International Conference on Harmonization: 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/

12.3 Prioritization of Intratumoral Lesion Injection

The selection and prioritization of lesions for intratumoral 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 intratumoral 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 (eg, 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

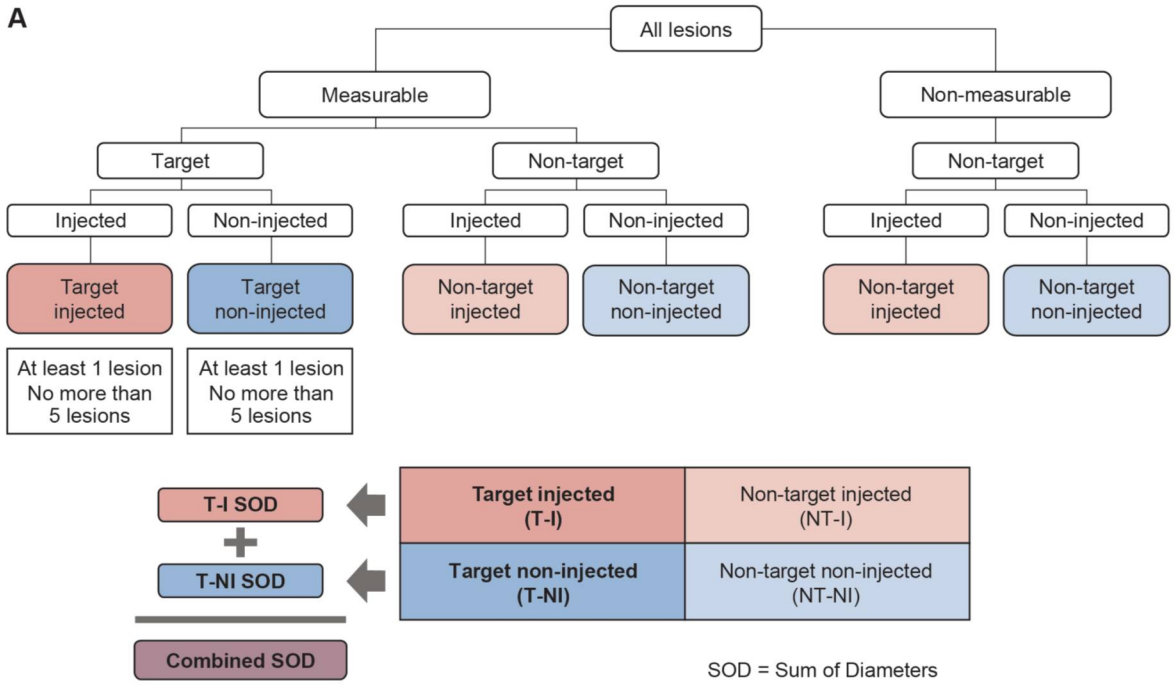
At the initiation of therapy, the next factors that should guide lesion prioritization are the size of the lesion, and the amount of viable tumor tissue present in the lesion. Other factors being equal, larger lesions are preferred. Larger lesions may have a greater amount of tumor tissue, and are generally 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 intratumoral 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 intratumoral 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 intratumoral immunotherapeutic, and a subsequent improved systemic antitumor response. New lesions may contain novel tumor antigens compared to previously injected lesions.

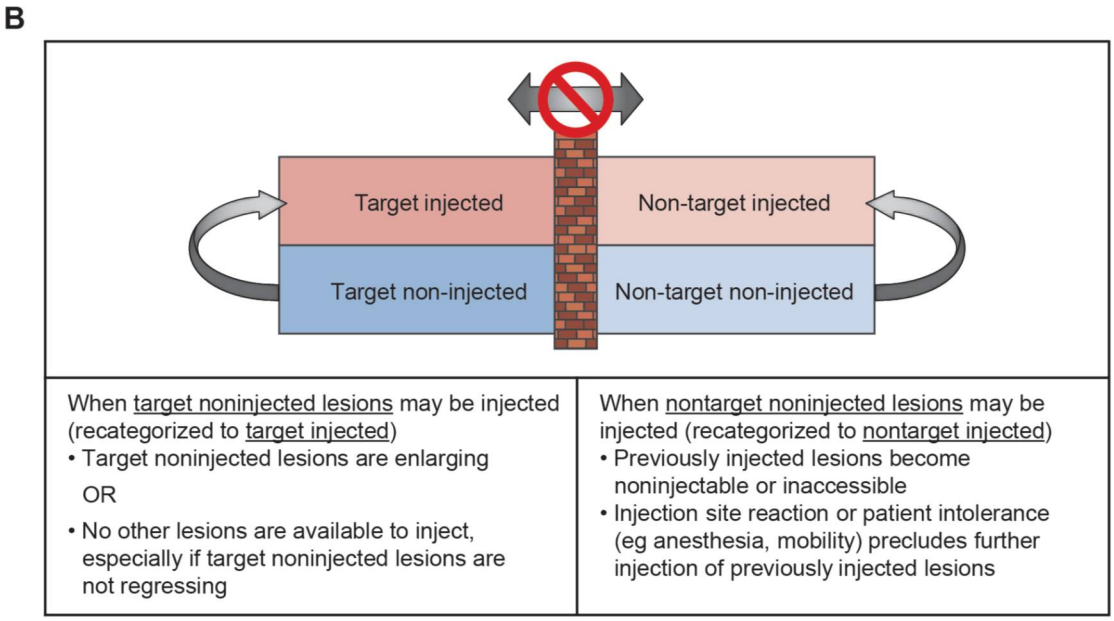
12.4 itRECIST Supplementary Figures

Figure 5 Algorithm for Classification of Lesions at Baseline



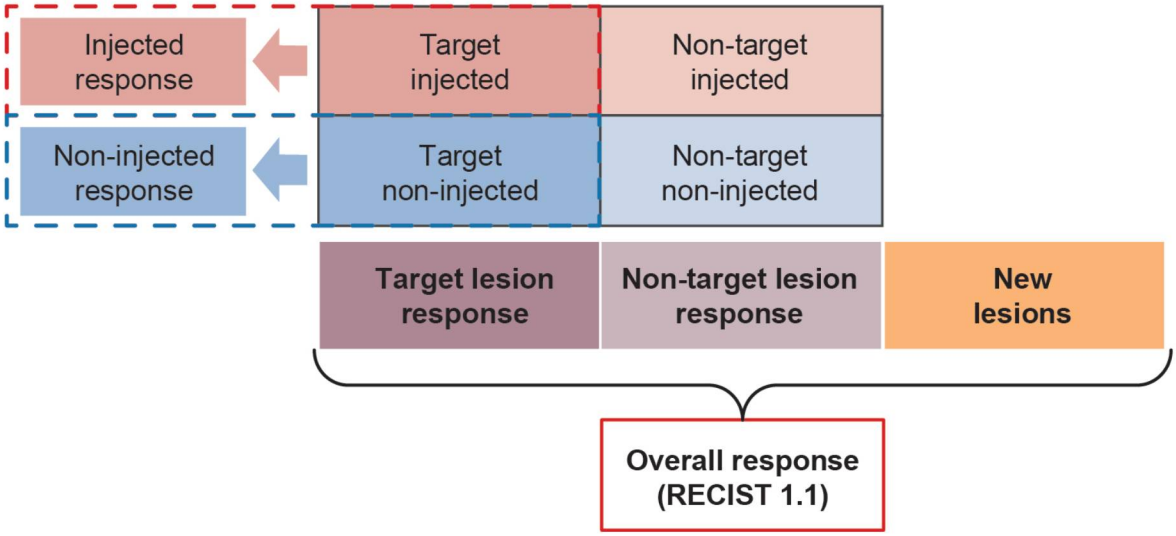
Lesions are classified first as measurable or nonmeasurable using the standard RECIST 1.1 rules for measurability. Measurable lesions (those eligible for selection as target lesions) are then classified as target (selected to be followed quantitatively) or nontarget (selected to be followed qualitatively), 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 5 lesions should be classified as target injected, and between 1 and 5 should be classified as target noninjected, for a maximum of 10 target lesions. All lesions not chosen as target are followed qualitatively as nontarget, and some of these may be selected for injection at baseline. T-I lesions and T-NI lesions each have their own distinct SOD. A combined SOD also includes all target lesions, injected and noninjected. NT-I and NT-NI lesions are followed qualitatively, exactly as in RECIST 1.1, classified in aggregate as showing complete response, unequivocal progression, or neither (called non-CR/non-PD in RECIST 1.1).

Figure 6 Reclassification of Noninjected Lesions



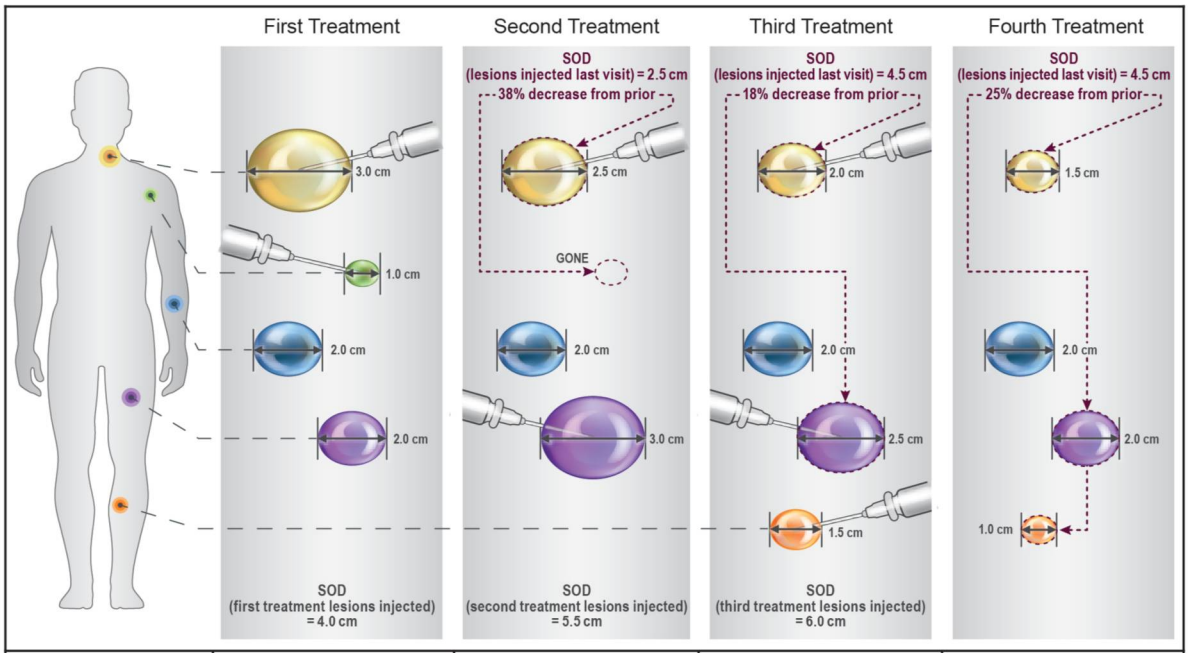
Target or nontarget noninjected lesions can be recategorized as injected lesions if the decision is made to inject them after baseline assessment. Nontarget noninjected lesions may be injected if previously injected nontarget lesions regress completely or become inaccessible or if a patient factor such 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.

Figure 7 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 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.

Figure 8 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; iRECIST 1.1 = immunotherapeutic Response Evaluation Criteria in Solid Tumors; NE = not evaluable; NT-I = nontarget injected; NT-NI = nontarget noninjected; PD = progressive disease; PR = partial response; 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 purple lesion. If this lesion were to grow later, it could contribute to an overall response of PD.

Source: [3]

12.5 Country-specific Requirements

For countries or sites that follow the CTFG guidance requiring monthly pregnancy testing, please use the following:

Section 6.1.2 Schedule of Activities for the Treatment Period, Intratumoral Administration for Arm 1 (Monotherapy) and Arm 2 (Combination Therapy – Including Crossover to Arm 2)

Trial Period	**Treatment Phase MK-1454 Monotherapy Cycle = 21 Days MK-1454 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**	
Administrative Procedures											
Pregnancy Test for WOCBP – Urine or Serum hCG	X			X			X			X	Required within 24 h prior to first dose of study medication. Does not need to be repeated if screening test was done within 24 hours of C1D1. If a urine pregnancy test cannot be confirmed as negative, a serum pregnancy test is required. Thereafter, pregnancy testing should be performed Day 1 of each subsequent cycle.

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

Trial Period	**Treatment Phase MK-1454 Monotherapy Cycle = 21 Days MK-1454 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**	
Administrative Procedures											
Pregnancy Test for WOCBP – Urine or Serum hCG	X			X			X			X	Required within 24 h prior to first dose of study medication. Does not need to be repeated if screening test was done within 24 hours of C1D1. If a urine pregnancy test cannot be confirmed as negative, a serum pregnancy test is required. Thereafter, pregnancy testing should be performed Day 1 of each subsequent cycle.

6.2.1 Schedule of Activities for Part II - Expansion Cohorts Screening and Treatment Period, MK-1454 Intratumoral Administration With Pembrolizumab Combination Therapy

Trial Period	Screening	Treatment Phase MK-1454 Cycle = CCI then Q3W; or Q3W Pembrolizumab Cycle = 21 Days										
Cycle		Cycle 1			Cycle 2			Cycle 3			Cycle 4 and Beyond	Notes
Scheduling Day	**-28 to -1**	**1**	**8**	**15**	**1**	**8**	**15**	**1**	**8**	**15**	**1**	
Scheduled Window		**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	
	Administrative Procedures											
Pregnancy Test for WOCBP – Urine or Serum hCG	X	X			X			X			X	Required within 24 h prior to first dose of study medication. Does not need to be repeated if screening test was done within 24 hours of C1D1. If a urine pregnancy test cannot be confirmed as negative, a serum pregnancy test is required. Thereafter, pregnancy testing should be performed Day 1 of each subsequent cycle.

12.6 List of Abbreviations and Definitions

Abbreviation	Definition
Abscopal	A phenomenon in the treatment of metastatic cancer where localized treatment of a tumor causes not only a shrinking of the treated tumor, but also a shrinking of tumors outside the scope of the localized treatment
ADA	Anti-drug antibody
ADL	Activities of daily living
ADME	Absorption, distribution, metabolism, and excretion
AE	Adverse event
AJCC	American Joint Committee on Cancer
ALT	Alanine aminotransferase
AMP	Adenosine monophosphate
aPTT	Activated partial thromboplastin time
ART	Antiretroviral therapy
ASaT	All-Subjects-as-Treated
ASCO-CAP	American Society of Clinical Oncology/College Of American Pathologists
AST	Aspartate aminotransferase
ATD	Accelerated titration design
C1D1	Cycle 1 Day 1
CBC	Complete blood count
CD	Cluster of differentiation (eg, CD8, CD28)
CDN	Cyclic dinucleotide
cGAMP	Cyclic GMP-AMP
cGAS	Cyclic (guanosine monophosphate-adenosine monophosphate) synthase
CI	Confidence interval
CR	Complete response
CRC	Colorectal cancer
CrCl	Creatinine clearance
CRF	Case report form
CRP	C-reactive protein
CRS	Cytokine release syndrome
CRU	Clinical research unit
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTFG	Clinical Trials Facilitation and Coordination Group
CTLA-4	Cytotoxic T-lymphocyte-associated protein 4

Abbreviation	Definition
CXCL11	Chemokine C-X-C motif ligand 11
DLT	Dose-limiting toxicity
DLTe	DLT-evaluable
dMMR	Deficient mismatch repair
dsDNA	Double-stranded deoxyribonucleic acid
DNA	Deoxynucleic acid
ECI	Event of clinical interest
E/CIA	Enzyme or chemiluminescence immunoassay
ECG	Electrocardiogram
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
FBR	Future biomedical research
FDAAA	Food and Drug Administration Amendments Act
FDG-PET	Fluorodeoxyglucose-positron emission tomography
FIH	First in human
FSH	Follicle-stimulating hormone
GCP	Good Clinical Practice
GFR	Glomerular filtration rate
GGT	Gamma glutamyl transferase
GMP	Guanosine monophosphate
GRI	Growth rate inhibition
GVHD	Graft-versus-host disease
HBsAg/HBV	Hepatitis B surface antigen/Hepatitis B virus
hCG	Human chorionic gonadotropin
HCV	Hepatitis C virus
Hep C Ab	Hepatitis C Antibody
HIV	Human immunodeficiency virus
HNSCC	Head and neck squamous cell carcinoma
HRT	Hormone replacement therapy
IB	Investigator's Brochure
ICF	Informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use

Abbreviation	Definition
IEC	Institutional Ethics Committee
IFN	Interferon
IFNβ	Interferon beta
Ig	Immunoglobulin
IHC	Immunohistochemistry
IL-6	Interleukin-6
INR	International normalized ratio
IO	Immuno-oncology
IP-10	Interferon gamma-induced protein 10
IRB	Institutional Review Board
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
IUD	Intrauterine device
IUS	Intrauterine system
IWG	International Working Group
IWRS	Integrated web response system
LAM	Lymphangioleiomyomatosis
LDH	Lactate dehydrogenase
LLOQ	Lower limit of quantification
mAb	Monoclonal antibody
MAD	Maximum administered dose
MCP-2	Monocyte chemoattractant protein-2
MIP-1α	Macrophage inflammatory protein-1 alpha
MOA	Mechanism of action
MRI	Magnetic resonance imaging
mRNA	Messenger ribonucleic acid
MSI	Microsatellite instability
MSI-H	Microsatellite instability-high
mSWAT	Modified Severity Weighted Assessment Tool
MTD	Maximum tolerated dose
mTPI	Modified toxicity probability interval
NASBA	Nucleic acid sequence-based amplification
NCI	National Cancer Institute

Abbreviation	Definition
NOAEL	No observed adverse effect level
NT-I	Nontarget injected
NT-NI	Nontarget noninjected
NSCLC	Nonsmall-cell lung cancer
OS	Overall survival
OTC	Over-the-counter
PCR	Polymerase chain reaction
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
PIN	Patient identification number
PK	Pharmacokinetic
PP	Per-Protocol
PT	Prothrombin time
PTT	Partial thromboplastin time
QD	Once daily
QW	Once a week
CCI [redacted]	
Q3W	Every 3 weeks
RECIST	Response Evaluation Criteria In Solid Tumors
RNA	Ribonucleic acid
RP2D	Recommended Phase 2 Dose
SAE	Serious adverse events
SCCHN	Squamous cell carcinoma of the head and neck
SD	Stable disease
SHP-1	Src homology region 2 domain-containing phosphatase-1
SHP-2	Src homology region 2 domain-containing phosphatase-2
SNP	Single nucleotide polymorphism
SoA	Schedule of Activities
SOD	Sum of diameters
sSAP	Supplemental Statistical Analysis Plan
STING	Stimulator of Interferon Genes

Abbreviation	Definition
TBK1	TANK-binding kinase 1
T-I	Target injected
T-NI	Target noninjected
TNBC	Triple-negative breast cancer
TNF-α	Tumor necrosis factor-alpha
TNM	Tumor, node, metastases
TSH	Thyroid-stimulating hormone
ULN	Upper limit of normal
VL	Viral load
VS	Vital sign(s)
WOCBP	Woman of childbearing potential
WT	Wild-type
ZAP70	Zeta-chain-associated protein kinase 70

13.0 SIGNATURES

13.1 Sponsor's Representative

TYPED NAME	
TITLE	
SIGNATURE	
DATE SIGNED	

13.2 Investigator

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 (including other manuals and documents referenced from this protocol). I agree to conduct the trial in accordance with generally accepted standards of Good Clinical Practice. I also agree to report all information or data in accordance with the protocol and, in particular, I agree to report any serious adverse events as defined in Section 7.0 – TRIAL PROCEDURES (Assessing and Recording Adverse Events). I also agree to handle all clinical supplies provided by the Sponsor and collect and handle all clinical specimens in accordance with the protocol. I understand that information that identifies me will be used and disclosed as described in the protocol, and that such information may be transferred to countries that do not have laws protecting such information. Since the information in this protocol and the referenced Investigator's Brochure is confidential, I understand that its disclosure to any third parties, other than those involved in approval, supervision, or conduct of the trial is prohibited. I will ensure that the necessary precautions are taken to protect such information from loss, inadvertent disclosure or access by third parties.

TYPED NAME	
TITLE	
SIGNATURE	
DATE SIGNED	