Official Protocol Title:	A Phase 2 Study in First Line Metastatic or Unresectable, Recurrent Head and Neck Squamous Cell Carcinoma to Evaluate Intratumoral MK-1454 in Combination with IV Pembrolizumab vs IV Pembrolizumab Monotherapy
NCT number:	NCT04220866
Document Date:	20 OCT 2022

Title Page

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Protocol Title: A Phase 2 Study in First Line Metastatic or Unresectable, Recurrent Head and Neck Squamous Cell Carcinoma to Evaluate Intratumoral MK-1454 in Combination with IV Pembrolizumab vs IV Pembrolizumab Monotherapy

Protocol Number: 002-03

Compound Number: MK-1454

Sponsor Name:

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

Legal Registered Address:

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P.O. Box 2000

Rahway, NJ 07065 USA

Regulatory Agency Identifying Number(s):

IND	144743
EudraCT	2019-003060-42
NCT	NCT04220866

Approval Date: 20 October 2022

Sponsor Signatory

Typed Name:
Title:

Date

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

Investigator Signatory

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

Typed Name:
Title:

Date

DOCUMENT HISTORY

Document	Date of Issue	Overall Rationale
MK-1454-002-03	20-OCT-2022	Merck Sharp & Dohme Corp. underwent an entity name and address change to Merck Sharp & Dohme LLC, Rahway, NJ, USA. This conversion resulted only in an entity name change and update to the address.
MK-1454-002-02	22-JUL-2021	To update the dose modification and toxicity management guidelines for irAEs associated with pembrolizumab.
MK-1454-002-01	05-AUG-2020	To address Health Authority requests, including to provide rationale for minimum creatinine clearance in the eligibility criteria, to add clarification for PD-L1 testing to the protocol, to clarify ongoing safety monitoring during the conduct of the clinical trial, and to provide additional clarifications.
Original Protocol	31-OCT-2019	Not applicable.

PROTOCOL AMENDMENT SUMMARY OF CHANGES

Amendment: 03

Overall Rationale for the Amendments:

Sponsor underwent an entity name change and update to the address.

Summary of Changes Table:

Section # and Name	Description of Change	Brief Rationale
Title Page Section 10.1.1 Code of Conduct for Clinical Trials Throughout	Sponsor entity name and address change.	Merck Sharp & Dohme Corp. underwent an entity name and address change to Merck Sharp & Dohme LLC, Rahway, NJ, USA. This conversion resulted only in an entity name change and update to the address.

Table of Contents

DOCUMENT HISTORY **3**
PROTOCOL AMENDMENT SUMMARY OF CHANGES **4**
1 PROTOCOL SUMMARY **13**
1.1 Synopsis **13**
1.2 Schema **17**
1.3 Schedule of Activities **18**
1.3.1 Schedule of Activities for Screening for All Participants 18
1.3.2 Schedule of Activities for the Treatment Period for Arm 1 (Combination Therapy: IT MK-1454 + IV Pembrolizumab) 20
1.3.3 Schedule of Activities for the Treatment Period for Arm 2 IV Pembrolizumab Monotherapy 24
1.3.4 Schedule of Activities for the End of Treatment and Posttreatment Follow-Up Periods 27
2 INTRODUCTION **29**
2.1 Study Rationale **29**
2.2 Background **29**
2.2.1 Pharmaceutical and Therapeutic Background 30
2.2.1.1 MK-1454 Pharmaceutical and Therapeutic Background 30
2.2.1.2 Pembrolizumab (MK-3475) Pharmaceutical and Therapeutic Background 31
2.2.2 Preclinical and Clinical Studies 32
2.2.3 Ongoing Clinical Studies 32
2.2.3.1 MK-1454 Clinical Studies 32
2.2.3.2 Pembrolizumab (MK-3475) Clinical Studies 33
2.3 Benefit/Risk Assessment **35**
3 HYPOTHESES, OBJECTIVES, AND ENDPOINTS **35**
4 STUDY DESIGN **37**
4.1 Overall Design **37**
4.2 Scientific Rationale for Study Design **39**
4.2.1 Rationale for the Study and Selected Participant Population 39
4.2.2 Rationale for Entry Criteria 40
4.2.2.1 Use of Combined Positive Scoring for PD-L1 Status 40
4.2.2.2 Rationale for Minimum Creatinine Clearance 40
4.2.3 Rationale for Endpoints 41
4.2.3.1 Efficacy Endpoints 41

4.2.3.1.1 Response Rate Assessed by RECIST Version 1.1 41
4.2.3.2 Safety Endpoints 41
4.2.3.3 Pharmacokinetic Endpoints 42
4.2.3.4 Pharmacodynamic Endpoints 42
4.2.3.5 Planned Exploratory Biomarker Research 42
4.2.3.6 Future Biomedical Research 44
4.2.4 Rationale for the Use of Comparator 44
4.3 Justification for Dose 44
4.3.1 Rationale for Dose of MK-1454 44
4.4 Beginning and End of Study Definition 45
4.4.1 Clinical Criteria for Early Study Termination 45
5 STUDY POPULATION 45
5.1 Inclusion Criteria 45
5.2 Exclusion Criteria 49
5.3 Lifestyle Considerations 52
5.3.1 Meals and Dietary Restrictions 52
5.4 Screen Failures 52
5.5 Participant Replacement Strategy 52
6 STUDY INTERVENTION 53
6.1 Study Intervention(s) Administered 53
6.2 Preparation/Handling/Storage/Accountability 55
6.2.1 Dose Preparation 55
6.2.2 Timing of Study Interventions 56
6.2.2.1 Timing for Administration for MK-1454 56
6.2.2.2 Timing for Administration of Pembrolizumab 57
6.2.3 Handling, Storage, and Accountability 57
6.3 Measures to Minimize Bias: Randomization and Blinding 57
6.3.1 Intervention Assignment 57
6.3.2 Stratification 58
6.3.3 Blinding 58
6.4 Study Intervention Compliance 58
6.5 Concomitant Therapy 58
6.5.1 Acceptable Concomitant Medications 58
6.5.2 Prohibited Concomitant Medications 59
6.5.3 Supportive Care 59
6.6 Dose Modification (Escalation/Titration/Other) 60
6.6.1 Dose Modification due to Adverse Events 60
6.6.1.1 Dose Modification for MK-1454 61

6.6.1.1.1 Guidelines for Management of Intratumoral Injection Site Reactions....61
6.6.1.1.2 Treatment for Cytokine Release Syndrome....62
6.6.1.2 Immune-Related Events and Dose Modification (Withhold, Treat, Discontinue)....65
6.6.1.2.1 Other Allowed Dose Interruption(s) for Pembrolizumab....71
6.7 Intervention After the End of the Study....71
6.8 Clinical Supplies Disclosure....71
6.9 Standard Policies....71
7 DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT WITHDRAWAL....71
7.1 Discontinuation of Study Intervention....71
7.2 Participant Withdrawal From the Study....73
7.3 Lost to Follow-up....73
8 STUDY ASSESSMENTS AND PROCEDURES....73
8.1 Administrative and General Procedures....74
8.1.1 Informed Consent....74
8.1.1.1 General Informed Consent....74
8.1.1.2 Consent and Collection of Specimens for Future Biomedical Research....75
8.1.2 Inclusion/Exclusion Criteria....75
8.1.3 Participant Identification Card....75
8.1.4 Medical History....75
8.1.5 Prior and Concomitant Medications Review....76
8.1.5.1 Prior Medications....76
8.1.5.2 Concomitant Medications....76
8.1.6 Assignment of Screening Number....76
8.1.7 Assignment of Treatment/Randomization Number....76
8.1.8 Study Intervention Administration....76
8.1.8.1 Timing of Dose Administration....77
8.1.9 Discontinuation and Withdrawal....77
8.1.9.1 Withdrawal From Future Biomedical Research....77
8.1.10 Participant Blinding/Unblinding....77
8.1.11 Calibration of Equipment....78
8.2 Efficacy/Immunogenicity Assessments....78
8.2.1 Tumor Imaging and Assessment of Disease....78
8.2.2 Initial Tumor Imaging....78
8.2.3 Tumor Imaging During the Study....79
8.2.4 End of Treatment and Follow-up Tumor Imaging....79

8.2.5 iRECIST 1.1 Assessment of Disease 80
8.2.6 itRECIST 85
8.2.7 Eastern Cooperative Oncology Group Performance Scale 86
8.3 Safety Assessments 86
8.3.1 Physical Examinations 86
8.3.1.1 Full Physical Examination 86
8.3.1.2 Directed Physical Examination 86
8.3.2 Vital Signs 86
8.3.3 Electrocardiograms 87
8.3.4 Clinical Safety Laboratory Assessments 87
8.3.4.1 Laboratory Safety Evaluations (Hematology, Chemistry, and Urinalysis) 87
8.3.4.2 Pregnancy Test 88
8.4 Adverse Events, Serious Adverse Events, and Other Reportable Safety Events 88
8.4.1 Time Period and Frequency for Collecting AE, SAE, and Other Reportable Safety Event Information 88
8.4.2 Method of Detecting AEs, SAEs, and Other Reportable Safety Events 90
8.4.3 Follow-up of AE, SAE, and Other Reportable Safety Event Information 90
8.4.4 Regulatory Reporting Requirements for SAE 90
8.4.5 Pregnancy and Exposure During Breastfeeding 91
8.4.6 Disease-related Events and/or Disease-related Outcomes Not Qualifying as AEs or SAEs 91
8.4.7 Events of Clinical Interest 91
8.5 Treatment of Overdose 92
8.6 Pharmacokinetics 92
8.6.1 Blood Collection for Serum Pembrolizumab and Plasma MK-1454 92
8.6.2 Blood Collection for Antidrug Antibodies 93
8.7 Pharmacodynamics 93
8.8 Biomarkers 93
8.8.1 Planned Genetic Analysis Sample Collection 93
8.9 Future Biomedical Research Sample Collection 93
8.10 Visit Requirements 94
8.10.1 Screening 94
8.10.2 Treatment Period Visit 95
8.10.3 Discontinued Participants Continuing to be Monitored in the Study 95
8.10.3.1 Safety Follow-up Visit 95
8.10.3.2 Imaging Follow-up Visits 95
8.10.3.3 Survival Follow-up Visits 95

9 STATISTICAL ANALYSIS PLAN 96
9.1 Statistical Analysis Plan Summary 96
9.2 Responsibility for Analyses/In-house Blinding 98
9.3 Hypotheses/Estimation 98
9.4 Analysis Endpoints 99
9.4.1 Efficacy/Immunogenicity/Pharmacokinetics Endpoints 99
9.4.2 Safety Endpoints 99
9.5 Analysis Populations 99
9.5.1 Efficacy Analysis Populations 99
9.5.2 Safety Analysis Populations 100
9.5.3 Pharmacokinetic Analysis Populations 100
9.6 Statistical Methods 100
9.6.1 Statistical Methods for Efficacy Analysis 100
9.6.1.1 Objective Response 100
9.6.1.2 Progression-free Survival 101
9.6.1.3 Overall Survival 102
9.6.1.4 Duration of Response 102
9.6.1.5 Analysis Strategy for Key Efficacy Endpoints 103
9.6.2 Statistical Methods for Safety Analysis 104
9.6.3 Summaries of Baseline Characteristics, Demographics, and Other Analyses 106
9.6.3.1 Demographic and Baseline Characteristics 106
9.6.3.2 Pharmacokinetic and Pharmacodynamic Modeling Analysis 106
9.7 Interim Analyses 106
9.8 Multiplicity 107
9.9 Sample Size and Power Calculations 108
9.10 Subgroup Analyses 110
9.11 Compliance (Medication Adherence) 111
9.12 Extent of Exposure 111
10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS 112
10.1 Appendix 1: Regulatory, Ethical, and Study Oversight Considerations 112
10.1.1 Code of Conduct for Clinical Trials 112
10.1.2 Financial Disclosure 114
10.1.3 Data Protection 114
10.1.3.1 Confidentiality of Data 115
10.1.3.2 Confidentiality of Participant Records 115
10.1.3.3 Confidentiality of IRB/IEC Information 115

10.1.4 Committees Structure....116
10.1.4.1 Stage Gate Review Committee....116
10.1.5 Publication Policy....116
10.1.6 Compliance with Study Registration and Results Posting Requirements....116
10.1.7 Compliance with Law, Audit, and Debarment....116
10.1.8 Data Quality Assurance....117
10.1.9 Source Documents....118
10.1.10 Study and Site Closure....118
10.2 Appendix 2: Clinical Laboratory Tests....119
10.3 Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting....121
10.3.1 Definition of AE....121
10.3.2 Definition of SAE....122
10.3.3 Additional Events Reported in the Same Manner as SAE....123
10.3.4 Recording AE and SAE....123
10.3.5 Reporting of AEs, SAEs, and Other Reportable Safety Events to the Sponsor....127
10.4 Appendix 4: Device Events, Adverse Device Events, and Medical Device Incidents: Definitions, Collection, and Documentation....129
10.5 Appendix 5: Contraceptive Guidance....130
10.5.1 Definitions....130
10.5.2 Contraception Requirements....131
10.5.2.1 Contraception Requirements: Female Participants....131
10.5.2.2 Contraception Requirements: Male Participants....132
10.6 Appendix 6: Collection and Management of Specimens for Future Biomedical Research....133
10.7 Appendix 7: Country-specific Requirements....138
10.8 Appendix 8: Guidelines for Prioritization of Intratumoral Lesion Injection....142
10.9 Appendix 9: Eastern Cooperative Oncology Group Performance Status....144
10.10 Appendix 10: itRECIST Supplementary Figures....145
10.11 Appendix 11: Abbreviations....150
11 REFERENCES....154

LIST OF TABLES

Table 1 Adequate Organ Function 46
Table 2 Study Interventions 54
Table 3 Determination of Intratumoral MK-1454 Injection Volume Per Lesion Based on Lesion Size 56
Table 4 Determination of Intratumoral MK-1454 Total Injectate Volume Based on Number of Lesions Injected Per Treatment Visit 56
Table 5 Intratumoral Injection Site Reaction Management Guidelines 62
Table 6 Cytokine Release Syndrome Treatment Guidelines 63
Table 7 Dose Modification and Toxicity Management Guidelines for Immune-related Adverse Events Associated with Pembrolizumab Monotherapy, Coformulations or IO Combinations 66
Table 8 Pembrolizumab Infusion Reaction Dose Modification and Treatment Guidelines 70
Table 9 Imaging and Treatment after First Radiologic Evidence of Progressive Disease 84
Table 10 Reporting Time Periods and Time Frames for Adverse Events and Other Reportable Safety Events 89
Table 11 Censoring Rules for Primary and Sensitivity Analyses of PFS 102
Table 12 Censoring Rules for Duration of Response 103
Table 13 Analysis Strategy for Key Efficacy Variables 104
Table 14 Analysis Strategy for Safety Parameters 106
Table 15 Probability of Continuing Enrollment in the Study 107
Table 16 Power of ORR After Continuing Enrollment in the Study (200 participants in total) 109
Table 17 Power of ORR without Continuing Enrollment in the Study (130 participants in total) 110
Table 18 Protocol-required Safety Laboratory Assessments 119

LIST OF FIGURES

Figure 1 Study Schema....17
Figure 2 Schematic Diagram Showing Mechanism of the Enhancement of T-cell Driven Antitumor Immunity Through the Action of STING Agonists....31
Figure 3 Imaging and Treatment for Clinically Stable Participants after First Radiologic Evidence of PD Assessed by the Investigator....85
Figure 4 Multiplicity Diagram....108
Figure 5 Algorithm for Classification of Lesions at Baseline....145
Figure 6 Reclassification of Noninjected Lesions....146
Figure 7 Overall Response Assessment Until Disease Progression....147
Figure 8 Example of Iterative Assessment of Injected Lesion Response During Treatment....148

1 PROTOCOL SUMMARY

1.1 Synopsis

Protocol Title: A Phase 2 Study in First Line Metastatic or Unresectable, Recurrent Head and Neck Squamous Cell Carcinoma to Evaluate Intratumoral MK-1454 in Combination with IV Pembrolizumab vs IV Pembrolizumab Monotherapy

Short Title: Phase 2 Study in 1L HNSCC of IT MK-1454 / MK-3475 IV vs MK-3475 IV

Acronym:

Hypotheses, Objectives, and Endpoints:

In males and females who are at least 18 years of age with metastatic or with unresectable, recurrent HNSCC with a tumor PD-L1 IHC CPS ≥1:

Objectives	Endpoints
Primary	
• Objective: To evaluate participants treated with IT MK-1454 in combination with pembrolizumab or pembrolizumab alone with regard to the objective response rate (ORR) per Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST 1.1) by blinded independent central review (BICR). • Hypothesis (H1): IT MK-1454 in combination with pembrolizumab results in a superior ORR, per RECIST 1.1 based on BICR, compared to pembrolizumab alone in participants with tumor combined positive scoring (CPS) ≥1. • Hypothesis (H2): IT MK-1454 in combination with pembrolizumab results in a superior ORR, per RECIST 1.1 based on BICR, compared to pembrolizumab alone in participants with tumor CPS ≥20. The study is considered to have met its primary objective if IT MK-1454, in combination with pembrolizumab, results in a superior ORR, per RECIST 1.1 based on BICR, compared to pembrolizumab alone either in participants with tumor CPS ≥1 or in participants with tumor CPS ≥20.	• Objective response is a confirmed complete response (CR) or partial response (PR)

Objectives	Endpoints
Secondary	
• Objective: To evaluate participants treated with IT MK-1454 in combination with pembrolizumab or pembrolizumab alone with regard to progression-free survival (PFS) per RECIST 1.1 by BICR.	• PFS, defined as the time from randomization to the first documented progressive disease (PD) or death from any cause, whichever occurs first
• Objective: To evaluate participants treated with IT MK-1454 in combination with pembrolizumab or pembrolizumab alone with regard to Duration of Response (DOR) per RECIST 1.1 by BICR.	• DOR, defined as the time from the first documented evidence of CR or PR until PD or death due to any cause, whichever occurs first, in participants demonstrating CR or PR
• Objective: To evaluate participants treated with IT MK-1454 in combination with pembrolizumab or pembrolizumab alone with regard to overall survival (OS).	• OS, defined as the time from randomization to the date of death from any cause
• Objective: To assess participants treated with IT MK-1454 in combination with pembrolizumab or pembrolizumab alone with regard to the safety and tolerability of study intervention.	• Adverse events (AEs) • Discontinuing study intervention due to an AE

Overall Design:

Study Phase	Phase 2
Primary Purpose	Treatment
Indication	Metastatic or unresectable, recurrent HNSCC
Population	Participants with a histologically or cytologically confirmed diagnosis of metastatic or unresectable, recurrent HNSCC with tumor CPS $\geq$1
Study Type	Interventional
Intervention Model	Parallel This is a multi-site study.
Type of Control	Active control without placebo

Study Blinding	Unblinded Open-label
Blinding Roles	No Blinding
Estimated Duration of Study	The Sponsor estimates that the study will require approximately 60 months from the time the first participant signs the informed consent until the last participant's last study-related telephone call or visit.

Number of Participants:

Approximately 200 participants will be randomized in the study, as described in Section 9.9.

Intervention Groups and Duration:

Intervention Groups

Intervention Group Name	Drug	Dose Strength	Dose Frequency	Route of Administration	Treatment Period	Use
Arm 1	MK 1454	CCI [redacted]	Q1W × 6, then Q3W	Intratumoral	Up to 35 cycles	Experimental
	MK 3475	200 mg	Q3W	Intravenous		Experimental
Arm 2	MK 3475	200 mg	Q3W	Intravenous	Up to 35 cycles	Comparator

Q1W once each week; Q3W once every 3 weeks

Other current or former name(s) or alias(es) for study intervention(s) are as follows: MK-3475 pembrolizumab KEYTRUDA®.

Total Number	2 arms
Duration of Participation	Each participant will participate in the study for up to approximately 2 years from the time the participant signs the informed consent form (ICF) through the final contact. After a screening phase of up to 28 days, each participant may receive assigned intervention for up to approximately 35 cycles. After the end of treatment, each participant will be followed up for 30 days for the occurrence of AEs and spontaneously reported pregnancy. All participants will be followed by telephone for OS until death, withdrawal of consent, or end of the study.

Study Governance Committees:

Steering Committee	No
Executive Oversight Committee	No
Data Monitoring Committee	No
Clinical Adjudication Committee	No
Stage Gate Review Committee	Yes
Study governance considerations are outlined in Appendix 1.	

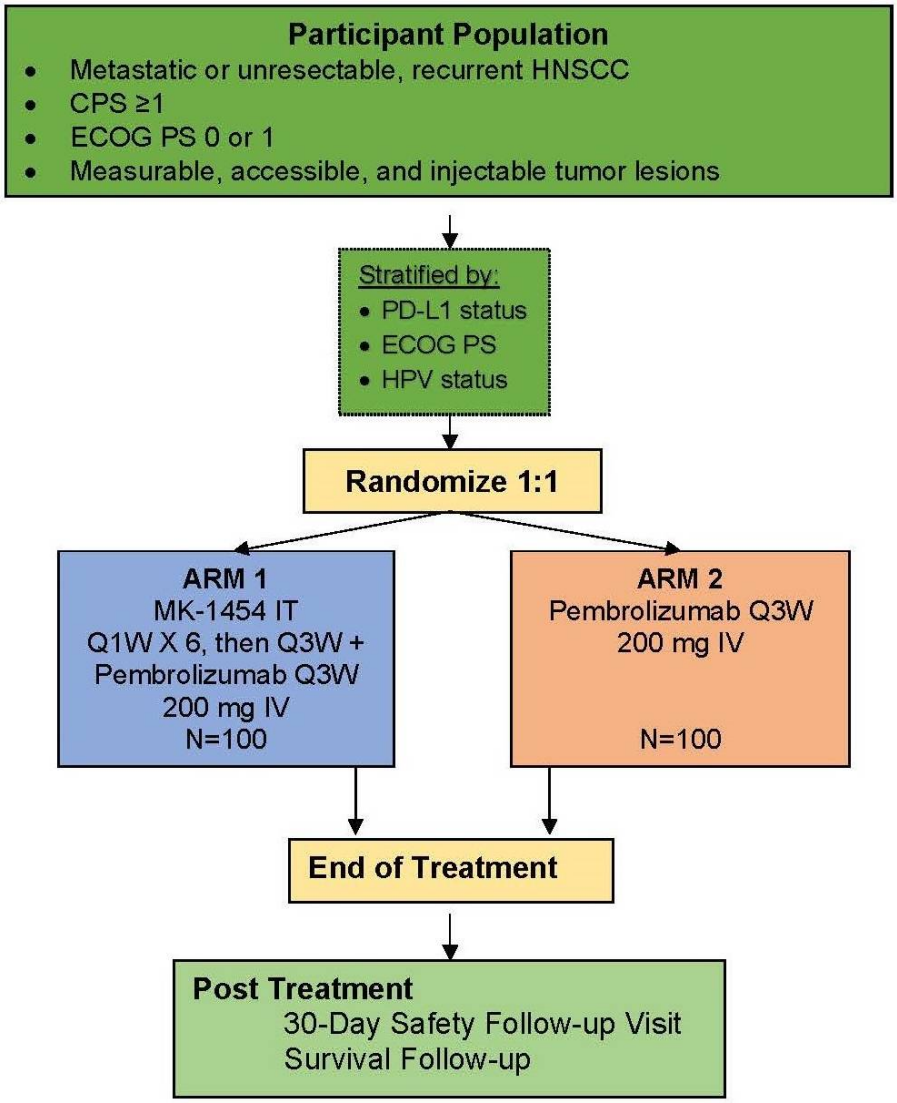
Study Accepts Healthy Volunteers: No

A list of abbreviations used in this document can be found in Appendix 10.

1.2 Schema

The study design is depicted in Figure 1.

Figure 1 Study Schema



CPS = combined positive score; ECOG = Eastern Cooperative Oncology Group; HNSCC = head and neck squamous cell carcinoma; HPV = human papilloma virus; IT = intratumoral; IV = intravenous; PD-L1 = programmed cell death ligand 1; Q1W = once each week; Q3W = once every 3 weeks.

1.3 Schedule of Activities

1.3.1 Schedule of Activities for Screening for All Participants

Study Period	Screening	Notes
Visit Days	-28 to -1	
Administrative Procedures		
Informed Consent	X	Informed consent must be documented prior to performing any protocol specific procedures. Tests performed prior to consent as part of routine clinical management are acceptable if performed within the specified timeframe.
Informed Consent for FBR (Optional)	X	Consent for FBR is not required to participate in the study.
Inclusion/Exclusion Criteria	X	
Participant Identification Card	X	Participant identification card to be updated with treatment number at the time of treatment randomization.
Demographics and Medical History	X	
Current Disease Details	X	
Prior Treatment for Head and Neck Cancer	X	
Mutational Status / Tumor Genetic Alteration(s)	X	Tumor genetic alteration(s) per standard of care, by history if available, as determined by local testing results (eg, MSI, dMMR).
Prior Medication	X	
Clinical Procedures/Assessments		
Tumor Imaging, RECIST 1.1, and iRECIST Response Assessment	X	Baseline tumor imaging (CT or MRI) and/or medical photography of cutaneous lesions should be performed within 28 days prior to the date of enrollment and submitted to the iCRO for confirmation of measurable disease (allow 14 days). Please refer to Imaging Manual for detailed information.
Medical Photography (Cutaneous Lesions)	X	
Full Physical Examination	X	
Vital Signs	X	Vital signs include heart rate, respiratory rate, 0_2 saturation, blood pressure, and temperature.
Weight and Height	X	Height will only be measured at screening.
ECOG performance status	X	To be performed within 7 days prior to the first dose of study intervention.
12 Lead Electrocardiogram (Local)	X	
AE Monitoring	X	All AEs that occur after the consent form is signed but before treatment allocation must be reported by the investigator if the event causes the participant to be excluded from the study or is the result of a protocol specified intervention. There is to be continuous AE reporting from the time of treatment allocation.

Study Period	Screening	Notes
Visit Days	**-28 to -1**	
Laboratory Procedures/Assessments - LOCAL		
CBC with Differential	X	Perform these screening clinical laboratory tests, with exception of hepatitis and thyroid testing, within 7 days prior to the first dose of study intervention. Participants on anticoagulant therapy should be monitored throughout the study with PT or INR and PTT or aPTT as clinically indicated.
Chemistry Panel	X	
PT or INR and PTT or aPTT	X	
LDH, GGT	X	
Urinalysis	X	
Thyroid Function (TSH, T3, FT3, T4, FT4)	X	Thyroid function: Total T3 and Total T4 are preferred over FT3 and FT4.
Pregnancy test for WOCBP only (urine or serum β hCG)	X	Perform within 7 days prior to C1D1. Urine pregnancy test to be performed as indicated; if test is positive or cannot be confirmed as negative, a serum pregnancy test is required. Additional pregnancy testing can be conducted if required by local regulations or if clinically indicated.
HIV, Hepatitis B and C Screen	X	Acceptable to be based on history unless testing is required by local regulation. Include HCV antibody or HCV RNA (qualitative) and HBsAg.
Pharmacokinetics/Pharmacodynamics/Future Biomedical Research/Biomarkers		
Tumor Tissue for HPV Status	X	Archival or newly obtained tissue will be collected from participants with oropharyngeal cancer to be tested for HPV status for stratification, if HPV status was not previously determined by IHC P16 testing according to the Procedures Manual. If test method is not available locally, sample is to be sent to the central laboratory at least 14 days prior to randomization. A single sample may be obtained for testing for HPV and assessing PD L1 status.
Tumor Tissue for PD L1 Status	X	Archival or newly obtained tissue will be collected from all participants for testing by central laboratory. Sample is to be sent to the central laboratory at least 14 days prior to randomization. This tissue sample will be analyzed using the IUO version of the US FDA approved PD L1 IHC 22C3 kit to confirm the PD L1 CPS ≥1 status for eligibility and for stratification by CPS (≥1 to <20 vs. ≥20).

Abbreviations: AE adverse event; aPTT activated partial thromboplastin time; β hCG β human chorionic gonadotropin; C1D1 Cycle 1 Day 1; CBC complete blood count; CPS combined positive score; CT computed tomography; ctDNA circulating tumor deoxyribonucleic acid; dMMR deficient mismatch repair; ECOG Eastern Cooperative Oncology Group; FBR future biomedical research; FDA Food and Drug Administration; FT3 free triiodothyronine; FT4 free thyroxine; GGT gamma glutamyl transpeptidase; HBsAg Hepatitis B surface antigen; HCV hepatitis C virus; HIV human immunodeficiency virus; HPV human papilloma virus;; iCRO imaging contract research organization; IHC immunohistochemistry; INR International Normalized Ratio; iRECIST modified RECIST 1.1 for immune based therapeutics; IUO Investigational Use Only; LDH lactate dehydrogenase; MRI magnetic resonance imaging; MSI microsatellite instability; PD L1 programmed cell death ligand 1; PT prothrombin time; PTT partial thromboplastin time; RECIST 1.1 Response Evaluation Criteria in Solid Tumors; version 1.1; RNA ribonucleic acid; T3 triiodothyronine; T4 thyroxine; TSH thyroid stimulating hormone; US United States; vs. versus; WOCBP women of childbearing potential.

1.3.2 Schedule of Activities for the Treatment Period for Arm 1 (Combination Therapy: IT MK-1454 + IV Pembrolizumab)

Study Period:	**Combination Treatment Phase (3-Week Cycles)**								**Notes**
Treatment Cycle/Title:	**Cycle 1**			**Cycle 2**			**Cycle 3**	**Cycle 4 and Beyond**	
Treatment Days:	**1**	**8**	**15**	**1**	**8**	**15**	**1**	**1**	
Scheduled Day and Window:	**+3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	
Administrative Procedures									
Informed Consent	X								Additional consent is required for treatment beyond disease progression.
Prior/Concomitant Medication Review	X	X	X	X	X	X	X	X	
Participant Identification Card	X								Participant identification card to be updated with treatment/randomization number at the time of intervention randomization.
Treatment Randomization	X								Treatment must occur within 72 h of intervention randomization.
MK-1454 Administration/ Dispensing	X	X	X	X	X	X	X	X	On days when both MK-1454 and pembrolizumab are to be administered, MK-1454 will be administered within 0.5 to 4 h after completion of pembrolizumab IV infusion.
Pembrolizumab Administration/ Dispensing	X			X			X	X	See Pembrolizumab Pharmacy Manual.
Efficacy Procedures									
Tumor Imaging, RECIST 1.1, iRECIST, and/or itRECIST Response Assessment							X	X	Tumor imaging (CT or MRI) and medical photography (for cutaneous lesions) to be performed 6 weeks (42-49 days) after the first dose, and then every 6 weeks (42 days ± 7 days) for the first year, then every 9 weeks (63 days ± 7 days) thereafter. Imaging schedule should follow **calendar days** and should not be adjusted for delays in cycle starts. Continue imaging schedule until confirmed disease progression, discontinuation from study, or start of new anticancer treatment. Medical photography can be performed more often as medically warranted.

Study Period:	**Combination Treatment Phase (3-Week Cycles)**								**Notes**
Treatment Cycle/Title:	**Cycle 1**			**Cycle 2**			**Cycle 3**	**Cycle 4 and Beyond**	
Treatment Days:	**1**	**8**	**15**	**1**	**8**	**15**	**1**	**1**	
Scheduled Day and Window:	**+3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	
Medical Photography (Cutaneous Lesions)							X	X	
Safety Procedures									
Directed Physical Examination	X			X			X	X	
Weight	X			X			X	X	
Vital Signs	X	X	X	X	X	X	X	X	Measure prior to study intervention. Vital signs include heart rate, respiratory rate, blood pressure, 0_2 saturation, and temperature.
ECOG performance status	X			X			X	X	Performed within 72 h prior to study intervention dosing on Day 1 of each cycle. Additional ECOG can be performed as clinically indicated.
12-Lead Electrocardiogram (Local)							X		
Pregnancy test – Urine or Serum β-hCG for WOCBP	X								Required within 24 h prior to first dose of study medication. Does not need to be repeated if screening pregnancy test was done within 24 h of the first dose of study medication on 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. Refer to Appendix 7 for country-specific requirements.
Urinalysis	X			X			X	X	Required within 72 h of C1D1. Does not need to be repeated if screening labs were done within 72 h of C1D1. May be performed up to 72 h prior to dosing for subsequent cycles when scheduled. PTT may be performed if the local lab is unable to perform aPTT. Any participant receiving anticoagulant therapy should have coagulation factors monitored closely throughout the study.
CBC with Differential	X	X	X	X	X	X	X	X	
PT or 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	

Study Period:	**Combination Treatment Phase (3-Week Cycles)**								**Notes**
Treatment Cycle/Title:	**Cycle 1**			**Cycle 2**			**Cycle 3**	**Cycle 4 and Beyond**	
Treatment Days:	**1**	**8**	**15**	**1**	**8**	**15**	**1**	**1**	
Scheduled Day and Window:	**+3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	
Thyroid Function Testing (TSH, T3 [or FT3], T4 [or FT4])	X						X	X*	Total T3 and Total T4 are preferred over FT3 and FT4. Required within 72 h 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 h of C1D1. *Cycle 4 not required.
AE Monitoring	X								
CCI	[redacted]								

Study Period:	**Combination Treatment Phase (3-Week Cycles)**								**Notes**
Treatment Cycle/Title:	**Cycle 1**			**Cycle 2**			**Cycle 3**	**Cycle 4 and Beyond**	
Treatment Days:	**1**	**8**	**15**	**1**	**8**	**15**	**1**	**1**	
Scheduled Day and Window:	**+3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	

Abbreviations: AE adverse event; aPTT activated partial thromboplastin time; β hCG β human chorionic gonadotropin; C Cycle; CBC complete blood count; CT computed tomography; ctDNA circulating tumor deoxyribonucleic acid; D Day; ECOG Eastern Cooperative Oncology Group; FT3 free triiodothyronine; FT4 free thyroxine; GGT gamma glutamyl transferase; INR international normalized ratio; iRECIST immune related RECIST; itRECIST intratumoral immunotherapy RECIST; IV intravenous; LDH lactate dehydrogenase; MRI magnetic resonance imaging; PK pharmacokinetics; PT prothrombin time; PTT partial thromboplastin time; RECIST v1.1 Response Evaluation Criteria In Solid Tumors, version 1.1; RNA ribonucleic acid; T3 total triiodothyronine; T4 total thyroxine; TSH thyroid stimulating hormone; WOCBP women of childbearing potential.

1.3.3 Schedule of Activities for the Treatment Period for Arm 2 – IV Pembrolizumab Monotherapy

Study Period:	**Treatment Phase (3-Week Cycles)**				**Notes**
Treatment Cycle/Title:	**Cycle 1**	**Cycle 2**	**Cycle 3**	**Cycle 4 and Beyond**	
Treatment Days:	**1**	**1**	**1**	**1**	
Scheduled Day and Window:	**+3**	**±3**	**±3**	**±3**	
Administrative Procedures					
Informed Consent	X				Additional consent is required for treatment beyond disease progression.
Prior/Concomitant Medication Review	X	X	X	X	
Participant Identification Card	X				Participant identification card to be updated with treatment number at the time of treatment intervention randomization.
Treatment Randomization	X				Treatment must occur within 72 h of intervention randomization.
Pembrolizumab Administration/ Dispensing	X	X	X	X	See Pembrolizumab Pharmacy Manual.
Efficacy Procedures					
Tumor Imaging, RECIST 1.1, iRECIST, and/or itRECIST Response Assessment			X	X	Tumor imaging (CT or MRI) and medical photography (for cutaneous lesions) to be performed 6 weeks (42-49 days) after the first dose, and then every 6 weeks (42 days ± 7 days) for the first year, then every 9 weeks (63 days ± 7 days) thereafter. Imaging schedule should follow **calendar days** and should not be adjusted for delays in cycle starts. Continue imaging schedule until confirmed disease progression, discontinuation from study, or start of a new antitumor treatment. Medical photography can be performed more often as medically warranted.
Medical Photography (cutaneous lesions)			X	X	

Study Period:	**Treatment Phase (3-Week Cycles)**				**Notes**
Treatment Cycle/Title:	**Cycle 1**	**Cycle 2**	**Cycle 3**	**Cycle 4 and Beyond**	
Treatment Days:	**1**	**1**	**1**	**1**	
Scheduled Day and Window:	**+3**	**±3**	**±3**	**±3**	
Safety Procedures					
Directed Physical Examination	X	X	X	X	
Weight	X	X	X	X	
Vital Signs	X	X	X	X	Measure prior to study intervention. Vital signs include heart rate, respiratory rate, blood pressure, 0_2 saturation, and temperature.
ECOG performance status	X	X	X	X	Performed within 72 h prior to study intervention dosing on Day 1 of each cycle. Additional ECOG can be performed as clinically indicated.
12-Lead Electrocardiogram (Local)			X		
Pregnancy test – Urine or Serum β-hCG for WOCBP	X				Required within 24 h prior to first dose of study medication. Does not need to be repeated if screening pregnancy test was done within 24 h of C1D1. If a urine pregnancy test cannot be confirmed as negative, a serum pregnancy test is required. Pregnancy testing must be done as required by local regulation. Refer to Appendix 7 for country-specific requirements.
Urinalysis	X	X	X	X	Required within 72 h of C1D1. Does not need to be repeated if screening labs were done within 72 h of C1D1. May be performed up to 72 h prior to dosing for subsequent cycles when scheduled.
CBC with Differential	X	X	X	X	
Chemistry Panel	X	X	X	X	
LDH, GGT	X	X	X	X	
Thyroid Function Testing (TSH, T3 [or FT3], T4 [or FT4])	X		X	X*	Total T3 and T4 are preferred over FT3 and FT4. Required within 72 h 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 h of C1D1. *Cycle 4 not required.
AE Monitoring	X				

Study Period:	**Treatment Phase (3-Week Cycles)**				**Notes**
Treatment Cycle/Title:	**Cycle 1**	**Cycle 2**	**Cycle 3**	**Cycle 4 and Beyond**	
Treatment Days:	**1**	**1**	**1**	**1**	
Scheduled Day and Window:	**+3**	**±3**	**±3**	**±3**	
CCI					

Abbreviations: AE adverse event; aPTT activated partial thromboplastin time; β hCG β human chorionic gonadotropin; C Cycle; CBC complete blood count; CT computed tomography; ctDNA circulating tumor deoxyribonucleic acid; D Day; ECOG Eastern Cooperative Oncology Group; FT3 free triiodothyronine; FT4 free thyroxine; GGT gamma glutamyl transferase; INR international normalized ratio; iRECIST immune related RECIST; itRECIST intratumoral immunotherapy RECIST; LDH lactate dehydrogenase; MRI magnetic resonance imaging; PK pharmacokinetics; PT prothrombin time; PTT partial thromboplastin time; RECIST v1.1 Response Evaluation Criteria In Solid Tumors, version 1.1; RNA ribonucleic acid; T3 total triiodothyronine; T4 total thyroxine; TSH thyroid stimulating hormone.; WOCBP women of childbearing potential.

1.3.4 Schedule of Activities for the End of Treatment and Posttreatment Follow-Up Periods

Study Period	EOT/ Discontinuation	Posttreatment Period			Notes
		30-Day Safety Follow-up Visit	Imaging Follow-up	Survival Follow-up	
Visit Timing		**30 days after the last dose**	**Every 6 weeks for 1 year, then every 9 weeks**	**Approxi-mately every 12 weeks**	
Visit Window (Days)	**±7**	**+7**	**±7**	**±14**	
Administrative Procedures					
Concomitant Medication	X	X			
Efficacy Procedures					**See Imaging Manual All imaging visits have a ± 7-day window**
Tumor Imaging, RECIST 1.1, iRECIST, and/or itRECIST Response Assessment	X		X		
Medical Photography (Cutaneous Lesions)	X		X		
New Anticancer Therapy Status	X	X	X		
Survival Status Monitoring	←	—	—	→	Upon Sponsor request, participants may be contacted for survival status at any time during the course of the study. After confirmed disease progression, each participant will be contacted for survival status until participant withdrawal of consent, becoming lost to follow-up, death, or the end of the study.
Safety Assessments and Procedures					**See Procedures Manual for collection and management of samples.**
AE Monitoring	X	X	X		
Full Physical Examination	X				
Directed Physical Examination		X			

Study Period	EOT/ Discontinuation	Posttreatment Period			Notes
		30-Day Safety Follow-up Visit	Imaging Follow-up	Survival Follow-up	
Visit Timing		**30 days after the last dose**	**Every 6 weeks for 1 year, then every 9 weeks**	**Approxi-mately every 12 weeks**	
Visit Window (Days)	**±7**	**+7**	**±7**	**±14**	
Weight	X	X			
Vital Signs	X	X			Heart rate, respiratory rate, blood pressure, 0_2 saturation, and temperature.
ECOG performance status	X	X			
CBC with Differential	X	X			
Chemistry Panel	X	X			
Urinalysis		X			
Pregnancy Test for WOCBP – Urine or Serum β-hCG		X			For WOCBP, perform as required locally. If a urine pregnancy test cannot be confirmed as negative, a serum pregnancy test is required. Refer to Appendix 7 for country-specific requirements.
Thyroid Function (TSH, T3 [or FT3], T4 [or FT4])	X				Total T3 and T4 are preferred over FT3 and FT4.
Pharmacokinetics (PK)/Pharmacodynamics/ Future Biomedical Research/Biomarkers					**See Procedures Manual for collection and management of samples.**
Blood for ctDNA Analysis	X				

Abbreviations: AE adverse event; β hCG β human chorionic gonadotropin; CBC complete blood count; ECOG Eastern Cooperative Oncology Group; EOT end of treatment; FT3 free triiodothyronine; FT4 free thyroxine; iRECIST immune related RECIST; itRECIST intratumoral immunotherapy RECIST; RECIST v1.1 Response Evaluation Criteria In Solid Tumors, version 1.1; T3 total triiodothyronine; T4 total thyroxine; TSH thyroid stimulating hormone; WOCBP women of childbearing potential.

2 INTRODUCTION

MK-1454 is a novel CDN that is a STING agonist under study for the treatment of HNSCC as monotherapy and as combination therapy with pembrolizumab. This is a Phase 2 study to assess the efficacy, safety, and tolerability of IT MK-1454 in combination with pembrolizumab versus pembrolizumab monotherapy.

2.1 Study Rationale

Endogenous STING pathway activation within the tumor induces spontaneous T-cell priming that is necessary for the generation of adaptive immunity. The scientific rationale for combining MK-1454 with PD-1 blockade is based on the ability of STING agonists to induce type I IFNs and induce strong T-cell activation by promoting cross-presentation of tumor antigens. As strong T-cell activation is accompanied by up-regulation of PD-1, which mediates T-cell inhibition by tumors, combination therapy with anti-PD-1 will prevent the inhibition of T-cell activation. The initial empirical rationale for combining MK-1454 with PD-1 blockade is based on the efficacy observed in anti-PD-1 nonresponsive syngeneic mouse tumor models where subefficacious MK-1454 doses in combination with anti-PD-1 induced improved antitumor responses and complete tumor regression compared to either monotherapy treatment alone (see MK-1454 IB for details).

This response was demonstrated in a Phase 1 study, in which IT injection of STING agonist in combination with pembrolizumab induced regression of established tumors and generated systemic immune responses, mediating rejection of distant metastases, and providing immunologic (T cell) memory. Preliminary results reported from the ongoing FIH study showed a PR to IT MK-1454 in combination with IV pembrolizumab in participants with HNSCC, TNBC, and anaplastic thyroid cancer [Harrington, K. J., et al 2018]. Dose-response data from this study led to the proposed [redacted] total dose per treatment visit of MK-1454 for IT injection into multiple sites. See Section 2.2.3.1 for further details of the FIH study.

Pembrolizumab monotherapy is approved as first-line treatment of patients with metastatic or with unresectable, recurrent HNSCC for patients whose tumors express PD-L1 (CPS ≥1) or in combination with platinum and fluorouracil regardless of PD-L1 expression. Refer to the IB/approved local product label for list of approvals for pembrolizumab. Clinical experience with MK-1454 in combination with pembrolizumab thus far, indicates that this combination may provide a greater benefit as a cancer therapeutic in the HNSCC patient population.

2.2 Background

Refer to the IB/approved labeling for detailed background information on MK-1454, and the MK-3475 IB for detailed background information on pembrolizumab.

2.2.1 Pharmaceutical and Therapeutic Background

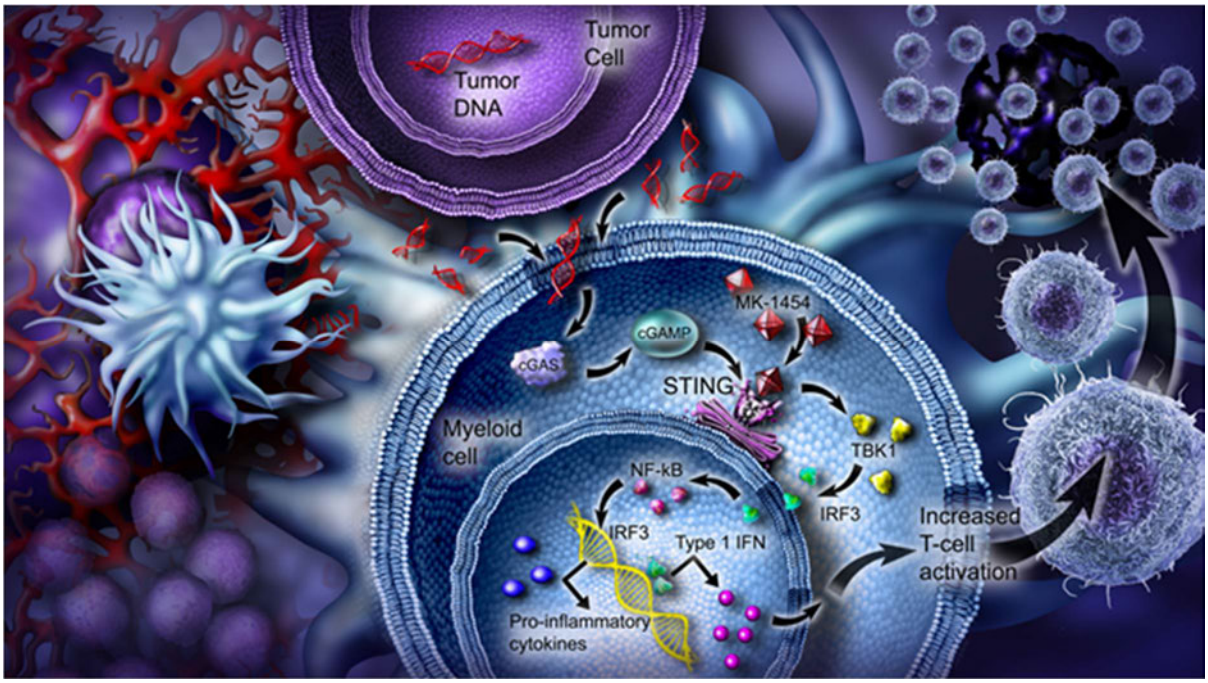
2.2.1.1 MK-1454 Pharmaceutical and Therapeutic Background

MK-1454 is a CDN STING agonist with activity across species. The presence of DNA in the cytoplasm of mammalian cells represents a cellular danger signal, and the cGAS/STING pathway is activated to respond to that potentially infectious threat [Barber GN 2015]. Free cytosolic DNA is recognized by cGAS, catalyzing the generation of the cyclic GMP-AMP. cGAMP strongly binds to the ER-transmembrane adapter protein STING, inducing the activation of transcription factor IRF-3 [Sun, L., et al 2013] [Burdette, D. L., et al 2011]. This ultimately leads to a strong induction of type 1 IFN and proinflammatory cytokines such as IL-6, TNF-α, and IFN-γ, which potentiate T-cell activation through multiple mechanisms.

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. SNP 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% [Yi, G., et al 2013]. Recent studies showed that all tested STING variants demonstrated comparable response to synthetic CDN-derivative STING agonists.

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 [Deng, L., et al 2014] [Woo S. R., et al 2014] as illustrated in Figure 2.

Figure 2 Schematic Diagram Showing Mechanism of the Enhancement of T-cell Driven Antitumor Immunity Through the Action of STING Agonists



cGAMP Cyclic guanosine monophosphate adenosine monophosphate, cGAS Cyclic guanosine monophosphate adenosine monophosphate synthase; IFN interferon; IRF3 interferon regulatory factor 3, NF κB nuclear factor kappa light chain enhancer of activated B cells; STING stimulator of interferon genes, TBK1 TANK binding kinase 1.

Working model of pharmacological STING activation leading to antitumor immune responses in vivo.
Therapeutically, the STING pathway can be stimulated by STING agonists when the compounds are injected into the tumor site, leading to the activation of intratumoral dendritic cells (DC). This results in the phosphorylation of TBK1 and activation of the transcription factors that induce expression of the type 1 IFN genes, proinflammatory cytokines, chemokines, etc. Type 1 IFN signaling in CD8α+ CD103+ cross presenting DC leads to antigen specific T cell priming and generation of spontaneous antitumor T cell responses in vivo. Recruitment of effector T cells into the tumor microenvironment is facilitated by the release of CXCL9/CXCL10 chemokines from DCs and other cells at the tumor site. Successfully recruited activated T cells additionally induce direct tumor cell killing, leading to measurable tumor shrinkage.

Source: Figure adapted from [Woo, S. R., et al 2015] [Corrales, L. 2016].

Published and internal data show that IT 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 [Corrales, L., et al 2015] [Fu, J., et al 2015] [Baird, J. R., et al 2016]. Finally, 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 [Fu, J., et al 2015].

2.2.1.2 Pembrolizumab (MK-3475) Pharmaceutical and Therapeutic Background

The importance of intact immune surveillance function in controlling outgrowth of neoplastic transformations has been known for decades [Disis, M. L. 2010]. Accumulating evidence shows a correlation between 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+ T-regs correlates with improved prognosis and long-term survival in solid malignancies such as ovarian, colorectal, pancreatic cancer, hepatocellular carcinoma, malignant melanoma, and renal cell carcinoma. Tumor-infiltrating lymphocytes can be expanded ex vivo and reinfused, inducing durable objective tumor responses in cancers such as melanoma [Dudley, M. E., et al 2005] [Hunder, N. N., et al 2008].

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

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

Pembrolizumab is currently approved for treatment of a variety of neoplasms, including metastatic or unresectable, recurrent HNSCC with disease progression on or after platinum-containing chemotherapy [U.S. Prescribing Information 2019].

2.2.2 Preclinical and Clinical Studies

For a review of preclinical studies of MK-1454, please see the IB.

2.2.3 Ongoing Clinical Studies

2.2.3.1 MK-1454 Clinical Studies

The ongoing FIH study, as of 06-JUN-2019, MK-1454-001, has evaluated IT MK-1454 doses of up to CCI as monotherapy, and IT MK-1454 doses of up to CCI in combination with pembrolizumab 200 mg IV Q3W. Dose-dependent increases in exposure to MK-1454 were observed, with a half-life of approximately 1.5 hours. Serum cytokines increased in a dose-dependent manner up to CCI followed by a plateau seen at CCI in monotherapy (n 27) and CCI in combination therapy (n 33). The expression of STING-

induced genes in blood increased in a dose-dependent manner up to [redacted] followed by plateau in participants receiving either monotherapy or combination therapy.

Early efficacy response data from participants with ≥1 postbaseline tumor assessment were available from 32 participants treated with IT MK-1454 monotherapy and from 67 participants treated with IT MK-1454 in combination with pembrolizumab as of 06-JUN-2019. No CR or PR was reported in the MK-1454 monotherapy treatment arm; 2 participants treated with MK-1454 monotherapy had ≥30% tumor reduction in target injected lesions among 18 participants with imaging assessments. Responses were observed in 7 participants who received combination therapy with IT MK-1454 and pembrolizumab, including a CR in 1 of 8 participants with TBNC; and PRs in 3 of 11 participants with HNSCC, 2 of 5 participants with anaplastic thyroid cancer, and 1 participant with in Merkel cell carcinoma. Reductions in volume of both injected and noninjected target lesions in combination therapy were observed, with a greater reduction over the [redacted] to [redacted] dose range compared to [redacted] to [redacted]

Safety data has shown the IT MK-1454 and IV pembrolizumab combination to have a manageable safety profile. [redacted]

Dose-limiting toxicities reported in MK-1454 monotherapy Arm 1 of the Phase 1 study included [redacted]

Dose-limiting toxicities reported in MK-1454 combination therapy with pembrolizumab 200 mg Arm 2 of the Phase 1 study included [redacted]

To date, 6 participants have been treated in Arm 3 with IT MK-1454 administered to visceral lesions in combination with pembrolizumab IV. This treatment arm is currently enrolling.

2.2.3.2 Pembrolizumab (MK-3475) Clinical Studies

Pembrolizumab is approved as monotherapy in patients whose tumors express PD-L1 CPS ≥1 or in combination with platinum and fluorouracil, a standard chemotherapy regimen, for the first-line treatment of patients with metastatic or with unresectable, recurrent HNSCC. Refer to the IB/approved local product label for list of approvals for pembrolizumab. The approval is based on results from a prespecified IA of the Phase 3 KEYNOTE-048 study, a randomized, multicenter, open-label, active-controlled study conducted in 882 patients with metastatic HNSCC who had not previously received systemic therapy and who were considered incurable by local therapies.

Among the 882 patients, the study population characteristics were: median age of 61 years (range, 20 to 94), 36% age 65 or older; 83% male; 73% white, 20% Asian, and 2.4% black; 61% had ECOG performance status of 1; and 79% were former or current smokers. Twenty-two percent of patients' tumors were HPV-positive; 23% had PD-L1 TPS ≥50%; and 95% had stage IV disease (19% were stage IVA, 6% were stage IVB, and 70% were stage IVC). Eighty-five percent of patients' tumors had PD-L1 expression of CPS ≥1, and 43% had CPS ≥20. The median duration of exposure to pembrolizumab 200 mg Q3W was 3.5 months (range, 1 day to 24.2 months) in the monotherapy arm and was 5.8 months (range, 3 days to 24.2 months) in the combination arm.

The main efficacy outcome measures were OS and PFS as assessed by BICR according to RECIST v1.1 (modified to follow a maximum of 10 target lesions and a maximum of 5 target lesions per organ) sequentially analyzed in the subgroup of patients with CPS ≥20, the subgroup of patients with CPS ≥1 and the overall population.

Pembrolizumab demonstrated a significant improvement in OS compared with the EXTREME regimen (cetuximab with carboplatin or cisplatin plus fluorouracil), as monotherapy in patients whose tumors expressed PD-L1 (CPS ≥1) with a median OS of 13.6 months versus 10.4 months, respectively; (HR 0.65 [95% CI, 0.53-0.80]; p 0.00002) and in combination with chemotherapy in the total study population (HR 0.77 [95% CI, 0.63-0.93]; p 0.0067).

Among participants whose tumors were CPS ≥20, OS was also significantly improved in those treated with pembrolizumab plus chemotherapy versus the EXTREME regimen: HR 0.60 (95% CI, 0.45, 0.82); p 0.00044. Assessment by HPV status (participants with oropharyngeal cancer) indicated that among those who were HPV-positive, pembrolizumab plus chemotherapy showed clear improvement; median OS was 23.9 months (95% CI: 16.2, 34.5) compared with 15.9 months for standard treatment HR 0.56 (95%CI: 0.36, 0.87). Assessment of OS by the ECOG subgroups were consistent with the CIs of the primary findings overlapping the primary HR outcome CI.

Pembrolizumab was discontinued for adverse reactions in 12% of patients in the monotherapy arm. The most common adverse reactions resulting in permanent discontinuation of pembrolizumab were sepsis (1.7%) and pneumonia (1.3%). Adverse reactions leading to the interruption of pembrolizumab occurred in 31% of patients; the most common adverse reactions leading to the interruption of pembrolizumab (≥2%) were pneumonia (2.3%), pneumonitis (2.3%) and hyponatremia (2%). The most common adverse reactions (≥20%) with pembrolizumab as monotherapy were fatigue (33%), constipation (20%), and rash (20%).

Pembrolizumab is approved for use in the treatment of multiple tumor types [U.S. Prescribing Information 2019], and ongoing clinical studies with pembrolizumab are being conducted in multiple solid tumors. In addition, multiple combinations with pembrolizumab are also being investigated. Refer to pembrolizumab IB for study details.

2.3 Benefit/Risk Assessment

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

For MK-1454-001, drug-related AEs reported most frequently by investigators (>10% of participants) were[redacted]. The most frequently reported SAEs in treated participants were[redacted]

Efficacy data from participants dosed with MK-1454 are available from 30 participants dosed in monotherapy (Arm 1) and 60 participants dosed in combination therapy (Arm 2) (including crossover participants). There have been no objective responses in monotherapy. In combination therapy, including crossover, there has been 1 CR in a participant with TNBC, and an additional 9 participants with a PR.

Based on composite evaluation of safety, pharmacodynamic, and efficacy data,[redacted] was selected as the recommended Phase 2 dose. Safety and efficacy data to date support the conclusion that MK-1454 has an acceptable benefit/risk profile for continued investigation.

Additional details regarding specific benefits and risks for participants participating in this clinical study may be found in the MK-1454 IB and pembrolizumab label/IB and informed consent documents.

3 HYPOTHESES, OBJECTIVES, AND ENDPOINTS

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

In males and females who are at least 18 years of age with metastatic or with unresectable, recurrent HNSCC with a tumor PD-L1 IHC CPS ≥1:

Objectives	Endpoints
Primary	
• Objective: To evaluate participants treated with IT MK-1454 in combination with pembrolizumab or pembrolizumab alone with regard to the ORR per RECIST 1.1 by BICR. • Hypothesis (H1): IT MK-1454 in combination with pembrolizumab results in a superior ORR, per RECIST 1.1 based on BICR, compared to pembrolizumab alone, in participants with tumor CPS ≥1. • Hypothesis (H2): IT MK-1454 in combination with pembrolizumab results in a superior ORR, per RECIST 1.1 based on BICR, compared to pembrolizumab alone, in participants with tumor CPS ≥20. The study is considered to have met its primary objective if IT MK-1454, in combination with pembrolizumab, results in a superior ORR, per RECIST 1.1 based on BICR, compared to pembrolizumab alone either in participants with tumor CPS ≥1 or in participants with tumor CPS ≥20.	• Objective response is a confirmed CR or PR
Secondary	
• Objective: To evaluate participants treated with IT MK-1454 in combination with pembrolizumab or pembrolizumab alone with regard to progression-free survival (PFS) per RECIST 1.1 by BICR.	• PFS, defined as the time from randomization to the first documented PD or death from any cause, whichever occurs first.
• Objective: To evaluate participants treated with IT MK-1454 in combination with pembrolizumab or pembrolizumab alone with regard to DOR per RECIST 1.1 by BICR.	• DOR, defined as the time from the first documented evidence of CR or PR until PD or death due to any cause, whichever occurs first, in participants demonstrating CR or PR.

Objectives	Endpoints
• Objective: To evaluate participants treated with IT MK-1454 in combination with pembrolizumab or pembrolizumab alone with regard to OS.	• OS, defined as the time from randomization to the date of death from any cause.
• Objective: To assess participants treated with IT MK-1454 in combination with pembrolizumab or pembrolizumab alone with regard to the safety and tolerability of study intervention.	• AEs • Discontinuing study intervention due to an AE.
Tertiary/Exploratory	
CCI [redacted]	

4 STUDY DESIGN

4.1 Overall Design

This is a randomized, active-controlled, parallel group, multicenter, open-label, Phase 2 study of IT MK-1454 in combination with pembrolizumab versus pembrolizumab monotherapy in participants with a histologically or cytologically confirmed diagnosis of metastatic or unresectable, recurrent HNSCC with a tumor CPS ≥1 [Kulangara, K., et al 2018] as first-line

treatment. Participants need to have at least 1 measurable lesion that is amenable to IT injection for RECIST assessment.

This study will evaluate the efficacy, safety, and tolerability of IT MK-1454 in combination with pembrolizumab IV versus pembrolizumab IV alone. Figure 1 depicts a summary of the study design. Approximately 200 participants will be randomized 1:1 using IRT to receive IT MK-1454 at a dose of CCI in combination with pembrolizumab (Arm 1) or pembrolizumab monotherapy (Arm 2). Randomization will be stratified by PD-L1 expression level defined by CPS (≥1 to <20 vs ≥20), ECOG performance status (0 vs. 1) and tumor HPV status (positive, negative). In Arm 1, study intervention will be IT MK-1454 CCI administered Q1W for 6 weeks, then Q3W, in combination with pembrolizumab 200 mg IV Q3W. In Arm 2, study intervention will be pembrolizumab 200 mg IV Q3W.

After a screening period of up to 28 days, participants will be randomized 1:1 to Arm 1 or Arm 2. Participants may be treated for up to 35 cycles (approximately 24 months) after initiation of treatment with pembrolizumab alone or in combination with MK-1454. Discontinuation Follow-Up will be 30 days after the last dose.

Participants will be treated until PD, unacceptable toxicity, or other protocol-specified criterion for cessation of treatment, at which point they will be discontinued from the study intervention. Participants who discontinue study intervention will have posttreatment follow-up for disease status (including imaging) until PD, initiating a new anticancer therapy, withdrawing consent for study participation, or becoming lost to follow-up. This protocol does not allow participants to cross over to the other arm if they experience progression.

After confirmed PD, each participant will be followed up for safety at 30 days after the EOT, then will be contacted by telephone every 12 weeks (84±7 days) for survival until death, end of the study, withdrawal of consent to participate in the study, or becoming lost to follow-up, whichever occurs first.

The primary efficacy objective will be ORR based on the RECIST 1.1 as assessed by BICR. PFS and DOR based on RECIST 1.1 per BICR, and OS will be evaluated as secondary objectives. ORR, PFS, and DOR will also be assessed by iRECIST. Participants may continue to receive study intervention until tumor assessment is repeated 4 to 8 weeks later, in order to confirm PD by iRECIST per site assessment.

AEs will be evaluated by the investigator, according to criteria outlined in the NCI CTCAE, Version 5.0, to establish the safety and tolerability of MK-1454 when administered in monotherapy or in combination with pembrolizumab. Sponsor assessment of safety will be ongoing from the start of the study. Assessment of safety will be monitored continuously throughout this Phase 2 study, including ongoing frequent medical monitoring of AEs as they occur. SAEs will be followed until resolution, stabilization, until the event is otherwise explained, or the participant is lost to follow-up.

CCI

CCI

[redacted]

Specific procedures to be performed during the study, as well as their prescribed times and associated visit windows, are outlined in the SoA in Section 1.3. Details of each procedure are provided in Section 8.

4.2 Scientific Rationale for Study Design

The current study is randomized but is not blinded due to the unfavorable risk/benefit of injecting placebo saline into lesions of participants randomized to Arm 2, monotherapy pembrolizumab. Such risks include bleeding, infection, and injection site pain. BICR will be used for primary endpoints to minimize bias in ORR and PFS determinations. An IA will be performed after 70 participants (~35 in each arm) are enrolled and participants have at least 2 postbaseline scans.

4.2.1 Rationale for the Study and Selected Participant Population

Head and neck cancers are an anatomically heterogeneous group of cancers that arise most often from the oral cavity, oropharynx, hypopharynx, and larynx [Salazar, C. R., et al 2014]. Approximately 90% of all new cases are squamous cell carcinoma of the head and neck and HNSCC is the ninth leading cancer by incidence worldwide [Gupta, B., et al 2016]. Although the head and neck region contains a wide diversity of structures and cell types, the vast majority of head and neck cancers arise from the mucosa of the upper aerodigestive tract and are predominantly squamous cell in origin.

A large number of patients with head and neck cancer initially present with locally advanced, Stage III/IV disease that is initially treated with combinations of chemotherapy, radiation and/or surgery. This initial treatment is generally designated as “definitive” therapy, which typically combines chemoradiation and surgery and can result in disease control rates ranging between 33% to 86% of patients. Patients who progress after initial definitive therapy require subsequent treatment for recurrent disease. Patients who initially present with metastatic disease generally receive the same therapy as those with recurrent disease after definitive treatment. Together, patients with recurrent or metastatic disease receive the first-line chemotherapies.

In this study, participants with oropharynx cancer will be stratified by HPV status (positive or negative). HNSCC is based on HPV status, as HPV-positive and HPV-negative tumors are 2 different diseases, each with a distinct biology, clinical presentation, and prognosis [Price, K. A. 2012] [Dorsey, K. 2013]. Preliminary data of single-agent pembrolizumab in head and neck cancer patients in KEYNOTE-012 demonstrate efficacy in both HPV-positive and HPV-negative patients. Investigator site assessment of HPV using IHC staining for the p16 protein will be used for the participants with oropharyngeal cancer prior to randomization.

4.2.2 Rationale for Entry Criteria

4.2.2.1 Use of Combined Positive Scoring for PD-L1 Status

The CPS levels selected, CPS ≥1 for inclusion, and CPS ≥1 to <20 versus CPS ≥20 level for stratification, were selected based on prior experience in pembrolizumab studies. Biomarker results from KEYNOTE-012 and KEYNOTE-055 showed that inclusion of both tumor cells and inflammatory cells in IHC scoring CPS improves the ability to predict response based on PD-L1 status compared to tumor cells alone (TPS) in patients with recurrent/metastatic HNSCC.

Based on the results from the KEYNOTE-048 study in first-line recurrent/metastatic HNSCC, 85% of participants' tumors had PD-L1 expression levels of CPS ≥1 and 43% had CPS ≥20. Pembrolizumab significantly improved OS over the EXTREME regimen (cetuximab 400 mg/m^2 loading/250 mg/m^2 QW + cisplatin) in the PD-L1 CPS ≥20 and ≥1 populations and was noninferior in the total population with favorable safety. These results showed that CPS correlates with responsiveness to PD-1 inhibition and is a useful guide for the selection of treatment. This study will evaluate PD-L1 expression using a CPS ≥1 and ≥20, which balance all factors including positive predictive value, prevalence, and the biomarker specificity/sensitivity. This tissue sample will be analyzed using the IUO version of the US FDA-approved PD-L1 IHC 22C3 kit to confirm the PD-L1 CPS ≥1 status for eligibility and for stratification by CPS (≥1 to <20 vs ≥20). Randomization will be stratified according to CPS ≥1 and <20 versus CPS ≥20, and PD-L1 expression will be correlated with clinical outcome according to both IHC criteria.

4.2.2.2 Rationale for Minimum Creatinine Clearance

In preclinical studies with tritiated MK-1454, 20% and 28% of MK-1454-derived radioactivity (<5% as MK-1454) was renally excreted in dogs and rats, respectively, suggesting renal excretion is not a major component of MK-1454 clearance preclinically. Clinically, MK-1454 has been tested in combination with pembrolizumab at doses up to CCI MK-1454, without reaching MTD. This is a 3.7-fold margin compared to the proposed dose of CCI in the Phase 2 study. Therefore, including participants with creatinine clearance of ≥30 mL/min poses minimal safety risk based on available data [Kim, E. S., et al 2017]. Furthermore, MSD is collecting urine to measure renal clearance of MK-1454 in the clinic in the Phase 1 study to assess the impact on renal function. Historically, pembrolizumab clinical studies have included participants with creatine clearance of ≥30 mL/min, with no adverse outcomes. Pembrolizumab is an IgG4 monoclonal antibody. Therefore, it is not expected that pembrolizumab has significant renal clearance based on the large molecular weight. This rationale is confirmed by PK analysis in subjects with normal and impaired renal function which has evaluated the safety of pembrolizumab in participants with impaired renal function. Based on the population PK analysis, both clearance and exposure of pembrolizumab are similar regardless of renal impairment status based on eGFR. Evaluation of safety data indicates that the risk of AEs and AEOSIs in participants receiving pembrolizumab is not impacted by their renal function.

4.2.3 Rationale for Endpoints

4.2.3.1 Efficacy Endpoints

The efficacy objective of this study is to evaluate the antitumor activity of the MK-1454 and pembrolizumab combination. The primary efficacy endpoint will be ORR, as assessed by BICR, according to tumor response criteria. ORR is an acceptable measure of clinical benefit to demonstrate a new antineoplastic combination therapy. The use of BICR and RECIST 1.1 criteria to evaluate ORR is considered acceptable by regulatory authorities for this stage of development.

The secondary objectives include assessment of PFS, DOR, and OS.

Progression-free survival is an acceptable measure of clinical benefit for a study that demonstrates superiority of a new antineoplastic therapy, especially if the magnitude of the effect is large and the therapy has an acceptable risk/benefit profile. The use of BICR and RECIST 1.1 to assess PFS is typically considered acceptable by regulatory authorities. Images will be submitted to an iCRO and read by an independent central review blinded to treatment assignment to minimize bias in the response assessments. In addition, the final determination of radiologic progression will be based on the central assessment of progression, rather than a local site investigator/radiology assessment.

DOR per RECIST 1.1, assessed by BICR, will serve as an additional measure of efficacy and is a commonly accepted endpoint by both regulatory authorities and the oncology community.

The endpoint of OS is a standard for demonstrating superiority of antineoplastic therapy in clinical studies. Additionally, as seen in multiple studies with pembrolizumab, there is a proportion of patients who experience long-term benefit and are represented in the tail-end of the survival curve.

4.2.3.1.1 Response Rate Assessed by RECIST Version 1.1

RECIST 1.1 will be used to determine the objective response. Although RECIST 1.1 references a maximum of 5 target lesions in total and 2 per organ, MSD allows a maximum of 10 target lesions in total and 5 per organ, if clinically relevant, to enable a broader sampling of tumor burden.

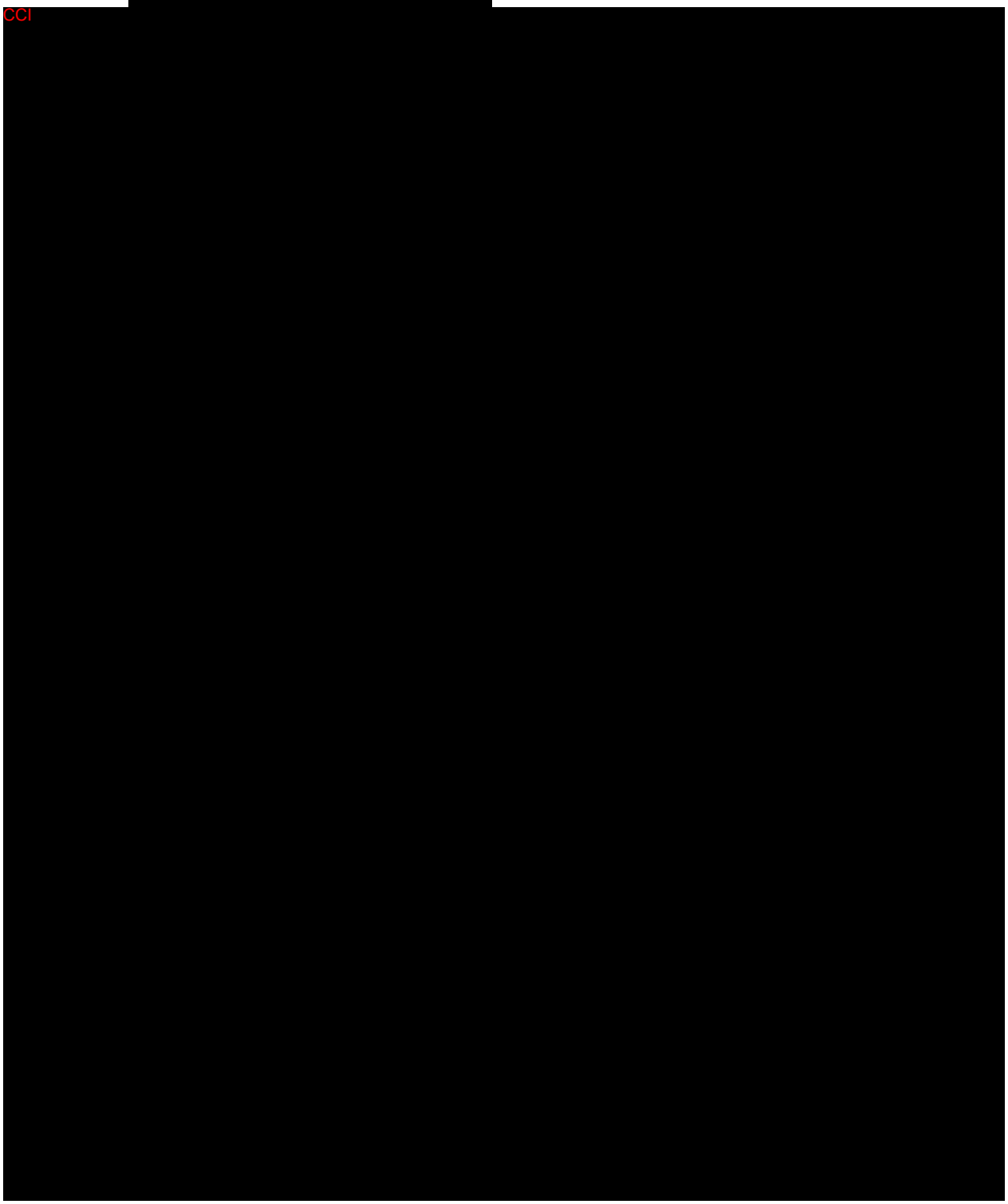
4.2.3.2 Safety Endpoints

The safety analysis will be based on participants who experience toxicities, as defined by CTCAE Version 5.0 criteria. Safety will be assessed by quantifying the toxicities and grades of toxicities experienced by participants who have received MK-1454 in combination with pembrolizumab versus pembrolizumab monotherapy.

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

4.2.3.3 CCI

CCI



CCI

[redacted]

4.2.3.6 CCI [redacted]

CCI [redacted]

4.2.4 Rationale for the Use of Comparator

The comparator, pembrolizumab 200 mg IV Q3W monotherapy, is currently approved for first-line treatment of patients with metastatic or with unresectable, recurrent HNSCC as monotherapy for patients whose tumors express PD-L1 (CPS ≥1) or in combination with platinum and fluorouracil regardless of PD-L1 expression.

4.3 Justification for Dose

4.3.1 Rationale for Dose of MK-1454

The recommended Phase 2 dose for MK-1454 was based on analysis of the safety, pharmacodynamic, and early efficacy data from Part I of the Phase 1 study (Section 2.2.3.1). In the Part 1 dose escalation, responses were observed at doses of CCI [redacted] CCI [redacted] and CCI [redacted] 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 [redacted] to CCI [redacted] compared to MK-1454 doses of CCI [redacted] to CCI [redacted] suggesting improved efficacy at the lower MK-1454 doses evaluated in the Phase 1 study. Pharmacodynamic analysis demonstrated nanostring gene signature and IP-10 dose-dependent increases, which peaked at CCI [redacted] and plateaued thereafter. The overall safety profile of MK-1454 was tolerable. Based on composite evaluation of safety, pharmacodynamic, and efficacy data, CCI [redacted] was selected as the recommended Phase 2 dose. To assure that the dose per lesion remains in the efficacious dose range when more than 1 lesion is injected per treatment visit, the total MK-1454 CCI [redacted] dose may be administered to a maximum of 3 lesions per treatment visit, with a minimum injectate volume of 1 mL to be injected in a single lesion, and a maximum injectate volume of 3 mL to be injected per participant per treatment visit.

4.4 Beginning and End of Study Definition

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

4.4.1 Clinical Criteria for Early Study Termination

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

5 STUDY POPULATION

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

5.1 Inclusion Criteria

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

Type of Participant and Disease Characteristics

1. Has histologically or cytologically confirmed diagnosis of metastatic or unresectable, recurrent HNSCC that is considered incurable by local therapies.

    - Has not had prior systemic therapy administered in the recurrent or metastatic setting. Systemic therapy, which was completed more than 6 months prior to signing consent, if given as part of multimodal treatment for locally advanced disease, is allowed.

    - The eligible primary tumor must be located in oropharynx, oral cavity, hypopharynx, or larynx. Participants may *not* have a primary tumor site of nasopharynx (any histology).

2. Has tumor PD-L1 expression of CPS ≥1.
   Note: Tumor tissue must be provided for PD-L1 biomarker analysis. An archival tissue sample is acceptable, otherwise a newly obtained biopsy may be obtained (please see the Procedures Manual for details).

3. Has measurable disease per RECIST 1.1, as assessed by BICR. Lesions situated in a previously irradiated area are considered measurable if progression has been demonstrated in such lesions.

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

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

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

5. Has an ECOG performance status of 0 or 1.

6. Demonstrates adequate organ function, as defined by Table 1.

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

Table 1 Adequate Organ Function

System	Laboratory Value
Hematological	
Absolute neutrophil count	≥1,500/µL
Platelets	≥100,000/µL
Hemoglobin	≥9 g/dL or ≥5.6 mmol/L[a]
Renal	
Creatinine **OR** CrCl (measured or calculated[b]) (GFR can also be used in place of CrCl)	≤1.5 × ULN **OR** ≥30 mL/min for participants with serum creatinine >1.5 × ULN [Kim, E. S., et al 2017]
Hepatic	
Total bilirubin (serum)	≤1.5 × ULN **or** Direct bilirubin ≤ ULN for participants with total bilirubin levels >1.5 × ULN
AST and ALT	≤2.5 × ULN **or** ≤5 × ULN for participants with liver metastases
Coagulation	
INR or PT PTT or aPTT	≤1.5 × ULN

Abbreviations: aPTT = activated partial thromboplastin time; ALT = Alanine aminotransferase; AST = aspartate aminotransferase; GFR = glomerular filtration rate; 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. Participants can be on stable dose of erythropoietin (≥ approximately 3 months).

[b] CrCl should be calculated per institutional standard.

7. Has results from testing of HPV status for oropharyngeal cancer defined as p16 IHC testing using CINtec® p16 Histology assay and a 70% cutoff point (please see the Procedures Manual for details). If HPV status was previously tested, then no additional testing is required.

    Note: Tumor p16 expression must be evaluated by assessment of IHC analysis with CINtec® p16 Histology assay (Ventana Medical Systems Inc., Tucson AZ) using "Benchmark Ultra" autostainer (Ventana, Tucson, AZ) and standard protocol. Positive p16 expression is defined as strong and diffuse nuclear and cytoplasmic staining in 70% or more of the tumor cells.

    Note: HPV stratification in this study in participants with oropharyngeal cancer will be performed according to HPV status using the specified method.

    Note: If local p16 testing results are not available, or cannot be assessed by the specified method, a tumor tissue sample must be submitted for p16 testing at the designated central laboratory.

    Note: Oral cavity, hypopharynx, and larynx cancer are not required to undergo HPV testing by p16 IHC as stratification by HPV status will only be assessed for oropharyngeal cancer. Other tumor locations are assumed to be HPV-negative for stratification purposes only.

Demographics

8. Is male or female, from 18 years to unlimited years of age inclusive, at the time of signing the informed consent.

Male Participants

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

9. Male participants are eligible to participate if they agree to the following during the intervention period with MK-1454 and for at least 120 days after the last dose of MK-1454:

- Refrain from donating sperm

    PLUS either:

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

    OR

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

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

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

  Note: Contraceptive requirements do not apply to participants taking pembrolizumab monotherapy.

Female Participants

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

- Is not a WOCBP

  OR

- Is a WOCBP and using a contraceptive method that is highly effective (with a failure rate of <1% per year), with low user dependency, or be abstinent from heterosexual intercourse as their preferred and usual lifestyle (abstinent on a long term and persistent basis), as described in Appendix [5] during the intervention period and for at least 120 days after the last dose of study intervention and agrees not to donate eggs (ova, oocytes) to others or freeze/store for her own use for the purpose of reproduction during this period. The investigator should evaluate the potential for contraceptive method failure (ie, noncompliance, recently initiated) in relationship to the first dose of study intervention.

- A WOCBP must have a negative highly sensitive pregnancy test (urine or serum) 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 Appendix [2].

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

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

Informed Consent

12. Has voluntarily agreed to participate by providing documented informed consent. The participant may also provide consent for FBR. However, the participant may participate in the main study without participating in FBR.

Additional Categories

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

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

    b) Have well-controlled HIV on anti-retroviral therapy, defined as:

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

        2) must have achieved and maintained virologic suppression, defined as confirmed HIV RNA level below 50 copies/mL or below the LLOQ using the locally available assay at the time of screening and for at least 12 weeks prior to screening;

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

5.2 Exclusion Criteria

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

Medical Conditions

1. Has disease that is suitable for local therapy administered with curative intent.

2. Has PD within 6 months of completion of curatively intended systemic treatment for locoregionally advanced HNSCC.

3. Has had chemotherapy or biological cancer therapy in the recurrent or metastatic setting for the treatment of HNSCC.

4. Has had radiation therapy (or other nonsystemic therapy) within 2 weeks prior to randomization or participant has not fully recovered (ie, ≤Grade 1 or at baseline) from AEs due to a previously administered treatment.

   Note: Subjects with ≤Grade 2 neuropathy, ≤Grade 2 alopecia, or laboratory values on Table 1 are an exception to this criterion and may qualify for the study.

   Note: If participant received major surgery, they must have recovered adequately from the toxicity and/or complications from the intervention prior to starting therapy.

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

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

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

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

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 and is allowed (prednisone ≤10 mg/day is acceptable). Use of nonsystemic steroids is permitted.

9. Has a diagnosis of immunodeficiency or is receiving systemic steroid therapy or any other form of immunosuppressive therapy within 7 days prior to the first dose of study treatment. Corticosteroid use as premedication for allergic reactions (eg, IV contrast) is allowed.

10. Has had an allogenic tissue/solid organ transplant.

11. Has a history of vasculitis.

12. Has a history of interstitial lung disease.

13. Has an active infection requiring systemic therapy.

14. Has a known history of active tuberculosis (TB; Bacillus tuberculosis).

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

16. Has had a severe hypersensitivity reaction to treatment a monoclonal antibody/components of the study intervention.

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

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

19. Has received prior therapy with an anti-PD-1, anti-PD-L1, or anti-PD-L2 agent or if the participant has previously participated in MSD MK-3475 clinical studies.

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

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

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

23. Is pregnant, breastfeeding, or expecting to conceive or father children within the projected duration of the study, starting with the Screening Visit through 120 days after the last dose of study intervention.

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

25. Has a tumor(s) in direct contact or encases a major blood vessel with or without ulceration and/or fungation onto the skin surface at the projected injection site in the head or neck.

26. Has a history of reirradiation for HNSCC at the projected injection site in the head and neck.

Prior/Concomitant Therapy

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

28. 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 mechanism of action of the study intervention. Participants 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.

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

Prior/Concurrent Clinical Study Experience

30. Is currently participating and receiving study therapy or has participated in a study of an investigational agent and received study therapy, or used an investigational device, any of which occurred within 4 weeks of the first dose of treatment. Note: Participation in the Follow-up Phase (receiving no study treatment) of a prior study is allowed.

5.3 Lifestyle Considerations

5.3.1 Meals and Dietary Restrictions

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

5.4 Screen Failures

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

Subjects may be rescreened after initially failing to meet the inclusion/exclusion criteria. Results from assessments performed during the initial screening period are acceptable in lieu of a repeat screening test if performed within the specified time frame and the inclusion/exclusion criteria are met. Subjects may be rescreened more than once at the discretion of the investigator.

5.5 Participant Replacement Strategy

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

6 STUDY INTERVENTION

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

Clinical supplies (study interventions provided by the Sponsor) will be packaged to support enrollment as required. Clinical supplies will be affixed with a clinical label in accordance with regulatory requirements.

6.1 Study Intervention(s) Administered

The study intervention(s) to be used in this study are outlined in Table 2.

Table 2 Study Interventions

Arm Name	Arm Type	Intervention Name	Type	Dose Formulation	Unit Dose Strength(s)	Dosage Level(s)	Route of Administration	Regimen/ Treatment Period/ Vaccination Regimen	Use	IMP/ NIMP	Sourcing
Arm 1	Experimental	Pembrolizumab	Drug	Solution for Infusion	100 mg /4 mL	200 mg	IV Infusion	200 mg IV Q3W	Experimental	IMP	Sponsor
Arm 1	Experimental	MK-1454	Drug	Sterile Solution	CCI mg/mL	CCI	Intratumoral	CCI IT Q1W × 6, then Q3W	Experimental	IMP	Sponsor
Arm 2	Active Comparator	Pembrolizumab	Drug	Solution for Infusion	100 mg /4 mL	200 mg	IV Infusion	200 mg IV Q3W	Experimental	IMP	Sponsor

IMP Investigational Medicinal Product; IV intravenous; NIMP Noninvestigational Medicinal Product; Q1W once each week; Q3W every 3 weeks.

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

All supplies indicated in Table 2 will be provided per the "Sourcing" column depending upon local country operational requirements. If local sourcing, every attempt should be made to source these supplies from a single lot/batch number where possible (eg, not applicable in the case where multiple lots or batches may be required due to the length of the study, etc.).

1. Refer to Section 8.1.8 for details regarding administration of the study intervention.

6.2 Preparation/Handling/Storage/Accountability

6.2.1 Dose Preparation

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

Each participant randomized to Arm 1 will receive a CCI dose of MK-1454 diluted in a volume of 1.0 mL to 3 mL of injectate. The volume of injectate delivered to each lesion will be based on the longest dimension of the lesion(s) intended for injection as shown in Table 3, and on the total number of lesions injected at the treatment visit. Injection of more than 1 lesion, if feasible, is suggested.

Regarding prioritization of lesions to be injected at a treatment visit, any new or progressing lesion should be prioritized first for injection, followed by injection of the largest lesion, with up to a total volume of injectate of 3 mL per treatment visit (Appendix 8).

A maximum of 3 lesions may be injected per treatment visit, with a minimum injectate volume of 1.0 mL (Table 4). The maximum total injectate volume per treatment visit per participant is 3 mL for all participants. Documentation of dose volume administered per lesion will be recorded. For image-guided procedures, document the needle tip within the lesion during IT injection. Detailed guidance on injectate volume and lesion injection is provided in the Procedures Manual.

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 3 and Table 4 for individual lesions may be permitted upon approval by the Sponsor Medical Monitor or designee.

Table 3 Determination of Intratumoral MK-1454 Injection Volume Per Lesion Based on Lesion Size

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

Table 4 Determination of Intratumoral MK-1454 Total Injectate Volume Based on Number of Lesions Injected Per Treatment Visit

Deliverable Volume		1 mL	2 mL	3 mL
Number of Lesions	1	1 × 1 mL	1 × 2 mL	1 × 3 mL
	2	NA	2 × 1 mL	1 × 1 mL + 1 × 2 mL
	3	NA	NA	3 × 1 mL

NA not applicable.

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

6.2.2 Timing of Study Interventions

Treatment cycles for this study are 21 days each cycle. All study interventions will begin after all predose study procedures and assessments have been completed, as detailed in Section 1.3. Every effort should be made to begin the first dose of study intervention on the day of randomization; however, if this is not achieved, study intervention is be initiated no later than 3 days from the date of randomization. All subsequent cycles of study intervention may be administered up to 3 days before or 3 days after the scheduled day due to administrative reasons per the investigator's judgment.

The reason for any variability in the administration of the study intervention(s) outside of the protocol-specified windows is to be documented in the participant's chart and recorded in the eCRFs.

6.2.2.1 Timing for Administration for MK-1454

MK-1454 will be administered as an IT injection on Day 1, Day 8, and Day 15 of the first 2 cycles (Q1W for Cycles 1 and 2), then on Day 1 of every 21-day cycle (Q3W) from Cycle 3 onward.

On days when both MK-1454 and pembrolizumab are to be administered, MK-1454 will be administered within 0.5 to 4 h after completion of the pembrolizumab IV infusion.

6.2.2.2 Timing for Administration of Pembrolizumab

Pembrolizumab will be administered as an IV infusion on Day 1 of each 21-day cycle after all predose study procedures and assessments have been completed, as detailed in Section 1.3.

The Pembrolizumab Pharmacy Manual contains specific instructions for dose preparation and administration.

6.2.3 Handling, Storage, and Accountability

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

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

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

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

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

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

6.3 Measures to Minimize Bias: Randomization and Blinding

6.3.1 Intervention Assignment

Intervention allocation will occur centrally using an IRT. There are 2 intervention arms. Participants will be randomized to 1 of 2 intervention arms: MK-1454 in combination with pembrolizumab (Arm 1) or pembrolizumab monotherapy (Arm 2).

6.3.2 Stratification

Intervention randomization will be stratified according to the following factors:

1. PD-L1 status (CPS ≥1 to <20 vs CPS ≥20)
2. ECOG performance status (0 vs 1)
3. HPV status (positive vs negative): HPV status for oropharynx cancer is determined by p16 IHC (positive vs negative); HPV status for participants without oropharynx cancer (eg, cancers of the oral cavity, hypopharynx and larynx) is considered HPV-negative.

6.3.3 Blinding

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

6.4 Study Intervention Compliance

Interruptions from the protocol-specified treatment plan for >12 weeks between MK-1454 or pembrolizumab doses for non drug-related or administrative reasons require consultation between the investigator and the Sponsor and written documentation of the collaborative decision on participant management.

6.5 Concomitant Therapy

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

6.5.1 Acceptable Concomitant Medications

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

All concomitant medications received within 30 days before the first dose of study intervention and up to 30 days after the last dose of study intervention should be recorded. Concomitant medications administered after 30 days after the last dose of study intervention should be recorded for SAEs and ECIs as defined in Section 8.4.

6.5.2 Prohibited Concomitant Medications

Participants are prohibited from receiving the following therapies during the Screening and Treatment Phases (including retreatment for post-CR relapse) of this study:

- Antineoplastic systemic chemotherapy or biological therapy
- Immunotherapy not specified in this protocol
- Chemotherapy not specified in this protocol
- Investigational agents other than pembrolizumab or MK-1454
- Radiation therapy

  Note: Radiation therapy to a symptomatic solitary lesion or to the brain may be considered on an exceptional case-by-case basis after consultation with Sponsor. The participant must have clear measurable disease outside the radiated field. Administration of palliative radiation therapy will be considered clinical progression for the purposes of determining PFS.

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

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

6.5.3 Supportive Care

Treatment guidelines for participants who experience drug-related AEs are provided in Section 6.6.

Participants should receive appropriate supportive care measures, as deemed necessary by the treating investigator including, but not limited to, the items outlined below:

- Nausea/vomiting: Nausea and vomiting should be treated aggressively, and consideration should be given in subsequent cycles to the administration of prophylactic antiemetic

therapy according to standard institutional practice. Participants should be strongly encouraged to maintain liberal oral fluid intake.

- Anemia: Transfusions and/or erythropoietin may be utilized as clinically indicated for the treatment of anemia but should be clearly noted as concomitant medications.
- Neutropenia: Prophylactic use of colony-stimulating factors including G-CSF, pegylated G-CSF, or GM-CSF is not allowed in this study. Therapeutic use of G-CSF is allowed in participants with Grade 3-4 febrile neutropenia.
- Thrombocytopenia: Transfusion of platelets may be used if clinically indicated. ITP should be ruled out before initiation of platelet transfusion.
- Anti-infectives: Participants with a documented infectious complication should receive oral or IV antibiotics or other anti-infective agents, as considered appropriate by the treating investigator for a given infectious condition, according to standard institutional practice.

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. Subsequently, all interventions, including continuation of study intervention, should be discussed with the Sponsor Clinical Director or designee.

6.6 Dose Modification (Escalation/Titration/Other)

6.6.1 Dose Modification due to Adverse Events

AEs (both nonserious and serious) associated with MK-1454 and/or pembrolizumab exposure may represent an immunologic etiology. These AEs may occur shortly after the first dose or several months after the last dose of treatment.

The CTCAE Version 5.0 must be used to grade the severity of AEs. The investigator may attribute each toxicity event to MK-1454 alone, to pembrolizumab alone, or to the combination, and modify the dose according to Table 5, Table 6, and Table 7. 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. If 1 (or more) treatment is held for toxicity, the schedule for restarting the agents should correspond with the next treatment cycle once the toxicity is resolved.

Holding of 1 treatment and not the other treatment is appropriate if, in the opinion of the investigator, the toxicity is clearly related to one of the study interventions. For example, in the combination arm (Arm 1), if MK-1454 is held due to an AE attributed to it, then pembrolizumab may continue to be administered. Appropriate documentation is required with regard to which treatment the investigator is attributing the AE. If, in the opinion of the investigator, the toxicity is related to the combination of 2 treatments, then both treatments should be held according to recommended dose modifications.

Participants may have only 1 dose modification of MK-1454 throughout the course of the study. If further toxicity occurs or the criteria for resuming treatment are not met, the participant must be discontinued from MK-1454. If a participant experiences several toxicities and there are conflicting recommendations, follow the most conservative recommendation.

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

6.6.1.1 Dose Modification for MK-1454

Guidelines for dose modification and/or treatment discontinuation for drug-related injection site reactions and for CRS AEs are provided in Table 5 and Table 6, respectively.

The investigator should first assess an AE to determine the CTCAE Version 5.0 severity grade. For AEs that are ≤ Grade 2, the decision to hold treatment is per medical assessment by the investigator. Once the AE has resolved to Grade 0 or 1, treatment with MK-1454 can be restarted. If the AE persists, discuss with the Sponsor with regard to selecting a different injection site or discontinuation. MK-1454 should be discontinued permanently following a severe or life-threatening AE.

In case toxicity does not resolve to Grade 0-1 within 12 weeks after last intervention, MK-1454 should be discontinued after consultation with the Sponsor.

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

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

Pembrolizumab treatment will be modified for the AEs described in Section 6.6.1.4.

6.6.1.1.1 Guidelines for Management of Intratumoral Injection Site Reactions

Guidelines for management of injection site reaction from intratumoral injection of MK-1454 are detailed in Table 5.

Table 5 Intratumoral Injection Site Reaction Management Guidelines

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 CCI and limit injections to mum 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 CCI 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.

AE adverse events; CTCAE Common Terminology Criteria for Adverse Events (Version 5.0); IT intratumoral; NCI National Cancer Institute.

6.6.1.1.2 Treatment for Cytokine Release Syndrome

CRS is defined in CTCAE Version 5.0 as a disorder characterized by nausea, headache, tachycardia, hypotension, rash, and shortness of breath. CRS occurs when lymphocytes (B cells, T cells, and/or natural killer cells) and/or myeloid cells (macrophages, dendritic cells, and monocytes) become activated and release inflammatory cytokines [Lee, D. W., et al 2014]. In addition to the symptomatology defined under CTCAE, CRS may present with fever, chills, myalgias, and malaise. Table 6 shows treatment guidelines for participants who experience CRS.

Table 6 Cytokine Release Syndrome Treatment Guidelines

NCI CTCAE Grade	MK-1454 Dose Modification	Treatment	Premedication at Subsequent Dosing
Grade 1 Mild reaction: Therapy interruption not indicated. Intervention not indicated.	No dose reduction warranted.	Increase monitoring of vital signs and oxygen saturation, as medically indicated, until the participant is deemed medically stable, in the opinion of the investigator.	None.
Grade 2 Therapy interruption indicated but responds promptly to symptomatic treatment (eg, NSAIDs, narcotics, IV fluids). Prophylactic medications indicated for ≤24 hours.	Per medical assessment of the investigator: • Consider holding dose until resolution to Grade 1 or baseline. • Consider decreasing dose of IT MK-1454 to [redacted] and limit injections to a maximum of 2 lesions per study visit. • If AE persists, discuss continuation with Sponsor.	Increase monitoring of vital signs and oxygen saturation, as medically indicated, until the participant is deemed medically stable, in the opinion of the investigator. Additional appropriate medical therapy may include, but is not limited to: IV fluids NSAIDs Acetaminophen Narcotics Oxygen Perform fever workup to exclude infectious etiologies; treat neutropenia if present.	Participant may be premedicated with acetaminophen 1.5 hours (± 30 minutes) prior to study intervention administration 500 to 1000 mg po (or equivalent dose of antipyretic).

NCI CTCAE Grade	MK-1454 Dose Modification	Treatment	Premedication at Subsequent Dosing
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).	• Hold dose until resolution to Grade 1 or baseline. • Decrease dose of IT MK-1454 to [CCI redacted] and limit injections to a maximum of 2 lesions per study visit. • If AE persists, discuss continuation with Sponsor.	Additional appropriate medical therapy may include, but is not limited to: IV fluids NSAIDS Acetaminophen Narcotics Oxygen Vasopressors Corticosteroids Anti-IL6 (eg, tocilizumab) Empiric antibiotics Participants with ≥ Grade 3 CRS need to be monitored very closely, likely in an intensive care setting.	For Grade 3 CRS, discuss with Sponsor prior to restart of study intervention. Upon approval by Sponsor, MK-1454 may be restarted at [CCI redacted] after AE resolves back to baseline or to Grade 1. Participant may be premedicated 1.5 hours(± 30 minutes) prior to study intervention administration with acetaminophen 500 to 1000 mg po (or equivalent dose of antipyretic).
Grade 4 Life-threatening consequences; pressor or ventilatory support indicated.	• Permanently discontinue IT MK 1454 treatment.	Additional appropriate medical therapy may include, but is not limited to: IV fluids NSAIDs Acetaminophen Narcotics Oxygen Vasopressors Corticosteroids Anti-IL6 (eg, tocilizumab) Empiric antibiotics Participants with ≥ Grade 3 CRS need to be monitored very closely, likely in an intensive care setting.	Permanently discontinue study intervention in participants who develop Grade 4 CRS.

AE adverse events; CRS cytokine release syndrome; CTCAE Common Terminology Criteria for Adverse Events (Version 5.0); IT intratumoral; IV intravenous; NCI National Cancer Institute; NSAID nonsteroidal anti inflammatory drug; po orally.

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

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

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

Dose Modification and Toxicity Management Guidelines for irAEs associated with pembrolizumab monotherapy, coformulations, or IO combinations are provided in Table 7.

Table 7 Dose Modification and Toxicity Management Guidelines for Immune-related Adverse Events Associated with Pembrolizumab Monotherapy, Coformulations or IO Combinations

General instructions:

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

irAEs	Toxicity Grade (CTCAE v5.0)	Action With Pembrolizumab Monotherapy, Coformulations or IO Combinations	Corticosteroid and/or Other Therapies	Monitoring and Follow-up
Pneumonitis	Grade 2	Withhold	• Administer corticosteroids (initial dose of 1 to 2 mg/kg prednisone or equivalent) followed by taper • Add prophylactic antibiotics for opportunistic infections	• Monitor participants for signs and symptoms of pneumonitis • Evaluate participants with suspected pneumonitis with radiographic imaging and initiate corticosteroid treatment
	Recurrent Grade 2, Grade 3 or 4	Permanently discontinue		
Diarrhea/Colitis	Grade 2 or 3	Withhold	• Administer corticosteroids (initial dose of 1 to 2 mg/kg prednisone or equivalent) followed by taper	• Monitor participants for signs and symptoms of enterocolitis (ie, diarrhea, abdominal pain, blood or mucus in stool with or without fever) and of bowel perforation (ie, peritoneal signs and ileus) • Participants with ≥Grade 2 diarrhea suspecting colitis should consider GI consultation and performing endoscopy to rule out colitis • Participants with diarrhea/colitis should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion
	Recurrent Grade 3 or Grade 4	Permanently discontinue		

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

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

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

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

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

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

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

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

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

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

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

Pembrolizumab may cause severe or life-threatening infusion-reactions including severe hypersensitivity or anaphylaxis. Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion. Dose modification and toxicity management guidelines on pembrolizumab associated infusion reaction are provided in Table 8.

Table 8 Pembrolizumab Infusion Reaction Dose Modification and Treatment Guidelines

NCI CTCAE Grade	Treatment	Premedication at Subsequent Dosing
Grade 1 Mild reaction; infusion interruption not indicated; intervention not indicated	Increase monitoring of vital signs, as medically indicated, until the participant is deemed medically stable, in the opinion of the investigator.	None.
Grade 2 Requires therapy or infusion interruption but responds promptly to symptomatic treatment (eg, antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for ≤24 h	**Stop Infusion.** Additional appropriate medical therapy may include but is not limited to: IV fluids Antihistamines NSAIDs Acetaminophen Narcotics Increase monitoring of vital signs, as medically indicated, until the participant is deemed medically stable, in the opinion of the investigator. If symptoms resolve within 1 hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (eg, from 100 mL/h to 50 mL/h). Otherwise, dosing will be held until symptoms resolve, and the participant should be premedicated for the next scheduled dose. Participants who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further study intervention treatment	Participant may be premedicated 1.5 h (± 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).
Grades 3 or 4 Grade 3: Prolonged (ie, not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (eg, renal impairment, pulmonary infiltrates) Grade 4: Life threatening; pressor or ventilatory support indicated	**Stop Infusion.** Additional appropriate medical therapy may include but is not limited to: Epinephrine** IV fluids Antihistamines NSAIDs Acetaminophen Narcotics Oxygen Pressors Corticosteroids Increase monitoring of vital signs, as medically indicated, until the participant is deemed medically stable, in the opinion of the investigator. Hospitalization may be indicated. **In cases of anaphylaxis, epinephrine should be used immediately. **Participant is permanently discontinued from further study intervention treatment.**	No subsequent dosing.

NCI CTCAE Grade	Treatment	Premedication at Subsequent Dosing
CTCAE Common Terminology Criteria for Adverse Events (Version 5.0); h hours; IV intravenous; NCI National Cancer Institute; NSAID nonsteroidal anti inflammatory drug; po orally. 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 CTCAE Version 5.0 at http://ctep.cancer.gov		

6.6.1.2.1 Other Allowed Dose Interruption(s) for Pembrolizumab

Pembrolizumab may be interrupted for situations other than treatment-related AEs, such as medical/surgical events or logistical reasons not related to study intervention. Participants should be placed back on study therapy within 3 weeks of the scheduled interruption, unless otherwise discussed with the Sponsor. The reason for interruption is to be documented in the participant's study record.

6.7 Intervention After the End of the Study

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

6.8 Clinical Supplies Disclosure

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

6.9 Standard Policies

Study site personnel will have access to a central electronic treatment allocation/randomization system (IRT system) to allocate subjects, to assign treatment to subjects and to manage the distribution of clinical supplies. Each person accessing the IRT 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.

7 DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT WITHDRAWAL

7.1 Discontinuation of Study Intervention

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

As certain data on clinical events beyond study intervention discontinuation may be important to the study, they must be collected through the participant's last scheduled follow-up, even if the participant has discontinued study intervention. Therefore, all participants who discontinue study intervention prior to completion of the protocol-specified treatment period will still continue to participate in the study as specified in Section 1.3 and Section 8.1.9, or if available, Protocol Clarification Letter.

Participants may discontinue study intervention at any time for any reason or be discontinued from the study intervention at the discretion of the investigator should any untoward effect occur. In addition, a participant may be discontinued from study intervention by the investigator or the Sponsor if study intervention is inappropriate, the study plan is violated, or for administrative and/or other safety reasons. Specific details regarding procedures to be performed at study intervention discontinuation are provided in Section 8.1.9.

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

- The participant or participant's legally acceptable representative requests to discontinue study intervention.
- The participant interrupts study intervention administration for more than 12 consecutive weeks.
- The participant has a medical condition or personal circumstance which, in the opinion of the investigator and/or Sponsor, placed the participant at unnecessary risk from continued administration of study intervention.
- The participant has a confirmed positive serum pregnancy test.
- Confirmed radiographic disease progression outlined in Section 8.2 (exception if the Sponsor approves treatment continuation).
- Progression or recurrence of any malignancy, or any occurrence of another malignancy that requires active treatment.
- Any study-intervention-related toxicity specified as a reason for permanent discontinuation in the guidelines for dose modification due to AEs in Section 6.6.
- Intercurrent illness other than another malignancy, as noted above, that prevents further administration of treatment.
- Investigator's decision to discontinue treatment.
- Completion of 35 treatments with pembrolizumab.

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

  Side effects and/or concomitant medications required for treatment of HIV and/or its complications that are incompatible with continued study treatment (Exceptions are permissible but should be discussed with the Sponsor.).

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

7.2 Participant Withdrawal From the Study

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

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

Specific details regarding procedures to be performed at the time of withdrawal from the study, as well as specific details regarding withdrawal from FBR, are outlined in Section 8.1.9. The procedures to be performed should a participant repeatedly fail to return for scheduled visits and/or if the study site is unable to contact the participant are outlined in Section 7.3.

7.3 Lost to Follow-up

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

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

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

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

8 STUDY ASSESSMENTS AND PROCEDURES

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

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

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

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

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

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

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

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

8.1 Administrative and General Procedures

8.1.1 Informed Consent

The investigator or medically qualified designee (consistent with local requirements) must obtain documented consent from each potential participant or each participant's legally acceptable representative prior to participating in a clinical study or 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 consent is in place.

8.1.1.1 General Informed Consent

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

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

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

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

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

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

8.1.1.2 Consent and Collection of Specimens for Future Biomedical Research

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

8.1.2 Inclusion/Exclusion Criteria

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

8.1.3 Participant Identification Card

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

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

8.1.4 Medical History

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

8.1.5 Prior and Concomitant Medications Review

8.1.5.1 Prior Medications

The investigator or qualified designee will review prior medication use, including any protocol-specified washout requirement, and record prior medication taken by the participant within 28 days before administration of the first dose of study medication. Details regarding prior treatments for head and neck cancer will be recorded separately.

8.1.5.2 Concomitant Medications

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

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

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

8.1.6 Assignment of Screening Number

All consented participants will be given a unique screening number that will be used to identify the participant for all procedures that occur prior to randomization. Each participant will be assigned only 1 screening number. Screening numbers must not be re-used for different participants.

8.1.7 Assignment of Treatment/Randomization Number

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

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

8.1.8 Study Intervention Administration

For infusion:

Pembrolizumab 200 mg will be administered in 30 minutes, with a window of -5 minutes and +10 minutes, as an IV infusion on Day 1 of each 21-day cycle. Do not administer pembrolizumab as an IV push nor as a bolus injection. Administration of study medication

will be monitored by the investigator and/or study staff. The total volume of study intervention infused will be compared to the total volume prepared to determine compliance with each dose administered. Please refer to the pembrolizumab (MK-3475) Pharmacy Manual.

For IT injection:

Refer to Section 6 for MK-1454 dose and treatment details, and to the SoA (Section 1.3) for timing of IT injections. Guidelines for prioritization of lesions for IT injection are provided in Appendix 8.

8.1.8.1 Timing of Dose Administration

See the SoA in Section 1.3.

8.1.9 Discontinuation and Withdrawal

Participants who discontinue study intervention prior to completion of the treatment period should be encouraged to continue to be followed for all remaining study visits as outlined in the SoA and Section 8.10.3.

When a participant withdraws from participation in the study, all applicable activities scheduled for the End of Treatment/Discontinuation visit should be performed (at the time of withdrawal). Any AEs that are present at the time of withdrawal should be followed in accordance with the safety requirements outlined in Section 8.4.3.

8.1.9.1 Withdrawal From Future Biomedical Research

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

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

8.1.10 Participant Blinding/Unblinding

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

8.1.11 Calibration of Equipment

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

8.2 Efficacy/Immunogenicity Assessments

8.2.1 Tumor Imaging and Assessment of Disease

Tumor imaging should be acquired by CT (strongly preferred). MRI should be used when CT is contraindicated or for imaging of the brain. The same imaging technique, ie, modality and use of contrast, should be used for a participant throughout the study to optimize the visualization of existing and new tumor burden. Required anatomical images, as well as the process for image collection and transmission to the iCRO, can be found in the Site Imaging Manual.

8.2.2 Initial Tumor Imaging

The process for image collection and transmission to the central vendor can be found in the Site Imaging Manual. Tumor imaging may be performed by CT (preferred) or MRI; however, the same imaging technique should be used on a participant throughout the study. CT scan is the more commonly used modality and is preferred for the majority of subjects. An MRI can be utilized, if clinically appropriate.

Imaging should include the head and neck, chest, and abdomen at all timepoints specified in the Study Flow Chart. Imaging of the pelvis is optional. For an individual participant, imaging should be consistent at all timepoints, (ie, follow-up imaging should cover the same areas as the baseline area, using the same imaging modality).

Initial tumor imaging at screening must be performed within 28 days prior to the date of allocation. The screening imaging must be submitted to the iCRO for confirmation of measurable disease per RECIST 1.1 for eligibility prior to randomization. Tumor imaging performed as part of routine clinical management is acceptable for use as screening tumor imaging if they are of diagnostic quality and performed within 28 days prior to the date of randomization.

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

carcinomatous meningitis, as participants with carcinomatous meningitis are excluded regardless of clinical stability.

8.2.3 Tumor Imaging During the Study

The first on-study imaging assessment should be performed at 6 weeks (42-49 days) from the date of first dose. Subsequent tumor imaging should be performed every 6 weeks (42 days ±7 days) (or more frequently if clinically indicated). After 1 year, participants who remain on treatment will have imaging performed every 9 weeks (63 days ±7 days). Imaging timing should follow **calendar days** and should not be adjusted for delays in cycle starts. Imaging should continue to be performed until disease progression is identified by the investigator, the start of new anticancer treatment, withdrawal of consent, or death, or notification by the Sponsor, whichever occurs first. All supplemental imaging must be submitted to the iCRO.

Objective response should be confirmed by a repeat imaging assessment. Tumor imaging to confirm PR or CR should be performed at least 4 weeks after the first indication of response is observed. Participants will then return to regularly scheduled imaging, starting with the next scheduled imaging time point. Participants who receive additional imaging for confirmation do not need to undergo the next scheduled tumor imaging if it is less than 4 weeks later; tumor imaging may resume at the subsequent scheduled imaging time point. Note: Response does not typically need to be verified in real time by the BICR.

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

8.2.4 End of Treatment and Follow-up Tumor Imaging

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

For participants who discontinue study intervention without documented disease progression, every effort should be made to continue monitoring their disease status by tumor imaging using the same imaging schedule used while on treatment (every 6 weeks in Year 1 or 9 weeks after Year 1). Monitor disease status until the start of a new anticancer treatment, disease progression, pregnancy, death, withdrawal of consent, or the end of the study, whichever occurs first.

8.2.5 iRECIST 1.1 Assessment of Disease

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

For participants who show evidence of radiological PD by RECIST 1.1 as determined by the investigator, the investigator will decide whether to continue a participant on study intervention until repeat imaging is obtained using iRECIST for participant management (see Table 9 and Figure 3). This decision by the investigator should be based on the participant's overall condition.

Clinical stability is defined as the following:

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

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

If the investigator decides to continue treatment, the participant may continue to receive study intervention and the tumor assessment should be repeated 4 to 8 weeks later to confirm PD by iRECIST per investigator assessment. Images should continue to be sent in to the central imaging vendor for potential retrospective BICR.

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

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

- Development of new lesion(s)

iRECIST defines new response categories, including iUPD (unconfirmed progressive disease) and iCPD (confirmed progressive disease). For purposes of iRECIST assessment, the first visit showing progression according to RECIST 1.1 will be assigned a visit (overall) response of iUPD, regardless of which factors caused the progression.

At this visit, target and nontarget lesions identified at baseline by RECIST 1.1 will be assessed as usual.

New lesions will be classified as measurable or nonmeasurable, using the same size thresholds and rules as for baseline lesion assessment in RECIST 1.1. From measurable new lesions, up to 5 lesions total (up to 2 per organ), may be selected as New Lesions Target. The sum of diameters of these lesions will be calculated, and kept distinct from the sum of diameters for target lesions at baseline. All other new lesions will be followed qualitatively as New Lesions Nontarget.

Assessment at the Confirmatory Imaging

On the confirmatory imaging, the participant will be classified as progression confirmed (with an overall response of iCPD), or as showing persistent unconfirmed progression (with an overall response of iUPD), or as showing disease stability or response (iSD/iPR/iCR).

Confirmation of Progression

Progression is considered confirmed, and the overall response will be iCPD, if ANY of the following occurs:

- Any of the factors that were the basis for the initial iUPD show worsening:
    - For target lesions, worsening is a further increase in the sum of diameters of ≥5 mm, compared to any prior iUPD time point
    - For nontarget lesions, worsening is any significant growth in lesions overall, compared to a prior iUPD time point; this does not have to meet the “unequivocal” standard of RECIST 1.1
    - For new lesions, worsening is any of these:
        - An increase in the new lesion sum of diameters by ≥5 mm from a prior iUPD time point
        - Visible growth of new nontarget lesions
        - The appearance of additional new lesions
- Any new factor appears that would have triggered PD by RECIST 1.1

Persistent iUPD

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

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

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

Resolution of iUPD

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

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

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

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

Management Following the Confirmatory Imaging

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

Note: If a participant has confirmed radiographic progression (iCPD) as defined above, but the participant is achieving a clinically meaningful benefit, an exception to continue treatment may be considered following consultation with the Sponsor. In this case, if study intervention is continued, tumor imaging should continue to be performed following the intervals as outlined in Section 1.3 and submitted to the central imaging vendor.

Detection of Progression at Visits after Pseudoprogression Resolves

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

- Target lesions
    - Sum of diameters reaches the PD threshold (20% and 5 mm increase from nadir) either for the first time, or after resolution of previous pseudoprogression. The nadir is always the smallest SOD seen during the entire study, either before or after an instance of pseudoprogression.
- Nontarget lesions
    - If nontarget lesions have never shown unequivocal progression, their doing so for the first time results in iUPD
    - If nontarget lesions had shown previous unequivocal progression, and this progression has not resolved, iUPD results from any significant further growth of nontarget lesions, taken as a whole
- New lesions
    - New lesions appear for the first time
    - Additional new lesions appear
    - Previously identified new target lesions show an increase of ≥5 mm in the new lesion sum of diameters, from the nadir value of that sum
    - Previously identified nontarget lesions show any significant growth

If any of the events above occur, the overall response for that visit is iUPD, and the iUPD evaluation process (see Assessment at the Confirmatory Imaging above) is repeated. Progression must be confirmed before iCPD can occur.

The decision process is identical to the iUPD confirmation process for the initial PD, with one exception: if new lesions occurred at a prior instance of iUPD, and at the confirmatory imaging the burden of new lesions has increased from its smallest value (for new target lesions, the sum of diameters is ≥5 mm increased from its nadir), then iUPD cannot resolve to iSD or iPR. It will remain iUPD until either a decrease in the new lesion burden allows resolution to iSD or iPR, or until a confirmatory factor causes iCPD. If any of the factors above indicate iUPD, the iUPD evaluation process repeats, just as on the first occurrence of iUPD.

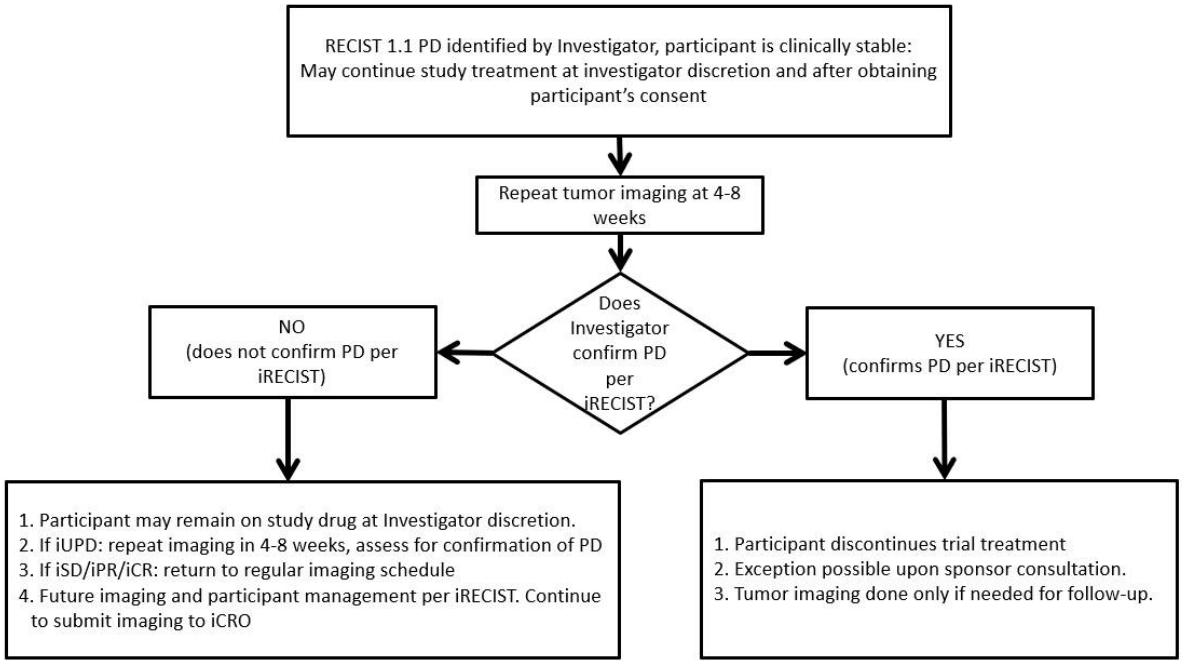
Additional details about iRECIST are provided in the iRECIST publication.

Table 9 Imaging and Treatment after First Radiologic Evidence of Progressive Disease

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

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

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



iCRO = imaging contract research organization; iCR = immune complete response; iPR = immune partial response; iSD = immune stable disease; iUPD = immune unconfirmed progressive disease; PD = progressive disease; iRECIST = Response Evaluation Criteria in Solid Tumors 1.1 for immune-based therapeutics; RECIST = Response Evaluation Criteria in Solid Tumors

8.2.6 itRECIST

itRECIST is a response assessment that is tailored to intratumoral immunotherapy, is aligned with RECIST 1.1 overall response assessment [Goldmacher, G. V., et al 2020], and is further described in Section 10.10.

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 intratumoral immunotherapy (an example is provided in Figure 8)
- provides guidelines on prioritization of lesion injection during the course of intratumoral immunotherapy (see Section 10.8)

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

8.2.7 Eastern Cooperative Oncology Group Performance Scale

The investigator or qualified designee will assess ECOG status (Appendix 9), prior to the administration of study intervention on Day 1 of each cycle at the timepoints identified in the SoA.

8.3 Safety Assessments

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

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

8.3.1 Physical Examinations

Physical examinations (full or directed) will be conducted by an investigator or medically qualified designee (consistent with local requirements) as per institutional standard. The time points for full physical examinations are described in Section 1.3.

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

8.3.1.1 Full Physical Examination

The investigator or qualified designee will perform a complete physical examination during the screening period. Height and weight will also be measured and recorded. Clinically significant abnormal findings should be recorded as medical history. After the first dose of study intervention, new clinically significant abnormal findings should be recorded as AEs.

8.3.1.2 Directed Physical Examination

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

8.3.2 Vital Signs

The investigator or qualified designee will take vital signs at screening, prior to the administration of each dose of study intervention and during the follow-up period as specified in the SoA. Vital signs include heart rate, respiratory rate, 0_2 saturation, blood pressure, and temperature.

8.3.3 Electrocardiograms

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

8.3.4 Clinical Safety Laboratory Assessments

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

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

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

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

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

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

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

Laboratory tests for screening should be performed within 7 days prior to the first dose of study intervention. An exception is hepatitis and thyroid serologies, which may be performed within 28 days prior to first dose. After Cycle 1, predose laboratory safety tests can be conducted up to 72 hours prior to dosing unless otherwise noted on the flow charts.

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

8.3.4.2 Pregnancy Test

All women who are being considered for participation in the study, and who are not surgically sterilized or postmenopausal, must be tested for pregnancy within 24 hours of the first dose of study medication on C1D1 and 30 days posttreatment. Additional pregnancy testing can be conducted if required by local regulations or if clinically indicated. If a urine test is positive or not evaluable, a serum test will be required. Participants must be excluded/discontinued from the study in the event of a positive or borderline-positive test result. Refer to Appendix 7 for country-specific requirements.

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

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

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

The investigator and any designees are responsible for detecting, documenting, and reporting events that meet the definition of an AE or SAE as well as other reportable safety events. Investigators remain responsible for following up AEs, SAEs, and other reportable safety events for outcome according to Section 8.4.3.

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

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

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

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

- All pregnancies and exposure during breastfeeding, from the time of intervention randomization through 120 days following cessation of study intervention, or 30 days following cessation of study intervention if the participant initiates new anticancer therapy must be reported by the investigator.
- Additionally, any SAE brought to the attention of an investigator at any time outside of the time period specified above must be reported immediately to the Sponsor if the event is considered related to study intervention.

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

All initial and follow-up AEs, SAEs, and other reportable safety events will be recorded and reported to the Sponsor or designee within the time frames as indicated in Table 10.

Table 10 Reporting Time Periods and Time Frames for Adverse Events and Other Reportable Safety Events

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

Type of Event	Reporting Time Period: Consent to Randomization/ Allocation	Reporting Time Period: Randomization/ Allocation through Protocol-specified Follow-up Period	Reporting Time Period: After the Protocol-specified Follow-up Period	Time Frame to Report Event and Follow-up Information to Sponsor:
Event of Clinical Interest (ECI) (require regulatory reporting)	Report if: - due to intervention - causes exclusion	Report - potential drug-induced liver injury (DILI) - require regulatory reporting	Not required	Within 24 hours of learning of event
Event of Clinical Interest (do not require regulatory reporting)	Report if: - due to intervention - causes exclusion	Report - non-DILI ECIs and those not requiring regulatory reporting	Not required	Within 5 calendar days of learning of event

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

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

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

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

8.4.4 Regulatory Reporting Requirements for SAE

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

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

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

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

8.4.5 Pregnancy and Exposure During Breastfeeding

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

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

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

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

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

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

8.4.7 Events of Clinical Interest

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

Events of clinical interest for this study include:

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

2. An elevated AST or ALT lab value that is greater than or equal to 3 × ULN and an elevated total bilirubin lab value that is greater than or equal to 2 × ULN and, at the same time, an alkaline phosphatase lab value that is less than 2 × 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 study site guidance for

assessment and follow-up of these criteria can be found in the Investigator Study File Binder (or equivalent).

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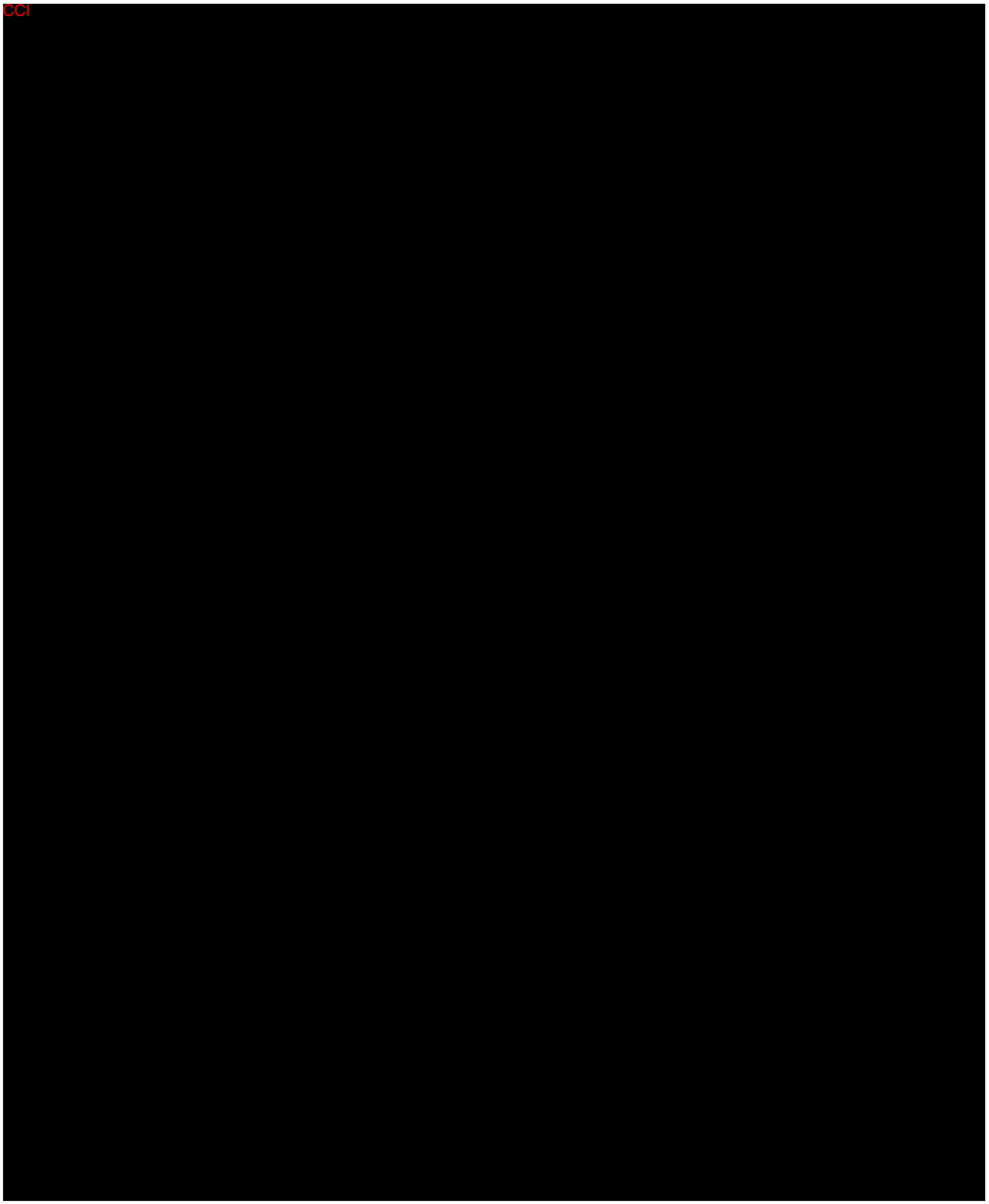

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[redacted]

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[redacted]

8.10 Visit Requirements

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

8.10.1 Screening

Approximately 28 days prior to treatment randomization, potential participants will be evaluated to determine that they fulfill the entry requirements as set forth in Section 5.

Subjects may be rescreened after initially failing to meet the inclusion/exclusion criteria. Results from assessments performed during the initial screening period are acceptable in lieu of a repeat screening test if performed within the specified time frame and the inclusion/exclusion criteria are met.

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

- Laboratory tests are to be performed within 7 days prior to the first dose of study intervention. An exception is hepatitis and thyroid function testing, which may be done up to 28 days prior to the first dose of study intervention.
- Evaluation of ECOG is to be performed within 7 days prior to the first dose of study intervention.
- For women of reproductive potential, a urine or serum pregnancy test will be performed within 24 hours prior to the first dose of study intervention. If urine pregnancy results cannot be confirmed as negative, a serum pregnancy test will be required (performed by the local study site laboratory). Refer to Appendix 7 for country-specific requirements.
- Tumor tissue testing for PD-L1 status (all participants) and HPV status (oropharyngeal cancer participants) are required for stratification prior to randomization. The sample should be sent to the central laboratory at least 14 days prior to randomization, unless testing locally (see Procedures Manual for details regarding tumor tissue collection). If testing locally, or reporting HPV status by history, tumor p16 expression must be evaluated by assessment of IHC analysis with CINtec® p16 Histology assay (Ventana Medical Systems Inc., Tucson AZ) using the “Benchmark Ultra” autostainer (Ventana, Tucson, AZ) and standard protocol.

8.10.2 Treatment Period Visit

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

8.10.3 Discontinued Participants Continuing to be Monitored in the Study

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

8.10.3.1 Safety Follow-up Visit

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

All AEs that occur prior to the Safety Follow-up Visit should be recorded up to 30 days following EOT.

8.10.3.2 Imaging Follow-up Visits

Participants who discontinue study intervention for reasons other than documented PD should continue with imaging assessments per the protocol-defined schedule until: (1) PD is assessed by the investigator, (2) initiation of a new anticancer treatment, (3) death, (4) withdrawal of consent, or (5) study conclusion or early termination, whichever occurs first.

8.10.3.3 Survival Follow-up Visits

Participants who experience confirmed PD 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.

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

9 STATISTICAL ANALYSIS PLAN

This section outlines the statistical analysis strategies and procedures for the primary and secondary analyses of the study. Exploratory and other nonconfirmatory analyses will be outlined in a separate sSAP.

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

CCI

9.1 Statistical Analysis Plan Summary

Key elements of the SAP are summarized. The comprehensive plan is provided in Sections 9.2 through 9.12.

Study Design Overview	This is a randomized, active-controlled, parallel group, multicenter, open-label, Phase 2 study of IT MK-1454 in combination with pembrolizumab IV versus pembrolizumab IV monotherapy in participants with a histologically or cytologically confirmed diagnosis of metastatic, or unresectable, recurrent HNSCC with a tumor CPS ≥1 as first-line therapy.
Intervention Assignment	Approximately 200 participants will be randomized in a 1:1 ratio to Arm 1 (IT MK-1454 plus pembrolizumab IV) and Arm 2 (pembrolizumab IV). The stratification factors are PD-L1 expression level defined by CPS (≥1 to <20 vs ≥20), ECOG performance status (0 versus 1) and HPV status (positive, negative for participants with oropharyngeal cancer).
Analysis Populations	Efficacy (Primary and Secondary): ITT Safety (Secondary): APaT
Primary Endpoint(s)	OR is a confirmed CR or PR) by RECIST 1.1 as assessed by BICR.
Secondary Endpoints	• PFS by RECIST 1.1 as assessed by BICR • DOR by RECIST 1.1 as assessed by BICR • OS • AEs • Discontinuing study intervention due to AE

Statistical Methods for Key Efficacy Analyses	The dual primary hypotheses comparing Arm 1 to Arm 2 for participants with CPS ≥1 and CPS ≥20 with regard to ORR will be evaluated using the stratified Miettinen and Nurminen method [Miettinen, O. and Nurminen, M. 1985]. The difference in ORR will be estimated using the stratified Miettinen and Nurminen method with strata weighting by sample size.
Statistical Methods for Key Safety Analyses	The analysis of safety results will follow a tiered approach for the comparison of Arm 1 versus Arm 2. The tiers differ with respect to the analyses that will be performed. There is no Tier 1 safety endpoint for this study. Tier 2 parameters will be assessed via point estimates with 95% CIs provided for between-arm comparisons; only point estimates by treatment arm are provided for Tier 3 safety parameters. The 95% CIs for the between-treatment differences in percentages will be provided using the Miettinen and Nurminen method [Miettinen, O. and Nurminen, M. 1985].
Interim Analyses	CCI [redacted]
Multiplicity	The overall type I error rate for the primary endpoint (OR) CCI [redacted] will be strongly controlled at α =2.5% (one-sided) [Chen, C., et al 2018]. CCI [redacted] CCI [redacted] α=1% (one-sided) will be allocated to ORR in participants with CPS ≥1 and α=1.5% (one-sided) will be allocated to ORR in participants with CPS ≥20. The graphical approach of Maurer and Bretz [Maurer, W. and Bretz, F. 2013] will be applied to reallocate alpha between the dual primary hypotheses if either primary hypothesis is rejected. CCI [redacted]

Sample Size and Power	The overall sample size will be approximately CCI 200, CCI CCI CCI CCI it provides approximate 84.0% power to detect a 21% difference in ORR (40% in Arm 1 versus 19% in Arm 2) at the type I error of 1% (one-sided) for participants with CPS ≥1. Based on MK-3475 KN048 data, the prevalence rate of the participants with CPS≥20 among participants with CPS ≥1 is assumed to be 50%. With 50 participants per arm, the study has approximately 86.3% power to detect a 31% difference in ORR (55% in Arm 1 versus 24% in Arm 2) at the type I error of 1.5% (one-sided) for participants with CPS ≥20. It has approximately 91.5% power to show that Arm 1 is superior to Arm 2 in at least 1 population (participants with CPS ≥1 or participants with CPS ≥20) at an overall type I error of 2.5% (one-sided). CCI

9.2 Responsibility for Analyses/In-house Blinding

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

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

Although the study is an open-label study, analyses or summaries generated by randomized treatment assignment, and actual treatment received will be limited and documented. Further documentation will be provided in the sSAP. In addition, independent radiologist(s) will perform the central imaging review without knowledge of treatment assignments.

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9.3 Hypotheses/Estimation

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

9.4 Analysis Endpoints

9.4.1 Efficacy/Immunogenicity/Pharmacokinetics Endpoints

Primary Efficacy Endpoint

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

Secondary Efficacy Endpoints

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

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

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

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9.4.2 Safety Endpoints

Safety endpoint is the number/proportion of participants with AEs, and who discontinue study treatment due to AEs. In addition, safety and tolerability will be assessed by clinical review of all relevant parameters including AEs, laboratory tests, and vital signs.

A description of safety measures is provided in Section 8.3 Safety Assessments.

9.5 Analysis Populations

9.5.1 Efficacy Analysis Populations

The analyses of efficacy endpoints (ORR, PFS, and OS) are based on the ITT population. All randomized participants will be included in this population. Participants will be analyzed in the treatment arm to which they are randomized. For the analysis of DOR, only participants with a CR or PR in the ITT population will be included.

A supportive approach using a modified ITT population may be performed for the efficacy endpoints. The modified ITT population consists of all randomized participants who receive scheduled treatments without substantial dose interruption as defined in the sSAP. These details will be documented in the sSAP.

9.5.2 Safety Analysis Populations

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

At least 1 laboratory or vital sign measurement obtained 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.

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9.6 Statistical Methods

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

9.6.1 Statistical Methods for Efficacy Analysis

Efficacy results that will be deemed to be statistically significant after consideration of the Type I error control strategy are described in Section 9.8. Nominal *p*-values will be computed for other efficacy analyses but should be interpreted with caution due to potential issues of multiplicity. For the stratified analyses, if the number of participants or events in a cell is small, the stratification factor(s) may be removed.

9.6.1.1 Objective Response

The stratified Miettinen and Nurminen method [Miettinen, O. and Nurminen, M. 1985] will be used for the ORR comparison (Arm 1 vs Arm 2) in participants with CPS ≥1 and in participants with CPS ≥20. The difference in ORR, 95% CI and p-values from the stratified

Miettinen and Nurminen method [Miettinen, O. and Nurminen, M. 1985] with strata weighting by sample size will be reported. The stratification factor used for randomization (Section 6.3.2) will be applied to the analysis. In the IA for continuing enrollment decision-making, the stratification will be based on PD-L1 CPS (≥1 to <20 vs ≥20). Sensitivity analyses will be performed for comparison of ORR based on the investigator's assessment.

9.6.1.2 Progression-free Survival

The nonparametric Kaplan-Meier method [Kaplan, E. L. 1958] will be used to estimate the PFS curve for each treatment group in participants with CPS ≥1 and in participants with CPS ≥20. The treatment difference in PFS will be assessed by the stratified log-rank test. A stratified Cox proportional hazard model [Cox, D. R. 1972] with Efron's method [Efron, B. 1977] of tie handling will be used to assess the magnitude of the treatment difference (ie, the HR) between the treatment arms. The HR and its 95% CI from the stratified Cox model with Efron's method of tie handling and with a single treatment covariate will be reported. The stratification factor used for randomization (Section 6.3.2) will be applied to both the stratified log-rank test and the stratified Cox model.

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

In order to evaluate the robustness of the PFS endpoint per RECIST 1.1 by BICR, 1 primary and 2 sensitivity analyses with a different set of censoring rules will be performed. For the primary analysis, if the events (PD or death) are immediately after more than 1 missed disease assessment, the data are censored at the last disease assessment prior to the missed visits. Also, data after new anticancer therapy are censored at the last disease assessment prior to the initiation of new anticancer therapy. The first sensitivity analysis follows the ITT principle. That is, PDs/deaths are counted as events regardless of missed study visits or initiation of new anticancer therapy. The second sensitivity analysis considers initiation of new anticancer treatment or discontinuation of treatment due to reasons other than CR to be a PD event for participants without documented PD or death. If a participant meets multiple criteria for censoring, the censoring criterion that occurs earliest will be applied. The censoring rules for primary and sensitivity analyses are summarized in Table 11.

In case there is an imbalance between the treatment groups on disease assessment schedules or censoring patterns, we may also perform a sensitivity analysis for PFS using interval censored data [Finkelstein, D. M. 1986], which modifies the Cox proportional hazard model for interval censored data. The interval will be constructed so that the left endpoint is the date of the last disease assessment without documented PD and the right endpoint is the date of documented PD or death, whichever occurs earlier.

Table 11 Censoring Rules for Primary and Sensitivity Analyses of PFS

Situation	Primary Analysis	Sensitivity Analysis 1	Sensitivity Analysis 2
PD or death documented after ≤1 missed disease assessment, and before new anticancer therapy, if any	Progressed at date of documented PD or death	Progressed at date of documented PD or death	Progressed at date of documented PD or death
PD or death documented immediately after ≥2 consecutive missed disease assessments or after new anticancer therapy, if any	Censored at last disease assessment prior to the earlier date of ≥2 consecutive missed disease assessments and new anticancer therapy, if any	Progressed at date of documented PD or death	Progressed at date of documented PD or death
No PD and no death; new anticancer treatment is not initiated	Censored at last disease assessment	Censored at last disease assessment	Progressed at treatment discontinuation due to reasons other than CR; otherwise censored at last disease assessment if participant is still receiving study treatment or has completed study treatment
No PD and no death; new anticancer treatment is initiated	Censored at last disease assessment before new anticancer treatment	Censored at last disease assessment	Progressed at date of new anticancer treatment

PD progressive disease; PFS progression free survival.

9.6.1.3 Overall Survival

The nonparametric Kaplan-Meier method [Kaplan, E. L. 1958] will be used to estimate the survival curves. The treatment difference in survival will be assessed by the stratified log-rank test in participants with CPS ≥1 and in participants with CPS ≥20. A Cox proportional hazard model with Efron's method [Efron, B. 1977] of tie handling will be used to assess the magnitude of the treatment difference (ie, the HR). The HR and its 95% CI from the Cox model with a single treatment covariate will be reported. The stratification factors used for randomization (Section 6.3.2) will be applied to both the stratified log-rank test and the stratified Cox model. Participants without documented death at the time of analysis will be censored at the date of last known contact.

9.6.1.4 Duration of Response

For participants with a CR or PR, whichever occurs first, censoring rules for DOR are summarized in Table 12. DOR will be assessed using RECIST 1.1 by BICR.

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

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

Table 12 Censoring Rules for Duration of Response

Situation	Date of Progression or Censoring	Outcome
No progression nor death, no new anticancer therapy initiated	Last adequate disease assessment	Censor (non-event)
No progression nor death, new anticancer therapy initiated	Last adequate disease assessment before new anticancer therapy was initiated	Censor (non-event)
Death or progression immediately after ≥2 consecutive missed disease assessments or after new anticancer therapy, if any	Earlier date of last adequate disease assessment prior to ≥2 missed adequate disease assessments and new anticancer therapy, if any	Censor (non-event)
Death or progression after ≤1 missed disease assessments and before new anticancer therapy, if any	PD or death	End of response (Event)

PD progressive disease.
A missed disease assessment includes any assessment that is not obtained or is considered inadequate for evaluation of response.

9.6.1.5 Analysis Strategy for Key Efficacy Endpoints

Table 13 summarizes the analysis strategy for the primary and secondary efficacy endpoints.

Table 13 Analysis Strategy for Key Efficacy Variables

Endpoint/Variable	Statistical Method	Analysis Population	Missing Data Approach
Primary Analyses			
OR/ORR (RECIST 1.1by BICR)	Test and estimation: Stratified Miettinen and Nurminen method.	ITT	Participants with missing data are considered nonresponders.
Secondary Analyses			
PFS (RECIST 1.1 by BICR)	Summary statistics using Kaplan-Meier method Estimation: stratified Cox model with Efron's tie-handling method	ITT	Censored according to rules in Table 11.
DOR (RECIST 1.1 by BICR)	Summary statistics using Kaplan-Meier method	All responders in ITT	Censored according to rules in Table 12.
OS	Summary statistics using Kaplan-Meier method Estimation: stratified Cox model with Efron's tie-handling method	ITT	Censored at last known alive date.

BICR blinded independent central review; DOR duration of response; ITT intention to treat; ORR objective response rate; OS overall survival; PFS progression free survival; RECIST 1.1 Response Evaluation Criteria in Solid Tumors Version 1; iRECIST modified RECIST 1.1 for immune based therapeutics.

Sensitivity analyses will be performed for ORR, PFS, and DOR using RECIST 1.1 and iRECIST based on investigator's assessment.

9.6.2 Statistical Methods for Safety Analysis

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

The analysis of safety results will follow a tiered approach (Table 14). The tiered approach will be used for the comparisons of Arm 1 versus Arm 2. The tiers differ with respect to the analyses that will be performed. AEs (specific terms as well as system organ class terms) and events in laboratory, vital sign, and ECG parameters are either prespecified as Tier 1 events or will be classified as belonging to Tier 2 or Tier 3 based on the percentage of events observed.

Tier 1 Events

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

AEOSIs that are immune-mediated or potentially immune-mediated are well documented and will be evaluated separately; however, these events have been characterized consistently

throughout the pembrolizumab clinical development program and determination of statistical significance is not expected to add value to the safety evaluation. Based on review of historic data from ongoing MK-1454 and pembrolizumab clinical studies, there are no known AEs associated with participants for which determination of a p-value is expected to impact the safety assessment. Therefore, there are no Tier 1 events for this protocol.

Tier 2 Events

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

Membership in Tier 2 requires that at least 10% of participants in any treatment arm exhibit the event. The threshold of at least 10% was chosen because participants enrolled in this study are in critical condition and usually experience various AEs of similar types regardless of treatment, events reported less frequently than in 10% of participants would obscure the assessment of the overall safety profile and add little to the interpretation of potentially meaningful treatment differences. In addition, Grades 3 to 5 AEs (≥5% of participants in one of the treatment arms) and SAEs (≥5% of participants in one of the treatment arms) will be considered Tier 2 events. Because many 95% CIs may be provided without adjustment for multiplicity, the CIs should be regarded as a helpful descriptive measure to be used in safety review, not a formal method for assessing the statistical significance of the between treatment differences.

Tier 3 Events

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

Continuous Safety Measures

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

Table 14 Analysis Strategy for Safety Parameters

Safety Tier	Safety Endpoint	95% CI for Treatment Comparison	Descriptive Statistics
Tier 2	Any AE (≥10% of participants in one of the treatment arms)	X	X
	Any Grades 3 to 5 AE (≥5% of participants in one of the treatment arms)	X	X
	Any serious AE (≥5% of participants in one of the treatment arms)	X	X
Tier 3	Any AE		X
	Any change from baseline results (laboratory tests, vital signs, ECGs)		X

AE adverse event, CI confidence interval; ECG electrocardiogram

9.6.3 Summaries of Baseline Characteristics, Demographics, and Other Analyses

9.6.3.1 Demographic and Baseline Characteristics

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

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[redacted]

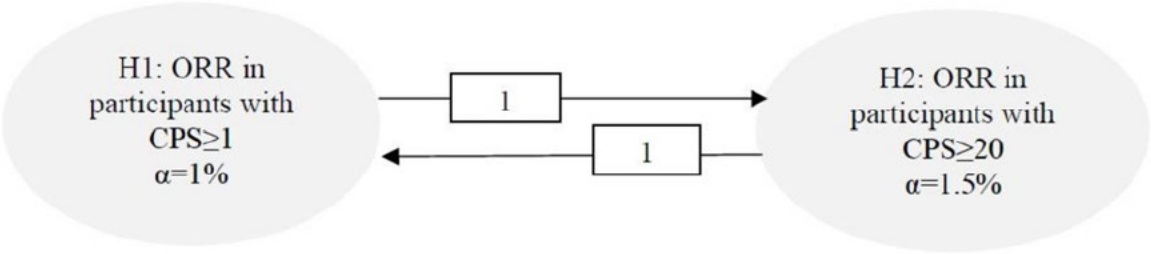
9.8 Multiplicity

The overall type I error rate for the primary endpoint (OR) CCI [redacted] in this study will be strongly controlled at α 2.5% (one-sided) [Chen, C., et al 2018]. CCI

CCI [redacted]

The overall type I error rate across the dual primary hypotheses (ORR in participants with CPS ≥1 and ORR in participants with CPS ≥20) will be strongly controlled at α 2.5% (1-sided) [redacted] α 1% (1-sided) will be initially allocated to ORR in participants with CPS ≥1 and α 1.5% (1-sided) will be allocated to ORR in participants with CPS ≥20. The graphical approach of Maurer and Bretz [Maurer, W. and Bretz, F. 2013] will be applied to reallocate alpha between the dual primary hypotheses if either primary hypothesis is rejected. According to this approach, study hypotheses may be tested more than once, and, when a particular null hypothesis is rejected, the α allocated to that hypothesis can be reallocated to other hypothesis tests. Figure 4 shows the multiplicity diagram that will be used to implement the graphical method. The initial 1-sided α allocation for each hypothesis is shown in the ellipse representing the hypothesis. The weights for reallocation from each hypothesis to the others are represented in the boxes on the lines connecting hypotheses.

Figure 4 Multiplicity Diagram



CPS combined positive scoring; H hypothesis; ORR objective response rate

[redacted]

9.9 Sample Size and Power Calculations

The overall sample size will be approximately [redacted] 200, [redacted]

Based on MK-3475 KN048 data, the prevalence rate of the participants with CPS ≥20 among participants with CPS ≥1 is assumed to be 50%. Table 16 provides the power to claim superior ORR of Arm 1 in participants with CPS ≥1 or CPS ≥20 if study continues to enroll up to approximately 200 participants. A study with 100 participants per arm provides approximate 84.0% power to detect a 21% difference in ORR (40% in Arm 1 vs 19% in Arm 2) at the type I error of 1% (1-sided) for participants with CPS ≥1. With 50 participants per arm, the study has approximately 86.3% power to detect a 31% difference in ORR (55% in Arm 1 vs 24% in Arm 2) at the type I error of 1.5% (1-sided) for participants with CPS ≥20. It has approximately 91.5% power to show that Arm 1 is superior to Arm 2 in at least 1 population (participants with CPS ≥1 or participants with CPS ≥20) at an overall type I error of 2.5% (one-sided). An observed ORR difference of approximately 15% (e.g., 34% vs. 19%) in CPS ≥ 1 or 21% (eg, 45% vs 24%) in CPS≥ 20 is needed to achieve a positive ORR outcome. The powers to claim superior ORR of Arm 1 at the type I error of 2.5% (1-sided) are also provided in Table 16 when one of null hypotheses is rejected and the α allocated to that hypothesis is reallocated to the other hypothesis test.

Table 16 Power of ORR CCI [redacted] in the Study (200 participants in total)

Hypothesis	Population	Alpha Level (one-sided)	True difference in ORR (Arm 1 versus Arm 2)	Power	Power at study level (at least one population win)
H1	CPS ≥1	0.010	21%	84.0%	91.5%
		0.025	21%	91.8%	
H2	CPS ≥20	0.015	31%	86.3%	
		0.025	31%	90.4%	

CPS combined positive scoring; H hypothesis; ORR objective response rate.
Assume true ORR of Arm 2 is 19% and 24% in participants with CPS ≥1 and CPS ≥20, respectively.

CCI [redacted]

CCI

[redacted]

9.10 Subgroup Analyses

To determine whether the treatment effect is consistent across various subgroups, the estimate of the between-group treatment effect (with a nominal 95% CI) for ORR, PFS and OS will be estimated within each category of each subgroup. The following are examples of classification variables:

- Stratification factors
  - PD-L1 expression level (defined by CPS ≥1 to <20 vs CPS ≥20)
  - ECOG status (0 vs. 1)
  - HPV status as determined by p16 IHC (positive vs. negative) (for participants with oropharyngeal cancer only)
- Age category (<65 vs ≥65 years)
- Sex (female vs male)
- Race (white vs non-white)
- Region (North America [NAm] vs EU vs Rest of the World [ROW])
- Smoking status (never vs former vs current)
- Disease status (metastatic vs. unresectable, recurrent)

9.11 Compliance (Medication Adherence)

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

9.12 Extent of Exposure

The extent of exposure will be summarized as duration of treatment in number of cycles or administrations as appropriate. Summary statistics will be provided on extent of exposure for the APaT population.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

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

10.1.1 Code of Conduct for Clinical Trials

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

Code of Conduct for Interventional Clinical Trials

I. Introduction

A. Purpose

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

B. Scope

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

II. Scientific Issues

A. Trial Conduct

1. Trial Design

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

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

2. Site Selection

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

3. Site Monitoring/Scientific Integrity

Investigative trial sites are monitored to assess compliance with the trial protocol and Good Clinical Practice (GCP). MSD reviews clinical data for accuracy, completeness, and consistency. Data are verified versus source documentation according to standard operating procedures. Per MSD policies and procedures, if fraud,

scientific/research misconduct or serious GCP non compliance is suspected, the issues are investigated. When necessary, the clinical site will be closed, the responsible regulatory authorities and ethics review committees notified.

B. Publication and Authorship

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

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

III. Participant Protection

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

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

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

B. Safety

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

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

C. Confidentiality

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

D. Genomic Research

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

IV. Financial Considerations

A. Payments to Investigators

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

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

B. Clinical Research Funding

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

C. Funding for Travel and Other Requests

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

V. Investigator Commitment

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

10.1.2 Financial Disclosure

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

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

10.1.3 Data Protection

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

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

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

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

10.1.3.1 Confidentiality of Data

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

10.1.3.2 Confidentiality of Participant Records

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

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

10.1.3.3 Confidentiality of IRB/IEC Information

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

10.1.4 Committees Structure

10.1.4.1 Stage Gate Review Committee

An internal Stage Gate Review Committee will review results of [redacted] accumulative safety data for decision-making. Logistical details and review guidance will be provided in the Stage Gate Review Committee Charter.

10.1.5 Publication Policy

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

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

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

10.1.6 Compliance with Study Registration and Results Posting Requirements

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

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

10.1.7 Compliance with Law, Audit, and Debarment

By signing this protocol, the investigator agrees to conduct the study in an efficient and diligent manner and in conformance with this protocol; generally accepted standards of GCP (eg, International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use GCP: Consolidated Guideline and other generally

accepted standards of GCP); and all applicable federal, state and local laws, rules and regulations relating to the conduct of the clinical study.

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

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

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

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

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

10.1.8 Data Quality Assurance

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

Detailed information regarding data management procedures for this protocol will be provided separately.

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

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

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

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

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

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

10.1.9 Source Documents

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

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

10.1.10 Study and Site Closure

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

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

10.2 Appendix 2: Clinical Laboratory Tests

- The tests detailed in Table 18 will be performed by the local laboratory. Laboratory samples, which cannot be processed locally, may be sent to the central laboratory.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Sections 5.1 and 5.2 of the protocol.
- Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.
- Pregnancy testing:
  - Pregnancy testing requirements for study inclusion are described in Section 5.1.
  - Pregnancy testing (urine or serum as required by local regulations) should be conducted 120 days after the last dose of study intervention.
  - Additional serum or urine pregnancy tests may be performed, as determined necessary by the investigator or required by local regulation, to establish the absence of pregnancy at any time during the participant's participation in the study.

Table 18 Protocol-required Safety Laboratory Assessments

Hematology	Chemistry	Urinalysis	Other
Hematocrit	Albumin	Blood	Pregnancy test (serum or urine)[a]
Hemoglobin	Alkaline phosphatase	Glucose	FSH [b]
Platelet count	Alanine aminotransferase	Protein	T3 or FT3 [c]
WBC (total and differential)[d]	Aspartate aminotransferase	Specific gravity	T4 or FT4 [c]
RBC	Bicarbonate or Carbon Dioxide	Microscopic exam, if abnormal results are noted	TSH
PT or INR	Calcium		Anti-HCV
aPTT or PTT	Chloride		HCV viral load
	Serum Creatinine		HCV genotype
	Creatinine clearance (measured or calculated)[e]		anti-HBs
	GGT		HbsAg
	Glucose		Anti-HBc (total and IgM)
	Phosphorus		HBeAg
	Potassium		anti-HBe
	Sodium		Anti-HDV

Hematology	Chemistry	Urinalysis	Other
	Total bilirubin		HPV viral load[f]
	Direct bilirubin		
	Total protein		
	BUN or Urea[g]		
	LDH		

aPTT activated partial thromboplastin time; BUN blood urea nitrogen; FT3 free triiodothyronine; FT4 free thyroxine; FSH follicle stimulating hormone; GFR glomerular filtration rate; GGT gamma glutamyl transpeptidase; HBc hepatitis B core antigen; HBeAg hepatitis B e antigen; HBsAg hepatitis B surface antigen; HCV hepatitis C virus; HDV hepatitis D virus; HPV human papilloma virus; INR International Normalized Ratio; LDH lactic dehydrogenase; PT prothrombin time; PTT partial thromboplastin time; RBC red blood count; T3 total triiodothyronine; T4 total thyroxine; TSH thyroid stimulating hormone; WBC white blood count.

[a] Perform on women of childbearing potential only 24 hours prior to C1D1. Pregnancy tests must be repeated prior to every cycle if required or as specified per local regulatory guidance. Refer to Appendix 7 for country specific requirements.

[b] 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.

[c] Total T3 and Total T4 are preferred; if not available, Free T3 or Free T4 may be tested.

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

[e] For participants 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.

[f] For participants diagnosed with oropharyngeal cancer only, HPV p16 IHC must be performed by central lab if not previously tested per the Procedures Manual.

[g] BUN is preferred; if not available urea may be tested

Investigators must document their review of each laboratory safety report.

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

10.3.1 Definition of AE

AE definition

- An AE is any untoward medical occurrence in a clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention.
- NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a study intervention.
- NOTE: For purposes of AE definition, study intervention (also referred to as Sponsor's product) includes any pharmaceutical product, biological product, vaccine, diagnostic agent, or protocol-specified procedure whether investigational or marketed (including placebo, active comparator product, or run-in intervention), manufactured by, licensed by, provided by, or distributed by the Sponsor for human use in this study.

Events meeting the AE definition

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator.
- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication.
- For all reports of overdose (whether accidental or intentional) with an associated AE, the AE term should reflect the clinical symptoms or abnormal test result. An overdose without any associated clinical symptoms or abnormal laboratory results is reported using the terminology "accidental or intentional overdose without adverse effect."

Events NOT meeting the AE definition

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

10.3.2 Definition of SAE

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

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

1. Results in death

2. Is life-threatening

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

3. Requires inpatient hospitalization or prolongation of existing hospitalization

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

4. Results in persistent or significant disability/incapacity

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.
- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza,

and accidental trauma (eg, sprained ankle) that may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

5. Is a congenital anomaly/birth defect

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

6. Other important medical events

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

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

10.3.3 Additional Events Reported in the Same Manner as SAE

Additional events that require reporting in the same manner as SAE

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

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

10.3.4 Recording AE and SAE

AE and SAE recording

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory, and diagnostics reports) related to the event.
- The investigator will record all relevant AE/SAE information on the AE eCRFs/worksheets at each examination.
- It is not acceptable for the investigator to send photocopies of the participant's medical records to the Sponsor in lieu of completion of the AE eCRF page.

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

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

Assessment of intensity/toxicity

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

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

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

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

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

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

Grade 5: Death related to AE.

Assessment of causality

- Did the Sponsor's product cause the AE?

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

- **The following components are to be used to assess the relationship between the Sponsor's product and the AE; the greater the correlation with the components and**

their respective elements (in number and/or intensity), the more likely the Sponsor's product caused the AE:

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

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

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

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

  - If yes, did the AE resolve or improve?

  - If yes, this is a positive dechallenge.

  - If no, this is a negative dechallenge.

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

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

  - If yes, did the AE recur or worsen?

  - If yes, this is a positive rechallenge.

  - If no, this is a negative rechallenge.

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

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

MODIFICATION GUIDELINES IN THE PROTOCOL, AND IF REQUIRED, THE INIRB/IEC.

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

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

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

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

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

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

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

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

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

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

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

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

may be assigned to a single agent if in the investigator's opinion, there is sufficient data to support full attribution of the AE to the single agent.

Follow-up of AE and SAE

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by Sponsor to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- New or updated information will be recorded in the eCRF.
- The investigator will submit any updated SAE data to the Sponsor within 24 hours of receipt of the information.

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

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

- The primary mechanism for reporting to the Sponsor will be the EDC tool.
    - Electronic reporting procedures can be found in the EDC data entry guidelines (or equivalent).
    - If the electronic system is unavailable for more than 24 hours, then the site will use the paper AE Reporting form.
        - Reference Section 8.4.1 for reporting time requirements.
- The site will enter the SAE data into the electronic system as soon as it becomes available.
- After the study is completed at a given site, the EDC tool will be taken off-line to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the EDC tool has been taken off-line, then the site can report this information on a paper SAE form or by telephone (see next section).
- Contacts for SAE reporting can be found in the Investigator Study File Binder (or equivalent).

SAE reporting to the Sponsor via paper CRF

- If the EDC tool is not operational, facsimile transmission or secure e-mail of the SAE paper CRF is the preferred method to transmit this information to the Sponsor.
- In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the SAE data collection tool sent by overnight mail or courier service.
- Initial notification via telephone does not replace the need for the investigator to complete and sign the SAE CRF pages within the designated reporting time frames.
- Contacts and instructions for SAE reporting and paper reporting procedures can be found in the Investigator Study File Binder (or equivalent).

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

Not applicable.

10.5 Appendix 5: Contraceptive Guidance

10.5.1 Definitions

Women of Childbearing Potential (WOCBP)

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

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

Women in the following categories are not considered WOCBP:

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

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

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

10.5.2 Contraception Requirements

10.5.2.1 Contraception Requirements: Female Participants

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

10.5.2.2 Contraception Requirements: Male Participants

Male participants are eligible to participate if they agree to the following during the intervention period with MK-1454 and for at least 120 days after the last dose of MK-1454:

- Refrain from donating sperm

PLUS either:

- Be abstinent from heterosexual intercourse as their preferred and usual lifestyle (abstinent on a long term and persistent basis) and agree to remain abstinent
- Must agree to use contraception unless confirmed to be azoospermic (vasectomized or secondary to medical cause) as detailed below:
  - Agree to use a male condom plus partner use of an additional contraceptive method when having penile-vaginal intercourse with a WOCBP who is not currently pregnant. Note: Men with a pregnant or breastfeeding partner must agree to remain abstinent from penile-vaginal intercourse or use a male condom during each episode of penile-vaginal penetration.
- Contraceptive use by men should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies
- Note: Contraceptive requirements do not apply to participants taking pembrolizumab monotherapy.

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

1. Definitions

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

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

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

d. DNA: Deoxyribonucleic acid.

e. RNA: Ribonucleic acid.

2. Scope of Future Biomedical Research

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

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

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

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

3. Summary of Procedures for Future Biomedical Research

a. Participants for Enrollment

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

b. Informed Consent

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

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

c. eCRF Documentation for Future Biomedical Research Specimens

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

d. Future Biomedical Research Specimen(s)

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

4. Confidential Participant Information for Future Biomedical Research

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

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

At the clinical study site, unique codes will be placed on the future biomedical research specimens. This code is a random number which does not contain any personally

identifying information embedded within it. The link (or key) between participant identifiers and this unique code will be held at the study site. No personal identifiers will appear on the specimen tube.

5. Biorepository Specimen Usage

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

Participants may withdraw their consent for future biomedical research and ask that their biospecimens not be used for future biomedical research. Participants may withdraw consent at any time by contacting the investigator for the main study. If medical records for the main study are still available, the investigator will contact the Sponsor using the designated mailbox (clinical.specimen.management@MSD.com). Subsequently, the participant's specimens will be flagged in the biorepository and restricted to main study use only. If specimens were collected from study participants specifically for future biomedical research, these specimens will be removed from the biorepository and destroyed. Documentation will be sent to the investigator confirming withdrawal and/or destruction, if applicable. It is the responsibility of the investigator to inform the participant of completion of the withdrawal and/or destruction, if applicable. Any analyses in progress at the time of request for withdrawal/destruction or already performed prior to the request being received by the Sponsor will continue to be used as part of the overall research study data and results. No new analyses would be generated after the request is received.

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

7. Retention of Specimens

Future biomedical research specimens will be stored in the biorepository for potential analysis for up to 20 years from the end of the main study. Specimens may be stored for longer if a regulatory or governmental authority has active questions that are being answered. In this special circumstance, specimens will be stored until these questions have been adequately addressed.

Specimens from the study site will be shipped to a central laboratory and then shipped to the Sponsor-designated biorepository. If a central laboratory is not utilized in a particular study, the study site will ship directly to the Sponsor-designated biorepository. The specimens will be stored under strict supervision in a limited access facility which operates to assure the integrity of the specimens. Specimens will be destroyed according to Sponsor policies and procedures and this destruction will be documented in the biorepository database.

8. Data Security

Databases containing specimen information and test results are accessible only to the authorized Sponsor representatives and the designated study administrator research personnel and/or collaborators. Database user authentication is highly secure, and is accomplished using network security policies and practices based on international standards to protect against unauthorized access.

9. Reporting of Future Biomedical Research Data to Participants

No information obtained from exploratory laboratory studies will be reported to the participant, family, or physicians. Principle reasons not to inform or return results to the participant include: Lack of relevance to participant health, limitations of predictive capability, and concerns regarding misinterpretation.

If important research findings are discovered, the Sponsor may publish results, present results in national meetings, and make results accessible on a public website in order to rapidly report this information to doctors and participants. Participants will not be identified by name in any published reports about this study or in any other scientific publication or presentation.

10. Future Biomedical Research Study Population

Every effort will be made to recruit all participants diagnosed and treated on Sponsor clinical studies for future biomedical research.

11. Risks Versus Benefits of Future Biomedical Research

For future biomedical research, risks to the participant have been minimized and are described in the future biomedical research informed consent.

The Sponsor has developed strict security, policies, and procedures to address participant data privacy concerns. Data privacy risks are largely limited to rare situations involving possible breach of confidentiality. In this highly unlikely situation, there is risk that the information, like all medical information, may be misused.

12. Questions

Any questions related to the future biomedical research should be emailed directly to clinical.specimen.management@MSD.com.

13. References

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

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

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

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

10.7 Appendix 7: Country-specific Requirements

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

Section 1.3.2 Schedule of Activities for the Treatment Period for Arm 1 (Combination Therapy: IT MK-1454 and IV Pembrolizumab)

Study Period:	**Combination Treatment Phase (3-Week Cycles)**								**Notes**
Treatment Cycle/Title:	**Cycle 1**			**Cycle 2**			**Cycle 3**	**Cycle 4 and Beyond**	
Treatment Days:	**1**	**8**	**15**	**1**	**8**	**15**	**1**	**1**	
Scheduled Day and Window:	**+3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	
Pregnancy test – Urine or Serum β-hCG for WOCBP	X			X			X	X	Required within 24 h prior to first dose of study medication. Does not need to be repeated if screening pregnancy test was done within 24 h of the first dose of study medication on 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.

β-hCG = β-human chorionic gonadotropin; EOT = end of treatment; WOCBP = women of childbearing potential.

Section 1.3.3 Schedule of Activities for the Treatment Period for Arm 2 IV Pembrolizumab Monotherapy)

Study Period:	**Treatment Phase (3-Week Cycles)**				**Notes**
Treatment Cycle/Title:	**Cycle 1**	**Cycle 2**	**Cycle 3**	**Cycle 4 and Beyond**	
Treatment Days:	**1**	**1**	**1**	**1**	
Scheduled Day and Window:	**+3**	**±3**	**±3**	**±3**	
Pregnancy test – Urine or Serum β-hCG for WOCBP	X	X	X	X	Required within 24 h prior to first dose of study medication. Does not need to be repeated if screening pregnancy test was done within 24 h 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.

Section 1.3.4 Schedule of Activities for the End of Treatment and Post-treatment Follow-Up Periods)

Study Period	EOT/ Discontinuation	Post-treatment Period			Notes
		30-Day Safety Follow-up Visit	Imaging Follow-up	Survival Follow-up	
Visit Timing		**30 days after the last dose**	**Every 6 weeks for 1 year, then every 9 weeks**	**Approxi-mately every 12 weeks**	
Visit Window (Days)	**±7**	**+7**	**±7**	**±14**	
Pregnancy Test for WOCBP – Urine or Serum β-hCG		X			For WOCBP, perform as required locally. If a urine pregnancy test cannot be confirmed as negative, a serum pregnancy test is required. **Thereafter, pregnancy testing should be performed approximately monthly up to 120 days following the discontinuation of study intervention.**

β-hCG = β-human chorionic gonadotropin; EOT = end of treatment; WOCBP = women of childbearing potential.

8.3.4.2 Pregnancy Test

All women who are being considered for participation in the study, and who are not surgically sterilized or postmenopausal, must be tested for pregnancy within 24 hours of the first dose of study medication on C1D1 and 30 days post-treatment. Additional pregnancy testing can be conducted if required by local regulations or if clinically indicated. If a urine test is positive or not evaluable, a serum test will be required. Participants must be excluded/discontinued from the study in the event of a positive or borderline-positive test result. During study treatment, pregnancy testing should be repeated on Day 1 of each cycle and then again 30 days after the last study dose of study treatment, and approximately monthly up to 120 days after the last study dose of study treatment.

8.10.1 Screening

For women of reproductive potential, a urine or serum pregnancy test will be performed within 24 hours prior to the first dose of study intervention. If urine pregnancy results cannot be confirmed as negative, a serum pregnancy test will be required (performed by the local study site laboratory). Thereafter, pregnancy testing should be conducted Day 1 of each subsequent cycle.

Appendix 2 Clinical Laboratory Tests

Footnote to Table 18 reads:

a. Perform on WOCBP only 24 hours prior to Cycle 1 Day 1 (C1D1). Thereafter, pregnancy testing should be conducted Day 1 of each subsequent cycle.

10.8 Appendix 8: Guidelines for Prioritization of Intratumoral Lesion Injection

The selection and prioritization of lesions for intratumoral injection may be a complex set of decisions made by the clinician at each treatment visit. Ultimately, lesion prioritization is based on clinical judgment and patient tolerance. A set of guiding principles is provided.

Patient Safety

The first priority is patient safety. Lesions are to be selected that minimize the potential for procedural complications and maximize patient comfort. Important safety factors are vascularity within a lesion, and vascularity adjacent to a lesion. Injection into intratumoral vasculature should be avoided to minimize systemic administration. Vessels adjacent to a tumor should ideally not be traversed to minimize bleeding risk. Areas of vascular encasement should be avoided in high risk locations, such as 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 therefore have a greater breadth of tumor-specific antigens to stimulate a broader repertoire of antigen-specific T-cells. Radiographically visible necrosis should be avoided for injection with an intratumoral immunotherapeutic. Direct the intratumoral immunotherapeutic into viable portions of a lesion, such as at the periphery 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 Enlarging Lesions

During therapy, lesions that are new or enlarging should be given higher priority over lesions selected on the basis of size. 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 repertoire of antigen-specific T cells in response to injection with an intratumoral immunotherapeutic, and subsequent improved systemic antitumor response. New lesions may contain novel tumor antigens compared to previously injected lesions.

Note: Detailed guidance on injectate volume and lesion injection is provided in the Procedures Manual.

10.9 Appendix 9: Eastern Cooperative Oncology Group Performance Status

Developed by the Eastern Cooperative Oncology Group, Robert L. Comis, MD, Group Chair.*

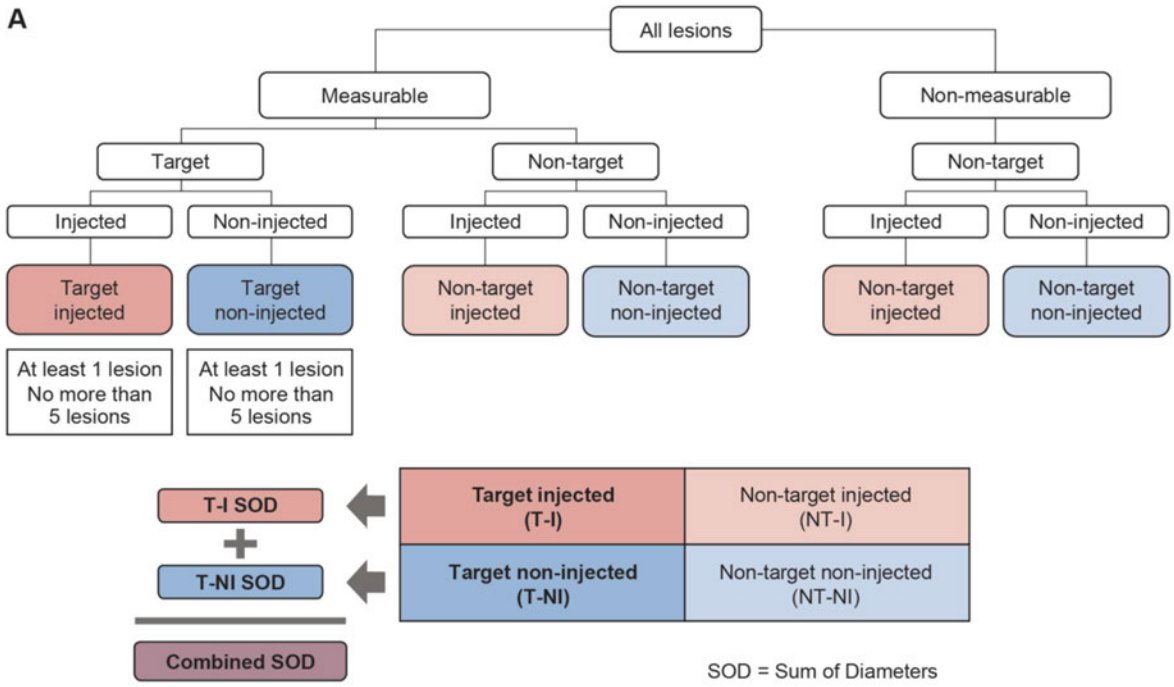
GRADE	ECOG PERFORMANCE STATUS
0	Fully active, able to carry on all predisease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework, office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities; up and about more than 50% of waking hours
3	Capable of only limited self-care; confined to bed or chair more than 50% of waking hours
4	Completely disabled; cannot carry on any self-care; totally confined to bed or chair
5	Dead

* Oken M, Creech R, Tormey D, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol. 1982;5:649-655

http://ecog-acrin.org/resources/ecog-performance-status

10.10 Appendix 10: itRECIST Supplementary Figures

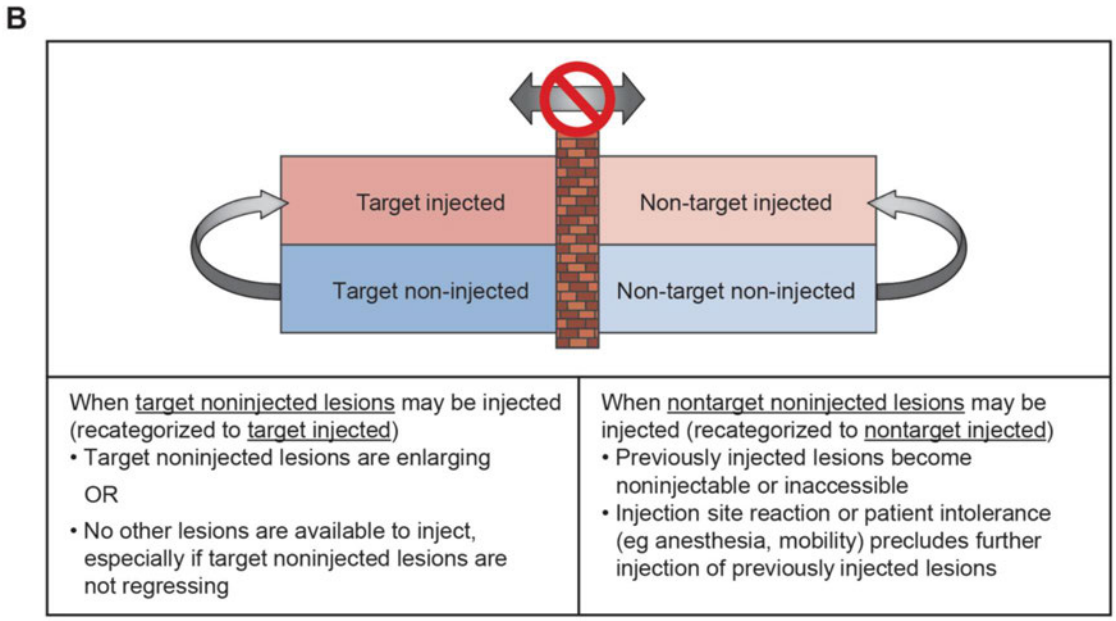
Figure 5 Algorithm for Classification of Lesions at Baseline



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

Lesions are classified first as measurable or nonmeasurable using the standard RECIST 1.1 rules for measurability. Measurable lesions (those eligible for selection as target lesions) are then classified as target (selected to be followed quantitatively) or nontarget (selected to be followed qualitatively), and the decisions about which lesions are to be injected are made based on the prioritization rules discussed. Lesions selected for injection may be either target or nontarget in RECIST 1.1 terms. Between 1 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).

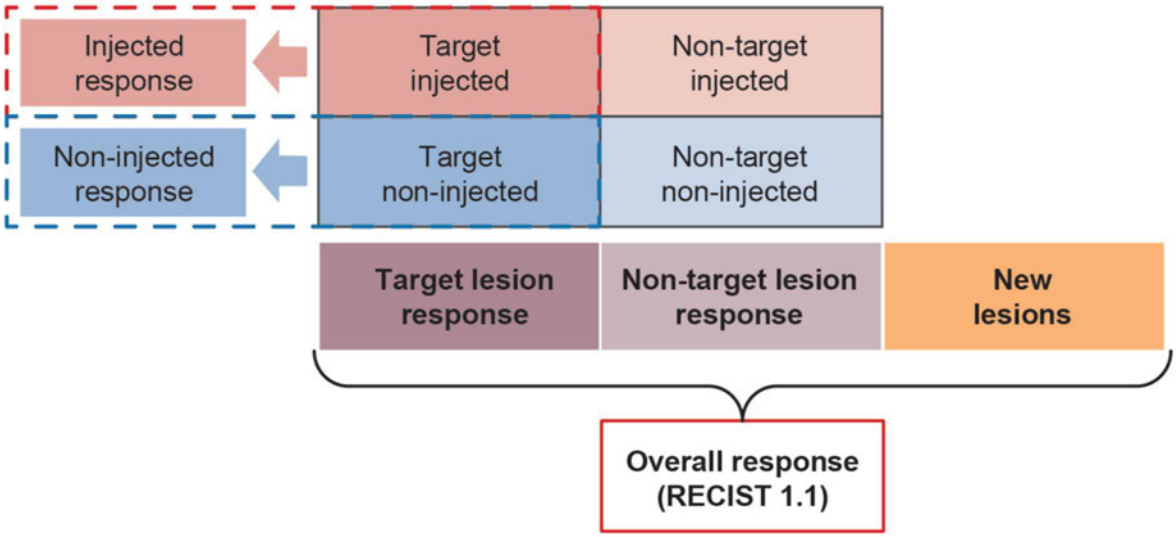
Figure 6 Reclassification of Noninjected Lesions



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

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

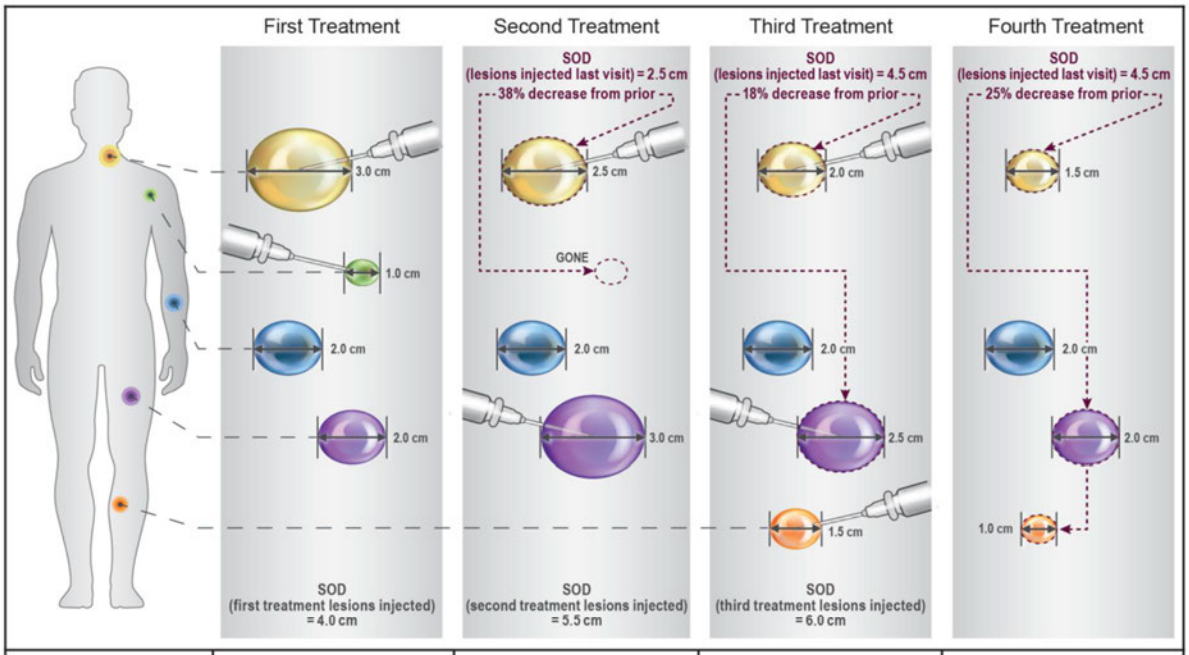
Figure 7 Overall Response Assessment Until Disease Progression



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

Overall response until disease progression per RECIST 1.1. The injected response at each visit is based on only the changes in the SODs of the lesions designated as target injected. The noninjected response at each visit is based on only the changes in the SODs of the target noninjected lesions. The overall response is based on the changes in the SODs of all target lesions together, the qualitative assessment of all nontarget lesions together, and the evaluation for possible new lesions and uses the same response categories and logical combination of these that RECIST 1.1 uses. 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; NE = not evaluable; NT-I = nontarget injected; NT-NI = nontarget noninjected; PD = progressive disease; PR = partial response; iRECIST 1.1 = immunotherapeutic Response Evaluation Criteria in Solid Tumors; SD = stable disease; SOD = sum of diameters (longest diameters for extranodal lesions, short axis for lymph nodes); T-I = target injected; T-NI = target noninjected.

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

This is an illustration of overall, injected, and noninjected response assessment, with a particular focus on the iterative assessment of injected lesions. All lesions from a single 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.

10.11 Appendix 11: Abbreviations

Abbreviation	Expanded Term
ADA	antidrug antibodies
ADL	activities of daily living
AE	adverse event
AEOSI	adverse event of special interest
APaT	All-Participants-as-Treated
aPTT	activated partial thromboplastin time
AR	adverse reaction
ART	antiretroviral therapy
ATD	accelerated titration design
ATP	adenosine triphosphate
AUC	area under the curve
BCG	Bacillus Calmette–Guérin
BDS	blood drug screen
BICR	blinded independent central review
BID	twice daily
BMI	body mass index
BP	blood pressure
C1D1	Cycle 1 Day 1
CBC	complete blood count
CD28	cluster of differentiation 28
CD3ζ	cluster of differentiation 3 zeta
CDN	cyclic dinucleotide
CF	compact flash
CG	Cockcroft-Gault
cGAS	cyclic GMP-AMP (guanosine monophosphate-adenosine monophosphate) synthase
CI	confidence interval
CI	confidence interval
CL	clearance
C_{max}	maximum concentration
CONSORT	Consolidated Standards of Reporting Trials
CPS	combined positive scoring
CR	Complete response
CrCl	creatinine clearance
CRF	Case Report Form
CRS	cytokine release syndrome
CRU	clinical research unit
CSR	Clinical Study Report
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
ctDNA	Circulating tumor deoxyribonucleic acid
CTFG	Clinical Trial Facilitation Group
CTLA-4	cytotoxic T-lymphocyte-associated protein 4
C_{trough}	minimum concentration
DC	dendritic cells
DILI	drug-induced liver injury
DLT	dose-limiting toxicity
dMMR	deficient mismatch repair indicated by the loss of expression of one or more of the MLH1, MSH2, MSH6, and PMS2 proteins
DNA	deoxyribonucleic acid
DOR	duration of response

Abbreviation	Expanded Term
dsDNA	double-stranded DNA
E/CIA	enzyme or chemiluminescence immunoassay
ECG	electrocardiogram
ECI	event of clinical interest
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic Case Report Form
EDC	electronic data collection
eGFR	estimated glomerular filtration rate
ELISA	enzyme-linked immunosorbent assay
EMA	European Medicines Agency
EOT	end of treatment
EQ-5D	EuroQoL-5D
ER	endoplasmic-reticulum
FAS	Full Analysis Set
FBR	Future biomedical research
FDAAA	Food and Drug Administration Amendments Act
FFPE	formalin-fixed, paraffin embedded
FIH	first in human
FSH	follicle-stimulating hormone
FT3	free triiodothyronine
FT4	free thyroxin
GCP	Good Clinical Practice
G-CSF	Granulocyte Colony-stimulating Factor
GFR	glomerular filtration rate
GGT	gamma-glutamyl transpeptidase
GI	gastrointestinal
GM-CSF	Granulocyte Macrophage Colony-Stimulating Factor
GMP-AMP	(guanosine monophosphate-adenosine monophosphate) synthase
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HIV	human immunodeficiency virus
HNSCC	head and neck squamous cell carcinoma
HPV	human papilloma virus
HR	hazard ratio
HRT	hormone replacement therapy
CCI [redacted]	
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
iCPD	immune confirmed progressive disease
iCR	immune complete response
iCRO	imaging CRO
IEC	Independent Ethics Committee
IFN	interferon
Ig	immunoglobulin
IgG4	immunoglobulin G4
IgV	immunoglobulin-variable
IHC	immunohistochemistry
IL	interleukin
IND	Investigational New Drug

Abbreviation	Expanded Term
INR	international normalized ratio
IO	immuno-oncology
iPR	immune partial response
irAEs	immune-related AEs
IRB	Institutional Review Board
iRECIST	Response Evaluation Criteria in Solid Tumors 1.1 for immune-based therapeutics
IRT	interactive response technology
iSD	immune stable disease
IT	intratumoral
ITP	idiopathic thrombocytopenic purpura
itRECIST	intratumoral immunotherapy RECIST
ITT	intention-to-treat
IUD	intrauterine device
IUO	Investigational use only
iUPD	Immune unconfirmed progressive disease
IUS	intrauterine hormone-releasing system
IV	intravenous
LDH	lactate dehydrogenase
LLOQ	lowest limit of quantitation
mAb	monoclonal antibody
MAD	maximum administered dose
MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging
mRNA	messenger RNA
MSI	microsatellite instability
MTD	maximum tolerated dose
NA	not applicable
NAm	North America
NCI	National Cancer Institute
NF-κB	nuclear factor kappa light chain enhancer of activated B cells
NOAEL	no observed adverse effect level
NSCLC	non–small cell lung cancer
O_2	oxygen
OR	objective response
ORR	objective response rate
OS	overall survival
OTC	over-the-counter
PD	progressive disease
PD-1	programmed cell death 1
PD-L1	programmed cell death ligand 1
PD-L2	programmed cell death ligand 2
PET	positron emission tomography
PFS	progression-free survival
PIN	personal identification number
PK	pharmacokinetic
PKCθ	protein kinase C-theta
po	orally
PP	per protocol
PR	partial response
PT	prothrombin time
PTT	partial thromboplastin time
Q1W	once each week

Abbreviation	Expanded Term
Q3W	every 3 weeks
RECIST	Response Evaluation Criteria in Solid Tumors
RNA	ribonucleic acid
RP2D	recommended Phase 2 dose
SAE	serious adverse event
SAP	Statistical Analysis Plan
SoA	schedule of activities
SOD	Sum of diameters
sSAP	supplemental Statistical Analysis Plan
STING	stimulator of interferon genes
SUSAR	suspected unexpected serious adverse reaction
T3	triiodothyronine
T4	thyroxine
TNBC	triple negative breast cancer
TPS	Tumor proportion scoring
T-regs	Regulatory T-cells
TSH	Thyroid-stimulating hormone
V	Volume of distribution
VS	vital sign
WBC	white blood cell
WOCBP	woman/women of childbearing potential
WT	Wild-type
ZAP70	zeta-chain-associated protein kinase
β-hCG	β-human chorionic gonadotropin

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