Official Protocol Title:	A Phase 1/2 Open-Label Rolling-Arm Umbrella Platform Design of Investigational Agents With or Without Pembrolizumab or Pembrolizumab Alone in Participants with Melanoma (KEYMAKER-U02): Substudy 02C
NCT number:	NCT04303169
Document Date:	05-Mar-2025

Title Page

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Protocol Title: A Phase 1/2 Open-Label Rolling-Arm Umbrella Platform Design of Investigational Agents With or Without Pembrolizumab or Pembrolizumab Alone in Participants with Melanoma (KEYMAKER-U02): Substudy 02C

Protocol Number: 02C-07

Compound Number: MK-3475

Sponsor Name:

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

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Approval Date: 05 March 2025

Sponsor Signatory

Typed Name: Title:	Date

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

Investigator Signatory

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

Typed Name: Title:	Date

DOCUMENT HISTORY

Document	Date of Issue	Overall Rationale
Amendment 7	05-MAR-2025	The Sponsor has decided to discontinue the arm evaluating MK-7684 + pembrolizumab (Arm 1) based on lack of efficacy observed in other studies. Additionally, the Sponsor has decided to discontinue arms evaluating V937 + pembrolizumab (Arm 2), pembrolizumab monotherapy (Arm 3), MK-4830 + pembrolizumab (Arm 4), MK-4280A monotherapy (Arm 5), and ATRA + pembrolizumab (Arm 6), based on Sponsor prioritization strategy. The decision to deprioritize development of V937, MK-4830, MK-4280A, and ATRA was made after a thorough evaluation of the data from these clinical programs and is not based on any safety concerns with any of these investigational agents.
Amendment 6	25-JUL-2022	To add 2 investigational treatment arms [MK-4280A] and [ATRA + pembrolizumab]
Amendment 5	09-FEB-2022	To clarify enrollment procedures for the rolling arm design of the trial and to update omissions in study intervention tables (Table 2 and Table 11)
Amendment 4	20-DEC-2021	To add one investigational arm [MK-4830 + pembrolizumab]
Amendment 3	07-JUL-2021	To update the dose modification and toxicity management guidelines for irAEs
Amendment 2	16-NOV-2020	To address Regulatory and Health Authority Feedback
Amendment 1	12-APR-2020	To address Regulatory and Health Authority Feedback
Original Protocol	13-NOV-2019	Not applicable

PROTOCOL AMENDMENT SUMMARY OF CHANGES

Amendment: 07

Overall Rationale for the Amendment:

The Sponsor has decided to discontinue the arm evaluating MK-7684 + pembrolizumab (Arm 1) based on lack of efficacy observed in other studies.

Additionally, the Sponsor has decided to discontinue arms evaluating V937 + pembrolizumab (Arm 2), pembrolizumab monotherapy (Arm 3), MK-4830 + pembrolizumab (Arm 4), MK-4280A monotherapy (Arm 5), and ATRA + pembrolizumab (Arm 6), based on Sponsor prioritization strategy. The decision to deprioritize development of V937, MK-4830, MK-4280A, and ATRA was made after a thorough evaluation of the data from these clinical programs and is not based on any safety concerns with any of these investigational agents.

Summary of Changes Table

Section Number and Name	Description of Change	Brief Rationale
Primary Reason for Amendment		
Section 1, Protocol Summary	Evaluation of Arms 1 through 6 will be discontinued and posttreatment efficacy and survival follow-up will cease. Participants receiving adjuvant pembrolizumab may continue study therapy per protocol.	The Sponsor has decided to discontinue the arm evaluating MK-7684 + pembrolizumab (Arm 1) based on lack of efficacy observed in other studies. Additionally, the Sponsor has decided to discontinue arms evaluating V937 + pembrolizumab (Arm 2), pembrolizumab monotherapy (Arm 3), MK-4830 + pembrolizumab (Arm 4), MK-4280A monotherapy (Arm 5), and ATRA + pembrolizumab (Arm 6), based on Sponsor prioritization strategy. The decision to deprioritize development of V937, MK-4830, MK-4280A, and ATRA was made after a thorough evaluation of the data from these clinical programs and is not based on any safety concerns with any of these investigational agents. As of Amendment 7, Arm 6 participants receiving adjuvant pembrolizumab monotherapy are the only participants actively receiving study therapy. All other study participants have completed or discontinued study therapy and completed safety follow-up.

Section Number and Name	Description of Change	Brief Rationale
Additional Changes		
Title Page	Regulatory Agency Identifying Number(s): Added NCT, EU CT, and WHO/UTN numbers.	To provide new information.
Section 1, Protocol Summary	A brief summary of new data from MK-7684A studies was added.	To provide context for the discontinuation of the vibostolimab/MK-7684A clinical program.
Section 1, Protocol Summary Section 4, Study Design Section 7, Discontinuation of Study Intervention and Participant Withdrawal Section 8, Study Assessments and Procedures Section 9, Statistical Considerations Section 10.6, Appendix 6: Substudy Combination-specific Requirements	At implementation of Amendment 7, the following changes apply to Arms 1 through 6. The changes listed below supersede any content/instructions from previous amendments: • Participants receiving adjuvant pembrolizumab monotherapy may continue on study therapy per protocol. • Imaging scans should no longer be submitted to CIV. However, for participants who are still on study treatment and deriving clinical benefit and will continue on study treatment until criteria for discontinuation are met, local tumor imaging should continue per local SOC schedule and local SOC method of assessment of imaging. All imaging as well as relevant objectives and endpoints will be assessed locally. • PK/ADA samples will no longer be collected. • Biomarker samples will no longer be collected. • Participants who complete study treatment or otherwise meet EOT criteria will be discontinued from the study after the EOT visit and any required safety follow-up visit. • There will be no follow-up for survival status. Participants currently in imaging follow-up or survival follow-up are considered to have completed the study and therefore should obtain imaging and further oncological care per local standard of care. However, standard safety reporting should continue, as applicable. • Those participants remaining on the study at the time of Amendment 7 should continue to be monitored in the study through the AE reporting period (Section 8.4). • All analyses prespecified in Section 9.7 for Arms 1 through 6 are complete at the time of Amendment 7.	Refer to Section 1 rationale for discontinuation of Arms 1 through 6.

Section Number and Name	Description of Change	Brief Rationale
Section 1.1 Synopsis	Overall Design: Revised estimated study duration from approximately 2.5 to 7 years per investigational agent treatment arm.	To align with efficacy follow-up schedule.
	Duration of Participation: Added duration for each participant from the time of providing documented informed consent through the final protocol-specified contact and specified duration of follow-up after the end of adjuvant treatment.	To meet EU CTR requirement.
Section 4.4, Beginning and End of Study Definition	Added definition of end of study for analyses and reporting purposes.	Refer to Section 1.1 rationale regarding EU CTR requirement.
	Added definition of local start of the study for countries in the EEA.	Refer to Section 1.1 rationale regarding EU CTR requirement.
	Added the estimated duration of the study.	Refer to Section 1.1 rationale regarding EU CTR requirement.
Section 5, Study Population	Added text related to code of conduct for clinical trials.	Refer to Section 1.1 rationale regarding EU CTR requirement.
Section 8.4, Adverse Events, Serious Adverse Events, and Other Reportable Safety Events	Added requirement for investigators to document if an SAE was associated with a medication error, misuse, or abuse.	Refer to Section 1.1 rationale regarding EU CTR requirement.
Section 8.4.1, Time Period and Frequency for Collecting AE, SAE, and Other Reportable Safety Event Information	Table 10: Updated periods and duration for potential DILI/DILI reporting.	To maintain continued regulatory reporting compliance in alignment with new Health Authority DILI reporting requirements.
Section 8.4.3, Follow-up of AE, SAE, and Other Reportable Safety Event Information	Added potential DILI/DILI to reportable events.	Refer to Section 8.4.1 rationale.
Section 8.4.4, Regulatory Reporting Requirements for SAE	Added a note on SUSAR reporting requirements.	To align with Regulation (EU) 536/2014.
Section 8.4.7, Events of Clinical Interest	ECI updated to potential DILI injury/DILI injury, with associated reporting requirements.	Refer to Section 8.4.1 rationale.
Section 10.1.1, Code of Conduct for Clinical Trials	Incorporated updates for EU Regulation 536/2014.	Refer to Section 8.4.4 rationale.
Section 10.1.3, Data Protection	Added reference to Sponsor's EU-approved Binding Corporate Rules and Global Privacy Program in pursuit of EU-US Data Privacy Framework	Refer to Section 1.1 rationale regarding EU CTR requirement.
Section 10.1.6, Compliance with Study Registration and Results Posting Requirements	Replaced reference to EMA clinical trial Directive 2001/20/EC with EU Regulation 536/2014.	Refer to Section 8.4.4 rationale.
	Added link to EU clinical trial register.	Refer to Section 1.1 rationale regarding EU CTR requirement.

Section Number and Name	Description of Change	Brief Rationale
Section 10.1.7, Compliance with Law, Audit, and Debarment	Added serious breach reporting requirements.	Refer to Section 1.1 rationale regarding EU CTR requirement.
Section 10.1.8, Data Quality Assurance	Added records retention period for EU CTR countries.	Refer to Section 1.1 rationale regarding EU CTR requirement.
Section 10.3.1, Definitions of Medication Error, Misuse, and Abuse	Added definitions of medication error, misuse, and abuse.	Refer to Section 1.1 rationale regarding EU CTR requirement.
Section 10.3.3, Definition of SAE	Added DILI to definition of SAE.	Refer to Section 8.4.1 rationale.
Section 10.6.1, Status of Investigational Agents in this Substudy	Table 9: Updated to reflect that no arms are activated for randomization/allocation as of Amendment 7.	Refer to Section 1 rationale for discontinuation of Arms 1 through 6.
	Table 10: Updated to reflect that Arms 4, 5, and 6 are no longer activated for randomization/allocation as of Amendment 7 and added rationale for closing Arms 1 to 6.	Refer to Section 1 rationale for discontinuation of Arms 1 through 6.

Table of Contents

DOCUMENT HISTORY **3**
PROTOCOL AMENDMENT SUMMARY OF CHANGES **4**
1 PROTOCOL SUMMARY **18**
1.1 Synopsis **19**
1.2 Schema **24**
1.3 Schedule of Activities **25**
2 INTRODUCTION **26**
2.1 Study Rationale **26**
2.1.1 Rationale for the Use of Standard of Care Pembrolizumab 26
2.1.2 Rationale for Choice of Investigational Agent in This Substudy Protocol 26
2.2 Background **26**
2.2.1 Melanoma Epidemiology and Current Therapeutic Options 26
2.2.2 Melanoma Medical Needs 28
2.2.2.1 PD-1 Refractory Melanoma 28
2.2.2.2 First-line (1L) Advanced Melanoma 28
2.2.2.3 Neoadjuvant Melanoma 29
2.2.2.4 Melanoma Brain Metastasis 30
2.3 Pembrolizumab Pharmaceutical and Therapeutic Background **31**
2.4 Investigational Agent Pharmaceutical and Therapeutic Background **32**
2.5 Scientific Rationale for the Combination of Investigational Agents With or Without Pembrolizumab **32**
2.6 Clinical Data on the Combination of Investigational Agents With or Without Pembrolizumab **33**
2.7 Benefit/Risk Assessment **33**
3 HYPOTHESES, OBJECTIVES, AND ENDPOINTS **34**
4 STUDY DESIGN **37**
4.1 Overall Design of the Substudy **37**
4.1.1 Investigational Treatment Arms 38
4.1.1.1 Efficacy Phase 38
4.1.1.2 All Substudy Participants 39
4.1.2 Stratification 41
4.1.3 Randomization/Allocation 41
4.1.3.1 Rationale for Randomization 41
4.1.4 Criteria for Adding Arms 41
4.1.5 Criteria for Removing Arms 41
4.2 Scientific Rationale for Substudy Design **42**

4.2.1 Rationale for Endpoints 43
4.2.1.1 Efficacy Endpoints 43
4.2.1.1.1 RECIST 1.1 44
4.2.1.2 Safety Endpoints 44
4.2.1.3 Pharmacokinetic Endpoints 44
4.2.1.4 Pharmacodynamic Endpoints 44
4.2.1.4.1 Antidrug Antibody Assessments 44
4.2.1.5 Planned Exploratory Biomarker Research 44
4.3 Justification for Dose 46
4.3.1 Rationale for Pembrolizumab Dosing Plan 46
4.3.2 Rationale for Investigational Agent Dosing Plan 48
4.4 Beginning and End of Study Definition 48
4.4.1 Clinical Criteria for Early Study Termination 49
5 STUDY POPULATION 50
5.1 Inclusion Criteria 50
5.2 Exclusion Criteria 53
5.3 Lifestyle Considerations 56
5.3.1 Meals and Dietary Restrictions 56
5.3.2 Caffeine, Alcohol, and Tobacco Restrictions 56
5.3.3 Activity Restrictions 56
5.3.4 Investigational Agent Contraception, Pregnancy, and Use in Nursing Women 56
5.4 Screen Failures 57
5.5 Participant Replacement Strategy 57
6 STUDY INTERVENTION 58
6.1 Study Intervention(s) Administered 58
6.2 Preparation/Handling/Storage/Accountability 60
6.2.1 Dose Preparation 60
6.2.2 Handling, Storage, and Accountability 60
6.3 Measures to Minimize Bias: Randomization and Blinding 61
6.3.1 Intervention Assignment 61
6.3.2 Stratification 61
6.3.3 Blinding 61
6.4 Study Intervention Compliance 61
6.5 Concomitant Therapy 62
6.5.1 Allowed Concomitant Medications 63
6.5.2 Prohibited Concomitant Medications 63
6.5.3 Rescue Medications and Supportive Care 64

6.5.4 Hematopoietic Growth Factors 65
6.6 Dose Modification (Escalation/Titration/Other) 65
6.6.1 Dose Modification for Pembrolizumab 65
6.6.1.1 Immune-Related Events and Dose Modification (Withhold, Treat, Discontinue) 65
6.6.1.2 Dose Modification and Toxicity Management of Infusion Reactions Related to Pembrolizumab 70
6.6.1.3 Other Allowed Dose Interruptions for Pembrolizumab 73
6.6.2 Dose Modification for Investigational Agent Intervention 73
6.6.3 Dose Modifications for Overlapping Toxicities 73
6.7 Intervention After the End of the Study 73
6.8 Clinical Supplies Disclosure 73
6.9 Standard Policies 73
6.9.1 Study Site Retention Samples 73
7 DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT WITHDRAWAL 74
7.1 Discontinuation of Study Intervention 74
7.2 Participant Withdrawal From the Study 75
7.3 Lost to Follow-up 76
8 STUDY ASSESSMENTS AND PROCEDURES 77
8.1 Administrative and General Procedures 78
8.1.1 Informed Consent 78
8.1.1.1 General Informed Consent 78
8.1.1.2 Specific Informed Consent 79
8.1.1.3 Consent and Collection of Specimens for Future Biomedical Research 79
8.1.2 Inclusion/Exclusion Criteria 79
8.1.3 Participant Identification Card 79
8.1.4 Medical History 79
8.1.5 Prior and Concomitant Medications Review 80
8.1.5.1 Prior Medications 80
8.1.5.2 Concomitant Medications 80
8.1.6 Assignment of Screening Number 80
8.1.7 Assignment of Treatment/Randomization Number 80
8.1.8 Study Intervention Administration 81
8.1.8.1 Timing of Dose Administration 81
8.1.8.1.1 Pembrolizumab Administration 81
8.1.8.1.2 Investigational Agents Administration 81
8.1.9 Discontinuation and Withdrawal 81

8.1.10 Participant Blinding/Unblinding 81
8.1.11 Domiciling 81
8.1.12 Calibration of Equipment 82
8.2 Efficacy/Immunogenicity Assessments 82
8.2.1 Tumor Imaging and Assessment of Disease 82
8.2.1.1 Initial Tumor Imaging 82
8.2.1.2 Tumor Imaging During the Substudy 83
8.2.1.3 End of Treatment and Follow-up Tumor Imaging 84
8.2.1.4 RECIST 1.1 Assessment of Disease 84
8.2.2 Quality of Life Assessments 84
8.3 Safety Assessments 84
8.3.1 Physical Examinations 84
8.3.2 Vital Signs 85
8.3.3 Electrocardiograms 85
8.3.4 Multiple-gated Acquisition Scan or Echocardiogram 85
8.3.5 Clinical Safety Laboratory Assessments 85
8.3.5.1 Urine Dipstick 86
8.3.6 Pregnancy Testing 86
8.3.7 Performance Assessments 86
8.4 Adverse Events, Serious Adverse Events, and Other Reportable Safety Events 86
8.4.1 Time Period and Frequency for Collecting AE, SAE, and Other Reportable Safety Event Information 86
8.4.2 Method of Detecting AEs, SAEs, and Other Reportable Safety Events 89
8.4.3 Follow-up of AE, SAE, and Other Reportable Safety Event Information 89
8.4.4 Regulatory Reporting Requirements for SAE 89
8.4.5 Pregnancy and Exposure During Breastfeeding 90
8.4.6 Disease-related Events and/or Disease-related Outcomes Not Qualifying as AEs or SAEs 90
8.4.7 Events of Clinical Interest 90
8.5 Treatment of Overdose 91
8.6 Pharmacokinetics 91
8.6.1 Blood Collection for Serum MK-3475 91
8.6.2 Blood Collection for Investigational Agents 91
8.7 Pharmacodynamics 92
8.8 Patient-Reported Outcomes 92
8.9 Biomarkers 92
8.9.1 Planned Genetic Analysis Sample Collection 93

8.10 Future Biomedical Research Sample Collection 93
8.11 Health Economics Medical Resource Utilization and Health Economics 93
8.12 Visit Requirements 93
8.12.1 Screening 94
8.12.1.1 Rescreening 94
8.12.2 Treatment Period 94
8.12.3 Participants Discontinued From Study Intervention but Continuing to be Monitored in This Substudy 95
8.12.4 Safety Follow-up Visit 95
8.12.5 Imaging Follow-up Visit(s) 95
8.12.5.1 Follow-up Visits 95
8.12.5.2 Survival Follow-up 95
8.12.6 Vital Status 96
9 STATISTICAL ANALYSIS PLAN 97
9.1 Statistical Analysis Plan Summary 97
9.2 Responsibility for Analyses/In-house Blinding 99
9.3 Hypotheses/Estimation 99
9.4 Analysis Endpoints 99
9.4.1 Efficacy Endpoints 99
9.4.1.1 Primary 99
9.4.1.2 Secondary 99
9.4.1.3 Exploratory 100
9.4.2 Safety Endpoints 100
9.4.3 Patient-Reported Outcome Endpoints 100
9.4.4 Pharmacokinetic Endpoints 101
9.5 Analysis Populations 101
9.5.1 Efficacy Analysis Populations 101
9.5.2 Safety Analysis Population 101
9.5.3 Pharmacokinetic Analysis Populations 101
9.6 Statistical Methods 101
9.6.1 Statistical Methods for Efficacy Analysis 102
9.6.1.1 Objective Response Rate (ORR), Pathological Complete Response (pCR) Rate, Near Pathological Complete Response (Near pCR) Rate, and Pathological Partial Response (pPR) Rate 102
9.6.1.2 Recurrence-free Survival (RFS) 102
9.6.2 Statistical Methods for Safety Analysis 102
9.6.3 Demographic and Baseline Characteristics 102
9.6.4 Statistical Methods for Pharmacokinetics (PK) Analyses 102

9.7 Interim Analyses 103
9.8 Multiplicity 103
9.9 Sample Size and Power Calculations 103
9.10 Subgroup Analyses 104
9.11 Compliance (Medication Adherence) 104
9.12 Extent of Exposure 104
10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS 105
10.1 Appendix 1: Regulatory, Ethical, and Study Oversight Considerations 105
10.1.1 Code of Conduct for Interventional Clinical Trials 105
10.1.2 Financial Disclosure 108
10.1.3 Data Protection 108
10.1.3.1 Confidentiality of Data 108
10.1.3.2 Confidentiality of Participant Records 109
10.1.3.3 Confidentiality of IRB/IEC Information 109
10.1.4 Committees Structure 109
10.1.4.1 Scientific Advisory Committee 109
10.1.4.2 Internal Data Monitoring Committee 109
10.1.5 Publication Policy 109
10.1.6 Compliance with Study Registration and Results Posting Requirements 110
10.1.7 Compliance with Law, Audit, and Debarment 110
10.1.8 Data Quality Assurance 111
10.1.9 Source Documents 112
10.1.10 Study and Site Closure 112
10.2 Appendix 2: Clinical Laboratory Tests 113
10.3 Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting 115
10.3.1 Definitions of Medication Error, Misuse, and Abuse 115
10.3.2 Definition of AE 115
10.3.3 Definition of SAE 116
10.3.4 Additional Events Reported in the Same Manner as SAE 117
10.3.5 Recording AE and SAE 118
10.3.6 Reporting of AEs, SAEs, and Other Reportable Safety Events to the Sponsor 121
10.4 Appendix 4: Device Events, Adverse Device Events, and Medical Device Incidents: Definitions, Collection, and Documentation 123
10.5 Appendix 5: Contraceptive Guidance 124
10.5.1 Definitions 124
10.5.2 Contraception Requirements 125

10.6 Appendix 6: Substudy Combination-specific Requirements 126
10.6.1 Status of Investigational Agents in this Substudy Protocol 126
10.6.2 Investigational Agent Information Summary 129
10.6.2.1 Section 1.3 Schedule of Activities 129
10.6.2.1.1 Section 1.3.1 Screening 129
10.6.2.1.2 Section 1.3.2 Pembrolizumab + MK-7684 (anti-TIGIT) 133
10.6.2.1.3 Section 1.3.3 Pembrolizumab + V937 154
10.6.2.1.4 Section 1.3.4 Pembrolizumab Monotherapy 169
10.6.2.1.5 Section 1.3.5 Pembrolizumab + MK-4830 (anti-ILT4) 181
10.6.2.1.6 Section 1.3.6 MK-4280A (Coformulation of MK-4280 + Pembrolizumab) 200
10.6.2.1.7 Section 1.3.7 Pembrolizumab + ATRA 217
10.6.2.2 Section 2.4 Investigational Agent Pharmaceutical and Therapeutic Background 228
10.6.2.2.1 Section 2.4.1 Preclinical Studies 230
10.6.2.2.2 Section 2.4.2 Ongoing Clinical Studies 238
10.6.2.3 Section 2.5 Scientific Rationale for the Combination of Investigational Agents With or Without Pembrolizumab 243
10.6.2.4 Section 2.6 Clinical Data on the Combination of Investigational Agents With or Without Pembrolizumab 247
10.6.2.5 Section 4.1 Overall Design of the Substudy 249
10.6.2.5.1 Section 4.1.1 Investigational Treatment Arms 249
10.6.2.6 Section 4.3 Justification for Dose 250
10.6.2.6.1 Section 4.3.2 Rationale for Investigational Agents Dosing Plan 250
10.6.2.7 Section 5.1 Inclusion Criteria Specific to the Investigational Agents Being Evaluated 254
10.6.2.8 Section 5.2 Exclusion Criteria Specific to the Investigational Agents Being Evaluated 255
10.6.2.9 Section 5.3 Lifestyle Considerations 256
10.6.2.9.1 Section 5.3.2 Caffeine, Alcohol, and Tobacco Restrictions 256
10.6.2.9.2 Section 5.3.4 Investigational Agent Contraception, Pregnancy, and Use in Nursing Women 257
10.6.2.10 Section 6.1 Study Intervention(s) Administered 257
10.6.2.11 Section 6.2 Preparation/Handling/Storage/Accountability 263
10.6.2.11.1 Section 6.2.1 Dose Preparation 263
10.6.2.11.2 Section 6.2.2 Handling, Storage, and Accountability 263
10.6.2.12 Section 6.3 Measures to Minimize Bias: Randomization and Blinding 264

10.6.2.12.1 Section 6.3.1 Intervention Assignment....264
10.6.2.13 Section 6.4 Study Intervention Compliance....264
10.6.2.14 Section 6.5 Concomitant Therapy....265
10.6.2.14.1 Section 6.5.2 Prohibited Concomitant Medications....265
10.6.2.14.2 Section 6.5.3 Rescue Medications and Supportive Care....266
10.6.2.15 Section 6.6 Dose Modification (Escalation/Titration/Other)....266
10.6.2.15.1 Section 6.6.2 Dose Modification for Investigational Agent Intervention....266
10.6.2.15.2 Section 6.6.3 Dose Modification for Overlapping Toxicities 270
10.6.2.16 Section 7.1 Discontinuation of Study Intervention....270
10.6.2.17 Section 8.1 Administrative and General Procedures....270
10.6.2.17.1 Section 8.1.1.2 Specific Informed Consent....270
10.6.2.17.2 Section 8.1.8 Study Intervention Administration....271
10.6.2.17.2.1 Section 8.1.8.1.2 Investigational Agents Administration....271
10.6.2.18 Section 8.5 Treatment of Overdose – Investigational Agents....271
10.6.2.19 Section 8.6 Pharmacokinetics....272
10.6.2.19.1 Blood Collection for Investigational Agents....272
10.7 Appendix 7: Collection and Management of Specimens for Future Biomedical Research....274
10.8 Appendix 8: AJCC 8th Edition Staging Criteria and Overall Staging Table....275
10.9 Appendix 9: ECOG Performance Status....279
10.10 Appendix 10: Surgery....280
10.11 Appendix 11: Country-specific Requirements....281
10.11.1 France....281
10.11.2 Germany....281
10.12 Appendix 12: Abbreviations....282
11 REFERENCES....287

LIST OF TABLES

Table 1 Adequate Organ Function Laboratory Values 53
Table 2 Study Interventions 59
Table 3 Dose Modification and Toxicity Management Guidelines for Immune-related Adverse Events Associated with Pembrolizumab Monotherapy, Coformulations or IO Combinations 66
Table 4 Pembrolizumab Infusion Reaction Dose Modification and Treatment Guidelines 71
Table 5 Reporting Time Periods and Time Frames for Adverse Events and Other Reportable Safety Events 88
Table 6 Operating Characteristics of Substudy 02C Interim Analysis for pCR 103
Table 7 Confidence Intervals for Different Observed pCR Rates in Each Investigational Treatment Arm in Substudy 02C 104
Table 8 Protocol-required Safety Laboratory Assessments 113
Table 9 Summary of Investigational Agents Activated for Randomization/Allocation 126
Table 10 Summary of Investigational Agents No Longer Activated for Randomization/Allocation 127
Table 11 Study Intervention 259
Table 12 Determination of Minimum Injectable Target Lesion Diameter at Treatment Initiation by Dose Level 262
Table 13 Dose Modification Guidelines for ATRA-Related Adverse Events 269
Table 14 Melanoma T Category Definition 275
Table 15 Melanoma N Category Definition 276
Table 16 Melanoma M Category Definition 277
Table 17 AJCC Clinical Prognostic Stage Groups (cTNM) 277
Table 18 AJCC Pathological (pTNM) Staging Groups 278

LIST OF FIGURES

Figure 1 Substudy 02C Design Overview 24
Figure 2 Substudy 02C Design 41
Figure 3 Results of a Dose Titration Study of Anti-TIGIT 18G10-IgG2a in the MC38 Colon Carcinoma Mouse Model 231
Figure 4 Antitumor Efficacy of Anti-TIGIT 18G10-IgG2a as a Single Agent and in Combination With Anti-PD-1 (muDX400) Therapy in the Murine Subcutaneous CT26 Colon Carcinoma Tumor-bearing Model .. 232

1 PROTOCOL SUMMARY

Four Phase 3 studies met prespecified futility criteria for OS or RFS: MK-7684A-003 in metastatic NSCLC with PD-L1 TPS ≥50% (OS HR, 1.06; 95% CI, 0.83-1.35), MK-7684A-007 in metastatic NSCLC with PD-L1 TPS ≥1% (OS HR, 1.14; 95% CI, 0.87 1.50), MK-7684A-008 in ES-SCLC (OS HR, 1.26; 95% CI, 1.00-1.59; presented at Society for Immunotherapy of Cancer 2024), and MK-7684A-010 in adjuvant melanoma (RFS HR, 1.25; 95% CI, 0.87-1.80; presented at Society for Melanoma Research 2024) (data on file). Overall, the lack of efficacy observed with MK-7684A rendered the risk-benefit balance unfavorable, so treatment with this investigational therapy was stopped in all studies. Based on these data, the Sponsor has made a strategic decision to discontinue the arm evaluating MK-7684 + pembrolizumab (Arm 1) in this study.

Additionally, the Sponsor has decided to discontinue arms evaluating V937 + pembrolizumab (Arm 2), pembrolizumab monotherapy (Arm 3), MK-4830 + pembrolizumab (Arm 4), MK-4280A monotherapy (Arm 5), and ATRA + pembrolizumab (Arm 6), based on Sponsor prioritization strategy. The decision to deprioritize development of V937, MK-4830, MK-4280A, and ATRA was made after a thorough evaluation of the data from these clinical programs and is not based on any safety concerns with any of these investigational agents

As of Amendment 7, enrollment is complete in Arms 1 through 6. All participants in Arms 1 to 5 have either completed or discontinued all study interventions and completed the safety follow-up. All participants in Arm 6 have either completed neoadjuvant study interventions, undergone surgical resection, and initiated adjuvant pembrolizumab monotherapy or have discontinued neoadjuvant or adjuvant study intervention.

At implementation of Amendment 7, the following changes apply to Arms 1 through 6. The changes listed below supersede any content/instructions from previous amendments:

- Participants receiving adjuvant pembrolizumab monotherapy may continue on study therapy per protocol.
- Imaging scans should no longer be submitted to CIV. However, for participants who are still on study treatment and deriving clinical benefit and will continue on study treatment until criteria for discontinuation are met, local tumor imaging should continue per local SOC schedule and local SOC method of assessment of imaging. All imaging as well as relevant objectives and endpoints will be assessed locally.
- PK/ADA samples will no longer be collected.
- Biomarker samples will no longer be collected.
- Participants who complete study treatment or otherwise meet EOT criteria will be discontinued from the study after the EOT visit and any required safety follow-up visit.
- There will be no follow-up for survival status. Participants currently in imaging follow-up or survival follow-up are considered to have completed the study and therefore should

obtain imaging and further oncological care per local standard of care. However, standard safety reporting should continue, as applicable.

- Those participants remaining on the study at the time of Amendment 7 should continue to be monitored in the study through the AE reporting period (Section 8.4).
- All analyses prespecified in Section 9.7 for Arms 1 through 6 are complete at the time of Amendment 7.

Existing protocol content is retained for historical reference.

1.1 Synopsis

Protocol Title: A Phase 1/2 Open-Label Rolling-Arm Umbrella Platform Design of Investigational Agents With or Without Pembrolizumab or Pembrolizumab Alone in Participants with Melanoma (KEYMAKER-U02): Substudy 02C

Short Title: Ph 1/2 Substudy of Neoadjuvant Oncological Treatment(s) in MEL

Acronym: Not applicable

Hypotheses, Objectives, and Endpoints:

Formal hypothesis testing will not be performed in this substudy protocol. The objectives will be evaluated by investigational treatment arm.

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

In Stage IIIB to Stage IIID melanoma participants who are candidates for neoadjuvant treatment receiving investigational agents in combination with or without pembrolizumab or pembrolizumab alone:

Primary Objectives	Primary Endpoints
- To assess the safety and tolerability of investigational treatment combinations based on the proportion of participants with adverse events (AEs).	- Adverse events - Study intervention discontinuations due to AEs
- To evaluate pathological complete response (pCR) rate as assessed by central review of the pathology results.	- pCR: Complete absence of viable tumor in the treated tumor bed.

Secondary Objectives	Secondary Endpoints
- To evaluate the near pathological complete response (near pCR) rate as assessed by central review of the pathology results.	- Near pCR: More than 0% but less than or equal to 10% of viable tumor cells in the treated tumor bed.
- To evaluate pathological partial response (pPR) rate as assessed by central review of the pathology results.	- pPR: More than 10% but less than or equal to 50% of viable tumor cells in the treated tumor bed.
- To evaluate recurrence-free survival (RFS) as assessed by the investigator.	- RFS: the time from the date of surgery to (1) any recurrence (local, regional, or distant) or (2) death due to any cause (both cancer and noncancer causes of death).

Overall Design:

Study Phase	Phase 1/Phase 2
Primary Purpose	Treatment
Indication	Melanoma
Population	Male/female participants with melanoma who are at least 18 years of age
Study Type	Interventional
Intervention Model	Parallel This is a multi-site rolling-arm substudy
Type of Control	No Control Arm
Study Blinding	Unblinded Open-label
Blinding Roles	No Blinding
Estimated Duration of Substudy	The Sponsor estimates that the substudy will require approximately 7 years per investigational treatment arm from the time the first participant (or their legally acceptable representative) provides documented informed consent until the last participant's last substudy-related contact.

Number of Participants:

This substudy protocol employs a design in which new investigational treatment arms will be open for enrollment on a rolling basis to evaluate investigational treatment agents with pembrolizumab. Therefore, the total number of participants will depend on the number of investigational treatment arms open for enrollment.

A maximum of approximately 25 participants in each pembrolizumab-based combination investigational treatment arm and approximately 15 participants in the pembrolizumab monotherapy arm.

Intervention Groups and Duration:

<table>
<tr><td>Intervention Groups</td><td>
<table>
<tr><th></th><th>Drug</th><th>Dose Strength</th><th>Dose Frequency</th><th>Route of Administration</th><th>Regimen/ Treatment Period</th><th>Use</th></tr>
<tr><td rowspan="2">Substudy 02C</td><td>Pembrolizumab</td><td>200 mg
400 mg</td><td>Q3W
Q6W</td><td>IV</td><td>~1 year</td><td>Test Product</td></tr>
<tr><td>Investigational Agent(s)[a]</td><td colspan="3">Please see Appendix 6, Section 10.6.1.</td><td>~6 weeks</td><td>Test Product</td></tr>
<tr><td colspan="7">Abbreviations: Q3W = every 3 weeks; Q6W = every 6 weeks; IV = intravenously
a An investigational treatment arm refers to a combination of investigational agent(s) with or without pembrolizumab, or pembrolizumab alone. There can be 1 or more than 1 investigational treatment arm open for enrollment at any given time. The investigational treatment arm(s) open for enrollment are described in Appendix 6, Section 10.6.1.</td></tr>
</table>
</td></tr>
<tr><td>Total Number</td><td>The total number of investigational treatment arms will depend on the number of investigational agents evaluated. This substudy protocol will include a minimum of 3 investigational treatment arms. Refer to Appendix 6, Section 10.6.1.</td></tr>
<tr><td>Duration of Participation</td><td>Each participant will participate in this substudy for approximately 6 years from the time the participant provides documented informed consent through the final protocol-specified contact.

This substudy protocol will include participants with Stage IIIB to Stage IIID melanoma who are candidates for neoadjuvant treatment. This substudy protocol will consist of multiple investigational treatment arms evaluating a combination of investigational agents with or without pembrolizumab or pembrolizumab alone. If more than 1 investigational treatment arm is open at any given time, participants will be randomly assigned to 1 of the investigational treatment arms open for enrollment.

After a Screening Phase of up to 28 days, each participant will receive neoadjuvant study intervention with pembrolizumab alone or a combination of investigational treatment agents for approximately 5 weeks from the first dose of study intervention followed by surgical resection of the tumor (also called definitive surgery or surgery with curative intent). No additional doses of neoadjuvant study intervention with an investigational treatment arm beyond the ones specified in the protocol may be given. Surgical</td></tr>
</table>

	resection of the tumor includes lymphadenectomy of the tumor-involved lymph node disease and/or in-transit metastases and resection of the primary cutaneous melanoma lesion ± wide local excision, if not resected previously. Prior to the surgical resection of the tumor, a radiologic evaluation will be performed at Week 6 from the first dose of study intervention (±7 days). Surgical resection of the tumor should be scheduled for Week 6 (42 days ±7 days) and performed by experienced melanoma surgeons. Neoadjuvant treatment will be discontinued if any of the following occur: disease progression is radiographically documented per RECIST 1.1 by the investigator prior to surgical resection of the tumor such that the participant cannot receive the planned surgical resection or requires additional surgery, unacceptable AEs are reported, or any other discontinuation criterion has been met (Section 7.1). After disease progression per RECIST1.1, but the tumor is still resectable and the participant is achieving a clinically meaningful benefit, continued study treatment requires consultation with the Sponsor. Participant who develops distant metastasis must be discontinued from study treatment. Following the Week 6 surgical tumor resection, participants will have a tumor imaging assessment performed at Week 12 to establish a new baseline prior to the start of adjuvant therapy. Prior to the initiation of the adjuvant phase of the study, the investigator will also conduct a physical examination and review the pathology report of the surgical resection specimen(s) to ensure the participant is disease-free and the surgical margins are tumor-free (R0). Sponsor approval is required prior to initiation of adjuvant therapy. Once disease-free status has been confirmed, participants will receive adjuvant therapy with pembrolizumab monotherapy (dosing schedule specified in Appendix 6, Section 10.6.1) starting as soon as possible after surgery (interval between surgical resection and adjuvant pembrolizumab should not exceed 12 weeks) and continuing until the total treatment duration including both neoadjuvant and adjuvant therapy is approximately 1 year or until they experience disease recurrence, unacceptable AEs are reported, consent is withdrawn, death, intercurrent illness that prevents further administration of study intervention, investigator's decision to discontinue the participant, noncompliance with study intervention or procedure, or administrative reasons requiring cessation of study intervention, whichever occurs first. Disease recurrence will be documented by the investigator radiographically and/or by examination and, when clinically appropriate, pathologically confirmed by the site. After the end of adjuvant treatment each participant will be followed for approximately 5 years.

	After the EOT, each participant will be followed for the occurrence of AEs and spontaneously reported pregnancy. Participants who discontinue due to disease recurrence will move into posttreatment Safety and Survival Follow-up. Participants who discontinue for reasons other than disease recurrence will have posttreatment Safety and Follow-up imaging for disease status until disease recurrence is documented, a nonstudy cancer treatment is initiated, consent is withdrawn, pregnancy, death, or becoming lost to follow-up. All participants will be followed for OS until death, withdrawal of consent, or the end of this substudy. Please see Appendix 6, Section 10.6.2 for additional details. Once the substudy objectives are achieved or the substudy has ended, participants will be discontinued from this substudy protocol and may be enrolled in an extension study to continue assessments and treatment, if available. All pembrolizumab-based combinations that will be evaluated in this substudy protocol have safety data from a separate study, precluding the need for an internal data monitoring committee.

Study Governance Committees:

Executive Oversight Committee	No
Data Monitoring Committee	No
Clinical Adjudication Committee	No
Substudy governance considerations are outlined in Appendix 1.	

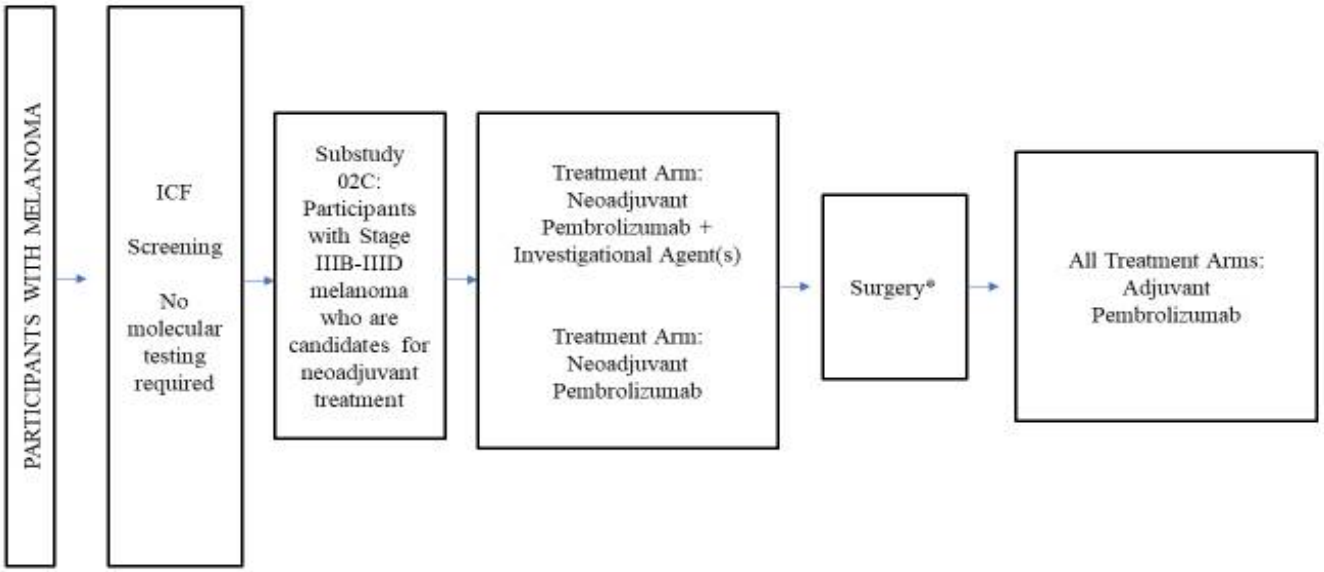
Study Accepts Healthy Volunteers: No

A list of abbreviations used in this document can be found in Appendix 12.

1.2 Schema

The overall substudy design is depicted in Figure 1.

Figure 1 Substudy 02C Design Overview



*Each participant will receive neoadjuvant study intervention with an investigational treatment arm for up to approximately 5 weeks from first dose of study intervention followed by surgical resection of the tumor (also called definitive surgery or surgery with curative intent).

1.3 Schedule of Activities

Refer to Appendix 6, Section 10.6.2.1 for the SoA for each investigational treatment arm.

2 INTRODUCTION

2.1 Study Rationale

Despite clear advances that have been taking place in the treatment of early as well as advanced melanoma in recent years, there are still medical needs and opportunities to improve the overall outcome of melanoma patients. This substudy protocol provides the framework for evaluating investigational agents (added to the backbone of a PD-1 receptor inhibitor or without an anti-PD-1 backbone) and anti-PD-1 monotherapy in substudies of patients who might benefit from these drugs and who need new treatment options. The infrastructure of this substudy protocol enables the rolling assignment of investigational agents as they become available in an efficient and cost-effective manner. This substudy protocol will include Stage IIIB to Stage IIID melanoma patients who are candidates for neoadjuvant treatment. The rationale for this substudy protocol is described in Section 2.2.2.

2.1.1 Rationale for the Use of Standard of Care Pembrolizumab

Pembrolizumab is standard of care in high-risk Stage III melanoma with lymph node involvement following complete resection (adjuvant treatment), in 1L advanced melanoma, and in patients with previously treated advanced melanoma. Pembrolizumab will be offered alone or in combination with other candidate investigational agents during the neoadjuvant phase of this substudy protocol and, per standard of care, as monotherapy to all participants during the adjuvant phase of this substudy protocol.

2.1.2 Rationale for Choice of Investigational Agent in This Substudy Protocol

Investigational agents that successfully attain a RP2D in Phase 1 studies, and whose mechanisms of action and toxicity profile make them logical candidates for subsequent study in Phase 1/2 in oncology will be tested in this substudy protocol. The candidate investigational agents are currently being evaluated in early phase studies as monotherapy alone and in combination with pembrolizumab.

See Appendix 6, Section 10.6.2.3 for a detailed rationale for each investigational agent.

2.2 Background

2.2.1 Melanoma Epidemiology and Current Therapeutic Options

Melanoma is the most serious form of skin cancer and affects adults of all ages. The 5-year prevalence of melanoma in the EU is approximately 326,000 patients with an incidence of approximately 83,000 new cases per year and approximately 16,000 deaths annually [WHO Health Organization 2012]. Melanoma accounts for approximately 5% of all new cases of cancer in the US. The incidence of melanoma continues to increase by almost 3% per year in the US. This translates to approximately 76,000 new cases a year with approximately 9000 associated deaths. The male-to-female incidence ratio of melanoma is 1.4:1 [Siegel, R., et al 2012]. The 5-year survival rate prior to the use of anti-PD-1 agents was 17% once patients had Stage IV disease [American Cancer Society 2016].

High-dose interleukin-2 was the first treatment to modify the natural history of patients with metastatic melanoma and may be curative for a small fraction of patients. However, its severe toxicity limited its application to carefully selected patients treated at centers with experience in managing the side effects of treatment. More recent research led to the development of immunotherapy using checkpoint inhibitors such as anti-PD-1 antibodies (pembrolizumab and nivolumab), and the anti-CTLA-4 antibody (ipilimumab) and targeted therapy such as BRAF and/or MEK inhibition (dabrafenib and/or trametinib, respectively). Both approaches prolong PFS and OS compared with chemotherapy [UpToDate, Inc. 2015]; thus, they are standard therapeutic options for patients with melanoma. More recently, the combination of a BRAF inhibitor plus a MEK inhibitor demonstrated increased efficacy and a better safety profile compared to BRAF inhibition alone as 1L therapy in patients with advanced melanoma. Both the combination of dabrafenib and trametinib or vemurafenib and cobimetinib are approved as 1L therapy in BRAF V600E mutation-positive melanoma patients [Robert, C., et al 2015] [Larkin, J., et al 2014]. The KEYNOTE-006 Phase 3 study demonstrated superior efficacy of pembrolizumab compared to ipilimumab in PFS and OS [Eggermont, A. M. M., et al 2018]. Similarly, nivolumab was studied in patients with previously untreated advanced melanoma compared to dacarbazine, and nivolumab showed superior efficacy compared to dacarbazine among previously untreated patients who had metastatic melanoma without BRAF mutation [Robert, C., et al 2015].

In 2014, the FDA approved both nivolumab and pembrolizumab for the treatment of patients with unresectable or metastatic melanoma and disease progression following ipilimumab and, if BRAF V600E mutation-positive, a BRAF inhibitor. The European Commission also approved pembrolizumab and nivolumab, for both 1L and previously treated patients with advanced melanoma.

Combination immunotherapy (anti-PD-1 + anti-CTLA-4) has shown high ORRs in patients with metastatic melanoma (ORR 58%); however, half of patients experienced significant toxicity from the treatment regimen [Valsecchi, M. E. 2015] [Postow, M. A., et al 2015] and survival benefit for this approach compared to anti-PD-1 agents has yet to be demonstrated.

There have also been recent advances in the treatment of earlier melanoma tumor settings, such as Stage IIB and IIC and Stage III patients following complete surgical resection of the primary tumor. Both PD-1 inhibitors pembrolizumab and nivolumab and the combination of BRAF and MEK inhibitors administered in the adjuvant setting have led to a decrease in the risk of recurrence compared to their respective controls [Eggermont, A. M. M., et al 2018a] [Weber, J., et al 2017] [Long, G. V., et al 2017] [Luke, J. J., et al 2022]. The combination of BRAF and MEK inhibitors has also demonstrated an increase in OS compared to placebo in the COMBI-AD study (ie, Dabrafenib With Trametinib in the Adjuvant Treatment of High risk BRAF V600 Mutation-positive Melanoma). The SWOG clinical trial S1404 was a randomized Phase III trial that found that adjuvant pembrolizumab for 1 year (647 patients) improved RFS in comparison with high-dose IFNα-2b for 1 year or ipilimumab for up to 3 years (654 patients), the approved SOC [Grossmann, K. F., et al 2022]. With all this significant advancement in the treatment of both adjuvant and advanced melanoma, which has led to a change in the treatment paradigm of melanoma patients, new medical needs have emerged as well as opportunities to continue to improve the outcomes of these patients.

2.2.2 Melanoma Medical Needs

2.2.2.1 PD-1 Refractory Melanoma

Analyses of clinical study data have identified 2 broad patterns of resistance to PD-1 inhibitors in patients with advanced melanoma: patients who fail to respond to PD-1 inhibitors administered as 1L therapy (also known as innate resistance), and patients who initially respond to therapy but eventually develop disease progression (also known as acquired resistance) [Pitt, J. M., et al 2016] [Restifo, N. P., et al 2016] [O'Donnell, J. S., et al 2017] [Sharma, P., et al 2017].

In addition, with the approval of anti-PD-1 agents in Stage III melanoma, while the majority of patients treated with adjuvant pembrolizumab are recurrence-free at 1 year (pembrolizumab 1-year RFS is 75.4% [95% CI: 71.3 to 78.9]), some patients do not benefit from adjuvant therapy and experience disease recurrence while on anti-PD-1 therapy or shortly thereafter [Eggermont, A. M. M., et al 2018a] [Weber, J., et al 2017] [Long, G. V., et al 2017].

Several mechanisms have been proposed to explain resistance to PD-1 inhibition, such as insufficient antitumor T-cell generation, inadequate antitumor T-cell effector function, or impaired T-cell memory. However, these mechanisms remain largely unknown [Jenkins, R. W., et al 2018].

Clinical data in this setting is very limited and unsatisfactory. Retrospective data in melanoma patients previously exposed to anti-PD-1 inhibitors showed an ORR to available checkpoint inhibitors (CTLA-4 and CTLA-4 + PD-1 combination) of 16% and 21%, respectively [Zimmer, L., et al 2017].

Phase 2 data of pembrolizumab plus ipilimumab immediately following progression on anti-PD-1 therapy in 17 evaluable melanoma patients showed an ORR of 47% and a disease control rate of 76% [Olsonm, D., et al 2018]. Recent results from the Phase 2 ILLUMINATE-204 study investigating tilsotolimod, an intratumorally delivered toll-like receptor agonist in combination with ipilimumab in 17 patients with unresectable or metastatic melanoma following failure of PD-1 inhibitor treatment, demonstrated an ORR of 47% and a disease control rate of 67% [Olsonm, D., et al 2018].

Therefore, this population represents a high medical need and effective therapies are urgently needed.

2.2.2.2 First-line (1L) Advanced Melanoma

Unresectable Stage III or Stage IV melanoma has historically been resistant to anticancer therapies and was associated with a median OS of less than 1 year. However, with the arrival of new therapies including targeted therapies such as BRAF and/or MEK inhibition for BRAF-mutant melanoma and immune checkpoint-based immunotherapy (anti-CTLA-4 and anti-PD-1 inhibitors), OS for patients with metastatic melanoma has tripled [Robert, C., et al 2015a] [Robert, C., et al 2015b] [Robert, C., et al 2015].

Mature data from KEYNOTE-006, with a median follow-up of 57.7 months (range: 0.03 to 62.1 months) confirms the long-term benefit of pembrolizumab in patients with advanced melanoma. The 5-year OS rate for patients treated with pembrolizumab was 38.7% and the 4-year PFS rate was 23.0% [Robert, C., et al 2019].

Despite these results, there is a large population of advanced melanoma patients (approximately 60% of all unresectable Stage III or Stage IV melanoma patients who receive anti-PD-1 inhibitors as 1L therapy for their advanced disease) who do not respond to therapy with anti-PD-1 agents.

More recently, the combination of anti-PD-1 and anti-LAG-3 was evaluated in RELATIVITY-047, a randomized, double-blinded trial in 714 patients with previously untreated metastatic or unresectable Stage III or IV melanoma. The trial demonstrated a statistically significant improvement in PFS by BICR for anti-PD-1 nivolumab plus anti-LAG-3 relatlimab, compared to nivolumab monotherapy (HR=0.75; 95% CI: 0.62, 0.92; *p*-value=0.006) [Tawbi, H. A., et al 2022].

Thus, the goal of evaluating combination strategies in this setting is to improve the overall outcome of patients with 1L advanced melanoma.

2.2.2.3 Neoadjuvant Melanoma

Surgery is the main treatment for Stage I or Stage II melanoma (tumor limited to the primary site) and Stage III melanoma (tumor invading regional lymph nodes). Although the long-term RFS rates for most patients with low-risk Stage I and Stage II melanoma are excellent following surgery, patients who have high risk features such as tumor-involved lymph nodes (Stage III) have poorer outcomes, with an average 5-year OS of approximately 50% [Gershenwald, J. E., et al 2017]. As mentioned above, adjuvant therapy with PD-1 inhibitors pembrolizumab and nivolumab and the combination of BRAF and MEK inhibitors is standard of care in patients with high-risk Stage III melanoma with lymph node involvement following complete resection.

While adequate and effective surgery is the goal of early treatment of primary melanoma, some cases with bulky nodal involvement are at high risk of local and distant recurrence despite upfront surgical resection. Neoadjuvant treatment offers the benefit of an early on-treatment pathological specimen that can be profiled for additional biomarkers and correlated with survival (pathological response as a surrogate marker for RFS and OS). Neoadjuvant treatment also allows to determine the efficacy of a treatment-of-interest within an individual patient and reduce the tumor burden before surgery, facilitating the procedure. Recent preclinical data also provide support for the superior activity of T-cell checkpoint blockade when given before surgery [Liu, J., et al 2016].

Patients with bulky resectable disease have been treated in pilot studies using a neoadjuvant approach with targeted therapy, and more recently, checkpoint inhibitors.

A Phase 2 clinical study of melanoma patients receiving neoadjuvant plus adjuvant dabrafenib and trametinib showed a RECIST 1.1 response rate after neoadjuvant-targeted

therapy of 85% (11 of 13 participants) and a pCR rate of 58% (7 of 12 participants). Compared to patients randomized to surgery followed by adjuvant targeted therapy, there was a statistically significant difference in the 12-month EFS favoring the neoadjuvant arm [Amaria, R. N., et al 2018].

Another Phase 2 clinical study in 20 participants with palpable Stage III melanoma randomized participants to receive ipilimumab 3 mg/kg and nivolumab 1 mg/kg, as either 4 doses after surgery (adjuvant arm) or 2 doses before surgery and 2 doses after surgery (neoadjuvant arm). Neoadjuvant therapy was feasible, with all participants undergoing surgery at the preplanned time point. However, in both arms, 9 of 10 participants experienced 1 or more Grade 3 or Grade 4 AEs. Pathological responses were achieved in 7 of 9 participants treated in the neoadjuvant arm, and 3 out of 9 participants had pCRs. None of these participants have relapsed with a median follow-up of 25.6 months [Blank, C. U., et al 2018].

Results from a separate randomized Phase 2 study of 2 doses of neoadjuvant nivolumab 3 mg/kg versus 2 doses of combined ipilimumab 3 mg/kg with nivolumab 1 mg/kg in 23 patients with high risk resectable melanoma yielded high response rates (RECIST 1.1 ORR 73%, pCR 45%) with substantial toxicity (73% Grade 3 treatment-related AEs) for the combination, whereas treatment with nivolumab monotherapy yielded modest responses (ORR 25%, pCR 25%) and lower toxicity (8% Grade 3 treatment-related AEs) [Amaria, R. N., et al 2018a].

Data with 1 dose of neoadjuvant pembrolizumab 200-mg fixed dose in 27 participants with resectable Stage III and Stage IV melanoma followed by curative resection and pembrolizumab therapy for 1 year confirmed that all participants were able to undergo surgery with no perioperative complications and the safety profile was consistent with the overall safety profile of pembrolizumab. Complete or near complete pathologic response was seen in 30% (n = 8) of participants at the time of resection and 1-year RFS was 55% [MedPage Today, LLC 2019].

The neoadjuvant clinical data described above is based on a small number of treated patients. However, because of the high risk of recurrence in Stage III melanoma with bulky resectable disease, the changing role of lymph node surgery in Stage III disease [Faries, M. B., et al 2017] and the advantages of neoadjuvant approaches described above, including an early prognostic readout, there is a high need to identify active combinations in this setting with an acceptable benefit-risk profile.

2.2.2.4 Melanoma Brain Metastasis

Melanoma has a high propensity to metastasize to the brain, with an incidence of 28.2% [Cagney, D. N., et al 2017]. A retrospective analysis of patients who presented with advanced regional melanoma (Stage IIIB and IIIC) treated with surgery and adjuvant therapy observed a 15% incidence of subsequent brain metastases [Sloan, A. E., et al 2009]. More than one third (37%) of patients with Stage IV melanoma eventually develop brain metastases, and the risk of brain metastases in advanced melanoma increases with disease

duration [Sloan, A. E., et al 2009]. In autopsy series of patients who die from melanoma, 55% to 75% have brain metastases at the time of death [Sloan, A. E., et al 2009].

Melanoma brain metastases have a high risk of spontaneous hemorrhage. Patients presenting with larger, symptomatic metastases are at higher risk for deteriorating performance status and worsening prognosis, and symptomatic patients often do not recover to baseline neurologic function following treatment, underscoring the importance of diagnosing brain metastases early and before symptoms develop [Raizer, J. J., et al 2008].

Locoregional therapies such as neurosurgical intervention, conformal radiation therapy, and SRS were once the mainstay of MBM treatment. In 54 patients with MBM treated with single fraction SRS before the development of effective systemic therapy, the rate of local control at 6 months was 87% and at 12 months, 68%. The overall survival rates at 6 and 12months were 50% and 25%, respectively [Bernard, M. E., et al 2012]. Single-agent BRAF inhibitors provide an intracranial response rate of 16% to 39%, whereas the combination of BRAFi/MEKi leads to response rate of up to 58% [Long, G. V., et al 2012] [Dummer, R., et al 2014]. The durability of responses induced by BRAFi/MEKi is shorter than in extracranial disease [Davies, M. A., et al 2017]. A pooled retrospective analysis of melanoma patients treated with pembrolizumab monotherapy in KEYNOTE-001, KEYNOTE-002, and KEYNOTE-006 demonstrated an ORR of 38.2% in patients with stable baseline brain metastasis and a disease control rate of 61.8%, compared to an ORR of 38.5% and DCR of 61.4% in patients with no baseline brain metastasis [Hamid, O., et al 2018]. CheckMate-204 and ABC independently confirmed that combination of ipilimumab and nivolumab is safe and has a high rate of durable intracranial responses (~55%) in patients with asymptomatic MBM [Long, G. V., et al 2017a] [Tawbi, H. A. H., et al 2017]. Antiangiogenic agents such as bevacizumab have also proven to enhance outcomes for patients with melanoma brain metastasis; a study of pembrolizumab with the VEGF-inhibiting agent bevacizumab in patients with MTM demonstrated an intracranial ORR of 60%, with an extracranial ORR of 62.5% [Kluger, H. M., et al 2019]. Additionally, it has been observed that anti-angiogenic therapy may be able to reduce serious brain toxicity (eg, brain edema) which is often caused by immune-oncologic agents [Tran, T. T., et al 2019] [Gerstner, E. R., et al 2009]. Finally, a Phase 1b/2 trial of pembrolizumab plus lenvatinib in patients with advanced solid tumors established promising antitumor activity for this combination in patients with metastatic melanoma with a manageable safety profile [Taylor, M. H., et al 2020].

2.3 Pembrolizumab Pharmaceutical and Therapeutic Background

The importance of intact immune surveillance function in controlling outgrowth of neoplastic transformations has been known for decades [Disis, M. L. 2010]. Accumulating evidence shows a correlation between tumor-infiltrating lymphocytes in cancer tissue and favorable prognosis in various malignancies. In particular, the presence of CD8+ T-cells and the ratio of CD8+ Teffs/FoxP3+ Tregs correlates with improved prognosis and long-term survival in solid malignancies such as ovarian, colorectal, and pancreatic cancer; hepatocellular carcinoma; malignant melanoma; and RCC. 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) [Dudley, M. E., et al 2005] [Hunder, N. N., et al 2008].

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 Ig-variable-type domain responsible for ligand binding and a cytoplasmic tail responsible for the binding of signaling molecules. The cytoplasmic tail of PD-1 contains 2 tyrosine-based signaling motifs, an immunoreceptor tyrosine-based inhibition motif, and an immunoreceptor tyrosine-based switch motif. Following T-cell stimulation, PD-1 recruits the tyrosine phosphatases, SHP-1 and SHP-2, to the immunoreceptor tyrosine-based switch motif within its cytoplasmic tail, leading to the dephosphorylation of effector molecules such as CD3 zeta, protein kinase C theta, and zeta-chain-associated protein kinase, which are involved in the CD3 T-cell signaling cascade [Okazaki, T., et al 2001] [Chemnitz, J. M., et al 2004] [Sheppard, K-A, et al 2004] [Riley, J. L. 2009]. The mechanism by which PD-1 down-modulates T-cell responses is similar to but distinct from that of CTLA-4, because both molecules regulate an overlapping set of signaling proteins [Parry, R. V., et al 2005] [Francisco, L. M., et al 2010]. Consequently, the PD-1/PD-L1 pathway is an attractive target for therapeutic intervention in melanoma.

Pembrolizumab is a potent humanized IgG4 mAb with high specificity of binding to the PD-1 receptor, thus inhibiting its interaction with PD-L1 and PD-L2. Preclinical in vitro data show that pembrolizumab has high affinity and potent receptor blocking activity for PD-1. Pembrolizumab has an acceptable preclinical safety profile and is in clinical development as an IV immunotherapy for advanced malignancies. Refer to the IB/approved labeling for detailed background information on pembrolizumab.

2.4 Investigational Agent Pharmaceutical and Therapeutic Background

Please refer to Appendix 6, Section 10.6.2.2 for background information on the investigational agents that are currently being assessed in this substudy protocol.

2.5 Scientific Rationale for the Combination of Investigational Agents With or Without Pembrolizumab

Please refer to Appendix 6, Section 10.6.2.3 for information on the scientific rationale for the combination of investigational agents with pembrolizumab or without pembrolizumab that are currently being assessed in this substudy protocol.

2.6 Clinical Data on the Combination of Investigational Agents With or Without Pembrolizumab

Please refer to Appendix 6, Section 10.6.2.4 for information on the clinical data on the combination of investigational agents with or without pembrolizumab that are currently being assessed in this substudy protocol.

2.7 Benefit/Risk Assessment

Beneficial effects of pembrolizumab have been seen in several melanoma studies to date. Publications of a significantly positive benefit/risk ratio have been reported for melanoma in single-arm and randomized studies as monotherapy (KEYNOTE-001, KEYNOTE-002, KEYNOTE-006, KEYNOTE-054, and KEYNOTE-716).

Given the relevance of improving and expanding treatment options for patients with melanoma, there is a high need for novel combinations in different tumor settings, as described in Section 2.2.2.

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

An advantage of the adaptive design of this substudy protocol is that it will allow rapid evaluation of multiple investigational agents with pembrolizumab in Stage IIIB to Stage IIID melanoma patients who are candidates for neoadjuvant treatment. This may identify new combination interventions with improved response rates over those described in the literature. Therefore, a potential benefit may be faster clinical development of novel interventions benefiting Stage IIIB Stage IIID melanoma patients while reducing exposure of patients to interventions that do not demonstrate improved clinical benefit. The combination of interventions may improve responsiveness in previously untreated tumors, where overall efficacy outcomes need to be improved. Potential risks of these novel combination interventions may be increased toxicity, intolerability, or unanticipated ADRs.

Additional details regarding specific benefits and risks for participants participating in this clinical substudy may be found in the accompanying IB and ICF documents.

3 HYPOTHESES, OBJECTIVES, AND ENDPOINTS

Formal hypothesis testing will not be performed in this substudy protocol. The objectives will be evaluated by investigational treatment arm.

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

In Stage IIIB to Stage IIID melanoma participants who are candidates for neoadjuvant treatment receiving investigational agents in combination with or without pembrolizumab or pembrolizumab alone:

Objectives	Endpoints
Primary	
• To assess the safety and tolerability of investigational treatment combinations based on the proportion of participants with adverse events (AEs).	• Adverse events • Study intervention discontinuations due to AEs
• To evaluate pathological complete response (pCR) rate as assessed by central review of the pathology results.	• pCR: Complete absence of viable tumor in the treated tumor bed.
Secondary	
• To evaluate the near pathological complete response (near pCR) rate as assessed by central review of the pathology results.	• Near pCR: More than 0% but less than or equal to 10% of viable tumor cells in the treated tumor bed.
• To evaluate pathological partial response (pPR) rate as assessed by central review of the pathology results.	• pPR: More than 10% but less than or equal to 50% of viable tumor cells in the treated tumor bed.
• To evaluate recurrence-free survival (RFS) as assessed by the investigator.	• RFS: the time from the date of surgery to (1) any recurrence (local, regional, or distant) or (2) death due to any cause (both cancer and noncancer causes of death).

Objectives	Endpoints
Tertiary/Exploratory	
• To evaluate overall survival (OS).	• OS: the time from the date of randomization/allocation to the date of death from any cause.
• To evaluate objective response rate (ORR) as assessed by investigator per Response Evaluation Criteria in Solid Tumors 1.1 (RECIST 1.1).	• Objective Response: CR or PR
• To characterize the pharmacokinetic (PK) profile of select agents in the pembrolizumab-based/non-pembrolizumab-based combinations.	• Serum concentration of agents combined with pembrolizumab/other investigational agents.
• To evaluate the development of circulating antidrug antibodies, of select agents, following administration of pembrolizumab-based/non-pembrolizumab-based combinations.	• Antidrug antibody (ADA) and/or neutralizing antibody levels.
• To identify molecular (genomic, metabolic, and/or proteomic) biomarkers that may be indicative of clinical response/resistance, safety, and/or the mechanism of action of pembrolizumab and investigational agents.	• Molecular (genomic, metabolic, and/or proteomic) determinants of response or resistance to treatments, using blood and/or tumor tissue.
• To evaluate the effects of neoadjuvant treatment on surgical outcomes.	• Surgical outcomes (episodes of infection at the wound site requiring IV antibiotics and/or wound drainage, number of episodes of seroma formation at the wound site requiring any intervention and volume of seroma drainage, number of episodes of bleeding from the wound requiring transfusion(s), incidence of lymphoedema).

Objectives	Endpoints
• To evaluate event-free survival (EFS) as assessed by the investigator.	• EFS: the time from the date of randomization/allocation to the date of the first progression during neoadjuvant therapy (only in case of distant metastasis or local progression that precludes surgery with curative intent), recurrence (local, regional, or distant metastasis), or death from any cause, whichever occurs first.

4 STUDY DESIGN

At implementation of Amendment 7, the following changes apply to Arms 1 through 6. The changes listed below supersede any content/instructions from previous amendments:

- Participants receiving adjuvant pembrolizumab monotherapy may continue on study therapy per protocol.
- Imaging scans should no longer be submitted to CIV. However, for participants who are still on study treatment and deriving clinical benefit and will continue on study treatment until criteria for discontinuation are met, local tumor imaging should continue per local SOC schedule and local SOC method of assessment of imaging. All imaging as well as relevant objectives and endpoints will be assessed locally.
- PK/ADA samples will no longer be collected.
- Biomarker samples will no longer be collected.
- Participants who complete study treatment or otherwise meet EOT criteria will be discontinued from the study after the EOT visit and any required safety follow-up visit.
- There will be no follow-up for survival status. Participants currently in imaging follow-up or survival follow-up are considered to have completed the study and therefore should obtain imaging and further oncological care per local standard of care. However, standard safety reporting should continue, as applicable.
- Those participants remaining on the study at the time of Amendment 7 should continue to be monitored in the study through the AE reporting period (Section 8.4).
- All analyses prespecified in Section 9.7 for Arms 1 through 6 are complete at the time of Amendment 7.

Existing protocol content is retained for historical reference.

4.1 Overall Design of the Substudy

The Master Protocol study is a Phase 1/2, rolling arm, multicenter, open-label, adaptive design study that will evaluate within this substudy protocol the efficacy of investigational treatment arms for the treatment of Stage IIIB to Stage IIID melanoma who are candidates for neoadjuvant therapy. Preliminary efficacy from this substudy protocol will be evaluated by using pCR rate, as determined by analysis of the surgical pathology specimen after surgical resection of the tumor. Throughout this protocol, the term RECIST 1.1 refers to the modification of RECIST 1.1 to include a maximum of 10 target lesions and a maximum of 5 target lesions per organ. Refer to Section 4.2.1.1.1 for further details.

In this substudy protocol, an investigational treatment arm refers to a unique investigational agent or a combination of investigational agents with pembrolizumab or pembrolizumab alone. Investigational agents will only be added to this substudy protocol after an initial

evaluation of safety and tolerability when administered alone and in combination with pembrolizumab has been completed and a RP2D has been identified.

Specific procedures to be performed during the substudy, as well as their prescribed times and associated visit windows, are outlined in the SoA in Appendix 6, Section 10.6.2.1. Details of each procedure are provided in Section 8 and in Appendix 6, Section 10.6.2.17, Section 10.6.2.18, and Section 10.6.2.19.

4.1.1 Investigational Treatment Arms

Please refer to Appendix 6, Section 10.6.2.5.1 for information on the investigational treatment arms that are currently being assessed in this substudy protocol.

This substudy protocol will include participants with Stage IIIB to Stage IIID melanoma who are candidates for neoadjuvant treatment. This substudy protocol will consist of multiple investigational treatment arms evaluating a combination of investigational agents with or without pembrolizumab or pembrolizumab alone. If more than 1 investigational treatment arm is open at any given time, participants will be randomly assigned to 1 of the investigational treatment arms open for enrollment. The substudy design is shown in Figure 2.

This substudy protocol will have 1 phase, an Efficacy Phase. A Safety Lead-in Phase is not part of this substudy protocol because all pembrolizumab-based combinations that will be evaluated have an established preliminary RP2D.

One IA is planned.

Endpoints are described in Section 4.2.1.

4.1.1.1 Efficacy Phase

This substudy protocol will enroll a minimum of 15 and a maximum of 25 participants in each investigational treatment arm.

One IA futility will be conducted for each investigational treatment arm after approximately 15 participants have been enrolled and the last participant has undergone surgical resection of the tumor. There is no enrollment pause during this IA futility assessment. The criteria of stopping enrollment for futility are specified below:

(1) If >4 out of 15 participants, or more than 30% of participants in the cohort, have progressive disease on neoadjuvant therapy, and as a result, their tumor(s) become unresectable prior to surgery.

OR

(2) If the observed pCR rate is 27% or less (≤4 of 15 participants with a pCR rate). Analysis of the surgical pathology specimen after surgical resection of the tumor will be used to evaluate pCR.

If neither is met, enrollment of the investigational treatment arm(s) will continue for a total of 25 participants. Enrollment in the neoadjuvant pembrolizumab monotherapy arm will not continue after 15 participants have been enrolled.

4.1.1.2 All Substudy Participants

A maximum of 25 participants are targeted for enrollment per pembrolizumab-based combination investigational treatment arm and 15 participants for the pembrolizumab monotherapy arm. Participants will be randomized equally to the combination investigational treatment arm(s) and to the pembrolizumab monotherapy arm until the pembrolizumab monotherapy arm reaches a total of 15 participants. Thereafter, participants will be randomized equally to all the open combination investigational treatment arms.

All participants will receive neoadjuvant pembrolizumab monotherapy or a combination of 1 or more investigational agent(s) with pembrolizumab for approximately 5 weeks from first dose of study intervention. Neoadjuvant treatment will be followed by surgical resection of the tumor. Surgical resection of the tumor includes lymphadenectomy of the tumor-involved lymph node disease and/or in-transit metastases and resection of the primary cutaneous melanoma lesion ± wide local excision (Appendix 10), if not resected previously. Prior to the surgical resection of the tumor, a radiologic evaluation will be performed at Week 6 from first dose of study intervention (±7 days). Surgical resection of the tumor should be scheduled for Week 6 (42 days ±7 days) from neoadjuvant C1D1 and performed by experienced melanoma surgeons. Surgery earlier than 5 weeks (35 days) from neoadjuvant C1D1 may be allowed in cases of progressive disease requiring surgery. This must be discussed with the Sponsor for approval. Neoadjuvant treatment will be discontinued if any of the following occur: disease progression is radiographically documented per RECIST 1.1 by the investigator prior to surgical resection of the tumor such that the participant cannot receive the planned surgical resection or requires additional surgery, unacceptable AEs are reported, or any other discontinuation criterion has been met (Section 7.1). After disease progression per RECIST1.1, but the tumor is still resectable and the participant is achieving a clinically meaningful benefit, continued study treatment requires consultation with the Sponsor. Participant who develops distant metastasis must be discontinued from study treatment.

Following the Week 6 surgical tumor resection, participants will have a tumor imaging assessment performed at Week 12 to establish new baseline prior to the start of adjuvant therapy. Prior to the initiation of the adjuvant phase of the study, the investigator will also conduct a physical examination and review the pathology report of the surgical resection specimen(s) to ensure the participant is disease-free and the surgical margins are tumor-free (R0). Sponsor approval is required prior to initiation of adjuvant therapy. Additionally, the surgical specimen will be sent for central pathology review. The investigator assessment is used to determine adjuvant study intervention, whereas central review is used for endpoint determination. Once disease-free status has been confirmed, participants will receive adjuvant therapy with pembrolizumab monotherapy (dosing schedule specified in Appendix 6, Section 10.6.1) starting as soon as possible after surgery (interval between surgical resection and adjuvant pembrolizumab can be as early as 4 weeks per investigator's discretion and should not exceed 12 weeks) (interval between post-surgery baseline imaging

and first dose of adjuvant dosing should not exceed 28 days) and continuing until the total treatment duration including both neoadjuvant and adjuvant therapy is approximately 1 year or until they experience disease recurrence, unacceptable AEs are reported, or any other discontinuation criteria has been met (Section 7.1). If more time is needed to start adjuvant treatment, consult with sponsor. If an incomplete resection of the tumor is performed, re-resection of the tumor followed by adjuvant therapy with pembrolizumab monotherapy will be allowed. If participants do not achieve a complete surgical resection of the tumor after resection or re-resection, subsequent adjuvant therapy with pembrolizumab will not be allowed in this substudy protocol.

Complete surgical resection of the tumor is defined as a disease-free status documented by new baseline imaging and a complete physical examination after surgical resection of the tumor prior to the start of adjuvant therapy, as well as tumor-free surgical margins (R0) after review of the pathology report of the surgical resection specimen(s) by the investigator. If participants experience disease progression per RECIST 1.1 that does not preclude surgery with curative intent during/after completion of neoadjuvant therapy and achieve a complete surgical resection of the tumor after surgical resection or re-resection of the tumor, they will be allowed to receive subsequent adjuvant therapy with pembrolizumab.

Participants who discontinue study intervention due to disease recurrence will move into posttreatment safety and survival follow-up. Participants who discontinue study intervention for reasons other than disease recurrence will have posttreatment safety assessments and follow-up imaging for disease status until disease recurrence is documented, a nonstudy cancer treatment is initiated, consent is withdrawn, pregnancy, death, or becoming lost to follow-up. All participants will be followed for OS until death, withdrawal of consent, or the end of this substudy (see Section 8.12.6).

An investigational treatment arm will be discontinued if the totality of the data does not support a favorable benefit-risk profile (see Section 4.1.5).

Follow-up visits and imaging schedules will be scheduled per the SoA (Appendix 6, Section 10.6.2.1). The primary safety endpoints of this substudy protocol are the proportion of participants with AEs and the proportion of participants who discontinue study intervention due to AEs; and the primary efficacy endpoint is the pCR rate as assessed by analysis of the surgical pathology specimen after surgical resection of the tumor.

Safety evaluations will include AE monitoring, physical examinations, clinical laboratory parameters (hematology and chemistry), vital signs, and assessment of ECOG performance status (see Appendix 9). Adverse events will be monitored throughout this substudy and graded in severity according to the guidelines outlined in the NCI CTCAE version 5.0. This substudy will be conducted in conformance with Good Clinical Practices.

Figure 2 Substudy 02C Design

4.1.2 Stratification

No stratification factors will be used in this substudy protocol.

4.1.3 Randomization/Allocation

Participants in this substudy protocol will be randomly allocated across all open investigational treatment if more than one investigational treatment arm is open for enrollment (Figure 1). If only 1 investigational treatment arm is available for enrollment, the treatment assignment will be deterministic.

4.1.3.1 Rationale for Randomization

Even though there is no intent to compare the treatment effect across investigational treatment arms, whenever 2 or more investigational treatment arms are open at the same time, randomization to investigational treatment arms will be used to decrease bias. Randomization to investigational treatment arms will occur centrally using an IRT system. More details on randomization are provided in Section 6.3.1.

4.1.4 Criteria for Adding Arms

The Sponsor will decide if an investigational agent should be studied in this substudy protocol based on the mechanism of action and toxicity profile observed in the Phase 1 studies. Once an investigational agent has been chosen, the Sponsor will decide in which investigational treatment arm(s) the investigational agent will be open for enrollment. The decision for which investigational treatment arm(s) a specific investigational agent will be assigned will be proposed by each study team based on the mechanism of action and the clinical development landscape.

New investigational agents will be added to this substudy protocol through an amendment by adding a new section in Appendix 6, Section 10.6.1, specific to that investigational agent (eg, Appendix 6, Section 10.6.2). In addition, Table 9 will be revised accordingly.

4.1.5 Criteria for Removing Arms

The enrollment in an arm may stop early after an interim futility analysis if the futility criteria is met. The totality of the data across all substudies, including the safety profile, pCR

rate, and change in tumor size from baseline will be included in the evaluation of either dropping or continuing an investigational treatment arm at an IA. Additionally, enrollment into an arm may stop early for issues related to enrollment or if risk/benefit is deemed unacceptable for a given investigational combination.

Investigational treatment arms may be inactivated from the substudy if they appear to offer a low probability of increased efficacy over the current treatment options/historical control available, based on the results of the IA. The IA may be performed for each investigational treatment arm after at least 15 participants have been enrolled in this substudy protocol and have undergone surgical resection of the tumor.

Following the IA, if the investigational treatment arm is to be discontinued, enrollment in the investigational treatment arm will be terminated and the participants will continue follow-up. However, the decision to further study the investigational agent(s) will be based on the totality of data from all substudies in the umbrella platform study, the data from other studies for the same investigational agent, as well as other factors such as the landscape for melanoma treatment at the time.

Investigational agents terminated for randomization/allocation will be inactivated from each substudy through an amendment. In addition, Table 9 and Table 10 will be revised accordingly.

4.2 Scientific Rationale for Substudy Design

The goal of this substudy protocol is to evaluate, on a rolling basis, the efficacy of investigational treatment arms in participants with Stage III melanoma candidates for neoadjuvant therapy to identify the investigational agent(s) that, when used in combination, are superior to the current treatment options/historical control available.

The umbrella platform study design provides the framework for testing investigational agents in this substudy protocol of patients with Stage IIIB to Stage IIID melanoma candidates for neoadjuvant therapy who might benefit from adding these drugs to the backbone of a PD-1 receptor blockade or to PD-1 blockade alone. The infrastructure of this substudy protocol enables the rolling assignment of investigational agents that are entering this Phase 1/2 study in an efficient and cost-effective manner to study the impact of each investigational treatment arm for these patients in need.

This substudy protocol employs an adaptive design in which treatments are added and/or inactivated from the substudy on an ongoing basis. Refer to Section 4.1.4 and Section 4.1.5, respectively.

4.2.1 Rationale for Endpoints

4.2.1.1 Efficacy Endpoints

The primary efficacy objective of this substudy protocol is to evaluate the antitumor effect of various investigational agents with or without pembrolizumab or pembrolizumab alone in participants with melanoma.

This substudy protocol will use the pCR rate as the primary efficacy endpoint. Pathologic complete response is defined as the complete absence of viable tumor in the treated tumor bed. The International Neoadjuvant Melanoma Consortium has recently standardized the pathologic evaluation of resected melanoma following neoadjuvant therapy including the assessment of pretreatment biopsies, initial specimen handling, histopathologic assessment of excised tumor-involved lymph nodes, and definition of pathologic response, including the definition of pCR described above [Tetzlaff, M. T., et al 2018]. The FDA has designated pCR as a surrogate endpoint to justify accelerated approval of a particular agent administered in the neoadjuvant (and adjuvant) setting for breast cancer [Center for Drug Evaluation and Research 2014] [Fumagalli, D., et al 2012].

This substudy protocol will use RFS, the near pCR rate, and the pPR rate as secondary efficacy endpoints. Recurrence-free survival is defined as the time from surgery to (1) any recurrence (local, regional, or distant) or (2) death due to any cause (both cancer and noncancer causes of death). Recurrence-free survival has been used as the primary outcome measure in a number of Phase 3 studies assessing anti-PD-1 therapy in the setting of Stage III adjuvant melanoma, including S1404/KN053, EORTC1325/KN054, CheckMate 238, and COMBI-AD [Eggermont, A. M. M., et al 2018a] [Weber, J., et al 2017] [Long, G. V., et al 2017]. Recurrence-free survival has also demonstrated to be a valid surrogate endpoint for OS for adjuvant randomized studies assessing checkpoint inhibitors in high risk melanoma after surgical resection [Suciu, S., et al 2018]. Preliminary data from neoadjuvant melanoma studies suggest a correlation of pCR with improved RFS among patients treated with neoadjuvant targeted and immune checkpoint therapies [Rozeman, E. A., et al 2017] [Spickard, A., et al 1963] [Amaria, R. N., et al 2018a]. Near pCR is defined as > 0% but ≤10% of viable tumor cells in the treated tumor bed. Pathologic response rate is defined as the proportion of participants who have >10% but ≤50% of the treated tumor bed occupied by viable tumor cells.

This substudy protocol will use ORR and EFS an exploratory efficacy endpoints. Objective response rate is defined as the proportion of participants who have best response as CR or PR. Responses are based on investigator assessment using RECIST 1.1, modified to follow a maximum of 10 target lesions and a maximum of 5 target lesions per organ. Event-free survival is defined as the time from randomization to the date of first progression during neoadjuvant therapy (only in case of distant metastasis or local progression that precludes surgery with curative intent), recurrence (local, regional, or distant metastasis), or death from any cause, whichever occurs first. Objective response rate is an appropriate endpoint to evaluate the antitumor activity of investigational treatment arms. Treatment effect measured by ORR can be a surrogate endpoint to support accelerated approval, a surrogate endpoint to support traditional approval, or it can represent direct clinical benefit based on the specific

disease, context of use, magnitude of the effect, the number of CRs, the durability of response, the disease setting, the location of the tumors, available therapy, and the benefit-risk relationship.

Additionally, this substudy protocol uses OS as an exploratory endpoint. OS has been recognized as the gold standard for the demonstration of superiority of a new antineoplastic therapy in randomized clinical studies. OS is defined as the time from date of randomization/allocation to date of death due to any cause.

4.2.1.1.1 RECIST 1.1

RECIST 1.1 (modified to follow a maximum of 10 target lesions and a maximum of 5 target lesions per organ) will be used when assessing images for efficacy measures and by the local site when determining eligibility. Eligibility will also be prospectively assessed based on RECIST 1.1.

4.2.1.2 Safety Endpoints

Safety parameters commonly used for evaluating investigational systemic anticancer treatments are included as safety endpoints including, but not limited to, the incidence of, causality, and outcome of AEs/SAEs, and changes in vital signs and laboratory values. Adverse events will be assessed as defined by the NCI CTCAE, version 5.0.

4.2.1.3 Pharmacokinetic Endpoints

An exploratory objective of this substudy protocol is to characterize the PK profile of select investigational agents with or without pembrolizumab. The PK profile will be done for select agents separately. The serum concentrations of select investigational agents will be used to determine PK parameters (eg, C_{max}, AUC) for different investigational agents with or without pembrolizumab. Furthermore, the results of these analyses may be used in conjunction with safety and ADA endpoints to facilitate dosing strategies for the treatment combination.

4.2.1.4 Pharmacodynamic Endpoints

4.2.1.4.1 Antidrug Antibody Assessments

Formation of ADAs can potentially confound drug exposures at therapeutic doses, and prime for subsequent infusion-related toxicity. Antidrug antibody response at the beginning of some selected cycles of treatment will be determined to potentially understand drug metabolism, exposure, and safety. Antidrug antibody response to select investigational antibody agents and pembrolizumab will be evaluated in validated immunogenicity assays.

4.2.1.5 Planned Exploratory Biomarker Research

CCI [redacted]

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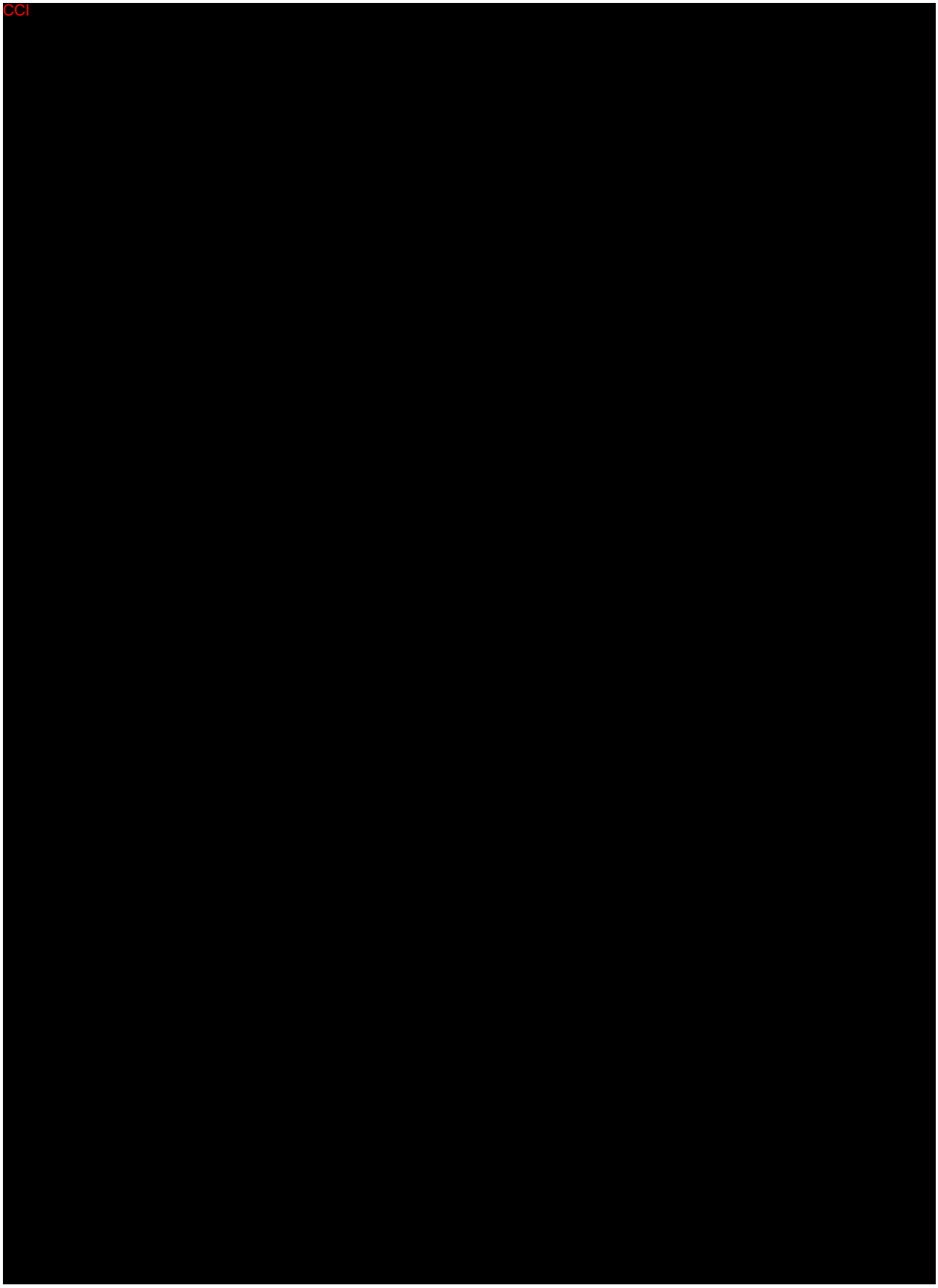

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4.3 Justification for Dose

4.3.1 Rationale for Pembrolizumab Dosing Plan

The planned doses of pembrolizumab for this substudy protocol are 200 mg Q3W and 400 mg Q6W.

Rationale for 200 mg Q3W dosing:

Based on the totality of data generated in the KEYTRUDA® development program, 200 mg Q3W is an appropriate dose of pembrolizumab for adults across all indications. As outlined below, this dose is justified by:

- Clinical data from 8 randomized studies in melanoma and NSCLC indications demonstrating flat dose- and exposure-efficacy relationships from 2 mg/kg Q3W to 10 mg/kg Q2W representing an approximate 5 to 7.5 fold exposure range (refer to the pembrolizumab IB, Section 5.2.

- Population PK analysis showing that both fixed dosing and weight-based dosing provides similar control of PK variability with considerable overlap in the distributions of exposures, supporting suitability of 200 mg Q3W,

- Clinical data showing meaningful improvement in benefit-risk including OS at 200 mg Q3W across multiple indications, and

- Pharmacology data showing full target saturation in both systemic circulation (inferred from PK data) and tumor (inferred from PBPK analysis) at 200 mg Q3W.

Among the 8 randomized, dose-comparison studies, a total of 2262 participants were enrolled with melanoma and NSCLC, covering different disease settings (treatment-naïve, previously treated, PD-L1 enriched, and all-comers) and different treatment settings (monotherapy and in combination with chemotherapy). Five studies compared 2 mg/kg Q3W versus 10 mg/kg Q3W (KN001 Cohort B2, KN001 Cohort D, KN002, KN010, and KN021), and 3 studies compared 10 mg/kg Q3W versus 10 mg/kg Q2W (KN001 Cohort B3, KN001 Cohort F2, and KN006). All of these studies demonstrated flat dose- and exposure-response relationships across the doses studied representing an approximate 5- to 7.5-fold difference in exposure.

The 2 mg/kg (or 200 mg fixed dose) Q3W provided similar responses to the highest doses studied. Subsequently, flat dose-/exposure-response relationships were also observed in other tumor types including head and neck cancer, bladder cancer, gastric cancer, and classical Hodgkin lymphoma, confirming 200 mg Q3W as the appropriate dose independent of the tumor type. These findings are consistent with the mechanism of action of pembrolizumab, which acts by interaction with immune cells, and not via direct binding to cancer cells.

Additionally, pharmacology data clearly show target saturation at 200 mg Q3W. First, PK data in KN001 evaluating target-mediated drug disposition conclusively demonstrated saturation of PD-1 in systemic circulation at doses much lower than 200 mg Q3W. Second, a PBPK analysis was conducted to predict tumor PD-1 saturation over a wide range of tumor penetration and PD-1 expression. This evaluation concluded that pembrolizumab at 200 mg Q3W achieves full PD-1 saturation in both blood and tumor. Finally, population PK analysis of pembrolizumab, which characterized the influence of body weight and other participant covariates on exposure, has shown that the fixed dosing provides similar control of PK variability as weight-based dosing, with considerable overlap in the distribution of exposures from the 200 mg Q3W fixed dose and 2 mg/kg Q3W dose. Supported by these PK

characteristics and given that fixed dose has advantages of reduced dosing complexity and reduced potential of dosing errors, the 200 mg Q3W fixed dose was selected for evaluation across all pembrolizumab protocols.

Rationale for 400 mg Q6W dosing:

A 400 mg Q6W dosing regimen of pembrolizumab is expected to have a similar benefit-risk profile as 200 mg Q3W in all treatment settings in which 200 mg Q3W pembrolizumab is currently approved [Lala, M., et al 2020]. Specifically, the dosing regimen of 400 mg Q6W for pembrolizumab is considered adequate based on M&S analyses, given the following rationale:

Pharmacokinetic simulations demonstrating that in terms of pembrolizumab exposures:

- C_{avg} (or AUC) at 400 mg Q6W is similar to that at the approved 200 mg Q3W dose, thus bridging efficacy between dosing regimens.

- C_{min} at 400 mg Q6W are generally within the range of those achieved with 2 mg/kg or 200 mg Q3W in the majority (>99%) of patients.

- C_{max} at 400 mg Q6W are well below the C_{max} for the highest clinically tested dose of 10 mg/kg Q2W, supporting that the safety profile for 400 mg Q6W should be comparable to the established safety profile of pembrolizumab.

- E-R for pembrolizumab has been demonstrated to be flat across indications, and OS predictions in melanoma and NSCLC demonstrate that efficacy at 400 mg Q6W is expected to be similar to that at 200 mg or 2 mg/kg Q3W, given the similar exposures; thus, 400 mg Q6W is expected to be efficacious across indications.

- The EMA has adopted a positive opinion recommending the approval of a new extended dosing schedule for KEYTRUDA® for all approved monotherapy indications in the EU. The CHMP opinion supports a new recommended dose of 400 mg Q6W delivered intravenously over 30 minutes. The 400 mg Q6W dosing schedule would provide patients in the EU with 2 approved dosing options of pembrolizumab [Merck & Co., Inc. 2019].

4.3.2 Rationale for Investigational Agent Dosing Plan

Please refer to Appendix 6, Section 10.6.2.6.1 for rationale for dosing information for the investigational agents that are currently being assessed in this substudy protocol.

4.4 Beginning and End of Study Definition

The overall study begins when the first participant (or their legally acceptable representative) provides documented informed consent. The overall study ends when the last participant completes the last study-related contact, withdraws consent, or is lost to follow-up (ie, the participant is unable to be contacted by the investigator), or the last participant on active treatment is consented in the extension study (if applicable). For purposes of analysis and

reporting, the overall study ends when the Sponsor receives the last laboratory test result or at the time of final contact with the last participant, whichever comes last.

If the study includes countries in the European Economic Area (EEA), the local start of the study in the EEA is defined as First Site Ready (FSR) in any Member State.

The Sponsor estimates that the maximum duration of the study from first participant entered through long-term follow-up will be 7 years (~5 years after study intervention has been completed) to attain the final assessment of the study (eg, to evaluate safety and/or long-term efficacy) for all evaluable participants. Refer to the Synopsis, Section 1.1, for the duration of participation of participants.

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 as a whole 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.

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

5 STUDY POPULATION

As stated in the Code of Conduct for Clinical Trials (Appendix 1.1), this study includes participants of varying age, race, ethnicity, and sex (as applicable). The collection and use of these demographic data will follow all local laws and participant confidentiality guidelines while supporting the study of the disease, its related factors, and the IMP under investigation.

Male and female participants with melanoma who are at least 18 years of age will be enrolled in this substudy protocol.

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

Refer to Appendix 6, Section 10.6.2.7 and Section 10.6.2.8 for additional inclusion or exclusion criteria, respectively, specific to the investigational agent(s) prior to randomization/allocation to ensure the participant meets all eligibility criteria.

5.1 Inclusion Criteria

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

Type of Participant and Disease Characteristics

1. Has histologically or cytologically confirmed melanoma.

2. Has clinically detectable and resectable Stage IIIB or IIIC or IIID melanoma per AJCC 8th Edition Staging Criteria (see Appendix 8), with 1 or more macroscopic lymph node metastases that can be biopsied, and no current or history of in-transit metastases within the last 6 months. Melanoma must be amenable to surgery with curative intent. At baseline, patients may have a primary cutaneous melanoma lesion in addition to tumor-involved lymph node disease. “Resectable” is defined as lesion(s) without significant vascular, central nervous system or bony involvement as per the surgeon’s judgment, where tumor-free margins (R0) can safely be achieved with surgery. Participants with multiple regional tumor-involved lymph nodes are eligible. Participants with gross or microscopic extracapsular nodal extension are eligible.

3. Has the presence of at least 1 measurable lesion by CT or MRI per RECIST 1.1 (≥ 1.5 cm in short axis for a tumor-involved lymph node).

4. Has been untreated for Stage IIIB, IIIC or IIID melanoma except as follows:

    a. Surgical resection and re-resection of the primary melanoma is allowed.

    b. Prior radiotherapy to the primary melanoma, including after prior surgical resection, is allowed.

    c. No other prior anticancer therapy is allowed.

5. Has provided a baseline tumor biopsy.

    a. Participants must submit a tumor sample during Screening for confirmation of adequacy of tumor tissue at a central pathology laboratory. If participants have only 1 measurable lesion per RECIST 1.1, the biopsy specimen should be obtained from the nontarget lesion or archival tissue from the primary tumor. If biopsy specimen was obtained from a lone target lesion, a repeat screening CT must be obtained post biopsy and measurable disease. Confirmation of presence of adequate tumor tissue by central pathology laboratory is required prior to randomization/allocation.

    b. The sites should submit tumor samples to the central pathology laboratory for assessment of the adequacy of tumor tissue and for biomarker analysis.

Demographics

6. Is male or female from 18 years to 120 years at the time of documented informed consent.

7. Has an ECOG performance status 0 to 1 (as assessed within 7 days of the first dose of study intervention, see Appendix 9).

Male Participants

8. Contraceptive use by men should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies. Contraception measures for the investigational agents are specified in Appendix 6, Section 10.6.2.7.

    Male participants are eligible to participate if they agree to the following during treatment with the investigational agents.

    - 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)

    - Note: Men with a pregnant or breastfeeding partner must agree to remain abstinent from penile-vaginal intercourse.

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

    - 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 the time specified in Appendix 6, Section 10.6.2.7 after the last dose of study intervention. Refer to Appendix 6, Section 10.6.1 for specific investigational agents. The investigator should evaluate the potential for contraceptive method failure (ie, noncompliance, recently initiated) in relationship to the first dose of study intervention.

- A WOCBP must have a negative highly sensitive pregnancy test (urine or serum as required by local regulations) within 24 hours before the first dose of study intervention.

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

- 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.

    Note: For female participants, contraception measures for the investigational agents are specified in Appendix 5 and Appendix 6, Section 10.6.2.7.

Informed Consent

10. The participant (or legally acceptable representative if applicable) has provided documented informed consent/assent for the study.

Additional Categories

11. Have adequate organ function as detailed in Table 1. Specimens must be collected within 7 days prior to the first dose of study intervention.

Table 1 Adequate Organ Function Laboratory Values

System	Laboratory Value
Hematological	
Absolute neutrophil count (ANC)	≥1500/µL
Platelets	≥100 000/µL
Hemoglobin	≥9.0 g/dL or ≥5.6 mmol/L[a]
Renal	
Creatinine OR Measured or calculated[b] creatinine clearance (GFR can also be used in place of creatinine or CrCl)	≤1.5 × ULN OR ≥30 mL/min for participant with creatinine levels >1.5 × institutional ULN
Hepatic	
Total bilirubin	≤1.5 × ULN OR direct bilirubin ≤ULN for participants with total bilirubin levels >1.5 × ULN except for unconjugated hyperbilirubinemia of Gilbert's syndrome.
AST (SGOT) and ALT (SGPT), and ALP	≤2.5 × ULN (≤5 × ULN for participants with liver metastases)[c]
Coagulation	
International normalized ratio (INR) OR prothrombin time (PT) Activated partial thromboplastin time (aPTT)/PTT	≤1.5 × ULN unless participant is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants

Abbreviations: ALP = alkaline phosphatase; ALT (SGPT) = alanine aminotransferase (serum glutamic pyruvic transaminase); AST (SGOT) = aspartate aminotransferase (serum glutamic oxaloacetic transaminase); CrCl = creatinine clearance; GFR = glomerular filtration rate; ULN = upper limit of normal.

a Criteria must be met without erythropoietin dependency and without packed red blood cell (pRBC) transfusion within last 2 weeks.

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

c Participants with ALP values >3 times the ULN and known to have bone metastases can be included.
Note: This table includes eligibility-defining laboratory value requirements for treatment; laboratory value requirements should be adapted according to local regulations and guidelines for the administration of specific chemotherapies.

12. Has resolution of toxic effect(s) of the most recent prior therapy to Grade 1 or less (except alopecia). If the participant received major surgery or radiation therapy of >30 Gy, they must have recovered from the toxicity (resolved to ≤ Grade 1) and/or complications from the intervention. Note: Grade 2 hypothyroidism will be allowed.

5.2 Exclusion Criteria

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

Medical Conditions

1. Has a diagnosis of immunodeficiency or is receiving chronic systemic steroid therapy (in dosing exceeding 10 mg daily of prednisone equivalent) or any other form of immunosuppressive therapy within 7 days before the first dose of study intervention. Participants with asthma that require intermittent use of bronchodilators, inhaled steroids, or local steroid injections would not be excluded from the study.

2. Has a known additional malignancy that is progressing or requires active treatment within the past 2 years. Exceptions to the secondary malignancy exclusion include basal cell carcinoma of the skin, squamous cell carcinoma of the skin, new non-ulcerated primary melanoma <1 mm in depth with no nodal involvement, Grade 1 follicular lymphoma, or carcinoma in situ (eg, breast carcinoma, cervical cancer in situ) that have undergone potentially curative therapy.

3. Participants must not have any evidence of CNS metastasis and/or carcinomatous meningitis.

4. Has ocular or mucosal melanoma.

5. Has known hypersensitivity to active substances or any of their excipients including previous clinically significant hypersensitivity reaction to treatment with another mAb. For a list of excipients, refer to the respective IB.

6. 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). Replacement therapy (eg, thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency) is not considered a form of systemic treatment and is allowed.

7. Has an active infection requiring systemic therapy.

8. Has known history of HIV (HIV 1/2 antibodies). No testing of HIV is required unless mandated by local health authority (see Appendix 11 for country-specific requirements).

9. Has known history of hepatitis B (defined as HBsAg reactive) or known hepatitis C virus (defined as HCV RNA [qualitative] is detected) infection.
Note: No testing for hepatitis B and hepatitis C is required unless mandated by local health authority (see Appendix 11 for country-specific requirements).

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

11. Has a history of active tuberculosis (TB; *Bacillus* tuberculosis). (See Appendix 11 for country-specific requirements).

12. A WOCBP who has a positive urine pregnancy test within 24 hours prior to randomization or treatment allocation (see Appendix 5). If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required.
Note: If more than 24 hours have elapsed between the Screening pregnancy test and the first dose of study intervention, another pregnancy test (urine or serum) must be performed and must be negative in order for the participant to start receiving study intervention.

Prior/Concomitant Therapy

13. Has received prior therapy with an anti-PD-1, anti-PD-L1, or anti-PD-L2 agent or with an agent directed to another stimulatory or co-inhibitory T-cell receptor (eg, CTLA-4, OX-40, CD137, TIGIT).

14. Has received prior systemic anticancer therapy including investigational agents within 4 weeks prior to randomization/allocation.

    Note: Participants must have recovered from all AEs due to previous therapies to ≤Grade 1 or baseline. Participants with ≤Grade 2 neuropathy and/or ≤Grade 2 endocrinopathy may be eligible.

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

15. Has received prior radiotherapy within 2 weeks of the first dose of study intervention. Participants must have recovered from all radiation-related toxicities, not require corticosteroids, and not have had radiation pneumonitis.

16. Has had major surgery (<3 weeks prior to the first dose of study intervention).
    Note: If the participant received major surgery, they must have recovered adequately from the toxicity and/or complications from the intervention prior to the first dose of study intervention. Adequate wound healing after major surgery must be assessed clinically, independent of time elapsed for eligibility.

17. Has received a live or live-attenuated vaccine within 30 days before the first dose of study intervention. Administration of killed vaccines are allowed.

    Refer to Section 6.5 for information on COVID-19 vaccines.

Prior/Concurrent Clinical Study Experience

18. Is currently participating in or has participated in a study of an investigational agent or has used an investigational device within 4 weeks prior to the first dose of study intervention.
    Note: Participants who have entered the Follow-up phase of an investigational study may participate if it has been 4 weeks since the last dose of the previous investigational agent.

Diagnostic Assessments

None.

Other Exclusions

19. Had a history or has current evidence of any condition, therapy, or laboratory abnormality that might confound the results of this substudy, interfere with the participation for the full duration of this substudy, or is not in the best interest of the participant to participate, in the opinion of the treating investigator.

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

21. Has had an allogeneic tissue/solid organ transplant.

5.3 Lifestyle Considerations

None for pembrolizumab. Please refer to Appendix 6, Section 10.6.2.9 for lifestyle considerations for specific investigational agents.

5.3.1 Meals and Dietary Restrictions

Participants should maintain a normal diet unless modifications are required to manage an AE such as diarrhea, nausea, or vomiting. Please refer to Appendix 6, 10.6.2.9 for investigational-agent-specific meals and dietary restrictions.

5.3.2 Caffeine, Alcohol, and Tobacco Restrictions

None for pembrolizumab. Please refer to Appendix 6, 10.6.2.9 for caffeine, alcohol, and tobacco considerations for specific investigational agents.

5.3.3 Activity Restrictions

None for pembrolizumab. Please refer to Appendix 6, 10.6.2.9 for activity restrictions for specific investigational agents.

5.3.4 Investigational Agent Contraception, Pregnancy, and Use in Nursing Women

Study intervention may have adverse effects on a fetus in utero. Refer to Appendix 5 for approved methods of contraception.

Participants should be informed that taking the study intervention may involve unknown risks to the fetus (unborn baby) if pregnancy were to occur during this substudy. To participate in this substudy, participants of childbearing potential must adhere to the contraception requirements (Appendix 5) from the day of study intervention initiation (or 14 days prior to the initiation of study intervention for oral contraception) throughout this substudy period up to 120 days after the last dose of study intervention. If there is any question that a participant of childbearing potential will not reliably comply with the requirements for contraception, that participant should not be entered into this substudy.

5.4 Screen Failures

Screen failures are defined as participants who provide documented consent to participate in the clinical substudy but are subsequently not randomized in this substudy. 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 entry guidelines.

5.5 Participant Replacement Strategy

A participant who discontinues from study intervention or withdraws from this substudy 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 substudy participant according to the substudy protocol.

Clinical supplies will be packaged to support enrollment. Clinical supplies will be affixed with a clinical label in accordance with regulatory requirements.

6.1 Study Intervention(s) Administered

The study interventions to be used in this substudy protocol are outlined in Table 2. See also Appendix 6, Section 10.6.2.10 for specific details on particular investigational agents to be used in this substudy protocol.

Table 2 Study Interventions

Inter-vention Group	Arm Type	Intervention Name	Type	Dose Formu-lation	Unit Dose Strengths	Dosage Levels	Route of Adminis-tration	Regimen/ Treatment Period	Use	IMP/ NIMP	Sourcing
Substudy 02C	Experi mental	Pembrolizumab	Drug	Solution for Infusion	25 mg/mL	200 mg 400 mg	IV Infusion	Q3W Q6W	Test Product	IMP	Central
Substudy 02C	Experi mental	Investigational Agent	Drug	TBD	TBD	TBD	TBD	TBD	Test Product	IMP	Central
Arm 3	Experi mental	Pembrolizumab (MK-3475)	Drug	Solution for Infusion	25 mg/mL	400 mg	IV Infusion	Q6W; 1 cycle in the neoadjuvant phase (C1D1) and up to 8 cycles in the adjuvant phase	Test Product	IMP	Central

Abbreviations: IMP = investigational medicinal product; IV = intravenous; NIMP = noninvestigational medicinal product; Q3W = every 3 weeks, Q6W = every 6 weeks; TBD = to be determined.

Note: 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.

Refer to Appendix 6, Section 10.6.2.10 for specific dosing information on the investigational agent(s).

All study interventions will be administered on an outpatient basis.

Pembrolizumab, as indicated in Table 2, will be provided centrally by the Sponsor. Investigational agents indicated in Appendix 6 Table 11 will be provided centrally by the Sponsor or locally by the study site, subsidiary or designee, depending on local country operational or regulatory requirements.

For any commercially available product that is provided by the study site, subsidiary, or designee, every attempt will be made to source these supplies from a single lot/batch number. The study site is responsible for recording the lot number, manufacturer, and expiry date for any locally purchased product as per local guidelines unless otherwise instructed by the Sponsor.

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

6.2 Preparation/Handling/Storage/Accountability

6.2.1 Dose Preparation

Details on preparation and administration of pembrolizumab and the investigational agents are provided in the Pharmacy Manual.

Refer to Appendix 6, Section 10.6.2.11.1 for a description of dose preparation and handling, storage, and accountability of the investigational agents.

6.2.2 Handling, Storage, and Accountability

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

Only participants enrolled in the substudy 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

This substudy protocol has no control arm (standard of care pembrolizumab monotherapy). When more than 1 investigational treatment arm is open for enrollment, randomization/allocation will be utilized to minimize bias. Randomization to investigational treatment arms will occur centrally using an IRT system.

6.3.2 Stratification

No stratification factors will be used in this substudy protocol.

6.3.3 Blinding

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

6.4 Study Intervention Compliance

Study intervention(s) will be administered by the investigator and/or study staff. The total volume of study medication infused will be compared with the total volume prepared to determine compliance with each dose administered.

Interruptions from the protocol-specified treatment ≥12 weeks require consultation between the investigator and the Sponsor and written documentation of the collaborative decision on participant management.

If participants are unable to undergo complete surgical resection due to development of irAE or an unrelated event such as intercurrent medical illness or life event, additional doses of neoadjuvant study intervention must be discussed with the Sponsor for approval with a plan to reschedule surgical resection at the safest and earliest timepoint.

Inability to coordinate surgical resection with the local surgeon is not an acceptable reason to administer additional doses of neoadjuvant study intervention.

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

time of dosing by a member of the study site staff other than the person administering the study intervention.

See Appendix 6, Section 10.6.2.13 for investigational agent-specific compliance information.

6.5 Concomitant Therapy

Medications or vaccinations specifically prohibited in the exclusion criteria are not allowed during the treatment period. If a clinical indication for any medication or vaccination is 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 or vaccination 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.

The following medications and vaccinations are prohibited during the study:

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

Note: Radiation therapy to a symptomatic solitary lesion or to the brain may be allowed at the investigator's discretion. Please refer to Section 6.5.2 Prohibited Concomitant Medications.

Live or live attenuated vaccines within 30 days before the first dose of study intervention and while participating in the study. Note: Killed vaccines are allowed.

Any medication (including over-the-counter medications) or therapy administered to the participant during this substudy (starting at the date of informed consent) will be recorded on the appropriate CRF. The investigator will record the AE for which the concomitant medication/therapy was administered on the appropriate CRF. If the concomitant medication/therapy is being administered for a medical condition present at the time of entry into this substudy, the investigator will record the medical condition on the appropriate CRF.

All prior medications (including over-the-counter medications) administered within 28 days prior to the first dose of study intervention and any concomitant therapy administered to the participant during the study (starting at the date of informed consent) and up to 30 days after the last dose of study intervention should be recorded. Additionally, all diagnostic, therapeutic, or surgical procedures relating to malignancy should be recorded. Any medication that is considered necessary for the participant's health, and that is not expected

to interfere with the evaluation of or interact with the study intervention, may be continued during this substudy.

6.5.1 Allowed Concomitant Medications

Treatment of complications or AEs or therapy to ameliorate symptoms (including blood products, blood transfusions, fluid transfusions, antibiotics, and antidiarrheal drugs) may be given at the discretion of the investigator, unless it is expected to interfere with the evaluation of (or to interact with) the study intervention. Anti-emetic or any other prophylaxis should be considered in accordance with institutional guidelines.

Any additional procedural or participant-specific particularities should be discussed with the investigator and the Sponsor.

6.5.2 Prohibited Concomitant Medications

Participants are prohibited from receiving the following therapies during the Screening, Treatment Phase, and Posttreatment Safety Follow-up Visit of this substudy protocol:

- Concurrent anticancer therapies such as chemotherapy, targeted therapies, antitumor interventions (surgical resection, surgical debulking of tumor, etc.), or cancer immunotherapy not specified in this protocol.

Note: Topical anticancer agents to treat skin lesions (eg, in situ melanoma or squamous cell carcinoma) are allowed, excluding skin metastasis of melanoma.

- Preoperative/Neoadjuvant Phase: Palliative surgery to treat a nontarget symptomatic solitary lesion or to the brain will be allowed after documented progressive disease. Palliative surgery to treat nontarget lesions without documentation of progressive disease will need Sponsor consultation and approval. Palliative surgery of target lesions without documentation of progressive disease is not allowed.

- Preoperative/Neoadjuvant Phase: Palliative radiotherapy to treat a nontarget symptomatic solitary lesion(s) or to the brain, will be allowed after documented progressive disease. Palliative radiotherapy to treat nontarget lesions without documentation of progressive disease will need Sponsor consultation and approval. Palliative radiotherapy of target lesions without documentation of progressive disease is not allowed.

- Other concurrent investigational drugs not specified in this protocol.

- Live or live attenuated vaccines within 30 days before the first dose of study intervention and while participating in the study.

  Note: Injectable killed vaccines are allowed.

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

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

- Systemic glucocorticoids for any purpose other than to modulate symptoms from an AE that is suspected to have immunologic etiology. Physiologic doses of corticosteroids not exceeding 10 mg daily of prednisone equivalent may be used during this substudy. Note: Inhaled steroids are allowed for management of asthma or seasonal allergies.

For participants who, in an assessment by the investigator, require the use of any of the aforementioned treatments for clinical management, continuation of study intervention, and further participation in the substudy must be discussed and agreed upon with the Sponsor. If participants receive additional anticancer therapies, this will be judged to represent evidence of disease progression (preoperative/neoadjuvant phase) or disease recurrence (postoperative phase) and study intervention will be discontinued. These participants should complete all EOT assessments and continue to be followed for survival in the Follow-up Period.

After the Posttreatment Safety Follow-up Visit, there are no prohibited therapies.

6.5.3 Rescue Medications and Supportive Care

Participants should receive appropriate supportive care measures as deemed necessary by the treating investigator. Suggested supportive care measures for the management of AEs with potential immunologic etiology for immunotherapeutic agents and other etiologies for investigational agents with a different mechanism of action are outlined along with the dose modification guidelines in each substudy. Where appropriate, these guidelines include the use of oral or IV treatment with corticosteroids, as well as additional anti-inflammatory agents if symptoms do not improve with administration of corticosteroids. Note that several courses of steroid tapering may be necessary as symptoms may worsen when the steroid dose is decreased. For each disorder, attempts should be made to rule out other causes such as metastatic disease or bacterial or viral infection, which might require additional supportive care. The treatment guidelines are intended to be applied when the investigator determines the events to be related to pembrolizumab or investigational agent(s) being explored in this protocol.

Note: If after the evaluation of an event it is determined to be not related to pembrolizumab or any other investigational agents, the investigator does not need to follow the treatment guidance.

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

6.5.4 Hematopoietic Growth Factors

Primary prophylactic use of G-CSF may be used per the discretion of the treating physician and in line with local guidelines.

6.6 Dose Modification (Escalation/Titration/Other)

6.6.1 Dose Modification for Pembrolizumab

Pembrolizumab dose reductions are not permitted. Pembrolizumab treatment may be interrupted or discontinued due to toxicity. Pembrolizumab may be interrupted for a maximum of 12 weeks. An interruption of pembrolizumab for more than 12 weeks will require Sponsor approval before treatment can be resumed (see Section 6.4).

6.6.1.1 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 3.

Please see Appendix 6, Section 10.6.2.15 for additional details, and Appendix 11 for country-specific requirements.

Table 3 Dose Modification and Toxicity Management Guidelines for Immune-related Adverse Events Associated with Pembrolizumab Monotherapy, Coformulations or IO Combinations

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

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

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

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

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

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

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

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

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

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

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

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

6.6.1.2 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 reactions are provided in Table 4.

Table 4 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.**	Participant may be premedicated 1.5 hours (± 30 minutes) prior to infusion of pembrolizumab with: • Diphenhydramine 50 mg orally (or equivalent dose of antihistamine). • Acetaminophen 500-1000 mg orally (or equivalent dose of analgesic).

NCI CTCAE Grade	Treatment	Premedication at Subsequent Dosing
Grades 3 or 4 **Grade 3:** Prolonged (ie, not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (eg, renal impairment, pulmonary infiltrates) **Grade 4:** Life-threatening; pressor or ventilatory support indicated	**Stop Infusion.** Additional appropriate medical therapy may include but is not limited to: - Epinephrine** - IV fluids - Antihistamines - NSAIDs - Acetaminophen - Narcotics - Oxygen - Pressors - Corticosteroids Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator. Hospitalization may be indicated. **In cases of anaphylaxis, epinephrine should be used immediately. **Participant is permanently discontinued from further study intervention.**	No subsequent dosing

Abbreviations: CTCAE = Common Terminology Criteria for Adverse Events; IV = intravenous; NCI = National Cancer Institute; NSAIDs = nonsteroidal anti-inflammatory drugs; PO = by mouth.
Note: 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 v5.0 at http://ctep.cancer.gov

6.6.1.3 Other Allowed Dose Interruptions 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 intervention within 3 weeks of the scheduled interruption for pembrolizumab, unless otherwise discussed with the Sponsor. The reason for interruption should be documented in the participant's substudy record. Imaging should not be delayed for delays in cycle treatment.

6.6.2 Dose Modification for Investigational Agent Intervention

Please refer to Appendix 6, Section 10.6.2.15.1 for dose modification information on the investigational agents that are currently being assessed in this substudy protocol.

6.6.3 Dose Modifications for Overlapping Toxicities

For overlapping toxicities where it is unclear if the event is related to pembrolizumab or the investigational agent(s), it is recommended to hold all study intervention, and initiate management as outlined in Section 6.6.1 and Appendix 6, Section 10.6.2.15.2. If toxicity does not improve, the investigator should consider discontinuing the participant.

6.7 Intervention After the End of the Study

No study-specified intervention following the end of this substudy is planned.

6.8 Clinical Supplies Disclosure

This substudy is open-label; therefore, the participant, the study site personnel, the Sponsor, and/or designee are aware of the specific treatment assignments. Study intervention is included in the label text; random code/disclosure envelopes or lists are not provided.

6.9 Standard Policies

Not applicable.

6.9.1 Study Site Retention Samples

Not applicable.

7 DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT WITHDRAWAL

At implementation of Amendment 7, the following changes apply to Arms 1 through 6. The changes listed below supersede any content/instructions from previous amendments:

- Participants receiving adjuvant pembrolizumab monotherapy may continue on study therapy per protocol.
- Imaging scans should no longer be submitted to CIV. However, for participants who are still on study treatment and deriving clinical benefit and will continue on study treatment until criteria for discontinuation are met, local tumor imaging should continue per local SOC schedule and local SOC method of assessment of imaging. All imaging as well as relevant objectives and endpoints will be assessed locally.
- PK/ADA samples will no longer be collected.
- Biomarker samples will no longer be collected.
- Participants who complete study treatment or otherwise meet EOT criteria will be discontinued from the study after the EOT visit and any required safety follow-up visit.
- There will be no follow-up for survival status. Participants currently in imaging follow-up or survival follow-up are considered to have completed the study and therefore should obtain imaging and further oncological care per local standard of care. However, standard safety reporting should continue, as applicable.
- Those participants remaining on the study at the time of Amendment 7 should continue to be monitored in the study through the AE reporting period (Section 8.4).
- All analyses prespecified in Section 9.7 for Arms 1 through 6 are complete at the time of Amendment 7.

Existing protocol content is retained for historical reference.

7.1 Discontinuation of Study Intervention

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

As certain data on clinical events beyond study intervention discontinuation may be important to the substudy, 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 continue to participate in the substudy as specified in the SoA and Section 8.12.3.

Participants may discontinue study intervention at any time for any reason or be discontinued from the study intervention at the discretion of the investigator should any untoward effect

occur. In addition, a participant may be discontinued from study intervention by the investigator or the Sponsor if study intervention is inappropriate, the substudy 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 substudy intervention but continue to be monitored in the substudy for any of the following reasons:

- The participant or participant's legally acceptable representative requests to discontinue study intervention.
- 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.
- Documented disease progression such that the patient cannot receive the planned surgical resection or requires additional surgery (preoperative/neoadjuvant phase) or documented disease recurrence (postoperative/adjuvant phase).
- Any progression or recurrence of any malignancy, or any occurrence of another malignancy, which requires active treatment. Exceptions to secondary malignancy include basal cell carcinoma of the skin, squamous cell carcinoma of the skin, new non-ulcerated primary melanoma <1 mm in depth with no nodal involvement, Grade 1 follicular lymphoma, or carcinoma in situ (eg, breast carcinoma, cervical cancer in situ) that have undergone potentially curative therapy. Exceptions should be discussed with the Sponsor prior to continuing therapy.
- Recurrent Grade 2 pneumonitis and other AEs that may require treatment discontinuation per Section 6.6 (Dose Modification).
- Completion of approximately 1 year of study intervention.

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

Discontinuation from substudy intervention is "permanent." Once a participant is discontinued from study intervention, the participant shall not be allowed to restart study intervention.

7.2 Participant Withdrawal From the Study

Specific details regarding procedures to be performed at the time of withdrawal from the substudy, 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 substudy 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

At implementation of Amendment 7, the following changes apply to Arms 1 through 6. The changes listed below supersede any content/instructions from previous amendments:

- Participants receiving adjuvant pembrolizumab monotherapy may continue on study therapy per protocol.
- Imaging scans should no longer be submitted to CIV. However, for participants who are still on study treatment and deriving clinical benefit and will continue on study treatment until criteria for discontinuation are met, local tumor imaging should continue per local SOC schedule and local SOC method of assessment of imaging. All imaging as well as relevant objectives and endpoints will be assessed locally.
- PK/ADA samples will no longer be collected.
- Biomarker samples will no longer be collected.
- Participants who complete study treatment or otherwise meet EOT criteria will be discontinued from the study after the EOT visit and any required safety follow-up visit.
- There will be no follow-up for survival status. Participants currently in imaging follow-up or survival follow-up are considered to have completed the study and therefore should obtain imaging and further oncological care per local standard of care. However, standard safety reporting should continue, as applicable.
- Those participants remaining on the study at the time of Amendment 7 should continue to be monitored in the study through the AE reporting period (Section 8.4).
- All analyses prespecified in Section 9.7 for Arms 1 through 6 are complete at the time of Amendment 7.

Existing protocol content is retained for historical reference.

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

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

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

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

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

8.1 Administrative and General Procedures

8.1.1 Informed Consent

The investigator or medically qualified designee (consistent with local requirements) must obtain documented consent from each potential participant or each participant's legally acceptable representative prior to participating in a clinical substudy. If there are changes to the participant's status during the substudy (eg, health or age of majority requirements), the investigator or medically qualified designee must ensure the appropriate consent is in place. Refer to Appendix 11 for country-specific requirements.

8.1.1.1 General Informed Consent

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

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

The initial ICF, any subsequent revised ICF, and any 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 substudy. The communication of this information will be provided and documented via a revised consent form or addendum to the original consent

form that captures the participant's or the participant's legally acceptable representative's dated signature.

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

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

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

8.1.1.2 Specific Informed Consent

Refer to Appendix 6, Section 10.6.2.17.1 for information about specific informed consent for the investigational agents that are currently being assessed in this substudy protocol.

8.1.1.3 Consent and Collection of Specimens for Future Biomedical Research

Not applicable.

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 this substudy protocol.

8.1.3 Participant Identification Card

All participants will be given a participant identification card identifying them as participants in a research substudy. The card will contain substudy 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/allocation, site personnel will add the treatment/randomization number to the participant identification card.

8.1.4 Medical History

A medical history will be obtained by the investigator or qualified designee. The medical history will collect all active conditions and any condition diagnosed within the prior 10 years that the investigator considers to be clinically important. Details regarding the disease for which the participant has enrolled in this substudy protocol will be recorded separately and not listed as medical history. If a medical condition is diagnosed at the time of screening due to the physical examination, laboratory tests, radiologic assessment, other assessment, and/or a combination of these evaluations, the medical condition is to be recorded as a baseline condition along with the participant's other medical history unless due to any

protocol-specified intervention (eg, procedure, washout or run-in treatment including placebo run-in).

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 starting this substudy. Treatment for the disease for which the participant has enrolled in this substudy protocol will be recorded separately and not listed as a prior medication.

8.1.5.2 Concomitant Medications

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

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 study intervention, the 30-day Safety Follow-up Visit should occur before the first dose of the new therapy.

8.1.6 Assignment of Screening Number

All consented participants will be given a unique screening number that will be used to identify the participant for all procedures that occur prior to randomization/allocation. 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/allocation. Once a treatment/randomization number is assigned to a participant, it can never be re-assigned to another participant.

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

8.1.8 Study Intervention Administration

Study intervention will be administered by the investigator and/or substudy staff.

8.1.8.1 Timing of Dose Administration

Study intervention will be administered on Day 1 of every treatment cycle. Study intervention should begin within 24 hours of randomization. See SoA for timing of administration of investigational agents.

8.1.8.1.1 Pembrolizumab Administration

During the preoperative/neoadjuvant phase, pembrolizumab will be administered as a 30-minute IV infusion on Day 1 or Day 8 of the first 2 treatment cycles if given Q3W or on Day 1 or Day 8 of the first treatment cycle if given Q6W and on Day 1 of each Q3W or Q6W treatment cycle during the postoperative/adjuvant phase. Sites should make every effort to target infusion timing to be as close to 30 minutes as possible. However, given the variability of infusion pumps from site to site, a window of -5 minutes and +10 minutes is permitted (ie, infusion time is 30 minutes: –5 min/ +10 min).

The Pharmacy Manual contains specific instructions for pembrolizumab reconstitution, preparation of the infusion fluid, and administration.

8.1.8.1.2 Investigational Agents Administration

See Appendix 6, Section 10.6.2.17 and Pharmacy Manual for specific details on the timing and administration procedures for each investigational agent. Investigational agents will be administered after pembrolizumab.

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 substudy visits.

When a participant withdraws from participation in this substudy protocol, all applicable activities scheduled for the final substudy 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.

8.1.10 Participant Blinding/Unblinding

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

8.1.11 Domiciling

Participants will not be domiciled.

8.1.12 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

Immunogenicity assessments will not be performed in this substudy protocol.

8.2.1 Tumor Imaging and Assessment of Disease

The process for image collection and transmission to the CIV can be found in the SIM. Diagnostic quality CT of the chest, abdomen, pelvis, and neck (if disease present) is required at baseline and at all scheduled follow-up visits. Tumor imaging is strongly preferred to be acquired by CT; the CT portion of PET/CT may be used in place of stand-alone CT if it is of diagnostic quality per the Site Imaging Manual. For the abdomen and pelvis, contrast-enhanced MRI may be used when CT with iodinated contrast is contraindicated, or when mandated by local practice. Magnetic resonance imaging is the strongly preferred modality for imaging the brain.

The same imaging technique regarding modality, ideally the same scanner, and the use of contrast should be used in a participant throughout this substudy to optimize the reproducibility of the assessment of existing and new tumor burden and improve the accuracy of the assessment of response or progression based on imaging. Note: for the purposes of assessing tumor imaging, the term “investigator” refers to the local investigator at the site and/or the radiological reviewer at the site or at an offsite facility.

Brain imaging is required for all participants at Screening. Magnetic resonance imaging is preferred; however, CT imaging will be acceptable, if MRI is medically contraindicated.

All scheduled images for all substudy participants from the sites will be submitted to the CIV. In addition, images (including via other modalities) that are obtained at an unscheduled time point to determine disease progression, as well as imaging obtained for other reasons, but captures radiologic progression based on investigator assessment, should also be submitted to the CIV.

8.2.1.1 Initial Tumor Imaging

Initial tumor imaging at Screening must be performed within 28 days prior to the date of the first dose of study intervention. An extension of the screening window of up to 7 days may be approved following mandatory Sponsor consultation. Tumor imaging performed as part of routine clinical management is acceptable for use as Screening tumor imaging if it is of diagnostic quality and performed within 28 days prior to the first dose of study intervention.

Digital photographs documenting measurable cutaneous lesions should be obtained if the cutaneous lesion is included as part of the nontarget lesions for disease assessment according to RECIST 1.1. Copies of the photograph should be forwarded to the central imaging vendor for potential retrospective analysis. The timing for capturing cutaneous lesion photographs should follow the same schedule as the imaging scans. The requirements for the digital photographs and the process for transmitting photographs to the central imaging vendor are in the Site Imaging Manual.

8.2.1.2 Tumor Imaging During the Substudy

The first on study imaging assessment should be performed at 6 weeks (42 days ±7 days) from first dose of study intervention and prior to surgical resection of the tumor. Surgical resection specimens taken at Week 6 (42 days ±7 days from neoadjuvant C1D1) must be submitted to a central pathology laboratory for pathological assessment of resection specimens after neoadjuvant therapy.

After surgical resection of the tumor, disease-free status must be documented by a complete physical examination and radiographic imaging at Week 12 (84 days ±7 days) from neoadjuvant C1D1, new baseline imaging prior to start of adjuvant therapy) and then receive adjuvant therapy with pembrolizumab monotherapy. The interval between post-surgery baseline imaging and first dose of adjuvant dosing should not exceed 28 days. Patients with gross positive residual disease at the time of surgery do not qualify as having disease-free status and are not eligible for adjuvant pembrolizumab. Patients with microscopic residual disease (ie, positive surgical margins) can be treated with re-excision or radiation, at the investigator's discretion, to render the participant disease-free prior to adjuvant pembrolizumab.

Subsequent tumor imaging should be performed every 12 weeks from adjuvant C1D1 (±7 days) for the first 2 years, after which imaging will be performed every 24 weeks (168 days ±7 days) until Year 5 or more frequently if clinically indicated or until documented disease recurrence. Imaging timing should follow calendar days and should not be adjusted for delays in cycle starts. Imaging should continue to be performed until disease recurrence is identified by the investigator, the start of new anticancer treatment, withdrawal of consent, or death, whichever occurs first. All supplemental imaging must be submitted to the CIV.

Participants who develop in-transit metastases will be followed with calipers by physical examination and skin lesion photography until surgical resection is performed.

Disease recurrence is defined as the appearance of any metastatic lesion. Appearance of a new melanoma in situ or Stage I melanoma which can be treated curatively by wide excision does not constitute recurrence. Any enlargement in lymph nodes >1 cm in short axis and >50% from baseline must be biopsied to rule out relapse of disease followed-up with subsequent imaging to document disease recurrence. Appearance of new pleural effusions or increase in the size of an existing effusion does not constitute unequivocal progression unless cytologically proven of neoplastic origin, since some effusions are a toxicity related to therapy or other medical conditions.

8.2.1.3 End of Treatment and Follow-up Tumor Imaging

For participants who discontinue study intervention, tumor imaging should be performed at the time of treatment discontinuation (±4-week window). If previous imaging was obtained within 4 weeks prior to the date of discontinuation, then imaging at treatment discontinuation is not mandatory. For participants who discontinue study intervention due to documented disease progression (preoperative/neoadjuvant phase) or disease recurrence (postoperative/adjuvant phase), this is the final required tumor imaging.

For participants who discontinue study intervention without documented disease recurrence (postoperative/adjuvant phase), every effort should be made to continue monitoring disease status by tumor imaging using the same imaging schedule used while on treatment (every 12 weeks for the first 2 years), from Week 12 (new baseline imaging prior to start of adjuvant therapy), and every 24 weeks thereafter until Year 5 or until the start of a new anticancer treatment, disease recurrence, pregnancy, death, withdrawal of consent, or the end of this substudy, whichever occurs first.

8.2.1.4 RECIST 1.1 Assessment of Disease

RECIST 1.1 will be used as the primary measure for assessment of tumor response, date of disease progression, and as a basis for all protocol guidelines related to disease status (eg, discontinuation of study intervention). Although RECIST 1.1 references a maximum of 5 target lesions in total and 2 per organ, this protocol allows a maximum of 10 target lesions in total and 5 per organ, if clinically relevant to enable a broader sampling of tumor burden.

8.2.2 Quality of Life Assessments

Not applicable for this substudy.

8.3 Safety Assessments

Details regarding specific safety procedures/assessments to be performed in this substudy protocol are provided; refer to Appendix 11 for country-specific requirements. The total amount of blood/tissue to be drawn/collected over the course of this substudy (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 and/or Laboratory Manual.

The sites should submit tumor samples to the central pathology laboratory for adequacy of tumor tissue and for biomarker analysis.

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

8.3.1 Physical Examinations

Complete physical examinations and brief directed physical examinations will be conducted by an investigator or medically qualified designee (consistent with local requirements) as per institutional standard at the timepoints specified in the SoAs (Appendix 6, Section 10.6.2.1).

Investigators should pay special attention to clinical signs related to previous serious illnesses. For all complete physical examinations and directed physical examinations, the investigator or qualified designee should conduct a visual inspection of local recurrence and palpation of lymph nodes to assess recurrence.

8.3.2 Vital Signs

The investigator or qualified designee will measure vital signs at the timepoints specified in the SoA (Appendix 6, Section 10.6.2.1). Vital signs include temperature, pulse, respiratory rate, and blood pressure. Weight will be monitored as per vital signs. Height will be measured at Screening only.

8.3.3 Electrocardiograms

A standard 12-lead ECG will be performed during Screening using local standard procedures. Clinically important abnormal findings should be recorded as medical history. Additional ECGs may be performed as clinically necessary.

8.3.4 Multiple-gated Acquisition Scan or Echocardiogram

Not applicable for this substudy protocol.

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

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

8.3.5.1 Urine Dipstick

Not applicable for this substudy protocol.

8.3.6 Pregnancy Testing

All women who are being considered for participation in this substudy and who are not surgically sterilized or postmenopausal, must be tested for pregnancy within 24 hours before the first dose of study intervention. If a urine test is positive or not evaluable, a serum test will be required. Participants must be excluded/discontinued from this substudy in the event of a positive test result. Repeated pregnancy testing (such as monthly testing) may be conducted if required by local regulation.

8.3.7 Performance Assessments

ECOG Performance Scale: The investigator or qualified designee will assess ECOG status (Appendix 9) at the timepoints specified in the SoA (Appendix 6, Section 10.6.2.1).

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.

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

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

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

Investigators remain responsible for following up AEs, SAEs, and other reportable safety events for outcome according to Section 8.4.3. The investigator, who is a qualified physician, will assess events that meet the definition of an AE or SAE as well as other reportable safety events with respect to seriousness, intensity/toxicity and causality.

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

All AEs, SAEs, and other reportable safety events that occur after the participant provides documented informed consent, but before intervention randomization/allocation must be reported by the investigator if the participant is receiving placebo run-in or other run-in treatment, if the event causes 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/allocation through 90 days following cessation of study intervention must be reported by the investigator 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 AEs meeting serious criteria, from the time of intervention randomization/allocation through the time required to eliminate systemic exposure 120 days following after cessation of study intervention as described in Section 5.1 and 8.3.5, or 30 days following cessation of study intervention if the participant initiates new anticancer therapy must be reported by the investigator.

- All pregnancies and exposure during breastfeeding, from the time of intervention randomization/allocation through the time required to eliminate systemic exposure after cessation of study intervention as described in Section 5.1 and 8.3.6, or 30 days after 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 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 substudy, and he/she considers the event to be reasonably related to the study intervention or substudy 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 5.

Table 5 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 AE Collection Period	**Reporting Time Period:** After the Protocol-specified AE Collection Period	Time Frame to Report Event and Follow-up Information to Sponsor:
NSAE	Report if: - due to protocol-specified intervention - causes exclusion - participant is receiving placebo run-in or other run-in treatment	Report all	Not required	Per data entry guidelines
SAE including Cancer[a] 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
Potential DILI/DILI (requiring regulatory reporting)	Report if: - due to intervention - causes exclusion	Report - potential DILI/DILI - to be reported as a SAE with OME criteria in the absence of other serious criteria	Previously reported – Follow to completion/ termination; report outcome	Within 24 hours of learning of event
ECI (require regulatory reporting)	Report if: - due to intervention - causes exclusion	Report - requiring regulatory reporting	Previously reported – Follow to completion/ termination; report outcome	Within 24 hours of learning of event
ECI (do not require regulatory reporting)	Report if: - due to intervention - causes exclusion	Report - those not requiring regulatory reporting	Not required	Within 5 calendar days of learning of event

Type of Event	Reporting Time Period: Consent to Randomization/ Allocation	Reporting Time Period: Randomization/ Allocation through Protocol-specified AE Collection Period	Reporting Time Period: After the Protocol-specified AE Collection Period	Time Frame to Report Event and Follow-up Information to Sponsor:
Cancer	Report if: - due to intervention - causes exclusion	Report all	Not required	Within 5 calendar days of learning of event (unless an SAE)
Overdose	Report if: - receiving placebo run-in or other run-in medication	Report all	Not required	Within 5 calendar days of learning of event (unless an SAE)

Potential DILI/DILI = drug-induced liver injury; ECI = event of clinical interest; NSAE = nonserious adverse event; OME=other important medical event; SAE = serious adverse event.
a Progression of cancer under study is not reportable as per protocol-specified criteria (refer to Section 8.4.6).

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

Care will be taken not to introduce bias when detecting AE and/or SAE and other reportable safety events. Open-ended and 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. SAEs and other reportable safety events, including potential DILI/DILI, 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). The investigator will also make every attempt to follow 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.

Note: To meet EU CTR requirements, the Sponsor will report SUSARs to the Eudravigilance database via E2B(R3) electronic ICSR form in compliance with CTR 536/2014.

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), including the pregnancy of a male participant's female partner, 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 this substudy. Any suspected endpoint which 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 substudy include:

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

- All potential DILI events/DILI will be reported to the Sponsor as a SAE, within 24 hours, with OME criteria in the absence of other SAE criteria. DILI is defined as follows:

  - Potential DILI events defined as an elevated AST or ALT laboratory value that is greater than or equal to 3× the ULN and an elevated total bilirubin laboratory value that is greater than or equal to 2× the ULN and, at the same time, an alkaline phosphatase laboratory value that is less than 2× the ULN, as determined by way of protocol-specified laboratory testing or unscheduled laboratory testing.*

  *Note: These criteria are based upon available regulatory guidance documents. The purpose of the criteria is to specify a threshold of abnormal hepatic tests that must trigger an additional evaluation for an underlying etiology. The study site guidance for assessment and follow-up of these criteria can be found in the Investigator Study File Binder (or equivalent).

8.5 Treatment of Overdose

For this substudy, an overdose of pembrolizumab will be defined as any dose of 1000 mg or greater (≥5 times the indicated dose for 200 mg Q3W or ≥2.5 times the indicated dose for 400 mg Q6W).

No specific information is available on the treatment of overdose of pembrolizumab. In the event of overdose, the participant should be observed closely for signs of toxicity. Appropriate supportive treatment should be provided if clinically indicated.

Refer to Appendix 6, Section 10.6.2.18 for the definition and treatment of an overdose associated with investigational agents.

8.6 Pharmacokinetics

8.6.1 Blood Collection for Serum MK-3475

Sample collections for MK-3475 PK and ADA are currently planned as shown in the SoA (Appendix 6, Section 10.6.2.1). Substudy sites must have appropriately trained staff and adequate equipment for procuring and processing specimens. Instructions for the collection, handling and shipping procedures of MK-3475 ADA and PK samples will be provided in the Laboratory Manual. If ongoing PK and/or ADA sampling is deemed to be unnecessary by the Sponsor, it may be reduced or discontinued, and sites will be notified accordingly. Pharmacokinetic and ADA analyses of MK-3475 will be reported separately.

8.6.2 Blood Collection for Investigational Agents

Refer to Appendix 6, Section 10.6.2.19 for information about serum blood collection associated with investigational agents.

8.7 Pharmacodynamics

Sample collection, storage, and shipment instructions for plasma samples is provided in the Laboratory Manual.

8.8 Patient-Reported Outcomes

Not applicable for this substudy protocol.

8.9 Biomarkers

To identify novel biomarkers, the following biospecimens to support exploratory analyses of cellular components (eg, protein, RNA, DNA, metabolites) and other circulating molecules will be collected from all participants in this substudy as specified in the SoA for confirmation of adequacy of tumor tissue at a central pathology laboratory:

CCI

[redacted]

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

Preoperative research tumor tissue collection:

- Baseline Biopsy

  Participants must submit a tumor sample during Screening for confirmation of adequacy of tumor tissue at a central pathology laboratory. Confirmation of presence of tumor tissue is required prior to randomization/allocation. In the event a participant has tumor tissue left after confirmation of adequacy of tumor tissue, the tumor tissue sample will be used for biomarker analysis.

- On treatment Biopsy

  Participants must submit a tumor sample at the end of Cycle 1 (Days 15 to 21). Tumor sample must be collected prior to C2D1 (neoadjuvant arm with 21-day cycles) or C1D22 (neoadjuvant arm with 42-day cycles) for biomarker analysis. This biopsy at the end of Cycle 1 is required but only to be performed if adequate tumor volume is left as determined by the investigator. If participants have only 1 measurable lesion per RECIST 1.1, the biopsy specimen should be obtained from the nontarget lesion. This

on-treatment biopsy will be used for research only and will be done at the investigator's discretion.

Surgical research tumor tissue collection taken at Week 6:

Surgical resection of the tumor includes lymphadenectomy of the tumor-involved lymph node disease and/or in-transit metastases and resection of the primary cutaneous melanoma lesion ± wide local excision, if not resected previously. All resected tumor specimens and all sampled regional lymph nodes should be submitted to the central pathology laboratory. In the event a participant has tumor tissue left after diagnostic assessment, the tumor tissue sample will be used for biomarker analysis.

8.9.1 Planned Genetic Analysis Sample Collection

The planned genetic analysis sample should be drawn for planned analysis of the association between genetic variants in DNA and drug response. This sample will not be collected at the site if there is either a local law or regulation prohibiting collection, or if the IRB/IEC does not approve the collection of the sample for these purposes.

Sample collection, storage, and shipment instruction for planned genetic analysis samples will be provided in the operations/laboratory manual.

8.10 Future Biomedical Research Sample Collection

Not applicable.

8.11 Health Economics Medical Resource Utilization and Health Economics

Medical resource utilization and health economics data associated with medical encounters will be collected in the CRF by the investigator and substudy site personnel for all participants throughout this substudy. Protocol-mandated procedures, tests, and encounters are excluded.

The data collected may be used to conduct exploratory economic analyses and will include:

- All-cause hospitalizations and emergency room visits, from the time of treatment randomization/allocation through 90 days following cessation of study intervention, or 30 days following cessation of study intervention if the participant initiates new anticancer therapy, whichever is earlier.

8.12 Visit Requirements

Visit requirements are outlined in Appendix 6, Section 10.6.2.1. Specific procedure-related details are provided in Section 8.

8.12.1 Screening

Documented informed consent must be obtained prior to performing any protocol-specific procedure. Results of a test performed prior to the participant providing documented consent as part of routine clinical 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 HIV testing which may be done up to 28 days prior to the first dose of study intervention if mandated by local health authorities (see Table 8 in Appendix 2).

- Evaluation of ECOG performance status is to be performed within 7 days prior to the first dose of study intervention.

- Complete physical examination is to be performed within 7 days of the first dose of study intervention.

- 12-lead ECG is to be performed within 7 days prior to the first dose of study intervention.

- Any additional procedure or assessment for specific investigational agents, which will also be required at Screening for all participants (see Appendix 6, Section 10.6.2.1.1).

- 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 substudy site laboratory).

- An archival tumor sample should have been collected within 5 years prior to entering the screening period. Newly obtained tumor tissue may be obtained within 90 days of treatment initiation. The sites should submit tumor samples to the central pathology laboratory for adequacy of tumor tissue and for biomarker analysis.

8.12.1.1 Rescreening

Participants may be rescreened after initially failing to meet the inclusion/exclusion criteria. Results from assessments during the initial screening period are acceptable in lieu of a repeat screening test if performed within the specified time frame and the corresponding inclusion/exclusion criteria is met. Participants who are rescreened will retain their original screening number.

8.12.2 Treatment Period

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

8.12.3 Participants Discontinued From Study Intervention but Continuing to be Monitored in This Substudy

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 combined. Visit requirements are outlined in the SoA. Additional details regarding participant withdrawal and discontinuation are presented in Section 8.1.9.

8.12.4 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.

8.12.5 Imaging Follow-up Visit(s)

Participants who discontinue treatment for reasons other than documented progressive disease (preoperative/neoadjuvant phase) or disease recurrence (postoperative phase) should continue with imaging assessments per the protocol defined schedule until: (1) progressive disease (preoperative/neoadjuvant phase) or disease recurrence (postoperative/adjuvant phase) is documented, (2) initiation of a new anticancer treatment, (3) death, (4) withdrawal of consent, or (5) substudy conclusion or early termination, whichever occurs first.

8.12.5.1 Follow-up Visits

Participants who discontinue study intervention for a reason other than disease progression (preoperative/neoadjuvant phase) or disease recurrence (postoperative phase) will move into the Follow-up Phase and should be assessed every 12 weeks (84 days ±7 days) for ~2 years, then every 24 weeks (168 days ±7 days) until Year 5, or more frequently if clinically indicated. Every effort should be made to collect information regarding disease status until the start of new anticancer therapy, disease progression, death, end of study. Information regarding poststudy anticancer treatment will be collected if new treatment is initiated.

8.12.5.2 Survival Follow-up

Participants who experience confirmed disease progression or start a new anticancer therapy will move into the Survival Follow-up Phase and should be contacted by telephone approximately every 12 weeks to assess for survival status until death, withdrawal of consent, or the end of this substudy, whichever occurs first.

8.12.6 Vital Status

To ensure current and complete survival information (vital status) is available at the time of database locks, updated vital status may be requested during the study by the Sponsor. Upon Sponsor notification, all participants who do not/will not have a scheduled study visit or study contact during the Sponsor-defined time period will be contacted for their vital status.

9 STATISTICAL ANALYSIS PLAN

At implementation of Amendment 7, the following changes apply to Arms 1 through 6. The changes listed below supersede any content/instructions from previous amendments:

- Participants receiving adjuvant pembrolizumab monotherapy may continue on study therapy per protocol.
- Imaging scans should no longer be submitted to CIV. However, for participants who are still on study treatment and deriving clinical benefit and will continue on study treatment until criteria for discontinuation are met, local tumor imaging should continue per local SOC schedule and local SOC method of assessment of imaging. All imaging as well as relevant objectives and endpoints will be assessed locally.
- PK/ADA samples will no longer be collected.
- Biomarker samples will no longer be collected.
- Participants who complete study treatment or otherwise meet EOT criteria will be discontinued from the study after the EOT visit and any required safety follow-up visit.
- There will be no follow-up for survival status. Participants currently in imaging follow-up or survival follow-up are considered to have completed the study and therefore should obtain imaging and further oncological care per local standard of care. However, standard safety reporting should continue, as applicable.
- Those participants remaining on the study at the time of Amendment 7 should continue to be monitored in the study through the AE reporting period (Section 8.4).
- All analyses prespecified in Section 9.7 for Arms 1 through 6 are complete at the time of Amendment 7.

Existing protocol content is retained for historical reference.

9.1 Statistical Analysis Plan Summary

This section outlines the statistical analysis strategies and procedures for the primary analyses of this substudy. Secondary, exploratory, and other nonconfirmatory analyses will be outlined in a separate supplemental sSAP.

If, after this substudy has begun, changes are made to the primary objectives, or to the statistical methods related to those objectives, then the protocol will be amended (consistent with ICH Guideline E9). Changes to the secondary, 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 this substudy. Post hoc exploratory analyses will be clearly identified in the CSR.

Full details are in the SAP, Section 9.6.

Study Design Overview	A Phase 1/2 Open-Label Rolling-Arm Umbrella Platform Design of Investigational Agents with or without Pembrolizumab or Pembrolizumab Alone in Participants with Melanoma (KEYMAKER-U02): Substudy 02C This substudy protocol includes participants with Stage IIIB-IIID melanoma who are candidates for neoadjuvant treatment.
Treatment Assignment	This is an open-label substudy. Participants will be randomized equally to one of the investigational treatment arms open for enrollment and there are no stratification factors considered.
Analysis Populations	Efficacy: • APaT and FAS Safety: • APaT
Primary Endpoints	• pCR rate as assessed by central review of the pathology results. • AEs and study intervention discontinuations due to AEs.
Secondary Endpoint(s)	Near pCR and pPR rate as assessed by central review of the pathology results, and RFS.
Statistical Methods for Efficacy Analyses	Point estimates and the corresponding 90% and 95% CIs will be provided for the treatment-specific pCR rate, the near pCR rate, and the pPR rate using the Clopper and Pearson method [Clopper, C. J. 1934]. The nonparametric Kaplan-Meier method will be used to estimate the RFS curve in each treatment group.
Statistical Methods for Safety Analyses	Summary statistics will be provided for the safety endpoints.
Interim Analyses	Depending on the enrollment rate, 1 interim efficacy analysis may be conducted in each investigational treatment arm separately.
Multiplicity	No multiplicity adjustment is planned in this Phase 1/2 study.

Sample Size and Power	This is an estimation substudy. A maximum of 25 participants will be enrolled in each investigational treatment arm, and approximately 15 participants will be enrolled in the neoadjuvant pembrolizumab monotherapy arm. The total sample size for this substudy will depend on the number of investigational agents to be evaluated in this substudy protocol. The sample size for each arm was calculated to ensure adequate "power" to detect certain response rates (even though this is an estimation study). See Section 9.9 for details.

9.2 Responsibility for Analyses/In-house Blinding

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

This substudy is open-label (ie, participants, investigators, and Sponsor personnel will be aware of participant treatment assignment after each participant is enrolled and study intervention is assigned).

9.3 Hypotheses/Estimation

Objectives of this substudy are stated in Section 3. This is an estimation substudy and no formal hypothesis testing will be performed.

9.4 Analysis Endpoints

9.4.1 Efficacy Endpoints

9.4.1.1 Primary

- **Pathological Complete Response (pCR) Rate**

  pCR rate is defined as the proportion of participants with complete absence of viable tumor in the treated tumor bed as assessed by central review of the pathology results. Participants without pathology results data due to any reason will be counted as non-responders.

9.4.1.2 Secondary

- Near Pathological Complete Response (near pCR) Rate

  Near pCR is defined as the proportion of participants with > 0% but ≤10% of viable tumor cells in the treated tumor bed as assessed by central review of the pathology

results. Participants without pathology results data due to any reason will be counted as nonresponders.

- Pathological Partial Response (pPR) Rate

  pPR rate is defined as the proportion of participants with >10% but ≤50% of the treated tumor bed occupied by viable tumor cells as assessed by central review of the pathology results. Participants without pathology results data due to any reason will be counted as nonresponders.

- Recurrence-free Survival (RFS)

  RFS is defined as the time from date of surgery to (1) any recurrence (local, regional, or distant) as assessed by the investigator or (2) death due to any cause (both cancer and noncancer causes of death).

9.4.1.3 Exploratory

- **Overall Survival (OS)**

  Overall survival is defined as the time from date of randomization/allocation to date of death from any cause.

- **Objective Response Rate (ORR)**

  Objective response rate is defined as the percentage of participants who achieve a confirmed CR or PR per RECIST 1.1 as assessed by investigator. Participants without follow-up scans will be considered nonresponders.

- **Event-free Survival (EFS)**

  Event-free survival is defined as the time from randomization/allocation to the date of first progression during neoadjuvant therapy (only in case of distant metastasis or local progression that precludes surgery with curative intent), recurrence (local, regional, or distant metastasis) as assessed by the investigator, or death from any cause, whichever occurs first.

9.4.2 Safety Endpoints

The safety endpoints include AEs, SAEs, and study intervention discontinuation 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.

9.4.3 Patient-Reported Outcome Endpoints

Patient-reported outcome endpoints will not be evaluated in this substudy protocol.

9.4.4 Pharmacokinetic Endpoints

Pharmacokinetic endpoints include serum concentrations of investigational agents in combination with or without pembrolizumab, as well as derived PK parameters such as AUC, C_{min}, and C_{max}.

9.5 Analysis Populations

9.5.1 Efficacy Analysis Populations

The APaT population will be used for the pCR rate, the near pCR rate, the pPR rate, the ORR, and OS. Participants who were treated in the neoadjuvant setting, regardless whether they undergo surgery to completely resect the tumors, will be included in the APaT population. The FAS population will be used for RFS. Participants who were treated in the neoadjuvant setting and undergo surgery to completely resect the tumors will be included in the FAS population. In both populations, participants will be analyzed according to the treatment to which they were assigned (even if it is different from the treatment they actually received).

9.5.2 Safety Analysis Population

The APaT population will be used for the analysis of safety in this substudy. Participants will be analyzed according to the investigational treatment arm in which they were treated.

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

9.5.3 Pharmacokinetic Analysis Populations

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

9.6 Statistical Methods

This section describes the statistical methods that address the primary and secondary objectives. Methods related to the exploratory endpoints will be described in the sSAP. This is an estimation substudy. The primary and secondary endpoints will be summarized for each investigational treatment arm separately. Formal hypothesis tests will not be conducted.

9.6.1 Statistical Methods for Efficacy Analysis

9.6.1.1 Objective Response Rate (ORR), Pathological Complete Response (pCR) Rate, Near Pathological Complete Response (Near pCR) Rate, and Pathological Partial Response (pPR) Rate

The ORR, pCR rate, near pCR rate, and pPR rate estimates in each investigational treatment arm will be reported along with the 90% and 95% CI using the Clopper and Pearson method [Clopper, C. J. 1934].

9.6.1.2 Recurrence-free Survival (RFS)

The nonparametric Kaplan-Meier method will be used to estimate the RFS curve in each treatment group. Since disease assessment is performed periodically, events such as progression or recurrence can occur any time during the time interval between the last assessment where the event was not documented and the assessment when the event is documented. To evaluate the robustness of the RFS endpoint, sensitivity analyses with a different set of censoring rules may be performed. Details of the sensitivity analyses and the censoring rules for the sensitivity analyses will be included in the sSAP.

9.6.2 Statistical Methods for Safety Analysis

Safety and tolerability will be assessed by clinical review of all relevant parameters including AEs, SAEs, laboratory tests, vital signs, and ECG measurements. The broad AE categories consisting of the percentage of participants with any AE, any drug-related AE, any Grade 3 to 5 AE, any serious AE, any AE that is both drug-related and Grade 3 to 5, any AE that is both drug-related and serious, any discontinuation due to an AE, and death will be summarized via point estimates by each treatment arm.

9.6.3 Demographic and Baseline Characteristics

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

9.6.4 Statistical Methods for Pharmacokinetics (PK) Analyses

Pharmacokinetic parameters (ie, AUC, C_{min}, and C_{max}) of investigational agents in combination with or without pembrolizumab will be summarized by non-compartmental analysis. Plasma concentration versus time data may be pooled with data from existing studies and may be analyzed using a population PK approach to estimate population PK parameters. The detailed methods will be included in a separate analysis plan.

9.7 Interim Analyses

One IA futility will be conducted for each respective investigational treatment arm when a total of 15 participants have been enrolled and undergo the tumor resection surgery. Enrollment will not pause for the IA. The criteria of stopping enrollment for futility are specified below:

(1) If >4 out of 15 participants, or more than 30% of participants in the cohort, have progressive disease on neoadjuvant therapy, and as a result, their tumor(s) become unresectable prior to surgery, then the enrollment in the respective arm may be stopped early.

OR

(2) If ≤4 participants with a pCR are observed out of the first 15 participants or pCR rate ≤27%, then the enrollment in the respective arm may be stopped early. This criterion was chosen because it corresponds to a <1% predictive probability of success for observing a 40% or higher pCR rate at the end of the substudy given the IA data. A noninformative prior distribution of Beta (1.1) is used in the predictive probability success calculation.

The totality of the data including near pCR results will be provided for IA decision making. Table 6 shows the operating characteristics of the IA for pCR. The neoadjuvant pembrolizumab monotherapy arm will enroll a total of 15 participants only and no IA is planned for the neoadjuvant pembrolizumab monotherapy arm.

Table 6 Operating Characteristics of Substudy 02C Interim Analysis for pCR

True pCR Rate in Investigational Treatment Arm	**Prob. Stopping Enrollment Early for Futility (≤4 pCRs out of 15)**
20%	84%
25%	69%
30%	52%
40%	22%
50%	6%

Abbreviations: pCR = pathological complete response

9.8 Multiplicity

No multiplicity adjustment is planned for this substudy.

9.9 Sample Size and Power Calculations

This is an estimation substudy. Although the hypothesis testing is not intended, power calculations are provided as a reference for the sample size justification.

A total of 25 participants has approximately 78%/62% power to detect 50%/45% pCR rate, assuming the historical pCR rate is 25% at 7% type I error (one-sided). Table 7 shows the 2-sided 90% and 95% CIs of pCR for different pCRs for each pembrolizumab-based combination arm (N = 25) based on the method of Clopper and Pearson[Clopper, C. J. 1934]. The neoadjuvant pembrolizumab monotherapy arm will enroll a total of 15 participants and will be used only for reference.

Table 7 Confidence Intervals for Different Observed pCR Rates in Each Investigational Treatment Arm in Substudy 02C

Total Sample Size per Arm	Observed Number of pCRs	Observed pCR Rate	95% CI	90% CI
25	8	32%	(15%, 54%)	(17%, 50%)
25	10	40%	(21%, 61%)	(24%, 58%)
25	12	48%	(28%, 69%)	(31%, 66%)
25	14	56%	(35%, 76%)	(38%, 73%)
15	4	27%	(8%, 55%)	(10%, 51%)
15	5	33%	(12%, 62%)	(14%, 57%)

Abbreviations: CI = confidence interval; pCR = pathological complete response.

9.10 Subgroup Analyses

Details of subgroup analyses will be documented in the sSAP.

9.11 Compliance (Medication Adherence)

Drug accountability data for study intervention will be collected during this substudy. Any deviation from protocol-directed administration will be reported. If there are oral medications in the respective treatment arm, details of the compliance definition will be provided according in the sSAP.

9.12 Extent of Exposure

The extent of exposure will be evaluated by summary statistics for duration of treatment.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

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

10.1.1 Code of Conduct for Interventional Clinical Trials

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

I. Introduction

A. Purpose

Merck Sharp & Dohme LLC, Rahway, NJ, USA (MSD), through its subsidiaries, conducts clinical trials worldwide to evaluate the safety and effectiveness of our products. As such, we are committed to conducting these trials in compliance with the highest ethical and scientific standards. Trial conduct includes processes from design to reporting, including planning, initiating, performing, recording, oversight, evaluation, analysis and reporting activities as appropriate. 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 MSD's global standards, local and/or national regulations (including all applicable data protection laws and regulations), Regulation (EU) 536/2014, the International Council for Harmonisation Good Clinical Practice (ICH GCP) E6 and ICH General Considerations for Clinical Studies E8, and in accordance with the ethical principles that have their origin in the Declaration of Helsinki.

B. Scope

Highest ethical and scientific standards shall be endorsed for all clinical interventional investigations sponsored by MSD irrespective of the party (parties) employed for their execution (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, randomization, and blinding) must be adequate to address the specific purpose of the trial and shall respect the data protection rights of all participants, trial site staff and, where applicable, third parties. Input may be considered from a broad range of stakeholders, including patient advocacy groups/patients representing the trial population, caregivers, and healthcare providers to ensure operational feasibility. The use of innovative digital health technologies will be considered. Factors critical to the quality of the trial should also be identified. These factors are attributes of a trial that are fundamental to the protection of participants, the reliability and interpretability of the trial results and the decisions made based on those trial results. Risks to critical to quality factors should be managed prospectively and adjusted when new or unanticipated issues arise once the trial has begun. All trial protocols are and will be assessed for the need and capability to enroll underrepresented groups. Participants must meet protocol entry criteria to be enrolled in the trial.

2. Site Selection

MSD's clinical trials are conducted globally in many different countries and in diverse populations, including people of varying age, race, ethnicity, gender, and accounting for other potential disease related factors. MSD

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

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

3. Site Monitoring/Scientific Integrity

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

B. Publication and Authorship

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

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

III. Participant Protection

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

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

The protocol, protocol amendment(s), informed consent form, investigator's brochure, and other relevant trial documents must be reviewed and approved by an IRB/IEC before being implemented at each site, in compliance with local and/or national regulations and ICH Guidelines. 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. Informed consents include relevant aspects of the trial, such as trial design, anticipated benefits and risks of medical intervention(s), trial setting, and the potential use of technology. Trial designs include procedures and systems for the identification, monitoring, and reporting of safety concerns. 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.

During trial planning, the need for an independent Data Monitoring Committee (DMC) is assessed.

C. Confidentiality

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

D. Genomic Research

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

E. Trial Results

At the time of providing informed consent and in accordance with local laws and regulations, participants should be informed about the plans for availability of trial results.

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 medical record 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.

The Sponsor has EU-approved Binding Corporate Rules since 2017, covering all aspects of its Global Privacy Program (Corporate Policy 20), and is self-certified pursuant to the EU-US Data Privacy Framework.

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 Scientific Advisory Committee

This substudy was developed in collaboration with a SAC. The SAC comprises both Sponsor and non-Sponsor scientific experts who provide input with respect to study design, interpretation of study results, and subsequent peer-reviewed scientific publications.

10.1.4.2 Internal Data Monitoring Committee

Not applicable to this substudy. All pembrolizumab-based combinations that will be evaluated in this substudy protocol have safety data from a separate study, precluding the need for an internal data monitoring committee.

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 trials Regulation 536/2014, 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, https://euclinicaltrials.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 Regulation 536/2014 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 Regulation 536/2014, 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.

For investigators located in countries with serious breach reporting requirements, the investigator will promptly report to the Sponsor any serious breach or suspected serious breach that occurs in compliance with those requirements. Unless more specifically defined in the applicable requirements, a serious breach is any breach of the applicable clinical trial regulation or of the clinical trial protocol that is likely to affect to a significant degree: (i) the safety or rights of a trial participant, or (ii) the reliability and robustness of the data generated in the clinical trial.

10.1.8 Data Quality Assurance

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

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

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

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

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

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

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

Records and documents, including participants' documented informed consent, pertaining to the conduct of this study must be retained by the investigator for 15 years after study completion unless local regulations or institutional policies require a longer retention period (eg, EU CTR: 25 years after the end of the study). 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 8 will be performed by the local laboratory.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5.1 and Section 5.2, respectively and Appendix 6, Section 10.6.2.7 and Section 10.6.2.8 of the substudy protocol.
- Additional tests may be performed at any time during this substudy as determined necessary by the investigator or required by local regulations.

Table 8 Protocol-required Safety Laboratory Assessments

Laboratory Assessments	Parameters			
Hematology	Platelet Count RBC Count Hemoglobin Hematocrit	RBC Indices: MCV[c] MCH[c] %Reticulocytes[c]	WBC count with Differential[a]: Neutrophils Lymphocytes Monocytes Eosinophils Basophils	
Chemistry	Blood Urea Nitrogen (BUN)[b]	Potassium	AST/SGOT	Total bilirubin (and direct bilirubin, if total bilirubin is elevated above the upper limit of normal)
	Albumin	Bicarbonate[c]	Chloride[c]	Phosphorus[c]
	Creatinine[d]	Sodium	ALT/SGPT	Total Protein[c]
	Glucose	Calcium	Alkaline phosphatase	Magnesium
	TSH	Free thyroxine[e]	LDH	Amylase
	Lipase	Cholesterol[c]	Triglycerides[c]	CPK[f]
	Pregnancy test	Triiodothyronine (Total T3)[e]		
Routine Urinalysis[g]	• Specific gravity • pH, glucose, protein, hemoglobin or blood, ketones by dipstick • Microscopic examination (if blood or protein is abnormal)			
Other Screening Tests	• PT/INR and aPTT/PTT[h] • Serology (HIV antibody, HBsAg, and hepatitis C virus antibody) NOTE: certain ex-US sites require testing for HIV and hepatitis B and C during screening. Consult with regional health authorities and institutional standards to confirm if such testing is applicable. • Serum or urine β hCG pregnancy test (as needed for WOCBP) • Coagulation factors (PT or INR and aPTT/PTT). Additional testing to be conducted as clinically indicated for participants taking anticoagulation therapy.			

Laboratory Assessments	Parameters

Abbreviations: ALT = alanine aminotransferase; aPTT = activated partial thromboplastin; AST = aspartate aminotransferase; β hCG = β human chorionic gonadotropin; BUN = blood urea nitrogen; CPK = creatine phosphokinase; HBsAg = hepatitis B surface antigen; HIV = human immunodeficiency virus; RNA = ribonucleic acid; LDH = lactate dehydrogenase; MCV = mean corpuscular volume; MCH = mean corpuscular hemoglobin, PT/INR = prothrombin time/international normalize ratio; PTT = partial prothrombin time; RBC = red blood cell; SGOT = serum glutamic pyruvic transaminase; WBC = white blood cell count; WOCBP = women of childbearing potential; T3 = triiodothyronine; TSH = thyroid stimulating hormone; ULN = upper limit of normal

a Absolute or % acceptable per institutional standard.
b Urea is acceptable if BUN is not available as per institutional standard.
c Performed only if considered local standard of care. Serum LDH at Screening is required.
d GFR (measured or calculated) or creatinine clearance can be used in place of creatinine.
e Free T4, Total T3, and TSH levels will be performed during screening, at cycles specified in the SoA, and at the time of discontinuation (End of Treatment). Free T3 is acceptable where Total T3 cannot be determined. There may be instances when sites are unable to obtain thyroid function testing results prior to the scheduled dosing. After C1, retrospective review of thyroid function testing results after dosing is acceptable.
f CPK isoenzymes (CK-MB) should be evaluated if CPK is greater than 3 × ULN.
g If urine dipstick testing suggests a urinary tract infection, or if clinically indicated, a urine microscopy, culture, and sensitivity should be performed at the institution's laboratory.
h Performed as part of the screening assessment and as clinically indicated for participants taking anticoagulation therapy.

Laboratory samples collected within 3 days prior to the first dose of study intervention need not be repeated on C1D1. The investigator (or medically qualified designee) must document their review of each laboratory safety report. Results must be known and acceptable prior to dosing.

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

10.3.1 Definitions of Medication Error, Misuse, and Abuse

Medication error

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

Misuse

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

Abuse

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

10.3.2 Definition of AE

AE definition

- An AE is any untoward medical occurrence in a clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention.
- NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a study intervention.
- NOTE: For purposes of AE definition, study intervention (also referred to as Sponsor's product) includes any pharmaceutical product, biological product, vaccine, diagnostic agent, 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."
- Any new cancer (that is not a condition of the study). Progression of the cancer under study is not a reportable event. Refer to Section 8.4.6 for additional details.

Events NOT meeting the AE definition

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

10.3.3 Definition of SAE

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

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

a. **Results in death**

b. **Is life-threatening**

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

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

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

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

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

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

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

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

f. **Other important medical events**

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

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

- All events of potential DILI/DILI will be reported as a SAE with OME criteria in the absence of other serious criteria.

10.3.4 Additional Events Reported in the Same Manner as SAE

Additional events that require reporting in the same manner as SAE:

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

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

10.3.5 Recording AE and SAE

AE and SAE recording

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory, and diagnostics reports) related to the event.
- The investigator will record all relevant AE/SAE information on the AE CRFs/worksheets at each examination.
- It is not acceptable for the investigator to send photocopies of the participant's medical records to the Sponsor in lieu of completion of the AE CRF page.
- There may be instances when copies of medical records for certain cases are requested by the Sponsor. In this case, all participant identifiers, with the exception of the participant number, will be blinded on the copies of the medical records before submission to the Sponsor.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of intensity/toxicity

- An event is defined as "serious" when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, not when it is rated as severe.
- The investigator will make an assessment of intensity for each AE and SAE (and other reportable safety event) according to the NCI CTCAE, version v5.0. Any AE that changes CTCAE grade over the course of a given episode will have each change of grade recorded on the AE CRFs/worksheets.
    - Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
    - Grade 2: Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL.
    - Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL.

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

- Grade 5: Death related to AE.

Assessment of causality

- Did the Sponsor's product cause the AE?

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

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

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

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

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

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

    - If yes, did the AE resolve or improve?

    - If yes, this is a positive dechallenge.

    - If no, this is a negative dechallenge.

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

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

  - If yes, did the AE recur or worsen?

  - If yes, this is a positive rechallenge.

  - If no, this is a negative rechallenge.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Follow-up of AE and SAE

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

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

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

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

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

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

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

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

- Reference Section 8.4.1 for reporting time requirements.

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

- After the study is completed at a given site, the EDC tool will be taken off-line to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the EDC tool has been taken off-line, then the site can report this information on a paper SAE form or by telephone (see next section).
- Contacts for SAE reporting can be found in the Investigator Study File Binder (or equivalent).

SAE reporting to the Sponsor via paper CRF

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

10.4 Appendix 4: 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

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]
- IUS[c]
- 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. IUS is a progestin releasing IUD.

Note: The following are not acceptable methods of contraception:
- Periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and LAM.
- Male condom with cap, diaphragm, or sponge with spermicide.
- Male and female condom should not be used together (due to risk of failure with friction).

10.6 Appendix 6: Substudy Combination-specific Requirements

At implementation of Amendment 7, the following changes apply to Arms 1 through 6. The changes listed below supersede any content/instructions from previous amendments:

- Participants receiving adjuvant pembrolizumab monotherapy may continue on study therapy per protocol.
- Imaging scans should no longer be submitted to CIV. However, for participants who are still on study treatment and deriving clinical benefit and will continue on study treatment until criteria for discontinuation are met, local tumor imaging should continue per local SOC schedule and local SOC method of assessment of imaging. All imaging as well as relevant objectives and endpoints will be assessed locally.
- PK/ADA samples will no longer be collected.
- Biomarker samples will no longer be collected.
- Participants who complete study treatment or otherwise meet EOT criteria will be discontinued from the study after the EOT visit and any required safety follow-up visit.
- There will be no follow-up for survival status. Participants currently in imaging follow-up or survival follow-up are considered to have completed the study and therefore should obtain imaging and further oncological care per local standard of care. However, standard safety reporting should continue, as applicable.
- Those participants remaining on the study at the time of Amendment 7 should continue to be monitored in the study through the AE reporting period (Section 8.4).
- All analyses prespecified in Section 9.7 for Arms 1 through 6 are complete at the time of Amendment 7.

Existing protocol content is retained for historical reference.

10.6.1 Status of Investigational Agents in this Substudy Protocol

Table 9 Summary of Investigational Agents Activated for Randomization/Allocation

Investigational Agent	Active Cohorts	Dosing Schedule	Section
N/A	N/A	N/A	N/A

Table 10 Summary of Investigational Agents No Longer Activated for Randomization/Allocation

Investigational Agent	Active Cohorts	Section	Rationale for Closing Arm
MK-7684 (anti-TIGIT)	Arm 1	10.6.2	Enrollment is complete. Sponsor decision to discontinue the arm is based on lack of efficacy observed in other studies and is not based on any safety concerns. As of Amendment 7, all participants have either completed or discontinued all neoadjuvant and adjuvant study interventions and completed the safety follow-up.
V937 (oncolytic virus)	Arm 2	10.6.2	Enrollment is complete. Sponsor decision to discontinue the arm is based on internal prioritization strategy and is not based on any safety concerns. As of Amendment 7, all participants have either completed or discontinued all neoadjuvant and adjuvant study interventions and completed the safety follow-up.
MK-3475 (pembrolizumab; anti-PD-1)[a]	Arm 3	10.6.2	Enrollment is complete. Sponsor decision to discontinue the arm is based on the decision to discontinue Arms 1, 2, 4, 5, and 6, and is not based on any safety concerns. As of Amendment 7, all participants have either completed or discontinued all neoadjuvant and adjuvant study interventions and completed the safety follow-up.
MK-4830 (anti-ILT4)	Arm 4	10.6.2	Enrollment is complete. Sponsor decision to discontinue the arm is based on internal prioritization strategy and is not based on any safety concerns. As of Amendment 7, all participants have either completed or discontinued all neoadjuvant and adjuvant study interventions and completed the safety follow-up.
MK-4280A (Coformulation of: MK-4280 + Pembrolizumab)	Arm 5	10.6.2	Enrollment is complete. Sponsor decision to discontinue the arm is based on internal prioritization strategy and is not based on any safety concerns. As of Amendment 7, all participants have either completed or discontinued all neoadjuvant and adjuvant study interventions and completed the safety follow-up.
ATRA (tretinoin)	Arm 6	10.6.2	Enrollment is complete. Sponsor decision to discontinue the arm is based on internal prioritization strategy and is not based on any safety concerns. As of Amendment 7, all participants have either completed neoadjuvant study interventions, undergone surgical resection, and initiated adjuvant pembrolizumab monotherapy or have discontinued neoadjuvant or adjuvant study intervention.

C=Cycle; D=Day; Q3W=every 3 weeks; $TCID_{50}$=tissue culture infectious dose 50%.

[a] Although Arm 3 is no longer activated for randomization/allocation, single-agent pembrolizumab may still be active in other arms (eg, as adjuvant therapy).

Investigational Treatment Arm 1: Two neoadjuvant administrations of pembrolizumab 200 mg Q3W IV on C1D1 and C2D1 + 2 neoadjuvant administrations of MK-7684 200 mg Q3W IV on C1D1 and C2D1 followed by surgical resection of the tumor followed by adjuvant pembrolizumab monotherapy 400 mg Q6W IV for 8 cycles (total treatment duration including neoadjuvant and adjuvant treatment of approximately 1 year). The SoAs described in Section 1.3.1 and Section 1.3.2 of this appendix should be followed.

When more than 1 agent is to be given on the same day, the order of administration is pembrolizumab followed by MK-7684. Refer to the Pharmacy Manual for additional information.

Investigational Treatment Arm 2: One neoadjuvant administration of pembrolizumab 400 mg Q6W IV on C1D8 + V937 3×10^8 TCID50 on C1D1, C1D3, C1D5, C1D8, and C1D22 intratumorally followed by surgical resection of the tumor followed by adjuvant pembrolizumab monotherapy 400 mg Q6W IV for 8 cycles (total treatment duration including neoadjuvant and adjuvant treatment of approximately 1 year). The SoAs described in Section 1.3.1 and Section 1.3.3 of this appendix should be followed.

When more than 1 agent is to be given on the same day, the order of administration is pembrolizumab followed by V937. Participants must submit a tumor sample at the end of Cycle 1 (Days 15 to 21) for biomarker analysis; biopsy sample should be collected prior to V937 administration on C1D22. Refer to the Pharmacy Manual for additional information.

Investigational Treatment Arm 3: One neoadjuvant administration of pembrolizumab 400 mg Q6W IV on C1D1 followed by complete resection of the tumor followed by adjuvant pembrolizumab monotherapy 400 mg Q6W IV for 8 cycles (total treatment duration including neoadjuvant and adjuvant treatment of approximately 1 year). The SoAs described in Section 1.3.1 and Section 1.3.4 of this appendix should be followed.

Investigational Treatment Arm 4: Two neoadjuvant administrations of pembrolizumab 200 mg Q3W IV on C1D1 and C2D1 + 2 neoadjuvant administrations of MK-4830 800 mg Q3W IV on C1D1 and C2D1 followed by surgical resection of the tumor followed by adjuvant pembrolizumab monotherapy 400 mg Q6W IV for 8 cycles (total treatment duration including neoadjuvant and adjuvant treatment of approximately 1 year). The SoAs described in Section 1.3.1 and Section 1.3.5 of this appendix should be followed.

When more than 1 agent is to be given on the same day, the order of administration is pembrolizumab followed by MK-4830. Refer to the Pharmacy Manual for additional information.

Investigational Treatment Arm 5: Two neoadjuvant cycles of MK-4280A (coformulation of MK-4280 800 mg + pembrolizumab 200 mg) Q3W IV on C1D1 and C2D1, followed by surgical resection of the tumor, and then followed by adjuvant pembrolizumab monotherapy 400 mg Q6W for 8 cycles (total treatment duration including neoadjuvant and adjuvant treatment of approximately 1 year). The SoAs described in Section 1.3.1 and Section 1.3.6 of this appendix should be followed.

Investigational Treatment Arm 6: Two neoadjuvant cycles of ATRA 75 mg/m^2 PO twice daily (total daily dose: 150 mg/m^2) on C1 Days 1, 2, and 3 and C2 Days 1, 2, and 3 + pembrolizumab 400 mg IV on C1 Day 1, followed by surgical resection of the tumor, and then followed by adjuvant pembrolizumab monotherapy 400 mg Q6W for 8 cycles (total treatment duration including neoadjuvant and adjuvant treatment of approximately 1 year). The SoAs described in Section 1.3.1 and Section 1.3.7 of this appendix should be followed.

NOTE: ATRA should be administered twice daily in the morning and evening. Pembrolizumab is administered on Day 1 of each cycle Q6W. On those days where both ATRA and pembrolizumab are administered, pembrolizumab may be infused approximately 30 minutes after the ATRA am dose.

10.6.2 Investigational Agent Information Summary

Procedures and assessments specific for MK-7684, V937, MK-4830, MK-4280A, and ATRA are detailed in the following sections. Refer to the main body of the substudy protocol for general aspects that govern the overall conduct of this substudy.

Note: Within this appendix, the subsections that follow correspond numerically with those in the main body of the protocol.

10.6.2.1 Section 1.3 Schedule of Activities

10.6.2.1.1 Section 1.3.1 Screening

Study Period	Screening (applicable to all participants in Substudy 2C)	Notes
Visit Timing/Cycle Number	**-28 to -1**	**All procedures and assessments are to be performed prior to administration of study intervention unless otherwise indicated. Refer to Section 8.12 for Visit Requirements.**
Cycle Day		
Scheduling Window (Days)	**-28 to -1**	
Administrative Procedures		
Informed consent	X	Informed Consent Form can be signed at any time prior to any protocol-specific screening procedures being performed.
Inclusion/exclusion	X	
Participant identification card	X	
Medical/surgical history	X	Significant medical/surgical history will be captured for last 10 years.
Demographics	X	
Staging	X	At study entry (assessed during Screening).

Study Period	Screening (applicable to all participants in Substudy 2C)	Notes
Visit Timing/Cycle Number	**-28 to -1**	**All procedures and assessments are to be performed prior to administration of study intervention unless otherwise indicated. Refer to Section 8.12 for Visit Requirements.**
Cycle Day		
Scheduling Window (Days)	**-28 to -1**	
BRAF status	X	BRAF V600 mutation analysis should be performed locally by the sites during Screening in participants without documented BRAF status. If the local laboratory is unable to perform BRAF testing, the site should submit the sample to the central pathology laboratory for testing. Due to the potential small size of the tumor sample, there might not be sufficient tumor tissue available to perform BRAF testing. In that case, BRAF V600 mutation analysis should be performed during the pathological assessment of the resected tumor specimen(s) (after the preoperative/neoadjuvant phase).
Prior medication review	X	
Efficacy/Immunogenicity Procedures		
Tumor assessment: chest, abdomen, and pelvis (CT/MRI)	X	Scans performed within the screening period but before signing the ICF may be used if consistent with protocol requirements per SIM. Imaging of any anatomy that shows disease at Screening or in subsequent evaluations will be required and should be submitted to the CIV. All imaging visits have a scheduling window of ±7 days. Tumor imaging is strongly preferred to be acquired by CT; the CT portion of PET-CT may be used in place of a stand-alone CT if it is of diagnostic quality per Site Imaging Manual.
Digital Photography	X	Qualitative digital photography should be performed at baseline and at time of scheduled tumor assessments for cutaneous lesions. Cutaneous lesions are not considered measurable for the purposes of this protocol but may be considered to be nontarget lesions for tumor assessments by investigators. Copies of digital photographs should also be submitted to the CIV.
Brain MRI	X	A brain MRI is required at Screening. Brain CT scan should only be used when MRI is contraindicated.
Safety Procedures		
AE monitoring	X	Record AEs if the event causes the participant to be excluded from the study or is the result of a protocol-specified intervention (eg, procedure).
Complete physical examination	X	To be performed within 7 days of first dose of study intervention.

Study Period	Screening (applicable to all participants in Substudy 2C)	Notes
Visit Timing/Cycle Number	**-28 to -1**	**All procedures and assessments are to be performed prior to administration of study intervention unless otherwise indicated. Refer to Section 8.12 for Visit Requirements.**
Cycle Day		
Scheduling Window (Days)	**-28 to -1**	
Vital signs (resting BP, heart rate, RR, and temp), weight, and height	X	Blood pressure and heart rate will be measured after the participant has been resting for 5 minutes. See Section 8.3.2 for vital signs. Height is measured at Screening only.
12-lead ECG	X	Single 12-lead ECG. Participants must be in the recumbent position for a period of 5 minutes prior to the ECG. Additional assessments may be performed if clinically indicated. To be performed within 7 days of first dose of study intervention. See Section 8.3.3 for ECG.
Hematology and chemistry laboratory assessment	X	Screening samples collected within 7 days of first dose of study intervention. Laboratory samples collected within 3 days prior to the first dose of study intervention need not be repeated on C1D1. The investigator (or medically qualified designee) must document their review of each laboratory safety report. Serum LDH is required at Screening.
Urinalysis	X	Screening samples collected within 7 days of first dose of study intervention. Additional assessments may be performed if clinically indicated.
PT/INR and aPTT/PTT	X	Screening samples collected within 7 days of first dose of study intervention. Additional testing to be conducted as clinically indicated for participants taking anticoagulant therapy.
T3, FT4, TSH	X	Screening samples to be collected within 7 days of first dose of study intervention. Free T3 is acceptable where Total T3 cannot be determined.
Pregnancy test (WOCBP only)	X	To be assessed within 24 hours before the first dose of study intervention. A serum or urine pregnancy test will be performed as indicated, prior to first dose of study intervention. See Appendix 11 for country-specific guidelines.
Serum FSH or estradiol	X	Only for women <45 years old with no menses for ≥1 year (12 months) and not currently on HRT or hormonal contraception.
HIV, HBV, HCV	X	Testing is not required unless mandated by local health authorities.
ECOG performance status	X	To be assessed within 7 days of first dose of study intervention.
Biomarkers		
Tumor blocks or slides	X	Collected during Screening for confirmation of adequacy of tumor tissue at a central pathology laboratory. See Section 8.9 for details on biomarker assessments.

Study Period	Screening (applicable to all participants in Substudy 2C)	Notes
Visit Timing/Cycle Number	**-28 to -1**	**All procedures and assessments are to be performed prior to administration of study intervention unless otherwise indicated. Refer to Section 8.12 for Visit Requirements.**
Cycle Day		
Scheduling Window (Days)	**-28 to -1**	

Abbreviations: AE = adverse event; aPTT = activated partial thromboplastin time; BP = blood pressure; BRAF = v-raf murine sarcoma viral oncogene homolog B1; C1 = Cycle 1; CIV = central imaging vendor; CT = computed tomography; D1 = Day 1; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; FSH = follicle stimulating hormone; FT4 = free thyroxine; HBV = hepatitis B virus; HCV = hepatitis C virus; HIV = human immunodeficiency virus; HRT = hormone replacement therapy; ICF = informed consent form; INR = international normalized ratio; LDH = lactate dehydrogenase; MRI = magnetic resonance imaging; PD-1/L1 = programmed cell death protein 1/programmed cell death- ligand 1; PET-CT = positron emissions tomography-computed tomography; PT = prothrombin time; PTT = partial thromboplastin time; RR = respiratory rate; SIM = site imaging manual; T3 = triiodothyronine; TSH = thyroid-stimulating hormone; WOCBP = women of childbearing potential.

10.6.2.1.2 Section 1.3.2 Pembrolizumab + MK-7684 (anti-TIGIT)

Pembrolizumab + MK-7684 (anti-TIGIT)											
Study Period	**Treatment**					**EOT[b]**	**Posttreatment**				**Notes**
	Cycle = 21 days		**Cycle = 42 days**				**Safety[b]**	**Follow-up[c]**		**Survival**	
Visit Timing/Cycle Number	**Cycle 1 (Neo-adjuvant Phase)**	**Cycle 2 (Neo-adjuvant Phase)**	**Post-Surgical Resection Visit to confirm Disease-free Status**	**Cycle 1 and Onwards[a] (Adjuvant Phase)**		**At D/C**	**30 Days After Last Dose**	**Q12W**	**Q24W**	**Q12W**	**All procedures and assessments are to be performed prior to administration of study intervention unless otherwise indicated. Refer to Section 8.12 for visit details.**
Cycle Day	**1**	**1**	**1**	**1**	**22[d]**						
Scheduling Window (Days)		**±3**	**±3**	**±3**	**±3**		**+7**	**±7**	**±7**	**±7**	
Administrative Procedures											
BRAF status			X								BRAF V600 mutation analysis should be performed locally by the sites during the pathological assessment of the resected tumor specimen(s), if not performed during Screening. If the local laboratory is unable to perform BRAF testing, the site should submit the sample to the central pathology laboratory for testing.

Pembrolizumab + MK-7684 (anti-TIGIT)											
Study Period	**Treatment**					**EOT[b]**	**Posttreatment**				**Notes**
	Cycle = 21 days		**Cycle = 42 days**				**Safety[b]**	**Follow-up[c]**		**Survival**	
Visit Timing/Cycle Number	**Cycle 1 (Neo-adjuvant Phase)**	**Cycle 2 (Neo-adjuvant Phase)**	**Post-Surgical Resection Visit to confirm Disease-free Status**	**Cycle 1 and Onwards[a] (Adjuvant Phase)**		**At D/C**	**30 Days After Last Dose**	**Q12W**	**Q24W**	**Q12W**	**All procedures and assessments are to be performed prior to administration of study intervention unless otherwise indicated. Refer to Section 8.12 for visit details.**
Cycle Day	**1**	**1**	**1**	**1**	**22[d]**						
Scheduling Window (Days)		**±3**	**±3**	**±3**	**±3**		**+7**	**±7**	**±7**	**±7**	
Concomitant medication review	-X	X	X	X	X	X	X	X			Concomitant medications will be recorded for 90 days after last dose (or for up to 120 days after last dose for SAEs).
Randomization/allocation	X										Presurgery/ Neoadjuvant Phase: Participants may be randomized/allocated 24 hours prior to first dose of study intervention and after confirmation of eligibility. All procedures and assessments on first dose of study intervention should be performed after randomization/ allocation.

Pembrolizumab + MK-7684 (anti-TIGIT)											
Study Period	**Treatment**					**EOT[b]**	**Posttreatment**				**Notes**
	Cycle = 21 days		**Cycle = 42 days**				**Safety[b]**	**Follow-up[c]**		**Survival**	
Visit Timing/Cycle Number	**Cycle 1 (Neo-adjuvant Phase)**	**Cycle 2 (Neo-adjuvant Phase)**	**Post-Surgical Resection Visit to confirm Disease-free Status**	**Cycle 1 and Onwards[a] (Adjuvant Phase)**		**At D/C**	**30 Days After Last Dose**	**Q12W**	**Q24W**	**Q12W**	**All procedures and assessments are to be performed prior to administration of study intervention unless otherwise indicated. Refer to Section 8.12 for visit details.**
Cycle Day	**1**	**1**	**1**	**1**	**22[d]**						
Scheduling Window (Days)		**±3**	**±3**	**±3**	**±3**		**+7**	**±7**	**±7**	**±7**	
Dispensation of pembrolizumab drug kit	X	X		X							Presurgery/Neoadjuvant Phase: C1D1 and C2D1 Postsurgery/Adjuvant Phase: Day 1 of every cycle (eg, C1D1, C2D1, C3D1, etc.)
Pembrolizumab administration	X	X		X							Presurgery/ Neoadjuvant Phase: Pembrolizumab will be administered Q3W for 2 doses prior to surgical resection. Postsurgery/Adjuvant Phase: After surgical resection, pembrolizumab will be administered Q6W on Day 1 of each cycle (total treatment duration including neoadjuvant and adjuvant phase of approximately 1 year)

Pembrolizumab + MK-7684 (anti-TIGIT)											
Study Period	**Treatment**					**EOT[b]**	**Posttreatment**				**Notes**
	Cycle = 21 days		**Cycle = 42 days**				**Safety[b]**	**Follow-up[c]**		**Survival**	
Visit Timing/Cycle Number	**Cycle 1 (Neo-adjuvant Phase)**	**Cycle 2 (Neo-adjuvant Phase)**	**Post-Surgical Resection Visit to confirm Disease-free Status**	**Cycle 1 and Onwards[a] (Adjuvant Phase)**		**At D/C**	**30 Days After Last Dose**	**Q12W**	**Q24W**	**Q12W**	**All procedures and assessments are to be performed prior to administration of study intervention unless otherwise indicated. Refer to Section 8.12 for visit details.**
Cycle Day	**1**	**1**	**1**	**1**	**22[d]**						
Scheduling Window (Days)		**±3**	**±3**	**±3**	**±3**		**+7**	**±7**	**±7**	**±7**	
Dispensation of MK-7684 drug kit	X	X									Presurgery/ Neoadjuvant Phase: C1D1 and C2D1 only.
MK-7684 administration	X	X									Presurgery/ Neoadjuvant Phase: MK-7684 will be administered Q3W for 2 doses prior to surgical resection.
Subsequent antineoplastic treatment							X	X	X	X	All anticancer therapy will be recorded until time of death or termination of survival FU. If a clinic visit is not feasible, follow-up information may be obtained via telephone or email.
Survival status	<----------									---------->	Participants may be contacted for survival status at any time during the course of this substudy.

Pembrolizumab + MK-7684 (anti-TIGIT)											
Study Period	**Treatment**					**EOT[b]**	**Posttreatment**				**Notes**
	Cycle = 21 days		**Cycle = 42 days**				**Safety[b]**	**Follow-up[c]**		**Survival**	
Visit Timing/Cycle Number	**Cycle 1 (Neo-adjuvant Phase)**	**Cycle 2 (Neo-adjuvant Phase)**	**Post-Surgical Resection Visit to confirm Disease-free Status**	**Cycle 1 and Onwards[a] (Adjuvant Phase)**		**At D/C**	**30 Days After Last Dose**	**Q12W**	**Q24W**	**Q12W**	**All procedures and assessments are to be performed prior to administration of study intervention unless otherwise indicated. Refer to Section 8.12 for visit details.**
Cycle Day	**1**	**1**	**1**	**1**	**22[d]**						
Scheduling Window (Days)		**±3**	**±3**	**±3**	**±3**		**+7**	**±7**	**±7**	**±7**	
Efficacy/Immunogenicity Procedures											
Tumor assessment: chest, abdomen, and pelvis (CT/MRI)[e]	<---------->					X		X	X		All imaging visits have a scheduling window of ±7 days. Presurgery/ Neoadjuvant Phase: The first on study imaging assessment should be performed at 6 weeks (42 days ±7 days) from first dose of study intervention (prior to surgical resection of the tumor). After surgical resection of the tumor, disease-free status must be documented by radiographic imaging at Week 12 (new baseline imaging prior to start of adjuvant therapy), prior to the start of

Pembrolizumab + MK-7684 (anti-TIGIT)											
Study Period	**Treatment**					**EOT[b]**	**Posttreatment**				**Notes**
	Cycle = 21 days		**Cycle = 42 days**				**Safety[b]**	**Follow-up[c]**		**Survival**	
Visit Timing/Cycle Number	**Cycle 1 (Neo-adjuvant Phase)**	**Cycle 2 (Neo-adjuvant Phase)**	**Post-Surgical Resection Visit to confirm Disease-free Status**	**Cycle 1 and Onwards[a] (Adjuvant Phase)**		**At D/C**	**30 Days After Last Dose**	**Q12W**	**Q24W**	**Q12W**	**All procedures and assessments are to be performed prior to administration of study intervention unless otherwise indicated. Refer to Section 8.12 for visit details.**
Cycle Day	**1**	**1**	**1**	**1**	**22[d]**						
Scheduling Window (Days)		**±3**	**±3**	**±3**	**±3**		**+7**	**±7**	**±7**	**±7**	
											postoperative/ adjuvant pembrolizumab. Postsurgery/Adjuvant Phase: Subsequent tumor imaging should be performed every 12 weeks from adjuvant C1D1 (±7 days) for the first 2 years, after which imaging will be performed every 24 weeks (168 days ±7 days) until Year 5 or more frequently if clinically indicated. or until documented disease recurrence. For participants who discontinue study intervention without documented disease recurrence, every effort should be made

Pembrolizumab + MK-7684 (anti-TIGIT)											
Study Period	**Treatment**					**EOT[b]**	**Posttreatment**				**Notes**
	Cycle = 21 days		**Cycle = 42 days**				**Safety[b]**	**Follow-up[c]**		**Survival**	
Visit Timing/Cycle Number	**Cycle 1 (Neo-adjuvant Phase)**	**Cycle 2 (Neo-adjuvant Phase)**	**Post-Surgical Resection Visit to confirm Disease-free Status**	**Cycle 1 and Onwards[a] (Adjuvant Phase)**		**At D/C**	**30 Days After Last Dose**	**Q12W**	**Q24W**	**Q12W**	**All procedures and assessments are to be performed prior to administration of study intervention unless otherwise indicated. Refer to Section 8.12 for visit details.**
Cycle Day	**1**	**1**	**1**	**1**	**22[d]**						
Scheduling Window (Days)		**±3**	**±3**	**±3**	**±3**		**+7**	**±7**	**±7**	**±7**	
											to continue monitoring disease status by tumor imaging using the same imaging schedule used while on treatment. Imaging of any anatomy that shows disease at Screening will be required in subsequent evaluations and should be submitted to the CIV. Tumor imaging is strongly preferred to be acquired by CT; the CT portion of PET/CT may be used in place of a stand-alone CT if it is of diagnostic quality per site imaging manual. Imaging at EOT is not required if the previous tumor

Pembrolizumab + MK-7684 (anti-TIGIT)											
Study Period	**Treatment**					**EOT[b]**	**Posttreatment**				**Notes**
	Cycle = 21 days		**Cycle = 42 days**				**Safety[b]**	**Follow-up[c]**		**Survival**	
Visit Timing/Cycle Number	**Cycle 1 (Neo-adjuvant Phase)**	**Cycle 2 (Neo-adjuvant Phase)**	**Post-Surgical Resection Visit to confirm Disease-free Status**	**Cycle 1 and Onwards[a] (Adjuvant Phase)**		**At D/C**	**30 Days After Last Dose**	**Q12W**	**Q24W**	**Q12W**	**All procedures and assessments are to be performed prior to administration of study intervention unless otherwise indicated. Refer to Section 8.12 for visit details.**
Cycle Day	**1**	**1**	**1**	**1**	**22[d]**						
Scheduling Window (Days)		**±3**	**±3**	**±3**	**±3**		**+7**	**±7**	**±7**	**±7**	
											imaging assessment was within 4 weeks prior to the EOT visit.
Digital photography	<----------										Qualitative digital photography should be performed as clinically indicated. Cutaneous lesions are not considered measurable for the purposes of this protocol but may be considered to be nontarget lesions for tumor assessments by investigators. Copies of digital photographs should also be submitted to the central imaging vendor.

Pembrolizumab + MK-7684 (anti-TIGIT)											
Study Period	**Treatment**					**EOT[b]**	**Posttreatment**				**Notes**
	Cycle = 21 days		**Cycle = 42 days**				**Safety[b]**	**Follow-up[c]**		**Survival**	
Visit Timing/Cycle Number	**Cycle 1 (Neo-adjuvant Phase)**	**Cycle 2 (Neo-adjuvant Phase)**	**Post-Surgical Resection Visit to confirm Disease-free Status**	**Cycle 1 and Onwards[a] (Adjuvant Phase)**		**At D/C**	**30 Days After Last Dose**	**Q12W**	**Q24W**	**Q12W**	**All procedures and assessments are to be performed prior to administration of study intervention unless otherwise indicated. Refer to Section 8.12 for visit details.**
Cycle Day	**1**	**1**	**1**	**1**	**22[d]**						
Scheduling Window (Days)		**±3**	**±3**	**±3**	**±3**		**+7**	**±7**	**±7**	**±7**	
Safety Procedures											
AE monitoring	X	X	X	X	X	X	X	X			AEs: monitored up to 90 days after last dose. SAEs and pregnancy: monitored up to 120 days after last dose, or 30 days after last dose if participant starts a new anticancer therapy, whichever is sooner.
Complete physical examination			X								Postsurgical resection of the tumor, disease-free status must be documented by a complete physical examination at Week 12 (new baseline imaging), prior to the start of postoperative/adjuvant pembrolizumab.

Pembrolizumab + MK-7684 (anti-TIGIT)											
Study Period	**Treatment**					**EOT[b]**	**Posttreatment**				**Notes**
	Cycle = 21 days		**Cycle = 42 days**				**Safety[b]**	**Follow-up[c]**		**Survival**	
Visit Timing/Cycle Number	**Cycle 1 (Neo-adjuvant Phase)**	**Cycle 2 (Neo-adjuvant Phase)**	**Post-Surgical Resection Visit to confirm Disease-free Status**	**Cycle 1 and Onwards[a] (Adjuvant Phase)**		**At D/C**	**30 Days After Last Dose**	**Q12W**	**Q24W**	**Q12W**	**All procedures and assessments are to be performed prior to administration of study intervention unless otherwise indicated. Refer to Section 8.12 for visit details.**
Cycle Day	**1**	**1**	**1**	**1**	**22[d]**						
Scheduling Window (Days)		**±3**	**±3**	**±3**	**±3**		**+7**	**±7**	**±7**	**±7**	
Directed physical examination	X	X		X	X	X	X	X	X		In addition to the directed PEs in the flowchart, a symptom-directed PE may be performed at any time during this substudy, as clinically indicated. The investigator or qualified designee should conduct a visual inspection of local recurrence and palpation of lymph nodes to assess recurrence

Pembrolizumab + MK-7684 (anti-TIGIT)											
Study Period	**Treatment**					**EOT[b]**	**Posttreatment**				**Notes**
	Cycle = 21 days		**Cycle = 42 days**				**Safety[b]**	**Follow-up[c]**		**Survival**	
Visit Timing/Cycle Number	**Cycle 1 (Neo-adjuvant Phase)**	**Cycle 2 (Neo-adjuvant Phase)**	**Post-Surgical Resection Visit to confirm Disease-free Status**	**Cycle 1 and Onwards[a] (Adjuvant Phase)**		**At D/C**	**30 Days After Last Dose**	**Q12W**	**Q24W**	**Q12W**	**All procedures and assessments are to be performed prior to administration of study intervention unless otherwise indicated. Refer to Section 8.12 for visit details.**
Cycle Day	**1**	**1**	**1**	**1**	**22[d]**						
Scheduling Window (Days)		**±3**	**±3**	**±3**	**±3**		**+7**	**±7**	**±7**	**±7**	
Review of the pathology report postsurgical resection			X								Review of the pathology report of the surgical resection specimen(s) by the investigator is mandatory prior to the start of adjuvant therapy to ensure the participant is disease-free and the surgical margins are tumor-free (R0).
Vital signs (resting BP, heart rate, RR, and temp), and weight	X	X		X	X	X	X				Blood pressure and heart rate will be measured after the participant has been resting for 5 minutes. See Section 8.3.2 for vital signs.

Pembrolizumab + MK-7684 (anti-TIGIT)											
Study Period	**Treatment**					**EOT[b]**	**Posttreatment**				**Notes**
	Cycle = 21 days		**Cycle = 42 days**				**Safety[b]**	**Follow-up[c]**		**Survival**	
Visit Timing/Cycle Number	**Cycle 1 (Neo-adjuvant Phase)**	**Cycle 2 (Neo-adjuvant Phase)**	**Post-Surgical Resection Visit to confirm Disease-free Status**	**Cycle 1 and Onwards[a] (Adjuvant Phase)**		**At D/C**	**30 Days After Last Dose**	**Q12W**	**Q24W**	**Q12W**	**All procedures and assessments are to be performed prior to administration of study intervention unless otherwise indicated. Refer to Section 8.12 for visit details.**
Cycle Day	**1**	**1**	**1**	**1**	**22[d]**						
Scheduling Window (Days)		**±3**	**±3**	**±3**	**±3**		**+7**	**±7**	**±7**	**±7**	
12-lead ECG	<----------				---------->						As clinically indicated. Participants must be in the recumbent position for a period of 5 minutes prior to the ECG. See Section 8.3.3 for ECG.
Hematology and chemistry laboratory assessment	X	X	X	X	X	X	X				Procedures/ assessments should be performed prior to all scheduled substudy visits. Every effort should be made to collect samples at the same time of day. LDH testing is needed. Laboratory samples collected within 3 days prior to the first dose of study intervention need not be repeated on C1D1.

Pembrolizumab + MK-7684 (anti-TIGIT)											
Study Period	**Treatment**					**EOT[b]**	**Posttreatment**				**Notes**
	Cycle = 21 days		**Cycle = 42 days**				**Safety[b]**	**Follow-up[c]**		**Survival**	
Visit Timing/Cycle Number	**Cycle 1 (Neo-adjuvant Phase)**	**Cycle 2 (Neo-adjuvant Phase)**	**Post-Surgical Resection Visit to confirm Disease-free Status**	**Cycle 1 and Onwards[a] (Adjuvant Phase)**		**At D/C**	**30 Days After Last Dose**	**Q12W**	**Q24W**	**Q12W**	**All procedures and assessments are to be performed prior to administration of study intervention unless otherwise indicated. Refer to Section 8.12 for visit details.**
Cycle Day	**1**	**1**	**1**	**1**	**22[d]**						
Scheduling Window (Days)		**±3**	**±3**	**±3**	**±3**		**+7**	**±7**	**±7**	**±7**	
Urinalysis	←----------				----------→						As clinically indicated.
PT/INR and aPTT/PTT	←----------				----------→						As clinically indicated for participants taking anticoagulant therapy.
T3, FT4, TSH		X		X		X					Presurgery/ Neoadjuvant Phase: Thyroid function tests will be performed at Cycle 2. Postsurgery/Adjuvant Phase: Thyroid function tests will be performed at Cycle 1 and every cycle thereafter and at the time of discontinuation (EOT). Free T3 is acceptable where Total T3 cannot be determined. After C1 of the Presurgery/ Neoadjuvant Phase,

Pembrolizumab + MK-7684 (anti-TIGIT)											
Study Period	**Treatment**					**EOT[b]**	**Posttreatment**				**Notes**
	Cycle = 21 days		**Cycle = 42 days**				**Safety[b]**	**Follow-up[c]**		**Survival**	
Visit Timing/Cycle Number	**Cycle 1 (Neo-adjuvant Phase)**	**Cycle 2 (Neo-adjuvant Phase)**	**Post-Surgical Resection Visit to confirm Disease-free Status**	**Cycle 1 and Onwards[a] (Adjuvant Phase)**		**At D/C**	**30 Days After Last Dose**	**Q12W**	**Q24W**	**Q12W**	**All procedures and assessments are to be performed prior to administration of study intervention unless otherwise indicated. Refer to Section 8.12 for visit details.**
Cycle Day	**1**	**1**	**1**	**1**	**22[d]**						
Scheduling Window (Days)		**±3**	**±3**	**±3**	**±3**		**+7**	**±7**	**±7**	**±7**	
											retrospective review of thyroid function testing results is allowed when the results are not available prior to dosing.
Pregnancy test (WOCBP only)		X		X		X	X	X			To be assessed prior to all scheduled visits. A serum or urine pregnancy test will be performed as indicated, prior to every cycle, up to 120 days after last dose of study intervention or 30 days after last dose if participant starts a new anticancer therapy, whichever comes first. See Appendix 11 for country-specific guidelines.

Pembrolizumab + MK-7684 (anti-TIGIT)											
Study Period	**Treatment**					**EOT[b]**	**Posttreatment**				**Notes**
	Cycle = 21 days		**Cycle = 42 days**				**Safety[b]**	**Follow-up[c]**		**Survival**	
Visit Timing/Cycle Number	**Cycle 1 (Neo-adjuvant Phase)**	**Cycle 2 (Neo-adjuvant Phase)**	**Post-Surgical Resection Visit to confirm Disease-free Status**	**Cycle 1 and Onwards[a] (Adjuvant Phase)**		**At D/C**	**30 Days After Last Dose**	**Q12W**	**Q24W**	**Q12W**	**All procedures and assessments are to be performed prior to administration of study intervention unless otherwise indicated. Refer to Section 8.12 for visit details.**
Cycle Day	**1**	**1**	**1**	**1**	**22[d]**						
Scheduling Window (Days)		**±3**	**±3**	**±3**	**±3**		**+7**	**±7**	**±7**	**±7**	
ECOG performance status		X		X	X	X	X				To be assessed prior to dosing during all scheduled visits.
Pharmacokinetics/Pharmacodynamics/Biomarkers											
MK-3475 PK	X	X		X		X	X				Presurgery/ Neoadjuvant Phase: Collect predose of study intervention on C1D1 C2D1. Postsurgery/Adjuvant Phase: Collect predose on C1D1, C2D1. Samples should also be taken at EOT and at the 30-day Safety Follow-up visit. Note: Predose = Prior to the administration of any study intervention. Postdose = After the administration of all study interventions.

Pembrolizumab + MK-7684 (anti-TIGIT)											
Study Period	**Treatment**					**EOT[b]**	**Posttreatment**				**Notes**
	Cycle = 21 days		**Cycle = 42 days**				**Safety[b]**	**Follow-up[c]**		**Survival**	
Visit Timing/Cycle Number	**Cycle 1 (Neo-adjuvant Phase)**	**Cycle 2 (Neo-adjuvant Phase)**	**Post-Surgical Resection Visit to confirm Disease-free Status**	**Cycle 1 and Onwards[a] (Adjuvant Phase)**		**At D/C**	**30 Days After Last Dose**	**Q12W**	**Q24W**	**Q12W**	**All procedures and assessments are to be performed prior to administration of study intervention unless otherwise indicated. Refer to Section 8.12 for visit details.**
Cycle Day	**1**	**1**	**1**	**1**	**22[d]**						
Scheduling Window (Days)		**±3**	**±3**	**±3**	**±3**		**+7**	**±7**	**±7**	**±7**	
MK-3475 ADA	X	X		X		X	X				Presurgery/ Neoadjuvant Phase: Collect predose of study intervention on C1D1 C2D1. Postsurgery/Adjuvant Phase: Collect predose on C1D1, C2D1. Samples should also be taken at EOT and at the 30-day Safety Follow-up visit. Note: Predose = Prior to the administration of any study intervention. Postdose = After the administration of all study interventions.

Pembrolizumab + MK-7684 (anti-TIGIT)											
Study Period	**Treatment**					**EOT[b]**	**Posttreatment**				**Notes**
	Cycle = 21 days		**Cycle = 42 days**				**Safety[b]**	**Follow-up[c]**		**Survival**	
Visit Timing/Cycle Number	**Cycle 1 (Neo-adjuvant Phase)**	**Cycle 2 (Neo-adjuvant Phase)**	**Post-Surgical Resection Visit to confirm Disease-free Status**	**Cycle 1 and Onwards[a] (Adjuvant Phase)**		**At D/C**	**30 Days After Last Dose**	**Q12W**	**Q24W**	**Q12W**	**All procedures and assessments are to be performed prior to administration of study intervention unless otherwise indicated. Refer to Section 8.12 for visit details.**
Cycle Day	**1**	**1**	**1**	**1**	**22[d]**						
Scheduling Window (Days)		**±3**	**±3**	**±3**	**±3**		**+7**	**±7**	**±7**	**±7**	
MK-7684 PK	X	X		X		X	X				Presurgery/ Neoadjuvant Phase: Collect predose of study intervention on C1D1 C2D1. Postsurgery/Adjuvant Phase: Collect predose on C1D1, C2D1. Samples should also be taken at EOT and at the 30-day Safety Follow-up visit. Note: Predose = Prior to the administration of any study intervention. Postdose = After the administration of all study interventions.

Pembrolizumab + MK-7684 (anti-TIGIT)											
Study Period	**Treatment**					**EOT[b]**	**Posttreatment**				**Notes**
	Cycle = 21 days		**Cycle = 42 days**				**Safety[b]**	**Follow-up[c]**		**Survival**	
Visit Timing/Cycle Number	**Cycle 1 (Neo-adjuvant Phase)**	**Cycle 2 (Neo-adjuvant Phase)**	**Post-Surgical Resection Visit to confirm Disease-free Status**	**Cycle 1 and Onwards[a] (Adjuvant Phase)**		**At D/C**	**30 Days After Last Dose**	**Q12W**	**Q24W**	**Q12W**	**All procedures and assessments are to be performed prior to administration of study intervention unless otherwise indicated. Refer to Section 8.12 for visit details.**
Cycle Day	**1**	**1**	**1**	**1**	**22[d]**						
Scheduling Window (Days)		**±3**	**±3**	**±3**	**±3**		**+7**	**±7**	**±7**	**±7**	
MK-7684 ADA	X	X		X		X	X				Presurgery/ Neoadjuvant Phase: Collect predose of study intervention on C1D1 C2D1. Postsurgery/Adjuvant Phase: Collect predose on C1D1, C2D1. Samples should also be taken at EOT and at the 30-day Safety Follow-up visit. Note: Predose = Prior to the administration of any study intervention. Postdose = After the administration of all study interventions.

Pembrolizumab + MK-7684 (anti-TIGIT)											
Study Period	**Treatment**					**EOT[b]**	**Posttreatment**				**Notes**
	Cycle = 21 days		**Cycle = 42 days**				**Safety[b]**	**Follow-up[c]**		**Survival**	
Visit Timing/Cycle Number	**Cycle 1 (Neo-adjuvant Phase)**	**Cycle 2 (Neo-adjuvant Phase)**	**Post-Surgical Resection Visit to confirm Disease-free Status**	**Cycle 1 and Onwards[a] (Adjuvant Phase)**		**At D/C**	**30 Days After Last Dose**	**Q12W**	**Q24W**	**Q12W**	**All procedures and assessments are to be performed prior to administration of study intervention unless otherwise indicated. Refer to Section 8.12 for visit details.**
Cycle Day	**1**	**1**	**1**	**1**	**22[d]**						
Scheduling Window (Days)		**±3**	**±3**	**±3**	**±3**		**+7**	**±7**	**±7**	**±7**	
Blood for ctDNA analysis	X	X		X		X		X*	X*		Presurgery/ Neoadjuvant Phase: Collect predose on first dose of study intervention, and predose on C2D1. Postsurgery/Adjuvant Phase: Collect predose on C1D1. After C1D1 collection, the ctDNA samples should be collected at the time of all scheduled imaging assessments (±7 days), including EOT imaging assessment, and should be performed if possible for all unscheduled imaging assessments (±7 days) documenting recurrence. *During follow-up, if a clinic visit is not feasible, blood for ctDNA will not be collected

Pembrolizumab + MK-7684 (anti-TIGIT)											
Study Period	**Treatment**					**EOT[b]**	**Posttreatment**				**Notes**
	Cycle = 21 days		**Cycle = 42 days**				**Safety[b]**	**Follow-up[c]**		**Survival**	
Visit Timing/Cycle Number	**Cycle 1 (Neo-adjuvant Phase)**	**Cycle 2 (Neo-adjuvant Phase)**	**Post-Surgical Resection Visit to confirm Disease-free Status**	**Cycle 1 and Onwards[a] (Adjuvant Phase)**		**At D/C**	**30 Days After Last Dose**	**Q12W**	**Q24W**	**Q12W**	**All procedures and assessments are to be performed prior to administration of study intervention unless otherwise indicated. Refer to Section 8.12 for visit details.**
Cycle Day	**1**	**1**	**1**	**1**	**22[d]**						
Scheduling Window (Days)		**±3**	**±3**	**±3**	**±3**		**+7**	**±7**	**±7**	**±7**	
Blood for genetic analysis	X										Presurgery/ Neoadjuvant Phase: Collect predose on first dose of study intervention. See Section 8.9 for additional information.
Tumor blocks or slides	X		X								Presurgery/ Neoadjuvant Phase: Participants must submit a tumor sample at the end of Cycle 1 (Days 15-21) or C2D1 predose for biomarker analysis. A surgical resection specimen taken at Week 6 will also be submitted for pathologic assessment of resection specimens and for biomarker analysis. See Section 8.9 for details on biomarker assessments.

Pembrolizumab + MK-7684 (anti-TIGIT)											
Study Period	**Treatment**					**EOT[b]**	**Posttreatment**				**Notes**
	Cycle = 21 days		**Cycle = 42 days**				**Safety[b]**	**Follow-up[c]**		**Survival**	
Visit Timing/Cycle Number	**Cycle 1 (Neo-adjuvant Phase)**	**Cycle 2 (Neo-adjuvant Phase)**	**Post-Surgical Resection Visit to confirm Disease-free Status**	**Cycle 1 and Onwards[a] (Adjuvant Phase)**		**At D/C**	**30 Days After Last Dose**	**Q12W**	**Q24W**	**Q12W**	**All procedures and assessments are to be performed prior to administration of study intervention unless otherwise indicated. Refer to Section 8.12 for visit details.**
Cycle Day	**1**	**1**	**1**	**1**	**22[d]**						
Scheduling Window (Days)		**±3**	**±3**	**±3**	**±3**		**+7**	**±7**	**±7**	**±7**	

Abbreviations: AE = adverse event; BP = blood pressure; C1 = Cycle 1; C2 = Cycle 2; C3 = Cycle 3; C5 = Cycle 5; CIV = central imaging vendor; CT = computed tomography; ctDNA = circulating tumor DNA; ctRNA = circulating tumor RNA; D1 = Day 1; D15 = Day 15; D8 = Day 8; D/C = discontinue/discontinuing; ECG = electrocardiogram; ECHO = echocardiogram; ECOG = Eastern Cooperative Oncology Group; EOT = end of treatment; ePRO = electronic patient-reported outcome; FT4 = free thyroxine; FU = follow-up; HBV = hepatitis B virus; HCV = hepatitis C virus; HIV = human immunodeficiency virus; HRQoL = health-related quality of life; ICF = Informed Consent Form; INR = international normalized ratio; MRI = magnetic resonance imaging; MUGA = multigated acquisition; PE = physical examination; PK = pharmacokinetics; PT = prothrombin time; Q3W = every 3 weeks; Q9W = every 9 weeks; Q12W = every 12 weeks; Q24W = every 24 weeks; QD = once daily; RECIST = Response Evaluation Criteria in Solid Tumors; RR = respiratory rate; SAE = serious adverse event; SIM = site imaging manual; T3 = triiodothyronine; TSH = thyroid-stimulating hormone; UPCR=urine protein-to-creatinine; WOCBP = women of childbearing potential

a After surgical resection of the tumor, participants will receive 8 cycles of adjuvant therapy with pembrolizumab monotherapy as soon as possible after surgery - (interval between surgical resection and adjuvant pembrolizumab should not exceed 12 weeks; the interval between postsurgery baseline imaging and first dose of adjuvant dosing should not exceed 28 days; total treatment duration including neoadjuvant and adjuvant therapy of approximately 1 year) or until they experience disease recurrence, unacceptable AEs are reported, consent is withdrawn, death, intercurrent illness that prevents further administration of study intervention, investigator's decision to discontinue the participant, noncompliance with study intervention or procedure requirements, or administrative reasons requiring cessation of treatment, whichever occurs first.

b If EOT visit occurs ~30 days from last dose of study intervention, a 30-day Safety Follow-up visit is not required. In this situation, all procedures required at the 30-day Safety Follow-up visit and EOT are performed once and entered into the EOT visit only. End of treatment will be defined as the date when the participant discontinues all study interventions.

c For participants who DC study intervention for reasons other than documented disease recurrence, follow-up visits to monitor disease status continue until documented disease recurrence or initiation of a new anticancer therapy. Participants who D/C study intervention with documented disease recurrence proceed directly to Survival Follow-up.

d Optional visit; visit and laboratory assessments should be completed as clinically indicated.

e Brain imaging is required for all participants at Screening. Magnetic resonance imaging is preferred; however, CT imaging will be acceptable if MRI is medically contraindicated.

Note: Each participant will receive neoadjuvant study intervention with an investigational treatment arm for up to approximately 5 weeks from first dose of study intervention followed by surgical resection of the tumor 6 weeks (42 days ± 7 days) from neoadjuvant C1D1 (also called definitive surgery with curative intent). Surgery should occur no sooner than approximately 5 weeks from the first dose of study intervention.

10.6.2.1.3 Section 1.3.3 Pembrolizumab + V937

Pembrolizumab + V937														
Study Period	**Treatment Cycle = 42 days**								**EOT[b]**	**Posttreatment**				**Notes**
										Safety[b]	**Follow-up[c]**		**Survival**	
Visit Timing/Cycle Number	**Cycle 1 (Neoadjuvant Phase)**					**Post-Surgical Resection Visit to confirm Disease-free Status**	**Cycle 1 and Onward[a] (Adjuvant Phase)**		**At D/C**	**30 Days After Last Dose**	**Q12W**	**Q24 W**	**Q12W**	**All procedures and assessments are to be performed prior to administration of study intervention unless otherwise indicated. Refer to Section 8.12 for visit details.**
Cycle Day	**1**	**3**	**5**	**8**	**22**	**1**	**1**	**22[d]**						
Scheduling Window (Days)	**-**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**		**+7**	**±7**	**±7**	**±7**	
Administrative Procedures														
BRAF status						X								BRAF V600 mutation analysis should be performed locally by the sites during the pathological assessment of the resected tumor specimen(s), if not performed during Screening. If the local laboratory is unable to perform BRAF testing, the site should submit the sample to the central laboratory for testing.
Concomitant medication review	X	X	X	X	X	X	X	X	X	X	X			Concomitant medications will be recorded for 90 days after last dose (or for up to 120 days after last dose for SAEs).

Pembrolizumab + V937														
Study Period	**Treatment Cycle = 42 days**								**EOT[b]**	**Posttreatment**				**Notes**
										Safety[b]	**Follow-up[c]**		**Survival**	
Visit Timing/Cycle Number	**Cycle 1 (Neoadjuvant Phase)**					**Post-Surgical Resection Visit to confirm Disease-free Status**	**Cycle 1 and Onward[a] (Adjuvant Phase)**		**At D/C**	**30 Days After Last Dose**	**Q12W**	**Q24 W**	**Q12W**	**All procedures and assessments are to be performed prior to administration of study intervention unless otherwise indicated. Refer to Section 8.12 for visit details.**
Cycle Day	**1**	**3**	**5**	**8**	**22**	**1**	**1**	**22[d]**						
Scheduling Window (Days)	**-**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**		**+7**	**±7**	**±7**	**±7**	
Randomization/ allocation	X													Presurgery/ Neoadjuvant Phase: Participants may be randomized/allocated 24 hours prior to first dose of study intervention and after confirmation of eligibility. All procedures and assessments on first dose of study intervention should be performed after randomization/ allocation.
Dispensation of pembrolizumab drug kit				X			X							Presurgery/ Neoadjuvant Phase: C1D8. Postsurgery/Adjuvant Phase: Day 1 of every cycle (eg, C1D1, C2D1, C3D1, etc.)

Pembrolizumab + V937														
Study Period	**Treatment Cycle = 42 days**								**EOT[b]**	**Posttreatment**				**Notes**
										Safety[b]	**Follow-up[c]**		**Survival**	
Visit Timing/Cycle Number	**Cycle 1 (Neoadjuvant Phase)**					**Post-Surgical Resection Visit to confirm Disease-free Status**	**Cycle 1 and Onward[a] (Adjuvant Phase)**		**At D/C**	**30 Days After Last Dose**	**Q12W**	**Q24 W**	**Q12W**	**All procedures and assessments are to be performed prior to administration of study intervention unless otherwise indicated. Refer to Section 8.12 for visit details.**
Cycle Day	**1**	**3**	**5**	**8**	**22**	**1**	**1**	**22[d]**						
Scheduling Window (Days)	**-**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**		**+7**	**±7**	**±7**	**±7**	
Pembrolizumab administration				X			X							Presurgery/ Neoadjuvant Phase: Pembrolizumab will be administered for 1 dose prior to surgical resection on C1D8. Postsurgery/Adjuvant Phase: After surgical resection, pembrolizumab will be administered Q6W on Day 1 of each cycle (total treatment duration including neoadjuvant and adjuvant phase of approximately 1 year).
Dispensation of V937 drug kit	X	X	X	X	X									Presurgery/Neoadjuvant Phase: C1D1, C1D3, C1D5, C1D8, and C1D22.
V937 administration	X	X	X	X	X									Presurgery/ Neoadjuvant Phase: V937 will be administered for up to 5 doses prior to surgical resection.
Subsequent antineoplastic treatment										X	X	X	X	All anticancer therapy will be recorded until time of death or termination of survival FU. If a clinic visit is not feasible, follow-up information may be obtained via telephone or email.

Pembrolizumab + V937														
Study Period	**Treatment Cycle = 42 days**								**EOT[b]**	**Posttreatment**				**Notes**
										Safety[b]	**Follow-up[c]**		**Survival**	
Visit Timing/Cycle Number	**Cycle 1 (Neoadjuvant Phase)**					**Post-Surgical Resection Visit to confirm Disease-free Status**	**Cycle 1 and Onward[a] (Adjuvant Phase)**		**At D/C**	**30 Days After Last Dose**	**Q12W**	**Q24 W**	**Q12W**	**All procedures and assessments are to be performed prior to administration of study intervention unless otherwise indicated. Refer to Section 8.12 for visit details.**
Cycle Day	**1**	**3**	**5**	**8**	**22**	**1**	**1**	**22[d]**						
Scheduling Window (Days)	**-**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**		**+7**	**±7**	**±7**	**±7**	
Survival status	<----------							---------->						Participants may be contacted for survival status at any time during the course of this substudy.
Efficacy/Immunogenicity Procedures														
Tumor assessment: chest, abdomen, and pelvis (CT/MRI)[e]	<----------							---------->	X		X	X		All imaging visits have a scheduling window of ±7 days. Presurgery/Neoadjuvant Phase: The first on study imaging assessment should be performed at 6 weeks (42 days ±7 days) from first dose of study intervention (prior to surgical resection of the tumor). After surgical resection of the tumor, disease-free status must be documented by radiographic imaging at Week 12 (new baseline imaging prior to start of adjuvant therapy), prior to the start of postoperative/adjuvant pembrolizumab. Postsurgery/Adjuvant Phase: Subsequent tumor imaging should be performed every 12 weeks from adjuvant C1D1 (±7 days) for the first 2 years, after which imaging will be performed every 24 weeks (168 days ±7 days) until Year 5 or more frequently if clinically indicated. or until documented disease recurrence.

Pembrolizumab + V937														
Study Period	**Treatment Cycle = 42 days**								**EOT[b]**	**Posttreatment**				**Notes**
										Safety[b]	**Follow-up[c]**		**Survival**	
Visit Timing/Cycle Number	**Cycle 1 (Neoadjuvant Phase)**					**Post-Surgical Resection Visit to confirm Disease-free Status**	**Cycle 1 and Onward[a] (Adjuvant Phase)**		**At D/C**	**30 Days After Last Dose**	**Q12W**	**Q24 W**	**Q12W**	**All procedures and assessments are to be performed prior to administration of study intervention unless otherwise indicated. Refer to Section 8.12 for visit details.**
Cycle Day	**1**	**3**	**5**	**8**	**22**	**1**	**1**	**22[d]**						
Scheduling Window (Days)	**-**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**		**+7**	**±7**	**±7**	**±7**	
														For participants who discontinue study intervention without documented disease recurrence, every effort should be made to continue monitoring disease status by tumor imaging using the same imaging schedule used while on treatment. Imaging of any anatomy that shows disease at Screening will be required in subsequent evaluations and should be submitted to the CIV. Tumor imaging is strongly preferred to be acquired by CT; the CT portion of PET/CT may be used in place of a stand-alone CT if it is of diagnostic quality per site imaging manual. Imaging at EOT is not required if the previous tumor imaging assessment was within 4 weeks prior to the EOT visit.

Pembrolizumab + V937														
Study Period	**Treatment Cycle = 42 days**								**EOT[b]**	**Posttreatment**				**Notes**
										Safety[b]	**Follow-up[c]**		**Survival**	
Visit Timing/Cycle Number	**Cycle 1 (Neoadjuvant Phase)**					**Post-Surgical Resection Visit to confirm Disease-free Status**	**Cycle 1 and Onward[a] (Adjuvant Phase)**		**At D/C**	**30 Days After Last Dose**	**Q12W**	**Q24 W**	**Q12W**	**All procedures and assessments are to be performed prior to administration of study intervention unless otherwise indicated. Refer to Section 8.12 for visit details.**
Cycle Day	**1**	**3**	**5**	**8**	**22**	**1**	**1**	**22[d]**						
Scheduling Window (Days)	**-**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**		**+7**	**±7**	**±7**	**±7**	
Digital photography	<----------													Qualitative digital photography should be performed as clinically indicated. Cutaneous lesions are not considered measurable for the purposes of this protocol but may be considered to be nontarget lesions for tumor assessments by investigators. Copies of digital photographs should also be submitted to the central imaging vendor.
Safety Procedures														
AE monitoring	X	X	X	X	X	X	X	X	X	X	X			AEs: monitored up to 90 days after last dose. SAEs and pregnancy: monitored up to 120 days after last dose, or 30 days after last dose if participant starts a new anticancer therapy, whichever is sooner.

Pembrolizumab + V937														
Study Period	**Treatment Cycle = 42 days**								**EOT[b]**	**Posttreatment**				**Notes**
										Safety[b]	**Follow-up[c]**		**Survival**	
Visit Timing/Cycle Number	**Cycle 1 (Neoadjuvant Phase)**					**Post-Surgical Resection Visit to confirm Disease-free Status**	**Cycle 1 and Onward[a] (Adjuvant Phase)**		**At D/C**	**30 Days After Last Dose**	**Q12W**	**Q24 W**	**Q12W**	**All procedures and assessments are to be performed prior to administration of study intervention unless otherwise indicated. Refer to Section 8.12 for visit details.**
Cycle Day	**1**	**3**	**5**	**8**	**22**	**1**	**1**	**22[d]**						
Scheduling Window (Days)	**-**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**		**+7**	**±7**	**±7**	**±7**	
Complete physical examination						X								Postsurgical resection of the tumor, disease-free status must be documented by a complete physical examination at Week 12 (new baseline imaging), prior to the start of postoperative/adjuvant pembrolizumab
Directed physical examination	X				X		X	X	X	X	X	X		In addition to the directed PEs in the flowchart, a symptom-directed PE may be performed at any time during this substudy, as clinically indicated. The investigator or qualified designee should conduct a visual inspection of local recurrence and palpation of lymph nodes to assess recurrence.
Review of the pathology report postsurgical resection						X								Review of the pathology report of the surgical resection specimen(s) by the investigator is mandatory prior to the start of adjuvant therapy to ensure the participant is disease-free and the surgical margins are tumor-free (R0).

Pembrolizumab + V937														
Study Period	**Treatment Cycle = 42 days**								**EOT[b]**	**Posttreatment**				**Notes**
										Safety[b]	**Follow-up[c]**		**Survival**	
Visit Timing/Cycle Number	**Cycle 1 (Neoadjuvant Phase)**					**Post-Surgical Resection Visit to confirm Disease-free Status**	**Cycle 1 and Onward[a] (Adjuvant Phase)**		**At D/C**	**30 Days After Last Dose**	**Q12W**	**Q24 W**	**Q12W**	**All procedures and assessments are to be performed prior to administration of study intervention unless otherwise indicated. Refer to Section 8.12 for visit details.**
Cycle Day	**1**	**3**	**5**	**8**	**22**	**1**	**1**	**22[d]**						
Scheduling Window (Days)	**-**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**		**+7**	**±7**	**±7**	**±7**	
Vital signs (resting BP, heart rate, RR, and temp), and weight	X				X		X	X	X	X				Blood pressure and heart rate will be measured after the participant has been resting for 5 minutes. See Section 8.3.2 for vital signs.
12-lead ECG	←	----	----	----	----	----	----	----	----	→				As clinically indicated. Participants must be in the recumbent position for a period of 5 minutes prior to the ECG. See Section 8.3.3 for ECG.
Hematology and chemistry laboratory assessment	X				X	X	X	X	X	X				Procedures/assessments should be performed prior to all scheduled substudy visits. Every effort should be made to collect samples at the same time of day. LDH testing is needed. Laboratory samples collected within 3 days prior to the first dose of study intervention need not be repeated on C1D1.
Urinalysis	←	----	----	----	----	----	----	----	----	→				As clinically indicated.
PT/INR and aPTT/PTT	←	----	----	----	----	----	----	----	----	→				As clinically indicated for participants taking anticoagulant therapy.

Pembrolizumab + V937														
Study Period	**Treatment Cycle = 42 days**								**EOT[b]**	**Posttreatment**				**Notes**
										Safety[b]	**Follow-up[c]**		**Survival**	
Visit Timing/Cycle Number	**Cycle 1 (Neoadjuvant Phase)**					**Post-Surgical Resection Visit to confirm Disease-free Status**	**Cycle 1 and Onward[a] (Adjuvant Phase)**		**At D/C**	**30 Days After Last Dose**	**Q12W**	**Q24 W**	**Q12W**	**All procedures and assessments are to be performed prior to administration of study intervention unless otherwise indicated. Refer to Section 8.12 for visit details.**
Cycle Day	**1**	**3**	**5**	**8**	**22**	**1**	**1**	**22[d]**						
Scheduling Window (Days)	**-**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**		**+7**	**±7**	**±7**	**±7**	
T3, FT4, TSH					X		X		X					Presurgery/Neoadjuvant Phase: Thyroid function tests will be performed at C1D22. Postsurgery/Adjuvant Phase: Thyroid function tests will be performed at Cycle 1, and every cycle thereafter and at the time of discontinuation (EOT). Free T3 is acceptable where Total T3 cannot be determined. After C1 of the Presurgery/ Neoadjuvant Phase, retrospective review of thyroid function testing results is allowed when the results are not available prior to dosing.
Pregnancy test (WOCBP only)					X		X		X	X	X			To be assessed prior to all scheduled visits. A serum or urine pregnancy test will be performed as indicated, prior to every cycle, up to 120 days after last dose of study intervention or 30 days after last dose if participant starts a new anticancer therapy, whichever comes first. See Appendix 11 for country-specific guidelines.

Pembrolizumab + V937														
Study Period	**Treatment Cycle = 42 days**								**EOT[b]**	**Posttreatment**				**Notes**
										Safety[b]	**Follow-up[c]**		**Survival**	
Visit Timing/Cycle Number	**Cycle 1 (Neoadjuvant Phase)**					**Post-Surgical Resection Visit to confirm Disease-free Status**	**Cycle 1 and Onward[a] (Adjuvant Phase)**		**At D/C**	**30 Days After Last Dose**	**Q12W**	**Q24 W**	**Q12W**	**All procedures and assessments are to be performed prior to administration of study intervention unless otherwise indicated. Refer to Section 8.12 for visit details.**
Cycle Day	**1**	**3**	**5**	**8**	**22**	**1**	**1**	**22[d]**						
Scheduling Window (Days)	**-**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**		**+7**	**±7**	**±7**	**±7**	
ECOG performance status					X		X	X	X	X				To be assessed dosing during all scheduled visits.
Pharmacokinetics/Pharmacodynamics/Biomarkers														
MK-3475 PK				X			X		X	X				Presurgery/Neoadjuvant Phase: Predose and postdose on C1D8 Postsurgery/Adjuvant Phase: Predose on C1D1, C2D1, C3D1, and C7D1. All predose trough samples should be drawn within 24 hours before infusion of study intervention. Samples should also be taken at EOT and at the 30-day Safety Follow-up visit. Note: Predose = Prior to the administration of any study intervention. Postdose = After the administration of all study interventions.

Pembrolizumab + V937														
Study Period	**Treatment Cycle = 42 days**								**EOT[b]**	**Posttreatment**				**Notes**
										Safety[b]	**Follow-up[c]**		**Survival**	
Visit Timing/Cycle Number	**Cycle 1 (Neoadjuvant Phase)**					**Post-Surgical Resection Visit to confirm Disease-free Status**	**Cycle 1 and Onward[a] (Adjuvant Phase)**		**At D/C**	**30 Days After Last Dose**	**Q12W**	**Q24 W**	**Q12W**	**All procedures and assessments are to be performed prior to administration of study intervention unless otherwise indicated. Refer to Section 8.12 for visit details.**
Cycle Day	**1**	**3**	**5**	**8**	**22**	**1**	**1**	**22[d]**						
Scheduling Window (Days)	**-**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**		**+7**	**±7**	**±7**	**±7**	
MK-3475 ADA				X			X		X	X				Presurgery/Neoadjuvant Phase: Predose C1D8. Postsurgery/Adjuvant Phase: Predose on C1D1, C2D1, C3D1, and every 4 cycles thereafter. All predose trough samples should be drawn within 24 hours before infusion of study intervention. Samples should also be taken at EOT and at the 30-day Safety Follow-up visit. Note: Predose = Prior to the administration of any study intervention.

Pembrolizumab + V937														
Study Period	**Treatment Cycle = 42 days**								**EOT[b]**	**Posttreatment**				**Notes**
										Safety[b]	**Follow-up[c]**		**Survival**	
Visit Timing/Cycle Number	**Cycle 1 (Neoadjuvant Phase)**					**Post-Surgical Resection Visit to confirm Disease-free Status**	**Cycle 1 and Onward[a] (Adjuvant Phase)**		**At D/C**	**30 Days After Last Dose**	**Q12W**	**Q24 W**	**Q12W**	**All procedures and assessments are to be performed prior to administration of study intervention unless otherwise indicated. Refer to Section 8.12 for visit details.**
Cycle Day	**1**	**3**	**5**	**8**	**22**	**1**	**1**	**22[d]**						
Scheduling Window (Days)	**-**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**		**+7**	**±7**	**±7**	**±7**	
V937 PK	X	X	X	X	X				X	X				Presurgery/Neoadjuvant Phase: Predose 0-1 hour before V937 administration; 0.5, 2, 4, and 6 hours postdose on C1D1, C1D8, C1D22. Predose 0-1 hour before V937 administration; 0.5 and 2 hours postdose on C1D3, C1D5. Samples should also be taken at EOT and at the 30-day Safety Follow-up visit. The sample window preference is ± 15 min.
Anti-V937 Neutralizing Antibody	X	X	X	X	X				X	X				Presurgery/Neoadjuvant Phase: Predose 0-1 hour before V937 administration on C1D1, C1D3, C1D5, C1D8, C1D22. Samples should also be taken at EOT and at the 30-day Safety Follow-up Visit.

Pembrolizumab + V937														
Study Period	**Treatment Cycle = 42 days**								**EOT[b]**	**Posttreatment**				**Notes**
										Safety[b]	**Follow-up[c]**		**Survival**	
Visit Timing/Cycle Number	**Cycle 1 (Neoadjuvant Phase)**					**Post-Surgical Resection Visit to confirm Disease-free Status**	**Cycle 1 and Onward[a] (Adjuvant Phase)**		**At D/C**	**30 Days After Last Dose**	**Q12W**	**Q24 W**	**Q12W**	**All procedures and assessments are to be performed prior to administration of study intervention unless otherwise indicated. Refer to Section 8.12 for visit details.**
Cycle Day	**1**	**3**	**5**	**8**	**22**	**1**	**1**	**22[d]**						
Scheduling Window (Days)	**-**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**		**+7**	**±7**	**±7**	**±7**	
Blood for RNA analysis	X*			X*	X		X		X					Presurgery/Neoadjuvant Phase (pembrolizumab and V937): *Collect predose 0 to 4 hours prior to first dose of study intervention and 4 to 8 hours postdose of V937 administration on C1D1 and C1D8. Collect predose on C1D22. Postsurgery/Adjuvant Phase: Collect predose on C1D1 and at EOT.
Blood for ctDNA analysis	X			X	X		X		X		X*	X*		Presurgery/Neoadjuvant Phase: Collect predose on first dose of study intervention, predose on C1D8 and C1D22. Postsurgery/Adjuvant Phase: Collect predose on C1D1. After C1D1 collection, the ctDNA samples should be collected at the time of all scheduled imaging assessments (±7 days), including EOT imaging assessment, and should be performed if possible for all unscheduled imaging assessments (±7 days) documenting recurrence. *During follow-up, if a clinic visit is not feasible, blood for ctDNA will not be collected.

Pembrolizumab + V937														
Study Period	**Treatment Cycle = 42 days**								**EOT[b]**	**Posttreatment**				**Notes**
										Safety[b]	**Follow-up[c]**		**Survival**	
Visit Timing/Cycle Number	**Cycle 1 (Neoadjuvant Phase)**					**Post-Surgical Resection Visit to confirm Disease-free Status**	**Cycle 1 and Onward[a] (Adjuvant Phase)**		**At D/C**	**30 Days After Last Dose**	**Q12W**	**Q24 W**	**Q12W**	**All procedures and assessments are to be performed prior to administration of study intervention unless otherwise indicated. Refer to Section 8.12 for visit details.**
Cycle Day	**1**	**3**	**5**	**8**	**22**	**1**	**1**	**22[d]**						
Scheduling Window (Days)	**-**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**		**+7**	**±7**	**±7**	**±7**	
Blood for genetic analysis	X													Presurgery/Neoadjuvant Phase: Collect predose on first dose of study intervention. See Section 8.9 for additional information.
Tumor blocks or slides					X	X								Presurgery/Neoadjuvant Phase: Participants must submit a tumor sample at the end of Cycle 1 (Days 15-21) or C1D22 predose for biomarker analysis. A surgical resection specimen taken at Week 6 will also be submitted for pathologic assessment of resection specimens and for biomarker analysis. See Section 8.9 for details on biomarker assessments.

Pembrolizumab + V937														
Study Period	**Treatment Cycle = 42 days**								**EOT[b]**	**Posttreatment**				**Notes**
										Safety[b]	**Follow-up[c]**		**Survival**	
Visit Timing/Cycle Number	**Cycle 1 (Neoadjuvant Phase)**					**Post-Surgical Resection Visit to confirm Disease-free Status**	**Cycle 1 and Onward[a] (Adjuvant Phase)**		**At D/C**	**30 Days After Last Dose**	**Q12W**	**Q24 W**	**Q12W**	**All procedures and assessments are to be performed prior to administration of study intervention unless otherwise indicated. Refer to Section 8.12 for visit details.**
Cycle Day	**1**	**3**	**5**	**8**	**22**	**1**	**1**	**22[d]**						
Scheduling Window (Days)	**-**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**		**+7**	**±7**	**±7**	**±7**	

Abbreviations: AE = adverse event; BP = blood pressure; C1 = Cycle 1; C2 = Cycle 2; C3 = Cycle 3; C5 = Cycle 5; CIV = central imaging vendor; CT = computed tomography; ctDNA = circulating tumor DNA; ctRNA = circulating tumor RNA; D1 = Day 1; D15 = Day 15; D8 = Day 8; D/C = discontinue/discontinuing; ECG = electrocardiogram; ECHO = echocardiogram; ECOG = Eastern Cooperative Oncology Group; EOT = end of treatment; ePRO = electronic patient-reported outcome; FT4 = free thyroxine; FU = follow-up; HBV = hepatitis B virus; HCV = hepatitis C virus; HIV = human immunodeficiency virus; HRQoL = health-related quality of life; ICF = Informed Consent Form; INR = international normalized ratio; MRI = magnetic resonance imaging; MUGA = multigated acquisition; PE = physical examination; PK = pharmacokinetics; PT = prothrombin time; Q3W = every 3 weeks; Q9W = every 9 weeks; Q12W = every 12 weeks; Q24W = every 24 weeks; QD = once daily; RECIST = Response Evaluation Criteria in Solid Tumors; RR = respiratory rate; SAE = serious adverse event; SIM = site imaging manual; T3 = triiodothyronine; TSH = thyroid-stimulating hormone; UPCR=urine protein-to-creatinine; WOCBP = women of childbearing potential

a After surgical resection of the tumor, participants will receive 8 cycles of adjuvant therapy with pembrolizumab monotherapy as soon as possible after surgery (interval between surgical resection and adjuvant pembrolizumab should not exceed 12 weeks; the interval between postsurgery baseline imaging and first dose of adjuvant dosing should not exceed 28 days; total treatment duration including neoadjuvant and adjuvant therapy of approximately 1 year) or until they experience disease recurrence, unacceptable AEs are reported, consent is withdrawn, death, intercurrent illness that prevents further administration of study intervention, investigator's decision to discontinue the participant, noncompliance with study intervention or procedure requirements, or administrative reasons requiring cessation of treatment, whichever occurs first.

b If EOT visit occurs ~30 days from last dose of study intervention, a 30-day Safety Follow-up visit is not required. In this situation, all procedures required at the 30-day Safety Follow-up visit and EOT are performed once and entered into the EOT visit only. End of treatment will be defined as the date when the participant discontinues all study interventions.

c For participants who DC study intervention for reasons other than documented disease recurrence, follow-up visits to monitor disease status continue until documented disease recurrence or initiation of a new anticancer therapy. Participants who D/C study intervention with documented disease recurrence proceed directly to Survival Follow-up.

d Optional visit; visit and laboratory assessments should be completed as clinically indicated.

e. Brain imaging is required for all participants at Screening. Magnetic resonance imaging is preferred; however, CT imaging will be acceptable if MRI is medically contraindicated.

Note: Each participant will receive neoadjuvant study intervention with an investigational treatment arm for up to approximately 5 weeks from first dose of study intervention followed by surgical resection of the tumor 6 weeks (42 days ± 7 days) from neoadjuvant C1D1 (also called definitive surgery with curative intent). Surgery should occur no sooner than approximately 5 weeks from the first dose of study intervention.
Other current or former name(s) or alias(es) for V937 investigational agent are as follows: CAVATAK®; Coxsackievirus A21 (CVA21).

10.6.2.1.4 Section 1.3.4 Pembrolizumab Monotherapy

Pembrolizumab Monotherapy											
Study Period	**Treatment Cycle = 42 days**					**EOT[b]**	**Posttreatment**				**Notes**
							Safety[b]	**Follow-up[c]**		**Survival**	
Visit Timing/Cycle Number	**Cycle 1 (Neoadjuvant Phase)**		**Post-Surgical Resection Visit to confirm Disease-free Status**	**Cycle 1 and Onward[a] (Adjuvant Phase)**		**At D/C**	**30 Days After Last Dose**	**Q12 W**	**Q24 W**	**Q12W**	**All procedures and assessments are to be performed prior to administration of study intervention unless otherwise indicated. Refer to Section 8.12 for visit details.**
Cycle Day	**1**	**22**	**1**	**1**	**22[d]**						
Scheduling Window (Days)	**-**	**±3**	**±3**	**±3**	**±3**		**+7**	**±7**	**±7**	**±7**	
Administrative Procedures											
BRAF status			X								BRAF V600 mutation analysis should be performed locally by the sites during the pathological assessment of the resected tumor specimen(s), if not performed during Screening. If the local laboratory is unable to perform BRAF testing, the site should submit the sample to the central laboratory for testing.
Concomitant medication review	X	X	X	X	X	X	X	X			Concomitant medications will be recorded for 90 days after last dose (or for up to 120 days after last dose for SAEs).

Pembrolizumab Monotherapy											
Study Period	**Treatment Cycle = 42 days**					**EOT[b]**	**Posttreatment**				**Notes**
							Safety[b]	**Follow-up[c]**		**Survival**	
Visit Timing/Cycle Number	**Cycle 1 (Neoadjuvant Phase)**		**Post-Surgical Resection Visit to confirm Disease-free Status**	**Cycle 1 and Onward[a] (Adjuvant Phase)**		**At D/C**	**30 Days After Last Dose**	**Q12 W**	**Q24 W**	**Q12W**	**All procedures and assessments are to be performed prior to administration of study intervention unless otherwise indicated. Refer to Section 8.12 for visit details.**
Cycle Day	**1**	**22**	**1**	**1**	**22[d]**						
Scheduling Window (Days)	**-**	**±3**	**±3**	**±3**	**±3**		**+7**	**±7**	**±7**	**±7**	
Randomization/ allocation	X										Presurgery/Neoadjuvant Phase: Participants may be randomized/allocated 24 hours prior to first dose of study intervention and after confirmation of eligibility. All procedures and assessments on first dose of study intervention should be performed after randomization/allocation.
Dispensation of pembrolizumab drug kit	X			X							Presurgery/Neoadjuvant Phase: C1D1. Postsurgery/Adjuvant Phase: Day 1 of every cycle (eg, C1D1, C2D1, C3D1, etc.).
Pembrolizumab administration	X			X							Presurgery/Neoadjuvant Phase: Pembrolizumab will be administered for 1 dose prior to surgical resection. Postsurgery/Adjuvant Phase: After surgical resection, pembrolizumab will be administered Q6W on Day 1 of each cycle (total treatment duration including neoadjuvant and adjuvant phase of approximately 1 year).

Pembrolizumab Monotherapy											
Study Period	**Treatment Cycle = 42 days**					**EOT[b]**	**Posttreatment**				**Notes**
							Safety[b]	**Follow-up[c]**		**Survival**	
Visit Timing/Cycle Number	**Cycle 1 (Neoadjuvant Phase)**		**Post-Surgical Resection Visit to confirm Disease-free Status**	**Cycle 1 and Onward[a] (Adjuvant Phase)**		**At D/C**	**30 Days After Last Dose**	**Q12 W**	**Q24 W**	**Q12W**	**All procedures and assessments are to be performed prior to administration of study intervention unless otherwise indicated. Refer to Section 8.12 for visit details.**
Cycle Day	**1**	**22**	**1**	**1**	**22[d]**						
Scheduling Window (Days)	**-**	**±3**	**±3**	**±3**	**±3**		**+7**	**±7**	**±7**	**±7**	
Subsequent antineoplastic treatment							X	X	X	X	All anticancer therapy will be recorded until time of death or termination of survival FU. If a clinic visit is not feasible, follow-up information may be obtained via telephone or email.
Survival status	<----------				---------->						Participants may be contacted for survival status at any time during the course of this substudy.

Pembrolizumab Monotherapy											
Study Period	**Treatment Cycle = 42 days**					**EOT[b]**	**Posttreatment**				**Notes**
							Safety[b]	**Follow-up[c]**		**Survival**	
Visit Timing/Cycle Number	**Cycle 1 (Neoadjuvant Phase)**		**Post-Surgical Resection Visit to confirm Disease-free Status**	**Cycle 1 and Onward[a] (Adjuvant Phase)**		**At D/C**	**30 Days After Last Dose**	**Q12 W**	**Q24 W**	**Q12W**	**All procedures and assessments are to be performed prior to administration of study intervention unless otherwise indicated. Refer to Section 8.12 for visit details.**
Cycle Day	**1**	**22**	**1**	**1**	**22[d]**						
Scheduling Window (Days)	**-**	**±3**	**±3**	**±3**	**±3**		**+7**	**±7**	**±7**	**±7**	
Efficacy/Immunogenicity Procedures											
Tumor assessment: chest, abdomen, and pelvis (CT/MRI)[e]	<---------->					X		X	X		All imaging visits have a scheduling window of ±7 days. Presurgery/Neoadjuvant Phase: The first on-study imaging assessment should be performed at 6 weeks (42 days ±7 days) from first dose of study intervention (prior to surgical resection of the tumor). After surgical resection of the tumor, disease-free status must be documented by radiographic imaging at Week 12 (new baseline imaging prior to start of adjuvant therapy), prior to the start of postoperative/adjuvant pembrolizumab. Postsurgery/Adjuvant Phase: Subsequent tumor imaging should be performed every 12 weeks from adjuvant C1D1 (±7 days) for the first 2 years, after which imaging will be performed every 24 weeks (168 days ±7 days) until Year 5 or more frequently if clinically indicated. or until documented disease recurrence. For participants

Pembrolizumab Monotherapy											
Study Period	**Treatment Cycle = 42 days**					**EOT[b]**	**Posttreatment**				**Notes**
							Safety[b]	**Follow-up[c]**		**Survival**	
Visit Timing/Cycle Number	**Cycle 1 (Neoadjuvant Phase)**		**Post-Surgical Resection Visit to confirm Disease-free Status**	**Cycle 1 and Onward[a] (Adjuvant Phase)**		**At D/C**	**30 Days After Last Dose**	**Q12 W**	**Q24 W**	**Q12W**	**All procedures and assessments are to be performed prior to administration of study intervention unless otherwise indicated. Refer to Section 8.12 for visit details.**
Cycle Day	**1**	**22**	**1**	**1**	**22[d]**						
Scheduling Window (Days)	**-**	**±3**	**±3**	**±3**	**±3**		**+7**	**±7**	**±7**	**±7**	
											who discontinue study intervention without documented disease recurrence, every effort should be made to continue monitoring disease status by tumor imaging using the same imaging schedule used while on treatment. Imaging of any anatomy that shows disease at Screening will be required in subsequent evaluations and should be submitted to the CIV. Tumor imaging is strongly preferred to be acquired by CT; the CT portion of PET/CT may be used in place of a stand-alone CT if it is of diagnostic quality per site imaging manual. Imaging at EOT is not required if the previous tumor imaging assessment was within 4 weeks prior to the EOT visit.

Pembrolizumab Monotherapy											
Study Period	**Treatment Cycle = 42 days**					**EOT[b]**	**Posttreatment**				**Notes**
							Safety[b]	**Follow-up[c]**		**Survival**	
Visit Timing/Cycle Number	**Cycle 1 (Neoadjuvant Phase)**		**Post-Surgical Resection Visit to confirm Disease-free Status**	**Cycle 1 and Onward[a] (Adjuvant Phase)**		**At D/C**	**30 Days After Last Dose**	**Q12 W**	**Q24 W**	**Q12W**	**All procedures and assessments are to be performed prior to administration of study intervention unless otherwise indicated. Refer to Section 8.12 for visit details.**
Cycle Day	**1**	**22**	**1**	**1**	**22[d]**						
Scheduling Window (Days)	**-**	**±3**	**±3**	**±3**	**±3**		**+7**	**±7**	**±7**	**±7**	
Digital photography	<----------				---------->						Qualitative digital photography should be performed as clinically indicated. Cutaneous lesions are not considered measurable for the purposes of this protocol but may be considered to be nontarget lesions for tumor assessments by investigators. Copies of digital photographs should also be submitted to the central imaging vendor.
Safety Procedures											
AE monitoring	X	X	X	X	X	X	X	X			AEs: monitored up to 90 days after last dose. SAEs and pregnancy: monitored up to 120 days after last dose, or 30 days after last dose if participant starts a new anticancer therapy, whichever is sooner.

Pembrolizumab Monotherapy											
Study Period	**Treatment Cycle = 42 days**					**EOT[b]**	**Posttreatment**				**Notes**
							Safety[b]	**Follow-up[c]**		**Survival**	
Visit Timing/Cycle Number	**Cycle 1 (Neoadjuvant Phase)**		**Post-Surgical Resection Visit to confirm Disease-free Status**	**Cycle 1 and Onward[a] (Adjuvant Phase)**		**At D/C**	**30 Days After Last Dose**	**Q12 W**	**Q24 W**	**Q12W**	**All procedures and assessments are to be performed prior to administration of study intervention unless otherwise indicated. Refer to Section 8.12 for visit details.**
Cycle Day	**1**	**22**	**1**	**1**	**22[d]**						
Scheduling Window (Days)	**-**	**±3**	**±3**	**±3**	**±3**		**+7**	**±7**	**±7**	**±7**	
Complete physical examination			X								Postsurgical resection of the tumor, disease-free status must be documented by a complete physical examination at Week 12 (new baseline imaging), prior to the start of postoperative/adjuvant pembrolizumab.
Directed physical examination	X	X		X	X	X	X	X	X		In addition to the directed PEs in the flowchart, a symptom-directed PE may be performed at any time during this substudy, as clinically indicated. The investigator or qualified designee should conduct a visual inspection of local recurrence and palpation of lymph nodes to assess recurrence.
Review of the pathology report postsurgical resection			X								Review of the pathology report of the surgical resection specimen(s) by the investigator is mandatory prior to the start of adjuvant therapy to ensure the participant is disease-free and the surgical margins are tumor-free (R0).

Pembrolizumab Monotherapy											
Study Period	**Treatment Cycle = 42 days**					**EOT[b]**	**Posttreatment**				**Notes**
							Safety[b]	**Follow-up[c]**		**Survival**	
Visit Timing/Cycle Number	**Cycle 1 (Neoadjuvant Phase)**		**Post-Surgical Resection Visit to confirm Disease-free Status**	**Cycle 1 and Onward[a] (Adjuvant Phase)**		**At D/C**	**30 Days After Last Dose**	**Q12 W**	**Q24 W**	**Q12W**	**All procedures and assessments are to be performed prior to administration of study intervention unless otherwise indicated. Refer to Section 8.12 for visit details.**
Cycle Day	**1**	**22**	**1**	**1**	**22[d]**						
Scheduling Window (Days)	**-**	**±3**	**±3**	**±3**	**±3**		**+7**	**±7**	**±7**	**±7**	
Vital signs (resting BP, heart rate, RR, and temp), and weight	X	X		X	X	X	X				Blood pressure and heart rate will be measured after the participant has been resting for 5 minutes. See Section 8.3.2 for vital signs.
12-lead ECG	←----------		----------				----------→				As clinically indicated. Participants must be in the recumbent position for a period of 5 minutes prior to the ECG. See Section 8.3.3 for ECG.
Hematology and chemistry laboratory assessment	X	X	X	X	X	X	X				Procedures/assessments should be performed prior to all scheduled substudy visits. Every effort should be made to collect samples at the same time of day. LDH testing is needed. Laboratory samples collected within 3 days prior to the first dose of study intervention need not be repeated on C1D1
Urinalysis	←----------		----------				----------→				As clinically indicated.
PT/INR and aPTT/PTT	←----------		----------				----------→				As clinically indicated for participants taking anticoagulant therapy.

Pembrolizumab Monotherapy											
Study Period	**Treatment Cycle = 42 days**					**EOT[b]**	**Posttreatment**				**Notes**
							Safety[b]	**Follow-up[c]**		**Survival**	
Visit Timing/Cycle Number	**Cycle 1 (Neoadjuvant Phase)**		**Post-Surgical Resection Visit to confirm Disease-free Status**	**Cycle 1 and Onward[a] (Adjuvant Phase)**		**At D/C**	**30 Days After Last Dose**	**Q12 W**	**Q24 W**	**Q12W**	**All procedures and assessments are to be performed prior to administration of study intervention unless otherwise indicated. Refer to Section 8.12 for visit details.**
Cycle Day	**1**	**22**	**1**	**1**	**22[d]**						
Scheduling Window (Days)	**-**	**±3**	**±3**	**±3**	**±3**		**+7**	**±7**	**±7**	**±7**	
T3, FT4, TSH		X		X		X					Presurgery/Neoadjuvant Phase: Thyroid function tests will be performed at Cycle 1. Postsurgery/Adjuvant Phase: Thyroid function tests will be performed at Cycle 1 and every cycle thereafter and at the time of discontinuation (EOT). Free T3 is acceptable where Total T3 cannot be determined. After C1 of the Presurgery/Neoadjuvant Phase, retrospective review of thyroid function testing results is allowed when the results are not available prior to dosing.
Pregnancy test (WOCBP only)		X		X		X	X	X			To be assessed prior to all scheduled visits. A serum or urine pregnancy test will be performed as indicated, prior to every cycle, up to 120 days after last dose of study intervention or 30 days after last dose if participant starts a new anticancer therapy, whichever comes first. See Appendix 11 for country-specific guidelines.

Pembrolizumab Monotherapy											
Study Period	**Treatment Cycle = 42 days**					**EOT[b]**	**Posttreatment**				**Notes**
							Safety[b]	**Follow-up[c]**		**Survival**	
Visit Timing/Cycle Number	**Cycle 1 (Neoadjuvant Phase)**		**Post-Surgical Resection Visit to confirm Disease-free Status**	**Cycle 1 and Onward[a] (Adjuvant Phase)**		**At D/C**	**30 Days After Last Dose**	**Q12 W**	**Q24 W**	**Q12W**	**All procedures and assessments are to be performed prior to administration of study intervention unless otherwise indicated. Refer to Section 8.12 for visit details.**
Cycle Day	**1**	**22**	**1**	**1**	**22[d]**						
Scheduling Window (Days)	**-**	**±3**	**±3**	**±3**	**±3**		**+7**	**±7**	**±7**	**±7**	
ECOG performance status		X		X	X	X	X				To be assessed prior to dosing during all scheduled visits.
Biomarkers											
Blood for ctDNA analysis	X	X		X		X		X*	X*		Presurgery/Neoadjuvant Phase: Collect predose on the first dose of study intervention and C1D22. Postsurgery/Adjuvant Phase: Collect predose on C1D1. After C1D1 collection, the ctDNA samples should be collected at the time of all scheduled imaging assessments (±7 days), including EOT imaging assessment, and should be performed if possible for all unscheduled imaging assessments (±7 days) documenting recurrence. *During follow-up, if a clinic visit is not feasible, blood for ctDNA will not be collected
Blood for genetic analysis	X										Presurgery/Neoadjuvant Phase: Collect predose on first dose of study intervention. See Section 8.9 for additional information.

Pembrolizumab Monotherapy											
Study Period	**Treatment Cycle = 42 days**					**EOT[b]**	**Posttreatment**				**Notes**
							Safety[b]	**Follow-up[c]**		**Survival**	
Visit Timing/Cycle Number	**Cycle 1 (Neoadjuvant Phase)**		**Post-Surgical Resection Visit to confirm Disease-free Status**	**Cycle 1 and Onward[a] (Adjuvant Phase)**		**At D/C**	**30 Days After Last Dose**	**Q12 W**	**Q24 W**	**Q12W**	**All procedures and assessments are to be performed prior to administration of study intervention unless otherwise indicated. Refer to Section 8.12 for visit details.**
Cycle Day	**1**	**22**	**1**	**1**	**22[d]**						
Scheduling Window (Days)	**-**	**±3**	**±3**	**±3**	**±3**		**+7**	**±7**	**±7**	**±7**	
Tumor blocks or slides	X		X								Presurgery/Neoadjuvant Phase: Participants must submit a tumor sample at the end of Cycle 1 (Days 15-21) or C1D22 for biomarker analysis. A surgical resection specimen taken at Week 6 will also be submitted for pathologic assessment of resection specimens and for biomarker analysis. See Section 8.9 for details on biomarker assessments.

Pembrolizumab Monotherapy											
Study Period	**Treatment Cycle = 42 days**					**EOT[b]**	**Posttreatment**				**Notes**
							Safety[b]	**Follow-up[c]**		**Survival**	
Visit Timing/Cycle Number	**Cycle 1 (Neoadjuvant Phase)**		**Post-Surgical Resection Visit to confirm Disease-free Status**	**Cycle 1 and Onward[a] (Adjuvant Phase)**		**At D/C**	**30 Days After Last Dose**	**Q12 W**	**Q24 W**	**Q12W**	**All procedures and assessments are to be performed prior to administration of study intervention unless otherwise indicated. Refer to Section 8.12 for visit details.**
Cycle Day	**1**	**22**	**1**	**1**	**22[d]**						
Scheduling Window (Days)	**-**	**±3**	**±3**	**±3**	**±3**		**+7**	**±7**	**±7**	**±7**	

Abbreviations: AE = adverse event; BP = blood pressure; C1 = Cycle 1; C2 = Cycle 2; C3 = Cycle 3; C5 = Cycle 5; CIV = central imaging vendor; CT = computed tomography; ctDNA = circulating tumor DNA; ctRNA = circulating tumor RNA; D1 = Day 1; D15 = Day 15; D8 = Day 8; D/C = discontinue/discontinuing; ECG = electrocardiogram; ECHO = echocardiogram; ECOG = Eastern Cooperative Oncology Group; EOT = end of treatment; ePRO = electronic patient-reported outcome; FT4 = free thyroxine; FU = follow-up; HBV = hepatitis B virus; HCV = hepatitis C virus; HIV = human immunodeficiency virus; HRQoL = health-related quality of life; ICF = Informed Consent Form; INR = international normalized ratio; MRI = magnetic resonance imaging; MUGA = multigated acquisition; PE = physical examination; PK = pharmacokinetics; PT = prothrombin time; Q3W = every 3 weeks; Q9W = every 9 weeks; Q12W = every 12 weeks; Q24W = every 24 weeks; QD = once daily; RECIST = Response Evaluation Criteria in Solid Tumors; RR = respiratory rate; SAE = serious adverse event; SIM = site imaging manual; T3 = triiodothyronine; TSH = thyroid-stimulating hormone; UPCR=urine protein-to-creatinine; WOCBP = women of childbearing potential

a After surgical resection of the tumor, participants will receive 8 cycles of adjuvant therapy with pembrolizumab monotherapy as soon as possible after surgery (interval between surgical resection and adjuvant pembrolizumab should not exceed 12 weeks; the interval between postsurgery baseline imaging and first dose of adjuvant dosing should not exceed 28 days; total treatment duration including neoadjuvant and adjuvant therapy of approximately 1 year) or until they experience disease recurrence, unacceptable AEs are reported, consent is withdrawn, death, intercurrent illness that prevents further administration of study intervention, investigator's decision to discontinue the participant, noncompliance with study intervention or procedure requirements, or administrative reasons requiring cessation of treatment, whichever occurs first.

b If EOT visit occurs ~30 days from last dose of study intervention, a 30-day Safety Follow-up visit is not required. In this situation, all procedures required at the 30-day Safety Follow-up visit and EOT are performed once and entered into the EOT visit only. End of treatment will be defined as the date when the participant discontinues all study interventions.

c For participants who DC study intervention for reasons other than documented disease recurrence, follow-up visits to monitor disease status continue until documented disease recurrence or initiation of a new anticancer therapy. Participants who D/C study intervention with documented disease recurrence proceed directly to Survival Follow-up.

d Optional visit; visit and laboratory assessments should be completed as clinically indicated.

e. Brain imaging is required for all participants at Screening. Magnetic resonance imaging is preferred; however, CT imaging will be acceptable if MRI is medically contraindicated.

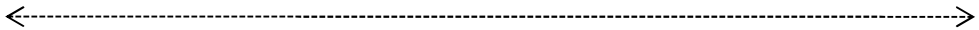
Note: Each participant will receive neoadjuvant study intervention with an investigational treatment arm for up to approximately 5 weeks from first dose of study intervention followed by surgical resection of the tumor 6 weeks (42 days ± 7 days) from neoadjuvant C1D1 (also called definitive surgery with curative intent). Surgery should occur no sooner than approximately 5 weeks from the first dose of study intervention.

10.6.2.1.5 Section 1.3.5 Pembrolizumab + MK-4830 (anti-ILT4)

Pembrolizumab + MK-4830 (anti-ILT4)												
Study Period	**Treatment**						**EOT[b]**	**Posttreatment**				**Notes**
	Cycle = 21 days			**Cycle = 42 days**				**Safety[b]**	**Follow-up[c]**		**Survival**	
Visit Timing/Cycle Number	**Cycle 1 (Neo-adjuvant Phase)**	**Cycle 2 (Neo-adjuvant Phase)**		**Post-Surgical Resection Visit to confirm Disease-free Status**	**Cycle 1 and Onwards[a] (Adjuvant Phase)**		**At D/C**	**30 Days After Last Dose**	**Q12W**	**Q24W**	**Q12W**	**All procedures and assessments are to be performed prior to administration of study intervention unless otherwise indicated. Refer to Section 8.12 for visit details.**
Cycle Day	**1**	**1**	**21**	**1**	**1**	**22[d]**						
Scheduling Window (Days)		**±3**	**±3**	**±3**	**±3**	**±3**		**+7**	**±7**	**±7**	**±7**	
Administrative Procedures												
BRAF status				X								BRAF V600 mutation analysis should be performed locally by the sites during the pathological assessment of the resected tumor specimen(s), if not performed during Screening. If the local laboratory is unable to perform BRAF testing, the site should submit the sample to the central pathology laboratory for testing.
Concomitant medication review	X	X	X	X	X	X	X	X	X			Concomitant medications will be recorded for 90 days after last dose (or for up to 120 days after last dose for SAEs).

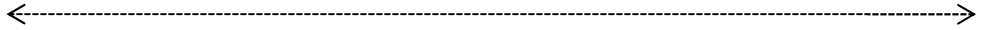
Pembrolizumab + MK-4830 (anti-ILT4)												
Study Period	**Treatment**						**EOT[b]**	**Posttreatment**				**Notes**
	Cycle = 21 days			**Cycle = 42 days**				**Safety[b]**	**Follow-up[c]**		**Survival**	
Visit Timing/Cycle Number	**Cycle 1 (Neo-adjuvant Phase)**	**Cycle 2 (Neo-adjuvant Phase)**		**Post-Surgical Resection Visit to confirm Disease-free Status**	**Cycle 1 and Onwards[a] (Adjuvant Phase)**		**At D/C**	**30 Days After Last Dose**	**Q12W**	**Q24W**	**Q12W**	**All procedures and assessments are to be performed prior to administration of study intervention unless otherwise indicated. Refer to Section 8.12 for visit details.**
Cycle Day	**1**	**1**	**21**	**1**	**1**	**22[d]**						
Scheduling Window (Days)		**±3**	**±3**	**±3**	**±3**	**±3**		**+7**	**±7**	**±7**	**±7**	
Randomization/allocation	X											Presurgery/ Neoadjuvant Phase: Participants may be randomized/allocated 24 hours prior to first dose of study intervention and after confirmation of eligibility. All procedures and assessments on first dose of study intervention should be performed after randomization/ allocation.
Dispensation of pembrolizumab drug kit	X	X			X							Presurgery/Neoadjuvant Phase: C1D1 and C2D1. Postsurgery/Adjuvant Phase: Day 1 of every cycle (eg, C1D1, C2D1, C3D1, etc.).

Pembrolizumab + MK-4830 (anti-ILT4)												
Study Period	**Treatment**						**EOT[b]**	**Posttreatment**				**Notes**
	Cycle = 21 days			**Cycle = 42 days**				**Safety[b]**	**Follow-up[c]**		**Survival**	
Visit Timing/Cycle Number	**Cycle 1 (Neo-adjuvant Phase)**	**Cycle 2 (Neo-adjuvant Phase)**		**Post-Surgical Resection Visit to confirm Disease-free Status**	**Cycle 1 and Onwards[a] (Adjuvant Phase)**		**At D/C**	**30 Days After Last Dose**	**Q12W**	**Q24W**	**Q12W**	**All procedures and assessments are to be performed prior to administration of study intervention unless otherwise indicated. Refer to Section 8.12 for visit details.**
Cycle Day	**1**	**1**	**21**	**1**	**1**	**22[d]**						
Scheduling Window (Days)		**±3**	**±3**	**±3**	**±3**	**±3**		**+7**	**±7**	**±7**	**±7**	
Pembrolizumab administration	X	X			X							Presurgery/ Neoadjuvant Phase: Pembrolizumab will be administered Q3W for 2 doses prior to surgical resection. Postsurgery/Adjuvant Phase: After surgical resection, pembrolizumab will be administered Q6W on Day 1 of each cycle (total treatment duration including neoadjuvant and adjuvant phase of approximately 1 year)
Dispensation of MK-4830 drug kit	X	X										Presurgery/ Neoadjuvant Phase: C1D1 and C2D1 only.
MK-4830 administration	X	X										Presurgery/ Neoadjuvant Phase: MK-4830 will be administered Q3W for 2 doses prior to surgical resection.

Pembrolizumab + MK-4830 (anti-ILT4)											
Study Period	**Treatment**						**EOT[b]**	**Posttreatment**			**Notes**
	Cycle = 21 days			**Cycle = 42 days**				**Safety[b]**	**Follow-up[c]**		**Survival**	
Visit Timing/Cycle Number	**Cycle 1 (Neo-adjuvant Phase)**	**Cycle 2 (Neo-adjuvant Phase)**		**Post-Surgical Resection Visit to confirm Disease-free Status**	**Cycle 1 and Onwards[a] (Adjuvant Phase)**		**At D/C**	**30 Days After Last Dose**	**Q12W**	**Q24W**	**Q12W**	**All procedures and assessments are to be performed prior to administration of study intervention unless otherwise indicated. Refer to Section 8.12 for visit details.**
Cycle Day	**1**	**1**	**21**	**1**	**1**	**22[d]**						
Scheduling Window (Days)		**±3**	**±3**	**±3**	**±3**	**±3**		**+7**	**±7**	**±7**	**±7**	
Subsequent antineoplastic treatment								X	X	X	X	All anticancer therapy will be recorded until time of death or termination of survival FU. If a clinic visit is not feasible, follow-up information may be obtained via telephone or email.
Survival status												Participants may be contacted for survival status at any time during the course of this substudy.

Pembrolizumab + MK-4830 (anti-ILT4)											
Study Period	**Treatment**						**EOT[b]**	**Posttreatment**				**Notes**
	Cycle = 21 days			**Cycle = 42 days**				**Safety[b]**	**Follow-up[c]**		**Survival**	
Visit Timing/Cycle Number	**Cycle 1 (Neo-adjuvant Phase)**	**Cycle 2 (Neo-adjuvant Phase)**		**Post-Surgical Resection Visit to confirm Disease-free Status**	**Cycle 1 and Onwards[a] (Adjuvant Phase)**		**At D/C**	**30 Days After Last Dose**	**Q12W**	**Q24W**	**Q12W**	**All procedures and assessments are to be performed prior to administration of study intervention unless otherwise indicated. Refer to Section 8.12 for visit details.**
Cycle Day	**1**	**1**	**21**	**1**	**1**	**22[d]**						
Scheduling Window (Days)		**±3**	**±3**	**±3**	**±3**	**±3**		**+7**	**±7**	**±7**	**±7**	
Efficacy/Immunogenicity Procedures												
Tumor assessment: chest, abdomen, and pelvis (CT/MRI)[e]	<---------->						X		X	X		All imaging visits have a scheduling window of ±7 days. Presurgery/ Neoadjuvant Phase: The first on-study imaging assessment should be performed at 6 weeks (42 days ±7 days) from first dose of study intervention (prior to surgical resection of the tumor). After surgical resection of the tumor, disease-free status must be documented by radiographic imaging at Week 12 (new baseline imaging prior to start of adjuvant therapy), prior to the start of postoperative/ adjuvant pembrolizumab. Postsurgery/Adjuvant Phase: Subsequent tumor imaging should be performed every 12 weeks from adjuvant C1D1 (±7 days) for the first

Pembrolizumab + MK-4830 (anti-ILT4)												
Study Period	**Treatment**						**EOT[b]**	**Posttreatment**				**Notes**
	Cycle = 21 days			**Cycle = 42 days**				**Safety[b]**	**Follow-up[c]**		**Survival**	
Visit Timing/Cycle Number	**Cycle 1 (Neo-adjuvant Phase)**	**Cycle 2 (Neo-adjuvant Phase)**		**Post-Surgical Resection Visit to confirm Disease-free Status**	**Cycle 1 and Onwards[a] (Adjuvant Phase)**		**At D/C**	**30 Days After Last Dose**	**Q12W**	**Q24W**	**Q12W**	**All procedures and assessments are to be performed prior to administration of study intervention unless otherwise indicated. Refer to Section 8.12 for visit details.**
Cycle Day	**1**	**1**	**21**	**1**	**1**	**22[d]**						
Scheduling Window (Days)		**±3**	**±3**	**±3**	**±3**	**±3**		**+7**	**±7**	**±7**	**±7**	
												2 years, after which imaging will be performed every 24 weeks (168 days ±7 days) until Year 5 or more frequently if clinically indicated. or until documented disease recurrence. For participants who discontinue study intervention without documented disease recurrence, every effort should be made to continue monitoring disease status by tumor imaging using the same imaging schedule used while on treatment. Imaging of any anatomy that shows disease at Screening will be required in subsequent evaluations and should be submitted to the CIV. Tumor imaging is strongly preferred to be acquired by CT; the CT portion of PET/CT may be used in

Pembrolizumab + MK-4830 (anti-ILT4)											
Study Period	**Treatment**						**EOT[b]**	**Posttreatment**			**Notes**
	Cycle = 21 days			**Cycle = 42 days**				**Safety[b]**	**Follow-up[c]**		**Survival**	
Visit Timing/Cycle Number	**Cycle 1 (Neo-adjuvant Phase)**	**Cycle 2 (Neo-adjuvant Phase)**		**Post-Surgical Resection Visit to confirm Disease-free Status**	**Cycle 1 and Onwards[a] (Adjuvant Phase)**		**At D/C**	**30 Days After Last Dose**	**Q12W**	**Q24W**	**Q12W**	**All procedures and assessments are to be performed prior to administration of study intervention unless otherwise indicated. Refer to Section 8.12 for visit details.**
Cycle Day	**1**	**1**	**21**	**1**	**1**	**22[d]**						
Scheduling Window (Days)		**±3**	**±3**	**±3**	**±3**	**±3**		**+7**	**±7**	**±7**	**±7**	
												place of a stand-alone CT if it is of diagnostic quality per site imaging manual. Imaging at EOT is not required if the previous tumor imaging assessment was within 4 weeks prior to the EOT visit.
Digital photography												Qualitative digital photography should be performed as clinically indicated. Cutaneous lesions are not considered measurable for the purposes of this protocol but may be considered to be nontarget lesions for tumor assessments by investigators. Copies of digital photographs should also be submitted to the central imaging vendor.

Pembrolizumab + MK-4830 (anti-ILT4)											
Study Period	**Treatment**						**EOT[b]**	**Posttreatment**				**Notes**
	Cycle = 21 days			**Cycle = 42 days**				**Safety[b]**	**Follow-up[c]**		**Survival**	
Visit Timing/Cycle Number	**Cycle 1 (Neo-adjuvant Phase)**	**Cycle 2 (Neo-adjuvant Phase)**		**Post-Surgical Resection Visit to confirm Disease-free Status**	**Cycle 1 and Onwards[a] (Adjuvant Phase)**		**At D/C**	**30 Days After Last Dose**	**Q12W**	**Q24W**	**Q12W**	**All procedures and assessments are to be performed prior to administration of study intervention unless otherwise indicated. Refer to Section 8.12 for visit details.**
Cycle Day	**1**	**1**	**21**	**1**	**1**	**22[d]**						
Scheduling Window (Days)		**±3**	**±3**	**±3**	**±3**	**±3**		**+7**	**±7**	**±7**	**±7**	
Safety Procedures												
AE monitoring	X	X		X	X	X	X	X	X			AEs: monitored up to 90 days after last dose. SAEs and pregnancy: monitored up to 120 days after last dose, or 30 days after last dose if participant starts a new anticancer therapy, whichever is sooner.
Complete physical examination				X								Postsurgical resection of the tumor, disease-free status must be documented by a complete physical examination at Week 12 (new baseline imaging), prior to the start of postoperative/adjuvant pembrolizumab.

Pembrolizumab + MK-4830 (anti-ILT4)											
Study Period	**Treatment**						**EOT[b]**	**Posttreatment**				**Notes**
	Cycle = 21 days			**Cycle = 42 days**				**Safety[b]**	**Follow-up[c]**		**Survival**	
Visit Timing/Cycle Number	**Cycle 1 (Neo-adjuvant Phase)**	**Cycle 2 (Neo-adjuvant Phase)**		**Post-Surgical Resection Visit to confirm Disease-free Status**	**Cycle 1 and Onwards[a] (Adjuvant Phase)**		**At D/C**	**30 Days After Last Dose**	**Q12W**	**Q24W**	**Q12W**	**All procedures and assessments are to be performed prior to administration of study intervention unless otherwise indicated. Refer to Section 8.12 for visit details.**
Cycle Day	**1**	**1**	**21**	**1**	**1**	**22[d]**						
Scheduling Window (Days)		**±3**	**±3**	**±3**	**±3**	**±3**		**+7**	**±7**	**±7**	**±7**	
Directed physical examination	X	X			X	X	X	X	X	X		In addition to the directed PEs in the flowchart, a symptom-directed PE may be performed at any time during this substudy, as clinically indicated. The investigator or qualified designee should conduct a visual inspection of local recurrence and palpation of lymph nodes to assess recurrence.
Review of the pathology report postsurgical resection				X								Review of the pathology report of the surgical resection specimen(s) by the investigator is mandatory prior to the start of adjuvant therapy to ensure the participant is disease-free and the surgical margins are tumor-free (R0).

Pembrolizumab + MK-4830 (anti-ILT4)											
Study Period	**Treatment**						**EOT[b]**	**Posttreatment**			**Notes**
	Cycle = 21 days			**Cycle = 42 days**				**Safety[b]**	**Follow-up[c]**		**Survival**	
Visit Timing/Cycle Number	**Cycle 1 (Neo-adjuvant Phase)**	**Cycle 2 (Neo-adjuvant Phase)**		**Post-Surgical Resection Visit to confirm Disease-free Status**	**Cycle 1 and Onwards[a] (Adjuvant Phase)**		**At D/C**	**30 Days After Last Dose**	**Q12W**	**Q24W**	**Q12W**	**All procedures and assessments are to be performed prior to administration of study intervention unless otherwise indicated. Refer to Section 8.12 for visit details.**
Cycle Day	**1**	**1**	**21**	**1**	**1**	**22[d]**						
Scheduling Window (Days)		**±3**	**±3**	**±3**	**±3**	**±3**		**+7**	**±7**	**±7**	**±7**	
Vital signs (resting BP, heart rate, RR, and temp), and weight	X	X			X	X	X	X				Blood pressure and heart rate will be measured after the participant has been resting for 5 minutes. See Section 8.3.2 for vital signs.
12-lead ECG	<----------	----------	----------	----------	----------	----------	----------	---------->				As clinically indicated. Participants must be in the recumbent position for a period of 5 minutes prior to the ECG. See Section 8.3.3 for ECG.
Hematology and chemistry laboratory assessment	X	X		X	X	X	X	X				Procedures/ assessments should be performed prior to all scheduled substudy visits. Every effort should be made to collect samples at the same time of day. LDH testing is needed. Laboratory samples collected within 3 days prior to the first dose of study intervention need not be repeated on C1D1.
Urinalysis	<----------	----------	----------	----------	----------	----------	----------	---------->				As clinically indicated.

Pembrolizumab + MK-4830 (anti-ILT4)											
Study Period	**Treatment**						**EOT[b]**	**Posttreatment**				**Notes**
	Cycle = 21 days			**Cycle = 42 days**				**Safety[b]**	**Follow-up[c]**		**Survival**	
Visit Timing/Cycle Number	**Cycle 1 (Neo-adjuvant Phase)**	**Cycle 2 (Neo-adjuvant Phase)**		**Post-Surgical Resection Visit to confirm Disease-free Status**	**Cycle 1 and Onwards[a] (Adjuvant Phase)**		**At D/C**	**30 Days After Last Dose**	**Q12W**	**Q24W**	**Q12W**	**All procedures and assessments are to be performed prior to administration of study intervention unless otherwise indicated. Refer to Section 8.12 for visit details.**
Cycle Day	**1**	**1**	**21**	**1**	**1**	**22[d]**						
Scheduling Window (Days)		**±3**	**±3**	**±3**	**±3**	**±3**		**+7**	**±7**	**±7**	**±7**	
PT/INR and aPTT/PTT	<----------							---------->				As clinically indicated for participants taking anticoagulant therapy.
T3, FT4, TSH		X			X		X					Presurgery/ Neoadjuvant Phase: Thyroid function tests will be performed at Cycle 2. Postsurgery/Adjuvant Phase: Thyroid function tests will be performed at Cycle 1 and every cycle thereafter and at the time of discontinuation (EOT). Free T3 is acceptable where Total T3 cannot be determined. After C1 of the Presurgery/ Neoadjuvant Phase, retrospective review of thyroid function testing results is allowed when the results are not available prior to dosing.

Pembrolizumab + MK-4830 (anti-ILT4)											
Study Period	**Treatment**						**EOT[b]**	**Posttreatment**				**Notes**
	Cycle = 21 days			**Cycle = 42 days**				**Safety[b]**	**Follow-up[c]**		**Survival**	
Visit Timing/Cycle Number	**Cycle 1 (Neo-adjuvant Phase)**	**Cycle 2 (Neo-adjuvant Phase)**		**Post-Surgical Resection Visit to confirm Disease-free Status**	**Cycle 1 and Onwards[a] (Adjuvant Phase)**		**At D/C**	**30 Days After Last Dose**	**Q12W**	**Q24W**	**Q12W**	**All procedures and assessments are to be performed prior to administration of study intervention unless otherwise indicated. Refer to Section 8.12 for visit details.**
Cycle Day	**1**	**1**	**21**	**1**	**1**	**22[d]**						
Scheduling Window (Days)		**±3**	**±3**	**±3**	**±3**	**±3**		**+7**	**±7**	**±7**	**±7**	
Pregnancy test (WOCBP only)		X			X		X	X	X			To be assessed prior to all scheduled visits. A serum or urine pregnancy test will be performed as indicated, prior to every cycle, up to 120 days after last dose of study intervention or 30 days after last dose if participant starts a new anticancer therapy, whichever comes first. See Appendix 11 for country-specific guidelines.
ECOG performance status		X			X	X	X	X				To be assessed prior to dosing during all scheduled visits.

Pembrolizumab + MK-4830 (anti-ILT4)											
Study Period	**Treatment**						**EOT[b]**	**Posttreatment**				**Notes**
	Cycle = 21 days			**Cycle = 42 days**				**Safety[b]**	**Follow-up[c]**		**Survival**	
Visit Timing/Cycle Number	**Cycle 1 (Neo-adjuvant Phase)**	**Cycle 2 (Neo-adjuvant Phase)**		**Post-Surgical Resection Visit to confirm Disease-free Status**	**Cycle 1 and Onwards[a] (Adjuvant Phase)**		**At D/C**	**30 Days After Last Dose**	**Q12W**	**Q24W**	**Q12W**	**All procedures and assessments are to be performed prior to administration of study intervention unless otherwise indicated. Refer to Section 8.12 for visit details.**
Cycle Day	**1**	**1**	**21**	**1**	**1**	**22[d]**						
Scheduling Window (Days)		**±3**	**±3**	**±3**	**±3**	**±3**		**+7**	**±7**	**±7**	**±7**	
Pharmacokinetics/Pharmacodynamics/Biomarkers												
MK-3475 PK	X	X	X		X		X	X				Presurgery/ Neoadjuvant Phase: Collect predose of study intervention on C1D1, C2D1 and C2D21. Postsurgery/Adjuvant Phase: Collect predose on C1D1, C2D1. Samples should also be taken at EOT and at the 30-day Safety Follow-up visit. Note: Predose = Prior to the administration of any study intervention. Postdose = After the administration of all study interventions.

Pembrolizumab + MK-4830 (anti-ILT4)											
Study Period	**Treatment**						**EOT[b]**	**Posttreatment**				**Notes**
	Cycle = 21 days			**Cycle = 42 days**				**Safety[b]**	**Follow-up[c]**		**Survival**	
Visit Timing/Cycle Number	**Cycle 1 (Neo-adjuvant Phase)**	**Cycle 2 (Neo-adjuvant Phase)**		**Post-Surgical Resection Visit to confirm Disease-free Status**	**Cycle 1 and Onwards[a] (Adjuvant Phase)**		**At D/C**	**30 Days After Last Dose**	**Q12W**	**Q24W**	**Q12W**	**All procedures and assessments are to be performed prior to administration of study intervention unless otherwise indicated. Refer to Section 8.12 for visit details.**
Cycle Day	**1**	**1**	**21**	**1**	**1**	**22[d]**						
Scheduling Window (Days)		**±3**	**±3**	**±3**	**±3**	**±3**		**+7**	**±7**	**±7**	**±7**	
MK-3475 ADA	X	X	X		X		X	X				Presurgery/ Neoadjuvant Phase: Collect predose of study intervention on C1D1, C2D1 and C2D21. Postsurgery/Adjuvant Phase: Collect predose on C1D1, C2D1. Samples should also be taken at EOT and at the 30-day Safety Follow-up visit. Note: Predose = Prior to the administration of any study intervention. Postdose = After the administration of all study interventions.

Pembrolizumab + MK-4830 (anti-ILT4)											
Study Period	**Treatment**						**EOT[b]**	**Posttreatment**				**Notes**
	Cycle = 21 days			**Cycle = 42 days**				**Safety[b]**	**Follow-up[c]**		**Survival**	
Visit Timing/Cycle Number	**Cycle 1 (Neo-adjuvant Phase)**	**Cycle 2 (Neo-adjuvant Phase)**		**Post-Surgical Resection Visit to confirm Disease-free Status**	**Cycle 1 and Onwards[a] (Adjuvant Phase)**		**At D/C**	**30 Days After Last Dose**	**Q12W**	**Q24W**	**Q12W**	**All procedures and assessments are to be performed prior to administration of study intervention unless otherwise indicated. Refer to Section 8.12 for visit details.**
Cycle Day	**1**	**1**	**21**	**1**	**1**	**22[d]**						
Scheduling Window (Days)		**±3**	**±3**	**±3**	**±3**	**±3**		**+7**	**±7**	**±7**	**±7**	
MK-4830 PK	X	X	X		X		X	X				Presurgery/ Neoadjuvant Phase: Collect predose of study intervention on C1D1, C2D1 and C2D21. Postsurgery/Adjuvant Phase: Collect predose on C1D1, C2D1. Samples should also be taken at EOT and at the 30-day Safety Follow-up visit. Note: Predose = Prior to the administration of any study intervention. Postdose = After the administration of all study interventions.

Pembrolizumab + MK-4830 (anti-ILT4)											
Study Period	**Treatment**						**EOT[b]**	**Posttreatment**				**Notes**
	Cycle = 21 days			**Cycle = 42 days**				**Safety[b]**	**Follow-up[c]**		**Survival**	
Visit Timing/Cycle Number	**Cycle 1 (Neo-adjuvant Phase)**	**Cycle 2 (Neo-adjuvant Phase)**		**Post-Surgical Resection Visit to confirm Disease-free Status**	**Cycle 1 and Onwards[a] (Adjuvant Phase)**		**At D/C**	**30 Days After Last Dose**	**Q12W**	**Q24W**	**Q12W**	**All procedures and assessments are to be performed prior to administration of study intervention unless otherwise indicated. Refer to Section 8.12 for visit details.**
Cycle Day	**1**	**1**	**21**	**1**	**1**	**22[d]**						
Scheduling Window (Days)		**±3**	**±3**	**±3**	**±3**	**±3**		**+7**	**±7**	**±7**	**±7**	
MK-4830 ADA	X	X	X		X		X	X				Presurgery/ Neoadjuvant Phase: Collect predose of study intervention on C1D1, C2D1 and C2D21. Postsurgery/Adjuvant Phase: Collect predose on C1D1, C2D1. Samples should also be taken at EOT and at the 30-day Safety Follow-up visit. Note: Predose = Prior to the administration of any study intervention. Postdose = After the administration of all study interventions.
Blood for serum biomarker analyses	X											Presurgery/ Neoadjuvant Phase: Collect predose on C1D1.

Pembrolizumab + MK-4830 (anti-ILT4)												
Study Period	**Treatment**						**EOT[b]**	**Posttreatment**				**Notes**
	Cycle = 21 days			**Cycle = 42 days**				**Safety[b]**	**Follow-up[c]**		**Survival**	
Visit Timing/Cycle Number	**Cycle 1 (Neo-adjuvant Phase)**	**Cycle 2 (Neo-adjuvant Phase)**		**Post-Surgical Resection Visit to confirm Disease-free Status**	**Cycle 1 and Onwards[a] (Adjuvant Phase)**		**At D/C**	**30 Days After Last Dose**	**Q12W**	**Q24W**	**Q12W**	**All procedures and assessments are to be performed prior to administration of study intervention unless otherwise indicated. Refer to Section 8.12 for visit details.**
Cycle Day	**1**	**1**	**21**	**1**	**1**	**22[d]**						
Scheduling Window (Days)		**±3**	**±3**	**±3**	**±3**	**±3**		**+7**	**±7**	**±7**	**±7**	
Blood for ctDNA analysis	X	X			X		X					Presurgery/ Neoadjuvant Phase: Collect predose on first dose of study intervention, and predose on C2D1. Postsurgery/Adjuvant Phase: Collect predose on C1D1, C2D1, C3D1, C5D1 & C7D1.
Blood for genetic analysis	X											Presurgery/ Neoadjuvant Phase: Collect predose on first dose of study intervention. See Section 8.9 for additional information.

Pembrolizumab + MK-4830 (anti-ILT4)											
Study Period	**Treatment**						**EOT[b]**	**Posttreatment**				**Notes**
	Cycle = 21 days			**Cycle = 42 days**				**Safety[b]**	**Follow-up[c]**		**Survival**	
Visit Timing/Cycle Number	**Cycle 1 (Neo-adjuvant Phase)**	**Cycle 2 (Neo-adjuvant Phase)**		**Post-Surgical Resection Visit to confirm Disease-free Status**	**Cycle 1 and Onwards[a] (Adjuvant Phase)**		**At D/C**	**30 Days After Last Dose**	**Q12W**	**Q24W**	**Q12W**	**All procedures and assessments are to be performed prior to administration of study intervention unless otherwise indicated. Refer to Section 8.12 for visit details.**
Cycle Day	**1**	**1**	**21**	**1**	**1**	**22[d]**						
Scheduling Window (Days)		**±3**	**±3**	**±3**	**±3**	**±3**		**+7**	**±7**	**±7**	**±7**	
Tumor blocks or slides	X			X								Presurgery/ Neoadjuvant Phase: Participants must submit a tumor sample at the end of Cycle 1 (Days 15-21) or C2D1 predose for biomarker analysis. A surgical resection specimen taken at Week 6 will also be submitted for pathologic assessment of resection specimens and for biomarker analysis. See Section 8.9 for details on biomarker assessments.

Pembrolizumab + MK-4830 (anti-ILT4)												
Study Period	**Treatment**						**EOT[b]**	**Posttreatment**				**Notes**
	Cycle = 21 days			**Cycle = 42 days**				**Safety[b]**	**Follow-up[c]**		**Survival**	
Visit Timing/Cycle Number	**Cycle 1 (Neo-adjuvant Phase)**	**Cycle 2 (Neo-adjuvant Phase)**		**Post-Surgical Resection Visit to confirm Disease-free Status**	**Cycle 1 and Onwards[a] (Adjuvant Phase)**		**At D/C**	**30 Days After Last Dose**	**Q12W**	**Q24W**	**Q12W**	**All procedures and assessments are to be performed prior to administration of study intervention unless otherwise indicated. Refer to Section 8.12 for visit details.**
Cycle Day	**1**	**1**	**21**	**1**	**1**	**22[d]**						
Scheduling Window (Days)		**±3**	**±3**	**±3**	**±3**	**±3**		**+7**	**±7**	**±7**	**±7**	

Abbreviations: AE = adverse event; BP = blood pressure; C1 = Cycle 1; C2 = Cycle 2; C3 = Cycle 3; C5 = Cycle 5; CIV = central imaging vendor; CT = computed tomography; ctDNA = circulating tumor DNA; ctRNA = circulating tumor RNA; D1 = Day 1; D15 = Day 15; D8 = Day 8; D/C = discontinue/discontinuing; ECG = electrocardiogram; ECHO = echocardiogram; ECOG = Eastern Cooperative Oncology Group; EOT = end of treatment; ePRO = electronic patient-reported outcome; FT4 = free thyroxine; FU = follow-up; HBV = hepatitis B virus; HCV = hepatitis C virus; HIV = human immunodeficiency virus; HRQoL = health-related quality of life; ICF = Informed Consent Form; INR = international normalized ratio; MRI = magnetic resonance imaging; MUGA = multigated acquisition; PE = physical examination; PK = pharmacokinetics; PT = prothrombin time; Q3W = every 3 weeks; Q9W = every 9 weeks; Q12W = every 12 weeks; Q24W = every 24 weeks; QD = once daily; RECIST = Response Evaluation Criteria in Solid Tumors; RR = respiratory rate; SAE = serious adverse event; SIM = site imaging manual; T3 = triiodothyronine; TSH = thyroid-stimulating hormone; UPCR=urine protein-to-creatinine; WOCBP = women of childbearing potential

a After surgical resection of the tumor, participants will receive 8 cycles of adjuvant therapy with pembrolizumab monotherapy as soon as possible after surgery (interval between surgical resection and adjuvant pembrolizumab should not exceed 12 weeks; the interval between postsurgery baseline imaging and first dose of adjuvant dosing should not exceed 28 days; total treatment duration including neoadjuvant and adjuvant therapy of approximately 1 year) or until they experience disease recurrence, unacceptable AEs are reported, consent is withdrawn, death, intercurrent illness that prevents further administration of study intervention, investigator's decision to discontinue the participant, noncompliance with study intervention or procedure requirements, or administrative reasons requiring cessation of treatment, whichever occurs first.

b If EOT visit occurs ~30 days from last dose of study intervention, a 30-day Safety Follow-up visit is not required. In this situation, all procedures required at the 30-day Safety Follow-up visit and EOT are performed once and entered into the EOT visit only. End of treatment will be defined as the date when the participant discontinues all study interventions.

c For participants who DC study intervention for reasons other than documented disease recurrence, follow-up visits to monitor disease status continue until documented disease recurrence or initiation of a new anticancer therapy. Participants who D/C study intervention with documented disease recurrence proceed directly to Survival Follow-up.

d Optional visit; visit and laboratory assessments should be completed as clinically indicated.

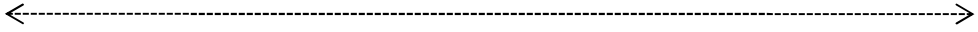
e Brain imaging is required for all participants at Screening. Magnetic resonance imaging is preferred; however, CT imaging will be acceptable if MRI is medically contraindicated.

Note: Each participant will receive neoadjuvant study intervention with an investigational treatment arm for up to approximately 5 weeks from first dose of study intervention followed by surgical resection of the tumor 6 weeks (42 days ± 7 days) from neoadjuvant C1D1 (also called definitive surgery with curative intent). Surgery should occur no sooner than approximately 5 weeks from the first dose of study intervention.

10.6.2.1.6 Section 1.3.6 MK-4280A (Coformulation of MK-4280 + Pembrolizumab)

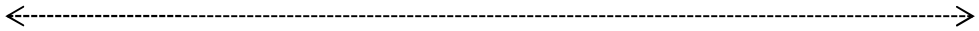
MK-4280A (Coformulation of MK-4280 + Pembrolizumab)												
Study Period	**Treatment**						**EOT[b]**	**Posttreatment**				**Notes**
	Cycle = 21 days			**Cycle = 42 days**				**Safety[b]**	**Follow-up[c]**		**Survival**	
Visit Timing/Cycle Number	**Cycle 1 (Neo-adjuvant Phase)**	**Cycle 2 (Neo-adjuvant Phase)**		**Post-Surgical Resection Visit to confirm Disease-free Status**	**Cycle 1 and Onwards[a] (Adjuvant Phase)**		**At D/C**	**30 Days After Last Dose**	**Q12W**	**Q24W**	**Q12W**	**All procedures and assessments are to be performed prior to administration of study intervention unless otherwise indicated. Refer to Section 8.12 for visit details.**
Cycle Day	**1**	**1**	**21**	**1**	**1**	**22[d]**						
Scheduling Window (Days)		**±3**	**±3**	**±3**	**±3**	**±3**		**+7**	**±7**	**±7**	**±7**	
Administrative Procedures												
BRAF status				X								BRAF V600 mutation analysis should be performed locally by the sites during the pathological assessment of the resected tumor specimen(s), if not performed during Screening. If the local laboratory is unable to perform BRAF testing, the site should submit the sample to the central pathology laboratory for testing.
Concomitant medication review	X	X	X	X	X	X	X	X	X			Concomitant medications will be recorded for 90 days after last dose (or for up to 120 days after last dose for SAEs).

MK-4280A (Coformulation of MK-4280 + Pembrolizumab)											
Study Period	**Treatment**					**EOT[b]**	**Posttreatment**				**Notes**
	Cycle = 21 days			**Cycle = 42 days**			**Safety[b]**	**Follow-up[c]**		**Survival**	
Visit Timing/Cycle Number	**Cycle 1 (Neo-adjuvant Phase)**	**Cycle 2 (Neo-adjuvant Phase)**		**Post-Surgical Resection Visit to confirm Disease-free Status**	**Cycle 1 and Onwards[a] (Adjuvant Phase)**		**At D/C**	**30 Days After Last Dose**	**Q12W**	**Q24W**	**Q12W**	**All procedures and assessments are to be performed prior to administration of study intervention unless otherwise indicated. Refer to Section 8.12 for visit details.**
Cycle Day	**1**	**1**	**21**	**1**	**1**	**22[d]**						
Scheduling Window (Days)		**±3**	**±3**	**±3**	**±3**	**±3**		**+7**	**±7**	**±7**	**±7**	
Randomization/ allocation	X											Presurgery/ Neoadjuvant Phase: Participants may be randomized/allocated 24 hours prior to first dose of study intervention and after confirmation of eligibility. All procedures and assessments on first dose of study intervention should be performed after randomization/ allocation.
Dispensation of MK-4280A drug kit	X	X										
MK-4280A administration	X	X										Presurgery/ Neoadjuvant Phase: MK-4280A will be administered IV Q3W for 2 doses prior to surgical resection.
Dispensation of Pembrolizumab drug kit					X							

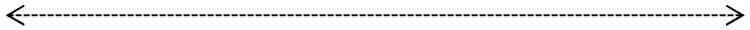
MK-4280A (Coformulation of MK-4280 + Pembrolizumab)											
Study Period	**Treatment**						**EOT[b]**	**Posttreatment**			**Notes**
	Cycle = 21 days			**Cycle = 42 days**				**Safety[b]**	**Follow-up[c]**		**Survival**	
Visit Timing/Cycle Number	**Cycle 1 (Neo-adjuvant Phase)**	**Cycle 2 (Neo-adjuvant Phase)**		**Post-Surgical Resection Visit to confirm Disease-free Status**	**Cycle 1 and Onwards[a] (Adjuvant Phase)**		**At D/C**	**30 Days After Last Dose**	**Q12W**	**Q24W**	**Q12W**	**All procedures and assessments are to be performed prior to administration of study intervention unless otherwise indicated. Refer to Section 8.12 for visit details.**
Cycle Day	**1**	**1**	**21**	**1**	**1**	**22[d]**						
Scheduling Window (Days)		**±3**	**±3**	**±3**	**±3**	**±3**		**+7**	**±7**	**±7**	**±7**	
Pembrolizumab administration					X							Postsurgery/Adjuvant Phase: After surgical resection, pembrolizumab 400 mg IV will be administered Q6W on Day 1 of each of 8 cycles (total treatment duration including neoadjuvant and adjuvant phase of approximately 1 year)
Subsequent antineoplastic treatment								X	X	X	X	All anticancer therapy will be recorded until time of death or termination of survival FU. If a clinic visit is not feasible, follow-up information may be obtained via telephone or email.
Survival status												Participants may be contacted for survival status at any time during the course of this substudy.

MK-4280A (Coformulation of MK-4280 + Pembrolizumab)												
Study Period	**Treatment**						**EOT[b]**	**Posttreatment**				**Notes**
	Cycle = 21 days			**Cycle = 42 days**				**Safety[b]**	**Follow-up[c]**		**Survival**	
Visit Timing/Cycle Number	**Cycle 1 (Neo-adjuvant Phase)**	**Cycle 2 (Neo-adjuvant Phase)**		**Post-Surgical Resection Visit to confirm Disease-free Status**	**Cycle 1 and Onwards[a] (Adjuvant Phase)**		**At D/C**	**30 Days After Last Dose**	**Q12W**	**Q24W**	**Q12W**	**All procedures and assessments are to be performed prior to administration of study intervention unless otherwise indicated. Refer to Section 8.12 for visit details.**
Cycle Day	**1**	**1**	**21**	**1**	**1**	**22[d]**						
Scheduling Window (Days)		**±3**	**±3**	**±3**	**±3**	**±3**		**+7**	**±7**	**±7**	**±7**	
Efficacy/Immunogenicity Procedures												
Tumor assessment: chest, abdomen, and pelvis (CT/MRI)[e]							X		X	X		All imaging visits have a scheduling window of ±7 days. Presurgery/ Neoadjuvant Phase: The first on-study imaging assessment should be performed at 6 weeks (42 days ±7 days) from first dose of study intervention (prior to surgical resection of the tumor). After surgical resection of the tumor, disease-free status must be documented by radiographic imaging at Week 12 (new baseline imaging prior to start of adjuvant therapy), prior to the start of postoperative/ adjuvant pembrolizumab. Postsurgery/Adjuvant Phase: Subsequent tumor imaging should be performed every 12 weeks from adjuvant C1D1 (±7 days) for the first 2 years, after which imaging will be performed every 24 weeks (168 days ±7 days) until Year 5 or more frequently if clinically indicated. or until documented disease recurrence. For

MK-4280A (Coformulation of MK-4280 + Pembrolizumab)											
Study Period	**Treatment**						**EOT[b]**	**Posttreatment**			**Notes**
	Cycle = 21 days			**Cycle = 42 days**				**Safety[b]**	**Follow-up[c]**		**Survival**	
Visit Timing/Cycle Number	**Cycle 1 (Neo-adjuvant Phase)**	**Cycle 2 (Neo-adjuvant Phase)**		**Post-Surgical Resection Visit to confirm Disease-free Status**	**Cycle 1 and Onwards[a] (Adjuvant Phase)**		**At D/C**	**30 Days After Last Dose**	**Q12W**	**Q24W**	**Q12W**	**All procedures and assessments are to be performed prior to administration of study intervention unless otherwise indicated. Refer to Section 8.12 for visit details.**
Cycle Day	**1**	**1**	**21**	**1**	**1**	**22[d]**						
Scheduling Window (Days)		**±3**	**±3**	**±3**	**±3**	**±3**		**+7**	**±7**	**±7**	**±7**	
												participants who discontinue study intervention without documented disease recurrence, every effort should be made to continue monitoring disease status by tumor imaging using the same imaging schedule used while on treatment. Imaging of any anatomy that shows disease at Screening will be required in subsequent evaluations and should be submitted to the CIV. Tumor imaging is strongly preferred to be acquired by CT; the CT portion of PET/CT may be used in place of a stand-alone CT if it is of diagnostic quality per site imaging manual. Imaging at EOT is not required if the previous tumor imaging assessment was within 4 weeks prior to the EOT visit.

MK-4280A (Coformulation of MK-4280 + Pembrolizumab)												
Study Period	**Treatment**						**EOT[b]**	**Posttreatment**				**Notes**
	Cycle = 21 days			**Cycle = 42 days**				**Safety[b]**	**Follow-up[c]**		**Survival**	
Visit Timing/Cycle Number	**Cycle 1 (Neo-adjuvant Phase)**	**Cycle 2 (Neo-adjuvant Phase)**		**Post-Surgical Resection Visit to confirm Disease-free Status**	**Cycle 1 and Onwards[a] (Adjuvant Phase)**		**At D/C**	**30 Days After Last Dose**	**Q12W**	**Q24W**	**Q12W**	**All procedures and assessments are to be performed prior to administration of study intervention unless otherwise indicated. Refer to Section 8.12 for visit details.**
Cycle Day	**1**	**1**	**21**	**1**	**1**	**22[d]**						
Scheduling Window (Days)		**±3**	**±3**	**±3**	**±3**	**±3**		**+7**	**±7**	**±7**	**±7**	
Digital photography												Qualitative digital photography should be performed as clinically indicated. Cutaneous lesions are not considered measurable for the purposes of this protocol but may be considered to be nontarget lesions for tumor assessments by investigators. Copies of digital photographs should also be submitted to the central imaging vendor.
Safety Procedures												
AE monitoring	X	X	X	X	X	X	X	X	X			AEs: monitored up to 90 days after last dose. SAEs and pregnancy: monitored up to 120 days after last dose, or 30 days after last dose if participant starts a new anticancer therapy, whichever is sooner.

MK-4280A (Coformulation of MK-4280 + Pembrolizumab)											
Study Period	**Treatment**						**EOT[b]**	**Posttreatment**				**Notes**
	Cycle = 21 days			**Cycle = 42 days**				**Safety[b]**	**Follow-up[c]**		**Survival**	
Visit Timing/Cycle Number	**Cycle 1 (Neo-adjuvant Phase)**	**Cycle 2 (Neo-adjuvant Phase)**		**Post-Surgical Resection Visit to confirm Disease-free Status**	**Cycle 1 and Onwards[a] (Adjuvant Phase)**		**At D/C**	**30 Days After Last Dose**	**Q12W**	**Q24W**	**Q12W**	**All procedures and assessments are to be performed prior to administration of study intervention unless otherwise indicated. Refer to Section 8.12 for visit details.**
Cycle Day	**1**	**1**	**21**	**1**	**1**	**22[d]**						
Scheduling Window (Days)		**±3**	**±3**	**±3**	**±3**	**±3**		**+7**	**±7**	**±7**	**±7**	
Complete physical examination				X								Postsurgical resection of the tumor, disease-free status must be documented by a complete physical examination at Week 12 (new baseline imaging), prior to the start of postoperative/adjuvant pembrolizumab.
Directed physical examination	X	X			X	X	X	X	X	X		In addition to the directed PEs in the flowchart, a symptom-directed PE may be performed at any time during this substudy, as clinically indicated. The investigator or qualified designee should conduct a visual inspection of local recurrence and palpation of lymph nodes to assess recurrence.

MK-4280A (Coformulation of MK-4280 + Pembrolizumab)											
Study Period	**Treatment**					**EOT[b]**	**Posttreatment**				**Notes**
	Cycle = 21 days			**Cycle = 42 days**			**Safety[b]**	**Follow-up[c]**		**Survival**	
Visit Timing/Cycle Number	**Cycle 1 (Neo-adjuvant Phase)**	**Cycle 2 (Neo-adjuvant Phase)**		**Post-Surgical Resection Visit to confirm Disease-free Status**	**Cycle 1 and Onwards[a] (Adjuvant Phase)**		**At D/C**	**30 Days After Last Dose**	**Q12W**	**Q24W**	**Q12W**	**All procedures and assessments are to be performed prior to administration of study intervention unless otherwise indicated. Refer to Section 8.12 for visit details.**
Cycle Day	**1**	**1**	**21**	**1**	**1**	**22[d]**						
Scheduling Window (Days)		**±3**	**±3**	**±3**	**±3**	**±3**		**+7**	**±7**	**±7**	**±7**	
Review of the pathology report postsurgical resection				X								Review of the pathology report of the surgical resection specimen(s) by the investigator is mandatory prior to the start of adjuvant therapy to ensure the participant is disease-free and the surgical margins are tumor-free (R0).
Vital signs (resting BP, heart rate, RR, and temp), and weight	X	X			X	X	X	X				Blood pressure and heart rate will be measured after the participant has been resting for 5 minutes. See Section 8.3.2 for vital signs.
12-lead ECG												As clinically indicated. Participants must be in the recumbent position for a period of 5 minutes prior to the ECG. See Section 8.3.3 for ECG.

MK-4280A (Coformulation of MK-4280 + Pembrolizumab)											
Study Period	**Treatment**						**EOT[b]**	**Posttreatment**			**Notes**
	Cycle = 21 days			**Cycle = 42 days**				**Safety[b]**	**Follow-up[c]**		**Survival**	
Visit Timing/Cycle Number	**Cycle 1 (Neo-adjuvant Phase)**	**Cycle 2 (Neo-adjuvant Phase)**		**Post-Surgical Resection Visit to confirm Disease-free Status**	**Cycle 1 and Onwards[a] (Adjuvant Phase)**		**At D/C**	**30 Days After Last Dose**	**Q12W**	**Q24W**	**Q12W**	**All procedures and assessments are to be performed prior to administration of study intervention unless otherwise indicated. Refer to Section 8.12 for visit details.**
Cycle Day	**1**	**1**	**21**	**1**	**1**	**22[d]**						
Scheduling Window (Days)		**±3**	**±3**	**±3**	**±3**	**±3**		**+7**	**±7**	**±7**	**±7**	
Hematology and chemistry laboratory assessment	X	X		X	X	X	X	X				Procedures/ assessments should be performed prior to all scheduled substudy visits. Every effort should be made to collect samples at the same time of day. LDH testing is needed. Laboratory samples collected within 3 days prior to the first dose of study intervention need not be repeated on C1D1.
Urinalysis	<---------->											As clinically indicated.
PT/INR and aPTT/PTT	<---------->											As clinically indicated for participants taking anticoagulant therapy.

MK-4280A (Coformulation of MK-4280 + Pembrolizumab)											
Study Period	**Treatment**						**EOT[b]**	**Posttreatment**				**Notes**
	Cycle = 21 days			**Cycle = 42 days**				**Safety[b]**	**Follow-up[c]**		**Survival**	
Visit Timing/Cycle Number	**Cycle 1 (Neo-adjuvant Phase)**	**Cycle 2 (Neo-adjuvant Phase)**		**Post-Surgical Resection Visit to confirm Disease-free Status**	**Cycle 1 and Onwards[a] (Adjuvant Phase)**		**At D/C**	**30 Days After Last Dose**	**Q12W**	**Q24W**	**Q12W**	**All procedures and assessments are to be performed prior to administration of study intervention unless otherwise indicated. Refer to Section 8.12 for visit details.**
Cycle Day	**1**	**1**	**21**	**1**	**1**	**22[d]**						
Scheduling Window (Days)		**±3**	**±3**	**±3**	**±3**	**±3**		**+7**	**±7**	**±7**	**±7**	
T3, FT4, TSH		X			X		X					Presurgery/ Neoadjuvant Phase: Thyroid function tests will be performed at Cycle 2. Postsurgery/Adjuvant Phase: Thyroid function tests will be performed at Cycle 1 and every cycle thereafter and at the time of discontinuation (EOT). Free T3 is acceptable where Total T3 cannot be determined. After C1 of the Presurgery/ Neoadjuvant Phase, retrospective review of thyroid function testing results is allowed when the results are not available prior to dosing.

MK-4280A (Coformulation of MK-4280 + Pembrolizumab)											
Study Period	**Treatment**						**EOT[b]**	**Posttreatment**				**Notes**
	Cycle = 21 days			**Cycle = 42 days**				**Safety[b]**	**Follow-up[c]**		**Survival**	
Visit Timing/Cycle Number	**Cycle 1 (Neo-adjuvant Phase)**	**Cycle 2 (Neo-adjuvant Phase)**		**Post-Surgical Resection Visit to confirm Disease-free Status**	**Cycle 1 and Onwards[a] (Adjuvant Phase)**		**At D/C**	**30 Days After Last Dose**	**Q12W**	**Q24W**	**Q12W**	**All procedures and assessments are to be performed prior to administration of study intervention unless otherwise indicated. Refer to Section 8.12 for visit details.**
Cycle Day	**1**	**1**	**21**	**1**	**1**	**22[d]**						
Scheduling Window (Days)		**±3**	**±3**	**±3**	**±3**	**±3**		**+7**	**±7**	**±7**	**±7**	
Pregnancy test (WOCBP only)		X			X		X	X	X			To be assessed prior to all scheduled visits. A serum or urine pregnancy test will be performed as indicated, prior to every cycle, up to 120 days after last dose of study intervention or 30 days after last dose if participant starts a new anticancer therapy, whichever comes first. See Appendix 11 for country-specific guidelines.
ECOG performance status		X			X	X	X	X				To be assessed prior to dosing during all scheduled visits.
Biomarkers/ Pharmacokinetics/Pharmacodynamics												
Blood for ctDNA analysis	X	X			X		X					Presurgery/ Neoadjuvant Phase: Collect predose on first dose of study intervention, and predose on C2D1. Postsurgery/Adjuvant Phase: Collect predose on C1D1, C2D1, C3D1, C5D1 & C7D1.

MK-4280A (Coformulation of MK-4280 + Pembrolizumab)												
Study Period	**Treatment**						**EOT[b]**	**Posttreatment**				**Notes**
	Cycle = 21 days			**Cycle = 42 days**				**Safety[b]**	**Follow-up[c]**		**Survival**	
Visit Timing/Cycle Number	**Cycle 1 (Neo-adjuvant Phase)**	**Cycle 2 (Neo-adjuvant Phase)**		**Post-Surgical Resection Visit to confirm Disease-free Status**	**Cycle 1 and Onwards[a] (Adjuvant Phase)**		**At D/C**	**30 Days After Last Dose**	**Q12W**	**Q24W**	**Q12W**	**All procedures and assessments are to be performed prior to administration of study intervention unless otherwise indicated. Refer to Section 8.12 for visit details.**
Cycle Day	**1**	**1**	**21**	**1**	**1**	**22[d]**						
Scheduling Window (Days)		**±3**	**±3**	**±3**	**±3**	**±3**		**+7**	**±7**	**±7**	**±7**	
Blood for genetic analysis	X											Presurgery/ Neoadjuvant Phase: Collect predose on first dose of study intervention. See Section 8.9 for additional information.
Tumor blocks or slides	X			X								Presurgery/ Neoadjuvant Phase: Participants must submit a tumor sample at the end of Cycle 1 (Days 15-21) or C2D1 predose for biomarker analysis. A surgical resection specimen taken at Week 6 will also be submitted for pathologic assessment of resection specimens and for biomarker analysis. See Section 8.9 for details on biomarker assessments.

MK-4280A (Coformulation of MK-4280 + Pembrolizumab)											
Study Period	**Treatment**					**EOT[b]**	**Posttreatment**				**Notes**
	Cycle = 21 days			**Cycle = 42 days**			**Safety[b]**	**Follow-up[c]**		**Survival**	
Visit Timing/Cycle Number	**Cycle 1 (Neo-adjuvant Phase)**	**Cycle 2 (Neo-adjuvant Phase)**		**Post-Surgical Resection Visit to confirm Disease-free Status**	**Cycle 1 and Onwards[a] (Adjuvant Phase)**		**At D/C**	**30 Days After Last Dose**	**Q12W**	**Q24W**	**Q12W**	**All procedures and assessments are to be performed prior to administration of study intervention unless otherwise indicated. Refer to Section 8.12 for visit details.**
Cycle Day	**1**	**1**	**21**	**1**	**1**	**22[d]**						
Scheduling Window (Days)		**±3**	**±3**	**±3**	**±3**	**±3**		**+7**	**±7**	**±7**	**±7**	
MK-3475 PK	X	X	X		X		X	X				Presurgery/Neoadjuvant Phase: Collect predose of study intervention on C1D1 and C2D1, and then on C2D21. Postsurgery/Adjuvant Phase: Collect predose on C1D1, C2D1. Samples should also be taken at EOT and at the 30-day Safety Follow-up visit. Note: Predose = Prior to the administration of any study intervention. Postdose = After the administration of all study interventions.

MK-4280A (Coformulation of MK-4280 + Pembrolizumab)											
Study Period	**Treatment**					**EOT[b]**	**Posttreatment**				**Notes**
	Cycle = 21 days			**Cycle = 42 days**			**Safety[b]**	**Follow-up[c]**		**Survival**	
Visit Timing/Cycle Number	**Cycle 1 (Neo-adjuvant Phase)**	**Cycle 2 (Neo-adjuvant Phase)**		**Post-Surgical Resection Visit to confirm Disease-free Status**	**Cycle 1 and Onwards[a] (Adjuvant Phase)**		**At D/C**	**30 Days After Last Dose**	**Q12W**	**Q24W**	**Q12W**	**All procedures and assessments are to be performed prior to administration of study intervention unless otherwise indicated. Refer to Section 8.12 for visit details.**
Cycle Day	**1**	**1**	**21**	**1**	**1**	**22[d]**						
Scheduling Window (Days)		**±3**	**±3**	**±3**	**±3**	**±3**		**+7**	**±7**	**±7**	**±7**	
MK-3475 ADA	X	X	X		X		X	X				Presurgery/Neoadjuvant Phase: Collect predose of study intervention on C1D1and C2D1, and then on C2D21. Postsurgery/Adjuvant Phase: Collect predose on C1D1, C2D1. Samples should also be taken at EOT and at the 30-day Safety Follow-up visit. Note: Predose = Prior to the administration of any study intervention. Postdose = After the administration of all study interventions.

MK-4280A (Coformulation of MK-4280 + Pembrolizumab)											
Study Period	**Treatment**					**EOT[b]**	**Posttreatment**				**Notes**
	Cycle = 21 days			**Cycle = 42 days**			**Safety[b]**	**Follow-up[c]**		**Survival**	
Visit Timing/Cycle Number	**Cycle 1 (Neo-adjuvant Phase)**	**Cycle 2 (Neo-adjuvant Phase)**		**Post-Surgical Resection Visit to confirm Disease-free Status**	**Cycle 1 and Onwards[a] (Adjuvant Phase)**		**At D/C**	**30 Days After Last Dose**	**Q12W**	**Q24W**	**Q12W**	**All procedures and assessments are to be performed prior to administration of study intervention unless otherwise indicated. Refer to Section 8.12 for visit details.**
Cycle Day	**1**	**1**	**21**	**1**	**1**	**22[d]**						
Scheduling Window (Days)		**±3**	**±3**	**±3**	**±3**	**±3**		**+7**	**±7**	**±7**	**±7**	
MK-4280 PK	X	X	X		X		X	X				Presurgery/Neoadjuvant Phase: Collect predose of study intervention on C1D1 and C2D1, and then on C2D21. Postsurgery/Adjuvant Phase: Collect predose on C1D1, C2D1. Samples should also be taken at EOT and at the 30-day Safety Follow-up visit. Note: Predose = Prior to the administration of any study intervention. Postdose = After the administration of all study interventions.

MK-4280A (Coformulation of MK-4280 + Pembrolizumab)											
Study Period	**Treatment**					**EOT[b]**	**Posttreatment**				**Notes**
	Cycle = 21 days			**Cycle = 42 days**			**Safety[b]**	**Follow-up[c]**		**Survival**	
Visit Timing/Cycle Number	**Cycle 1 (Neo-adjuvant Phase)**	**Cycle 2 (Neo-adjuvant Phase)**		**Post-Surgical Resection Visit to confirm Disease-free Status**	**Cycle 1 and Onwards[a] (Adjuvant Phase)**		**At D/C**	**30 Days After Last Dose**	**Q12W**	**Q24W**	**Q12W**	**All procedures and assessments are to be performed prior to administration of study intervention unless otherwise indicated. Refer to Section 8.12 for visit details.**
Cycle Day	**1**	**1**	**21**	**1**	**1**	**22[d]**						
Scheduling Window (Days)		**±3**	**±3**	**±3**	**±3**	**±3**		**+7**	**±7**	**±7**	**±7**	
MK-4280 ADA	X	X	X		X		X	X				Neoadjuvant Phase: Collect predose of study intervention on C1D1 and C2D1, and then on C2D21. Postsurgery/Adjuvant Phase: Collect predose on C1D1, C2D1. Samples should also be taken at EOT and at the 30-day Safety Follow-up visit. Note: Predose = Prior to the administration of any study intervention. Postdose = After the administration of all study interventions.

MK-4280A (Coformulation of MK-4280 + Pembrolizumab)											
Study Period	**Treatment**					**EOT[b]**	**Posttreatment**				**Notes**
	Cycle = 21 days			**Cycle = 42 days**			**Safety[b]**	**Follow-up[c]**		**Survival**	
Visit Timing/Cycle Number	**Cycle 1 (Neo-adjuvant Phase)**	**Cycle 2 (Neo-adjuvant Phase)**		**Post-Surgical Resection Visit to confirm Disease-free Status**	**Cycle 1 and Onwards[a] (Adjuvant Phase)**		**At D/C**	**30 Days After Last Dose**	**Q12W**	**Q24W**	**Q12W**	**All procedures and assessments are to be performed prior to administration of study intervention unless otherwise indicated. Refer to Section 8.12 for visit details.**
Cycle Day	**1**	**1**	**21**	**1**	**1**	**22[d]**						
Scheduling Window (Days)		**±3**	**±3**	**±3**	**±3**	**±3**		**+7**	**±7**	**±7**	**±7**	

Abbreviations: AE = adverse event; BP = blood pressure; C1 = Cycle 1; C2 = Cycle 2; C3 = Cycle 3; C5 = Cycle 5; CIV = central imaging vendor; CT = computed tomography; ctDNA = circulating tumor DNA; ctRNA = circulating tumor RNA; D1 = Day 1; D15 = Day 15; D8 = Day 8; D/C = discontinue/discontinuing; ECG = electrocardiogram; ECHO = echocardiogram; ECOG = Eastern Cooperative Oncology Group; EOT = end of treatment; ePRO = electronic patient-reported outcome; FT4 = free thyroxine; FU = follow-up; HBV = hepatitis B virus; HCV = hepatitis C virus; HIV = human immunodeficiency virus; HRQoL = health-related quality of life; ICF = Informed Consent Form; INR = international normalized ratio; MRI = magnetic resonance imaging; MUGA = multigated acquisition; PE = physical examination; PK = pharmacokinetics; PT = prothrombin time; Q3W = every 3 weeks; Q9W = every 9 weeks; Q12W = every 12 weeks; Q24W = every 24 weeks; QD = once daily; RECIST = Response Evaluation Criteria in Solid Tumors; RR = respiratory rate; SAE = serious adverse event; SIM = site imaging manual; T3 = triiodothyronine; TSH = thyroid-stimulating hormone; UPCR=urine protein-to-creatinine; WOCBP = women of childbearing potential

a After surgical resection of the tumor, participants will receive 8 cycles of adjuvant therapy with pembrolizumab monotherapy as soon as possible after surgery (interval between surgical resection and adjuvant pembrolizumab should not exceed 12 weeks; the interval between postsurgery baseline imaging and first dose of adjuvant dosing should not exceed 28 days; total treatment duration including neoadjuvant and adjuvant therapy of approximately 1 year) or until they experience disease recurrence, unacceptable AEs are reported, consent is withdrawn, death, intercurrent illness that prevents further administration of study intervention, investigator's decision to discontinue the participant, noncompliance with study intervention or procedure requirements, or administrative reasons requiring cessation of treatment, whichever occurs first.

b If EOT visit occurs ~30 days from last dose of study intervention, a 30-day Safety Follow-up visit is not required. In this situation, all procedures required at the 30-day Safety Follow-up visit and EOT are performed once and entered into the EOT visit only. End of treatment will be defined as the date when the participant discontinues all study interventions.

c For participants who DC study intervention for reasons other than documented disease recurrence, follow-up visits to monitor disease status continue until documented disease recurrence or initiation of a new anticancer therapy. Participants who D/C study intervention with documented disease recurrence proceed directly to Survival Follow-up.

d Optional visit; visit and laboratory assessments should be completed as clinically indicated.

e Brain imaging is required for all participants at Screening. Magnetic resonance imaging is preferred; however, CT imaging will be acceptable if MRI is medically contraindicated.

Note: Each participant will receive neoadjuvant study intervention with an investigational treatment arm for up to approximately 5 weeks from first dose of study intervention followed by surgical resection of the tumor 6 weeks (42 days ± 7 days) from neoadjuvant C1D1 (also called definitive surgery with curative intent). Surgery should occur no sooner than approximately 5 weeks from the first dose of study intervention.

10.6.2.1.7 Section 1.3.7 Pembrolizumab + ATRA

Pembrolizumab + ATRA											
Study Period	**Treatment**					**EOT[b]**	**Posttreatment**				**Notes**
	Cycle = 21 days		**Cycle = 42 days**				**Safety[b]**	**Follow-up[c]**		**Survival**	
Visit Timing/Cycle Number	**Cycle 1 (Neo-adjuvant Phase)**	**Cycle 2 (Neo-adjuvant Phase)**	**Post-Surgical Resection Visit to confirm Disease-free Status**	**Cycle 1 and Onwards[a] (Adjuvant Phase)**		**At D/C**	**30 Days After Last Dose**	**Q12W**	**Q24W**	**Q12W**	**All procedures and assessments are to be performed prior to administration of study intervention unless otherwise indicated. Refer to Section 8.12 for visit details.**
Cycle Day	**1**	**1**	**1**	**1**	**22[d]**						
Scheduling Window (Days)		**±3**	**±3**	**±3**	**±3**		**+7**	**±7**	**±7**	**±7**	
Administrative Procedures											
BRAF status			X								BRAF V600 mutation analysis should be performed locally by the sites during the pathological assessment of the resected tumor specimen(s), if not performed during Screening. If the local laboratory is unable to perform BRAF testing, the site should submit the sample to the central pathology laboratory for testing.
Concomitant medication review	X	X	X	X	X	X	X	X			Concomitant medications will be recorded for 90 days after last dose (or for up to 120 days after last dose for SAEs).
Randomization/allocation	X										Presurgery/ Neoadjuvant Phase: Participants may be randomized/allocated 24 hours prior to first dose of study intervention and after confirmation of eligibility. All procedures and assessments on first dose of study intervention should be performed after randomization/ allocation.

Pembrolizumab + ATRA											
Study Period	**Treatment**					**EOT[b]**	**Posttreatment**				**Notes**
	Cycle = 21 days		**Cycle = 42 days**				**Safety[b]**	**Follow-up[c]**		**Survival**	
Visit Timing/Cycle Number	**Cycle 1 (Neo-adjuvant Phase)**	**Cycle 2 (Neo-adjuvant Phase)**	**Post-Surgical Resection Visit to confirm Disease-free Status**	**Cycle 1 and Onwards[a] (Adjuvant Phase)**		**At D/C**	**30 Days After Last Dose**	**Q12W**	**Q24W**	**Q12W**	**All procedures and assessments are to be performed prior to administration of study intervention unless otherwise indicated. Refer to Section 8.12 for visit details.**
Cycle Day	**1**	**1**	**1**	**1**	**22[d]**						
Scheduling Window (Days)		**±3**	**±3**	**±3**	**±3**		**+7**	**±7**	**±7**	**±7**	
ATRA dispensed to participant	X	X									ATRA dispensed on D1 of each cycle for use during the cycle. ATRA will be centrally sourced.
ATRA administration	X	X									Presurgery/ Neoadjuvant Phase: ATRA 75 mg/m^2 twice daily PO 3 days Q3W will be administered for 2 doses prior to surgical resection. For Cycle 1, ATRA administration on Days 1, 2 and 3 For Cycle 2, ATRA administration on Days 1, 2, and 3 NOTE: ATRA should be administered twice daily in the morning and evening.
Dispensation of pembrolizumab drug kit to participant	X			X							

Pembrolizumab + ATRA											
Study Period	**Treatment**					**EOT[b]**	**Posttreatment**				**Notes**
	Cycle = 21 days		**Cycle = 42 days**				**Safety[b]**	**Follow-up[c]**		**Survival**	
Visit Timing/Cycle Number	**Cycle 1 (Neo-adjuvant Phase)**	**Cycle 2 (Neo-adjuvant Phase)**	**Post-Surgical Resection Visit to confirm Disease-free Status**	**Cycle 1 and Onwards[a] (Adjuvant Phase)**		**At D/C**	**30 Days After Last Dose**	**Q12W**	**Q24W**	**Q12W**	**All procedures and assessments are to be performed prior to administration of study intervention unless otherwise indicated. Refer to Section 8.12 for visit details.**
Cycle Day	**1**	**1**	**1**	**1**	**22[d]**						
Scheduling Window (Days)		**±3**	**±3**	**±3**	**±3**		**+7**	**±7**	**±7**	**±7**	
Pembrolizumab administration	X			X							Neoadjuvant Phase: Pembrolizumab: Pembrolizumab 400 mg IV on C1 Day 1. Postsurgery/Adjuvant Phase: After surgical resection, pembrolizumab 400 mg will be administered IV Q6W on Day 1 of each of 8 cycles (total treatment duration including neoadjuvant and adjuvant phase of approximately 1 year) Pembrolizumab is administered on Day 1 of each cycle Q6W. On those days where both ATRA and pembrolizumab are administered, pembrolizumab may be infused approximately 30 minutes after the ATRA am dose.
Subsequent antineoplastic treatment							X	X	X	X	All anticancer therapy will be recorded until time of death or termination of survival FU. If a clinic visit is not feasible, follow up information may be obtained via telephone or email.

Pembrolizumab + ATRA											
Study Period	**Treatment**					**EOT[b]**	**Posttreatment**				**Notes**
	Cycle = 21 days		**Cycle = 42 days**				**Safety[b]**	**Follow-up[c]**		**Survival**	
Visit Timing/Cycle Number	**Cycle 1 (Neo-adjuvant Phase)**	**Cycle 2 (Neo-adjuvant Phase)**	**Post-Surgical Resection Visit to confirm Disease-free Status**	**Cycle 1 and Onwards[a] (Adjuvant Phase)**		**At D/C**	**30 Days After Last Dose**	**Q12W**	**Q24W**	**Q12W**	**All procedures and assessments are to be performed prior to administration of study intervention unless otherwise indicated. Refer to Section 8.12 for visit details.**
Cycle Day	**1**	**1**	**1**	**1**	**22[d]**						
Scheduling Window (Days)		**±3**	**±3**	**±3**	**±3**		**+7**	**±7**	**±7**	**±7**	
Survival status											Participants may be contacted for survival status at any time during the course of this substudy.
Efficacy/Immunogenicity Procedures											
Tumor assessment: chest, abdomen, and pelvis (CT/MRI)[e]						X		X	X		All imaging visits have a scheduling window of ±7 days. Presurgery/ Neoadjuvant Phase: The first on-study imaging assessment should be performed at 6 weeks (42 days ±7 days) from first dose of study intervention (prior to surgical resection of the tumor). After surgical resection of the tumor, disease-free status must be documented by radiographic imaging at Week 12 (new baseline imaging prior to start of adjuvant therapy), prior to the start of postoperative/ adjuvant pembrolizumab. Postsurgery/Adjuvant Phase: Subsequent tumor imaging should be performed every 12 weeks from adjuvant C1D1 (±7 days) for the first 2 years, after which imaging will be performed every 24 weeks (168 days ±7 days) until Year 5 or more frequently if clinically indicated. or

Pembrolizumab + ATRA											
Study Period	**Treatment**					**EOT[b]**	**Posttreatment**				**Notes**
	Cycle = 21 days		**Cycle = 42 days**				**Safety[b]**	**Follow-up[c]**		**Survival**	
Visit Timing/Cycle Number	**Cycle 1 (Neo-adjuvant Phase)**	**Cycle 2 (Neo-adjuvant Phase)**	**Post-Surgical Resection Visit to confirm Disease-free Status**	**Cycle 1 and Onwards[a] (Adjuvant Phase)**		**At D/C**	**30 Days After Last Dose**	**Q12W**	**Q24W**	**Q12W**	**All procedures and assessments are to be performed prior to administration of study intervention unless otherwise indicated. Refer to Section 8.12 for visit details.**
Cycle Day	**1**	**1**	**1**	**1**	**22[d]**						
Scheduling Window (Days)		**±3**	**±3**	**±3**	**±3**		**+7**	**±7**	**±7**	**±7**	
											until documented disease recurrence. For participants who discontinue study intervention without documented disease recurrence, every effort should be made to continue monitoring disease status by tumor imaging using the same imaging schedule used while on treatment. Imaging of any anatomy that shows disease at Screening will be required in subsequent evaluations and should be submitted to the CIV. Tumor imaging is strongly preferred to be acquired by CT; the CT portion of PET/CT may be used in place of a stand-alone CT if it is of diagnostic quality per site imaging manual. Imaging at EOT is not required if the previous tumor imaging assessment was within 4 weeks prior to the EOT visit.

Pembrolizumab + ATRA											
Study Period	**Treatment**					**EOT[b]**	**Posttreatment**				**Notes**
	Cycle = 21 days		**Cycle = 42 days**				**Safety[b]**	**Follow-up[c]**		**Survival**	
Visit Timing/Cycle Number	**Cycle 1 (Neo-adjuvant Phase)**	**Cycle 2 (Neo-adjuvant Phase)**	**Post-Surgical Resection Visit to confirm Disease-free Status**	**Cycle 1 and Onwards[a] (Adjuvant Phase)**		**At D/C**	**30 Days After Last Dose**	**Q12W**	**Q24W**	**Q12W**	**All procedures and assessments are to be performed prior to administration of study intervention unless otherwise indicated. Refer to Section 8.12 for visit details.**
Cycle Day	**1**	**1**	**1**	**1**	**22[d]**						
Scheduling Window (Days)		**±3**	**±3**	**±3**	**±3**		**+7**	**±7**	**±7**	**±7**	
Digital photography	←	----------	----------	----------	----------	----------	----------	----------	----------	→	Qualitative digital photography should be performed as clinically indicated. Cutaneous lesions are not considered measurable for the purposes of this protocol but may be considered to be nontarget lesions for tumor assessments by investigators. Copies of digital photographs should also be submitted to the central imaging vendor.
Safety Procedures											
AE monitoring	X	X	X	X	X	X	X	X			AEs: monitored up to 90 days after last dose. SAEs and pregnancy: monitored up to 120 days after last dose, or 30 days after last dose if participant starts a new anticancer therapy, whichever is sooner.
Complete physical examination			X								Postsurgical resection of the tumor, disease-free status must be documented by a complete physical examination at Week 12 (new baseline imaging), prior to the start of postoperative/adjuvant pembrolizumab.

Pembrolizumab + ATRA											
Study Period	**Treatment**					**EOT[b]**	**Posttreatment**				**Notes**
	Cycle = 21 days		**Cycle = 42 days**				**Safety[b]**	**Follow-up[c]**		**Survival**	
Visit Timing/Cycle Number	**Cycle 1 (Neo-adjuvant Phase)**	**Cycle 2 (Neo-adjuvant Phase)**	**Post-Surgical Resection Visit to confirm Disease-free Status**	**Cycle 1 and Onwards[a] (Adjuvant Phase)**		**At D/C**	**30 Days After Last Dose**	**Q12W**	**Q24W**	**Q12W**	**All procedures and assessments are to be performed prior to administration of study intervention unless otherwise indicated. Refer to Section 8.12 for visit details.**
Cycle Day	**1**	**1**	**1**	**1**	**22[d]**						
Scheduling Window (Days)		**±3**	**±3**	**±3**	**±3**		**+7**	**±7**	**±7**	**±7**	
Directed physical examination	X	X		X	X	X	X	X	X		In addition to the directed PEs in the flowchart, a symptom-directed PE may be performed at any time during this substudy, as clinically indicated. The investigator or qualified designee should conduct a visual inspection of local recurrence and palpation of lymph nodes to assess recurrence.
Review of the pathology report postsurgical resection			X								Review of the pathology report of the surgical resection specimen(s) by the investigator is mandatory prior to the start of adjuvant therapy to ensure the participant is disease-free and the surgical margins are tumor-free (R0).
Vital signs (resting BP, heart rate, RR, and temp), and weight	X	X		X	X	X	X				Blood pressure and heart rate will be measured after the participant has been resting for 5 minutes. See Section 8.3.2 for vital signs.
12-lead ECG	<---------->										As clinically indicated. Participants must be in the recumbent position for a period of 5 minutes prior to the ECG. See Section 8.3.3 for ECG.

Pembrolizumab + ATRA											
Study Period	**Treatment**					**EOT[b]**	**Posttreatment**				**Notes**
	Cycle = 21 days		**Cycle = 42 days**				**Safety[b]**	**Follow-up[c]**		**Survival**	
Visit Timing/Cycle Number	**Cycle 1 (Neo-adjuvant Phase)**	**Cycle 2 (Neo-adjuvant Phase)**	**Post-Surgical Resection Visit to confirm Disease-free Status**	**Cycle 1 and Onwards[a] (Adjuvant Phase)**		**At D/C**	**30 Days After Last Dose**	**Q12W**	**Q24W**	**Q12W**	**All procedures and assessments are to be performed prior to administration of study intervention unless otherwise indicated. Refer to Section 8.12 for visit details.**
Cycle Day	**1**	**1**	**1**	**1**	**22[d]**						
Scheduling Window (Days)		**±3**	**±3**	**±3**	**±3**		**+7**	**±7**	**±7**	**±7**	
Hematology and chemistry laboratory assessment	X	X	X	X	X	X	X				Procedures/ assessments should be performed prior to all scheduled substudy visits. Every effort should be made to collect samples at the same time of day. LDH testing is needed. Laboratory samples collected within 3 days prior to the first dose of study intervention need not be repeated on C1D1.
Urinalysis	←----------	----------	----------	----------	----------→						As clinically indicated.
PT/INR and aPTT/PTT	←----------	----------	----------	----------	----------→						As clinically indicated for participants taking anticoagulant therapy.
T3, FT4, TSH		X		X		X					Presurgery/ Neoadjuvant Phase: Thyroid function tests will be performed at Cycle 2. Postsurgery/Adjuvant Phase: Thyroid function tests will be performed at Cycle 1 and every cycle thereafter and at the time of discontinuation (EOT). Free T3 is acceptable where Total T3 cannot be determined. After C1 of the Presurgery/ Neoadjuvant Phase, retrospective review of thyroid function testing results is allowed when the results are not available prior to dosing.

Pembrolizumab + ATRA											
Study Period	**Treatment**					**EOT[b]**	**Posttreatment**				**Notes**
	Cycle = 21 days		**Cycle = 42 days**				**Safety[b]**	**Follow-up[c]**		**Survival**	
Visit Timing/Cycle Number	**Cycle 1 (Neo-adjuvant Phase)**	**Cycle 2 (Neo-adjuvant Phase)**	**Post-Surgical Resection Visit to confirm Disease-free Status**	**Cycle 1 and Onwards[a] (Adjuvant Phase)**		**At D/C**	**30 Days After Last Dose**	**Q12W**	**Q24W**	**Q12W**	**All procedures and assessments are to be performed prior to administration of study intervention unless otherwise indicated. Refer to Section 8.12 for visit details.**
Cycle Day	**1**	**1**	**1**	**1**	**22[d]**						
Scheduling Window (Days)		**±3**	**±3**	**±3**	**±3**		**+7**	**±7**	**±7**	**±7**	
Pregnancy test (WOCBP only)		X	X	X		X	X	X			To be assessed prior to all scheduled visits. A serum or urine pregnancy test will be performed as indicated, prior to every cycle, up to 120 days after last dose of study intervention or 30 days after last dose if participant starts a new anticancer therapy, whichever comes first. See Appendix 11 for country-specific guidelines.
ECOG performance status		X		X	X	X	X				To be assessed prior to dosing during all scheduled visits.
Biomarkers/ Pharmacokinetics/Pharmacodynamics											
Blood for ctDNA analysis	X	X		X		X					Presurgery/ Neoadjuvant Phase: Collect predose on first dose of study intervention, and predose on C2D1. Postsurgery/Adjuvant Phase: Collect predose on C1D1, C2D1, C3D1, C5D1 & C7D1.
Blood for genetic analysis	X										Presurgery/ Neoadjuvant Phase: Collect predose on first dose of study intervention. See Section 8.9 for additional information.

Pembrolizumab + ATRA											
Study Period	**Treatment**					**EOT[b]**	**Posttreatment**				**Notes**
	Cycle = 21 days		**Cycle = 42 days**				**Safety[b]**	**Follow-up[c]**		**Survival**	
Visit Timing/Cycle Number	**Cycle 1 (Neo-adjuvant Phase)**	**Cycle 2 (Neo-adjuvant Phase)**	**Post-Surgical Resection Visit to confirm Disease-free Status**	**Cycle 1 and Onwards[a] (Adjuvant Phase)**		**At D/C**	**30 Days After Last Dose**	**Q12W**	**Q24W**	**Q12W**	**All procedures and assessments are to be performed prior to administration of study intervention unless otherwise indicated. Refer to Section 8.12 for visit details.**
Cycle Day	**1**	**1**	**1**	**1**	**22[d]**						
Scheduling Window (Days)		**±3**	**±3**	**±3**	**±3**		**+7**	**±7**	**±7**	**±7**	
Tumor blocks or slides	X		X								Presurgery/ Neoadjuvant Phase: Participants must submit a tumor sample at the end of Cycle 1 (Days 15-21) or C2D1 predose for biomarker analysis. A surgical resection specimen taken at Week 6 will also be submitted for pathologic assessment of resection specimens and for biomarker analysis. See Section 8.9 for details on biomarker assessments.

Pembrolizumab + ATRA											
Study Period	**Treatment**					**EOT[b]**	**Posttreatment**				**Notes**
	Cycle = 21 days		**Cycle = 42 days**				**Safety[b]**	**Follow-up[c]**		**Survival**	
Visit Timing/Cycle Number	**Cycle 1 (Neo-adjuvant Phase)**	**Cycle 2 (Neo-adjuvant Phase)**	**Post-Surgical Resection Visit to confirm Disease-free Status**	**Cycle 1 and Onwards[a] (Adjuvant Phase)**		**At D/C**	**30 Days After Last Dose**	**Q12W**	**Q24W**	**Q12W**	**All procedures and assessments are to be performed prior to administration of study intervention unless otherwise indicated. Refer to Section 8.12 for visit details.**
Cycle Day	**1**	**1**	**1**	**1**	**22[d]**						
Scheduling Window (Days)		**±3**	**±3**	**±3**	**±3**		**+7**	**±7**	**±7**	**±7**	

Abbreviations: AE = adverse event; BP = blood pressure; C1 = Cycle 1; C2 = Cycle 2; C3 = Cycle 3; C5 = Cycle 5; CIV = central imaging vendor; CT = computed tomography; ctDNA = circulating tumor DNA; ctRNA = circulating tumor RNA; D1 = Day 1; D15 = Day 15; D8 = Day 8; D/C = discontinue/discontinuing; ECG = electrocardiogram; ECHO = echocardiogram; ECOG = Eastern Cooperative Oncology Group; EOT = end of treatment; ePRO = electronic patient-reported outcome; FT4 = free thyroxine; FU = follow up; HBV = hepatitis B virus; HCV = hepatitis C virus; HIV = human immunodeficiency virus; HRQoL = health-related quality of life; ICF = Informed Consent Form; INR = international normalized ratio; MRI = magnetic resonance imaging; MUGA = multigated acquisition; PE = physical examination; PK = pharmacokinetics; PT = prothrombin time; Q3W = every 3 weeks; Q9W = every 9 weeks; Q12W = every 12 weeks; Q24W = every 24 weeks; QD = once daily; RECIST = Response Evaluation Criteria in Solid Tumors; RR = respiratory rate; SAE = serious adverse event; SIM = site imaging manual; T3 = triiodothyronine; TSH = thyroid-stimulating hormone; UPCR=urine protein-to-creatinine; WOCBP = women of childbearing potential

a After surgical resection of the tumor, participants will receive 8 cycles of adjuvant therapy with pembrolizumab monotherapy as soon as possible after surgery (interval between surgical resection and adjuvant pembrolizumab should not exceed 12 weeks; the interval between postsurgery baseline imaging and first dose of adjuvant dosing should not exceed 28 days; total treatment duration including neoadjuvant and adjuvant therapy of approximately 1 year) or until they experience disease recurrence, unacceptable AEs are reported, consent is withdrawn, death, intercurrent illness that prevents further administration of study intervention, investigator's decision to discontinue the participant, noncompliance with study intervention or procedure requirements, or administrative reasons requiring cessation of treatment, whichever occurs first.

b If EOT visit occurs ~30 days from last dose of study intervention, a 30-day Safety Follow-up visit is not required. In this situation, all procedures required at the 30-day Safety Follow-up visit and EOT are performed once and entered into the EOT visit only. End of treatment will be defined as the date when the participant discontinues all study interventions.

c For participants who DC study intervention for reasons other than documented disease recurrence, follow-up visits to monitor disease status continue until documented disease recurrence or initiation of a new anticancer therapy. Participants who D/C study intervention with documented disease recurrence proceed directly to Survival Follow up.

d Optional visit; visit and laboratory assessments should be completed as clinically indicated.

e Brain imaging is required for all participants at Screening. Magnetic resonance imaging is preferred; however, CT imaging will be acceptable if MRI is medically contraindicated.

Note: Each participant will receive neoadjuvant study intervention with an investigational treatment arm for up to approximately 5 weeks from first dose of study intervention followed by surgical resection of the tumor 6 weeks (42 days ± 7 days) from neoadjuvant C1D1 (also called definitive surgery with curative intent). Surgery should occur no sooner than approximately 5 weeks from the first dose of study intervention.

10.6.2.2 Section 2.4 Investigational Agent Pharmaceutical and Therapeutic Background

MK-7684 (anti-TIGIT)

MK-7684 is a humanized, antagonist IgG1 mAb that binds to the immune checkpoint receptor, TIGIT, and blocks the interaction between TIGIT and its ligand. This human IgG1 antibody is being developed as a cancer immunotherapeutic with the potential to be used as monotherapy or to be combined with pembrolizumab (a humanized anti-PD-1 receptor antibody) to increase the benefit to patients with various tumor types including melanoma.

TIGIT is an immunomodulatory receptor expressed primarily on activated CD4+ and CD8+ T-cells, NK cells, and NK T cells. Its structure reveals a single extracellular immunoglobulin domain, a transmembrane region, an ITT-like phosphorylation motif, and an ITIM.

TIGIT forms part of a comodulatory network that consists of a positive (CD226) and negative (TIGIT) immunomodulatory receptor on T-cells, and ligands (CD155 and CD112) expressed on tumor cells and antigen presenting cells [Levin, S. D., et al 2011]. Whereas CD226 is widely expressed on most immune cells, TIGIT is highly expressed on memory T-cells, Tregs, NK cells, and NK T cells [Dardalhon, V., et al 2005] [Stanietsky, N., et al 2013]. CD155/PVR/Necl5/Tage4 and CD112/PVRL-2 are 2 nectin family members that are widely expressed both on cells of the hematopoietic system and on fibroblasts and endothelial cells. Functionally, these receptor ligands are involved in cell adhesion and motility. CD155 is reported to be overexpressed in several tumor types and has been found to be induced by Ras activation and genotoxic stress [Carlsten, M., et al 2007] [Hirota, T., et al 2005] [Masson, D., et al 2001].

Significant single agent anti-TIGIT antitumor efficacy was observed in multiple preclinical tumor models as well as in combination with anti-PD-1 monotherapy. In addition, TIGIT is highly coexpressed with PD-1 on both CD4+ and CD8+ TILs including Tregs, in mouse and human tumors, and has been reported to be coexpressed with PD-1 and T-cell immunoglobulin and mucin domain containing-3 (Tim-3) on the TILs with the most exhausted phenotype [Chauvin, J. M., et al 2015] [Johnston, R. J., et al 2014]. Furthermore, enhanced antitumor efficacy is observed in preclinical models when an anti-TIGIT antibody is used with an anti-PD-1 antibody.

For additional information, refer to Section 2.1 of the MK-7684 IB.

V937

V937 is a live oncolytic virus preparation derived from the nongenetically altered prototype *Kuykendall* strain of V937 propagated in cell cultures. V937 is a naturally occurring human enterovirus. Coxsackieviruses are non-enveloped viruses with positive single-stranded RNA and 4 capsid proteins.

The primary mechanism by which V937 as an oncolytic virus can achieve differential infectivity between normal cells and neoplastic cells, in other words, can infect and kill

cancer cells while leaving normal cells relatively unaffected, is based on viral receptor surface expression. By targeting a viral receptor or receptor complex that is present or over-expressed on the surface of cancer cells compared to being absent or under-expressed on normal cells, degrees of selective cell destruction can, in principle, be achieved. Specifically, the rationale for the use of V937 as a potential therapeutic in human malignancy is based on its use of the proteins ICAM-1 and DAF for attachment and subsequent infection of a cell, the occurrence of DAF in abundance on the surface of many types of cancer cells, and the high expression rate of ICAM-1 on cancer cells (including breast cancer, head and neck cancer, prostate cancer, and melanoma), which are supported by results of studies in animal models.

Other current or former name(s) or alias(es) for this investigational agent are as follows: V937: CAVATAK®; Coxsackievirus A21 (CVA21).

For additional information, refer to Section 2.1 of the V937 IB.

MK-4830 (anti-ILT4)

MK-4830 is a human-ILT4 antagonistic monoclonal antibody (mAb) on an IgG4/Lambda framework. MK-4830 was selected based on its specificity to ILT4, its ability to block HLA G binding to ILT4 and its ability to rescue ILT4-related inhibitory function. The IgG4 isotype was chosen to minimize effector function and framework-mediated cross-linking ability leading to agonist activity. Based on in vitro data, MK-4830 has high affinity and potent receptor blocking activity to ILT4.

For additional information, refer to Section 2.1 of the MK-4830 IB.

MK-4280A (Coformulation of (MK-4280 + Pembrolizumab)

MK-4280 binds to the immune checkpoint receptor LAG-3 and blocks the interaction with its ligand, MHC class II. LAG-3 is an inhibitory immune modulatory receptor that regulates both effector T-cell homeostasis, proliferation and activation, and has a role in the suppressor activity of T_{regs} [Huang, C. T., et al 2004] [Baixeras, E., et al 1990] [Goldberg, M. V. and Drake, C. G. 2011]. LAG-3 is expressed on activated $CD8^+$ and $CD4^+$ T cells, T_{regs} and the Type 1 regulatory (Tr1) T-cell population, as well as on NK cells, NKT cells, and a subset of tolerogenic plasmacytoid dendritic cells [Huard, B., et al 1994] [Workman, C. J., et al 2009] [Gagliani, N., et al 2013]. Because of its proposed role on both effector T cells and T_{regs}, LAG-3 is 1 of several immune checkpoint molecules where blockade of both cell populations has the potential to enhance antitumor immunity [Andrews, L. P., et al 2017].

Given the observed enhanced antitumor activity of anti-LAG-3 when combined with PD-1 blockade in nonclinical models, the Sponsor has developed a coformulated product of MK-4280 and pembrolizumab (referred to as MK-4280A). MK-4280A is a fixed dose combination of MK-4280 and pembrolizumab antibodies. For additional information, refer to Section 2.1 of the MK-4280/MK-4280A IB.

Evidence of clinical efficacy of combination treatment with an anti-LAG and an anti-PD-1 monoclonal antibody was shown in data from a randomized, double-blind phase 2/3 trial (RELATIVITY-047, NCT03470922). In that study, the addition of relatlimab, a LAG-3 inhibitor, to nivolumab, a PD-1 inhibitor, significantly improved progression-free survival compared to nivolumab monotherapy in advanced melanoma, with a good safety profile [Tawbi, H. A., et al 2022].

ATRA (tretinoin)

ATRA is a vitamin A derivative that binds the retinoic acid receptor on MDSCs and differentiates immature monocytes into more mature dendritic cells [Nefedova, Y., et al 2007]. Tretinoin is the generic name of the trade name drug Vesanoid®. In some cases, health care professionals may use the trade name Vesanoid® or ATRA when referring to the generic drug name tretinoin. For additional information, refer to the tretinoin prescribing information.

ATRA is an FDA-approved commercially available retinoid that induces maturation of APL cells in culture. ATRA is a standard treatment currently approved for patients with APL. It is available in a 10 mg soft gelatin capsule for oral administration. The recommended dose (for APL) is 45 mg/m^2/day administered as 2 evenly divided doses until complete remission is documented.

ATRA is not approved in combination with pembrolizumab or for the treatment of patients with melanoma. Treatment with ATRA in combination with pembrolizumab has been investigated. A single arm, single institution, Phase I/II study (NCT03200847) enrolled 24 patients diagnosed with Stage IV melanoma and evaluated treatment consisted of 200 mg Q3W pembrolizumab plus the supplemental treatment of 150 mg/m^2 ATRA orally for 3 days surrounding each of the first four infusions of pembrolizumab. The combination of ATRA and pembrolizumab is well tolerated in melanoma patients and suggests that reducing MDSCs with ATRA may enhance the efficacy of pembrolizumab [McCarter, M., et al 2021].

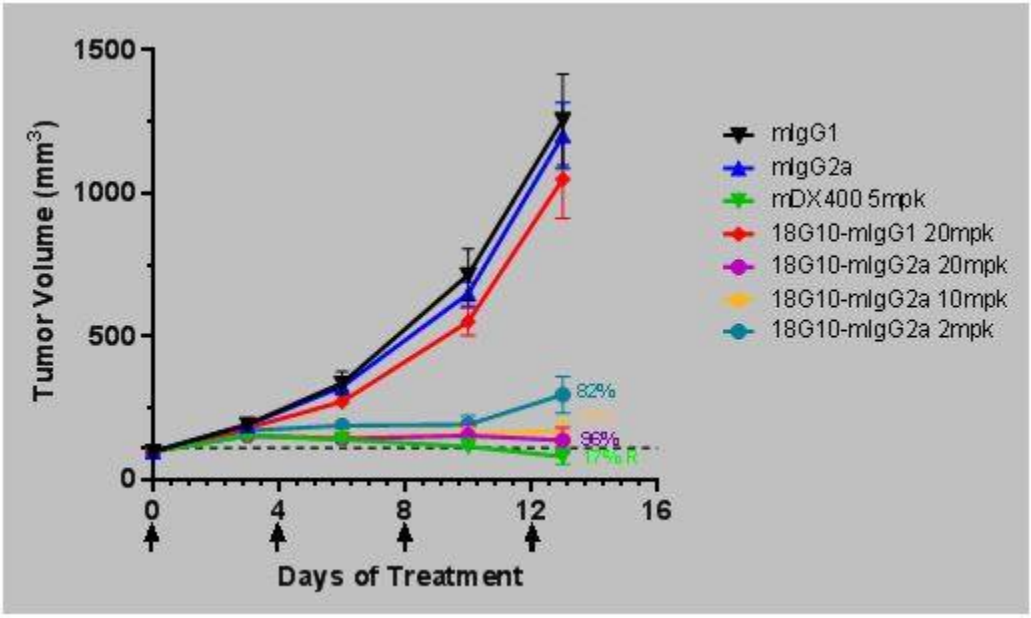
10.6.2.2.1 Section 2.4.1 Preclinical Studies

MK-7684 (anti-TIGIT)

Evaluation of TIGIT modulation as an approach to enhance tumor immunity was prompted by internal preclinical observations showing that antagonizing TIGIT has potent immunostimulatory effects. Results of studies performed at Merck demonstrated in vivo antitumor activity of rat anti-mouse TIGIT antibodies. In order to understand how antibody backbone differences may impact the antitumor efficacy of anti-TIGIT antibodies, parental rat anti-mouse TIGIT mAbs, or chimeric versions of these antibodies, were tested in multiple established (80 to 180 mm^3) syngeneic tumor models as single agents and in combination with an anti-mouse PD-1 mAb (muDX400). All anti-TIGIT mAbs tested resulted in a trend toward enhanced antitumor activity when combined with an anti-mouse PD-1 mAb (mDX400). The chimeric anti-TIGIT IgG2a mAbs (strong FcγR binding) showed the most robust single agent activity as compared to anti-TIGIT IgG1 (D265A mutant; minimal FcγR binding) mAbs and the most combination benefit when combined with anti-mouse PD-1.

A representative dose titration study demonstrating significant single agent efficacy of the anti-mouse TIGIT 18G10-mIgG2a antibody in the murine MC38 colon carcinoma tumor model is shown in Figure 3. Anti-mouse TIGIT (18G10-mIgG2a) displayed single agent activity comparable to anti-mouse PD-1 (mDX400). The MC38 tumor model has been classified as very responsive to anti-PD-1 treatment, and MC38 model selection was based on baseline TIGIT protein surface expression on CD8+ and CD4+ TILs, baseline mRNA expression of CD155, and induction of TIGIT and CD155 expression in tumors after anti-PD-1 treatment.

Figure 3 Results of a Dose Titration Study of Anti-TIGIT 18G10-IgG2a in the MC38 Colon Carcinoma Mouse Model



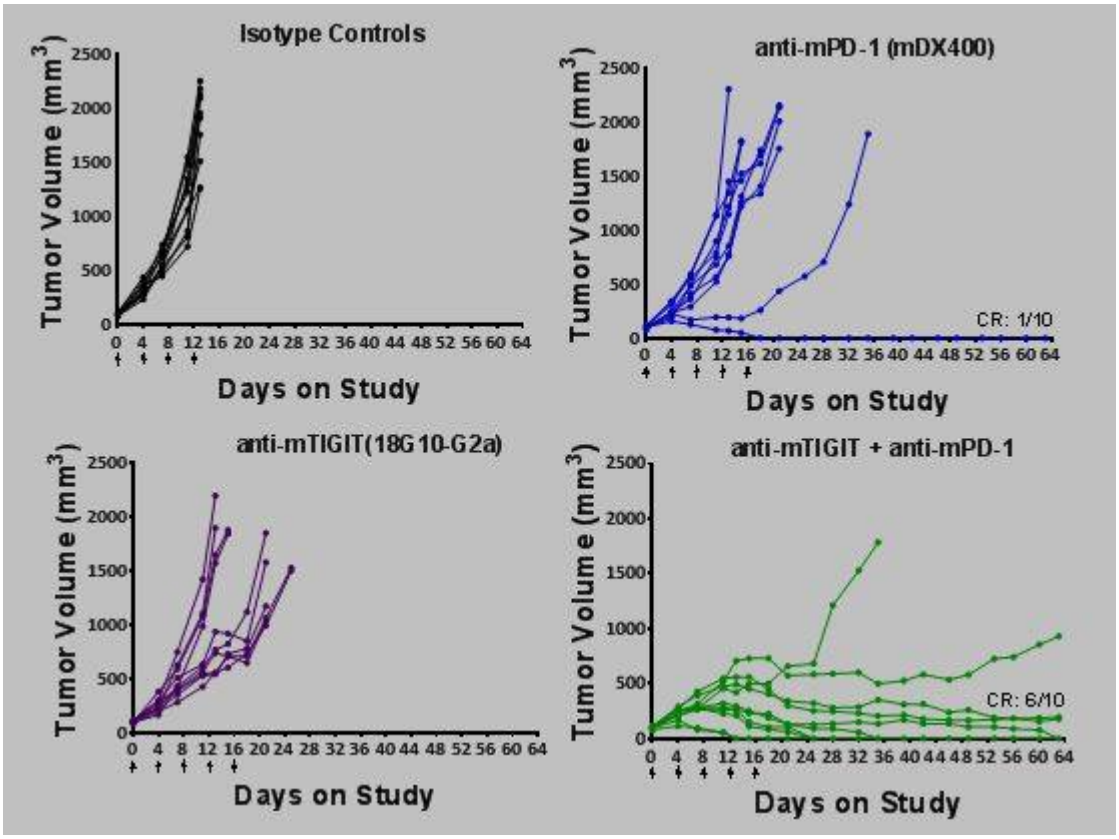
Abbreviations: Ig = immunoglobulin; mpk = mg/kg; PD-1 = programmed death 1; TIGIT = T-cell immunoglobulin and immunoreceptor tyrosine-based inhibitory motif.

C57BL/6 mice bearing MC38 mouse syngeneic tumors (mean tumor volume at start of treatment 98 mm^3) were administered anti-mouse TIGIT antibodies at doses of 2 mg/kg, 10 mg/kg, or 20 mg/kg, anti-mouse PD-1 (mDX400) at a dose of 5 mg/kg, or isotype controls every 4 days for 5 cycles (n=10/group). Tumor volume curves are presented for the average of 10 animals within each group. The anti-mouse TIGIT 18G10-IgG2a antibody resulted in 82%, 94%, and 96% tumor growth inhibition at the 2 mg/kg, 10 mg/kg, and 20 mg/kg doses, respectively. Anti-mouse PD-1 (mDX400) resulted in 17% tumor regression at the 5 mg/kg dose.

A representative study evaluating anti-TIGIT treatment as a single agent and in combination with anti-PD-1(muDX400) therapy in the murine subcutaneous CT26-tumor bearing model is shown in Figure 4. The CT26 colon carcinoma model has been classified as partially responsive to anti-PD-1 treatment with only partial tumor growth inhibition observed. CT26 model selection was based on baseline TIGIT protein surface expression on CD8+ and CD4+ TILs, baseline mRNA expression of CD155, and induction of TIGIT and CD155 expression in tumors after anti-PD-1 treatment. Combination treatment of 18G10-G2a with anti-PD-1 (mDX400) demonstrated significantly enhanced efficacy and survival as compared to

anti-TIGIT and anti-PD-1 monotherapy treatments. Animals with complete responses showed curative protection from tumor rechallenge, consistent with the development of immune memory (data not shown).

Figure 4 Antitumor Efficacy of Anti-TIGIT 18G10-IgG2a as a Single Agent and in Combination With Anti-PD-1 (muDX400) Therapy in the Murine Subcutaneous CT26 Colon Carcinoma Tumor-bearing Model



Abbreviations: CR = complete response; Ig = immunoglobulin; PD-1 = programmed death 1; TIGIT = T-cell immunoglobulin and immunoreceptor tyrosine-based inhibitory motif.

CT26 tumor-bearing BALB/cAnN mice (mean tumor volume at start of treatment ~100 mm3) were administered anti-TIGIT antibody (18G10-G2a) at a dose of 18 mg/kg and an anti-murine anti-PD-1 antibody (mDX400) at a dose of 10 mg/kg by intraperitoneal injection, every 4 days for 5 cycles. Tumor volume curves are presented for individual animals within each group (n=10/group).

These studies (and others) have demonstrated that anti-mouse TIGIT mAb treatment can augment antitumor T-cell responses and induce tumor rejection in several murine tumor models when used alone and in combination with an anti-mouse PD-1 mAb. In these studies, the combination of anti-mouse TIGIT and anti-mouse PD-1 led to an increased ratio of Teffs to Tregs in the tumor, but these effects were not observed in the draining lymph node (data not shown).

The results of studies conducted at Merck using chimeric anti-mouse TIGIT mAbs on the IgG2a backbone revealed that administration of single agent anti-mouse TIGIT mAbs are efficacious in treating multiple established subcutaneous murine tumors and that combining anti-mouse TIGIT 18G10-G2a with anti-mouse PD-1 leads to enhanced combination benefit over either single agent alone.

The potential toxicity profile of MK-7684 identified in nonclinical studies in nonhuman primates relates to transiently decreased lymphocyte or neutrophil counts in blood, and proinflammatory responses (eg, elevation of serum fibrinogen). A limited body of published literature describing TIGIT (Vstm3)-deficient KO mice indicate increased sensitivity to autoimmune diseases, using a model of myelin oligodendrocyte glycoprotein-induced autoimmune encephalomyelitis [Levin, S. D., et al 2011]. While specific target organs have not been identified for anti-TIGIT antibody, generally, immune-mediated adverse effects for immune-stimulating agents, including anti-TIGIT therapy, are anticipated to be observed in some patients.

Toxicology studies of MK-7684 monotherapy and pembrolizumab monotherapy in nonhuman primates did not demonstrate overlapping toxicities of these monoclonal antibodies. Moreover, using an in vitro cytokine release assay, the combination of MK-7684 and pembrolizumab did not enhance cytokine induction in human peripheral blood monocytes. Potential increase in immune-mediated adverse effects resulting from the combination of MK-7684 and pembrolizumab, however, cannot be ruled out.

For additional information, refer to the MK-7684 IB.

V937

In several SCID mouse animal models, V937 has demonstrated significant efficacy in reducing and eliminating solid human tumor xenografts using cancer cell lines that express high levels of ICAM-1 and/or DAF.

The major V937 toxicity observed in immunodeficient mice is HLP resulting from localized myositis. The capacity of Coxsackie group A viruses to cause flaccid paralysis in suckling mice was a key defining characteristic used to originally define the viral group. This paralysis was seen regardless of the route of administration, resulting from dramatic myopathy in skeletal muscles. In contrast to the findings with immunodeficient mice, challenge of Nu/Nu mice or immunocompetent mice (BALB/c and C57BL/6) with V937 failed to induce any signs of paralytic illness, suggesting myopathic effects are confined to severely immune-compromised animals. In clinical experience to date, no signs of the development of myositis have been observed in participants administered V937 by either intratumoral, intravesicular, or IV routes.

In immunocompetent animals, a 2-dose intraperitoneal (IP, 10^9 TCID50/dose) and single-dose IV (10^6 TCID50/dose) test for toxicity was performed in rats over a 14-day observation period. No clinically significant abnormalities in any biochemical parameters following administration of either of the V937 doses by either route compared to the saline controls were reported. Hematological profiles were similar across all groups with the exception of

the V937-treated males, which had significantly higher platelet counts than the saline-treated controls, although the results for both groups were well within the reference interval. All animals showed weight gain with no difference in mean weight between the groups. No gross or histological abnormalities attributable to the virus were found at necropsy.

A transgenic animal model expressing Hu Mu chimeric ICAM-1 in BALB/c immunocompetent mice was developed that appears to have the necessary characteristics for evaluating the pharmacology and nonclinical safety of V937. A single-dose challenge of Wt and Hu/Mu ICAM-1 Tg BALB/c mice with V937 (~10^7 TCID50) via IN and IP administration over a 14-day observation period did not induce clinical signs of viral infection or development of HLP. All animals showed weight gain over the experimental period, and no gross or histological abnormalities attributable to the virus were found at necropsy. Greater levels of infectious V937 and V937 viral RNA persisted in the lungs and BAL washings of Tg mice compared to Wt mice. Coupled with the finding that neutralizing anti-V937 antibody was detected in the serum of Tg mice and not Wt mice challenged with V937 via the IN route (route of natural infection), it is assumed that some level of V937 replication has probably occurred in the lungs of Tg mice following either IN or IP challenge.

In a repeat dose study, chimeric Hu/Mu ICAM-1 BALB/c mice were administered 10 SC doses of V937 (2.5 x 10^7 TCID50 or approximately 1.25 × 10^9 TCID50/kg assuming a 20 g mouse) or sucrose/saline (controls) over Days 1 to 22. No remarkable treatment-related clinical observations, no apparent effects on body weight, and no apparent changes in any evaluated clinical chemistry or hematology parameters were reported. There was no apparent toxic effect of V937, including no signs of HLP or other forms of myositis. On Day 9, anti-V937 antibody titers were 1:10 (the limit of detection for the assay) in serum in control animals and >1:120 in V937-treated animals. On Day 24, serum samples in CVA214-treated animals had anti-V937 antibody titers of >1:57. Gross pathology and histopathology examinations of the various organs/tissues showed no apparent changes that could be attributed to SC administration of V937. The results of a second study using the same dose regimen suggested that V937 treatment resulted in a minor exacerbation in the extent of inflammatory changes at the injection site. The NOAEL of SC-administered V937 to male and female chimeric Hu/Mu ICAM-1 transgenic BALB/C mice was ~1.25 × 10^9 TCID50/kg.

Repeated IV dosing of V937 in chimeric Hu/Mu ICAM-1 BALB/c mice was undertaken to support a future clinical study investigating IV V937 administration to late-stage cancer patients. Clinical pathology and histopathology examinations of the various organs/tissues showed no apparent changes that could be attributed to IV administration of V937, except for the transient appearance of inflammatory cells in the heart, which were graded as minimal in intensity.

In addition, repeated intrahepatic injections of V937 were administered to Hu/Mu ICAM-1 transgenic mice to support direct injection of liver metastases under image guidance in advanced cancer patients. A maximum total exposure of 3 x 10^9 TCID50/kg was administered over 3 intrahepatic injections, given 1 week apart, prior to a 28-day recovery period. No significant treatment-related clinical observations, clinical chemistry, organ weight, or histomorphological findings were reported in this study.

Nonclinical studies investigating the coadministration of intratumoral or IV V937 with 2 different immunostimulatory antibodies, showed that, regardless of the method of administration, V937 used in combination with anti-PD-1 and/or anti-CTLA-4 blocking antibodies was generally well tolerated in immunocompetent mouse models of melanoma and NSCLC, with gross observations not revealing AEs relating to the agents tested. These studies were the basis for subsequent clinical studies assessing V937 in combination with different checkpoint inhibitors.

For additional information, refer to the V937 IB.

MK-4830 (anti-ILT4)

MK-4830 binds to human ILT4 and enhances immune cell activated proinflammatory cytokine production in human primary cell based assays and reverses ILT4 mediated immune suppression in mouse engineered cell based assays. In healthy humans, ILT4 protein is detected in the myeloid compartment of immune cells comprised mostly of monocytes and granulocytes. In tumor samples from cancer patients, ILT4 protein is detected in tumor infiltrating myeloid cells in addition to monocytes and granulocytes. MK-4830 does not bind other human ILT family proteins tested or mouse ortholog PirB, nor does it bind rhesus monkey PBMC. Induction of cytokine release by MK-4830 as a single agent or in combination with pembrolizumab was comparable to that induced by a negative control therapeutic antibody in human PBMC and whole blood assays that assess potential for cytokine release. The level of binding to primary human and rhesus monkey RBCs and platelets was comparable between MK-4830 and negative control antibodies. MK-4830 does not cause ADCC or immune cell depletion in cell based assays and human whole blood in vitro assays. MK-4830 has significant single agent antitumor efficacy in the humanized mouse SK MEL 5 tumor model. MK-4830 has linear PK properties in rhesus monkeys following IV administration.

In light of undetectable relevant binding of MK-4830 to rhesus PBMC, the potential for off target effects upon administration of MK-4830 was assessed in rhesus monkey in a GLP compliant 4 week repeat dose toxicity study, followed by an exploratory 3 month study in radiotelemetry-instrumented rhesus monkeys. There were no findings to preclude evaluation of MK-4830 in human clinical studies.

In the 4 week GLP study, rhesus monkeys were administered MK-4830 IV at doses of 0, 2, 20, or 200 mg/kg once per week for a total of 4 doses followed with a 7 week treatment free period. MK-4830 was well tolerated in all animals. Findings detected in animals treated with MK-4830 were limited to minimal to mild segmental thickening of the intima in coronary arteries and/or branches of the hepatic artery in 1 or 2 monkeys in each dose group at the end of the dosing period that represented a reversible change (not observed at the end of the treatment-free period) of low severity and not associated with any compromise to integrity of the vessels (intact endothelial surface, intact internal elastic lamina, and intact tunica media and adventitia). There was no evidence of cellular accumulation or presence of lipid material or mineralization within the affected intima. Immunohistochemical staining with anti IgM or anti IgG showed no specific staining of intima, tunica media, or adventitia in affected

arteries, confirming an absence of immune complex deposition. The segmental and reversible changes in individual animals were not considered adverse.

In the exploratory 3 month repeat dose terminal cardiovascular telemetry study, MK-4830 was IV administered at 20 mg/kg once weekly for approximately 3 months to conscious, adult male and female, telemetered, rhesus monkeys, which were euthanized at the end of dosing period for histopathology evaluation of major organs and selected aorta and artery tissues. There were no test article related effects on any cardiovascular parameters monitored throughout the 3 month recording period, including BP parameters (group systolic BP, diastolic BP, mean BP) or PP, HR, ECG intervals (PR, QRS, RR, uncorrected QT, and HR corrected QTcB intervals), body temperature, or SLA. There were no test article related effects on ECG morphology following automated and manual review of ECG telemetry waveforms and surface ECGs. All animals survived to the scheduled termination and no test article related clinical observations, clinical pathology, or histopathology findings were observed.

Based on the 4 week repeat dose rhesus monkey toxicity study, the NOAEL of MK-4830 was at 200 mg/kg/week, corresponding to a mean exposure (AUC0 168h) of 923,000 µg/mL/h. A conservative approach to determining the FIH starting dose was utilized due to lack of pharmacologically relevant species. The selection of the MK-4830 FIH dose was based on an integrated approach including the in vitro binding of MK-4830 to human peripheral blood monocytes and granulocytes and predictions of human exposure based on rhesus monkey PK data. The starting dose of 0.045 mg/kg in patients with cancer represents a 2680 fold exposure margin to the NOAEL in the repeat dose rhesus monkey toxicity study.

For additional information, refer to the MK-4830 IB.

MK-4280A (Coformulation of MK-4280 + Pembrolizumab)

The expression of LAG-3 was evaluated in blood, normal tissues, and tumor tissues in human, cynomolgus monkey, and mouse (PD006). The qRT-PCR results revealed that LAG-3 mRNA is expressed primarily in lymphoid cells from lymphoid organs such as the appendix, lymph node, spleen, tonsil, and thymus in humans, cynomolgus monkeys, and mice. The expression pattern of LAG-3 mRNA was similar across all 3 species.

Expression of LAG-3 was evaluated using IHC in 10 syngeneic mouse tumors: CT26, 4T1, RENCA, MB49, CM3, EMT6, B16F10, LL/2, and MC38. Cells positive for LAG-3 uniformly had lymphoid morphology and were observed in all tumors except B16F10. Cancer cells expressing LAG-3 were not observed. Expression of LAG-3 was also evaluated using IHC in 10 panels of human tumors including 82 melanomas, 104 NSCLCs, 33 glioblastomas/high-grade gliomas, 41 head and neck cancers, 73 gastric cancers, 34 bladder cancers, 67 liver cancers, 73 triple negative breast cancers, 112 CRCs, and 76 esophageal cancers. All LAG-3 positive cells had lymphoid morphology; LAG-3 positive cancer cells were not observed. The highest percentage of samples scored with moderate or higher LAG 3 positive cell frequency was found in esophageal cancer, melanoma, and both the squamous and large cell subtypes of NSCLC.

The antitumor activity of 28G10 mG1, which lacks Fc effector function, was tested in vivo as a single agent and in combination with the anti-mouse PD 1 antibody muDX400 in the MBT 2 mouse syngeneic tumor model. Treatment with anti-LAG 3 28G10 mG1 alone did not show significant antitumor efficacy compared with the isotype treatment group over the study period with no CRs. Significant antitumor efficacy was noted with anti-PD 1 muDX400 treatment relative to isotype control treatment over the entire study period including CRs. Three studies (15 M320 6937, 15 M320 7007, 15 M320 7210) were performed that showed augmented efficacy of the combination therapy.

Coblockade of PD-1 and LAG-3 with blocking antibodies in syngeneic mouse tumor models was reported to result in greater tumor inhibition over either single agent in the Sal1N fibrosarcoma and MC38 colon adenocarcinoma tumor models [Woo, S. R., et al 2012]. However, coblockade had little effect on the poorly immunogenic B16F10 melanoma model [Chen, S., et al 2015]. Blockade of LAG-3 alone had modest antitumor activity in the MBT-2 bladder syngeneic mouse tumor model whereas coblockade of LAG-3 and PD-1 (with 28G10-mG1) resulted in greater numbers of animals with CRs and fewer numbers of animals with progressive disease compared with murinized anti-PD-1 treatment alone in 2 independent studies. Loss of drug exposures over the course of treatment, preferentially in the combination treatment group, may underestimate the combination antitumor benefit. Curative murinized anti-PD-1 treatment or murinized anti-PD-1 and anti-LAG-3 combination treatment resulted in the establishment of long-term immune memory to MBT-2 tumor rechallenge.

For additional information, refer to the MK-4280/MK-4280A IB [Edition 8].

ATRA (tretinoin)

Preclinical data suggest that ATRA abrogates the suppressive effects of MDSCs isolated from both human cancer patients and mouse cancer models in vitro [Breitman, T. R., et al 1981] [Hittelman, W. N., et al 1988]. Furthermore, mice treated with ATRA have decreased frequencies of MDSCs and increased frequencies of dendritic cells that improve T-cell responses against tumors [Kusmartsev, S., et al 2003] [Lee, J. M., et al 2012] [Song, X., et al 2011].

Preliminary research has identified a population of immunosuppressive MDSCs (Lineage negative, HLA-DR negative, CD11b positive, and CD33 positive) that are increased in Stage IV melanoma patients relative to healthy donors. To establish MDSCs as a potentially important contributor to immunosuppression in melanoma patients, the frequency and function of immunosuppressive MDSCs was compared in the peripheral blood of healthy donors, Stage I, and Stage IV melanoma patients [Jordan, K. R., et al 2013]. Significant increases were found in the frequency of MDSCs in the peripheral blood of Stage IV melanoma patients compared with healthy donors. The frequency of these cells correlated with an increase in regulatory T-cells and an increased level of IL-6 and IL-8 cytokines in the peripheral blood. Furthermore, patients with clinical disease progression had an increased frequency of these cells, and patients with a high frequency of MDSCs had decreased overall survival and an increased risk of death (hazard ratio 4.83, p=0.016). This increased risk of death was independent of other clinical factors including age, gender, and treatment

regimens. Finally, it was shown that MDSCs isolated from Stage IV melanoma patients were significantly more immunosuppressive than those isolated from healthy donors. Overall, these data suggest that MDSCs may be a significant contributor to immunosuppression in melanoma patients and that targeting these cells in a combinatorial approach may improve immune responses against melanoma.

ATRA induces the differentiation of immature monocytes into more mature cells of the dendritic cell lineage [Nagaraj, S., et al 2009] [Sendo, D., et al 2003] [Breitman, T. R., et al 1981]. In agreement with these results, preliminary data suggests that ATRA induces maturation of in vitro-derived MDSCs. Monocytes cultured from healthy donors with GM-CSF/IL-4 or GM-CSF/IL-6 were used to generate mature monocytes of the dendritic cell lineage (a control population) or MDSCs, respectively [Lechner, M. G., et al 2010] [Tedder, T. F. 1997]. In contrast to the control population, MDSCs express low levels of HLA-DR and maintain high expression of CD14, consistent with the phenotype of an immature monocyte. Furthermore, MDSCs express increased levels of molecules that inhibit T-cell responses such as Arginase I, NOX1, iNOS, and PD-L1. Conversely, MDSCs cultured with ATRA are phenotypically more similar to the control dendritic cell population, expressing decreased levels of inhibitory molecules and CD14 and increased levels of HLA-DR. Most importantly, MDSCs derived in vitro with GM-CSF and IL-6 suppress T-cell proliferation. However, treatment of these MDSCs with ATRA eliminates their suppressive effects and restores T-cell proliferation. Finally, MDSCs express higher levels of retinoic acid receptors RAR and RXR, suggesting that ATRA treatment may selectively target these inhibitory cells.

10.6.2.2.2 Section 2.4.2 Ongoing Clinical Studies

MK-7684 (anti-TIGIT)

Protocol 7684-001-08 is the first-in-human clinical study with MK-7684.

For additional information, refer to the MK-7684 IB. As accumulating safety data from human participants are available for MK-7684, the reference safety information of expected related AE terms (ie, AR) using current MedDRA Preferred terms will be updated in the IB.

V937

The clinical development of V937 so far has involved assessing for safety and efficacy signals using 3 different routes of administration: intratumoral, intravesicular, and IV. To date, 299 participants with different cancer indications (melanoma, head and neck cancer, prostate cancer, NSCLC, metastatic bladder cancer, and uveal melanoma) have received 1 or more doses of V937 in 11 ongoing or completed clinical studies, either as V937 monotherapy or in combination with a checkpoint inhibitor. Treatment has been well tolerated and the majority of treatment-related AEs were Grade 1 or 2 in severity.

Initial Phase 1 clinical studies explored single-dose and dose escalation designs using intratumoral administration of V937 in participants with advanced melanoma (Studies PSX-X01, PSX-X02, and PSX-X03) or head and neck cancer (Study PSX-X06). A multicenter, single-arm Phase 2 study conducted in the United States (VLA-007/008) further assessed the

safety and efficacy of intratumoral V937 in participants with Stage IIIC-IV melanoma receiving up to 19 sets of injections at a maximum dose of 3×10^8 TCID50 (about 4.5×10^6 TCID50/kg for a 70-kg participant). In this 57-participant study, the intratumoral administration was well tolerated. The ORR was 28.1% (16/57) with 8 participants achieving a CR and 8 a PR. Responses were seen in injected, noninjected nonvisceral, and distant, noninjected visceral lesions. Treatment-related AEs were limited to Grade 1 or 2 in severity, and included injection site pain and erythema, fatigue, chills, pyrexia, pain, myalgia, headache, and hyperhidrosis. A substudy of 13 additional participants receiving the same treatment regimen looked at changes in the tumor microenvironment through paired Baseline and Day 8 biopsies. V937 treatment significantly upregulated a number of interferon-response and immune checkpoint inhibitory genes in injected melanoma lesions, including CXCL10, CXCL11, CTLA-4, PD-L1, LAG-3, and IDO. More recently, the same intratumoral V937 regimen has been given in combination with either ipilimumab (Study VLA-013) or pembrolizumab (Study VLA-011) in participants with Stage IIIB-IV melanoma. Clinical responses in both studies have been promising, and all AEs related to V937 have been limited to Grade 1 or 2 in severity. Four participants in Study VLA-011 each experienced a Grade 3 AE related to pembrolizumab. One of these participants also experienced a fatal (Grade 5) event of *E. coli* septic shock, this was considered unrelated to V937. The incidence of participants with Grade 3 to 5 AEs is 13% (4/31). In Study VLA-013, 8 participants experienced Grade 3 or 4 AEs that were considered related to ipilimumab treatment. This incidence of participants with Grade 3 to 4 AEs (7/47 or 15%) is not different to what one would expect in this patient population treated with ipilimumab. In summary, a total of 166 participants have received a total of 3218 intratumoral V937 doses in 7 completed or ongoing clinical studies.

V937 has been given via intravesicular administration in 15 participants with newly diagnosed NMIBC. In Study VLA-012, V937 was given in a dose-escalation fashion, in 1 or 2 doses, with or without a prior intravesical administration of low-dose (10 mg) mitomycin C. Serial cystoscopy identified viral-induced hemorrhage and immune inflammation of the tumor microenvironment, and viral replication within the bladder tumors was highlighted by detection of secondary viral peak loads in urine taken in the days following treatment. The treatment was well tolerated with only 3 treatment-related AEs: Grade 1 abdominal distension, chills, and nausea.

V937 has been given via IV administration in 3 studies to date, with 118 participants having received a total of 768 infusions of V937. The first study (PSX-X04) assessed 1 or 2 infusions of 5 escalating doses in 10 participants with advanced prostate, melanoma, or breast cancer. Participants received V937 up to 3.3×10^9 TCID50. The treatment was well tolerated, with treatment-related AEs limited to Grade 1 facial flushing, flulike symptoms, and arthralgia. Study VLA-009 is a multicenter 2-Part Phase 1 study of IV administered V937 either as monotherapy, or in combination with pembrolizumab. In Part A, V937 alone was given in a dose-escalation fashion at 1.0×10^8 TCID50, 3.0×10^8 TCID50, or 1.0×10^9 TCID50 per infusion. Participants had advanced melanoma, castrate-resistant prostate cancer, NSCLC, or metastatic bladder cancer. No dose-limiting toxicities were seen, and the infusions were well tolerated, with no Grade 3 or higher treatment-related AEs. Participants in the final cohort were required to have a biopsy at Day 8, and V937 was

detected in biopsies from participants with melanoma, NSCLC, and bladder cancer. In Part B, V937 was given in the same 3 escalating doses in participants with NSCLC or bladder cancer, but in combination with pembrolizumab. No dose-limiting toxicities were noted, and AEs related to V937 or pembrolizumab were mainly Grade 1 or 2 in severity. Four Grade 3 events related to V937 were reported in 3 participants, or 4% (3/85) of participants treated. Nineteen Grade 3 AEs related to pembrolizumab were reported in 9 participants, or 11% (9/85) of treated participants. However, the nature and frequency of these events were not unexpected for pembrolizumab monotherapy. Enrollment has been completed and participant follow-up is ongoing. Study VLA-024 is a multicenter study of IV V937 at 1.0×10^9 TCID50 per infusion in combination with ipilimumab, in participants with uveal melanoma metastatic to liver. One Grade 3 AE related to ipilimumab has been reported, but no dose-limiting toxicities have occurred to date, with the AEs similar in frequency and grade to what would be expected for each drug given as monotherapy.

V937 is a naturally occurring virus that induces mild upper respiratory tract symptoms during infection in humans. As such, a potential risk is that participants may excrete virus from the respiratory tract or gastrointestinal tract for some days after V937 administration. In Study VLA-007/008, where V937 was administered intratumoral, nearly all participants displayed some levels of V937 RNA in the serum directly following viral injection, which in most cases decays before the following viral administration. Viral excretion was monitored through collection of samples and swabs of injection sites and outer dressings from many of the participants tested to date. No V937 viral RNA was detected in any throat swab or sample of urine, feces, or sputum. V937 viral RNA was detected in 33 of 493 dressing swabs. Low levels of V937 RNA have been detected in some swabs of the injection sites from 33 participants (no infectious virus detected, except for 13 samples from 7 participants at <320 TCID50/mL and 8 samples from 4 participants at <10,000 $TCID_{50}$/mL of transport media).

In Study VLA-009 Part A, where V937 was administered IV, 446 excretion samples were tested and 17 were positive for viral RNA. Of these 17, only 3 samples (0.7%) were positive for infectious virus (a minimal level of infectious V937 of <320 TCID50/mL was detected in 1 fecal and 2 sputum samples). No infectious V937 was detected in urine or infusion site swabs. In VLA-009 Part B/KEYNOTE-200, where V937 is administered IV in combination with pembrolizumab, 2531 excretion samples have been tested, and 109 were positive for viral RNA. Of these 109 samples, 32 (1.3%) were positive for infectious virus (10 sputum, 10 urine, 7 throat swab, 5 fecal). The majority (26/32) of these samples expressed low levels of infectious V937 (<320 TCID50). Five of 32 excretion samples (3 sputum, 1 fecal, and 1 throat swab) expressed <10,000 TCID50/mL and 1 sample of 32 (sputum) expressed <50,000 TCID50/mL during Days 3 to 8 and together with all excretion samples after Day 15 have not displayed detectable levels of infectious V937. Such a finding is not unexpected, as V937 neutralizing antibodies start to develop in the second week after treatment initiation. These results from study VLA-009 indicate that the risk for viral transmission remains low, with an overall excretion sample positive rate of 1.2%.

No known cases of V937 transmission from a V937-treated participant to a health care worker or to a participant in close contact have been confirmed. To date, there have been

18 reported cases of suspected V937 transmission, with samples submitted for testing in 14 of these, and all were found to be negative for V937.

For additional information, refer to the V937 IB. As accumulating safety data from human participants are available for V937, the reference safety information of expected related AE terms (ie, AR) using current MedDRA Preferred terms will be updated in the V937 IB.

MK-4830 (anti-ILT4)

MK-4830-001 is the first-in-human clinical study with MK-4830.

For additional information, refer to the MK-4830 IB. As accumulating safety data from human participants are available for MK-4830, the reference safety information of expected related AE terms (ie, AR) using current MedDRA Preferred terms will be updated in the IB.

MK-4280A (Coformulation of MK-4280 + Pembrolizumab)

For details on MK-4280 and MK-4280A, refer to the MK-3280/MK-3280A IB [Edition 8].

Study MK-4280-001 is evaluating the MK-4280A coformulation versus sequential administration of MK-4280 and pembrolizumab. As of the data cutoff date (21-MAR-2022), there were no remarkable differences in the frequencies or types of AEs observed for participants receiving MK-4280A (coformulation of 800 mg MK-4280 and 200 mg pembrolizumab) compared with those of participants receiving sequential administration of 800 mg MK-4280 and 200 mg pembrolizumab.

The RP2D for MK-4280 administered sequentially and in coformulation with pembrolizumab (ie, MK-4280A) is 800 mg.

Safety data from all participants enrolled in the MK-4280-001 study at the time of the data cutoff (21-MAR-2022) indicated that data were available from 476 participants including 38 participants treated with monotherapy (Parts A and B, including 9 participants who crossed over from monotherapy to MK-4280 + pembrolizumab combination therapy) and 359 participants treated with MK-4280 and 200 mg pembrolizumab (administered sequentially [323 participants] or as the MK-4280A coformulation [36 participants]) plus an additional 40 participants from MK-4280 + pembrolizumab + chemotherapy. As of the data cutoff date, there were no remarkable differences in the frequencies or types of AEs observed for participants receiving MK-4280A (coformulation of 800 mg MK-4280 and 200 mg pembrolizumab) compared with those of participants receiving sequential administration of 800 mg MK-4280 and 200 mg pembrolizumab.

In MK-4280-001, the most common AEs for participants receiving MK-4280 alone (occurring in >20% of participants) include fatigue (44.7%), nausea (26.3%), and cough (23.7%). The most common AEs for participants receiving MK-4280 in combination with pembrolizumab (occurring in >20% of participants, excluding the chemotherapy arm) include fatigue 27.2%), nausea (22.8%), and decreased appetite (20.7%).

Of the 378 participants (excluding the chemotherapy arm), 254 participants (64.0%) had at least 1 drug-related AE per investigator assessment: 24 participants (63.2%) in the monotherapy arm and 232 participants (63.0%) in the combination therapy arm (see Section 5.5.1.1 in the MK-4280/MK-4280A IB [Edition 8]). The only drug-related AE per investigator that occurred in ≥10% of participants receiving MK-4280 alone was fatigue (18.4%). Drug-related AEs as per investigator assessment occurring in >10% of participants receiving MK-4280 in combination with pembrolizumab included hypothyroidism (18.2%) and fatigue (16.0%).

A total of 131 participants (33.0%), excluding the chemotherapy arm, had an SAE on study: 8 participants (21.1%) in the monotherapy arm and 123 participants (33.4%) in the combination therapy arm (see Section 5.5.1.1 in MK-4280/MK-4280A IB [Edition 8]). A total of 25 participants (6.3%), excluding the chemotherapy arm, had SAEs deemed to be related to study treatment by the investigator, including 1 participant (2.6%) receiving MK-4280 monotherapy and 24 participants (6.5%) receiving combination therapy.

An analysis comparing the incidence of AEOSIs was similar in participants receiving MK-4280A with that in participants receiving the same doses of MK-4280 and pembrolizumab administered sequentially. Thus, the safety results of the coformulation are generally consistent with the established safety profile of pembrolizumab monotherapy.

Data from MK-4280-001 in solid tumors showed that the safety, efficacy, and PK of MK-4280A is generally similar to that of the sequentially administered MK-4280 and pembrolizumab.

ATRA (tretinoin)

Each year, >23,000 patients with advanced melanoma are eligible for systemic treatment after experiencing disease progression on a previous line of therapy for metastatic disease. According to recent data, roughly 12% of those patients (±2300) progressed on CTLA-4+PD-1. This number continues to grow with approximately 1 in every 3 newly diagnosed patients currently receiving CTLA-4+PD-1 as their first-line therapy.

MDSCs are potent suppressors of antitumor immunity and are frequently associated with poor outcomes in melanoma patients treated with immune checkpoint inhibitors. Inducing the differentiation of MDSCs using ATRA reduces MDSC frequency and function.

A single arm, single institution, phase 1/11 study (NCT03200847) enrolled 24 patients diagnosed with stage IV melanoma [McCarter, M., et al 2021]. Eligible patients were over the age of 18 and had not been previously treated anti-PD-1 therapy. Treatment consisted of 200mg Q3W pembrolizumab plus the supplemental treatment of 150 mg/m^2 ATRA orally for 3 days surrounding each of the first four infusions of pembrolizumab, with patients continuing pembrolizumab for up to two years until confirmed disease progression or unacceptable toxicity. This study seeks to assess the safety and efficacy of combining ATRA and pembrolizumab in advanced melanoma patients. The dose of ATRA was chosen based on the observed PK and effects on MDSCs [Nefedova, Y., et al 2007] [Iclozan, C., et al 2013].

At data cut off (FEB 2021) 22 patients were evaluable for tumor response. Median follow-up was 1.0 years (0.3-2 years). In general, the combination of pembrolizumab and ATRA was well tolerated. This study demonstrates that the combination of ATRA and pembrolizumab is well tolerated and suggests that reducing MDSCs with ATRA may enhance the efficacy of pembrolizumab [McCarter, M., et al 2021].

Renal cell carcinoma patients treated with ATRA followed by high-dose IL-2 had reduced frequencies of circulating MDSCs with reduced immunosuppressive function during the ATRA phase of the treatment regimen [Mirza, N., et al 2006]. However, the subsequent high-dose IL-2 treatment abrogated these effects and resulted in a lack of clinical benefit overall [Mirza, N., et al 2006]. In another recent study, ATRA was used in combination with a dendritic cell vaccine targeting p53 mutations in small cell lung cancer patients [Iclozan, C., et al 2013]. The survival outcomes have not yet been reported; however, the study showed that the frequency and function of MDSCs was reduced after ATRA treatment and that p53-specific T-cell responses were increased in more patients receiving the combinatorial therapy compared with patients receiving the dendritic cell vaccine alone [Iclozan, C., et al 2013]. A dose ranging PK analysis showed correlation between serum concentrations of ATRA and the desired target effect on circulating MDSCs, and determined that the optimal oral dose of ATRA was 150 mg/m^2/day. Lower doses of ATRA generally resulted in lower serum concentrations and less reliable effects on MDSCs.

Myeloid-derived suppressor cells (MDSCs) are potent suppressors of antitumor immunity citationand are commonly associated with poor outcomes in melanoma patients treated with immune checkpoint inhibitors. Inducing the differentiation of MDSCs using all-trans retinoic acid (ATRA) reduces MDSC frequency. This analysis seeks to assess the safety and efficacy of combining ATRA and pembrolizumab in advanced melanoma patients.

For additional information, refer to the tretinoin prescribing information.

10.6.2.3 Section 2.5 Scientific Rationale for the Combination of Investigational Agents With or Without Pembrolizumab

MK-7684 (anti-TIGIT)

Evaluation of TIGIT modulation as an approach to enhance tumor immunity was prompted by internal preclinical observations showing that antagonizing TIGIT has potent immunostimulatory effects. Results of studies performed at Merck demonstrated in vivo antitumor activity of rat anti-mouse TIGIT antibodies. In order to understand how antibody backbone differences may impact the antitumor efficacy of anti-TIGIT antibodies, parental rat anti-mouse TIGIT mAbs, or chimeric versions of these antibodies, were tested in multiple established (80 mm^3 to 180 mm^3) syngeneic tumor models as single agents and in combination with an anti-mouse PD-1 mAb (muDX400). All anti-TIGIT mAbs tested resulted in a trend toward enhanced antitumor activity when combined with an anti-mouse PD-1 mAb (mDX400). The chimeric anti-TIGIT IgG2a mAbs (strong FcγR binding) showed the most robust single agent activity as compared to anti-TIGIT IgG1 (D265A mutant; minimal FcγR binding) mAbs and the most combination benefit when combined with anti-mouse PD-1.

In the murine MC38 colon carcinoma tumor model, anti-mouse TIGIT (18G10-mIgG2a) displayed single agent activity comparable to anti-mouse PD-1 (mDX400). The MC38 tumor model has been classified as very responsive to anti-PD-1 treatment, and MC38 model selection was based on baseline TIGIT protein surface expression on CD8+ and CD4+ TILs, baseline mRNA expression of CD155, and induction of TIGIT and CD155 expression in tumors after anti-PD-1 treatment.

A representative study evaluated anti-TIGIT treatment as a single agent and in combination with anti-PD-1(muDX400) therapy in the murine subcutaneous CT26-tumor bearing model. The CT26 colon carcinoma model has been classified as partially responsive to anti-PD-1 treatment with only partial tumor growth inhibition observed. CT26 model selection was based on baseline TIGIT protein surface expression on CD8+ and CD4+ TILs, baseline mRNA expression of CD155, and induction of TIGIT and CD155 expression in tumors after anti-PD-1 treatment. Combination treatment of 18G10-G2a with anti-PD-1 (mDX400) demonstrated significantly enhanced efficacy and survival as compared to anti-TIGIT and anti-PD-1 monotherapy treatments. Animals with complete responses showed curative protection from tumor rechallenge, consistent with the development of immune memory.

These studies (and others) have demonstrated that anti-mouse TIGIT mAb treatment can augment antitumor T-cell responses and induce tumor rejection in several murine tumor models when used alone and in combination with an anti-mouse PD-1 mAb. In these studies, the combination of anti-mouse TIGIT and anti-mouse PD-1 led to an increased ratio of Teffs to Tregs in the tumor, but these effects were not observed in the draining lymph nodes. The results of studies conducted at Merck using chimeric anti-mouse TIGIT mAbs on the IgG2a backbone revealed that administration of single agent anti-mouse TIGIT mAbs are efficacious in treating multiple established subcutaneous murine tumors and that combining anti-mouse TIGIT 18G10-G2a with anti-mouse PD-1 leads to enhanced combination benefit over either single agent alone.

The potential toxicity profile of MK-7684 identified in nonclinical studies in nonhuman primates relates to transiently decreased lymphocyte or neutrophil counts in blood, and proinflammatory responses (eg, elevation of serum fibrinogen). A limited body of published literature describing TIGIT (Vstm3) -deficient KO mice indicate increased sensitivity to autoimmune diseases, using a model of myelin oligodendrocyte glycoprotein-induced autoimmune encephalomyelitis [Levin, S. D., et al 2011]. While specific target organs have not been identified for anti-TIGIT antibody, generally, immune-mediated adverse effects for immune-stimulating agents, including anti-TIGIT therapy, are anticipated to be observed in some patients.

Toxicology studies of MK-7684 monotherapy and pembrolizumab monotherapy in nonhuman primates did not demonstrate overlapping toxicities of these monoclonal antibodies. Moreover, using an in vitro cytokine release assay, the combination of MK-7684 and pembrolizumab did not enhance cytokine induction in human peripheral blood monocytes. Potential increase in immune-mediated adverse effects resulting from the combination of MK-7684 and pembrolizumab, however, cannot be ruled out.

V937

A strong rationale exists for combining oncolytic virus vaccination with immune checkpoint inhibition and initial clinical experience with this approach is promising. This result also supports the growing consensus that the effectiveness of extant T-cell enhancing immunotherapies such as pembrolizumab, ipilimumab, and interleukin-2 are dependent on preexisting T-cell recognition of melanoma. In recent preclinical studies performed in a fully immune-competent mouse model of melanoma, enhanced antitumor activity was observed in mice receiving a combination of intratumoral V937 and immune checkpoint antibody (anti-PD-1) compared to activity displayed from single agent use alone [Shafren, D., et al 2014].

V937, whether administered by the intratumoral, IV, or intravesical route, is well tolerated, with the majority of adverse reactions being of Grade 1 or 2 in severity. When given in combination with either ipilimumab or pembrolizumab, the incidence of checkpoint inhibitor-associated adverse reactions is similar to that reported in the literature as per single agent checkpoint inhibitor therapy. The overall the general safety profile of V937 continues to be favorable.

MK-4830 (anti-ILT4)

MK-4830 is a human-ILT4 antagonistic monoclonal antibody (mAb) on an IgG4/Lambda framework. MK-4830 was selected based on its specificity to ILT4, its ability to block HLA G binding to ILT4 and its ability to rescue ILT4-related inhibitory function. The IgG4 isotype was chosen to minimize effector function and framework-mediated cross-linking ability leading to agonist activity. Based on in vitro data, MK-4830 has high affinity and potent receptor blocking activity to ILT4.

MK-4830 has an acceptable preclinical safety profile and is in clinical development as an intravenous immunotherapy for advanced solid tumors. Significant antitumor efficacy, demonstrated by tumor growth inhibition, was observed in the humanized mice inoculated with SKMEL5 tumor cells with MK-4830 alone. This data provides the rationale to pursue MK-4830 as monotherapy. MK-4830 is being developed as a cancer immunotherapeutic with the potential to be used as monotherapy or to be combined with KEYTRUDA® (pembrolizumab; a humanized anti-programmed cell death 1 [PD-1] receptor antibody), to increase antitumor efficacy in participants with various tumor indications.

MK-4280A (Coformulation of MK-4280 + Pembrolizumab)

Emerging data suggest that combining PD-1/PD-L1 inhibitors with other immune modulatory agents might sensitize tumors to immunotherapy and/or provide additive efficacy. LAG-3 may be an appropriate target for co-inhibition with PD-1. In a mouse model, LAG-3 appears to play an immunosuppressive role, helping to prevent autoimmunity [Topalian, S. L., et al 2012].

CD8+ T-cells expressing both LAG-3 and PD-1 are the dominant TIL population in mice transplanted with CT26 colon carcinoma cells, in which LAG-3 was shown to control T-cell proliferation/cell cycle progression, resulting in a state of hypofunction

[Waugh, K. A., et al 2016]. Consistent with the landmark finding that immune cells within human colorectal tumors predict clinical outcome [Galon, J., et al 2006], both in vitro and in vivo data indicate that dual blockade of LAG-3 and PD-1 potentially can have a synergistic impact on reversing tumor-specific anergy [Andrews, L. P., et al 2017]. In 1 example, using the MC-38 mouse model of colon derived tumor cells, PD-1 inhibition resulted in expression of LAG-3 on T-cells [Beyrend, G., et al 2019]. In turn, combined PD-1 and LAG-3 blockade delayed tumor growth and enhanced survival.

In CRC patients, LAG-3 was overexpressed on colorectal immune cells, and correlated with poor differentiation, advanced stage, lymph node involvement, and invasion depth (T stage) [Chen, J. and Chen, Z. 2014]. Also, among MSI-H colon cancer patients LAG-3 expression was associated with a shorter relapse-free survival, and correlated with tumor cell PD-L1 expression [Lee, S. J., et al 2017].

In March 2022, the FDA approved Opudualag, which is a combination of anti-PD-1 nivolumab and anti-LAG-3 relatlimab for the treatment of unresectable or metastatic melanoma, based on RELATIVITY-047 (NCT03470922), that is a randomized, double-blinded phase 3 trial in patients with previously untreated metastatic or unresectable Stage III or IV melanoma. The trial demonstrated a statistically significant improvement in PFS by BICR for Opdualag compared to nivolumab, validating that blocking LAG-3 in combination with PD-1 as a therapeutic strategy for patients with melanoma [Tawbi, H. A., et al 2022].

ATRA (tretinoin)

NCT03200847 is a single-arm, single-institution, Phase 1/2 clinical study which has enrolled 24 patients diagnosed with Stage IV melanoma. Eligible patients were ≥18 and had not been previously treated with anti-PD-1 therapy. Treatment consisted of pembrolizumab 200 mg q3w plus the supplemental treatment of ATRA 150 mg/m^2 orally for 3 days surrounding each of the first 4 pembrolizumab infusions, with patients continuing pembrolizumab for up to 2 years until confirmed disease progression or unacceptable toxicity. The primary endpoints were to establish the MTD and RP2D. Secondary endpoints were safety, reduction in circulating MDSCs, assessments of antitumor activity.

At data cut off (February 2021) 22 patients were evaluable for tumor response. Median follow-up was 1.0 years (0.3-2 years). The ORR was 60% and DCR was 83%. Six-month PFS rate was 62%. Excluding patients diagnosed with uveal melanoma (n = 2) the ORR was 72%, DCR was 86%, and the six-month PFS rate was 68% [McCarter, M., et al 2021]. Paired analysis showed sustained decreases in absolute numbers (p=0.002) and percentage (p=0.007) of circulating MDSCs ($CD3^-CD19^-CD56^-CD11b^+CD33^+HLA\text{-}DR^{-/low}$) 4 to 6 weeks after stopping ATRA.

In general, the combination of pembrolizumab and ATRA was well tolerated. The most common treatment-related AEs were Grade 1 or 2, including headache (22 participants, 92%), fatigue (18 participants, 75%), rash (16 participants, 66%), and nausea (8 participants, 33%), most of which corresponded with the 3-day course of ATRA treatment. Ten patients had Grade 3 or higher AEs with most being common immune checkpoint inhibitor-related AEs. This study is ongoing [McCarter, M., et al 2021].

10.6.2.4 Section 2.6 Clinical Data on the Combination of Investigational Agents With or Without Pembrolizumab

Pembrolizumab with MK-7684 (anti-TIGIT)

A Phase 1, open-label, multiarm, multicenter dose-finding clinical study (NCT02964013) is currently ongoing. In Part A dose escalation, MK-7684 was evaluated as monotherapy (n = 34) and in combination with pembrolizumab (n = 34) in 68 participants with advanced solid tumors who failed standard treatment options. Thirteen participants who progressed on the monotherapy arm crossed over to the combination arm. MK-7684 (dose ranges: 2.1, 7, 21, 70, 210, and 700 mg) and pembrolizumab (200-mg fixed dose) were administered Q3W for up to 35 cycles or until progression, intolerable toxicity, or investigator or participant decision. Primary study objectives included evaluation of safety and tolerability, PK, and ORR as determined by RECIST 1.1. Preliminary data showed MK-7684 as monotherapy and in combination with pembrolizumab was generally well tolerated and had a manageable safety profile across all dose levels tested. No DLTs were recorded. Treatment-related AEs occurred in 56% of participants in the monotherapy arm and 60% in the combination arm of which 6% and 11%, respectively, were Grade 3 to 4 toxicities. No participants discontinued due to treatment-related AEs. The most common treatment-related AEs (occurring in ≥10% of participants) were fatigue and pruritus in the monotherapy arm and pruritus in the combination arm. In the monotherapy and combination arms, 1 partial response (3%; n = 1 out of 34 participants) and 8 partial responses (19%; n = 8 out of 43 participants) were observed, and the disease control rates were 35% and 47%, respectively.

The preclinical rationale described above, in addition to the encouraging efficacy data observed in the Phase 1 study and overall favorable safety profile makes this combination a suitable one to be further evaluated in participants with Stage IIIB to Stage IIID melanoma candidates for neoadjuvant therapy.

Pembrolizumab with V937

In melanoma, there are 2 studies where V937 has been administered intratumoral either as monotherapy or in combination with pembrolizumab: (1) CALM, monotherapy and (2) CAPRA, in combination with pembrolizumab.

CALM is a Phase 2 study with V937 administered intratumoral to participants with melanoma. The main cohort of this study consisted of 57 participants with histologically proven Stage IIIC or Stage IV melanoma who failed to qualify for curative surgery and who had one or more tumors that were accessible for direct injection and measurable by RECIST 1.1. The dose of V937 for this study was 3×10^8 TCID50 (about 4.5×10^6 TCID50/kg for a 70-kg patient) by intratumoral administration. Each participant received 4 separate V937 administrations during the first 8 days in the study (Days 1, 3, 5, and 8), followed by a fifth dose 2 weeks later (Day 22) and further administrations at 3-week intervals (Days 43, 64, 85, 106, and 127, up to a maximum of 10 sets of injections) or until confirmed disease progression or development of excessive toxicity. Participants responding to the treatment could receive an additional 9 intratumoral injections, given every 3 weeks following Day 169. Overall, a number of V937-injected lesions and noninjected

distant/visceral lesions displayed either detectable reductions in size or stabilization of tumor growth. The median immune-PFS at 6 months (irPFS: irCR, irPR, or irSD) was 38.6%. The current investigator-assessed ORR (irRECIST 1.1) was 28.1%. A durable response (ie, one lasting 6 months or more) was demonstrated in 21% of participants by irRECIST. The median time to response (first irPR or irCR) was 3.4 months and the median duration of response was 10.1 months. The median OS was 25.6 months, with 75% of participants alive at 12 months [Curti, B., et al 2017].

CAPRA is a multisite open-label study designed to assess the safety of intratumoral V937 when used in combination with pembrolizumab in patients with advanced melanoma. The V937 treatment regimen consists of 4 treatments within the first 8 days and then may continue to receive V937 Q3W for a maximum of 19 treatments. Pembrolizumab is given IV at a dose of 2 mg/kg body weight on Day 8 and continuing every 3 weeks for up to 2 years. As of 23 JUN 2018, 31 participants had been enrolled and 27 participants were evaluated for response. One participant discontinued prior to response assessment due to an unrelated AE, and 3 participants have not yet been evaluated for response. The best response rate for the 27 evaluable participants is 59% [Silk, A. W., et al 2017].

Among the 31 participants with advanced melanoma treated in Study VLA-011 treatment-emergent AEs are very similar to those reported in the VLA-007 intratumoral study reported in ≥3 participants and include rash, fatigue, diarrhea, dry mouth and decreased appetite. Adverse events considered related to V937 were limited to Grade 1 or 2, in severity. Adverse events considered related to pembrolizumab included 4 Grade 3 events, but the frequency and nature were not unexpected. Eleven SAEs have been reported; none were considered related to V937 but 4 events were considered related to pembrolizumab. To date, the combination of intratumoral V937 and pembrolizumab has been well tolerated.

The preclinical rationale described above, in addition to the encouraging efficacy data observed in the Phase 1 study and overall favorable safety profile makes this combination a suitable one to be further evaluated in participants with Stage IIIB to Stage IIID melanoma candidates for neoadjuvant therapy.

Pembrolizumab with MK-4830 (anti-ILT4)

MK-4830 is currently being evaluated as monotherapy and in combination with pembrolizumab (MK 3475) in an ongoing FIH, Phase 1 clinical study in participants with advanced solid tumors, Study PN001. Study objectives include evaluating the safety, PK, PD, and preliminary efficacy of MK-4830 at various dose levels as monotherapy and in combination with pembrolizumab (Study MK-4830-001). The ongoing dose escalation part of the study is intended to identify a maximum tolerated dose or maximum administered dose and a recommended Phase 2 dose of MK-4830 alone and in combination with pembrolizumab; the dose expansion part of the study is to identify the objective response rate by investigator in several advanced tumor indications and to evaluate safety and tolerability of the combination of MK-4830, pembrolizumab and chemotherapy (1L NSCLC) or lenvatinib (1L RCC). MK-4830 is also being evaluated in combination with pembrolizumab (MK 3475) in an ongoing Phase 2 clinical study in participants with NSCLC, Study MK 3475 U01.

MK-4280A (Coformulation of MK-4280 + Pembrolizumab)

Several ongoing clinical trials are examining pembrolizumab in combination with MK-4280 and in coformulation with pembrolizumab (MK-4280A) in participants with various solid and hematologic malignancies. For details, please refer to the current MK-4280/MK-4280A IB [Edition 8].

The safety profile for participants receiving MK-4280A was consistent with the known safety profile of participants receiving sequential administration of 800 mg MK-4280 and pembrolizumab. As of the data cutoff date, there were no remarkable differences in the frequencies or types of AEs observed for participants receiving MK-4280A (coformulation of 800 mg MK-4280 and 200 mg pembrolizumab) compared with those of participants receiving sequential administration of 800 mg MK-4280 and 200 mg pembrolizumab.

ATRA (tretinoin)

Refer to the tretinoin prescribing information for clinical study data. The 2004 label reports ATRA had been investigated in 114 previously treated APL patients and in 67 previously untreated ("de novo") patients in one open-label, uncontrolled single investigator clinical study (Memorial Sloan-Kettering Cancer Center) and in 2 cohorts of compassionate cases treated by multiple investigators under the auspices of the National Cancer Institute. All patients received 45 mg/m^2/day as a divided oral dose for up to 90 days or 30 days beyond the day that CR was reached [U.S. Product Circular 2004]. Additional studies have been done in patients with renal cell carcinoma [Mirza, N., et al 2006] and small cell lung cancer [Iclozan, C., et al 2013].

A study for melanoma is currently underway. NCT03200847 is a single-arm, single-institution, Phase 1/2 clinical study which has enrolled 24 patients diagnosed with Stage IV melanoma. Eligible patients were ≥18 and had not been previously treated with anti-PD-1 therapy. Treatment consisted of pembrolizumab 200 mg Q3W plus the supplemental treatment of ATRA 150 mg/m^2 orally for 3 days surrounding each of the first 4 pembrolizumab infusions, with patients continuing pembrolizumab for up to 2 years until confirmed disease progression or unacceptable toxicity. The primary endpoints were to establish the MTD and RP2D. Secondary endpoints were safety, reduction in circulating MDSCs, assessments of antitumor activity. The study is ongoing [McCarter, M. 2020].

10.6.2.5 Section 4.1 Overall Design of the Substudy

10.6.2.5.1 Section 4.1.1 Investigational Treatment Arms

Participants will receive treatment with:

Arm 1: Participants will receive 2 administrations of pembrolizumab (at a fixed dose of 200 mg Q3W) C1D1 and C2D1 in combination with MK-7684 (at a fixed dose of 200 mg Q3W) C1D1 and C2D1 followed by surgical resection of the tumor. After surgical resection of the tumor (Appendix 10), participants will receive 8 cycles of adjuvant therapy with

pembrolizumab monotherapy (at a fixed dose of 400 mg Q6W) on Day 1 of every cycle (total treatment duration including neoadjuvant and adjuvant therapy of approximately 1 year).

Arm 2: Participants will receive 1 administration of pembrolizumab (at a fixed dose of 400 mg Q6W) on C1D8 and V937 (at a fixed dose of 3×10^8 TCID50) on C1D1, C1D3, C1D5, C1D8, and C1D22 followed by surgical resection of the tumor. After surgical resection of the tumor (Appendix 10), participants will receive 8 cycles of adjuvant therapy with pembrolizumab monotherapy (at a fixed dose of 400 mg Q6W) on Day 1 of every cycle (total treatment duration including neoadjuvant and adjuvant therapy of approximately 1 year).

Arm 3: Participants will receive 1 administration of pembrolizumab monotherapy (at a fixed dose of 400 mg Q6W) C1D1 followed by surgical resection of the tumor. After surgical resection of the tumor (Appendix 10), participants will receive 8 cycles of adjuvant therapy with pembrolizumab monotherapy (at a fixed dose of 400 mg Q6W) on Day 1 of every cycle (total treatment duration including neoadjuvant and adjuvant therapy of approximately 1 year).

Arm 4: Participants will receive 2 administrations of pembrolizumab (at a fixed dose of 200 mg Q3W) C1D1 and C2D1 in combination with MK-4830 (at a fixed dose of 800 mg Q3W) C1D1 and C2D1 followed by surgical resection of the tumor. After surgical resection of the tumor (Appendix 10), participants will receive 8 cycles of adjuvant therapy with pembrolizumab monotherapy (at a fixed dose of 400 mg Q6W) on Day 1 of every cycle (total treatment duration including neoadjuvant and adjuvant therapy of approximately 1 year).

Arm 5: Two neoadjuvant cycles of MK-4280A (coformulation of MK-4280 800 mg + pembrolizumab 200 mg) Q3W IV on C1D1 and C2D1, followed by surgical resection of the tumor, and followed by adjuvant pembrolizumab monotherapy 400 mg Q6W for 8 cycles (total treatment duration including neoadjuvant and adjuvant treatment of approximately 1 year).

Arm 6: Two neoadjuvant cycles of ATRA 75 mg/m^2 ATRA PO twice daily (total daily dose: 150 mg/m^2) on C1 Days 1, 2, and 3 and C2 Days 1, 2, and 3 + pembrolizumab 400 mg IV on C1 Day 1, followed by surgical resection of the tumor, and then followed by adjuvant pembrolizumab monotherapy 400 mg Q6W for 8 cycles (total treatment duration including neoadjuvant and adjuvant treatment of approximately 1 year).

10.6.2.6 Section 4.3 Justification for Dose

10.6.2.6.1 Section 4.3.2 Rationale for Investigational Agents Dosing Plan

MK-7684 (anti-TIGIT)

Available preliminary PK data from participants treated with escalating doses of MK-7684 from 2.1 mg to 700 mg when given as monotherapy or in combination with 200 mg pembrolizumab in Study PN001 showed that serum MK-7684 exposures increased in a dose-

dependent manner. Preliminary PK profiles of MK-7684 exposures suggest that target-mediated clearance of MK-7684 is saturated at the 210-mg and 700-mg doses.

Available preliminary data for the exploratory target engagement pharmacodynamic marker from participants treated escalating doses of MK-7684 from 2.1 mg to 700 mg when given as monotherapy or in combination with 200 mg pembrolizumab in Study PN001 showed that increasing doses of MK-7684 resulted in decreasing TIGIT availability on CD4+, CD8+, CD4+CD25+, CD4+HLADR+, and CD8+HLADR+ TIGIT+ T cells, generally approaching saturation (>90%). These data indicate TIGIT engagement by MK-7684 in circulation.

Based on preliminary PK and pharmacodynamic observations, a preliminary RP2D of 200 mg was considered for MK-7684 monotherapy and in combination with pembrolizumab. Please see the MK-7684 IB for additional details.

V937

Based on the results from the repeat dose toxicology study on V937 administered SC to male and female chimeric Hu/Mu ICAM-1 transgenic Balb/C mice, the administered SC dose of approximately 1.25 x 10^9 TCID50/kg caused no apparent toxic effects, including any signs of HLP or other forms of myositis, and was considered to be the NOAEL dose for the study. This V937 SC dose in mice has a human equivalent dose of about 1 x 10^8 TCID50/kg, which provides a safety margin of about 20-fold for the human V937 dose of about 4.5 x 10^6 TCID50/kg (for a 70-kg patient) to be evaluated. Furthermore, Hu/Mu ICAM-1 transgenic mice tolerated systemic exposure to V937 at levels of approximately 8 x 10^4 TCID50/mL equivalents after primary SC injection (30 minutes after dosing), which is approximately 50 times the level (1.8 x 10^3 to 1.2 x 10^3 TCID50/mL equivalents) observed in the serum of patients in earlier clinical studies following the initial intratumoral injection with V937 at 3.2 x 10^8 TCID50.

Phase 1 studies have been completed for V937 monotherapy and pembrolizumab combinations in intratumoral and IV settings. All intratumoral studies have treated cutaneous or subcutaneous lesions only. No data are available for visceral intratumoral administration. In addition, Phase 1 dose escalation has been completed for intravesicular administration for V937 monotherapy. In all cases the highest doses tested were well tolerated, and evidence of biological activity has been demonstrated. Therefore, the proposed studies moving forward will use the current recommended Phase 2 doses and schedules.

For intratumoral and intravesicular applications, a total dose of 3 × 10^8 TCID50 has been administered. In the cases of intratumoral administration, the dose may be divided among several lesions. Doses were administered on Days 1, 3, 5, 8, and 22, and then every 3 weeks for a total of 11 or 19 doses.

For IV administration, the total dose is 1 × 10^9 TCID50, administered on Days 1, 3, 5, 8, 22, and then every 3 weeks for a total of 11 doses.

MK-4830 (anti-ILT4)

The human starting dose and dosing interval of MK-4830 were based on an integration of nonclinical toxicology and pharmacology data. Given the potential of MK-4830 to activate the immune system and the limitations of standard toxicology studies to model these effects in the preclinical setting, a conservative FIH starting dose was chosen. The FIH starting dose of MK-4830 was determined based on integration of the data obtained from in vitro studies evaluating MK-4830 binding to granulocytes and monocytes obtained from patients with cancer and normal volunteers, nonclinical PK in NHP, and safety and toxicology studies also in NHP. In particular, emphasis is placed on the in vitro receptor binding data due to lack of target homology, lack of orthologous protein expression, and lack of bio reactivity of MK-4830 in rodents and NHPs.

The FIH starting dose of 3 mg was conservatively determined based on projected C_{max} where the half-maximal effective concentration of the cell membrane bound immunoglobulin like transcript 4 in blood is bound to MK-4830. As MK-4830 is an antagonistic, rather than an agonistic mAb, 50% receptor occupancy is considered a conservative value that is unlikely to produce significant physiologic effects. Furthermore, the use of C_{max} as the exposure parameter to derive 50% receptor occupancy leads to an even more conservative estimate. Moreover, the starting dose of 3 mg Q3W is predicted to yield a steady state C_{max} of 1.2 µg/mL, providing an approximately 6,900 fold safety margin to the NOAEL observed in the rhesus GLP toxicity study.

In Study MK-4830-001, preliminary data for the serum target engagement pharmacodynamic marker from participants treated with escalating doses of MK-4830 demonstrated a dose dependent increase in membrane receptor occupancy, with an average membrane target occupancy of >90% at 800 mg or higher doses. Based on these findings and additional clinical safety data from Study MK-4830-001, the RP2D was determined to be MK-4830 800 mg Q3W. For additional information, refer to Sections 5.3 and 5.4 of the MK-4830 IB.

MK-4280A (Coformulation of MK-4280 + Pembrolizumab)

Given the Sponsor's observation of limited MK-4280 monotherapy activity and the observed efficacy and tolerability of MK-4280 when used in combination with pembrolizumab in the ongoing Phase 1 clinical study of MK-4280-001, the Sponsor developed MK-4280A, a coformulated product of MK-4280 in combination with pembrolizumab. PK, safety and efficacy are comparable in MSS CRC participants treated with MK-4280A compared to separately administered MK-4280 and pembrolizumab on MK-4280-001 (see MK-4280/MK-4280A IB for details). Compared with sequential administration of separate formulations, the single coformulation vial could provide significant benefit to patients and providers, including simplified preparation, reduced infusion times, reduction of potential errors in drug administration.

The planned dose of MK-4280 in the coformulation in this study is 800 mg Q3W. Preliminary PK data from participants treated on MK-4280-001 in participants receiving MK-4280 alone and in combination with pembrolizumab in advanced solid tumors at doses from 7 mg to 800 mg showed that serum MK-4280 exposures increased in a dose-dependent manner. Preliminary PK profiles of MK-4280 exposures suggest that target receptor-mediated clearance (reflecting target engagement of membrane LAG-3) of MK-4280 was more likely to stay saturated at ≥700 mg dose compared with lower doses considering PK C_{trough} variability observed. Additionally, efficacy data from a randomized dose finding study in participants with gastric cancer in MK-4280-001 suggested possible trend towards better efficacy at higher doses. MK-4280 given alone and in combination with pembrolizumab has been tolerable at all dose levels tested from 7 mg to 800 mg with no clear dose dependence in the type or frequency of AEs. For more detailed information, please refer to the MK-4280/ MK-4280A IB. Therefore, based on the totality of preliminary data accumulated so far, the Sponsor has elected 800 mg dose of MK-4280 in the coformulation.

ATRA (tretinoin)

MDSCs are potent suppressors of antitumor immunity and are frequently associated with poor outcomes in melanoma patients treated with immune checkpoint inhibitors. Inducing the differentiation of MDSCs using ATRA reduces MDSC frequency and function.

The dose of ATRA was chosen based on the observed PK and effects on MDSCs [Nefedova, Y., et al 2007] [Iclozan, C., et al 2013]. Renal cell carcinoma patients treated with ATRA followed by high-dose IL-2 had reduced frequencies of circulating MDSCs with reduced immunosuppressive function during the ATRA phase of the treatment regimen [Mirza, N., et al 2006]. However, the subsequent high-dose IL-2 treatment abrogated these effects and resulted in a lack of clinical benefit overall [Mirza, N., et al 2006]. In another recent study, ATRA was used in combination with a dendritic cell vaccine targeting p53 mutations in small cell lung cancer patients [Iclozan, C., et al 2013]. The survival outcomes have not yet been reported; however, the study showed that the frequency and function of MDSCs was reduced after ATRA treatment and that p53-specific T-cell responses were increased in more patients receiving the combinatorial therapy compared with patients receiving the dendritic cell vaccine alone [Iclozan, C., et al 2013]. A dose ranging PK analysis showed correlation between serum concentrations of ATRA and the desired target effect on MDSCs, and determined that the optimal oral dose of ATRA was 150 mg/m^2/day. Lower doses of ATRA generally resulted in lower serum concentrations and less reliable effects on MDSCs.

For additional information, refer to the tretinoin prescribing information.

10.6.2.7 Section 5.1 Inclusion Criteria Specific to the Investigational Agents Being Evaluated

These Inclusion Criteria are applicable to ALL PARTICIPANTS being screened to any open arm within this substudy.

Investigational-agent-specific inclusion criteria

Male Participants

13. Male participants are eligible to participate if they agree to the following during treatment with and for at least 120 days after the last dose of V937 or at least 7 days after last dose of ATRA:

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

OR

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

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

Note: For male participants who only receive pembrolizumab, MK-7684, MK-4830, MK-4280A, or a combination of the aforementioned drugs, no contraception measured are needed.

Female Participants

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

- A female participant is eligible to participate if she is not pregnant or breastfeeding, and at least 1 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 pembrolizumab, MK-7684, V937, MK-4830, and MK-4280A, or 30 days after the last dose of ATRA, whichever occurs last. The investigator should evaluate the potential for contraceptive method failure (ie, noncompliance, recently initiated) in relationship to the first dose of study intervention.

- WOCBP who choose to remain abstinent from heterosexual intercourse should do so during the entire period of risk associated with the study intervention.

- A WOCBP must have a negative highly sensitive pregnancy test (urine or serum as required by local regulations) within 24 hours before the first dose of study intervention.

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

- Additional requirements for pregnancy testing during and after study intervention are 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.

Type of Participant and Disease Characteristics

15. Participants in Germany only: with BRAF V600 mutation-positive melanoma are eligible for the study ONLY in the absence of rapidly progressing metastatic melanoma in the judgement of the investigator.

10.6.2.8 Section 5.2 Exclusion Criteria Specific to the Investigational Agents Being Evaluated

These Exclusion Criteria are applicable to ALL PARTICIPANTS being screened within this substudy.

The following additional exclusion criteria are specific to V937:

22. Participants with tumors close to an airway, major blood vessel, or spinal cord that, in the opinion of the investigators, could cause occlusion or compression in the case of tumor swelling or erosion into a major vessel in the case of necrosis.

23. Participants should not have lesions in mucosal areas (vulvar, anal, oral cavity, etc.) that are to be injected with V937. Participants requiring mucosal lesion injection, per substudy protocol (eg, only mucosal lesions are present), are not eligible.
24. Participants must be naïve to TVEC and other oncolytic viruses.

The following additional exclusion criteria are specific to MK-4830 (anti-ILT4):

25. Participant has received previous treatments with another agent targeting ILT4.

The following additional exclusion criteria are specific to MK-4280A (anti-LAG-3):

26. Participants who received prior treatment with an anti-LAG-3 agent

10.6.2.9 Section 5.3 Lifestyle Considerations

MK-7684 (anti-TIGIT)

None.

V937 a LAG-3 agent

None.

MK-4830 (anti-ILT4)

None.

MK-4280A (Coformulation of MK-4280 + Pembrolizumab)

None.

ATRA (tretinoin)

The following precautions appear in the ATRA package insert:

1. The ability to drive or operate machinery might be impaired in patients treated with ATRA, particularly if they are experiencing dizziness or severe headache.

2. As with other retinoids, ATRA must not be administered in combination with vitamin A because symptoms of hypervitaminosis A could be aggravated.

3. Cases of fatal thrombotic complications have been reported rarely in patients concomitantly treated with ATRA and anti-fibrinolytic agents. Therefore, caution should be exercised when administering ATRA concomitantly with these agents.

10.6.2.9.1 Section 5.3.2 Caffeine, Alcohol, and Tobacco Restrictions

MK-7684 (anti-TIGIT)

None.

V937

None.

MK-4830 (anti-ILT4)

None.

MK-4280A (Coformulation of MK-4280 + Pembrolizumab)

None.

ATRA (tretinoin)

None.

10.6.2.9.2 Section 5.3.4 Investigational Agent Contraception, Pregnancy, and Use in Nursing Women

MK-7684 (anti-TIGIT)

MK-7684 may have adverse effects on a fetus in utero. Contraception requirements for this substudy are outlined in Appendix 5.

V937

V937 may have adverse effects on a fetus in utero. Contraception requirements for this substudy are outlined in Appendix 5.

MK-4830 (anti-ILT4)

MK-4830 may have adverse effects on a fetus in utero. Contraception requirements for this substudy are outlined in Appendix 5.

MK-4280A (Coformulation of MK-4280 + Pembrolizumab)

MK-4280A may have adverse effects on a fetus in utero. Contraception requirements for this substudy are outlined in Appendix 5.

ATRA (tretinoin)

ATRA may have adverse effects on a fetus in utero. Contraception requirements for this substudy are outlined in Appendix 5.

10.6.2.10 Section 6.1 Study Intervention(s) Administered

Study interventions will be administered on an outpatient basis. The investigational agents to be used in this substudy protocol are outlined in Table 11.

MK-7684 (anti-TIGIT)

MK-7684 will be provided centrally by the Sponsor.

V937

V937 will be provided centrally by the Sponsor.

MK-4830 (anti-ILT4)

MK-4830 will be provided centrally by the Sponsor.

MK-4280A (Coformulation of MK-4280 + Pembrolizumab)

MK-4280A will be provided centrally by the Sponsor.

ATRA (tretinoin)

ATRA (tretinoin) will be provided centrally or locally by the Sponsor.

Table 11 Study Intervention

Arm Name	Arm Type	Intervention Name	Type	Dose Formulation	Unit Dose Strengths	Dosage Levels	Route of Administration	Regimen/ Treatment Period	Use	IMP/ NIMP	Sourcing
Arm 1	Experimental	MK-7684 (anti-TIGIT)	Drug	Solution for Infusion	50 mg/mL	200mg	IV Infusion	Q3W for 2 cycles in the neoadjuvant phase (C1D1, C2D1)	Test Product	IMP	Central
Arm 1	Experimental	Pembrolizumab (MK-3475)	Drug	Solution for Infusion	25 mg/mL	200 mg; 400 mg	IV Infusion	Q3W (200 mg); 2 cycles in the neoadjuvant phase (C1D1, C2D1) Q6W (400 mg); up to 8 cycles in the adjuvant phase	Test Product	IMP	Central
Arm 2	Experimental	V937 (oncolytic virus)	Other	Sterile Solution	7.5×10^7 TCID50/mL	3×10^8 TCID50	Intratumoral	C1D1, C1D3, C1D5, C1D8 & C1D22 of the neoadjuvant phase	Test Product	IMP	Central
Arm 2	Experimental	Pembrolizumab (MK-3475)	Drug	Solution for Infusion	25 mg/mL	400 mg	IV Infusion	Q6W; 1 cycle in the neoadjuvant phase (C1D8) and up to 8 cycles in the adjuvant phase	Test Product	IMP	Central

Arm Name	Arm Type	Intervention Name	Type	Dose Formulation	Unit Dose Strengths	Dosage Levels	Route of Administration	Regimen/ Treatment Period	Use	IMP/ NIMP	Sourcing
Arm 4	Experimental	MK-4830 (anti-ILT4)	Drug	Solution for Infusion	50 mg/mL	800 mg	IV Infusion	Q3W for 2 cycles in the neoadjuvant phase (C1D1, C2D1)	Test Product	IMP	Central
Arm 4	Experimental	Pembrolizumab (MK-3475)	Drug	Solution for Infusion	25 mg/mL	200 mg 400 mg	IV Infusion	Q3W (200 mg); 2 cycles in the neoadjuvant phase (C1D1, C2D1) Q6W (400 mg); for up to 8 cycles in the adjuvant phase	Test Product	IMP	Central
Arm 5	Experimental	MK-4280A (coform of MK-4280 + pembrolizumab)	Biological/ Vaccine	Solution for Infusion	20 mg/mL MK-4280 + 5 mg/mL pembrolizumab for a total protein content of 25 mg/mL	MK-4280A (co-formulation of MK-4280 800 mg + pembrolizumab 200 mg)	IV Infusion	Q3W for 2 cycles in the neoadjuvant phase (C1D1, C2D1).	Test Product	IMP	Central
Arm 5	Experimental	Pembrolizumab (MK-3475)	Biological/ Vaccine	Solution for Infusion	25 mg/mL	400 mg	IV Infusion	400 mg Q6W for up to 8 cycles in the adjuvant phase.	Test Product	IMP	Central

Arm Name	Arm Type	Intervention Name	Type	Dose Formulation	Unit Dose Strengths	Dosage Levels	Route of Administration	Regimen/ Treatment Period	Use	IMP/ NIMP	Sourcing
Arm 6	Experimental	ATRA (Tretinoin)	Drug	Capsule	10 mg	75 mg/m^2	Oral	Twice per day for 3 days Q3W for 2 cycles (ie, C1 Days 1, 2, and 3 and C2 Days 1, 2, and 3) in the neoadjuvant phase	Test Product	IMP	Central or Local
Arm 6	Experimental	Pembrolizumab (MK 3475)	Biological/ Vaccine	Solution for Infusion	25 mg/mL	400 mg	IV Infusion	400 mg Q6W for 1 cycle (ie, C1D1) in the neoadjuvant phase; and 400 mg Q6W for up to 8 cycles in the adjuvant phase	Test Product	IMP	Central

Abbreviations: IMP = investigational medicinal product; IV = intravenous; NIMP = noninvestigational medicinal product; Q3W = every 3 weeks, Q6W = every 6 weeks; TCID50 = tissue culture infectious dose 50%.

Note: 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.

NOTE: Although Arm 3 (pembrolizumab monotherapy) is no longer activated for randomization/allocation, single-agent pembrolizumab may be active in treatment arms as adjuvant therapy.

V937

V937 will be administered by intratumoral injection into cutaneous, subcutaneous, and/or nodal lesions that are visible, palpable, or detectable by ultrasound guidance. V937 will be administered with a total maximal volume of injectate of 4 mL per treatment visit for all injected lesions combined. **A maximum of 5 lesions can be injected per visit**.

V937 administration will be administered during Cycle 1 and will occur 0.5 to 4 hours after a 400-mg dose of pembrolizumab infused over 30 minutes.

Each participant will receive V937 in a volume of 0.5 to 4 mL of injectate. The amount of V937 administered will depend on the number of lesions injected and the size of those lesions. See Table 12 for dose level range. The volume of injectate delivered to each lesion will be based on the longest dimension of the injectable target lesion as shown in Table 12 (short axis diameter in the case of lymph nodes), and on the number of lesions injected. Documentation of dose volume administered per lesion will be obtained.

Prioritization of lesions to be injected should include consideration of the following order:

First: New or progressing lesion(s)

Second: The largest lesion(s)

If multiple lesions exist, a new or progressing lesion should be considered next for injection first, followed by injection of the largest lesion, then injection of any additional lesions, up to a total volume of injectate of 4 mL and a maximum number of 5 lesions.

The total volume administered to all lesions can range from 0.5 to 4 mL per participants, per visit.

Table 12 Determination of Minimum Injectable Target Lesion Diameter at Treatment Initiation by Dose Level

Target Lesion Size (longest dimension)	**Injection Volume[a]**
>2.5 cm	2 mL
1.5 to 2.5 cm	1 mL
0.5 to <1.5 cm	0.5mL

a Volumes are estimates; total volume injected per visit for all tumor lesions combined = 4 mL

Details on preparation and administration of V937 are provided in the Pharmacy Manual.

Injected tumor area should consist of vital tumor tissue (avoid injection into areas with significant necrosis, if feasible). The injected, single, sufficiently sized target lesion at treatment initiation should be the same lesion that underwent pretreatment biopsy.

If at any time after treatment initiation a dose cannot be fully injected into the single target lesion identified at the start of treatment (eg, due to tissue induration or tumor shrinkage), the

dose may be split and the remaining amount of V937 may be injected into another accessible target lesion(s). Documentation of dose volume administered per target lesion should be obtained. If no other target lesion is accessible for injection or lesions are no longer visible, the remaining amount may alternatively be injected subcutaneously into the tissue immediately surrounding the target lesion, if assessed feasible by the treating physician. Site and volume for each injection must be documented in the eCRF.

10.6.2.11 Section 6.2 Preparation/Handling/Storage/Accountability

10.6.2.11.1 Section 6.2.1 Dose Preparation

Details on preparation and administration of MK-7684, V937, MK-4830, and MK-4280A are provided in the Pharmacy Manual.

ATRA (tretinoin) is a capsule for oral administration and does not require preparation. See the Pharmacy Manual for additional details.

For additional information, refer to the MK-7684, V937, MK-4830, and MK-4280/ MK-4280A IBs.

10.6.2.11.2 Section 6.2.2 Handling, Storage, and Accountability

MK-7684 (anti-TIGIT)

Stability studies of MK-7684 solution for infusion are in progress to confirm that, throughout the duration of the clinical studies, clinical supplies remain within specifications. The proposed shelf-life for the solution for infusion is based on the available stability data when stored according to conditions specified in the clinical supplies labeling. As additional stability data become available, the shelf-life may be extended. For each individual study, clinical supplies are to be stored in accordance with specific instructions on the label.

Refer to Section 6.2.2 of this substudy protocol for accountability instructions.

For additional information, refer to the MK-7684 IB and the Pharmacy Manual.

V937

Refer to Section 6.2.2 of this substudy protocol for accountability instructions. For additional information, refer to the V937 IB and the Pharmacy Manual.

MK-4830 (anti-ILT4)

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

MK-4280A

Refer to Section 6.2.2 of this substudy protocol for accountability instructions. For additional information, refer to the MK-4280/MK-4280A IB and the Pharmacy Manual.

ATRA (tretinoin)

ATRA will be provided centrally. Refer to Section 6.2.2 of this substudy protocol for accountability instructions. For additional information, refer to the ATRA prescribing information.

10.6.2.12 Section 6.3 Measures to Minimize Bias: Randomization and Blinding

10.6.2.12.1 Section 6.3.1 Intervention Assignment

Participants eligible for this substudy protocol will be randomly assigned to open investigational treatment arms centrally using an IRT system. For additional details on study intervention assignment, refer to Section 6.3.1 of this substudy protocol.

10.6.2.13 Section 6.4 Study Intervention Compliance

MK-7684 (anti-TIGIT)

Refer to Section 6.4 of the main protocol for instructions that apply to study intervention compliance when study intervention is infused.

V937

Refer to Section 6.4 of the main protocol for instructions that apply to study intervention compliance when study intervention is infused.

MK-4830 (anti-ILT4)

Refer to Section 6.4 of the main protocol for instructions that apply to study intervention compliance when study intervention is infused.

MK-4280A (Coformulation of MK-4280 + Pembrolizumab)

Refer to Section 6.4 of the main protocol for instructions that apply to study intervention compliance when study intervention is infused.

ATRA (tretinoin)

A record of the number of ATRA capsules dispensed to and taken by each participant must be maintained and reconciled with study intervention and compliance records. Intervention start and stop dates, including dates for intervention delays, and missed doses and/or dose reductions will also be recorded in the CRF.

10.6.2.14 Section 6.5 Concomitant Therapy

10.6.2.14.1 Section 6.5.2 Prohibited Concomitant Medications

MK-7684 (anti-TIGIT)

None.

V937

None.

MK-4830 (anti-ILT4)

None.

MK-4280A (Coformulation of MK-4280 + Pembrolizumab)

None.

ATRA (tretinoin)

None.

There are no DDI-related concomitant medication prohibitions or restrictions. No DDI are expected between pembrolizumab and ATRA because ATRA is a small, non-protein molecule.

As ATRA is metabolized by the hepatic P450 system, there is a potential for alteration of PK parameters in patients administered concomitant medications that are also inducers or inhibitors of this system. Medications that generally induce hepatic P450 enzymes include rifampicin, glucocorticoids, phenobarbital, and pentobarbital. Medications that generally inhibit hepatic P450 enzymes include ketoconazole, cimetidine, erythromycin, verapamil, diltiazem, and cyclosporine. To date there are no data to suggest that co-use with these medications increases or decreases either efficacy or toxicity of ATRA.

10.6.2.14.2 Section 6.5.3 Rescue Medications and Supportive Care

MK-7684 (anti-TIGIT)

None. Refer to Section 6.5.3 of this substudy protocol for instructions that apply to immunomodulatory agents.

V937

None. Refer to Section 6.5.3 of this substudy protocol for instructions that apply to immunomodulatory agents.

MK-4830 (anti-ILT4)

None. Refer to Section 6.5.3 of this substudy protocol for instructions that apply to immunomodulatory agents.

MK-4280A (Coformulation of MK-4280 + Pembrolizumab)

None. Refer to Section 6.5.3 of this substudy protocol for instructions that apply to immunomodulatory agents.

ATRA (tretinoin)

None.

10.6.2.15 Section 6.6 Dose Modification (Escalation/Titration/Other)

10.6.2.15.1 Section 6.6.2 Dose Modification for Investigational Agent Intervention

MK-7684 (anti-TIGIT)

Adverse events associated with MK-7684 exposure may represent an immunologic etiology. These irAEs may occur shortly after the first dose or several months after the last dose of study intervention and may affect more than 1 body system simultaneously. Therefore, early recognition and initiation of treatment is critical to reduce complications.

Dose modification instructions provided for pembrolizumab in Section 6.6.1 of this protocol should be followed for MK-7684 as well as they generally apply to immunomodulatory agents.

V937

Adverse events (both nonserious and serious) associated with V937 exposure may represent an immunologic etiology. These AEs may occur shortly after the first dose or several months after the last dose of treatment.

The CTCAE v5.0 must be used to grade the severity of AEs. The investigator may attribute each toxicity event to V937 alone, to pembrolizumab alone, or to the combination, and modify the dose according to .

Holding of 1 agent and not the other agent is appropriate if, in the opinion of the investigator, the toxicity is clearly related to 1 of the study interventions. For example, in combination, if V937 is held due to an AE attributed to that drug, then pembrolizumab may continue to be administered, and vice versa. Appropriate documentation is required regarding to which drug the investigator is attributing the AE. If, in the opinion of the investigator, the toxicity is related to the combination of 2 investigational agents, then both drugs should be held according to recommended dose modifications.

The most common adverse reactions seen with V937 treatment continue to be fatigue, chills, pyrexia, and influenza-like illness. These events are mainly Garde 1 or 2 in severity, transient, and easily managed.

In addition, a group of treatment-related AEs is specific to studies where V937 is delivered by intratumoral administration. This includes injection site pain, injection site erythema, injection site reaction, injection site pruritis, injection site discharge, and injection site edema. These AEs are associated with the intralesional procedure and have not been reported when V937 has been given by the IV or intravesicular route. These symptoms are limited to being mild (Grade 1) in severity.

As common practice, anti-inflammatory or anti-allergic agents, such as acetaminophen or ibuprofen, should be initiated if Grade 2 fever, chill, or site injection reaction occurs. Permanently discontinue V937 if these Grade 2 AEs reoccur in the same participants or are >Grade 2.

MK-4830 (anti-ILT4)

Based on its mechanism of action, irAEs from MK-4830 may occur. AEs associated with pembrolizumab exposure may also represent an immunologic etiology. These irAEs may occur shortly after the first dose or several months after the last dose of treatment and may affect more than 1 body system simultaneously. Therefore, early recognition and initiation of treatment is critical to reduce complications.

The NCI CTCAE v5.0 must be used to grade the severity of AEs. The investigator may attribute each toxicity event to MK-4830 alone, to pembrolizumab alone, or to the combination.

Due to the lack of prior clinical data for MK-4830, the dose modification instructions provided for pembrolizumab in Section 6.6.1 of this protocol should be followed for MK-4830 as well as they generally apply to immunomodulatory agents.

MK-4280A (Coformulation of MK-4280 + Pembrolizumab)

Based on its mechanism of action, irAEs from MK-4280A may occur. These irAEs may occur shortly after the first dose or several months after the last dose of treatment and may affect more than 1 body system simultaneously. Therefore, early recognition and initiation of treatment is critical to reduce complications. Based on existing clinical study data, most irAEs were reversible and could be managed with interruptions of pembrolizumab monotherapy, coformulation, or IO combination administration of corticosteroids and/or other supportive care.

The NCI CTCAE v5.0 must be used to grade the severity of AEs. The investigator may attribute each toxicity event to MK-4280 alone, to pembrolizumab alone, or to the combination.

The dose modification instructions provided for pembrolizumab monotherapy, coformulations or IO combinations in Section 6.6.1 of this protocol should be followed for MK-4280A as they generally apply to immunomodulatory agents.

ATRA (tretinoin)

ATRA dose interruption for participants who experience ATRA-related toxicity will be in accordance with the dose modification guidelines described in Table 13, and in accordance with investigator's assessment of whether ATRA dose interruption is required to manage participant's toxicity. The dose of ATRA in this study is 150 mg/m^2/day. Dose may be reduced to 100 mg/m^2/day to manage toxicities upon Sponsor consultation and approval (Table 13).

AEs will be graded using NCI CTCAE version 5.0. Investigators will decide the probability of the event being related to a single drug or a combination of drugs as to whether dose modification of a single drug or the combination of drugs is required.

Once the ATRA dose has been reduced, it may not be increased at a later date, unless the dose has been mistakenly decreased; in this situation, the Sponsor's approval is required to increase the dose.

Note: If pembrolizumab is permanently discontinued, ATRA must also be discontinued.

Dose modification guidelines for ATRA-related AEs are provided in Table 13.

Table 13 Dose Modification Guidelines for ATRA-Related Adverse Events

Treatment-Related Toxicity[a,b]	**Management**	**Dose Adjustment**
Grade 1 or Tolerable Grade 2	Continue treatment	No change
Intolerable Grade 2[c] or Grade 3[d]		
First occurrence	Interrupt ATRA until resolved to Grade 0-1, or tolerable Grade 2.	Reduce ATRA dose to 50 mg/m^2 twice daily (100 mg/m^2 daily) x 3 days Q3W.
Second occurrence (same toxicity or new toxicity)	Interrupt ATRA.	Further dose reduction should be discussed with Sponsor, otherwise discontinue ATRA[e].
Grade 4[d]: Discontinue Study Intervention[e]		

ATRA=all-trans retinoic acid; CTCAE=Common Terminology Criteria for Adverse Events; q3w=once every 3 weeks.

Note: For grading see CTCAE version 5.0. Collect all AE grades (ie, decreasing and increasing CTCAE grade).

a An interruption of study intervention with ATRA for more than 28 days will require Sponsor approval before study intervention can be resumed.

b Initiate optimal medical management for headache before any ATRA interruption or dose reduction.

c Applicable only to Grade 2 toxicities judged by the participant and/or physician to be intolerable.

d For asymptomatic laboratory abnormalities, such as Grade ≥3 elevations of amylase and lipase that are not considered clinically relevant by the investigator, continuation of treatment should be discussed with Sponsor.

e If ATRA is discontinued, pembrolizumab may be continued if, in the opinion of the investigator, the toxicity is solely attributable to ATRA.

Toxicity Management of Infusion Reactions Related to MK-7684 (anti-TIGIT)

MK-7684 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 the infusion. Toxicity management guidelines for infusion reactions should be followed for MK-7684 (Table 4).

Toxicity Management of Infusion Reactions Related to MK-4830 (anti-ILT4)

MK-4830 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 the infusion. Toxicity management guidelines for infusion reactions should be followed for MK-4830 (Table 4).

Dose Modification and Toxicity Management of Infusion Reactions Related to MK-4280A

MK-4280A 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 MK-4280A associated infusion reaction are provided in Table 4 in Section 6.6.1.2.

10.6.2.15.2 Section 6.6.3 Dose Modification for Overlapping Toxicities

Holding pembrolizumab, MK-7684, V937, MK-4830, or ATRA and not the other(s) is appropriate if, in the opinion of the investigator, the toxicity is clearly related to 1 of the study interventions. For example, if MK-7684 is held due to an AE attributed to that treatment, then pembrolizumab may continue to be administered. If V937 is held due to an AE attributed to that treatment, then pembrolizumab may continue to be administered. If MK-4830 is held due to an AE attributed to that treatment, then pembrolizumab may continue to be administered. The investigator must appropriately document the attribution of the AE. If, in the opinion of the investigator, the toxicity is related to the combination of 2 agents, then both study interventions should be held according to recommended dose modifications.

10.6.2.16 Section 7.1 Discontinuation of Study Intervention

Interruptions from the protocol-specified treatment ≥12 weeks require consultation between the investigator and the Sponsor and written documentation of the collaborative decision on participant management.

10.6.2.17 Section 8.1 Administrative and General Procedures

No additional assessments or procedures are required for MK-7684, V937, MK-4830, MK-4280A, or ATRA. Refer to the SoA (Section 1.3 of this appendix) and Section 8 of this substudy protocol.

10.6.2.17.1 Section 8.1.1.2 Specific Informed Consent

MK-7684 (anti-TIGIT)

None.

V937

None.

MK-4830 (anti-ILT4)

None.

MK-4280A (Coformulation of MK-4280 + Pembrolizumab)

None.

ATRA (tretinoin)

None.

10.6.2.17.2 Section 8.1.8 Study Intervention Administration

10.6.2.17.2.1 Section 8.1.8.1.2 Investigational Agents Administration

MK-7684 (anti-TIGIT)

MK-7684 will be administered on C1D1 and C2D1 over a period of approximately 30 minutes for a total of 2 treatment cycles. MK-7684 will be administered approximately 30 minutes after completion of the pembrolizumab infusion.

V937

V937 will be administered on C1D1, C1D3, C1D5, C1D8, and C1D22. When V937 is to be administered on the same day as pembrolizumab (ie, Cycle 1 Day 8), V937 administration will occur 0.5 to 4 hours after the 400 mg dose of pembrolizumab is infused over 30 minutes. For administration details, see the Pharmacy Manual.

MK-4830 (anti-ILT4)

MK-4830 will be administered on C1D1 and C2D1 over a period of approximately 30 minutes for a total of 2 treatment cycles. MK-4830 will be administered approximately 30 minutes after completion of the pembrolizumab infusion.

MK-4280A (Coformulation of MK-4280 + Pembrolizumab)

MK-4280A (800 mg + pembrolizumab 200 mg) will be administered on C1D1 and C2D1 as a 30-minute IV infusion for a total of 2 treatments.

ATRA (tretinoin)

Two neoadjuvant cycles of ATRA 75 mg/m^2 PO twice daily (total daily dose: 150 mg/m^2) on C1 Days 1, 2, and 3 and C2 Days 1, 2, and 3 + pembrolizumab 400 mg IV on C1 Day 1 of the neoadjuvant phase.

10.6.2.18 Section 8.5 Treatment of Overdose – Investigational Agents

MK-7684 (anti-TIGIT)

For the purpose of this substudy, an overdose of MK-7684 will be defined as any dose exceeding the prescribed dose by ≥20%. No specific information is available on the treatment

of overdose of MK-7684. In the event of overdose, the participant should be observed closely for signs of toxicity. Appropriate supportive treatment should be provided if clinically indicated.

V937

For the purpose of this substudy, an overdose of V937 will be defined as any dose exceeding the prescribed dose by >50% of the indicated dose. No specific information is available on the treatment of overdose of V937. In the event of overdose, V937 should be discontinued and the participant should be observed closely for signs of toxicity. Appropriate supportive treatment should be provided if clinically indicated.

MK-4830 (anti-ILT4)

For purposes of this substudy, an overdose will be defined as any dose exceeding the prescribed dose for MK-4830 by ≥100%. No specific information is available on the treatment of overdose of MK-4830. In the event of overdose, MK-4830 should be discontinued and the participant should be observed closely for signs of toxicity. Appropriate supportive treatment should be provided if clinically indicated.

MK-4280A (Coformulation of MK-4280 + Pembrolizumab)

For this study, an overdose of MK-4280A will be defined as exceeding the prescribed dose by ≥100%.

No specific information is available on the treatment of overdose of MK-4280A. In the event of overdose, the participant should be observed closely for signs of toxicity. Appropriate supportive intervention should be provided if clinically indicated.

ATRA (tretinoin)

There has been no experience with acute overdosage in humans. Overdosage with other retinoids has been associated with transient headache, facial flushing, cheilosis, abdominal pain, dizziness, and ataxia. These symptoms have quickly resolved without apparent residual effects. Supportive symptomatic care can be provided at the investigator's discretion.

10.6.2.19 Section 8.6 Pharmacokinetics

10.6.2.19.1 Blood Collection for Investigational Agents

MK-7684 (anti-TIGIT)

Sample collections for MK-7684 PK and ADA are currently planned as shown in the SoA (Section 10.6.2.1 of this appendix). Study sites must have appropriately trained staff and adequate equipment for procuring and processing specimens. Instructions for the collection, handling, and shipping procedures of MK-7684 PK and ADA samples will be provided in the Laboratory Manual. Samples collected for PK and ADA may only be stored at this time. If ongoing PK and/or ADA sampling is deemed to be unnecessary by the Sponsor, it may be

reduced or discontinued, and sites will be notified accordingly. Pharmacokinetic and ADA analyses of MK-7684 will be reported separately.

V937

Sample collections for V937 PK and ADA are currently planned as shown in the SoA (Section 10.6.2.1 of this appendix). Study sites must have appropriately trained staff and adequate equipment for procuring and processing specimens. Instructions for the collection, handling, and shipping procedures of V937 PK and ADA samples will be provided in the Laboratory Manual. Samples collected for PK and ADA may only be stored at this time. If ongoing PK and/or ADA sampling is deemed to be unnecessary by the Sponsor, it may be reduced or discontinued, and sites will be notified accordingly. Pharmacokinetic and ADA analyses of V937 will be reported separately.

MK-4830 (anti-ILT4)

Sample collections for MK-4830 PK and ADA are currently planned as shown in the SoA (Section 10.6.2.1 of this appendix). Study sites must have appropriately trained staff and adequate equipment for procuring and processing specimens. Instructions for the collection, handling, and shipping procedures of MK-4830 PK and ADA samples will be provided in the Laboratory Manual. Samples collected for PK and ADA may only be stored at this time. If ongoing PK and/or ADA sampling is deemed to be unnecessary by the Sponsor, it may be reduced or discontinued, and sites will be notified accordingly. Pharmacokinetic and ADA analyses of MK-4830 will be reported separately.

MK-4280A (Coformulation of MK-4280 + Pembrolizumab)

To evaluate MK-4280A immunogenicity and exposure for the proposed dosing regimen, sample collections for analysis of ADA and PK are currently planned as shown in the SoA (Section 10.6.2.1 of this appendix). Blood samples will be obtained to measure serum PK of MK-4280 and pembrolizumab. Study sites must have appropriately trained staff and adequate equipment for procuring and processing specimens. Instructions for the collection, handling, and shipping procedures of samples will be provided in the Laboratory Manual. Samples collected for PK and ADA may only be stored at this time. If ongoing PK and/or ADA sampling is deemed to be unnecessary by the Sponsor, it may be reduced or discontinued, and sites will be notified accordingly. PK and ADA analyses of MK-4280A (ie, MK-4280 and pembrolizumab) will be reported separately.

ATRA (tretinoin)

Blood samples for PK and ADA will not be collected in Treatment Arm 6.

10.7 Appendix 7: Collection and Management of Specimens for Future Biomedical Research

Not applicable.

10.8 Appendix 8: AJCC 8th Edition Staging Criteria and Overall Staging Table

The AJCC has designated staging by TNM classification to define melanoma.

Staging tables (Table 14, Table 15, Table 16, Table 17, and Table 18) adapted from AJCC 8th edition. Refer to AJCC guidelines for more information [Gershenwald, J. E., et al 2017].

Table 14 Melanoma T Category Definition

T Stage	T Stage Definition (thickness and ulceration)
TX	Primary tumor thickness cannot be assessed (ulceration status not applicable)
T0	No evidence of primary tumor (ulceration status not applicable)
Tis	Melanoma in situ (ulceration status not applicable)
T1	≤1.0 mm (ulceration status unknown or unspecified)
T1a	<0.8 mm without ulceration
T1b	<0.8 mm with ulceration or 0.8-1.0 mm with or without ulceration
T2	>1.0-2.0 mm (ulceration status unknown or unspecified)
T2a	>1.0-2.0 mm without ulceration
T2b	>1.0-2.0 mm with ulceration
T3	>2.0-4.0 mm (ulceration status unknown or unspecified)
T3a	>2.0-4.0 mm without ulceration
T3b	>2.0-4.0 mm with ulceration
T4	>4.0 mm (ulceration status unknown or unspecified)
T4a	>4.0 mm without ulceration
T4b	>4.0 mm with ulceration

Abbreviations: T = primary tumor.

Table 15 Melanoma N Category Definition

N Category	Number of Tumor-involved Regional Lymph Nodes	Presence of In-transit, Satellite, and/or Microsatellite Metastases
NX	Regional Nodes not assessed (exception: pathological N category not required for T1 melanomas, use clinical N information)	No
N0	No regional metastases detected	No
N1	One tumor-involved node or any number of in-transit, satellite, and/or microsatellite metastases with no tumor-involved nodes	
N1a	One clinically occult (detected by SLN biopsy)	No
N1b	One clinically detected	No
N1c	No regional lymph node disease	Yes
N2	2 or 3 tumor-involved nodes or any number of in-transit, satellite, and/or microsatellite metastases with 1 tumor-involved node	
N2a	2 or 3 clinically occult (detected by SLN biopsy)	No
N2b	2 or 3, at least one of which was clinically detected	No
N2c	One clinically occult or clinically detected	Yes
N3	Four or more tumor-involved nodes or any number of in-transit, satellite, and/or microsatellite metastases with 2 or more tumor-involved nodes, or any number of matted nodes without or with in-transit, satellite, and/or microsatellite metastases.	
N3a	4 or more clinically occult (detected by SLN biopsy)	No
N3b	4 or more, at least one of which was clinically detected, or the presence of any number of matted nodes	No
N3c	2 or more clinically occult or clinically detected and/or presence of any number of matted nodes.	Yes

Abbreviations: N= regional lymph node; SLN = sentinel lymph node.

Table 16 Melanoma M Category Definition

M Category	Anatomic Site	Lactate Dehydrogenase Level
M0	No evidence of distant metastasis	Not applicable
M1	Evidence of distant metastasis	See below
M1a	Distant metastasis to skin, soft tissue including muscle, and/or nonregional lymph node	Not recorded or unspecified
M1a(0)		Not elevated
M1a(1)		Elevated
M1b	Distant metastasis to lung with or without M1a sites of disease	Not recorded or unspecified
M1b(0)		Not elevated
M1b(1)		Elevated
M1c	Distant metastasis to non-central nervous system visceral sites with or without M1a or M1b sites of disease	Not recorded or unspecified
M1c(0)		Not elevated
M1c(1)		Elevated
M1d	Distant metastasis to CNS with or without M1a, M1b, or M1c sites of disease	Not recorded or unspecified
M1d(0)		Not elevated
M1d(1)		Elevated

Abbreviations: CNS = central nervous system; M = distant metastasis.

Table 17 AJCC Clinical Prognostic Stage Groups (cTNM)

T	N	M	Clinical Stage Group
Tis	N0	M0	0
T1a	N0	M0	IA
T1b	N0	M0	IB
T2a	N0	M0	IB
T2b	N0	M0	IIA
T3a	N0	M0	IIA
T3b	N0	M0	IIB
T4a	N0	M0	IIB
T4b	N0	M0	IIC
Ant T, Tis	≥N1	M0	III
Any T	Any N	M1	IV

Abbreviations: cTNM = clinical prognostic tumor, node, and metastasis; M0 = No evidence of distant metastases; N0 = No regional metastasis detected including no tumor-involved nodes and no in-transit, satellite, and/or microsatellite metastasis.

Table 18 AJCC Pathological (pTNM) Staging Groups

Staging (AJCC 8th edition)			
0	Tis	N0	M0
IA	T1a	N0	M0
IA	T1b	N0	M0
IB	T2a	N0	M0
IIA	T2b	N0	M0
IIA	T3a	N0	M0
IIB	**T3b**	**N0**	**M0**
IIB	**T4a**	**N0**	**M0**
IIC	**T4b**	**N0**	**M0**
IIIB	T0	N1b, N1c	M0
IIIC	T0	N2b, N2c, N3b, N3c	M0
IIIA	T1a/b-T2a	N1a or N2a	M0
IIIB	T1a/b-t2a	N1b/c or N2b	M0
IIIB	T2b/T3a	N1a-N2b	M0
IIIC	T1a-T3a	N2c or N3a/b/c	M0
IIIC	T3b/T4a	Any N≥N1	M0
IIIC	T4b	N1a-N2c	M0
IIID	T4b	N3a/b/c	M0
IV	Any T, Tis	Any N	M1

Abbreviations: M0 = No evidence of distant metastases; N0 = No regional metastasis detected including no tumor-involved nodes and no in-transit, satellite, and/or microsatellite metastasis; pTNM = pathological tumor, node, and metastasis.

10.9 Appendix 9: ECOG Performance Status

Grade	Description
0	Normal activity. Fully active, able to carry on all predisease performance without restriction.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (eg, light housework, office work).
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about >50% of waking hours.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.
Abbreviations: ECOG = Eastern Cooperative Oncology Group [Oken, M. M., et al 1982]	

10.10 Appendix 10: Surgery

To be evaluable for the primary endpoint analysis, participants should undergo curative intent surgical of the tumor, which includes lymphadenectomy of the tumor-involved lymph node disease and/or in-transit metastases and resection of the primary cutaneous melanoma lesion ± wide local excision, if not resected previously.

Surgical Guidelines:

Surgical excision is the primary treatment for melanoma. Optimal surgical margins for primary melanoma should follow NCCN guidelines v1:2017 recommendations (0.5 to 1 cm for in situ melanoma, 1-cm margins for melanomas ≤1 mm in thickness, and 1- to 2-cm margins for melanomas measuring 1.01 to 2 mm in thickness).

Lymphadenectomy of the tumor-involved lymph node disease includes complete lymph node dissection of the involved nodal basin. In the setting of inguinal lymphadenopathy, a pelvic dissection is recommended if the PET/CT or pelvic CT scan reveals iliac and/or obturator lymph node involvement or if a positive Cloquet's lymph node is found on intraoperative frozen section. Pelvic dissection should also be considered for clinically positive inguinal-femoral nodes or if 3 or more inguinofemoral nodes are involved. The operative note should fully describe the anatomic boundaries of the lymph node dissection.

Excision of in-transit disease to obtain clear margins is the mainstay of treatment for limited resectable in-transit metastasis.

10.11 Appendix 11: Country-specific Requirements

10.11.1 France

Section 6.6.1 Dose Modification for Pembrolizumab

Participants should be discontinued from study intervention if any of the following AEs occur:

- Recurrent Grade 3 colitis
- Grade 4 skin rash
- Stevens-Johnson syndrome
- Toxic epidermal necrolysis

Please refer to the current European Summary of Product Characteristics for additional guidance on management of AEs associated with pembrolizumab administration.

10.11.2 Germany

Section 5.2 Exclusion Criteria

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

- Has a known history of human immunodeficiency virus (HIV) infection. HIV testing is required at Screening.
- Has a known history of hepatitis B (defined as hepatitis B surface antigen [HBsAg] reactive) or known active hepatitis C virus (defined as HCV RNA [qualitative] is detected) infection. Testing for hepatitis B or hepatitis C is required at Screening.
- Has a known history of active tuberculosis (TB; *Bacillus* tuberculosis). Testing for tuberculosis is required at Screening.

Legally Acceptable Representative: Applicable to the definition provided in protocol Section 8.1.1 – Informed Consent

In order for a participant to be eligible to participate in Germany, they must be capable of providing documented informed consent; therefore, all references to a participant's "legally acceptable representative" in the protocol are not applicable for participants in Germany.

10.12 Appendix 12: Abbreviations

Abbreviation	Expanded Term
1L	First-line
ADA	antidrug antibody
ADL	activities of daily living
ADR	adverse drug reaction
AE	adverse event
AJCC	American Joint Committee on Cancer
ALT	Alanine aminotransferase
anti-CTLA-4	anticytotoxic T-lymphocyte-associated protein 4
APaT	All Participants as Treated
APL	acute promyelocytic leukemia
aPTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
ATRA	all-trans retinoic acid
AUC	area under the curve
BAL	bronchoalveolar lavage
BCG	*Bacillus* Calmette-Guérin
BP	blood pressure
BRAF	v-raf murine sarcoma viral oncogene homolog B1
C1D1	Cycle 1 Day 1
C_{avg}	Average concentration over the dosing interval
CD	cluster of differentiation
CD28	cluster of differentiation 28
CHMP	Committee for Medicinal Products for Human Use (CHMP) is the European Medicines Agency committee responsible for human medicines.
CI	confidence interval
CIV	central imaging vendor
C_{max}	This pharmacokinetics term refers to the maximum (or peak) serum concentration that a drug achieves in a specified test area of the body after the drug has been administered. Which is the minimum (or trough) concentration that a drug achieves after dosing.
C_{min}	This pharmacokinetics term refers to the minimum (or trough) concentration that a drug achieves in a specified test area of the body after dosing.
CNS	central nervous system
CONSORT	Consolidated Standards of Reporting Trials
CR	complete response
CRF	Case Report Form
CSR	Clinical Study Report
C-SSRS	Columbia-Suicide Severity Rating Scale
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTCAE 5.0	Common Terminology Criteria for Adverse Events, version 5.0
ctDNA	circulating tumor DNA
CTFG	clinical trial facilitation group
CTLA-4	cytotoxic T–lymphocyte-associated protein 4
DAF	Decay-accelerating factor
DCR	disease control rate
DDI	drug-drug interaction
DILI	drug-induced liver injury
DLT	dose-limiting toxicity
DNA	deoxyribonucleic acid

Abbreviation	Expanded Term
DOR	Duration of Response
E-R	Exposure-response
ECG	electrocardiogram
ECI	event of clinical interest
ECOG	Eastern Cooperative Oncology Group
EDC	electronic data capture
EEA	European Economic Area
EFS	event-free survival
ELISA	enzyme-linked immunosorbent assay
EMA	European Medicines Agency
EORTC	European Organization for Research and Treatment of Cancer
EOT	End of treatment
EQ-5D-5L	European Quality of Life 5-dimension 5- level
EU	European Union
EU CTR	European Union Clinical Trials Regulation
FAS	Full Analysis Set
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act
FGF	fibroblast growth factor
FIH	First in Human
FSH	Follicle stimulating hormone
FSR	first site ready
FT4	free thyroxine
FU	follow up
G-CSF	Granulocyte Colony-Stimulating Factor
GCP	Good Clinical Practice
GITR	glucocorticoid-induced TNFR-related protein
GLP	Good Laboratory Practice
GM-CSF	Granulocyte-macrophage-colony-Stimulating Factor
GVHD	Graft-versus-host disease
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HIV	human immunodeficiency virus
HLA-DR	Human Leukocyte Antigen – DR isotype
HLP	hind-limb paralysis
HRQoL	health-related quality of life
HRT	hormone replacement therapy
HR	heart rate
Hu	human
IA	interim analysis
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ICSR	individual case safety reports
IDO	indoleamine-(2,3)-dioxygenase
IgG1	Immunoglobulin G, subclass 1
IgG	Immunoglobulin G
IgM	Immunoglobulin M
IHC	immunohistochemistry
IL-2R	interleukin-2 receptor

Abbreviation	Expanded Term
IMP	Investigational medicinal product
ILT4	Immunoglobulin-like transcript 4
IMP	investigational medicinal product
IN	intranasal
IND	Investigational New Drug
INR	International Normalized Ratio
IO	Immuno-oncology
IP	intraperitoneal
irAE	immune-related adverse event
IRB	Institutional Review Board
IRT	interactive response technology
ITIM	immunoreceptor tyrosine-based inhibitory motif
ITT	immunoglobulin tail tyrosine
IV	intravenous
IVD	in vitro diagnostic
KO	knock-out
LAG-3	Lymphocyte Activation Gene-3
LDH	lactate dehydrogenase
M&S	modeling and simulation
mAb	monoclonal antibody
MBM	melanoma brain metastasis
MDSCs	Myeloid derived suppressor cells
MedDRA	Medical Dictionary for Regulatory Activities
MEK	mitogen-activated protein kinase
MRI	magnetic resonance imaging
mRNA	messenger RNA
MSI	microsatellite instability
MTD	maximum tolerated dose
mTPI	modified Toxicity Probability Interval
Mu	mouse
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NCT	National Clinical Trial
NDA	New Drug Application
NHP	non-human primates
NIMP	noninvestigational medicinal product
NK	Natural killer (cells)
NK T	Natural killer T (cells)
NMIBC	nonmuscle-invasive bladder cancer
NOAEL	No observed adverse effect level
NSCLC	non–small cell lung cancer
OME	other important medical event
ORR	objective response rate
OS	overall survival
PBPK	physiologically-based PK
pCR	pathological complete response
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
PirB	Paired immunoglobulin-like receptor B

Abbreviation	Expanded Term
PK	pharmacokinetic
pPR	pathological partial response
PR	partial response
PRES/RPLS	Posterior Reversible Encephalopathy Syndrome/Reversible Posterior Leukoencephalopathy Syndrome
PRO	patient-reported outcome
PT	prothrombin time
PTT	partial thromboplastin time
PVR	poliovirus receptor
PVRL-2	poliovirus receptor-related 2
Q2W	every 2 weeks
Q3W	every 3 weeks
Q6W	every 6 weeks
QLQ-C30	Quality of Life Questionnaire-Core 30
QOL	quality of life
RBC	red blood cell
RCC	renal cell carcinoma
RECIST 1.1	Response Evaluation Criteria in Solid Tumors 1.1
RFS	recurrence-free survival
RNA	ribonucleic acid
RP2D	recommended Phase 2 dose
SAC	Scientific Advisory Committee
SAE	serious adverse event
SAP	Statistical Analysis Plan
SC	subcutaneous
SCID	severe combined immunodeficiency
SHP-1	Src homology 2 domain containing protein tyrosine phosphatase 1
SHP-2	Src homology 2 domain containing protein tyrosine phosphatase 2
SIM	Site Imaging Manual
SLN	sentinel lymph node
SNP	single-nucleotide polymorphism
SoA	Schedule of Activities
SOC	Standard of care
SRS	sequence retrieval system
sSAP	supplemental Statistical Analysis Plan
SUSAR	Suspected Unexpected Serious Adverse Reaction
T3	triiodothyronine
TB	*Bacillus* tuberculosis
TCID50	tissue culture infectious dose 50%/mL
Teffs	effector T cells
Tg	transgenic
TIGIT	T-cell immunoreceptor with Ig and ITIM domains
TNM	tumor, node, and metastasis
T_{regs}	regulatory T cells
TSH	thyroid-stimulating hormone
TTD	time to true deterioration
TVEC	talimogene laherparepvec
ULN	upper limit of normal
UPCR	urine protein-to-creatinine ratio
US/USA	United States/United States of America
UTN	Universal Trial Number
VEGF	Vascular endothelial growth factor

Abbreviation	Expanded Term
WHO	World Health Organization
WOCBP	woman/women of childbearing potential
Wt	wild-type

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