Official Protocol Title:	Adjuvant Therapy with Pembrolizumab versus Placebo in Resected Highrisk Stage II Melanoma: A Randomized, Double-blind Phase 3 Study (KEYNOTE 716)
NCT number:	NCT03553836
Document Date:	11-May-2021

Title Page

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Protocol Title: Adjuvant Therapy with Pembrolizumab versus Placebo in Resected High-risk Stage II Melanoma: A Randomized, Double-blind Phase 3 Study (KEYNOTE 716)

Protocol Number: 716-04

Compound Number: MK-3475

Sponsor Name and Legal Registered Address:

Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc.
(hereafter referred to as the Sponsor or MSD)

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Regulatory Agency Identifying Number(s):

IND NUMBER: 110,080

EudraCT NUMBER: 2018-000669-35

Approval Date: 11 May 2021

Sponsor Signatory

Typed Name: Date
Title:

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

Investigator Signatory

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

Typed Name: Date
Title:

DOCUMENT HISTORY

Document	Date of Issue	Overall Rationale
Amendment 4	11-MAY-2021	Alignment with the USPI requirement for Pembrolizumab Dose Modifications
Amendment 3	28-SEP-2020	Clarify imaging schedule
Amendment 2 Country Specific	05-AUG-2019	Alignment with UK-specific Requirements
Amendment 1	18-MAR-2019	Conformation with FDA and other country-specific requirements
Original Protocol	17-MAY-2018	N/A

PROTOCOL AMENDMENT SUMMARY OF CHANGES

Amendment 04

Overall Rationale for the Amendment:

Alignment with the USPI requirement for Pembrolizumab Dose Modifications

Summary of Changes Table:

Section # and Name	Description of Change	Brief Rationale
6.6 Immune-related Events and Dose Modification (Escalation/Titration/Other)	Updated 6.6 header. Deleted 6.6.1 header. The Dose Modification and Toxicity Management Guidelines for irAEs and table were updated	The Dose Modification and Toxicity Management Guidelines for irAEs and table were updated to align with the USPI as requested by the FDA
1.1 Synopsis 4.1 Overall Design	Removed "when clinically appropriate"	Compliance with FDA request
	Removed “by telephone”	Clarification of information
1.3.1 Part 1 Adjuvant Treatment: Pembrolizumab or Placebo 1.3.2 Part 1 Crossover/Rechallenge After First Recurrence 8.3.1.2 Directed Physical Exam	Added language related to inspection of local recurrence and palpation of regional lymph nodes	Clarification of Directed Physical Examination

Section # and Name	Description of Change	Brief Rationale
4.1 Overall Design	Removed “initiating a nonstudy cancer treatment," Removed language related to the development of second primary malignancies	The efficacy assessment is based on ITT follow-up regardless of initiation of nonstudy cancer treatment or secondary primary malignancies
4.2.1.1.1 Primary Efficacy Endpoint	Provided reference to Appendix 12 Guidance for Distinguishing Primary Cutaneous Melanomas From Cutaneous Metastases of Melanoma	Additional guidance for pathologist as requested by the FDA
4.3 Justification for Dose	PK data was summarized and a reference to the IB was added Deleted reference to tumor types	Update of information
6.5.1 Specific Restrictions	Updated vaccine language	Clarification of vaccines allowed
8.2.1 Tumor Scans and Assessment of Disease 8.2.1.1 Initial Tumor Scans 8.2.1.2 Tumor Scans During the Study 8.2.1.3 End of Treatment and Follow-up Tumor Scans 8.2.1.4 Summary of Scans	References to images/imaging changed to “scan” as appropriate	Clarification of language / information.

Section # and Name	Description of Change	Brief Rationale
8.2.1.4.1 Part 1 Adjuvant Treatment 8.2.1.4.2 Part 2 Crossover/Rechallenge After First Recurrence	References to images/imaging changed to “scan” as appropriate	Clarification of language / information.
8.3 Safety Assessment	Added reference to Procedures Manual	Text added for clarity
8.4.1 Time Period and Frequency for Collecting AE, SAE, and Other Reportable Safety Event Information	Added more language to pregnancy/lactation instructions to Table 7	Clarification of information regarding how to handle pregnancy/lactation exposure
8.11.3.1 Safety Follow-up Visit 8.11.3.2 Efficacy Follow-up Visits 8.11.3.3 Distant Metastases-free Survival Follow-up 8.11.3.4 Survival Follow-up Contacts 8.11.4 Vital Status	Updated language to clarify visit information	Clarification of information

Section # and Name	Description of Change	Brief Rationale
10.9 Appendix 9: Description of the iRECIST Process for Assessment of Disease Progression	Paragraph added to align with lack of clinical stability used in RECIST 1.1	Alignment with FDA requirement
10.12 Appendix 12: Guidance for Distinguishing Primary Cutaneous Melanomas from Cutaneous Metastases of Melanoma	Added new appendix	Provide guidance for distinguishing primary cutaneous melanomas from cutaneous metastases of melanoma
Minor grammatical and typographical changes have been made throughout the document		

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1. Protocol Summary

1.1 Synopsis

Protocol Title:

Adjuvant Therapy with Pembrolizumab versus Placebo in Resected High-risk Stage II Melanoma: A Randomized, Double-blind Phase 3 Study (KEYNOTE 716)

Short Title:

Adjuvant Therapy with Pembrolizumab versus Placebo in Resected High-risk Stage II Melanoma

Overall Design:

Study Phase	Phase 3
Clinical Indication	Adjuvant treatment of high-risk Stage II melanoma
Population	Participants with surgically resected high-risk Stage II melanoma
Study Type	Interventional
Type of Design	Randomized, Multisite, Parallel-group, with Crossover or Rechallenge
Type of Control	Placebo
Study Blinding	Part 1 - Double-blind Part 2 - Unblinded
Estimated Duration of Study	The Sponsor estimates that the study will require approximately 15 years from the time the first participant (or their legally acceptable representative) provides documented informed consent until the last participant's last study-related contact.

Number of Participants:

Approximately 954 participants will be randomized as described in Section 9.1.

Treatment Groups and Duration:

Treatment Groups	Part 1 (Adjuvant Treatment): • Pembrolizumab (Adult: 200 mg IV Q3W or Pediatric: 2 mg/kg IV Q3W up to a maximum of 200 mg Q3W) • Placebo (saline solution IV Q3W) Part 2 (Crossover/Rechallenge): • Pembrolizumab: o Adult: 200 mg IV Q3W o Pediatric: 2 mg/kg IV Q3W up to a maximum of 200 mg IV Q3W
Duration of Participation	Each participant will participate in the study for approximately 15 years from the time the participant (or their legally acceptable representative) provides documented informed consent through the final contact. After a screening phase of up to 28 days, each participant in Part 1 will be assigned to receive study treatment (pembrolizumab or placebo) for 17 cycles. Participants will be treated with pembrolizumab or placebo unless they experience disease recurrence, unacceptable AEs, or intercurrent illness that prevents further administration of treatment, investigator's decision to withdraw the participant, noncompliance with study treatment or procedure requirements or administrative reasons requiring cessation of treatment, or until the participant has received 17 cycles of pembrolizumab or placebo. Disease recurrence is confirmed by investigator radiographically and/or by exam/biopsy and pathologically confirmed by the site. Participants who have recurrence of disease will be unblinded after Sponsor consultation and approval. Participants who receive placebo (Part 1 placebo arm), OR who stop study treatment after receiving 17 cycles of pembrolizumab (Part 1 pembrolizumab arm), do not experience disease recurrence within 6 months of completing Part 1 treatment with pembrolizumab, and do not stop treatment with pembrolizumab for disease recurrence or intolerability, may be eligible for rechallenge (Part 2) and may receive up to 17 or 35 cycles of pembrolizumab therapy Q3W at recurrence per Part 2 eligibility guidelines (Section 6.7). Disease recurrence/progression is confirmed by investigator

	radiographically (with site radiologist) and/or by exam with subsequent biopsy. RECIST 1.1/iRECIST will be used to assess/confirm disease progression in participants with metastatic/unresectable disease identified at start of Part 2 therapy. After the end of treatment in Parts 1 and 2, each participant will be followed for the occurrence of AEs and spontaneously reported pregnancy as described under Section 8.4. Participants who discontinue for reasons other than confirmed metastatic disease recurrence will be followed for disease status until metastatic disease recurrence is confirmed (radiographically and/or by exam with subsequent biopsy). Participants who initiate a nonstudy cancer treatment will have posttreatment DMFS follow-up until metastatic disease recurrence is documented. All participants will be followed for overall survival until death or the end of the study.

Study Governance:

Study Governance Committees

Committee	Included in this study?
Steering Committee	N
Executive Oversight Committee	Y
Data Monitoring Committee	Y
Clinical Adjudication Committee	N

Study governance considerations are outlined in Appendix 1.

A list of abbreviations used in this document can be found in Appendix 7.

1.2 Schema

1.2.1 Study Design

The study design is depicted in Figure 1.

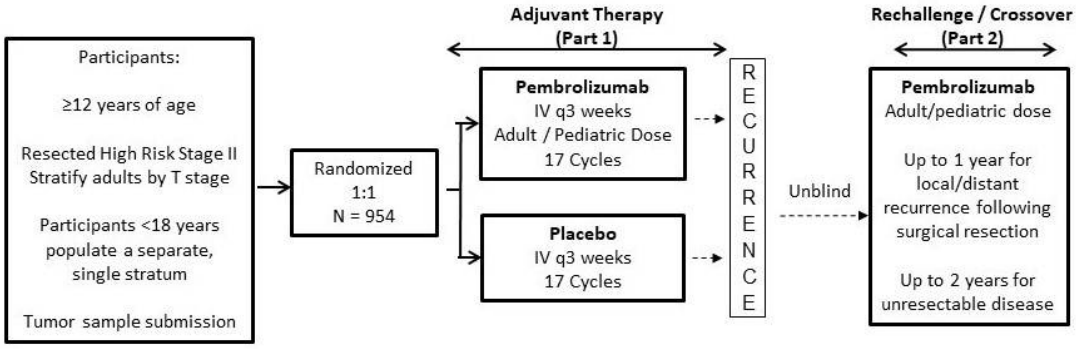


Figure 1 Study Design

1.2.2 Study Flow Schema

The study flow schema is depicted in Figure 2.

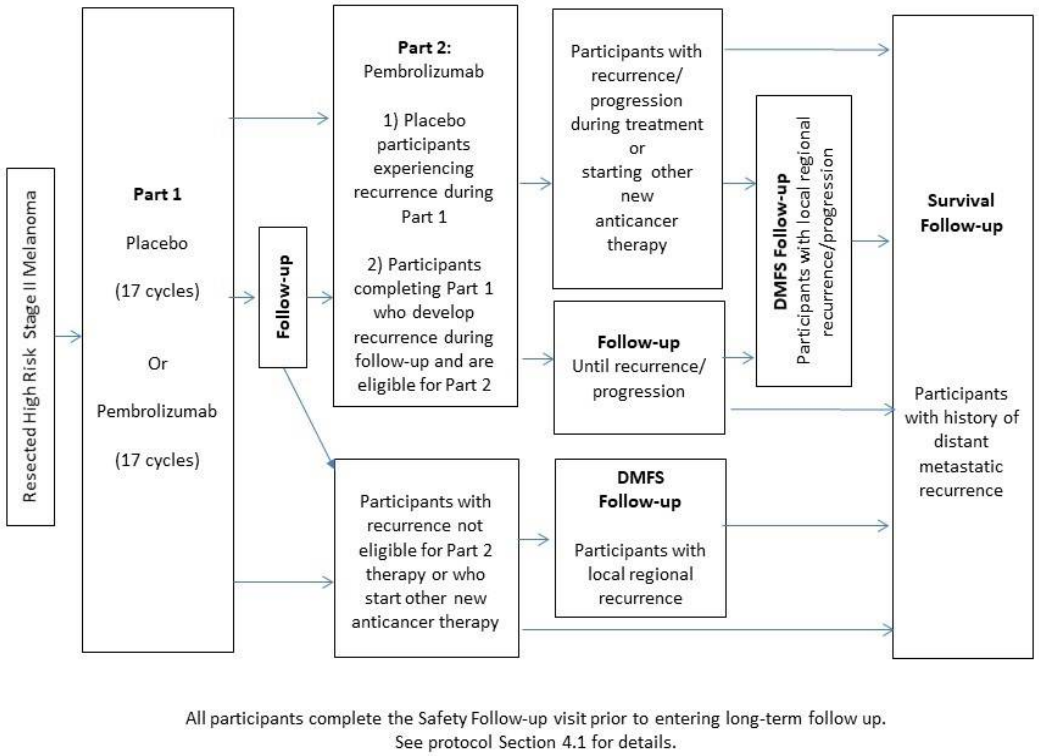


Figure 2 Study Flow Schema

1.3 Schedule of Activities (SoA)

1.3.1 Part 1 Adjuvant Treatment: Pembrolizumab or Placebo

Part I Adjuvant Treatment													
Trial Period	**Screening**		**During Treatment**			**End of Treatment**	**Posttreatment**						**Notes**
Treatment Cycle (Cycle = 21 days)			**1**	**2 and every even # cycle**	**3 and every odd # cycle**	**At time of treatment discontinuation**	**Safety Follow-up**	**Follow-Up Visits[d]**			**DMFS Follow-up**	**Survival Follow-up**	
							30 days post last dose	**Every 12 weeks for the 1st year from EOT**	**Every 6 months for the 2nd year to 5th year from EOT**	**Yearly thereafter starting at year 6 from EOT**	**Every 12 weeks**	**Every 12 weeks**	Procedures within a given treatment (TX) visit should occur on Day 1 of each cycle unless otherwise noted
Scheduling Window (Days):	**-28 to -1**	**-10 to -1**	**+3**	**±3**	**±3**		**+7**	**±14**	**±14**	**±28**	**±14**	**±14**	
Administrative Procedures													
Informed Consent/Assent	X												
Informed Consent/Assent for Future Biomedical Research	X												Not mandatory for participation in study
Participant Identification Card	X												
Eligibility Criteria	X												
Demographics and Medical History	X												
Prior and Concomitant Medication Review	X	X	X	X	X	X	X						Concomitant medications will be recorded beyond 30 days post-TX DC if related to SAE or ECI.
Treatment Assignment in IRT			X										
Trial Treatment Administration													
Pembrolizumab/Placebo			X	X	X								
Safety Procedures													
Full Physical Examination	X					X							

Part I Adjuvant Treatment													
Trial Period	**Screening**		**During Treatment**			**End of Treatment**	**Posttreatment**						**Notes**
Treatment Cycle (Cycle = 21 days)			**1**	**2 and every even # cycle**	**3 and every odd # cycle**	**At time of treatment discontinuation**	**Safety Follow-up**	**Follow-Up Visits[d]**			**DMFS Follow-up**	**Survival Follow-up**	
							30 days post last dose	**Every 12 weeks for the 1st year from EOT**	**Every 6 months for the 2nd year to 5th year from EOT**	**Yearly thereafter starting at year 6 from EOT**	**Every 12 weeks**	**Every 12 weeks**	Procedures within a given treatment (TX) visit should occur on Day 1 of each cycle unless otherwise noted
Scheduling Window (Days):	**-28 to -1**	**-10 to -1**	**+3**	**±3**	**±3**		**+7**	**±14**	**±14**	**±28**	**±14**	**±14**	
Directed Physical Examination			X	X	X		X	X	X	X			The investigator or qualified designee should conduct a visual inspection of local recurrence and palpation of regional lymph nodes to assess regional recurrence.
Vital Signs (pulse, blood pressure, respiratory rate, and temperature), Height and Weight	X		X	X	X	X	X	X	X	X			Pediatric only – height and weight to be measured at every visit. Adult height measured at screening only.
12-Lead ECG	X												6 lead ECG acceptable per local guidelines
Age Appropriate Performance Scale (Lansky/Karnofsky/ECOG)	X		X	X	X	X	X	X	X	X			Evaluated prior to dosing. Lansky scale to be used for participants ≤16 years old. Karnofsky scale to be used for participants >16 and <18 years old. ECOG to be used for participants ≥18 years old

Part I Adjuvant Treatment													
Trial Period	**Screening**		**During Treatment**			**End of Treatment**	**Posttreatment**						**Notes**
Treatment Cycle (Cycle = 21 days)			**1**	**2 and every even # cycle**	**3 and every odd # cycle**	**At time of treatment discontinuation**	**Safety Follow-up**	**Follow-Up Visits[d]**			**DMFS Follow-up**	**Survival Follow-up**	
							30 days post last dose	**Every 12 weeks for the 1st year from EOT**	**Every 6 months for the 2nd year to 5th year from EOT**	**Yearly thereafter starting at year 6 from EOT**	**Every 12 weeks**	**Every 12 weeks**	Procedures within a given treatment (TX) visit should occur on Day 1 of each cycle unless otherwise noted
Scheduling Window (Days):	**-28 to -1**	**-10 to -1**	**+3**	**±3**	**±3**		**+7**	**±14**	**±14**	**±28**	**±14**	**±14**	
HIV, Hepatitis B and C determination	X												No testing for HIV, Hepatitis B and C is required unless mandated by local health authority. Refer to Appendix 6 for country-specific requirements.
Review Adverse Events	X	X	X	X	X	X	X	X	X	X			
Submit Follow-up DMFS Imaging to Central Vendor											X		Site investigator must collect and review copy of clinical notes/reports, imaging reports, photographs and/or pathology reports (including imaging and biopsy/pathology assessment done external to site) to update disease status. A central imaging vendor will be used to collect, clean, and hold tumor imaging obtained during the DMFS phase of the study.

Part I Adjuvant Treatment													
Trial Period	**Screening**		**During Treatment**			**End of Treatment**	**Posttreatment**						**Notes**
Treatment Cycle (Cycle = 21 days)			**1**	**2 and every even # cycle**	**3 and every odd # cycle**	**At time of treatment discontinuation**	**Safety Follow-up**	**Follow-Up Visits[d]**			**DMFS Follow-up**	**Survival Follow-up**	
							30 days post last dose	**Every 12 weeks for the 1st year from EOT**	**Every 6 months for the 2nd year to 5th year from EOT**	**Yearly thereafter starting at year 6 from EOT**	**Every 12 weeks**	**Every 12 weeks**	Procedures within a given treatment (TX) visit should occur on Day 1 of each cycle unless otherwise noted
Scheduling Window (Days):	**-28 to -1**	**-10 to -1**	**+3**	**±3**	**±3**		**+7**	**±14**	**±14**	**±28**	**±14**	**±14**	
Submit Follow-up SFU Imaging to Central Vendor												X	Site investigator must collect and review copy of clinical notes/reports, imaging reports, photographs and/or pathology reports (including imaging and biopsy/pathology assessment done external to site) to update disease status if it is available. A central imaging vendor will be used to collect, clean, and hold submitted tumor imaging obtained during the SFU phase of the study.
Poststudy Anticancer Therapy Status							X	X	X	X	X	X	
Survival Status			←									→	After investigator determined recurrence or start of new anticancer TX. Upon Sponsor request, participants may be contacted for survival status at any time during the study.

Part I Adjuvant Treatment													
Trial Period	**Screening**		**During Treatment**			**End of Treatment**	**Posttreatment**						**Notes**
Treatment Cycle (Cycle = 21 days)			**1**	**2 and every even # cycle**	**3 and every odd # cycle**	**At time of treatment discontinuation**	**Safety Follow-up**	**Follow-Up Visits[d]**			**DMFS Follow-up**	**Survival Follow-up**	
							30 days post last dose	**Every 12 weeks for the 1st year from EOT**	**Every 6 months for the 2nd year to 5th year from EOT**	**Yearly thereafter starting at year 6 from EOT**	**Every 12 weeks**	**Every 12 weeks**	Procedures within a given treatment (TX) visit should occur on Day 1 of each cycle unless otherwise noted
Scheduling Window (Days):	**-28 to -1**	**-10 to -1**	**+3**	**±3**	**±3**		**+7**	**±14**	**±14**	**±28**	**±14**	**±14**	
Lab Procedures/Assessments													
Pregnancy Test – Urine or Serum		X		X	X	X	X						For women of childbearing potential, a urine pregnancy test should be performed within 72 hours prior to 1st dose of study TX. If urine pregnancy results cannot be confirmed as negative, a serum pregnancy test performed by the local study site laboratory is required.
PT/INR and aPTT		X											aPTT/PT/INR is mandatory at screening. PT/INR should be tested subsequently as needed for participants on warfarin based anticoagulation therapy.
CBC with Differential		X		X		X	X						

Part I Adjuvant Treatment													
Trial Period	**Screening**		**During Treatment**			**End of Treatment**	**Posttreatment**						**Notes**
Treatment Cycle (Cycle = 21 days)			**1**	**2 and every even # cycle**	**3 and every odd # cycle**	**At time of treatment discontinuation**	**Safety Follow-up**	**Follow-Up Visits[d]**			**DMFS Follow-up**	**Survival Follow-up**	
							30 days post last dose	**Every 12 weeks for the 1st year from EOT**	**Every 6 months for the 2nd year to 5th year from EOT**	**Yearly thereafter starting at year 6 from EOT**	**Every 12 weeks**	**Every 12 weeks**	Procedures within a given treatment (TX) visit should occur on Day 1 of each cycle unless otherwise noted
Scheduling Window (Days):	**-28 to -1**	**-10 to -1**	**+3**	**±3**	**±3**		**+7**	**±14**	**±14**	**±28**	**±14**	**±14**	
Comprehensive Chemistry Panel		X		X		X	X						Every 6 weeks (at the start of even # cycles) during treatment. Screening laboratory tests that cannot be done -10 to -1 day prior to C1D1 can be done on the day of C1D1 (before first dose in Part 1) if results are available for investigator's review before dosing
Urinalysis		X		X			X						Prior to first dose and then C4, C8, C12, C16 and 30 days after last study treatment.
T3(or Free T3), FT4 and TSH		X		X			X						After C1, retrospective review of thyroid function testing is allowed when results are not available prior to dosing
LDH			Recurrence only										Only required when recurrence is identified

Part I Adjuvant Treatment													
Trial Period	**Screening**		**During Treatment**			**End of Treatment**	**Posttreatment**						**Notes**
Treatment Cycle (Cycle = 21 days)			**1**	**2 and every even # cycle**	**3 and every odd # cycle**	**At time of treatment discontinuation**	**Safety Follow-up**	**Follow-Up Visits[d]**			**DMFS Follow-up**	**Survival Follow-up**	
							30 days post last dose	**Every 12 weeks for the 1st year from EOT**	**Every 6 months for the 2nd year to 5th year from EOT**	**Yearly thereafter starting at year 6 from EOT**	**Every 12 weeks**	**Every 12 weeks**	Procedures within a given treatment (TX) visit should occur on Day 1 of each cycle unless otherwise noted
Scheduling Window (Days):	**-28 to -1**	**-10 to -1**	**+3**	**±3**	**±3**		**+7**	**±14**	**±14**	**±28**	**±14**	**±14**	
Disease Evaluation													
Tumor Imaging (See Site Imaging Manual for more details)	X[a]			X[a]	X[a]			X[a]					Imaging timing should follow calendar days and should not be adjusted for delays in cycle starts. CT is preferred imaging modality for neck, chest, abdomen, and pelvis. CT portion of PET-CT may be used in place of stand-alone CT if it is of diagnostic quality per Site Imaging Manual. In the case of DC due to recurrence, scan date is the reference date for scheduling future scans. MRI of the brain may be performed as per site's SOC practice.
Pathology Report	X		Recurrence Only										See Appendix 10
Lesion Photograph			Recurrence Only										Submit diagnostic photograph for cutaneous recurrence if possible

Part I Adjuvant Treatment													
Trial Period	**Screening**		**During Treatment**			**End of Treatment**	**Posttreatment**						**Notes**
Treatment Cycle (Cycle = 21 days)			**1**	**2 and every even # cycle**	**3 and every odd # cycle**	**At time of treatment discontinuation**	**Safety Follow-up**	**Follow-Up Visits[d]**			**DMFS Follow-up**	**Survival Follow-up**	
							30 days post last dose	**Every 12 weeks for the 1st year from EOT**	**Every 6 months for the 2nd year to 5th year from EOT**	**Yearly thereafter starting at year 6 from EOT**	**Every 12 weeks**	**Every 12 weeks**	Procedures within a given treatment (TX) visit should occur on Day 1 of each cycle unless otherwise noted
Scheduling Window (Days):	**-28 to -1**	**-10 to -1**	**+3**	**±3**	**±3**		**+7**	**±14**	**±14**	**±28**	**±14**	**±14**	
Pharmacokinetics													
Blood for Serum pembrolizumab PK			X[b]	X[b]			X[b]						Pediatric Only (Less than 18 years old)
Blood for ADA			X[b]	X[b]			X[b]						
Translational Research/Biomarkers													
Archival Tumor Tissue	X												Submit archival tumor sample at screening if sufficient tumor tissue is available. See Procedure Manual for details.
Fresh Tumor Tissue Biopsy			Recurrence Only										Obtain and submit at recurrence if sufficient tumor tissue is available. See Procedure Manual for details.
Genetics/Gene Expression/Mutation Assessments	X		Recurrence Only										Information collected and recorded on eCRF only if available from standard of care testing completed by site
Blood for Genetic Analyses			X										Collect predose on Day 1 of C1.
Blood for RNA Analysis			X	X	X	X	Recurrence Only						Collect predose on Day 1 of C1, C2, C5, DC, and at recurrence.
Blood for Plasma Biomarker Analyses			X	X	X	X	Recurrence Only						
Blood for Serum Biomarker Analyses			X	X	X	X	Recurrence Only						

Part I Adjuvant Treatment													
Trial Period	**Screening**		**During Treatment**			**End of Treatment**	**Posttreatment**						**Notes**
Treatment Cycle (Cycle = 21 days)			**1**	**2 and every even # cycle**	**3 and every odd # cycle**	**At time of treatment discontinuation**	**Safety Follow-up**	**Follow-Up Visits[d]**			**DMFS Follow-up**	**Survival Follow-up**	
							30 days post last dose	**Every 12 weeks for the 1st year from EOT**	**Every 6 months for the 2nd year to 5th year from EOT**	**Yearly thereafter starting at year 6 from EOT**	**Every 12 weeks**	**Every 12 weeks**	Procedures within a given treatment (TX) visit should occur on Day 1 of each cycle unless otherwise noted
Scheduling Window (Days):	**-28 to -1**	**-10 to -1**	**+3**	**±3**	**±3**		**+7**	**±14**	**±14**	**±28**	**±14**	**±14**	
Stool for Biomarker Analysis			X	X	X	X	Recurrence Only[d]						Collection at home within 1 week prior to specified visit and brought into site on Day 1 of C1, C2, C5, DC, and disease recurrence
Blood for ctDNA			X	X	X	X	X	X	X	X			Collect predose on Day 1 of C1, C2, C3, subsequent odd cycles, DC, Safety Follow-up, every visit during Follow-up, and any unscheduled visit where there is a clinical suspicion of recurrence.

Part I Adjuvant Treatment													
Trial Period	**Screening**		**During Treatment**			**End of Treatment**	**Posttreatment**						**Notes**
Treatment Cycle (Cycle = 21 days)			**1**	**2 and every even # cycle**	**3 and every odd # cycle**	**At time of treatment discontinuation**	**Safety Follow-up**	**Follow-Up Visits[d]**			**DMFS Follow-up**	**Survival Follow-up**	
							30 days post last dose	**Every 12 weeks for the 1st year from EOT**	**Every 6 months for the 2nd year to 5th year from EOT**	**Yearly thereafter starting at year 6 from EOT**	**Every 12 weeks**	**Every 12 weeks**	Procedures within a given treatment (TX) visit should occur on Day 1 of each cycle unless otherwise noted
Scheduling Window (Days):	**-28 to -1**	**-10 to -1**	**+3**	**±3**	**±3**		**+7**	**±14**	**±14**	**±28**	**±14**	**±14**	
Patient-reported Outcomes													
EuroQoL EQ-5D-5L and EORTC QLQ-C30			X[c]		X[c]	X[c]	X[c]	X[c]	X[c]				PROs must be collected regardless of recurrence/progression status/treatment completion, unless participant withdraws from this portion of the study. PROs are administered prior to drug administration, AE evaluation, disease status evaluation and all procedures/assessments. If participant does not complete the PRO at designated time, the reason must be captured.

ADA = Antidrug Antibodies; aPTT = activated partial thromboplastin time; C1 = Cycle 1, etc.; CT = computed tomography; ctDNA = circulating tumor deoxyribonucleic acid; DC = discontinuation; DMFS = distant metastasis-free survival; ECG = electrocardiogram; ECI = event of clinical interest; ECOG = Eastern Cooperative Oncology Group; EOT = end of treatment; EORTC QLQ = European Organization for Research and Treatment of Cancer Quality of Life Questionnaire; IRT = Interactive Response Technology; LDH = Lactic Acid Dehydrogenase; MRI = magnetic resonance imaging; PET-CT = positron emission tomography -computed tomography; PK = Pharmacokinetic; PRO = patient-reported outcome; PT/INR = prothrombin time/international normalized ratio; RNA = ribonucleic acid; SAE = serious adverse event; SFU = survival follow-up; TSH = thyroid-stimulating hormone; TX = Treatment; WNL = Within normal ;imits.

a. See Section 8.2.1.4 and the Site Imaging Manual for more information. CT chest, abdomen, and pelvis, or CT chest with MRI abdomen and pelvis. Neck CT and/or MRI for head and neck primaries. MRI brain and spine only as clinically needed. A CT scan of the extremity where the primary melanoma was diagnosed (or MRI if CT scan is contraindicated) should be performed at the investigator's discretion or when clinically indicated.

b. PK/ADA (pediatric participants only): Predose trough PK and anti-pembrolizumab antibody samples will be collected at Cycles 1, 2, 4, 8 and every 4 cycles thereafter, and 30 days after discontinuation of study drug or until the participant starts new anticancer therapy whichever is earlier. All predose trough samples should be drawn within 24 hours before infusion of study drug from all pediatric participants. If Discontinuation Visit and 30-Day Safety Visit occur at the same visit refer to the data entry guidelines for required procedures. PK only: Additional postdose peak PK samples will be drawn within 30 minutes after end of study drug infusion at Cycles 1 and 8. An additional single PK sample should be drawn in Cycle 1 between 72 to 168 hours (Day 4 to Day 8) postdose and Cycle 1 at 264 to 408 hours (Day 12 to Day 18). Once a participant reaches the age of 18, PK/ADA samples should not be collected.

c. Patient-reported Outcomes (PROs) EuroQoL (EQ)-5D-5L and EORTC QLQ-C30 should be completed at baseline (Cycle 1), during treatment in year one (at Cycle 5, 9, 13, 17), every 12 weeks during year 2 (Week 60, 72, 84, and 96 from baseline), and every 6 months during year 3 (month 30 and 36 from baseline), at treatment discontinuation visit and the 30-day follow-up visit. PROs are administered in the following order: EQ-5D-5L, EORTC QLQ-C30. The EORTC QLQ-C30 will be administered only to adults (≥18 years of age at baseline) since the questionnaire is not validated in pediatric populations. The EQ-5D-5L will be administered to all study participants, since it is considered acceptable to use for persons 12 years and older.

d. The clinic visit at which imaging (or exam/biopsy) is performed to confirm suspected recurrence or the next scheduled or unscheduled visit at site if procedures performed at nonsite facility.

1.3.2 Part 2 Crossover/Rechallenge After First Recurrence

Part 2 Crossover/Rechallenge After First Recurrence											
Trial Period	**Screening**	**During Treatment**			**End of Treatment**	**Posttreatment**					**Notes**
Treatment Cycle:	**Prior to 1st dose in Part 2**	**1**	**2 and every even # cycle**	**3 and every odd # cycle**	**At time of treatment discontinuation**	**Safety Follow-up**	**Follow-up Visits**		**DMFS Follow-up**	**Survival Follow-up**	
						30 days post last dose	**Local Recurrence** **Every 12 weeks (±14 days) for 1st year, every 6 months (±14 days) years 2-5, then annually (±28 days) starting year 6 from EOT**	**Distant Recurrence** **Every 12 weeks (±14 days) for 2 years, then every 6 months (±14 days) during year 3 through year 5, then annually (±28 days) starting year 6 from EOT**	**Every 12 weeks**	**Every 12 weeks**	Procedures within a given treatment visit should occur on Day 1 of each cycle unless otherwise noted.
Scheduling Window (Days):	**-14 to -1**	**+3**	**±3**	**±3**		**+7**			**±14**	**±14**	
Administrative Procedures											
Informed Consent/Assent	X										Ensure that participants are re-consented with the most up-to-date IC within 14 days (+3 days) prior to the first dose in Part 2.
Eligibility Criteria	X										
Prior and Concomitant Medication Review	X	X	X	X	X	X					Concomitant medications taken will be recorded 28 days prior to C1D1 and beyond 30 days post-TX DC if related to SAE or ECI.

Part 2 Crossover/Rechallenge After First Recurrence											
Trial Period	**Screening**	**During Treatment**			**End of Treatment**	**Posttreatment**					**Notes**
						Safety Follow-up	**Follow-up Visits**		**DMFS Follow-up**	**Survival Follow-up**	
Treatment Cycle:	**Prior to 1st dose in Part 2**	**1**	**2 and every even # cycle**	**3 and every odd # cycle**	**At time of treatment discontinuation**	**30 days post last dose**	**Local Recurrence** **Every 12 weeks (±14 days) for 1st year, every 6 months (±14 days) years 2-5, then annually (±28 days) starting year 6 from EOT**	**Distant Recurrence** **Every 12 weeks (±14 days) for 2 years, then every 6 months (±14 days) during year 3 through year 5, then annually (±28 days) starting year 6 from EOT**	**Every 12 weeks**	**Every 12 weeks**	Procedures within a given treatment visit should occur on Day 1 of each cycle unless otherwise noted.
Scheduling Window (Days):	**-14 to -1**	**+3**	**±3**	**±3**		**+7**			**±14**	**±14**	
Trial Treatment Administration											
Pembrolizumab		X	X	X							Approximately 1 year (17 cycles) for local/distant recurrence following surgical resection. Approximately 2 years (up to 35 cycles) for unresectable disease; Participants with distant recurrence surgically resected will be treated for 17 cycles with pembrolizumab in part 2 and investigator may request Sponsor to approve up to 35 cycles total treatment in Part 2.

Part 2 Crossover/Rechallenge After First Recurrence											
Trial Period	**Screening**	**During Treatment**			**End of Treatment**	**Posttreatment**					**Notes**
						Safety Follow-up	**Follow-up Visits**		**DMFS Follow-up**	**Survival Follow-up**	
Treatment Cycle:	**Prior to 1st dose in Part 2**	**1**	**2 and every even # cycle**	**3 and every odd # cycle**	**At time of treatment discontinuation**	**30 days post last dose**	**Local Recurrence** **Every 12 weeks (±14 days) for 1st year, every 6 months (±14 days) years 2-5, then annually (±28 days) starting year 6 from EOT**	**Distant Recurrence** **Every 12 weeks (±14 days) for 2 years, then every 6 months (±14 days) during year 3 through year 5, then annually (±28 days) starting year 6 from EOT**	**Every 12 weeks**	**Every 12 weeks**	Procedures within a given treatment visit should occur on Day 1 of each cycle unless otherwise noted.
Scheduling Window (Days):	**-14 to -1**	**+3**	**±3**	**±3**		**+7**			**±14**	**±14**	
Safety Procedures											
Full Physical Examination	X[a]				X						
Directed Physical Exam		X	X	X		X	X	X			The investigator or qualified designee should conduct a visual inspection of local recurrence and palpation of regional lymph nodes to assess regional recurrence.
Vital Signs (pulse, blood pressure, respiratory rate, and temperature), Height, Weight	X[a]	X	X	X	X	X	X	X			Pediatric only – height and weight measured at every visit. Adult height measured at Part 1 screening only.
12-lead ECG	X										6 lead ECG acceptable per local guidelines

Part 2 Crossover/Rechallenge After First Recurrence											
Trial Period	**Screening**	**During Treatment**			**End of Treatment**	**Posttreatment**					**Notes**
Treatment Cycle:	**Prior to 1st dose in Part 2**	**1**	**2 and every even # cycle**	**3 and every odd # cycle**	**At time of treatment discontinuation**	**Safety Follow-up**	**Follow-up Visits**		**DMFS Follow-up**	**Survival Follow-up**	
						30 days post last dose	**Local Recurrence** **Every 12 weeks (±14 days) for 1st year, every 6 months (±14 days) years 2-5, then annually (±28 days) starting year 6 from EOT**	**Distant Recurrence** **Every 12 weeks (±14 days) for 2 years, then every 6 months (±14 days) during year 3 through year 5, then annually (±28 days) starting year 6 from EOT**	**Every 12 weeks**	**Every 12 weeks**	Procedures within a given treatment visit should occur on Day 1 of each cycle unless otherwise noted.
Scheduling Window (Days):	**-14 to -1**	**+3**	**±3**	**±3**		**+7**			**±14**	**±14**	
Age Appropriate Performance Scale (Lansky/Karnofsky/ ECOG)	X[a]	X	X	X	X	X	X	X			Evaluated prior to dosing. Lansky scale to be used for participants ≤16 years old. Karnofsky scale to be used for participants >16 and <18 years old. ECOG to be used for participants ≥18 years old
Review Adverse Events	X	X	X	X	X	X	X	X			
Poststudy Anticancer Therapy Status						X	X	X	X	X	

Part 2 Crossover/Rechallenge After First Recurrence											
Trial Period	**Screening**	**During Treatment**			**End of Treatment**	**Posttreatment**					**Notes**
						Safety Follow-up	**Follow-up Visits**		**DMFS Follow-up**	**Survival Follow-up**	
Treatment Cycle:	**Prior to 1st dose in Part 2**	**1**	**2 and every even # cycle**	**3 and every odd # cycle**	**At time of treatment discontinuation**	**30 days post last dose**	**Local Recurrence** **Every 12 weeks (±14 days) for 1st year, every 6 months (±14 days) years 2-5, then annually (±28 days) starting year 6 from EOT**	**Distant Recurrence** **Every 12 weeks (±14 days) for 2 years, then every 6 months (±14 days) during year 3 through year 5, then annually (±28 days) starting year 6 from EOT**	**Every 12 weeks**	**Every 12 weeks**	Procedures within a given treatment visit should occur on Day 1 of each cycle unless otherwise noted.
Scheduling Window (Days):	**-14 to -1**	**+3**	**±3**	**±3**		**+7**			**±14**	**±14**	
Submit Follow-up DMFS Imaging to Central Vendor									X		Site investigator must collect and review copy of clinical notes/reports, imaging reports, photographs and/or pathology reports (including imaging and biopsy/pathology assessment done external to site) to update disease status if it is available. A central imaging vendor will be used to collect, clean, and hold submitted tumor imaging obtained during the DMFS phase of the study.

Part 2 Crossover/Rechallenge After First Recurrence											
Trial Period	**Screening**	**During Treatment**			**End of Treatment**	**Posttreatment**					**Notes**
Treatment Cycle:	**Prior to 1st dose in Part 2**	**1**	**2 and every even # cycle**	**3 and every odd # cycle**	**At time of treatment discontinuation**	**Safety Follow-up**	**Follow-up Visits**		**DMFS Follow-up**	**Survival Follow-up**	
						30 days post last dose	**Local Recurrence** **Every 12 weeks (±14 days) for 1st year, every 6 months (±14 days) years 2-5, then annually (±28 days) starting year 6 from EOT**	**Distant Recurrence** **Every 12 weeks (±14 days) for 2 years, then every 6 months (±14 days) during year 3 through year 5, then annually (±28 days) starting year 6 from EOT**	**Every 12 weeks**	**Every 12 weeks**	Procedures within a given treatment visit should occur on Day 1 of each cycle unless otherwise noted.
Scheduling Window (Days):	**-14 to -1**	**+3**	**±3**	**±3**		**+7**			**±14**	**±14**	
Submit Follow-up SFU Imaging to Central Vendor										X	Site investigator must collect and review copy of clinical notes/reports, imaging reports, photographs and/or pathology reports (including imaging and biopsy/pathology assessment done external to site) to update disease status if it is available. A central imaging vendor will be used to collect, clean, and hold submitted tumor imaging obtained during the SFU phase of the study.

Part 2 Crossover/Rechallenge After First Recurrence											
Trial Period	**Screening**	**During Treatment**			**End of Treatment**	**Posttreatment**					**Notes**
Treatment Cycle:	**Prior to 1st dose in Part 2**	**1**	**2 and every even # cycle**	**3 and every odd # cycle**	**At time of treatment discontinuation**	**Safety Follow-up**	**Follow-up Visits**		**DMFS Follow-up**	**Survival Follow-up**	
						30 days post last dose	**Local Recurrence** Every 12 weeks (±14 days) for 1st year, every 6 months (±14 days) years 2-5, then annually (±28 days) starting year 6 from EOT	**Distant Recurrence** Every 12 weeks (±14 days) for 2 years, then every 6 months (±14 days) during year 3 through year 5, then annually (±28 days) starting year 6 from EOT	**Every 12 weeks**	**Every 12 weeks**	Procedures within a given treatment visit should occur on Day 1 of each cycle unless otherwise noted.
Scheduling Window (Days):	**-14 to -1**	**+3**	**±3**	**±3**		**+7**			**±14**	**±14**	
Survival Status		←----------	----------	----------	----------	----------	----------	----------	----------	----------→	1) After investigator determined recurrence or start of new anticancer TX. Upon Sponsor request, pts may be contacted for survival status at any time during the study. 2) When follow-up visits are spaced to every 6 months or yearly, pts will be contacted every 12 weeks between visits.

Part 2 Crossover/Rechallenge After First Recurrence											
Trial Period	**Screening**	**During Treatment**			**End of Treatment**	**Posttreatment**					**Notes**
Treatment Cycle:	**Prior to 1st dose in Part 2**	**1**	**2 and every even # cycle**	**3 and every odd # cycle**	**At time of treatment discontinuation**	**Safety Follow-up**	**Follow-up Visits**		**DMFS Follow-up**	**Survival Follow-up**	
						30 days post last dose	**Local Recurrence** **Every 12 weeks (±14 days) for 1st year, every 6 months (±14 days) years 2-5, then annually (±28 days) starting year 6 from EOT**	**Distant Recurrence** **Every 12 weeks (±14 days) for 2 years, then every 6 months (±14 days) during year 3 through year 5, then annually (±28 days) starting year 6 from EOT**	**Every 12 weeks**	**Every 12 weeks**	Procedures within a given treatment visit should occur on Day 1 of each cycle unless otherwise noted.
Scheduling Window (Days):	**-14 to -1**	**+3**	**±3**	**±3**		**+7**			**±14**	**±14**	
Laboratory Procedures/Assessments											
Pregnancy Test – Urine or Serum	X		X	X	X	X					For women of childbearing potential, a urine pregnancy test should be performed within 72 hours prior to 1st dose of study TX. If urine pregnancy results cannot be confirmed as negative, a serum pregnancy test performed by the local study site laboratory is required.

Part 2 Crossover/Rechallenge After First Recurrence											
Trial Period	**Screening**	**During Treatment**			**End of Treatment**	**Posttreatment**					**Notes**
Treatment Cycle:	**Prior to 1st dose in Part 2**	**1**	**2 and every even # cycle**	**3 and every odd # cycle**	**At time of treatment discontinuation**	**Safety Follow-up**	**Follow-up Visits**		**DMFS Follow-up**	**Survival Follow-up**	
						30 days post last dose	**Local Recurrence** Every 12 weeks (±14 days) for 1st year, every 6 months (±14 days) years 2-5, then annually (±28 days) starting year 6 from EOT	**Distant Recurrence** Every 12 weeks (±14 days) for 2 years, then every 6 months (±14 days) during year 3 through year 5, then annually (±28 days) starting year 6 from EOT	**Every 12 weeks**	**Every 12 weeks**	Procedures within a given treatment visit should occur on Day 1 of each cycle unless otherwise noted.
Scheduling Window (Days):	**-14 to -1**	**+3**	**±3**	**±3**		**+7**			**±14**	**±14**	
PT/INR and aPTT	X[a]										aPTT/PT/INR is mandatory at Part 2 screening. PT/INR should be tested subsequently as needed for participants on warfarin based anticoagulation therapy.
CBC with Differential	X[a]		X		X	X					Every 6 weeks (at the start of even # cycles) during treatment.
Comprehensive Chemistry Panel	X[a]		X		X	X					
Urinalysis	X[a]		X			X					Prior to 1st dose and then C4, C8, C12, C16 and 30 days after last dose of study treatment. Pts receiving 2 years of treatment will provide urine samples at C20, C24, C28 and C32.

Part 2 Crossover/Rechallenge After First Recurrence											
Trial Period	**Screening**	**During Treatment**			**End of Treatment**	**Posttreatment**					**Notes**
Treatment Cycle:	**Prior to 1st dose in Part 2**	**1**	**2 and every even # cycle**	**3 and every odd # cycle**	**At time of treatment discontinuation**	**Safety Follow-up**	**Follow-up Visits**		**DMFS Follow-up**	**Survival Follow-up**	
						30 days post last dose	**Local Recurrence** Every 12 weeks (±14 days) for 1st year, every 6 months (±14 days) years 2-5, then annually (±28 days) starting year 6 from EOT	**Distant Recurrence** Every 12 weeks (±14 days) for 2 years, then every 6 months (±14 days) during year 3 through year 5, then annually (±28 days) starting year 6 from EOT	**Every 12 weeks**	**Every 12 weeks**	Procedures within a given treatment visit should occur on Day 1 of each cycle unless otherwise noted.
Scheduling Window (Days):	**-14 to -1**	**+3**	**±3**	**±3**		**+7**			**±14**	**±14**	
T3 (or Free T3), FT4 and TSH	X[a]		X			X					After C1, retrospective review of thyroid function testing is allowed when results are not available prior to dosing.
LDH	X[a]		X			X					

Part 2 Crossover/Rechallenge After First Recurrence											
Trial Period	**Screening**	**During Treatment**			**End of Treatment**	**Posttreatment**					**Notes**
						Safety Follow-up	**Follow-up Visits**		**DMFS Follow-up**	**Survival Follow-up**	
Treatment Cycle:	**Prior to 1st dose in Part 2**	**1**	**2 and every even # cycle**	**3 and every odd # cycle**	**At time of treatment discontinuation**	**30 days post last dose**	**Local Recurrence** **Every 12 weeks (±14 days) for 1st year, every 6 months (±14 days) years 2-5, then annually (±28 days) starting year 6 from EOT**	**Distant Recurrence** **Every 12 weeks (±14 days) for 2 years, then every 6 months (±14 days) during year 3 through year 5, then annually (±28 days) starting year 6 from EOT**	**Every 12 weeks**	**Every 12 weeks**	Procedures within a given treatment visit should occur on Day 1 of each cycle unless otherwise noted.
Scheduling Window (Days):	**-14 to -1**	**+3**	**±3**	**±3**		**+7**			**±14**	**±14**	
Disease Evaluation											
Tumor Imaging • (See Site Imaging Manual for more details)	X[b]		X[b]		X[b]		X[b]				Imaging timing should follow calendar days and should not be adjusted for delays in cycle starts. CT is preferred imaging modality for neck, chest, abdomen, and pelvis. CT portion of PET-CT may be used in place of stand-alone CT if it is of diagnostic quality per Site Imaging Manual. In the case of DC due to recurrence, scan date is the reference date for scheduling future scans.
Pathology Report	X[a]	Recurrence or Progression of Melanoma									See Appendix 10

Part 2 Crossover/Rechallenge After First Recurrence											
Trial Period	**Screening**	**During Treatment**			**End of Treatment**	**Posttreatment**					**Notes**
Treatment Cycle:	**Prior to 1st dose in Part 2**	**1**	**2 and every even # cycle**	**3 and every odd # cycle**	**At time of treatment discontinuation**	**Safety Follow-up**	**Follow-up Visits**		**DMFS Follow-up**	**Survival Follow-up**	
						30 days post last dose	**Local Recurrence** Every 12 weeks (±14 days) for 1st year, every 6 months (±14 days) years 2-5, then annually (±28 days) starting year 6 from EOT	**Distant Recurrence** Every 12 weeks (±14 days) for 2 years, then every 6 months (±14 days) during year 3 through year 5, then annually (±28 days) starting year 6 from EOT	**Every 12 weeks**	**Every 12 weeks**	Procedures within a given treatment visit should occur on Day 1 of each cycle unless otherwise noted.
Scheduling Window (Days):	**-14 to -1**	**+3**	**±3**	**±3**		**+7**			**±14**	**±14**	
Lesion Photograph	X[a]	Recurrence or Progression of Melanoma									Submit diagnostic photograph for cutaneous recurrence if possible
Translational Research/Biomarkers											
Obtain Fresh Tumor Tissue Biopsy	X[a]	Recurrence or Progression of Melanoma									Obtain and submit at recurrence or progression if sufficient tumor tissue is available. See Procedure Manual for details.
Genetics/Gene Expression/Mutation Assessments	X	Recurrence or Progression of Melanoma									Information collected and recorded on eCRF only if available from standard of care testing completed by site

Part 2 Crossover/Rechallenge After First Recurrence											
Trial Period	**Screening**	**During Treatment**			**End of Treatment**	**Posttreatment**					**Notes**
						Safety Follow-up	**Follow-up Visits**		**DMFS Follow-up**	**Survival Follow-up**	
Treatment Cycle:	**Prior to 1st dose in Part 2**	**1**	**2 and every even # cycle**	**3 and every odd # cycle**	**At time of treatment discontinuation**	**30 days post last dose**	**Local Recurrence** **Every 12 weeks (±14 days) for 1st year, every 6 months (±14 days) years 2-5, then annually (±28 days) starting year 6 from EOT**	**Distant Recurrence** **Every 12 weeks (±14 days) for 2 years, then every 6 months (±14 days) during year 3 through year 5, then annually (±28 days) starting year 6 from EOT**	**Every 12 weeks**	**Every 12 weeks**	Procedures within a given treatment visit should occur on Day 1 of each cycle unless otherwise noted.
Scheduling Window (Days):	**-14 to -1**	**+3**	**±3**	**±3**		**+7**			**±14**	**±14**	
Blood for ctDNA		X	X	X	X	X	X	X			Collect predose on Day 1 of C1, C2, C3, subsequent odd cycles, DC, Safety Follow-up, and every visit during Follow-up, and any unscheduled visit where there is a clinical suspicion of recurrence or progression

Part 2 Crossover/Rechallenge After First Recurrence											
Trial Period	**Screening**	**During Treatment**			**End of Treatment**	**Posttreatment**					**Notes**
Treatment Cycle:	**Prior to 1st dose in Part 2**	**1**	**2 and every even # cycle**	**3 and every odd # cycle**	**At time of treatment discontinuation**	**Safety Follow-up**	**Follow-up Visits**		**DMFS Follow-up**	**Survival Follow-up**	
						30 days post last dose	**Local Recurrence** **Every 12 weeks (±14 days) for 1st year, every 6 months (±14 days) years 2-5, then annually (±28 days) starting year 6 from EOT**	**Distant Recurrence** **Every 12 weeks (±14 days) for 2 years, then every 6 months (±14 days) during year 3 through year 5, then annually (±28 days) starting year 6 from EOT**	**Every 12 weeks**	**Every 12 weeks**	Procedures within a given treatment visit should occur on Day 1 of each cycle unless otherwise noted.
Scheduling Window (Days):	**-14 to -1**	**+3**	**±3**	**±3**		**+7**			**±14**	**±14**	
Patient-reported Outcomes											
EuroQoL (EQ)-5D-5L		X[c]		X[c]			X[c]	X[c]			PROs must be collected regardless of recurrence/progression status/TX completion, unless participant withdraws from study. PROs are to be administered prior to drug administration, AE evaluation, disease status evaluation and all procedures/assessments. If participant does not complete the PRO at designated time, the reason must be captured.

C1 = Cycle 1, etc.; DC = Discontinuation; EOT = End of Treatment; ICF = Informed Consent Form; Q3W = every 3 weeks; TX= Treatment; WNL = Within normal limits.

a. Screening laboratory tests and full physical examination are required only if they did not occur within 14 days of start of Part 2 study treatment. Tumor biopsy, lesion photography and pathology report must be completed within 4 weeks prior to first dose in Part 2. Sponsor consultation and approval is required prior to entry into Part 2. Screening laboratory tests that cannot be done -14 to -1 day prior to C1D1 can be done on the day of C1D1 (before first dose in Part 2) if results are available for investigator's review before dosing.

b. See Section 8.2.1.4 and the Site Imaging Manual for more information. CT chest, abdomen, and pelvis, or CT chest with MRI abdomen and pelvis. Neck CT and/or MRI for head and neck primaries. MRI brain: If no metastatic disease found, repeat only as clinically needed. If disease present, reimage Q12W with other staging scans. MRI spine as clinically needed. A CT scan of the extremity where the primary melanoma was diagnosed (or MRI if CT scan is contraindicated) should be performed at the investigator's discretion or when clinically indicated.

c. EuroQoL 5 Dimension Questionnaire (EQ-5D-5L) should be completed during this phase at baseline (Cycle 1), during treatment at Cycles 9, 17 and 35, and at 24 and 48 weeks during first year off treatment. The EuroQoL EQ-5D-5L will be administered to all study participants, since it is considered acceptable to use for persons 12 years and older.

1.3.3 Imaging Schedule

	Imaging On Treatment	End of Treatment (EOT)	In Follow-up
Part 1 • **Stage IIB and IIC** • **No evidence of disease at study entry**	Every 6 months for one year from randomization	If previous imaging was obtained within 4 weeks prior to the date of discontinuation, imaging at treatment discontinuation is not mandatory.	• Every 6 months in years 2-4 from randomization • Once in year 5 from randomization
Part 2 • **Stage III** • **No evidence of disease at entry into Part 2 after loco-regional recurrence**	Every 12 weeks for one year from C1D1		• Every 12 weeks in year 2 from C1D1 • Every 6 months from years 3-5 from C1D1 • Yearly thereafter
Part 2 • **Stage IV** • **No evidence of disease at entry into Part 2 after distant recurrence**	Every 12 weeks for one year from C1D1		• Every 12 weeks in year 2 from C1D1 * • Every 6 months from years 3-5 from C1D1 • Yearly thereafter
Part 2 • **Stage III/IV** • **Have unresectable disease at entry into Part 2**	Every 12 weeks for two years from C1D1		• Every 12 weeks in year 3 from C1D1 • Every 6 months for years 4-5 from C1D1 • Yearly thereafter

C1D1= Cycle 1 Day 1 of Part 2 Treatment

Note: For participants who stop Part 1 or Part 2 without documented recurrence/progression. Every effort should be made to capture imaging based on Part 1 and Part 2 SoA instructions.

* Participants who enter Part 2 with history of Stage IV melanoma and have no evidence of disease may be treated for up to 35 cycles and will have year 2 of imaging while on treatment.

2. Introduction

2.1 Study Rationale

Recent clinical studies in melanoma have focused on treating high-risk Stage III patients with programmed cell death inhibitor-1 (PD-1) inhibitors and combination BRAF and MEK inhibitors in the adjuvant setting to decrease the risk of recurrence and improve Distant Metastasis-free Survival (DMFS) and Overall Survival (OS) (S1404/KN053, EORTC1325/KN054, CheckMate 238, COMBI-AD). Adult patients with Stage III A, B, C melanoma who received 18 doses (~1 year) of pembrolizumab postresection in EORTC1325/KN054 had a significantly longer recurrence-free survival (RFS) than placebo [hazard ratio (HR)=0.57; 98.4% confidence interval (CI), 0.43-0.74; $p<0.0001$] [Eggermont, A. M. M. 2017]. In CheckMate 238, resected Stage IIIB, IIIC and IV melanoma patients have improved RFS and fewer Grade 3 and 4 AEs after 1 year of adjuvant treatment with nivolumab compared to patients treated with ipilimumab, which was previously approved by the Food and Drug Administration as adjuvant therapy [Weber, J., et al 2017]. COMBI-AD has shown RFS benefit with 1 year of adjuvant treatment using dabrafenib and trametinib in patients whose tumors harbor BRAF V600E or V600K mutations with Stage IIIA, B, and C melanoma [Long, G. V., et al 2017].

All Stage II patients are at risk of recurrence after complete surgical resection, which is considered standard of care in this patient population. IFN alpha as adjuvant therapy in melanoma has shown modest results at best [consistent effect on RFS with a maintained HR of 0.86 and approximately a 3% absolute survival advantage at 5 years] [Ives, N. J., et al 2017]. IFN alpha is a regimen with well described significant toxicities, particularly at high-dose, and these can profoundly affect quality of life and can even be life-threatening. With high-dose IFN, approximately 40% of patients have treatment-related AEs that lead to dose delays or reductions [Trinh, V. A., et al 2017]. Adjuvant IFN offers a reduction in RFS but is not universally recommended because of the significant toxicity associated with treatment that can affect quality of life [Garbe, C., et al 2012]. Pegylated IFN alpha 2b was approved by the Food and Drug Administration on 29-MAR-2011 for adjuvant therapy. Today IFN alpha has a limited role in adjuvant treatment of melanoma and is now recommended only to patients with ulcerated primary melanomas and to patients without access to more modern treatments [Eggermont, A. M. M. 2017].

Some patients with Stage II melanoma have MSS outcomes similar to Stage III patients. Data from the American Joint Committee on Cancer suggest that 94% of Stage IIA, 87% of Stage IIB, and 82% of Stage IIC patients will be alive at 5 years and by 10 years 88, 82, and 75% respectively. Stage IIIB 5-year MSS rate of 83% is comparable to Stage IIC OS at 5 years (82%). Similarly, Stage IIIA (88%) and IIIB (77%) MSS at 10 years are comparable to Stage IIA (88%) and IIC (75%) MSS rate at 10 years, respectively [Gershenwald, J. E., et al 2017]. These data clearly show that survival outcomes can be as dismal for some Stage II patients as for Stage III patients. This population thus has an unmet medical need for adjuvant therapy with the goal of preventing disease recurrence and increasing survival by providing treatment with adjuvant pembrolizumab that now has a proven therapeutic benefit in Stage III and IV patients.

EORTC1325/KN054 is currently investigating whether there is a benefit in rechallenging Stage III patients who experience disease recurrence, resectable or unresectable disease, at least 6 months from their last dose of pembrolizumab. The purpose of rechallenge is to identify patients with an immune system that has already been primed to respond to treatment of melanoma with pembrolizumab and determine whether pembrolizumab is able to prevent recurrence in the treatment time period and for at least an additional 6 months after treatment is completed by mounting a response during rechallenge. As no data is currently available from EORTC1325/KN054 on rechallenge, KN716 will offer patients the opportunity for rechallenge with pembrolizumab in the event of disease recurrence.

Stage II melanoma also affects the pediatric population. KN051 is currently investigating the safety of pembrolizumab in the pediatric population and has established safe dosing guidelines (2 mg/kg dose IV Q3W with maximum dose administered of 200 mg Q3W). Data is currently not available on efficacy of pembrolizumab in advanced pediatric melanoma but pembrolizumab has shown efficacy in other pediatric cancers and is currently approved for treatment of classical Hodgkin lymphoma and microsatellite instability-high tumors. Pembrolizumab has been well tolerated in the pediatric populations studied in KN051 [Geoerger, B., et al 2017]. Patients who are naïve to intensive therapeutic regimens are expected to tolerate pembrolizumab well.

Adjuvant pembrolizumab PK data has been collected from EORTC1325/KN054 and S1404/KN053 patients in the adjuvant treatment setting. Adult PK data will not be collected and analyzed in KN716. Pediatric adjuvant PK data has not been collected in prior studies and will be collected in Part 1 of this study.

In summary, this study will examine whether the benefits achieved with pembrolizumab adjuvant therapy seen in Stage III and IV melanoma translates to the adult (≥18 years of age) and pediatric (age 12 and older) High-Risk Stage II melanoma populations, and leads to improved RFS, DMFS and OS, while identifying biomarker correlates. Tolerable AEs are expected in an otherwise untreated population, making this an ideal design in which to include pediatric and adult participants. Upon recurrence, this study will explore whether rechallenge with pembrolizumab after adjuvant therapy decreases the risk of another recurrence or disease progression.

2.2 Background

Pembrolizumab is a potent humanized IgG4 monoclonal antibody with high specificity of binding to the PD-1 receptor, thus inhibiting its interaction with PD-L1 and PD-L2. Based on preclinical in vitro data, 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. KEYTRUDA® (pembrolizumab) is indicated for the treatment of patients across a number of indications. Refer to IB and approved product labeling for specific indications and detailed background information on pembrolizumab.

2.2.1 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 cluster of differentiation 8+ (CD8+) T-cells and the ratio of CD8+ effector T-cells/FoxP3+ regulatory T-cells (T-regs) correlates with improved prognosis and long-term survival in solid malignancies, such as ovarian, colorectal, and pancreatic cancer; hepatocellular carcinoma; malignant melanoma; and renal cell carcinoma. Tumor-infiltrating lymphocytes can be expanded ex vivo and reinfused, inducing durable objective tumor responses in cancers such as melanoma [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 cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) that has been shown to negatively regulate antigen receptor signaling upon engagement of its ligands (PD L1 and/or PD-L2) [Greenwald, R. J., et al 2005] [Okazaki, T., et al 2001].

The structure of murine PD-1 has been resolved [Zhang, X., et al 2004]. PD-1 and its family members are type-I transmembrane glycoproteins containing an 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 (CD3ζ), protein kinase C-theta (PKCθ), and zeta-chain-associated protein kinase (ZAP70), which are involved in the CD3 T-cell signaling cascade [Okazaki, T., et al 2001] [Chemnitz, J. M., et al 2004] [Sheppard, K-A, et al 2004] [Riley, J. L. 2009]. The mechanism by which PD-1 down-modulates T-cell responses is similar to, but distinct from, that of CTLA-4, because both molecules regulate an overlapping set of signaling proteins [Parry, R. V., et al 2005] [Francisco, L. M., et al 2010].

As a consequence, the PD-1/PD-L1 pathway is an attractive target for therapeutic intervention in patients with melanoma.

2.2.2 Preclinical and Clinical Studies

KEYNOTE protocols 001, 002, and 006 have led to the approval of pembrolizumab for the treatment of unresectable or metastatic melanoma in both pretreated and untreated patients. As noted above, clinical studies such as S1404/KN053, EORTC1325/KN054, CheckMate 238, and COMBI-AD are currently exploring the role of adjuvant therapy in Stage III and Stage IV resected melanoma, trying to improve RFS, DMFS, and OS for patients by providing therapy earlier when patients have been deemed free from disease by surgical resection. Benefits of adjuvant therapy have been reported in 3 of these studies so far.

KN051 is currently investigating the safety of pembrolizumab in the pediatric population and has established safe dosing guidelines. Data are currently not available on efficacy of pembrolizumab in advanced pediatric melanoma but this drug has shown efficacy in other

pediatric cancers and is currently approved for treatment of classical Hodgkin lymphoma and microsatellite instability-high tumors [Geoerger, B., et al 2017].

Refer to the IB and approved product labeling for more details on preclinical and clinical studies of pembrolizumab.

2.2.3 Ongoing Clinical Studies

Clinical development of pembrolizumab is ongoing in a number of advanced solid tumor indications, including advanced melanoma, NSCLC, bladder cancer, head and neck squamous cell carcinoma, other solid tumors, and hematologic malignancies, such as HL.

For study details please refer to the IB**.**

2.3 Benefit/Risk Assessment

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

Pembrolizumab has shown activity in adult patients with melanoma, NSCLC, cHL, and head and neck cancer and may have similar effects in pediatric patients. Pembrolizumab has been approved in the United States for the treatment of unresectable or metastatic melanoma in adults and is currently under study in the pediatric population. Recent results from EORTC1325/KN054 show adult patients with Stage III melanoma who receive postresection therapy with pembrolizumab have a significantly longer recurrence-free survival than placebo) making study of adjuvant pembrolizumab in the high-risk Stage II population to improve RFS, DMFS, and OS a natural choice in the adult population (internal Merck data). Some high-risk Stage II patients have MSS rates similar to Stage III patients.

Based on current evidence, no difference in mechanism of action and activity are expected in melanoma between children and adults or between the adjuvant and relapsed/refractory settings. Thus, pembrolizumab has the potential to provide therapeutic benefit to adult and pediatric patients with newly diagnosed and resected high-risk Stage II melanoma. In addition, based on clinical data accrued to date, the safety profile of pembrolizumab in pediatric patients was similar to that seen in adults; therefore, pembrolizumab has the potential to offer children adjuvant therapy for melanoma that is expected to be well tolerated and expected to lead to decreased risk of recurrence, improved DMFS, and OS.

Pembrolizumab appears generally well tolerated at all doses and schedules evaluated to date. These considerations support a favorable benefit-risk assessment for the study of adjuvant pembrolizumab in adult and pediatric participants with high-risk Stage II melanoma.

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

3. Objectives/Hypotheses and Endpoints

In participants 12 years of age and older with surgically resected High-Risk Stage II melanoma:

Objective/Hypothesis	Endpoint
Primary	
• To compare Recurrence-free Survival (RFS) between treatment arms. Hypothesis (H1): Pembrolizumab is superior to placebo with respect to RFS as assessed by the site investigator.	• RFS: time from randomization to (1) any recurrence (local or regional [including invasive ipsilateral tumor and invasive loco-regional tumor], or distant) as assessed by the investigator, or (2) death due to any cause (both cancer and noncancer causes of death)
Secondary	
• Objective: To compare DMFS between treatment arms. Hypothesis (H2): Pembrolizumab is superior to placebo with respect to DMFS as assessed by the site investigator.	• DMFS: The time from randomization to appearance of a distant metastasis as assessed by the investigator. A distant metastasis refers to cancer that has spread from the original (primary) tumor to distant organs or distant lymph nodes.
• Objective: To compare OS between treatment arms. Hypothesis (H3): Pembrolizumab is superior to placebo with respect to OS.	• OS: The time from randomization to death due to any cause.
• Objective: To assess the safety and tolerability of pembrolizumab compared to placebo in the proportion of AEs.	• AEs. • Discontinuation of study treatment due to AEs.
Tertiary/Exploratory	
• Objective: To compare average change from baseline during the adjuvant treatment period (up to 21 days after last administration) in global quality of life between the 2 treatment arms using the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30) global health status/QoL scale	• EORTC QLQ-C30 global health status/QoL scale.

Objective/Hypothesis	Endpoint
• Objective: To compare average change from baseline after the adjuvant period (from 21 days after last administration) in global quality of life between the 2 treatment arms using the EORTC QLQ-C30 global health status/QoL scale	• EORTC QLQ-C30 global health status/QoL scale.
• Objective: To characterize health utilities using the EuroQoL-5 Dimension Questionnaire (EQ-5D-5L) healthy utility scores.	• EQ-5D-5L health utility score.
• Objective: to compare the time to subsequent therapy (TTST) between treatment arms	• TTST: The time from randomization to the date of first subsequent therapy (eg, surgery, radiation therapy, antineoplastic therapy) or death (whatever the cause), whichever occurs first.
• Objective: to compare Progression/recurrence-free Survival 2 (PRFS2) between treatment arms	• PRFS2: Time from randomization to the earliest of the following: (1) date of 1st disease progression per RECIST 1.1 beyond the initial unresectable disease recurrence; (2) date of 2nd recurrence in patients without evidence of disease after surgery of a resectable 1st recurrence; (3) death.
• Objective: To identify molecular (genomic, metabolic, and/or proteomic) biomarkers that may be indicative of clinical response/resistance, safety, pharmacodynamic activity, and/or the mechanism of action of pembrolizumab.	• Germline genetic variation, genetic deoxyribonucleic acid (DNA) mutations from tumor, tumor and blood RNA variation, proteomics and immunohistochemistry (IHC), and other biomarkers.

4. Study Design

4.1 Overall Design

This is a randomized, placebo-controlled, parallel-group, crossover/rechallenge, multicenter study of adjuvant pembrolizumab in participants 12 years of age and older with resected Stage IIB or IIC cutaneous melanoma. Stage IIB and IIC cutaneous melanoma are defined as **T category T3b, T4a, or T4b (**Table 3**),** with negative sentinel lymph node (SLN) biopsy, no regional metastases and no evidence of distant metastasis per AJCC 8th edition

(Appendix 11) [Gershenwald, J. E., et al 2017]. The study design is depicted in Figure 1 (Section 1.2). Treatment regimens are described in Section 8.

Approximately 954 participants will be enrolled in the study. Eligible participants must have newly diagnosed, pathologically confirmed, completely resected melanoma with negative margins and had a negative SLN biopsy (Appendix 10). Participants cannot have received prior systemic therapy for Stage II melanoma. Participants will be randomized in a 1:1 ratio to 1 of the 2 treatment groups.

In Part 1, participants with High-Risk Stage IIB or IIC melanoma will receive the pembrolizumab adult (≥18 years of age) dose of 200 mg IV or the pediatric (≥12 years old and <18 years old) dose of 2 mg/kg IV up to a maximum of 200 mg every 3 weeks, or saline placebo IV every 3 weeks for 17 cycles.

A participant randomized to receive pembrolizumab who is under 18 years of age at the beginning of Part 1 or Part 2 of the study will receive and remain on the pediatric dose of pembrolizumab (2 mg/kg up to 200 mg Q3W) throughout Part 1 or Part 2 respectively. Any participant who begins Part 2 as an adult will adhere to the fixed adult dose of pembrolizumab (200 mg Q3W) regardless of their Part 1 dosing regimen.

Participants will undergo imaging including chest/abdomen/pelvis computed tomography (CT) and/or magnetic resonance imaging (MRI), and neck CT and/or MRI for head and neck primaries, and other CT and/or MRI when clinically indicated every 6 months during treatment to be assessed by site radiologist and investigator for disease recurrence. PET alone will not be used for disease assessment but the CT component of PET will be allowed if of diagnostic quality per the Site Imaging Manual. Other images of acceptable diagnostic quality may be obtained at the discretion of the investigator.

Participants will be stratified in Part 1 as follows: one stratum for pediatric participants (≥12 years of age and <18 years of age) and 3 strata for adult participants (≥18 years of age) based on T-stage tumor thickness and ulceration (T3b, T4a, T4b). In Part 1, study treatment must begin within 12 weeks of complete surgical resection. PK/antidrug antibody (ADA) data will be collected during Part 1 for pediatric participants. Disease recurrence is confirmed by investigator radiographically and/or by exam/biopsy and confirmed by the site via pathology. All participants will be unblinded after Sponsor consultation and approval at recurrence prior to crossover/rechallenge.

In Part 2, participants may receive up to 17 cycles or 35 cycles of pembrolizumab as adjuvant therapy per Part 2 eligibility guidelines (Section 6.7). Participants will receive 17 cycles of pembrolizumab Q3W after resection of recurrent disease if feasible (local recurrence, including local metastatic lymph nodes, or distant metastasis). Participants will receive up to 35 cycles Q3W for unresectable disease recurrence [unresectable local (regional metastatic lymph nodes, in-transit, satellite, and/or microsatellite metastases) or unresectable distant recurrence]. Participants with distant metastasis who undergo complete resection should receive 17 cycles but with Sponsor approval may receive 35 cycles. Participants who achieve a complete response (CR) per RECIST 1.1 may discontinue pembrolizumab after at least 8 administrations of treatment, including 2 doses beyond the date when the initial CR was declared. Participants receiving 35 cycles of therapy in Part 2 with partial response (PR) or stable disease (SD) per RECIST 1.1 or iPR or iSD per iRECIST should complete all 35

cycles of therapy. Participants are not eligible for further treatment with pembrolizumab beyond 35 cycles within the confines of the study. Participants will not be treated beyond true progression confirmed by iRECIST (see Section 8.2.1.6 for additional details).

The imaging schedule for participants with local, surgically resected recurrence will be every 12 weeks during treatment. Investigators will assess recurrence radiographically (with site radiologist) and/or by examination with subsequent biopsy during treatment and follow-up. Lesions identified by physical examination should be photographed and submitted to the imaging vendor. For participants with unresectable local (regional metastatic lymph nodes, in-transit, satellite, and/or microsatellite metastases) or distant recurrence imaging will also be every 12 weeks during treatment. Investigators will use RECIST 1.1/iRECIST to assess disease response/progression for participants entering Part 2 therapy with unresectable/metastatic disease.

Follow-up visits and imaging schedules will be scheduled in Part 1 and Part 2 per the SoA (Section 1.3).

Detailed information on Parts 1 and 2 is found in Section 8.

The primary endpoint of the study is RFS. Secondary endpoints include DMFS and OS. Distant metastasis refers to cancer that has spread from the original (primary) tumor and beyond local or nearby tissues and lymph nodes to distant organs or distant lymph nodes. This study will also examine the safety and tolerability of adult or pediatric pembrolizumab doses administered every 3 weeks for 17 cycles and at recurrence for 17 or 35 cycles as a secondary endpoint. Safety evaluations will include AE monitoring, physical examinations, clinical laboratory parameters (hematology and chemistry), vital signs, and assessment of ECOG, KPS or LPS (Appendix 8: Performance Status Scales). Adverse events will be monitored throughout the study and graded in severity according to the guidelines outlined in the NCI CTCAE Version 4.0.

Patient-reported outcomes (PROs) are an exploratory endpoint evaluating any clinically relevant differences between the 2 treatment arms in global quality of life. Differences will only be considered clinically relevant if they exceed the 10-point threshold on the 100-point QLQ-C30 scale. Health utilities will be described using the EQ-5D-5L. Other exploratory endpoints include identification of molecular biomarkers that may be indicative of clinical response/resistance, safety, pharmacodynamic activity, and/or the mechanism of action of pembrolizumab. Blood samples will be obtained to measure the pharmacokinetics (PK) of serum pembrolizumab in pediatric participants. The pembrolizumab serum minimum concentration (C_{trough}) at planned visits and times will be summarized.

Treatment in Part 1 and Part 2 of the study will continue until documented disease recurrence, unacceptable AEs, intercurrent illness that prevents further administration of treatment, investigator's decision to withdraw the participant, participant withdraws consent, participant requests to discontinue study treatment, pregnancy of the participant, noncompliance with study treatment or procedure requirement, completion of 17 cycles of pembrolizumab or placebo in Part 1, completion of 17 or 35 cycles of pembrolizumab in Part 2, or administrative reasons requiring cessation of treatment (Section 6.3.1).

After the end of study treatment, participants will be followed for 30 days for AE monitoring (SAEs and events of clinical interest (ECIs) will be collected for 90 days after the end of

study treatment). Participants who discontinue treatment for reasons other than disease recurrence will have posttreatment follow-up for disease status until metastatic disease recurrence, withdrawing consent, or they become lost to follow-up (see Section 7.1 for additional details). Thereafter, participants will be followed for OS every 12 weeks (±7 days) or more frequently as needed until death, withdrawal of consent, or the end of the study, whichever comes first.

This study will be conducted in conformance with Good Clinical Practices.

Five interim efficacy analyses are planned for this study to determine RFS, DMFS, and OS as identified in Section 9.

Results of the interim analyses will be reviewed by an external Data Monitoring Committee (eDMC), which will make recommendations to the Sponsor to continue, modify or end the study according to the plan described briefly in Section 4.4.1 and in detail in Section 9. All participants will have been randomized into the study before the first interim analysis will be conducted.

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

4.2 Scientific Rationale for Study Design

4.2.1 Rationale for Endpoints

4.2.1.1 Efficacy Endpoints

4.2.1.1.1 Primary Efficacy Endpoint

This study will use RFS based on recurrence as assessed by the investigator as the primary endpoint. RFS is an acceptable measure of clinical benefit for a late stage study that demonstrates superiority of a new antineoplastic therapy, especially if the magnitude of the effect is large and the therapy has an acceptable risk/benefit profile.

Investigator identified recurrence will be used to make treatment decisions as well as for exploratory efficacy analyses where specified.

New incident cases of melanoma will be distinguished from recurrences by a local pathologist. A pathologist will review skin lesion biopsy specimens and resection samples to identify if an intraepidermal component exists in the sample. If an intraepidermal component does exist, it is consistent with a new primary melanoma as opposed to a regional (in-transit) or distant metastatic recurrence. Refer to Appendix 12 for details regarding Guidance for Distinguishing Primary Cutaneous Melanomas from Cutaneous Metastases of Melanoma. New incident cases of melanoma and second cancer diagnoses are not counted as events for recurrence-free survival. A central imaging vendor will be used to collect, clean, and hold tumor imaging.

4.2.1.1.2 Secondary Efficacy Endpoints

The secondary efficacy objectives of this study are to compare DMFS (time between the date of randomization and the date of 1st distant metastasis) and OS (time from the date of randomization to the date of death) between the 2 treatment arms in this study.

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/serious adverse events (SAEs), and changes in vital signs and laboratory values. Adverse events will be assessed as defined by CTCAE, Version 4.0.

4.2.1.3 Exploratory Endpoints

Exploratory endpoints for this study include patient-reported outcomes (Section 4.2.1.3.1) and biomarker studies (Section 4.2.1.5).

4.2.1.3.1 Rationale for Patient-reported Outcomes

The EORTC QLQ-C30 and EuroQoL-5D (EQ-5D) patient-reported outcomes (PROs) are not pure efficacy or safety endpoints because they are affected by both disease progression and treatment tolerability.

4.2.1.3.2 EORTC QLQ-C30

EORTC QLQ-C30 is the most widely used cancer specific health-related quality of life (QoL) instrument, which contains 30 items and measures 5 functional dimensions (physical, role, emotional, cognitive, and social), 3 symptom items (fatigue, nausea/vomiting, and pain), 6 single items (dyspnea, sleep disturbance, appetite loss, constipation, diarrhea, and financial impact), and a global health and QoL scale [Aaronson, N. K., et al 1993]. The EORTC QLQ-C30 is a psychometrically and clinically validated instrument appropriate for assessing QoL in oncology studies [Aaronson, N. K., et al 1993].

Note: The use of EORTC QLQ-C30 is restricted to adult participants.

4.2.1.3.3 EQ-5D-5L

The EQ-5D-5L is a standardized instrument for use as a measure of health outcome and will provide data to develop health utilities for use in health economic analyses [Rabin, R. 2001]. The 5 health state dimensions in the EQ-5D-5L include the following: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension is rated on a 5-point scale from 1 (no problem) to 5 (unable to/extreme problems). The EQ-5D-5L also includes a graded (0 to 100) vertical visual analog scale on which the participant rates his or her general state of health at the time of the assessment. This instrument has been used extensively in cancer studies and published results from these studies support its validity and reliability [Pickard, A. S., et al 2007].

4.2.1.4 Pharmacokinetic Endpoints

Blood samples will be obtained to measure the PK of serum pembrolizumab in all pediatric participants. The pembrolizumab serum minimum concentration (C_{trough}) at planned visits and times will be summarized.

4.2.1.5 Planned Exploratory Biomarker Research

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

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

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

Genetic (DNA) analyses from tumor

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

Tumor and blood RNA analyses

Both genome-wide and targeted messenger RNA (mRNA) expression profiling and sequencing in tumor tissue and in blood may be performed to define gene signatures that correlate to clinical response to treatment with immunotherapies and/or other treatments administered. Immunotherapies induce a response in tumors that likely reflects an inflamed/immune phenotype. Specific immune-related gene sets (ie, those capturing interferon-gamma transcriptional pathways) may be evaluated and new signatures may be identified. Individual genes related to the immune system may also be evaluated (eg, IL-10). MicroRNA profiling may also be pursued as well as exosomal profiling.

Proteomics and immunohistochemistry (IHC) using blood or tumor

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

Other biomarkers

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

Other molecular changes of interest include the subtype of T-cells in the tumor microenvironment. The T-cell repertoire from tumor tissue and blood components may be evaluated.

Biomarker Research using Stool

Landmark studies have demonstrated that the gut microbiome can shape anti-tumor immunity and responses to immune checkpoint blockade in mouse models, and that modulation of the gut microbiome may enhance responses to immune checkpoint blockade. This has also been studied in patients on immune checkpoint blockade (anti-CTLA-4 and anti-PD-1), with evidence that differential bacterial signatures exist in responders versus non-responders to therapy (with responders having higher diversity of the gut microbiome and differential composition compared with non-responders). Importantly, these differences in

the gut microbiome are associated with differential immune signatures in the tumor microenvironment [Lynch, S. V. 2016].

4.2.1.6 Future Biomedical Research

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

Such research is for biomarker testing to address emergent questions not described elsewhere in the protocol (as part of the main study) and will only be conducted on specimens from appropriately consented participants. The objective of collecting/retaining specimens for future biomedical research is to explore and identify biomarkers that inform the scientific understanding of diseases and/or their therapeutic treatments. The overarching goal is to use such information to develop safer, more effective drugs/vaccines, and/or to ensure that participants receive the correct dose of the correct drug/vaccine at the correct time. The details of this future biomedical research are presented in Appendix 2.

4.2.2 Rationale for the Use of Comparator/Placebo

In this study, participants will be will randomized at enrollment to the pembrolizumab or placebo treatment groups and are expected to be treated for 17 cycles in Part 1. Placebo will be normal saline solution prepared by the local unblinded pharmacist, dosed and administered in the same manner as the investigational product. Placebo is being used to allow for a blinded study thereby limiting bias and providing a comparator arm that is consistent with standard of care for patients with Stage II melanoma (ie, surgical resection).

4.3 Justification for Dose

The planned dose of pembrolizumab for this study in adults 18 years of age and older is 200 mg Q3W. Based on the totality of data generated in the KEYTRUDA® development program, 200 mg Q3W is the appropriate dose of pembrolizumab 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 every 2 weeks, representing an approximate 5 to 7.5-fold exposure range (refer to IB, Section 5.2.2)

- 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 overall survival at 200 mg Q3W across multiple indications, and

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

Among the 8 randomized dose-comparison studies, a total of 2262 participants were enrolled with melanoma and nonsmall cell lung cancer (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 every 2 weeks (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 (TMDD) 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.

A model-based PK bridging analysis, which included available pediatric PK data from the pembrolizumab pediatric study KN051, was conducted to determine the pediatric dose based on the approach of exposure matching with adults. This analysis showed that a dose of 2 mg/kg (up to 200 mg) Q3W in pediatric participants provided PK exposures similar to those achieved at 2 mg/kg (or 200 mg) Q3W in adults, and served as the basis for approval of a pediatric indication in cHL as well as MSI-H cancers in the US at a dose of 2 mg/kg (up to 200 mg) Q3W. In addition, the safety of this dose in pediatric participants is established based on data from KN051 [Geoerger, B., et al 2017]. The incidence of positive immunogenicity status after pembrolizumab treatment in pediatric participants (2.8%) was comparable with that in adults (2.1%) and had no impact on pembrolizumab exposure. Based on these results, the pediatric dose for evaluation in this study is 2 mg/kg Q3W (up to a maximum of 200 mg Q3W).

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).

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, Good Clinical Practice (GCP) and/or other applicable regulatory requirements, procedure-related problems or the number of discontinuations for administrative reasons is too high.

5. Study Population

Male/Female participants with Stage IIB or IIC cutaneous melanoma of at least 12 years of age will be enrolled in this study.

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

5.1 Inclusion Criteria

Participants are eligible to be included in Part 1 of the study only if all of the following criteria apply (See Section 6.7 for inclusion criteria for Part 2):

Type of Participant and Disease Characteristics

1. Male/female participants who are ≥12 years of age on the day of providing documented informed consent/assent [unless local regulations and/or institutional policies do not allow for participants <18 years of age to participate; for those sites, the eligible population is ≥18 years of age] with surgically resected and histologically/pathologically confirmed new diagnosis of Stage IIB or IIC cutaneous melanoma per AJCC 8th edition guidelines.

   Note: Participants must have T-stage of T3b, T4a, or T4b (Table 3) with pathologically confirmed negative SLN biopsy, and no evidence of regional (N0) or distant metastatic disease (M0) per AJCC 8th edition guidelines (Appendix 11). Surgical considerations can be found in Appendix 10.

2. Participants must not have been previously treated for melanoma beyond complete surgical resection.

   Note: Participants may not have been treated with radiation therapy for their melanoma prior to study entry.

3. No more than 12 weeks may elapse between final surgical resection and randomization. Treatment should start only after complete wound healing from the surgery. If there is a delay of 1 to 7 days exceeding 12 weeks due to unforeseen circumstances, the eligibility should be discussed with the Sponsor and the decision documented. A delay of 1 to 7 days for screening imaging requirements will be allowed if Sponsor has allowed 1-week extension between surgical resection and randomization.

   Note: Final surgical resection is defined in this protocol as complete resection of melanoma and a SLN biopsy. If the wide excision is followed by the SLN biopsy (ie, they are not performed at the same time), no more than 12 weeks may elapse between the 2 surgical procedures. If a second wide excision needs to be completed after SLN biopsy, this date will be used to calculate final surgical resection date.

4. Have no evidence of metastatic disease on imaging as determined by investigator assessment. All suspicious lesions amenable to biopsy should be confirmed negative for malignancy.

5. Have a performance status of 0 or 1 on the ECOG Performance Scale at the time of enrollment, LPS score ≥50 (for participants ≤16 years old.), or a KPS score ≥50 (for participants >16 and <18 years old). (Appendix 8: Performance Status Scales).

6. Participant must have recovered adequately from toxicity and/or complications from surgery prior to starting study treatment.

Male participants:

7. Removed.

Female participants:

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

   - Is not a woman of childbearing potential (WOCBP)

   OR

   - Is a WOCBP and using a contraceptive method that is highly effective (with a failure rate of <1% per year) or be abstinent from heterosexual intercourse as their preferred and usual lifestyle (abstinent on a long-term and persistent basis) as described in Appendix 3 during the intervention period and for at least 120 days after the last dose of study intervention. The investigator should evaluate the potential for contraceptive method failure (ie, noncompliance, recently initiated) in relationship to the first dose of study intervention.

- A WOCBP must have a negative highly sensitive pregnancy test ([urine or serum] as required by local regulations) within 72 hours before 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 3.

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

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

Informed Consent

9. The participant (or legally acceptable representative if applicable) provides documented informed consent/assent for the study and agrees to DMFS and OS data collection until these study endpoints are reached.

10. The participant provides consent/assent for future biomedical research. However, the participant may take part in the main study without participating in future biomedical research.

11. Have adequate organ function as defined in Table 1. Specimens must be collected within 10 days prior to the start of study treatment.

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
Renal	
Creatinine OR Measured or calculated[2] 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
AST (SGOT) and ALT (SGPT)	Part 1 ≤2.5 × ULN
AST (SGOT) and ALT (SGPT)	Part 2 ≤2.5 × ULN (<5 × ULN for participants with liver metastases)
Coagulation	
International normalized ratio (INR) OR prothrombin time (PT) Activated partial thromboplastin time (aPTT)	≤1.5 × ULN unless participant is receiving anticoagulant therapy as long as PT or aPTT is within therapeutic range of intended use of anticoagulants

ALT (SGPT) = alanine aminotransferase (serum glutamic-pyruvic transaminase); AST (SGOT) = aspartate aminotransferase (serum glutamic-oxaloacetic transaminase); GFR = glomerular filtration rate; ULN = upper limit of normal.

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

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

Note: This table includes eligibility-defining laboratory value requirements for treatment; laboratory value requirements should be adapted according to local regulations and guidelines for the administration of specific chemotherapies.

5.2 Exclusion Criteria

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

Medical Conditions

1. Has a known additional malignancy that is progressing or has required active antineoplastic therapy (including hormonal) within the past 5 years.

   Note: Participants with basal cell carcinoma of the skin, squamous cell carcinoma of the skin, or carcinoma in situ (eg, breast carcinoma, cervical cancer in situ) that have undergone potentially curative therapy are not excluded.

   Note: Participants with a history of nonulcerated cutaneous/acral primary melanoma <1 mm in depth with no nodal involvement are allowed in this study. Participants with any previous melanoma that was ulcerated, ≥1 mm in depth, with nodal involvement, metastasis, or was treated beyond surgical resection (for example, radiation therapy) are not eligible for this study. Participants with synchronous melanomas where lesions not under study are not ulcerated and <1 mm in depth are allowed on the study. Participants with a history of mucosal or uveal melanoma are excluded from this study even if diagnosis and treatment were completed >5 years ago.

2. 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 prior the first dose of study drug.

   Note: The use of inhaled or topical steroids and systemic steroids at physiologic doses of corticosteroids (up to 5 mg/m^2/day prednisone equivalent with maximum dose of 10 mg daily) is allowed on study.

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

4. A WOCBP who has a positive urine pregnancy test within 72 hours prior to randomization (see Appendix 5). If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required.

   Note: In the event that 72 hours have elapsed between the screening pregnancy test and the first dose of study treatment, another pregnancy test (urine or serum) must be performed and must be negative in order for participant to start receiving study medication.

Prior/Concomitant Therapy

5. 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 coinhibitory T-cell receptor (eg, CTLA-4, OX-40, CD137).

6. Has received prior systemic anticancer therapy for melanoma including investigational agents.

7. Has received a live vaccine within 30 days prior to the first dose of study drug. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, varicella/zoster (chicken pox), yellow fever, rabies, *Bacillus* Calmette–Guérin, and typhoid vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed; however, intranasal influenza vaccines (eg, FluMist®) are live attenuated vaccines and are not allowed.

Prior/Concurrent Clinical Study Experience

8. 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 treatment.

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

Diagnostic Assessments

9. Has severe hypersensitivity (≥Grade 3) to any pembrolizumab excipients.

10. Has an active autoimmune disease that has required systemic treatment in 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.

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

12. Has an active infection requiring systemic therapy.

13. Has a known history of human immunodeficiency virus (HIV) infection. No HIV testing is required unless mandated by local health authority.

[redacted]

14. Has a known history of Hepatitis B (defined as Hepatitis B surface antigen reactive) or known active Hepatitis C virus (defined as Hepatitis C virus RNA [qualitative] is detected) infection. No testing for Hepatitis B and Hepatitis C is required unless mandated by local health authority.

[redacted]

15. Has a history of active tuberculosis (*Bacillus* tuberculosis).

16. Has a history or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the study, interfere with the participant's participation for the full duration of the study, or is not in the best interest of the participant to participate, in the opinion of the treating investigator.

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

Other Exclusions

18. Removed.

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

5.3 Lifestyle Considerations

No restrictions are required.

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.

5.3.2 Caffeine, Alcohol, and Tobacco Restrictions

No restrictions are required.

5.3.3 Activity Restrictions

No restrictions are required.

5.3.4 Pregnancy

If a participant inadvertently becomes pregnant while on treatment with pembrolizumab, the participant will be immediately discontinued from study treatment. The site will contact the participant at least monthly and document the participant's status until the pregnancy has been completed or terminated. The outcome of the pregnancy will be reported to the Sponsor without delay and within 24 hours if the outcome is a serious adverse experience (eg, death, abortion, congenital anomaly, or other disabling or life-threatening complication to the mother or newborn). The study investigator will make every effort to obtain permission to follow the outcome of the pregnancy and report the condition of the fetus or newborn to the Sponsor. If a male participant impregnates his female partner, the study personnel at the site must be informed immediately and the pregnancy must be reported to the Sponsor and followed as described in Section 8.4.6.

5.4 Screen Failures

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

5.5 Participant Replacement Strategy

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

6. Treatments

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

Clinical supplies [study treatment(s) provided by the Sponsor] will be packaged to support enrollment. Clinical supplies will be affixed with a clinical label in accordance with regulatory requirements.

6.1 Treatments Administered

The study treatments to be used in this study are outlined below in Table 2.

Table 2 Study Treatments

Study Treatment Name	Dose Formulation	Unit Dose Strength(s)	Dosage Level(s)	Route of Administration	Regimen/ Treatment Period	Use	IMP/ NIMP	Sourcing
Pembrolizumab	Solution for infusion	25 mg/mL vial	2 mg/kg (max. 200 mg) Q3W for pediatric participants (≥12 and <18 years old); 200 mg Q3W for adults (≥18 years of age)	IV infusion via infusion pump	Part 1: 17 cycles Part 2: 17 or 35 cycles	Experimental	IMP	Provided centrally by the Sponsor
Saline placebo	Solution for infusion	None	None	IV infusion via infusion pump	Part 1: 17 cycles	Placebo	IMP	Provided locally by the study site, subsidiary, or designee
Definition Investigational Medicinal Product (IMP) is based on guidance issued by the European Commission. Regional and/or Country differences of the definition of IMP/NIMP may exist. In these circumstances, local legislation is followed.								

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

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

All study treatments will be administered on an outpatient basis.

6.2 Preparation/Handling/Storage/Accountability

6.2.1 Dose Preparation

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

6.2.2 Handling, Storage and Accountability

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

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

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

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

6.3 Measures to Minimize Bias: Randomization and Blinding

6.3.1 Method of Treatment Assignment

Treatment allocation/randomization will occur centrally using an interactive response technology (IRT) system. There are 2 study treatment arms. Participants will be assigned

randomly in a 1:1 ratio to pembrolizumab study treatment or saline placebo study treatment in Part 1.

6.3.1.1 Stratification

Treatment allocation/randomization will be stratified according to the following factors:

1. Melanoma T-Stage (Table 3) for adults only
2. A separate stratum for pediatric (age 12-17) participants

Table 3 Melanoma Stage Stratification Table

Melanoma Stage	T-Stage	T-Stage Definition (thickness and ulceration status)
IIB	T3b	>2.0-4.0 mm with ulceration
IIB	T4a	>4.0 mm without ulceration
IIC	T4b	>4.0 mm with ulceration

T-stage of disease as defined by thickness and ulceration status per AJCC guidelines 8th edition

6.3.2 Blinding

In Part 1 of this study a double-blinding technique will be used. Pembrolizumab and placebo will be prepared and/or dispensed in a blinded fashion by an unblinded pharmacist or unblinded qualified study site personnel. The participant and the investigator who is involved in the study treatment administration or clinical evaluation of the participants are unaware of the group assignments.
Participants in Part 2 will receive pembrolizumab as open-label treatment.

See Section 8.1.11 for a description of the method of unblinding a participant during the study, should such action be warranted.

6.4 Treatment Compliance

Administration of study medication(s) will be administered by the investigator and/or study staff according to the specifications within the Pharmacy Manual. The total volume of study medication infused will be compared with the total volume prepared to determine compliance with each dose administered.

Participants experiencing a greater than 12-week delay between doses due to a pembrolizumab-related AE(s) must be discontinued from treatment.

If there are interruptions in the study intervention schedule, the details of and reason for any interruption of study intervention will be documented in the participant's medical record.

Refer to Section 6.6 for dose modification and toxicity management for irAEs associated with pembrolizumab and for other allowed dose interruptions of pembrolizumab.

6.5 Concomitant Therapy

6.5.1 Specific Restrictions

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

Listed below are specific restrictions or prohibitions for concomitant therapy or vaccination during the course of the study:

- Antineoplastic systemic chemotherapy, immunotherapy or biological therapy not specified in this protocol

  Note: Topical 5-fluorouracil use is allowed prior to enrollment on study. Treatment of skin cancers other than melanoma with any topical anticancer agents may be allowed during follow-up.

- Investigational agents other than pembrolizumab.
- Radiation therapy (See exceptions noted in inclusion and exclusion criteria for Part 2 [Section 6.7]).
- 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.
- Systemic glucocorticoids for any purpose other than to modulate symptoms from an ECI that is suspected to have an immunologic etiology. Inhaled or topical steroids are allowed, and systemic steroids at doses ≤5mg/m^2/day (maximum allowed 10 mg/day) prednisone or equivalent for pediatric participants (≥12 years old and <18 years old) and ≤10 mg/day prednisone or equivalent are allowed for adults.

Participants who in the assessment of the Investigator require the use of any of the aforementioned treatments for clinical management should be removed from the study unless otherwise specified above.

All treatments the Investigator considers necessary for a participant’s welfare may be administered at the discretion of the Investigator in keeping with the community standards of medical care. All concomitant medication will be recorded on the electronic case report form (eCRF) including all prescription, over-the-counter (OTC) products, herbal supplements, and IV medications and fluids. If changes occur during the study period, documentation of drug dosage, frequency, route, and date should also be included on the eCRF.

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

6.5.2 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 are outlined along with the dose modification guidelines in Section 6.6, Table 4. Where appropriate, these guidelines include the use of oral or IV treatment with corticosteroids, as well as additional antiinflammatory agents if symptoms do not improve with administration of corticosteroids. Note that several courses of steroid tapering may be necessary as symptoms may worsen when the steroid dose is decreased. For each disorder, attempts should be made to rule out other causes such as metastatic disease or bacterial or viral infection, which might require additional supportive care. The treatment guidelines are intended to be applied when the Investigator determines the events to be related to pembrolizumab.

Note: If after the evaluation of the event, it is determined not to be related to pembrolizumab, the Investigator does not need to follow the treatment guidance. Refer to Section 6.6 for guidelines regarding dose modification and supportive care.

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

6.6 Immune-related Events and Dose Modification (Withhold, Treat, Discontinue)

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

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

Dose Modification and Toxicity Management Guidelines for irAEs associated with pembrolizumab monotherapy, coformulations, or IO combinations are provided in Table 4.

Table 4 Dose Modification and Toxicity Management Guidelines for Immune-related Adverse Events Associated with Pembrolizumab Monotherapy, Coformulations or IO Combinations

General instructions:

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

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

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

irAEs	Toxicity Grade (CTCAEv4.0)	Action With Pembrolizumab Monotherapy, Coformulations or IO Combinations	Corticosteroid and/or Other Therapies	Monitoring and Follow-up
Hypothyroidism	Grade 2-4	Continue	• Initiate thyroid replacement hormones (eg, levothyroxine or liothyronine) per standard of care	• Monitor for signs and symptoms of thyroid disorders
Nephritis and renal dysfunction	Grade 2	Withhold	• Administer corticosteroids (prednisone 1-2 mg/kg or equivalent) followed by taper	• Monitor changes of renal function
	Grade 3 or 4	Permanently discontinue		
Myocarditis	Grade 1	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 2, 3 or 4	Permanently discontinue		
All Other irAEs	Persistent Grade 2	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology or exclude other causes
	Grade 3	Withhold or discontinue [b]		
	Recurrent Grade 3 or Grade 4	Permanently discontinue		

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

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

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

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

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

Pembrolizumab may cause severe or life-threatening infusion-reactions including severe hypersensitivity or anaphylaxis. Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion. Dose modification and toxicity management guidelines on pembrolizumab associated infusion reaction are provided in Table 5.

Table 5 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 drug treatment	Participant may be premedicated 1.5h (±30 minutes) prior to infusion of pembrolizumab with: Diphenhydramine 50 mg po (or equivalent dose of antihistamine). Acetaminophen 500-1000 mg po (or equivalent dose of analgesic).
Grades 3 or 4 Grade 3: Prolonged (ie, not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (eg, renal impairment, pulmonary infiltrates) Grade 4: Life-threatening; pressor or ventilatory support indicated	Stop Infusion. Additional appropriate medical therapy may include but is not limited to: Epinephrine** IV fluids Antihistamines NSAIDs Acetaminophen Narcotics Oxygen Pressors Corticosteroids Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator. Hospitalization may be indicated. **In cases of anaphylaxis, epinephrine should be used immediately. Participant is permanently discontinued from further study drug treatment.	No subsequent dosing
Appropriate resuscitation equipment should be available at the bedside and a physician readily available during the period of drug administration. For further information, please refer to the CTCAE v4.0 at http://ctep.cancer.gov		

Other allowed dose interruption for pembrolizumab

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

6.7 Part 2 – Crossover or Rechallenge Treatment After Recurrence

The primary goal of the overall study is to compare RFS of pembrolizumab versus placebo, while ensuring access to pembrolizumab for all participants entering the study by allowing crossover/rechallenge after recurrence.

All participants will be unblinded at recurrence (Section 8.1.11) after Sponsor consultation and approval. The site should ensure data for disease recurrence is entered in the database prior to unblinding. Additionally, any AEs and/or SAEs should be reported and causality attributed in the database prior to unblinding. Participants will be encouraged to undergo full resection of the new lesion(s) if they experience local recurrence or have a biopsy if they experience unresectable or metastatic disease. Lymph node dissection should be undertaken per the recommendations of treating physician and surgeon.

For participants who decide to go on to Part 2 and otherwise meet criteria for crossover or rechallenge, resection or biopsy of unresectable or metastatic disease will be mandatory to confirm diagnosis. If biopsy is clinically contraindicated investigators should seek Sponsor review to start participant on Part 2 therapy. Participants should start Part 2 therapy within 4 weeks of recurrence. If participant requires longer time from surgical resection (eg, for recovery from surgery), Sponsor may be consulted to allow additional time before start of Part 2 therapy.

All participants who complete Part 1 study treatment with pembrolizumab or received placebo will be eligible for additional cycles of pembrolizumab if they meet Part 2 enrollment criteria listed below. Rechallenge/crossover is optional and is at the discretion of the Investigator upon notification of the Sponsor.

Participants assigned in the Part 1 initial treatment phase to the placebo arm who experience recurrence at any point during Part 1 therapy and follow-up and meet all crossover criteria will be offered crossover to pembrolizumab per dosing criteria in Section 4.3. Participants on the pembrolizumab arm during the initial phase of treatment who are greater than 6 months from last dose of pembrolizumab treatment and who experience a recurrence will be offered rechallenge with pembrolizumab per dosing criteria outlined in Section 4.3. Participants who have local recurrence, including local metastatic lymph nodes or distant metastases that are surgically resected may receive up to 17 cycles of therapy with pembrolizumab and participants with an unresectable local (regional metastatic lymph nodes, in-transit, satellite, and/or microsatellite metastases) or an unresectable distant recurrence may receive up to 35 cycles of therapy with pembrolizumab per Section 1.3.2.

All participants should have screening imaging within 28 days prior to C1D1 in Part 2 Crossover/Rechallenge phase. The Part 1 EOT scan can be used as baseline for Part 2 if done within 4 weeks of 1st dose in Part 2. Participants who have had surgical resection of lesion

captured on imaging must have a scan after surgery or radiation is complete to establish baseline imaging within 4 weeks prior to start of Part 2 therapy. Brain MRI must be obtained within 4 weeks prior to start of Part 2 treatment, unless contradicted; then CT may be acquired.

Disease recurrence/progression is confirmed by investigator (radiographically and/or by exam with subsequent biopsy) and RECIST 1.1/iRECIST will be used to identify disease progression in participants with metastatic/unresectable disease identified at the start of Part 2 therapy. Local recurrence should be documented with photo image.

Radiotherapy (palliative or adjuvant) is allowed prior to Part 2 (eg, post lymph node dissection radiotherapy when indicated). Radiotherapy has to be completed prior to first dose and complete wound healing is required prior to first dose. Radiotherapy is allowed during treatment in Part 2 as palliative therapy (treatment of pain, impending fracture, etc.) in participants with unresectable recurrence or metastatic disease. If surgery or radiotherapy other than described above is indicated while on Part 2 therapy Sponsor must be consulted.

All eligibility criteria from Part 1 Sections 5.1 and 5.2 remain valid and must be reconfirmed prior to enrollment into Part 2 of the study with the EXCEPTION of:

- Inclusion Criteria 2, 3, 4 and 5
- Exclusion Criteria 5, 6 and 11

Participants must also meet the following requirements for entry into Part 2:

- Participant must have experienced an investigator determined/confirmed disease recurrence radiographically and/or by exam with subsequent biopsy. Local recurrence must be documented with photo image. Participants will only be eligible for Part 2 treatment after the first recurrence. If a participant experiences a second recurrence, they will not be eligible for Part 2. Participants who are less than 6 months from their last Part 1 pembrolizumab dose at the time of recurrence are not eligible for Part 2 treatment.

  Note: Cutaneous lesions and other superficial lesions detectable only by physical exam must be categorized as nontarget lesions for Part 2 of the study.

- No new anticancer treatment was administered after the last dose of Part 1 study treatment.
- Participant is continuing from Part 1 and has completed 17 cycles of pembrolizumab or any number of cycles with placebo with no delays in treatment ≥12 weeks. If a ≥12-week treatment delay has occurred, Sponsor approval must be obtained before moving into Part 2 of the study.

  Note: For any participant who is not able to complete the required 17 cycles of pembrolizumab or have ≥12-week treatment delay on placebo arm, a notification to the Sponsor is required to determine if it would impact their eligibility for entry into Part 2.

- Surgical resection or biopsy of unresectable or metastatic disease completed within 4 weeks of first dose.

- Full resection of lesions or biopsy of unresectable or metastatic disease confirmed by site pathologist to be melanoma.

  Note: If biopsy is clinically contraindicated, investigators should seek Sponsor review and approval to start participant on Part 2 therapy.

  If participant is identified to have a thoracic lesion or lymph node suspicious for a recurrence (especially if solitary lesion), it is encouraged that a biopsy be performed to confirm metastatic melanoma versus another lung primary malignancy versus a nonmalignant lung disease (eg, sarcoidosis).

- Participants with focal or multifocal brain metastasis who are asymptomatic and do not require supraphysiologic steroid therapy per Section 5.2 are allowed in Part 2 of the study and may receive concurrent radiation to these lesions. Participants with leptomeningeal disease are not allowed to proceed to Part 2 of the study. A brain MRI is required to confirm presence of brain metastasis and evaluate for leptomeningeal disease prior to start of Part 2 treatment and if contraindicated a CT may then be used. Brain lesions are not to be recorded as target lesions but should be followed as nontarget lesions.

- ECOG performance status 0-2 in participants ≥18 years of age, LPS ≥50 for children up to and including 16 years of age, or KPS ≥50 for participants >16 and <18 years of age (Appendix 8).

- For Part 2 of the study, any participant who developed a severe hypersensitivity (≥Grade 3) to any pembrolizumab excipients or pembrolizumab during Part 1 of the study will not be eligible for Part 2 therapy, as treatment in Part 1 was stopped secondary to an unacceptable AE.

Participants who discontinued study treatment during Part 1 due to documented disease recurrence on the pembrolizumab arm, unacceptable AEs, intercurrent illness that prevents further administration of treatment, investigator's decision to withdraw the participant, participant withdraws consent, participant requests to discontinue study treatment, pregnancy of the participant, noncompliance with study treatment, procedure requirements, or administrative reasons, are not eligible for Part 2.

6.8 Treatment After the End of the Study

The participant may be enrolled in an extension study upon completion of this study to continue protocol-defined assessments and treatment.

6.9 Clinical Supplies Disclosure

The emergency unblinding call center will use the treatment/randomization schedule for the study to unblind participants and to unmask study treatment identity during Part 1 of this study. The emergency unblinding call center should only be used in cases of emergency (see Section 8.1.11). In the event that the emergency unblinding call center is not available for a given site in this study, the central electronic treatment allocation/randomization system (IRT) should be used in order to unblind participants and to unmask study treatment identity. The Sponsor will not provide random code/disclosure envelopes or lists with the clinical supplies.

Part 2 of the study is open-label; therefore, the participant, the study site personnel, the Sponsor and/or designee are not blinded. Study treatment (name, strength or potency) is included in the label text; random code/disclosure envelopes or lists are not provided.

See Section 8.1.11 for a description of the method of unblinding a participant during the study, should such action be warranted.

6.10 Standard Policies

At the close of the study after unblinding, a letter is to be sent by the investigator to those participants who received placebos in the image of the competitor's product to provide the following advice:

"You have participated in a study conducted by the Sponsor. This is to advise you that you were among those who received a look-alike infusion provided locally by the clinical site to resemble the drug Keytruda (pembrolizumab) as much as possible. You did not receive the active drug Keytruda (pembrolizumab) as manufactured by Merck."

7. Discontinuation of Study Treatment and Participant Withdrawal

7.1 Discontinuation of Study Treatment

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

As certain data on clinical events beyond study treatment discontinuation may be important to the study, they must be collected through the participant's last scheduled follow-up, even if the participant has discontinued study treatment. Therefore, all participants who discontinue study treatment prior to completion of the protocol-specified treatment period will still continue to participate in the study as specified in Section 1.3 and Section 8.11.3.

Participants may discontinue study treatment at any time for any reason or be discontinued from the study treatment at the discretion of the investigator should any untoward effect occur. In addition, a participant may be discontinued from study treatment by the investigator or the Sponsor if study treatment is inappropriate, the study plan is violated, or for administrative and/or other safety reasons. Specific details regarding procedures to be performed at study treatment discontinuation are provided in Section 8.1.10.

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

- The participant or participant's legally acceptable representative requests to discontinue study treatment.
- The participant's treatment assignment has been purposely unblinded by the investigator, MSD subsidiary or through the emergency unblinding call center during Part 1 prior to recurrence.
- Interruptions from the protocol-specified treatment plan for greater than or equal to 12 weeks between pembrolizumab doses for nondrug-related or administrative reasons require consultation between the investigator and the Sponsor and written documentation of the collaborative decision on participant management.

- A ≥12-week break in pembrolizumab treatment due to a drug-related AE.
- 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 treatment.
- The participant has a confirmed positive serum pregnancy test.
- Participant with confirmed disease recurrence radiographically and/or by exam with subsequent biopsy while on Part 1 treatment with pembrolizumab or placebo must stop Part 1 study treatment. Participants on Part 1 treatment with placebo can be screened for Part 2 therapy with pembrolizumab.
- Confirmed disease recurrence identified by investigator (radiographically and/or by exam with subsequent biopsy) or confirmed progression per iRECIST if clinically stable during Part 2 treatment outlined in Section 8.11 (exception if the Sponsor approves treatment continuation).
- Any progression or recurrence of any malignancy, or any occurrence of another malignancy that requires active treatment (hormonal and/or antineoplastic therapy).
    - Exceptions to secondary malignancy include basal cell carcinoma of the skin, squamous cell carcinoma of the skin, new nonulcerated primary melanoma <1mm in depth with no nodal involvement, 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 or remaining in follow-up.
    - Diagnosis of a new primary melanoma >1mm or <1mm with ulceration will result in discontinuation of therapy in Part 1 or Part 2 and make participant no longer eligible for Part 2 therapy.
    - Investigator may submit a Sponsor consultation form to request a participant be unblinded if the participant develops a second malignancy including a new primary melanoma >1mm or <1mm with ulceration.
- Noncompliance with study treatment or procedure requirements.
- Discontinuation of treatment may be considered for participants who have attained a confirmed CR and have been treated for at least 8 cycles (at least 24 weeks), receiving at least 2 doses of pembrolizumab beyond the date when the initial CR was declared.
- Recurrent Grade 2 pneumonitis.
- Completion of 17 cycles during Part 1 therapy.

  Note: Participants who complete Part 1 therapy are still eligible for Part 2 therapy if they meet Part 2 eligibility guidelines. For any participant who is not able to complete the

required 17 cycles, a notification to the Sponsor is required to determine if it would impact eligibility for entry into Part 2.

- Completion of 17 cycles or 35 cycles with pembrolizumab as assigned in Part 2.

  Note: The number of treatments is calculated starting with the first dose.

- Withdrawal of consent by participant to continue on study.

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

7.2 Participant Withdrawal From the Study

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

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

Specific details regarding procedures to be performed at the time of withdrawal from the study, as well as specific details regarding withdrawal from future biomedical research are outlined in Section 8.1.10.1. The procedures to be performed should a participant repeatedly fail to return for scheduled visits and/or if the study site is unable to contact the participant are outlined in Section 7.3.

7.3 Lost to Follow-up

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

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

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

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

8. Study Assessments and Procedures

- Study procedures and their timing are summarized in the SoA.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- The investigator is responsible for assuring that procedures are conducted by appropriately qualified or trained staff. Delegation of study site personnel responsibilities will be documented in the Investigator Trial File Binder (or equivalent).
- All study-related medical decisions must be made by an investigator who is a qualified physician.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the participant's routine clinical management (eg, blood count) and obtained before signing of ICF may be utilized for screening or baseline purposes provided the procedure met the protocol-specified criteria and were performed within the time frame defined in the SoA.
- Additional evaluations/testing may be deemed necessary by the investigator and or the Sponsor for reasons related to participant safety. In some cases, such evaluation/testing may be potentially sensitive in nature (eg, HIV, Hepatitis C, etc.), and thus local regulations may require that additional informed consent, and assent if applicable, be obtained from the participant. In these cases, such evaluations/testing will be performed in accordance with those regulations.

The maximum amount of blood collected from each pediatric participant will not exceed approximately 51 mL per cycle. The amount for adult participants will not exceed approximately 42 mL per cycle.

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/Assent

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

8.1.1.1 General Informed Consent

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

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

The initial informed consent/assent form, any subsequent revised informed consent/assent form, and any written information provided to the participant must receive the IRB/IEC's approval/favorable opinion in advance of use. The communication of this information will be provided and documented via a revised consent/assent form or addendum to the original consent/assent 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 written documented informed consent/assent.

Participants must be re-consented with the current informed consent/assent form before entering Part 2 of the study.

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

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

8.1.1.2 Consent/Assent and Collection of Specimens for Future Biomedical Research

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

8.1.2 Inclusion/Exclusion Criteria

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

8.1.3 Participant Identification Card

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

allocation/randomization, site personnel will add the treatment/randomization number to the Participant Identification Card.

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

8.1.4 Medical History

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

8.1.5 Prior and Concomitant Medications Review

8.1.5.1 Prior Medications

The Investigator or qualified designee will review prior medication use, including any protocol-specified washout requirement, and record prior medication taken by the participant within 28 days before starting the study.

8.1.5.2 Concomitant Medications

The Investigator or qualified designee will record medication, if any, taken by the participant during the study through the Safety Follow-up visit. In addition, new medications started during Part 2 through the Part 2 Safety visit should be recorded. All medications related to reportable SAEs and ECIs should be recorded.

8.1.6 Assignment of Screening Number

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

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

Specific details on the screening visit requirements (screening/rescreening) are provided in Section 8.11.1.

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 allocation/randomization. Once a treatment/randomization number is assigned to a participant, it can never be re-assigned to another participant.

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

8.1.8 Treatment Administration

Study medication will be administered by the investigator and/or study staff according to the specifications within the Pharmacy Manual.

After ensuring participants meet study-related inclusion/exclusion criteria, study personnel will access IRT to obtain treatment number.

First study treatment should be administered within 3 calendar days of treatment number assignment in IRT.

8.1.8.1 Timing of Dose Administration

Cycle 1 treatment should be administered starting with Day 1 of the first treatment cycle after all procedures/assessments have been completed as detailed on the SoA (Section 1.3). Study treatment may be administered up to 3 days before or after the scheduled day of administration due to administrative reasons. Participants may continue on treatment until disease progression or until meeting other discontinuation criteria outlines in Section 7.1.

8.1.9 Part 2 Crossover/Rechallenge Therapy

See Section 6.7 for details on the Part 2 Crossover/Rechallenge therapy.

8.1.10 Discontinuation and Withdrawal

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

When a participant withdraws from participation in the study, all applicable activities scheduled for the final study visit should be performed (at the time of withdrawal). Any AEs which are present at the time of withdrawal should be followed in accordance with the safety requirements outlined in Section 8.4 -Adverse Events.

8.1.10.1 Withdrawal From Future Biomedical Research

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

In the event that the medical records for the main study are no longer available (eg, if the investigator is no longer required by regulatory authorities to retain the main study records) or the specimens have been completely anonymized, there will no longer be a link between

the participant's personal information and their specimens. In this situation, the request for specimen withdrawal cannot be processed.

8.1.11 Participant Blinding/Unblinding

STUDY TREATMENT IDENTIFICATION INFORMATION IS TO BE UNMASKED DURING PART 1 ONLY IF NECESSARY FOR THE WELFARE OF THE PARTICIPANT. EVERY EFFORT SHOULD BE MADE NOT TO UNBLIND.

For emergency situations where the investigator or medically qualified designee (consistent with local requirements) needs to identify the drug used by a participant and/or the dosage administered, he/she will contact the emergency unblinding call center by telephone and make a request for emergency unblinding. As requested by the investigator or medically qualified designee the emergency unblinding call center will provide the information to him/her promptly and report unblinding to the Sponsor. Prior to contacting the emergency unblinding call center to request unblinding of a participant's treatment assignment, the investigator who is a qualified physician should make reasonable attempts to enter the toxicity grade of the AEs observed, the relation to study drug, the reason thereof, etc., in the medical chart. If it is not possible to record this assessment in the chart prior to the unblinding, the unblinding should not be delayed.

In the event that unblinding has occurred, the circumstances around the unblinding (eg, date, reason and person performing the unblinding) must be documented promptly, and the Sponsor notified as soon as possible.

Once an emergency unblinding has taken place, the principal investigator, site personnel, and Sponsor personnel (with the exception of the blinded study statisticians) may be unblinded so that the appropriate follow-up medical care can be provided to the participant.

For studies that require non-emergency unblinding as part of the study design (eg, disease progression) to support treatment decisions, instructions in Procedure Manual should be followed. The emergency unblinding center should not be used for this purpose.

Once a non-emergency unblinding has taken place (ie, after first recurrence), the principal investigator, site personnel, and Sponsor personnel (with the exception of the study blinded statisticians) may be unblinded to the participant's data so that the appropriate follow-up medical care can be provided to the participant.

Participants whose treatment assignment has been unblinded by the investigator/delegate and/or nonstudy treating physician should continue to be monitored. Participants who qualify for Part 2 per the eligibility criteria in Section 6.7 may continue on the study.

The process for nonemergent unblinding at the time of disease recurrence in Part 1 requires the investigator to submit a Sponsor consultation form to the study clinical team requesting authorization for official unblinding upon disease recurrence and consideration to proceed into Part 2 of the study (Crossover/Rechallenge treatment). After unblinding is complete, the site will assess the participant's eligibility for Part 2 of the study and notify the Sponsor prior to beginning Part 2. The entry criteria for Part 2 are detailed in Section 6.7.

During the study, all data should be entered as soon as possible after a protocol visit or procedure is conducted. Upon first recurrence, every effort must be made to have all pending data entered into the eCRFs within 1 business day or before the site is unblinded to the

participant's treatment assignment. The site should ensure data for disease recurrence is entered in the database prior to unblinding. Additionally, any AEs and/or SAEs should be reported and causality attributed in the database prior to unblinding.

The study will be considered unblinded once the RFS endpoint has been achieved and has been reviewed by the eDMC. The Sponsor will identify to the sites the specific unblinding procedures to be followed.

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 is reliable and/or reproducible. Documentation of equipment calibration must be retained as source documentation at the study site.

8.1.13 Participants Turning 18 Years of Age While on Study

For participants turning 18 years of age while on study, the following adjustments are to be observed:

- Performance Assessment – The original performance assessment scale (Lansky/Karnofsky/ECOG) assigned to the participant will be used throughout Part 1. A participant will be assigned the appropriate age-related performance scale when entering Part 2.
- Pharmacokinetics (PK and ADA Samples) – Sample collection will cease once a participant turns 18 years of age.
- Height – Height is not collected for adults entering Part 1 or Part 2 other than at Part 1 screening. A participant below the age of 18 entering Part 1 or Part 2 will continue to have their height collected regardless of age.
- Pembrolizumab dosing – A participant randomized to receive pembrolizumab who is under 18 years of age at the beginning of Part 1 or Part 2 of the study will receive and remain on the pediatric dose of pembrolizumab (2 mg/kg up to 200 mg Q3W) throughout Part 1 or Part 2 respectively. Any participant who begins Part 2 as an adult will adhere to the fixed adult dose of pembrolizumab (200 mg Q3W) regardless of their Part 1 dosing regimen.

8.2 Efficacy Assessments

8.2.1 Tumor Scans and Assessment of Disease

Throughout this section, the term 'scan' refers to any medical imaging data used to assess tumor burden and may include cross-sectional imaging (such as CT or MRI), medical photography, or other methods as specified in this protocol.

Tumor imaging is strongly preferred to be acquired by CT. 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. A CT scan of the extremity where the primary melanoma was diagnosed (or MRI if CT scan is contraindicated) should be performed at the investigator's discretion or when clinically indicated. The same scan technique regarding modality, ideally the same scanner, and the use of contrast should be used in a participant throughout the study 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 scans. Note: for the purposes of assessing tumor scans, the term "investigator" refers to the local investigator at the site and/or the radiological reviewer located at the site or at an offsite facility.

8.2.1.1 Initial Tumor Scans

Initial tumor scans at Screening must be performed within 28 days prior to the date of randomization. The site study team must review screening scans to confirm the participant has no evidence of disease at study entry into Part 1. Exceptions can be made if screening scan performed outside of 28-day screening period. Sponsor approval must be obtained prior to randomization.

8.2.1.2 Tumor Scans During the Study

For Part 1 the first on-study scan time point will be performed 6 months (26 weeks ± 7 days) from date of randomization. Subsequent tumor scans should be performed every 6 months (26 weeks ±7 days) while on treatment, at end of treatment, every 6 months (26 weeks ±14 days) from years 2 to 4 from randomization, and then once in year 5 (365 ±28 days) from randomization or until recurrence, whichever comes first. More frequent scans may occur if clinically indicated.

Participants entering Part 2 who have resection of lesion captured on scans should have repeat scans after surgery or radiation to establish baseline imaging within 4 weeks prior to start of Part 2 therapy. For all Part 2 participants the first on-study scan assessment should be performed at 12 weeks (84 ±7 days) after first dose of pembrolizumab in Part 2 (C1D1). For participants with local recurrence including local metastatic lymph nodes surgically resected and distant metastasis surgically resected, subsequent tumor scan should be performed every 12 weeks (84 ±7 days) for 1 year from C1D1 while on treatment, at end of treatment, every 12 weeks (84 ±7 days) in year 2 from C1D1, every 6 months (26 weeks ±14 days) from years 3-5 from C1D1 and yearly thereafter (365 days ±28 days) or until recurrence.

For participants entering Part 2 who have unresectable disease, the first on-study scan assessment should be performed at 12 weeks (84 ±7 days) after first dose of pembrolizumab (C1D1) in Part 2. Subsequent tumor scans should be performed every 12 weeks (84 ±7 days) for 2 years from C1D1 while on treatment, at end of treatment, every 12 weeks (84 ±7 days) in year 3 from C1D1, every 6 months for years 4-5 (26 weeks ±14 days) from C1D1 and yearly thereafter (365 days ±28 days) or until recurrence.

Scans will be performed more frequently if clinically indicated. Scan timing should follow calendar days and should not be adjusted for delays in cycle starts.

Scans should continue to be performed until one of the following occurs:

- Metastatic disease recurrence is identified by the investigator or
- Progression in Part 2 is assessed by investigator using RECIST 1.1/iRECIST criteria

- Participant enters DMFS follow-up
- Participant enters Survival Follow-up
- Withdrawal of consent
- Death
- End of study.

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

Response assessment in Part 2 will be based on RECIST 1.1/ iRECIST as assessed by investigator/local radiology review. Objective response to confirm PR/CR is based on RECIST 1.1, and iRECIST will be used to confirm PD after initial site-assessed radiologic PD per RECIST 1.1 in clinically stable participants. Per iRECIST (Section 8.2.1.5), disease progression should be confirmed by the site 4 to 8 weeks after site-assessed first radiologic evidence of PD in clinically stable participants. Participants with unconfirmed disease progression may continue on treatment at the discretion of the investigator until disease progression is confirmed by the site, provided they have met the conditions detailed in Section 8.2.1.5. Participants who receive confirmatory scans do not need to undergo the next scheduled tumor scan if it is less than 4 weeks later; tumor scans may resume at the subsequent scheduled scan time point, if clinically stable. Participants with confirmed disease progression by iRECIST, as assessed by the site, will discontinue study treatment. Exceptions are detailed in Section 8.2.1.5.

A central imaging vendor will be used to collect, clean, and hold tumor scans. Images will be collected for possible analysis by BICR. The same scan technique should be used at each time point and the schedule of disease assessment should not be adjusted for delays, if any, in cycle starts of disease assessment. The process for scan collection and transmission to the central imaging vendor can be found in the Site Imaging Manual (SIM).

8.2.1.3 End of Treatment and Follow-up Tumor Scans

For participants who discontinue study treatment, tumor scans should be performed at the time of treatment discontinuation (± 4 week window). If previous scan was obtained within 4 weeks prior to the date of discontinuation, then the scan at treatment discontinuation is not mandatory. If study required interval imaging is due within 4 weeks of EOT, interval scans are not mandatory if all required scans have been obtained at EOT.

For participants who discontinue study treatment without documented disease progression, every effort should be made to continue monitoring disease status by tumor scans using the same scan schedule used while on treatment until metastatic disease recurrence disease progression, death, withdrawal of consent, or the end of the study, whichever occurs first.

8.2.1.4 Summary of Scans

8.2.1.4.1 Part 1 Adjuvant Treatment

- Tumor scans at Screening must be performed within 28 days prior to randomization. Exceptions can be made if screening scan is performed outside of the 28-day screening period. Sponsor approval must be obtained prior to randomization.

- The first on-study scan time point will be performed 6 months (26 weeks ±7 days) from the date of randomization.

- All consecutive scans are to be performed every 6 months (26 weeks ±7 days) from randomization, at EOT (±7 days), every 6 months (26 weeks ±14 days) during years 2 to 4 from randomization, and once in year 5 from randomization (365 ±28 days; ie, 5 years from the date of randomization) or until disease recurrence. Imaging schedule may or may not coincide with visit schedule.

- Scan timing should follow calendar days and should not be adjusted for delays in cycle starts.

- DMFS follow-up and SFU scan collection is per local standard of care or scan requirements for new anticancer therapy.

- Participants who had the last scan performed in the preceding 4 weeks of planned EOT visit may have EOT scan omitted at the discretion of the investigator. For participants who discontinue study treatment without documented recurrence, every effort should be made to continue monitoring disease status every 6 months (26 weeks ±7 days) from randomization, at EOT (±7 days), every 6 months (26 weeks ±14 days) during years 2 to 4 from randomization, and once in year 5 from randomization (365 ±28 days; ie, 5 years from the date of randomization) or until disease recurrence. Scan schedule may or may not coincide with visit schedule.

- If study required interval scans are due within 4 weeks of EOT, interval scans are not mandatory if all required scans have been obtained at EOT.

- All scan assessments performed in Part 1 must be scheduled based on date of randomization.

- Scans of any anatomy that show disease after screening or in subsequent evaluations will be required and should be submitted to the Central Imaging Vendor.

- Brain CT may be acquired if MRI is contraindicated.

- Site investigator must collect and review copy of scans and reports (including scans done external to site), photographs and pathology reports to update disease status. A central imaging vendor will be used to collect, clean, and hold tumor scans obtained during the DMFS phase of the study. A central imaging vendor will be used to

collect, clean, and hold tumor scans obtained during the SFU phase of the study if scans are available.

- Scan schedule may or may not coincide with visit schedule.

8.2.1.4.2 Part 2 Crossover/Rechallenge After First Recurrence

- The EOT scan from Part 1 can be used as baseline for Part 2 if done within 4 weeks of 1st dose in Part 2. If the EOT scan (from Part 1) cannot be used as the screening scan for Part 2, the latest scan date should be within 4 weeks prior to first dose in Part 2. Participants who have resection or radiation of lesion captured on scan should have a repeat scan after surgery or radiation is complete to establish baseline imaging within 4 weeks prior to start of Part 2 therapy.

- All scans performed while on treatment and during the follow-up phase of Part 2 must be scheduled based on C1D1 of treatment in Part 2.

- EOT scan in Part 2 should be obtained at EOT (± 4 weeks).

- During Part 2 treatment phase (ie, in the absence of a second recurrence on-study), participants who had the last scan performed in the preceding 4 weeks of the planned Part 2 EOT visit may have Part 2 EOT scan omitted at the discretion of the investigator.

- For participants with local recurrence including local metastatic lymph nodes surgically resected, scan assessment should be done every 12 weeks (84 ±7 days) for 1 year from C1D1, at EOT (±7 days), every 12 weeks in year 2 from C1D1 (84 ±7 days), every 6 months (26 weeks ±14 days) from years 3-5 from C1D1, and yearly (365 days ±28 days) thereafter until recurrence or end of study, whichever comes first.

- For participants with local recurrence including local metastatic lymph nodes surgically resected who discontinue study treatment without documented recurrence, every effort should be made to continue monitoring disease status by tumor scan every 12 weeks (84 ±7 days) for 1 year from C1D1, every 12 weeks (84 ±7 days) in year 2 from C1D1, every 6 months in years 3-5 (26 weeks ±14 days) from C1D1, and yearly thereafter (365 ±28 days) until recurrence or end of study, whichever comes first.

- For participants with distant metastatic disease who have undergone complete surgical resection, scan assessments should be done every 12 weeks (84 ±7 days) for 1 year from C1D1, at EOT (±7 days), every 12 weeks (84 ±14 days) in year 2 from C1D1, every 6 months in years 3-5 (26 weeks ±14 days) from C1D1, and yearly thereafter (365 days ±28 days) until recurrence or end of study, whichever comes first.

- For participants with resectable distant recurrence who discontinue study treatment without documented recurrence every effort should be made to continue monitoring disease status by tumor scan every 12 weeks (84 ±7 days) for the first year from C1D1, every 12 weeks (84 ±7 days) in year 2 from C1D1, every 6 months (26 weeks ±14 days) in years 3-5 from C1D1, and yearly thereafter (365 days ±28 days) or until recurrence/progression or end of study, whichever comes first.

- For participants with unresectable local (regional metastatic lymph nodes, in-transit, satellite, and/or microsatellite metastases) or unresectable distant recurrence scans should be done every 12 weeks (84 ±7 days) from C1D1 during the first 2 years from C1D1, at EOT (±7 days), every 12 weeks (84 ±7 days) in year 3 from C1D1, every 6 months (26 weeks ±14 days) in years 4-5 from C1D1, and yearly thereafter (365 days ±28 days) until recurrence/progression or end of study, whichever comes first.

- For participants with unresectable local (regional metastatic lymph nodes, in-transit, satellite, and/or microsatellite metastases) or unresectable distant recurrence who discontinue study treatment without documented recurrence/progression on Part 2, every effort should be made to continue monitoring disease status by tumor scan every 12 weeks (84 ±7 days) during years 1-2 from C1D1, every 12 weeks (84 ±7 days) in year 3 from C1D1, every 6 months (26 weeks ±14 days) in years 4-5 from C1D1, and yearly thereafter (365 ±28 days).until recurrence/progression or end of study, whichever comes first.

- All target and nontarget lesions should be followed at every scan time point.

- Scans of any anatomy that shows disease either at screening or in subsequent evaluations will be required and should be submitted to the Central Imaging Vendor.

- Brain MRI must be obtained within 4 weeks prior to start of Part 2 TX, unless contraindicated; then CT may be acquired. Scan timing should follow calendar days and should not be adjusted for delays in cycle starts.

- Site investigator must collect and review copy of scans and reports (including scans done external to site) to update disease status. A central imaging vendor will be used to collect, clean, and hold tumor scans obtained during the DMFS phase of the study. A central imaging vendor will be used to collect, clean, and hold tumor scans obtained during the SFU phase of the study if it is available.

- Scan schedule may or may not coincide with visit schedule.

8.2.1.5 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 treatment). 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.

8.2.1.6 iRECIST Assessment of Disease

iRECIST is based on RECIST 1.1 but adapted to account for the unique tumor response seen with immunotherapeutic drugs (Appendix 9). iRECIST will be used by the investigator to assess tumor response and progression and make treatment decisions. When clinically stable, participants should not be discontinued until progression is confirmed by the investigator, working with local radiology. This allowance to continue treatment despite initial radiologic PD takes into account the observation that some participants can have a transient tumor flare in the first few months after the start of immunotherapy, and then experience subsequent disease response. This data will be captured in the clinical database.

Clinical stability is defined as the following:

- Absence of symptoms and signs indicating clinically significant progression of disease.
- No decline in ECOG performance status, KPS status, or LPS status (Appendix 8).
- No requirements for intensified management, including increased analgesia, radiation, or other palliative care.

Any participant deemed **clinically unstable** should be discontinued from study treatment at site-assessed first radiologic evidence of PD and is not required to have repeat tumor imaging for confirmation of PD by iRECIST. If the investigator decides to continue treatment, the participant may continue to receive study treatment and the tumor assessment should be repeated 4 to 8 weeks later to confirm PD by iRECIST, per investigator assessment.

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

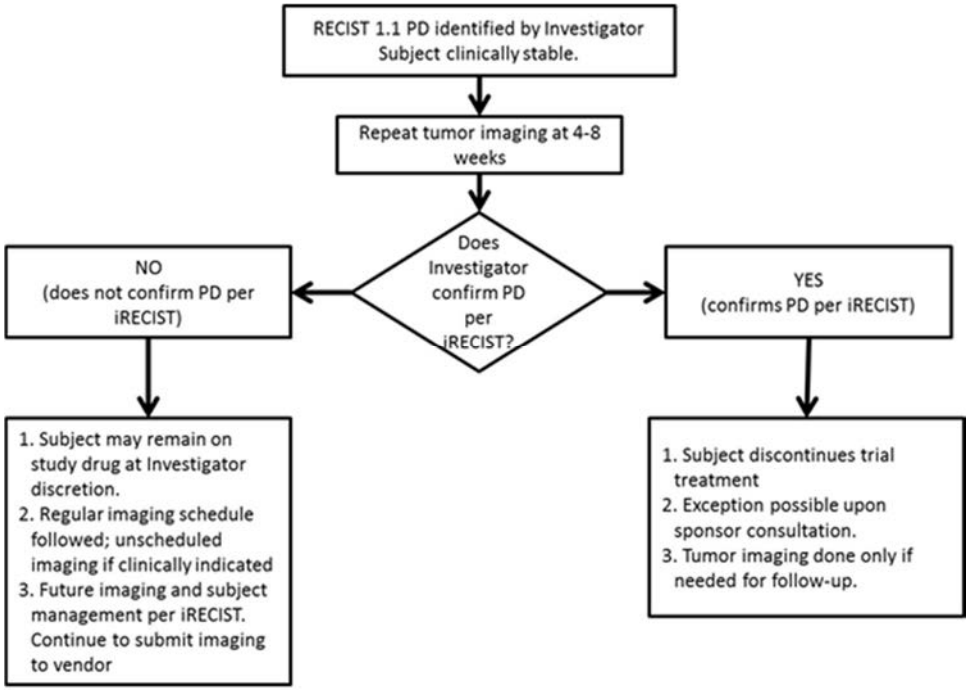
If a participant has confirmed radiographic progression (iCPD), study treatment should be discontinued; however, if the participant is achieving a clinically meaningful benefit, an exception to continue study treatment may be considered following consultation with the Sponsor. In this case, if study treatment is continued, tumor imaging should continue to be performed following the intervals as outlined in Section 1.3.

A description of the adaptations and iRECIST process are found in the iRECIST publication [Seymour, L., et al 2017]. A summary of imaging and treatment requirements after first radiologic evidence of progression is provided in Table 6 and illustrated as a flowchart in Figure 3.

Table 6 Imaging and Treatment After First Radiologic Evidence of Progressive Disease

	Clinically Stable		**Clinically Unstable**	
	Imaging	**Treatment**	**Imaging**	**Treatment**
First radiologic evidence of PD by RECIST 1.1	Repeat imaging at 4 to 8 weeks to confirm PD.	May continue study treatment at the investigator's discretion while awaiting confirmatory tumor imaging by site by iRECIST.	Repeat imaging at 4 to 8 weeks to confirm PD per investigator's discretion only.	Discontinue treatment.
Repeat tumor imaging confirms PD (iCPD) by iRECIST per investigator assessment.	No additional imaging required.	Discontinue treatment (exception is possible upon consultation with Sponsor).	No additional imaging required.	Not applicable.
Repeat tumor imaging shows iUPD by iRECIST per investigator assessment.	Repeat imaging at 4 to 8 weeks to confirm PD. May occur at next regularly scheduled imaging visit.	Continue study treatment at the investigator's discretion.	Repeat imaging at 4 to 8 weeks to confirm PD per investigator's discretion only.	Discontinue treatment.
Repeat tumor imaging shows iSD, iPR, or iCR by iRECIST per investigator assessment.	Continue regularly scheduled imaging assessments.	Continue study treatment at the investigator's discretion.	Continue regularly scheduled imaging assessments.	May restart study treatment if condition has improved and/or clinically stable per investigator's discretion. Next tumor imaging should occur according to the regular imaging schedule.

iCPD = iRECIST confirmed progressive disease; iCR = iRECIST complete response; iRECIST = modified Response Evaluation Criteria in Solid Tumors 1.1 for immune-based therapeutics; iSD = iRECIST stable disease; iUPD = iRECIST unconfirmed progressive disease; PD = progressive disease; RECIST 1.1 = Response Evaluation Criteria in Solid Tumors 1.1; VOP = verification of progression.



iRECIST = modified Response Evaluation Criteria in Solid Tumors 1.1 for immune-based therapeutics; PD = progressive disease; RECIST 1.1 = Response Evaluation Criteria in Solid Tumors 1.1.

Figure 3 Imaging and Treatment for Clinically Stable Participants Treated With Pembrolizumab After First Radiologic Evidence of PD Assessed by the Investigator

8.2.2 Lactic Acid Dehydrogenase

Lactic acid dehydrogenase (LDH) will be collected at the time of recurrence in Part 1 as a baseline. In Part 2 LDH will be collected as per the SoA (Section 1.3) in an advanced disease setting.

8.2.3 Quality of Life Assessments

8.2.3.1 Patient-reported Outcomes

The EuroQoL EQ-5D-5L and EORTC QLQ-C30 questionnaires will be administered by trained site personnel and completed electronically by participants in the following order: EuroQoL EQ-5D first, then EORTC QLQ-C30. In Part 1, EuroQoL EQ-5D-5L and EORTC QLQ-C30 should be completed at baseline (Cycle 1), during treatment in year one (at Cycle 5, 9, 13, 17), every 12 weeks during year 2 (Week 60, 72, 84, and 96 from baseline), and every 6 months during year 3 (month 30 and 36 from baseline). The EORTC QLQ-C30 will be administered only to adults (≥18 years of age at baseline) since the questionnaire is not validated in pediatric populations. The EuroQoL EQ-5D-5L will be administered to all study participants, since it is considered acceptable to use for persons 12 years and older.

In Part 2, EuroQoL EQ-5D-5L should be completed during this phase at baseline (Cycle 1), during treatment at Cycles 9, 17 and 35, and at 24 and 48 weeks during first year off treatment.

It is best practice and strongly recommended that electronic PROs are administered to randomized participants prior to drug administration, AE evaluation, and disease status notification. If the participant does not complete the electronic PROs at a scheduled time point, the MISS_MODE form must be completed to capture the reason the assessment was not performed.

8.3 Safety Assessments

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

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

8.3.1 Physical Examinations

8.3.1.1 Full Physical Exam

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

8.3.1.2 Directed Physical Exam

For cycles that do not required a full physical exam as defined in Section 1.3, the investigator or qualified designee will perform a directed physical exam as clinically indicated prior to the administration of the study treatment. New clinically significant abnormal findings should be recorded as AEs. The investigator or qualified designee should conduct a visual inspection of local recurrence and palpation of regional lymph nodes to assess regional recurrence.

Photographs of new skin lesions not visualized on imaging should be obtained and submitted to imaging vendor.

8.3.2 Vital Signs

- Temperature, pulse rate, respiratory rate, and blood pressure will be assessed.
- Blood pressure and pulse measurements will be assessed with a completely automated device. Manual techniques will be used only if an automated device is not available.
- Blood pressure and pulse measurements should be preceded by at least 5 minutes of rest for the participant in a quiet setting without distractions.

- Vital signs will be measured after 5 minutes rest and will include temperature, systolic and diastolic blood pressure, and pulse and respiratory rate.

The investigator or qualified designee will take vital signs at screening, prior to the administration of each dose of study treatment and at treatment discontinuation, and in follow-up as specified in Section 1.3. Vital signs are to be measured immediately before the start of study medication administration and as needed per standard of care.

For adult participants, height will be measured only at Screening in Part 1 and Part 2. For pediatric participants, height will be measured at study visits as specified in Section 1.3. Weight measurements may be conducted up to 3 days before the scheduled day of administration due to administrative reasons. Weight measurement is not required postinfusion.

8.3.3 Electrocardiograms

A standard 12-lead electrocardiogram (ECG) will be performed and reviewed by an investigator or medically qualified designee (consistent with local requirements) at screening in Part 1 and Part 2. Clinically significant abnormal findings should be recorded as medical history. Additional time points may be performed as clinically necessary.

Note: A 6-lead ECG is allowed per institutional standard.

8.3.4 Clinical Safety Laboratory Assessments

Refer to Appendix 5 for the list of clinical laboratory tests to be performed and to the SoA for the timing and frequency.

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

- All protocol-required laboratory assessments, as defined in Appendix 5, must be conducted in accordance with the SoA.

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

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

8.3.5 Pregnancy Test

All women who are being considered for participation in the study, and who are not surgically sterilized or postmenopausal, must be tested for pregnancy within 72 hours prior to the first dose of study treatment in Parts 1 and 2 of the study. If a urine test is positive or not evaluable, a serum test will be required. Participants must be excluded/discontinued from the study in the event of a positive test result. Repeated Pregnancy test should be performed according to the SoA (Section 1.3) and may be conducted as required by local regulations.

8.3.6 Performance Assessments

- Use of Performance scale is dependent upon age: LPS for participants up to and including 16 years of age; KPS for participants >16 and <18 years of age, or ECOG for participants ≥18 years of age. The original performance assessment scale (Lansky/Karnofsky/ECOG) assigned to the participant will be used throughout Part 1. A participant will be assigned the appropriate age-related performance scale when entering Part 2 and that scale will be used throughout Part 2.

8.3.6.1 ECOG Performance Status

The ECOG scale is a standard way of measuring the ability of participants to perform ordinary tasks, with scores ranging from 0 to 5. A lower score means the participant is better able to carry out daily activities. See Appendix 8 for a description of the full scale. The ECOG scale will be assessed as specified in the SoA (Section 1.3) in participants ≥18 years of age. An ECOG score of 0 or 1 is required for admission to the study.

8.3.6.2 Karnofsky Performance Scale

The KPS is a standard way of measuring the ability of cancer patients to perform ordinary tasks, with scores ranging from 0 to 100%. A higher score means the patient is better able to carry out daily activities. See Appendix 8 for a description of the full scale. The KPS will be assessed as specified in the SoA (Section 1.3) for participants >16 and <18 years of age. A KPS ≥50% is required for study eligibility.

8.3.6.3 Lansky Play-Performance Scale

The LPS score is a standard way of measuring the functionality of pediatric participants up to and including the age of 16. The LPS is rated by parents based on their child's activity over the past week. Parents fill out the assessment based on the directions on the form, and the form is readministered over time to assess for changes in performance status. A higher score means the child is functioning better. See Appendix 8 for a description of the full scale. The LPS will be assessed as specified in the SoA (Section 1.3). An LPS ≥50% is required for study eligibility.

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

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

Progression/recurrence of the cancer under study is not considered an AE as described in Section 8.4.5 and Appendix 4.

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

The investigator and any designees are responsible for detecting, documenting, and reporting events that meet the definition of an AE or SAE as well as other reportable safety events. Investigators remain responsible for following up AE, 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/assent but before intervention allocation/randomization must be reported by the investigator if the participant is receiving placebo run-in or other run-in treatment, if the event 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 treatment allocation/randomization through 30 days following cessation of study treatment must be reported by the investigator.

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

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

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

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

All initial and follow-up AEs, SAEs and other reportable safety events will be recorded and reported to the Sponsor or designee within the time frames as indicated in Table 7.

Table 7 Reporting Time Periods and Time Frames for Adverse Events and Other Reportable Safety Events

		Time Period				Time Frame to Report Event and Follow-up Information to SPONSOR:
Type of Event		**Consent to Randomization/ Allocation (Part 1) Consent to Time of First Dose (Part 2)**	**Randomization/ Allocation through Protocol-specified Follow-up Period (Part 1) Time of First Dose Through Protocol-specified Follow-up Period (Part 2)**	**After the Protocol-specified Follow-up Period**		
Non-Serious Adverse Event (NSAE)		Report if: - due to protocol-specified intervention - causes exclusion - participant is receiving placebo run-in or other run-in treatment	Report all	Not required		Per data entry guidelines
Serious Adverse Event (SAE) including Cancer and Overdose		Report if: - due to protocol-specified intervention - causes exclusion - participant is receiving placebo run-in or other run-in treatment	Report all	Report if: - drug/vaccine related. (Follow ongoing to outcome)		Within 24 hours of learning of event
Pregnancy/ Lactation Exposure		Report if: - participant has been exposed to any protocol-specified intervention (eg, procedure, washout or run-in treatment including placebo run-in). Exception: A positive pregnancy test at the time of initial screening is not a reportable event unless the participant has received study intervention.	Report all	Previously reported – Follow to completion/termination; report outcome		Within 24 hours of learning of event

Type of Event		Time Period: Consent to Randomization/ Allocation (Part 1) Consent to Time of First Dose (Part 2)	Time Period: Randomization/ Allocation through Protocol-specified Follow-up Period (Part 1) Time of First Dose Through Protocol-specified Follow-up Period (Part 2)	Time Period: After the Protocol-specified Follow-up Period		Time Frame to Report Event and Follow-up Information to SPONSOR:
Event of Clinical Interest (require regulatory reporting)		Report if: - due to intervention - causes exclusion	Report - Potential drug-induced liver injury (DILI) - Require regulatory reporting	Not required		Within 24 hours of learning of event
Event of Clinical Interest (Do not require regulatory reporting)		Report if: - due to intervention - causes exclusion	Report - non-DILI ECIs and those not requiring regulatory reporting	Not required		Within 5 calendar days of learning of event

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

Care will be taken not to introduce bias when detecting 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. All AE, SAE, and other reportable safety events including pregnancy and exposure during breastfeeding, events of clinical interest (ECIs), Cancer and Overdose will be followed until resolution, stabilization, until the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3). In addition, the investigator will make every attempt to follow all nonserious AEs that occur in randomized participants for outcome. Further information on follow-up procedures is given in Appendix 4.

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 treatment under clinical investigation are met.

- The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study treatment under clinical investigation. All AEs will be reported to regulatory authorities, IRB/IECs and investigators in accordance with all applicable global laws and regulations, ie, per ICH Topic E6 (R2) Guidelines for GCP.

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

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

8.4.5 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/recurrence of the cancer under study.

The Sponsor will monitor unblinded aggregated efficacy endpoint events and safety data to ensure the safety of the participants in the study. Any suspected endpoint 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/not recurrence of the cancer under study.

8.4.6 Pregnancy and Exposure During Breastfeeding

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

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

8.4.7 Events of Clinical Interest (ECIs)

Selected nonserious and serious adverse events are also known as ECIs and must be reported to the Sponsor.

Events of clinical interest for this study include:

1. an overdose of Sponsor's product, as defined in Section 8.5, that is not associated with clinical symptoms or abnormal laboratory results.
2. an elevated AST or ALT lab value that is greater than or equal to 3X the upper limit of normal and an elevated total bilirubin lab value that is greater than or equal to 2X the upper limit of normal and, at the same time, an alkaline phosphatase lab value that is less than 2X the upper limit of normal, as determined by way of protocol-specified laboratory testing or unscheduled laboratory testing.*

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

8.5 Treatment of Overdose

For this study, an overdose of pembrolizumab will be defined as any dose of 1000 mg or greater, or ≥5 times the indicated dose.

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.

Decisions regarding dose interruptions or modifications will be made by the investigator in consultation with the Sponsor based on the clinical evaluation of the participant.

8.6 Pharmacokinetics

To evaluate the immunogenicity and exposure of pembrolizumab in this indication in pediatric participants in Part I of this study, sample collections for analysis of PK and ADA are currently planned as shown in the SoA (Section 1.3.1). Blood samples for PK and ADA collected will be stored. Analysis will be performed only if required. If ongoing PK and/or ADA sampling is deemed to be unnecessary by the Sponsor, it may be reduced or discontinued.

8.6.1 Blood Collection for Serum MK-3475

Sample collection, storage and shipment instructions for serum samples will be provided in the operations/laboratory manual.

8.7 Pharmacodynamics

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

8.8 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 study as specified in the SoA:

- Blood for Genetic Analysis
- Blood for RNA Analysis
- Blood for Plasma Biomarker Analysis
- Blood for Serum Biomarker Analysis
- Stool for Biomarker Analysis

- Blood for circulating tumor DNA (ctDNA)
- Tumor tissue

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

The sample for genetic analysis should be drawn for planned exploratory biomarker research. 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. If leftover extracted DNA will be stored for future biomedical research if the participant provides documented informed consent/assent for future biomedical research. If the genetic sample collection is not approved, but future biomedical research is approved and consent/assent is given, this sample will be collected for the purpose of future biomedical research.

8.9 Future Biomedical Research Sample Collection

If the participant provides documented informed consent/assent for future biomedical research, the following specimens will be obtained as part of future biomedical research:

Leftover biomarkers listed in Section 8.8

8.10 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 study site personnel for all participants throughout the study. Protocol-mandated procedures, tests, and encounters are excluded.

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

- Number and duration of medical care encounters, including surgeries, and other selected procedures (inpatient and outpatient)
- Duration of hospitalization (total days or length of stay, including duration by wards [eg, intensive care unit])
- Number and type of diagnostic and therapeutic tests and procedures
- Outpatient medical encounters and treatments (including physician or emergency room visits, tests and procedures, and medications)

All cause hospitalization and emergency room visits must be reported in the eCRF from the time of treatment allocation/randomization through 90 days following cessation of study treatment, or 30 days following cessation of study treatment if the participant initiates new anticancer therapy, whichever is earlier.

8.11 Visit Requirements

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

8.11.1 Screening

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

8.11.2 Treatment Period

Visit requirements are outlined in the SoA (Section 1.3). Specific procedure-related details are provided in Section 8. Unless otherwise specified, assessments/procedures are to be performed prior to administration of study treatment. Unless otherwise specified, the window for each visit is ±3 days.

8.11.3 Discontinued Participants Continuing to be Monitored in the Study

8.11.3.1 Safety Follow-up Visit

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

8.11.3.2 Efficacy Follow-up Visits

Participants in Part 1 and 2 who complete study treatment or discontinue study treatment for a reason other than disease progression will begin Efficacy Follow-up and should be assessed per respective Part 1 and Part 2 SoA (Section 1.3) until PD to monitor disease status. Every effort should be made to collect information regarding disease status until disease progression, withdrawal of consent, pregnancy, or end of study, whichever occurs first. Information regarding post-study anticancer treatment will be collected if new treatment is initiated.

Participants who are eligible to receive retreatment with pembrolizumab according to the criteria in Section 6.7 will move from Efficacy Follow-up to Part 2 when they experience disease recurrence. Details are provided in the SoA (Section 1.3) for retreatment with pembrolizumab.

8.11.3.3 Distant Metastases-free Survival Follow-up

Part 1 participants who start a new anti-cancer therapy with history of local recurrence, or who do not qualify for or do not enter Part 2 therapy will move into DMFS Follow-up until distant metastatic recurrence is identified. Part 2 participants without a history of distant recurrence, with a history of local recurrence who experience a second local recurrence or local progression, or start a new anti-cancer therapy, will move into DMFS Follow-up until distant metastatic recurrence is identified. These participants should be assessed or contacted

by telephone or at an in-person visit approximately every 12 weeks to review disease status, recent imaging and current therapy until participants develop distant metastatic recurrence. Site investigator must collect and review copy of imaging reports, photographs and pathology reports (including imaging and biopsy/pathology assessment done external to site) to update disease status. A central imaging vendor will be used to collect, clean, and hold tumor imaging obtained during the DMFS phase of the study. Images will be collected for possible analysis by BICR. In the event that a participant refuses any further contact, or if a participant is discontinued from the study, the participant can authorize their site investigator to provide updated information about their tumor, anticancer treatment, well-being and overall status updates on their behalf. Radiographic imaging in the DMFS phase may be performed as clinically indicated per local standard of care or following new anticancer therapy imaging schedule and investigator assessments should be reported to the Sponsor. Information regarding post-study anti-cancer treatment will be collected if new treatment is initiated.

8.11.3.4 Survival Follow-up Contacts

Part 1 participants with distant metastases will move into Survival Follow-up if they do not qualify for or choose to not enter Part 2 of the study. Part 2 participants with a history of distant metastases or who develop new distant metastases during Part 2 will move into Survival Follow-up.

Participant Survival Follow-up status will be assessed approximately every 12 weeks until death, withdrawal of consent, or the end of the study, whichever occurs first. The collection of survival includes disease status (recurrence, progression, or new malignancy) if available or not already collected in imaging scans; record of further anticancer therapies and the outcomes in accordance with local regulations and participant consent.

The first Survival Follow-up assessment should be scheduled as described below:

- For participants who discontinue treatment intervention and who will not enter the efficacy follow-up phase, the first Survival Follow-up contact will be scheduled 12 weeks after the discontinuation visit and/or Safety Follow-up visit (whichever is last).

- For participants who completed assessments in Efficacy Follow-up, the first Survival Follow-up contact will be scheduled 12 weeks after the last Efficacy Follow-up visit has been performed.

These participants should be assessed or contacted by telephone or at an in-person visit approximately every 12 weeks to review disease status, recent imaging, and current therapy. Site investigator must collect and review copy of imaging reports, photographs, and pathology reports (including imaging and biopsy/pathology assessment done external to site) to update disease status if it is available. A central imaging vendor will be used to collect, clean, and hold submitted tumor imaging obtained during the SFU phase of the study. In the event that a participant refuses any further contact, or if a participant is discontinued from the study, the participant can authorize their site investigator to provide updated information about their tumor, anticancer treatment, well-being, and overall status updates on their behalf.

Radiographic imaging in Survival Follow-up may be performed as clinically indicated, per local standard of care, or following new anticancer therapy imaging schedule. Information regarding poststudy anticancer treatment will be collected if new treatment is initiated.

8.11.4 Vital Status

To ensure current and complete vital status for survival data is available at the time of database locks, updated vital status survival status may be requested during the study by the Sponsor. For example, updated vital status for survival data may be requested prior to but not limited to an eDMC review, interim analysis (IA), and/or final analysis (FA). 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 for survival data (excluding participants that have a previously recorded death event in the collection tool).

8.11.5 Post-study

Participants will be required to return to clinic approximately 30 days after the last dose of study treatment for the poststudy visit. If the poststudy visit occurs less than 30 days after the last dose of study treatment, a subsequent follow-up telephone call should be made at 30 days post the last dose of study treatment to determine if any AEs have occurred since the poststudy clinic visit.

9. Statistical Analysis Plan

This section outlines the statistical analysis strategy and procedures for the study. If, after the study has begun, changes are made to primary and/or key secondary hypotheses, or the statistical methods related to those hypotheses, then the protocol will be amended (consistent with International Council for Harmonisation [ICH] Guideline E-9). Changes to exploratory or other nonconfirmatory analyses made after the protocol has been finalized, but prior to the conduct of any analysis, will be documented in a supplemental Statistical Analysis Plan (sSAP) and referenced in the Clinical Study Report (CSR) for the study. Separate analysis plans may be developed for PK/modeling analysis, biomarker analysis, and genetic data analysis. Post hoc exploratory analyses will be clearly identified in the CSR. The PRO analysis plan will also be included in the sSAP.

9.1 Statistical Analysis Plan Summary

Key elements of the Statistical Analysis Plan (SAP) are summarized below. The comprehensive plan is provided in Section 9.2 – Responsibility for Analyses/In-house Blinding through Section 9.12 – Extent of Exposure.

Study Design Overview	A Randomized, Double-blind Phase 3 Study to Evaluate Pembrolizumab versus Placebo as Adjuvant Treatment for High-Risk Stage II melanoma
Treatment Assignment	Approximately 954 participants will be randomized in about 15 months (double-blind) in a 1:1 ratio between 2 treatment arms: (1) Pembrolizumab as adjuvant therapy or (2) Placebo as adjuvant therapy. Stratification factors are as follows: one stratum for pediatric (age 12-17) participants and 3strata for adult (age 18 and over) participants defined by T-stage (T3b, T4a, and T4b).
Analysis Populations	Efficacy: Intention-to-Treat Population (ITT) Safety: All Participants as Treated (APaT)
Primary Endpoint	Recurrence-free survival (RFS)
Key Secondary Endpoint(s)	1. Distant Metastasis-free Survival (DMFS) 2. Overall Survival (OS)
Statistical Methods for Key Efficacy Analyses	Treatment comparisons for time-to-event endpoints such as RFS, DMFS and OS will be evaluated using a stratified log-rank test. The hazard ratio (HR) will be estimated using a stratified Cox model.
Statistical Methods for Key Safety Analyses	The analysis of safety will follow a tiered approach. There are no Tier 1 events for this study. Point estimates and 95% confidence intervals (CIs) for between-treatment comparisons via the Miettinen and Nurminen method will be provided for Tier 2 safety endpoints; only point estimates by treatment group will be provided for Tier 3 safety endpoints [Miettinen, O. 1985].

Interim Analyses	Five efficacy interim analyses (IAs) and a final analysis will be performed. Results will be reviewed by an external Data Monitoring Committee (eDMC). Details are provided in Section 9.7 –Interim Analyses. Efficacy IAs • IA 1 (IA1): Scheduled at ~128 observed RFS events, about 33 months after the first participant is randomized o Primary purpose: First interim analysis of RFS • IA 2 (IA2): Scheduled at ~179 observed RFS events, about 48 months after the first participant is randomized o Primary purpose: Final analysis of RFS • IA 3 (IA3): Scheduled at ~146 DMFS events have been observed, about 60 months after the first participant is randomized o Primary purpose: First interim analysis of DMFS • IA 4 (IA4): Scheduled at ~195 observed DMFS events, about 108 months after the first participant is randomized o Primary purpose: Final analysis of DMFS • IA 5 (IA5): Scheduled at ~154 OS events have been observed, expected at ~120 months after the first participant is randomized o Primary purpose: First interim analysis of OS • Final analysis: Scheduled at ~204 OS events, 180 months after the first participant is randomized. o Primary purpose: Final analysis of OS
Multiplicity	The overall Type-I error rate over the 1 primary and 2 secondary efficacy endpoints will be strongly controlled at 2.5% (one-sided).
Sample Size and Power	The planned sample size is approximately 954 participants. The final analysis of RFS in this the study is expected to occur at ~ 48 months after first participant is randomized. It is estimated that approximately 179 RFS events will have been observed among all participants. The final analysis of DMFS in this the study is expected to occur at ~108 months after first participant is randomized. It is estimated that approximately 195 DMFS events will have been observed among all participants. The final analysis of OS in this the study is expected to occur at ~180 months after first participant is randomized. It is estimated that approximately 204 OS events will have been observed among all participants. (1) RFS: the study has an overall ~92% power at a one-sided 2.5% alpha level, if the true HR is 0.60. (2) DMFS: the study has an overall ~84% power at a one-sided 2.5% alpha level, if the true HR is 0.65. (3) OS: the study has an overall ~80% power at a one-sided 2.5% alpha level, if the true HR is 0.67.

9.2 Responsibility for Analyses/In-house Blinding

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

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

Part 1 of this study will be conducted as a double-blind study under in-house blinding procedures. Blinded Sponsor personnel will remain blinded throughout study conduct and the official, final database will not be unblinded until medical/scientific review has been performed, protocol deviations have been identified, and data have been declared final and complete. In addition, the site radiologist(s) will perform the imaging review without knowledge of treatment group assignment and provide their results to the site investigator.

Blinding with respect to planned efficacy interim analyses is described in Section 9.7 – Interim Analyses. Protocol-specified blinding to treatment assignment will be maintained at all investigational sites.

Part 2 of this study is open-label, so individuals participating in Part 2 will not remain blinded throughout the entire conduct of the study.

9.3 Hypotheses/Estimation

Objectives and hypotheses of the study are stated in Section 3 – Objectives/Hypotheses and Endpoints.

9.4 Analysis Endpoints

Efficacy and safety endpoints that will be evaluated are listed below.

9.4.1 Efficacy Endpoints

9.4.1.1 Primary Efficacy Endpoint

Recurrence-free Survival (RFS)

Recurrence-free Survival is defined as the time from randomization to any of the following events: recurrence of melanoma at any site (local, in-transit or regional lymph nodes or distant recurrence) or death due to any cause. New incident cases of melanoma and second cancer diagnoses are not counted as events for recurrence-free survival. See Section 9.6.1 – Statistical Methods for Efficacy Analyses for the definition of censoring.

9.4.1.2 Secondary Efficacy Endpoints

Distant Metastasis-free Survival (DMFS)

Distant Metastasis-free Survival is defined as the time from randomization to the first diagnosis of a distant metastasis. Distant metastasis refers to cancer that has spread from the original (primary) tumor and beyond local tissues and lymph nodes to distant organs or distant lymph nodes.

Overall Survival (OS)

Overall survival is defined as the time from randomization to death due to any cause.

9.4.1.3 Exploratory Endpoints

Time to Subsequent Therapy (TTST)

Time to subsequent therapy is defined as time from randomization to the date of first subsequent therapy (eg, surgery, radiation therapy, antineoplastic therapy) or death (whatever the cause) whichever occurs first.

Progression/Recurrence-free Survival 2 (PRFS2)

Progression/recurrence-free Survival 2 is defined as the time between the date of randomization and the earliest of the following:

- date of 1st disease progression per RECIST1.1 beyond the initial unresectable disease recurrence (unresectable local-regional disease recurrence or unresectable distant metastatic disease recurrence);
- date of 2nd recurrence in patients without evidence of disease after surgery of a resectable 1st recurrence (resectable local-regional recurrences or resectable distant metastatic disease recurrence);
- date of death.

9.4.2 Safety Endpoints

Safety measurements are described in Section 4.2.1 – Rationale for Endpoints and Section 8.3 – Safety Assessments.

9.4.3 PRO Endpoints

The PRO endpoints are exploratory endpoints and are assessed using the EORTC QLQ-C30 version 3 and the EQ-5D-5L utility score. The primary Health-Related Quality of Life endpoint that is considered relevant for this study is the EORTC QLQ-C30 global health status/QoL scale. The other EORTC QLQ-C30 scales will be considered secondary. Differences will only be considered clinically relevant if they exceed the 10-point threshold on the 100-point EORTC QLQ-C30 scale.

9.5 Analysis Populations

9.5.1 Efficacy Analysis Population

The intention-to-treat (ITT) population will serve as the population for primary efficacy analyses. All randomized participants will be included in this population. Participants will be included in the treatment group to which they are randomized.

Details on the approach to handling missing data are provided in Section 9.6 – Statistical Methods.

9.5.2 Safety Analysis Population

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

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

9.5.3 PRO Analysis Population

PRO analyses are based on the PRO Full Analysis Set (FAS) population, defined as participants who have at least one PRO assessment available and have received at least one dose of study treatment.

9.6 Statistical Methods

9.6.1 Statistical Methods for Efficacy Analyses

This section describes the statistical methods that address the primary and secondary objectives. Methods related to the tertiary objectives addressing PROs and other exploratory endpoints (eg, TTST) will be described in the sSAP.

Efficacy results that will be deemed to be statistically significant after consideration of the Type-I error control strategy are described in Section 9.8 – Multiplicity. Nominal p-values will be computed for other efficacy analyses but should be interpreted with caution due to potential issues of multiplicity.

9.6.1.1 Recurrence-free Survival (RFS)

The nonparametric Kaplan-Meier method will be used to estimate the RFS curve in each treatment group. The treatment difference in RFS will be assessed by the stratified log-rank test. A stratified Cox proportional hazard model with Efron’s method of tie handling will be used to assess the magnitude of the treatment difference (ie, HR) between the treatment arms. The HR and its 95% CI from the stratified Cox model with Efron's method of tie handling and with a single treatment covariate will be reported. Kaplan-Meier estimates and the

corresponding 95% CIs at specific follow-up time points will be provided for RFS. The stratification factors used for randomization (see Section 6.3.1.1 – Stratification) will be applied to both the stratified log-rank test and the stratified Cox model.

Since disease assessment is performed periodically, events such as disease recurrence and metastatic disease recurrence can occur any time in the time interval between the last assessment where the event was not documented and the assessment when the event is documented. For the primary analysis, the true date of the event will be approximated by the date of the first assessment at which event is objectively documented. Participants who do not experience a first recurrence event will be censored at the last disease assessment.

In order to evaluate the robustness of the RFS endpoint, a sensitivity analysis with a different set of censoring rules will be performed. For the sensitivity analysis, the true date of the event will be approximated by the date of the first assessment at which event is objectively documented, after ≤1 missed disease assessment and before new anticancer therapy is initiated, if any. Participants who experience a first recurrence immediately after ≥2 consecutive missed disease assessments or after new anticancer therapy is initiated will be censored at the last disease assessment prior to the earlier date of the ≥2 consecutive missed disease assessment or date the new anticancer therapy is initiated. Participants who do not experience a first recurrence event will be censored at the last disease assessment before new anticancer therapy is initiated, if any. The censoring rules for primary and sensitivity analyses of RFS are summarized in Table 8.

Table 8 Censoring Rules for Primary and Sensitivity Analyses of RFS

Situation	Primary Analysis	Sensitivity Analysis
Recurrence or death documented after ≤1 missed disease assessment, and before new anticancer therapy, if any	Event at earliest date of documented recurrence or death	Event at earliest date of documented recurrence or death
Recurrence or death documented immediately after ≥2 consecutive missed disease assessments or after new anticancer therapy, if any	Event at earliest date of documented recurrence or death	Censored at last disease assessment prior to the earlier date of ≥2 consecutive missed disease assessment and new anticancer therapy, if any
No recurrence and no death; and new anticancer treatment is not initiated	Censored at last disease assessment	Censored at last disease assessment
No recurrence and no death; new anticancer treatment is initiated	Censored at last disease assessment	Censored at last disease assessment before new anticancer treatment

The proportional hazards assumption on RFS will be examined using both graphical and analytical methods if warranted. The log[-log] of the survival function vs. time for RFS may be plotted for the comparison between the pembrolizumab and placebo arms. If the curves are not parallel, indicating that hazards are not proportional, supportive analyses may be conducted to account for the possible non-proportional hazards effect associated with immunotherapies using, for example, the Restricted Mean Survival Time method [Uno, H., et al 2014] or a parametric method [Odell, P. M., et al 1994].

One assumption for the stratified Cox proportional hazard model is that the treatment HR is constant across the strata. If strong departures from this assumption are observed (which can result in a notably biased and/or less powerful analysis), a sensitivity analysis may be performed based on a two-step weighted Cox model approach, in which the treatment effect is first estimated for each stratum, and then the stratum specific estimates are combined for overall inference using sample size weights [Mehrotra, D. V., et al 2012].

As indicated in Section 9.4.1.1, new primary melanomas will not be counted as RFS events for the primary RFS analysis. A sensitivity analysis to include new primary melanomas as RFS events will be performed to assess the robustness of the RFS endpoint.

Additional supportive unstratified analyses may also be provided. Further details of sensitivity analyses will be described in the sSAP.

9.6.1.2 Distant Metastases-free Survival

Nonparametric cumulative incidence curves will be used to estimate the ‘time to metastatic disease’ curves. The treatment difference in risk for metastatic disease will be assessed by the stratified log-rank test. A stratified Cox proportional hazard model with Efron’s method of tie handling will be used to assess the magnitude of the treatment difference (ie, the HR). The HR and its 95% CI from the stratified Cox model with a single treatment covariate will be reported. The stratification factors used for randomization (see Section 6.3.1.1 – Stratification) will be applied, as stratification factors used for analysis, to both the stratified log-rank test and the stratified Cox model. Participants without documented metastatic disease diagnosis (and alive) will be censored at the date of their last disease assessment.

9.6.1.3 Overall Survival

The nonparametric Kaplan-Meier method will be used to estimate the survival curves. The treatment difference in survival will be assessed by the stratified log-rank test. A stratified Cox proportional hazard model with Efron’s method of tie handling will be used to assess the magnitude of the treatment difference (the HR). The HR and its 95% CI from the stratified Cox model with a single treatment covariate will be reported. The stratification factors used for randomization (see Section 6.3.1.1 – Stratification) will be applied, as stratification factors used for analysis, to both the stratified log-rank test and the stratified Cox model. Kaplan-Meier estimates and the corresponding 95% CIs at specific follow-up time points will be provided for OS. Participants without documented death at the time of the analysis will be censored at the date of the last follow-up.

Additional supportive unstratified analyses may also be provided. Further details of OS sensitivity analyses will be described in the sSAP as needed.

9.6.1.4 Summary of Statistical Methods for Efficacy

Table 9 summarizes the primary analysis approach for primary and secondary efficacy endpoints. Sensitivity analysis methods are described above for each endpoint as applicable.

Methods related to exploratory objectives (and supportive analyses including TTST and PRFS2) will be described in the sSAP.

The strategy to address multiplicity issues with regard to multiple efficacy endpoints, multiple populations, and interim analyses is described in Section 9.7 – Interim Analyses and in Section 9.8 – Multiplicity.

Table 9 Analysis Strategy for Key Efficacy Endpoints

Endpoint/Variable (Description, Time Point)	Statistical Method†	Analysis Population	Missing Data Approach
Primary Hypothesis 1			
RFS	Test: Stratified log-rank test Estimation: Stratified Cox model with Efron's tie handling method	ITT	See Table 8 for censoring rules
Secondary Hypothesis 2			
DMFS	Test: Stratified log-rank test Estimation: Stratified Cox model with Efron's tie handling method	ITT	Censored at last known disease evaluation
Secondary Hypothesis 3			
OS	Test: Stratified log-rank test Estimation: Stratified Cox model with Efron's tie handling method	ITT	Censored at last known alive date

† Statistical models are described in further details in the text. For stratified analyses, the stratification factors used for randomization will be used as stratification factors for analysis.

9.6.2 Statistical Methods for Safety Analyses

Safety and tolerability will be assessed by clinical review of all relevant parameters including adverse experiences (AEs), laboratory tests and vital signs.

The analysis of safety results will follow a tiered approach as shown in Table 10. The tiers differ with respect to the analyses that will be performed. Adverse events (specific terms as well as system organ class terms) are either prespecified as "Tier 1" endpoints or will be classified as belonging to "Tier 2" or "Tier 3" based on the number of events observed.

Safety parameters or AEs of interest that are identified a priori constitute "Tier 1" safety endpoints that will be subject to inferential testing for statistical significance. There are no Tier 1 events for this protocol. Based on a review of historic chemotherapy data and data

from ongoing pembrolizumab clinical studies in gastric cancer, there are no AEs of interest that warrant inferential testing for comparison between treatment arms in this study.

Tier 2 parameters will be assessed via point estimates with 95% CIs provided for between-group comparisons.

Membership in Tier 2 requires that at least 10% of participants in any treatment group exhibit the event; all other adverse experiences and predefined limits of change will belong to Tier 3. The threshold of at least 10% of participants was chosen for Tier 2 event because the population enrolled in this study are in critical conditions and usually experience various adverse events of similar types regardless of treatment, events reported less frequent than 10% of participants would obscure the assessment of overall safety profile and add little to the interpretation of potentially meaningful treatment differences. In addition, the percentage of participants with any AE, any drug-related AE, any Grade 3-5 AE, any serious AE, any AE which is both drug-related and Grade 3-5, any AE which is both serious and drug-related, a dose modification due to AE, a discontinuation due to an AE, and death will be considered Tier 2 endpoints. Because many 95% confidence intervals may be provided without adjustment for multiplicity, the confidence intervals should be regarded as a helpful descriptive measure to be used in review, not a formal method for assessing the statistical significance of the between-group differences in adverse experiences and predefined limits of change. These analyses will be performed using the Miettinen and Nurminen method, an unconditional, asymptotic method [Miettinen, O. 1985].

Other safety parameters including AEs occurring in <10% of participants and continuous measures such as changes from baseline in laboratory and vital signs will be considered Tier 3 safety parameters. For laboratory tests and vital signs, summary statistics for baseline, on-treatment, and change from baseline values will be provided by treatment group in table format.

Table 10 Analysis Strategy for Safety Parameters

Safety Tier	Safety Endpoint	95% CI for Treatment Comparison	Descriptive Statistics
Tier 2	Any AE	X	X
	Any Serious AE	X	X
	Any Grade 3-5 AE	X	X
	Any Drug-related AE	X	X
	Any Serious and Drug-related AE	X	X
	Any Grade 3-5 and Drug-related AE	X	X
	Discontinuation due to AE	X	X
	Death		
	AEs (≥10% of participants in one of the treatment groups)	X	X
Tier 3	AEs or PDLCs		X
	Change from Baseline Results (Labs, ECGs, Vital Signs)		X

PDLC = Predefined Limit of Change; X = results will be provided.

9.6.3 Summaries of Demographic and Baseline Characteristics

The comparability of the treatment groups for each relevant characteristic will be assessed by the use of tables and/or graphs. No statistical hypothesis testing will be performed on these characteristics. The number and percentage of participants screened and randomized and the primary reasons for screening failure and discontinuation will be displayed. Demographic variables (eg, age) and baseline characteristics will be summarized by treatment either by descriptive statistics or categorical tables.

9.7 Interim Analyses

9.7.1 Safety Interim Analyses

The eDMC will conduct regular safety monitoring. The timing of the safety monitoring will be specified in the DMC charter.

9.7.2 Efficacy Interim Analyses

There are 5 efficacy interim analyses and a final analysis planned for this study (see Table 11). Details on how the planned analyses are incorporated into establishing statistical significance and the boundaries with regard to efficacy are discussed further in Section 9.8, Multiplicity.

Treatment level results of the efficacy interim analyses will be provided by an external unblinded statistician to the eDMC.

The eDMC will serve as the primary reviewer of the results of the interim analyses and will make recommendations for discontinuation of the study or modification to an Executive Oversight Committee (EOC) of the Sponsor. Depending on the recommendation of the eDMC, the Sponsor may prepare a regulatory submission. Participant-level unblinding to support regulatory filing will be restricted to a designate team at the Sponsor, who will have no other responsibilities associated with the study.

If the eDMC recommends modifications to the design of the protocol or discontinuation of the study, this EOC may be unblinded to study results at the treatment level in order to act on these recommendations or facilitate regulatory filing. Limited additional Sponsor personnel may also be unblinded to the treatment level results of the IA(s), if required, in order to act on the recommendations of the eDMC or facilitate regulatory filing. The extent to which individuals are unblinded with respect to results of interim analyses will be documented. Additional logistical details, revisions to the above plan and data monitoring guidance will be provided in the eDMC Charter.

Prior to final study unblinding, the external unblinded statistician will not be involved in any discussions regarding modifications to the protocol, statistical methods, identification of protocol deviations, or data validation efforts after the interim analyses.

Table 11 Analyses Planned, Endpoints Evaluated, and Drivers of Timing

Analysis	Endpoint	Criteria for Conduct of Analysis	Estimated Time after First Participant Randomized	Primary Purpose of Analysis
IA 1: Interim RFS analysis	RFS	(1) enrollment is completed, and (2) ~ 128 RFS events observed	~33 months	RFS IA
IA 2: Final RFS analysis	RFS	~179 RFS events observed	~48 months	RFS FA
IA 3: Interim DMFS analysis	DMFS	~146 DMFS events observed	~60 months	DMFS IA
IA 4: Final DMFS analysis;	DMFS	~195 DMFS events	~108 months	DMFS FA
IA 5: Interim OS analysis	OS	~154 OS events	~120 months	OS IA
FA: Final OS analysis	OS	~204 OS events	~180 months	OS FA
Abbreviations: RFS = Recurrence-free Survival; DMFS = distant metastatic-free survival; FA = final analysis; IA = interim analysis; OS = overall survival				

9.8 Multiplicity

The multiplicity strategy specified in this section will be applied to the primary hypothesis and 2 secondary hypotheses. The primary hypothesis tests the superiority of pembrolizumab to placebo with respect to RFS. The 2 secondary hypotheses test the superiority of pembrolizumab to placebo with respect to DMFS and OS. The overall Type-I error among the 3 hypotheses is strongly controlled at 2.5% (one-sided), with 2.5% initially allocated to the RFS hypothesis. The study will be considered a success if RFS is demonstrated to be statistically significant at either an interim analysis or the final analysis under multiplicity control.

The study uses the graphical method of Maurer and Bretz [Maurer, W. 2013] to control multiplicity for multiple hypotheses as well as interim analyses. According to this approach, when a particular null hypothesis is rejected, the alpha allocated to that hypothesis can be reallocated to other hypothesis tests.

Figure 4 shows that the initial one-sided α allocation is assigned to the RFS hypothesis. Should the RFS comparison be statistically significant, the 2.5% alpha will be reallocated to the DMFS comparison. Should the DMFS comparison be statistically significant, the 2.5% alpha will be reallocated to the OS comparison.

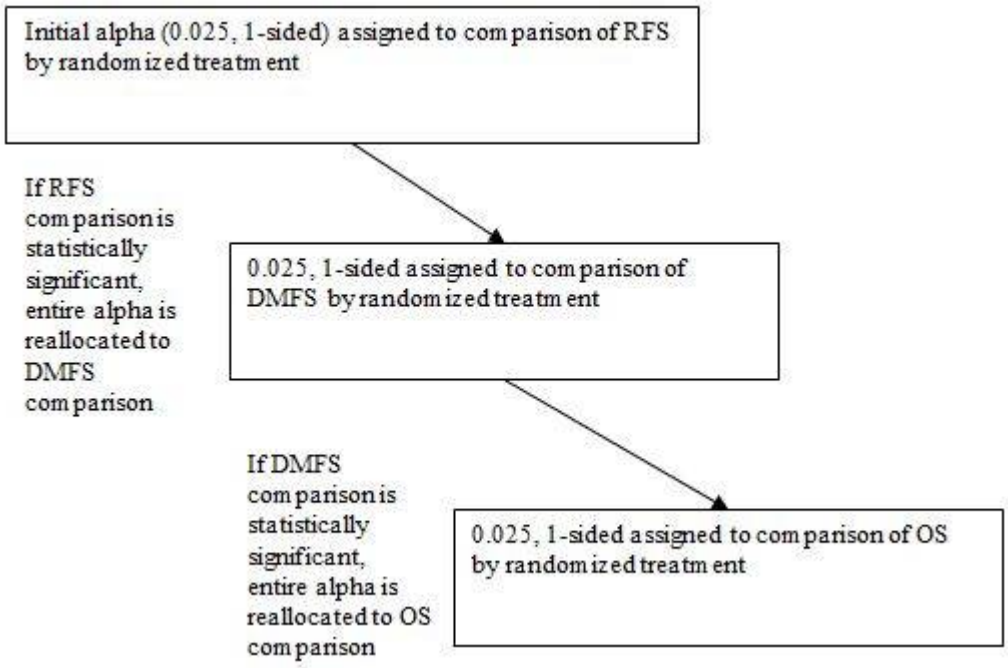


Figure 4 Multiplicity Graph for Type-I Error Control of Study Hypotheses

9.8.1 Recurrence-free Survival

The study initially allocates α = 2.5%, one-sided to test RFS. Table 12 shows the boundary properties for the interim analyses, which were derived using a Lan-DeMets O'Brien-Fleming approximation spending function. Note that the final row indicates the total power to reject the null hypothesis for RFS. If the actual number of RFS events differs from that specified in the table, the bounds will be adjusted using the O'Brien-Fleming alpha-spending function accordingly.

Table 12 Boundary Properties for Planned Analyses of the RFS Analyses Based on α = 0.025

Analysis	Value	Efficacy
IA 1: 71%[1]	Z[2]	2.4115
N: 954	p (1-sided)[2]	0.0079
Events: 128	HR[3] at bound	0.6522
Month: 33	P(Cross)[4] if HR=1	0.0079
	P(Cross)[4] if HR=0.6	0.6717
Final (IA2)	Z	2.0029
N: 954	p (1-sided)	0.0226
Events: 179	HR at bound	0.7410
Month: 48	P(Cross) if HR=1	0.0250
	P(Cross) if HR=0.6	0.9190

[1] Percentage of total number of events expected at final analysis

[2] Boundary values for statistical significance

[3] HR= hazard ratio

[4] Probability of crossing boundary for statistical significance

9.8.2 Distant Metastases-free Survival

The study initially allocates α=0.0, one-sided to test DMFS. If the null hypothesis for RFS is rejected, α=0.025 is fully reallocated to DMFS hypothesis testing.

Table 13 shows the boundary properties for the interim analysis (at 60 months from first participant enrolled) and final analysis (at 108 months), which were derived using a Lan-DeMets O'Brien-Fleming approximation spending function. Note that the final row indicates the total power to reject the null hypothesis for DMFS. If the actual number of events at the DMFS analyses differ from those specified in the table, the bounds will be adjusted using the Lan-DeMets O'Brien-Fleming approximation spending function accordingly.

Table 13 Efficacy Boundaries and Properties for the DMFS Analyses

Analysis	Value	Efficacy
IA 3: 75%	Z	2.3401
N: 954	p (1-sided)	0.0096
Events: 146	HR at bound	0.6788
Month: 60	P(Cross) if HR=1	0.0096
	P(Cross) if HR=0.65	0.5987
Final (IA4)	Z	2.0117
N: 954	p (1-sided)	0.0221
Events: 195	HR at bound	0.7494
Month: 108	P(Cross) if HR=1	0.0250
	P(Cross) if HR=0.65	0.8425

9.8.3 Overall Survival

The study initially allocates α=0, one-sided to test OS. If the null hypothesis for DMFS is rejected then α=0.025 is fully reallocated to OS hypothesis testing. Table 14 shows the boundary properties for the planned interim analysis (at 120 months from first participant enrolled) and final analysis (at 180 months), which were derived using a Lan-DeMets O'Brien-Fleming approximation spending function. Note that the final row indicates the total power to reject the null hypothesis for OS. If the actual number of events at the OS analyses differs from that specified in the table, the bounds will be adjusted using the Lan-DeMets O'Brien-Fleming approximation spending function accordingly.

Table 14 Efficacy Boundaries and Properties for the OS Analyses

Analysis	Value	Efficacy
IA 5: 76%	Z	2.3249
N: 954	p (1-sided)	0.0100
Events: 154	HR at bound	0.6875
Month: 120	P(Cross) if HR=1	0.0100
	P(Cross) if HR=0.67	0.5607
Final	Z	2.0138
N: 954	p (1-sided)	0.0220
Events: 204	HR at bound	0.7538
Month: 180	P(Cross) if HR=1	0.0250
	P(Cross) if HR=0.67	0.8050

9.8.4 Safety Analyses

The eDMC has responsibility for assessment of overall risk/benefit. When prompted by safety concerns, the eDMC can request corresponding efficacy data. External DMC review of efficacy data to assess the overall risk/benefit to study participants will not require a multiplicity adjustment typically associated with a planned interim efficacy analysis; however, to account for any multiplicity concerns raised by the eDMC review of unplanned efficacy data prompted by safety concerns, a sensitivity analysis for RFS adopting a conservative multiplicity adjustment will be prespecified in the sSAP. This analysis will be performed if efficacy data is requested by the eDMC during a safety evaluation to assess risk / benefit.

9.9 Sample Size and Power Calculations

The study will randomize approximately 954 participants in a 1:1 ratio between pembrolizumab adjuvant treatment and placebo adjuvant treatment.

9.9.1 Recurrence-free Survival

Recurrence-free survival is the primary endpoint. The final analysis of RFS is event-driven and will be conducted after approximately 179 RFS events have been observed, unless the study is terminated early. It may occur at ~ 48 months after the first participant is randomized (depending on enrollment rate and event accumulation rate).

With an alpha of 2.5% (one-sided) and sample size of 954, the study has an overall ~92% power for RFS, assuming the true HR (pembrolizumab vs. placebo) is 0.60. These calculations are based on the following assumptions: (1) RFS follows an “cure” model with a long-term RFS of 50% and the 60-month RFS estimated to be 68%; (2) an enrollment period of 16 months and at least 32 months follow-up; and (3) a yearly drop-out rate of 4.7%.

9.9.2 Distant Metastases-free Survival

Distant metastases-free survival is a secondary endpoint. The final analysis of DMFS is event-driven and will be conducted after approximately 195 DMFS events have been observed, unless the study is terminated early. It may occur at ~ 108 months after the first participant is randomized (depending on enrollment rate and event accumulation rate).

Should the comparisons of RFS be statistically significant, an alpha of 2.5% (one-sided) will be available for testing DMFS. With a sample size of 954, the study has ~84% power for DMFS, assuming the true HR (pembrolizumab vs. placebo) is 0.65. These calculations are based on the following assumptions: (1) DMFS follows an "cure" model with a long-term DMFS of 65% and the 60-month DMFS estimated to be 78%; (2) an enrollment period of 16 months and at least 92 months follow-up; and (3) a yearly drop-out rate of 4.7%.

9.9.3 Overall Survival

Overall survival is a secondary endpoint. The final analysis of OS is calendar driven and will be conducted at approximately 15 years after the first participant is randomized, when we expect to have observed ~204 OS events.

Should the comparisons of both RFS and DMFS be statistically significant, an alpha of 2.5% (one-sided) will be available for testing OS. With a sample size of 954, the study has ~80% power for OS, assuming the true HR (pembrolizumab vs. placebo) is 0.67. These calculations are based on the following assumptions: (1) OS follows an exponential distribution with the 120-month OS estimated to be 75%; (2) an enrollment period of 16 months and at least 164 months follow-up; and (3) a yearly drop-out rate of 4.7%. The sample size and power calculations were performed in the software R (package "gsDesign").

9.10 Subgroup Analyses

To determine whether the treatment effect is consistent across various subgroups, the estimate of the between-group treatment effect (with a nominal 95% CI) for the primary endpoints will be estimated and plotted within each category of the following classification variables:

- T-Stage (T3b versus T4a versus T4b)
- Age (<65 years versus ≥65 years)
- Sex (male versus female)
- Race (white versus nonwhite)
- ECOG performance status (0 versus 1) or equivalent KPS or LPS status

9.11 Compliance (Medication Adherence)

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

9.12 Extent of Exposure

The extent of exposure will be summarized as duration of treatment in number of cycles or administrations as appropriate.

10. Supporting Documentation and Operational Considerations

10.1 Appendix 1: Regulatory, Ethical and Study Oversight Considerations

10.1.1 Code of Conduct for Clinical Trials

Merck Sharp and Dohme Corp., a subsidiary of Merck & Co., Inc. (MSD)
Code of Conduct for Interventional Clinical Trials

I. Introduction

A. Purpose

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

B. Scope

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

II. Scientific Issues

A. Trial Conduct

1. Trial Design

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

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

2. Site Selection

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

3. Site Monitoring/Scientific Integrity

Investigative trial sites are monitored to assess compliance with the trial protocol and general principles of Good Clinical Practice (GCP). MSD reviews clinical data for accuracy, completeness, and consistency. Data are verified versus source documentation according to standard operating procedures. Per MSD policies and procedures, if fraud, scientific/research misconduct or serious GCP-noncompliance is suspected, the issues are investigated. When necessary, the clinical site will be closed, the responsible regulatory authorities and ethics review committees notified.

B. Publication and Authorship

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

MSD's policy on authorship is consistent with the recommendations published by the International Committee of Medical Journal Editors (ICMJE). In summary, authorship should reflect significant contribution to the design and

conduct of the trial, performance or interpretation of the analysis, and/or writing of the manuscript. All named authors must be able to defend the trial results and conclusions. MSD funding of a trial will be acknowledged in publications.

III. Participant Protection

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

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

B. Safety

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

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

C. Confidentiality

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

D. Genomic Research

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

IV. Financial Considerations

A. Payments to Investigators

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

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

B. Clinical Research Funding

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

C. Funding for Travel and Other Requests

Funding of travel by investigators and support staff (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

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

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

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

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 in order to verify worksheet/CRF data. By providing documented informed consent, 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 study was developed in collaboration with a Scientific Advisory Committee (SAC). The SAC is comprised of 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 Executive Oversight Committee

The Executive Oversight Committee (EOC) is comprised of members of Sponsor Senior Management. The EOC will receive and decide upon any recommendations made by the eDMC regarding the study.

10.1.4.3 Data Monitoring Committee

To supplement the routine study monitoring outlined in this protocol, an external DMC will monitor the interim data from this study. The voting members of the committee are external to the Sponsor. The members of the DMC must not be involved with the study in any other way (eg, they cannot be study investigators) and must have no competing interests that could affect their roles with respect to the study.

The DMC will make recommendations to the EOC regarding steps to ensure both participant safety and the continued ethical integrity of the study. Also, the DMC will review interim study results, consider the overall risk and benefit to study participants (see Section 9.7 Interim Analyses) and recommend to the EOC whether the study should continue in accordance with the protocol.

Specific details regarding composition, responsibilities, and governance, including the roles and responsibilities of the various members and the Sponsor protocol team; meeting facilitation; the study governance structure; and requirements for and proper documentation of DMC reports, minutes, and recommendations will be described in the DMC charter that is reviewed and approved by all the DMC members.

10.1.5 Publication Policy

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

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

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

10.1.6 Compliance with Study Registration and Results Posting Requirements

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

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

10.1.7 Compliance with Law, Audit, and Debarment

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

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

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

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

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

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

10.1.8 Data Quality Assurance

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

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

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

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

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

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

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

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

10.1.9 Source Documents

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

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

10.1.10 Study and Site Closure

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

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

10.2 Appendix 2: Collection and Management of Specimens for Future Biomedical Research

1. Definitions

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

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

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

d. DNA: Deoxyribonucleic acid.

e. RNA: Ribonucleic acid.

2. Scope of Future Biomedical Research

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

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

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

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

3. Summary of Procedures for Future Biomedical Research

a. Participants for Enrollment

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

b. Informed Consent

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

signed by the participant will be kept at the clinical study site under secure storage for regulatory reasons.

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

c. eCRF Documentation for Future Biomedical Research Specimens

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

d. Future Biomedical Research Specimen(s)

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

4. Confidential Participant Information for Future Biomedical Research

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

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

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

5. Biorepository Specimen Usage

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

6. Withdrawal From Future Biomedical Research

Participants may withdraw their consent for future biomedical research and ask that their biospecimens not be used for future biomedical research. Participants may withdraw consent at any time by contacting the principal investigator for the main study. If medical

records for the main study are still available, the investigator will contact the Sponsor using the designated mailbox (clinical.specimen.management@merck.com). Subsequently, the participant's specimens will be flagged in the biorepository and restricted to main study use only. If specimens were collected from study participants specifically for future biomedical research, these specimens will be removed from the biorepository and destroyed. Documentation will be sent to the investigator confirming withdrawal and/or destruction, if applicable. It is the responsibility of the investigator to inform the participant of completion of the withdrawal and/or destruction, if applicable. Any analyses in progress at the time of request for withdrawal/destruction or already performed prior to the request being received by the Sponsor will continue to be used as part of the overall research study data and results. No new analyses would be generated after the request is received.

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

7. Retention of Specimens

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

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

8. Data Security

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

9. Reporting of Future Biomedical Research Data to Participants

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

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

10. Future Biomedical Research Study Population

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

11. Risks Versus Benefits of Future Biomedical Research

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

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

12. Questions

Any questions related to the future biomedical research should be e-mailed directly to clinical.specimen.management@merck.com.

13. References

1. National Cancer Institute [Internet]: Available from https://www.cancer.gov/publications/dictionaries/cancer-terms?cdrid=45618
2. International Conference on Harmonization [Internet]: E15: Definitions for Genomic Biomarkers, Pharmacogenomics, Pharmacogenetics, Genomic Data and Sample Coding Categories. Available from http://www.ich.org/products/guidelines/efficacy/efficacy-single/article/definitions-for-genomic-biomarkers-pharmacogenomics-pharmacogenetics-genomic-data-and-sample-cod.html
3. Industry Pharmacogenomics Working Group [Internet]: Understanding the Intent, Scope and Public Health Benefits of Exploratory Biomarker Research: A Guide for IRBs/IECs and Investigational Site Staff. Available at http://i-pwg.org/
4. Industry Pharmacogenomics Working Group [Internet]: Pharmacogenomics Informational Brochure for IRBs/IECs and Investigational Site Staff. Available at http://i-pwg.org/

10.3 Appendix 3: Contraceptive Guidance and Pregnancy Testing

10.3.1 Definitions

Women of Childbearing Potential (WOCBP)

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

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

  Note: Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.
- Postmenopausal female
  - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
    - A high follicle-stimulating hormone level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormone replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, confirmation with 2 follicle-stimulating hormone 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.

10.3.2 Contraception Requirements

Female Participants

Female participants of childbearing potential are eligible to participate if they agree to use a highly effective method of contraception consistently and correctly as described in Table 15 during the protocol-defined time frame in Section 5.1.

Table 15 Highly Effective Contraception Methods

Highly Effective Contraceptive Methods That Are User Dependent [a] *Failure rate of <1% per year when used consistently and correctly.*
● Combined (estrogen- and progestogen-containing) hormonal contraception [b] ○ Oral ○ Intravaginal ○ Transdermal ○ Injectable
● Progestogen-only hormonal contraception [b] ○ Oral ○ Injectable
Highly Effective Methods That Have Low User Dependency *Failure rate of <1% per year when used consistently and correctly.*
● Progestogen-only contraceptive implant [b] ● Intrauterine hormone-releasing system (IUS) ● Intrauterine device (IUD) ● Bilateral tubal occlusion
● Vasectomized partner A vasectomized partner 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.
● 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 treatment. 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.
Notes: Use should be consistent with local regulations regarding the use of contraceptive methods for participants of clinical studies. a) Typical use failure rates are higher than perfect-use failure rates (ie, when used consistently and correctly). b) If locally required, in accordance with Clinical Trial Facilitation Group (CTFG) guidelines, acceptable hormonal contraceptives are limited to those which inhibit ovulation.

10.3.3 Pregnancy Testing

WOCBP should only be included after a negative highly sensitive urine or serum pregnancy test.

Following initiation of treatment, pregnancy testing will be performed whenever an expected menstrual cycle is missed or when pregnancy is otherwise suspected; at Q3W as specified in the Schedule of Activities (Section 1.3), after the last dose of study treatment, and as required locally.

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

10.4.1 Definition of AE

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

Events meeting the AE definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator. • Exacerbation of a chronic or intermittent preexisting condition including either an increase in frequency and/or intensity of the condition. • New conditions detected or diagnosed after study treatment administration even though it may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study treatment or a concomitant medication. • For all reports of overdose (whether accidental or intentional) with an associated AE, the AE term should reflect the clinical symptoms or abnormal test result. An overdose of study treatment 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). Note: Progression/recurrence of the cancer under study is not a reportable event. Refer to Section 8.4.5 for additional details.

Events NOT meeting the AE definition
● Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE. ● Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital). ● Anticipated day-to-day fluctuations of preexisting 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 preexisting condition that has not worsened. ● Refer to Section 8.4.5 for protocol-specific exceptions

10.4.2 Definition of SAE

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

An SAE is defined as any untoward medical occurrence that, at any dose:
a. Results in death
b. Is life-threatening ● The term 'life-threatening' in the definition of 'serious' refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
c. Requires inpatient hospitalization or prolongation of existing hospitalization ● Hospitalization is defined as an inpatient admission, regardless of length of stay, even if the hospitalization is a precautionary measure for continued observation. Note: Hospitalization for an elective procedure to treat a preexisting condition that has not worsened is not an SAE. A preexisting condition is a clinical condition that is diagnosed prior to the use of an MSD product and is documented in the patient's medical history.
d. Results in persistent or significant disability/incapacity ● The term disability means a substantial disruption of a person's ability to conduct normal life functions. ● This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect

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

f. Other important medical events:

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

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

10.4.3 Additional Events Reported in the Same Manner as SAE

Additional events which require reporting in the same manner as SAE

- In addition to the above criteria, 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.

10.4.4 Recording AE and SAE

AE and SAE recording

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

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

Assessment of intensity

- An event is defined as 'serious' when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.
- The investigator will make an assessment of intensity for each AE and SAE (and other reportable safety event) according to the NCI Common Terminology Criteria for Adverse Events (CTCAE), version 4.0. Any AE which 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 activities of daily living (ADL).
  - Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL.
  - Grade 4: Life threatening consequences; urgent intervention indicated.
  - Grade 5: Death related to AE.

Assessment of causality

- Did the Sponsor's product cause the AE?
  - The determination of the likelihood that the Sponsor's product caused the AE will be provided by an investigator who is a qualified physician. The investigator's signed/dated initials on the source document or worksheet that supports the causality noted on the AE form, ensures that a medically qualified assessment of causality was done. This initialed document must be retained for the required regulatory time frame. The criteria below are intended as reference guidelines to assist the investigator in assessing the likelihood of a relationship between the test product and the AE based upon the available information
  - **The following components are to be used to assess the relationship between the Sponsor's product and the AE;** the greater the correlation with the components and their respective elements (in number and/or intensity), the more likely the Sponsor's product caused the AE:
    - **Exposure:** Is there evidence that the participant was actually exposed to the Sponsor's product such as: reliable history, acceptable compliance assessment (pill count, diary, etc.), expected pharmacologic effect, or measurement of drug/metabolite in bodily specimen?

- **Time Course:** Did the AE follow in a reasonable temporal sequence from administration of the Sponsor's product? Is the time of onset of the AE compatible with a drug-induced effect (applies to studies with investigational medicinal product)?
- **Likely Cause:** Is the AE not reasonably explained by another etiology such as underlying disease, other drug(s)/vaccine(s), or other host or environmental factors
- **Dechallenge:** Was the Sponsor's product discontinued or dose/exposure/frequency reduced?
  - If yes, did the AE resolve or improve?
    - If yes, this is a positive dechallenge.
  - If no, this is a negative dechallenge.

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

NOTE: IF A RECHALLENGE IS PLANNED FOR AN AE WHICH WAS SERIOUS AND WHICH MAY HAVE BEEN CAUSED BY THE SPONSOR'S PRODUCT, OR IF 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 AS PER DOSE MODIFICATION GUIDELINES IN THE PROTOCOL, AND IF REQUIRED, THE IRB/IEC.

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

- The assessment of relationship will be reported on the CRFs/worksheets by an investigator who is a qualified physician according to his/her best clinical judgment, including consideration of the above elements.
- Use the following scale of criteria as guidance (not all criteria must be present to be indicative of a Sponsor's product relationship).

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

- For each AE/SAE, the investigator must document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to the Sponsor. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the Sponsor.
- The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements

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.

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

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

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

SAE reporting to the Sponsor via paper CRF

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

10.5 Appendix 5: Clinical Laboratory Tests

- The tests detailed in Table 16 will be performed by the local laboratory.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5 of the protocol.
- Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.

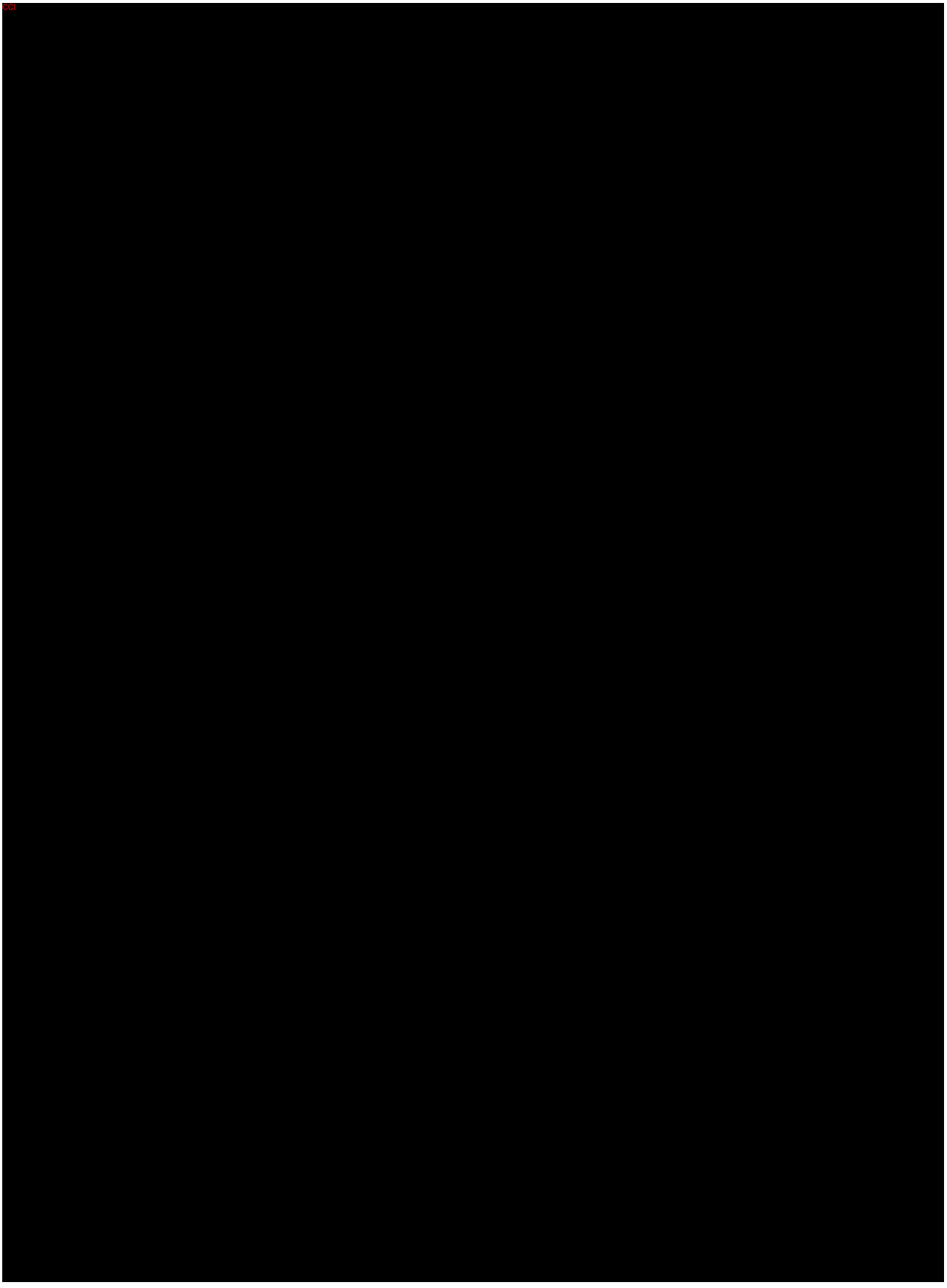
Table 16 Protocol-required Safety Laboratory Assessments

Laboratory Assessments	Parameters			
Hematology	Platelet Count RBC Count Hemoglobin Hematocrit	WBC count with Differential: Neutrophils Lymphocytes Monocytes Eosinophils Basophils		
Chemistry	Blood Urea Nitrogen (BUN)	Potassium	Aspartate Aminotransferase (AST)/ Serum Glutamic-Oxaloacetic Transaminase (SGOT)	Total bilirubin (and direct bilirubin, if total bilirubin is elevated above the upper limit of normal)
	Albumin	Bicarbonate or Carbon Dioxide*	Chloride	Phosphorus
	Creatinine	Sodium	Alanine Aminotransferase (ALT)/ Serum Glutamic-Pyruvic Transaminase (SGPT)	Magnesium
	Glucose	Calcium	Alkaline phosphatase	
Routine Urinalysis	• Specific gravity • pH, glucose, protein, blood, ketones by dipstick • Microscopic examination (if blood or protein is abnormal)			
Other Screening Tests	• Serum or urine hCG) pregnancy test (as needed for WOCBP) • Thyroid function tests (T3/FT3, FT4, and TSH) • Coagulation panel (prothrombin time [PT]/ International Normalized Ratio [INR], activated partial thromboplastin time[aPTT])			
Urea is acceptable if BUN is not available as per institutional standard. T3 is preferred; if not available, free T3 may be tested. *If these tests are not done as part of standard of care in your region then these tests do not need to be performed.				

The investigator (or medically qualified designee) must document their review of each laboratory safety report.

Laboratory/analyte results that could unblind the study will not be reported to investigative sites or other blinded personnel until the study has been unblinded.

10.6 Appendix 6: Country-specific Requirements



10.7 Appendix 7: Abbreviations

Abbreviation	Expanded Term
ADA	Antidrug Antibodies
ADL	Activities of daily living
AE	Adverse event
AJCC	American Joint Committee on Cancer
ALT	Alanine aminotransferase
APaT	All participants as treated (population)
aPTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
CBC	Complete blood count
CD	Cluster of differentiation
CI	Confidence interval
CR	Complete response
CrCl	Creatinine clearance
CRF	Case Report Form
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
ctDNA	Circulating tumor DNA
CTLA-4	Cytotoxic T-lymphocyte-associated protein 4
DMC	Data Monitoring Committee
DMFS	Distant metastasis-free survival
DNA	Deoxyribonucleic acid
ECG	Electrocardiogram
ECI	Event of clinical interest
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
EDC	Electronic data collection
eDMC	External Data Monitoring Committee
EMA	European Medicines Agency
EOC	Executive Oversight Committee
EORTC	European Organisation for Research and Treatment of Cancer

Abbreviation	Expanded Term
EORTC QLQ-C30	EORTC Quality of Life Questionnaire-C30
EOT	End of treatment
EQ-5D-5L	EuroQoL-5 Dimension - 5 Level Questionnaire
FA	Final analysis
FDAAA	Food and Drug Administration Amendments Act
GCP	Good Clinical Practice
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
HR	Hazard ratio
HRT	Hormone replacement therapy
IA	Interim analysis
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IFN	Interferon
Ig	Immunoglobulin
IHC	Immunohistochemistry
IL-10	Interleukin 10
IMP	Investigational Medicinal Product
INR	International normalized ratio
irAE	Immune-related adverse event
IRB	Institutional Review Board
iRECIST	Modified RECIST 1.1 for immune-based therapeutics
IRT	Interactive Response Technology
ITT	Intention-to-treat
IV	Intravenous
KPS	Karnofsky Performance Scale
LDH	Lactic acid dehydrogenase
LPS	Lansky Play-Performance Scale
MRI	Magnetic resonance imaging
mRNA	Messenger RNA

Abbreviation	Expanded Term
MSD	Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc.
MSS	Melanoma Specific Survival
MTD	Maximum tolerated dose
NCI	National Cancer Institute
NDA	New Drug Application
NIMP	Non-investigational Medicinal Product
OS	Overall survival
PD	Progressive disease
PD-1	Programmed cell death-1
PD-L1	Programmed cell death-ligand 1
PD-L2	Programmed cell death-ligand 2
PET	Positron emission tomography
PK	Pharmacokinetic
PR	Partial response
PRFS2	Progression/Recurrence-free Survival 2
PRO	Patient-reported outcome(s)
PT	Prothrombin time
Q3W	Every 3 weeks
QLQ	Quality of Life Questionnaire
QoL	Quality of life
RECIST 1.1	Response Evaluation Criteria in Solid Tumors version 1.1
RFS	Recurrence-free Survival
RNA	Ribonucleic acid
SAC	Scientific Advisory Committee
SAE	Serious adverse event
SFU	Survival Follow-up
SLN	Sentinel lymph node
SoA	Schedule of Activities
SOP	Standard Operating Procedure
sSAP	Supplemental Statistical Analysis Plan
SUSAR	Suspected unexpected serious adverse reaction
T1DM	Type 1 Diabetes Mellitus

Abbreviation	Expanded Term
TSH	Thyroid-stimulating hormone
TTST	Time to subsequent therapy
TX	Treatment
US	United States
WBC	White blood cells
WNL	Within normal limits
WOCBP	Woman/women of childbearing potential

10.8 Appendix 8: Performance Status Scales

10.8.1 ECOG Performance Scale

Grade	ECOG Status
0	Fully active, able to carry on all predisease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, eg, light house work, office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead

Source: [ECOG-ACRIN Cancer Research Group 2016]

10.8.2 Karnofsky Performance Scale

Score	Activity
100	Normal. No complaints. No evidence of disease.
90	Able to carry on normal activity. Minor signs or symptoms of disease.
80	Normal activity with effort. Some signs or symptoms of disease.
70	Care of self. Unable to carry on normal activity or to do active work.
60	Requires occasional assistance but is able to care for most of his needs.
50	Requires considerable assistance and frequent medical care.
40	Disabled. Requires special care and assistance.
30	Severely disabled. Hospitalization is indicated although death not imminent.
20	Hospitalization necessary, very sick active supportive treatment necessary.
10	Moribund. Fatal processes progressing rapidly.
0	Dead.

Source: [Karnofsky, D. A. 1949]

10.8.3 Lansky Play-Performance Scale

Score	Activity
100	Fully active, normal
90	Minor restrictions in physically strenuous activity
80	Active, but tires more quickly
70	Both greater restriction of, and less time spent in, active play
60	Up and around, but minimal active play; keeps busy with quieter activities
50	Gets dressed, but lies around much of the day; no active play; able to participate in all quiet play and activities
40	Mostly in bed; participates in quiet activities
30	In bed; needs assistance even for quiet play
20	Often sleeping; play entirely limited to very passive activities
10	No play; does not get out of bed
0	Unresponsive

Source: [Lansky, S. B., et al 1987]

10.9 Appendix 9: Description of the iRECIST Process for Assessment of Disease Progression

Assessment at Screening and Prior to RECIST 1.1 Progression

iRECIST is based on RECIST 1.1 but adapted to account for the unique tumor response seen with immunotherapeutic drugs. iRECIST will be used by the investigator to assess tumor response and progression, and to guide decisions about changes in management.

Until radiographic disease progression based on RECIST 1.1, there is no distinct iRECIST assessment.

Assessment and Decision at RECIST 1.1 Progression

For participants who show evidence of radiological PD by RECIST 1.1 as determined by the investigator, the investigator will decide whether to continue a participant on study treatment until repeat imaging is obtained using iRECIST for participant management. The decision by the investigator should be based on the participant's overall clinical condition.

Clinical stability is defined as the following:

- Absence of symptoms and signs indicating clinically significant progression of disease
- No decline in ECOG performance status for adults, LPS for children up to and including 16 years of age, or KPS for participants >16 or <18 years of age. (Appendix 8: Performance Status Scales)
- No requirements for intensified management, including increased analgesia, radiation, or other palliative care

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

If the investigator decides to continue treatment, the participant may continue to receive study treatment and the tumor assessment should be repeated 4 to 8 weeks later to confirm PD by iRECIST, per investigator assessment.

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

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

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

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

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

Assessment at the Confirmatory Imaging

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

Confirmation of Progression

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

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

Persistent iUPD

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

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

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

Resolution of iUPD

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

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

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

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

Management Following the Confirmatory Imaging

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

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

Detection of Progression at Visits after Pseudo-progression Resolves

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

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

- New lesions
  - New lesions appear for the first time
  - Additional new lesions appear
  - Previously identified new target lesions show an increase of ≥5 mm in the new lesion sum of diameters, from the nadir value of that sum
  - Previously identified nontarget lesions show any significant growth

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

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

Additional details about iRECIST are provided in the iRECIST publication [Seymour, L., et al 2017]. A summary of imaging and treatment requirements after first radiologic evidence of progression is illustrated as a flowchart in Figure 5.

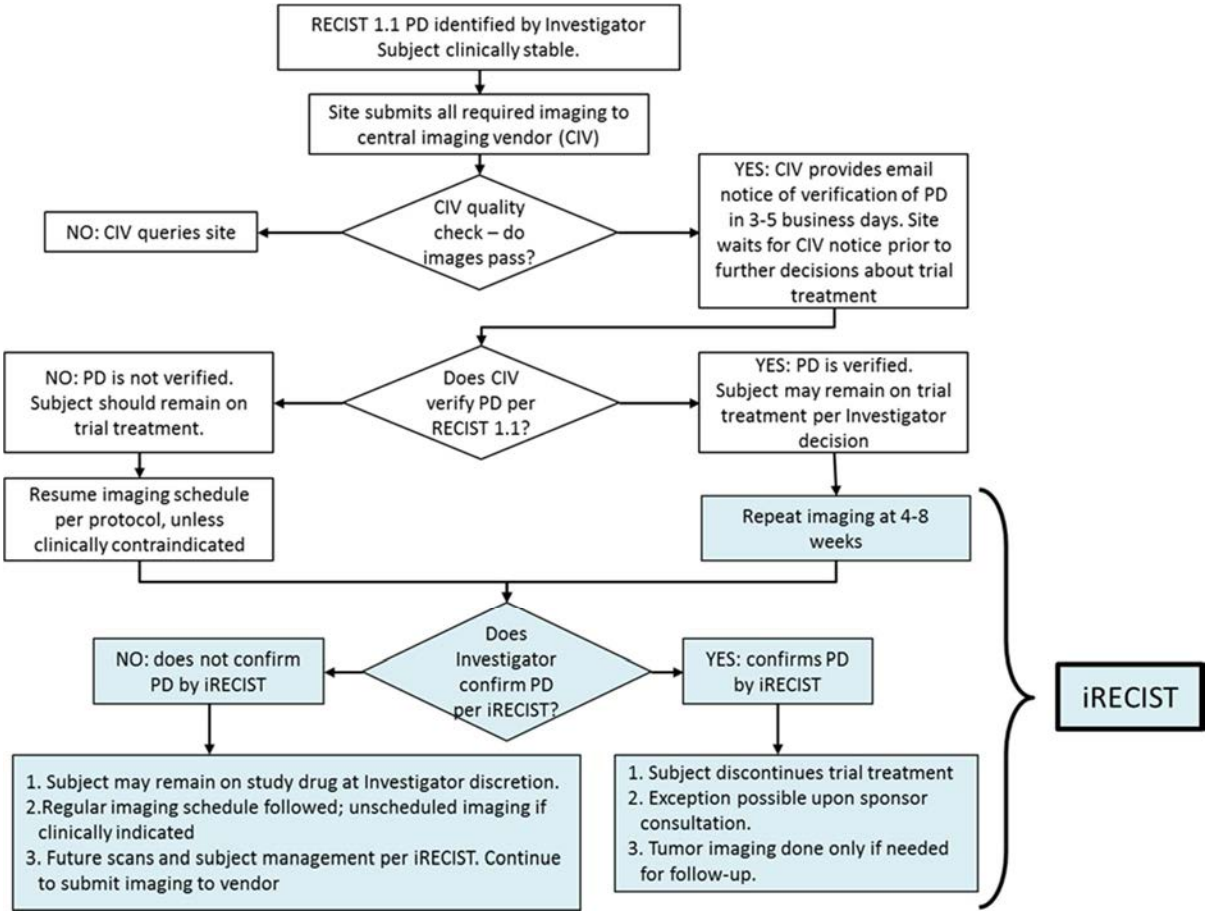


Figure 5 Imaging and Treatment for Clinically Stable Participants Treated With Pembrolizumab After First Radiologic Evidence of PD Assessed by the Investigator

10.10 Appendix 10: Surgical Considerations

1. Recommendation for Surgical Management:

a) Wide excision with a 1-2cm clinical margin surrounding the primary lesion or biopsy scar is recommended for entry on to this protocol. If the primary melanoma is completely resected within the wide excision margin, the resection is acceptable.

b) For lesions with Breslow's thickness >2 mm, a 2 cm minimum clinical margin is recommended when anatomically feasible. On other body sites with limited tissue availability a narrower margin is acceptable to avoid excessive morbidity.

c) For subungual melanoma, interphalangeal metacarpal/metatarsal-phalangeal amputation with histologically negative margins constitutes an adequate wide excision.

d) The specimen shall be excised to include skin and all subcutaneous tissue down to the muscular or deep fascia. Fascia may be included at the discretion of the operating surgeon.

e) The pathology report should report surgical margins and whether or not surgical resection margins are involved with the tumor, including close margin (eg, <1 mm between tumor and resection margin) and tumor abutting margin.

Closure of the defect (eg, primary advancement flap closure, split thickness skin graft, complex reconstruction) is at the discretion of the surgeon.

2. SLN Procedure:

A SLN is defined as any lymph node(s) receiving direct lymphatic drainage from a primary tumor site identified during lymphoscintigraphy with radioactive and/or visible tracer. There may be more than one sentinel node for some primary melanoma sites. The clinical rationale for SLN identification and separate evaluation is based on the assumption that metastatic lymph node involvement will first involve the SLN(s) that receive the majority of the lymphatic drainage from a given primary tumor before it involves more distant lymph nodes. Involvement of SLN(s) increases the likelihood that other, more distant node(s) may also contain metastatic disease. Conversely, if sentinel nodes are negative, other regional nodes are less likely to contain metastasis.

a) Pathological considerations for SLNs: AJCC and CAP guidelines should be followed for the pathologic examination and reporting of SLN biopsy specimens.

Parameters to include in the SLN pathology report are:

- Total number of sentinel nodes excised and submitted for pathologic review
- Number of sentinel nodes, if any, involved by tumor

b) Sequence of sectioning and staining in SLN protocol for melanoma

Pathologists should examine multiple hematoxylin– eosin (H&E) and immunohistochemically stained sections (for one or more melanocytic markers such as S100, HMB45, MelanA, SOX10 and/or tyrosinase) from each SLN. When S100 or SOX10 immunohistochemistry (IHC) is positive, a second IHC may be performed to assist in the interpretation of difficult cases. Any metastatic tumor cells identified within a lymph node, irrespective of how small they are or whether they are identified on H&E or immunostained sections, should be designated as a tumor-positive SLN. As per AJCC guidelines, if melanoma cells are identified within a lymphatic channel within or adjacent to a SLN, that SLN is regarded as tumor-involved. [Gershenwald, J. E., et al 2017] [College of American Pathologists 2018]

10.11 Appendix 11: AJCC 8th Edition Guidelines

The AJCC has designated staging by TNM classification to define melanoma.

Staging tables (Table 17, Table 18, Table 19, Table 20) adapted from AJCC 8th edition. Refer to AJCC guidelines for more information [Gershenwald, J. E., et al 2017].

Table 17 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	≤1.0mm (ulceration status unknown or unspecified)
T1a	<0.8mm without ulceration
T1b	<0.8mm with ulceration or 0.8-1.0mm with or without ulceration
T2	>1.0-2.0mm (ulceration status unknown or unspecified)
T2a	>1.0-2.0mm without ulceration
T2b	>1.0-2.0mm with ulceration
T3	>2.0-4.0mm (ulceration status unknown or unspecified)
T3a	>2.0-4.0mm without ulceration
T3b	>2.0-4.0 mm with ulceration
T4	>4.0mm (ulceration status unknown or unspecified)
T4a	>4.0 mm without ulceration
T4b	>4.0 mm with ulceration

AJCC = American Joint Committee on Cancer; T = primary tumor.

Table 18 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	Two or 3 tumor-involved nodes or any number of in-transit, satellite, and/or microsatellite metastases with one tumor-involved node	
N2a	Two or 3 clinically occult (detected by SLN biopsy)	No
N2b	Two 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	Four or more clinically occult (detected by SLN biopsy)	No
N3b	Four or more, at least one of which was clinically detected, or the presence of any number of matted nodes	No
N3c	Two or more clinically occult or clinically detected and/or presence of any number of matted nodes	Yes

N=Regional Lymph Node

Table 19 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 noncentral 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

M=Distant Metastasis

Table 20 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

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.

10.12 Appendix 12: Guidance for Distinguishing Primary Cutaneous Melanomas From Cutaneous Metastases of Melanoma

If the diagnosis is made in the context of an appropriate clinical history, it is usually not difficult to establish a correct pathologic diagnosis of either primary cutaneous melanoma or cutaneous metastasis of melanoma. Occasionally it may be extremely difficult to definitively determine whether a melanoma is a primary tumor, or a metastasis based upon pathological examination alone. This is particularly the case for a melanoma located in the dermis that lacks an in situ component in the overlying epidermis. In many instances, such tumors represent a primary melanoma with regression of the superficial dermal and epidermal components. The pathologist should recognize this phenomenon by the presence of some subtle clues such as:

- the presence of rare single atypical epidermal melanocytes,
- epidermal thinning with loss of rete ridges,
- fibrosis and vascular proliferation in the dermis overlying the lesion,
- defect in the band of superficial solar elastosis,
- band-like lymphohistiocytic inflammatory cell infiltrate which usually includes numerous pigment-laden macrophages.

In cases where difficulty remains, it is prudent to examine microscopically additional tissue from the lesion, including further sections cut from the original and additional tissue blocks.

In some instances, it is impossible to be certain from the pathologic features alone whether a melanoma is primary or metastatic. In such cases, correlation with clinical information is essential, as this may provide further and critical clues (eg, a history of a pigmented plaque that disappeared over time leaving a lump in the dermis would be strong evidence in favor of a primary melanoma with a regressed superficial/epidermal component). Furthermore, some primary melanomas may arise in the dermis without origin from the epidermis, including some cases of desmoplastic melanoma, melanomas arising in congenital nevi and blue nevus-like melanoma. The presence of an associated, benign nevus component is evidence favoring that a lesion is a primary melanoma and not metastatic melanoma.

Some metastatic melanomas can show prominent epidermotropism, mimicking a primary tumor. In most epidermotropic melanomas the overlying junctional change does not extend beyond the dermal component. The presence of multiple foci of intralymphatic tumor may be a clue to recognizing epidermotropic melanoma.

Although the presence of subtle nuclear pleomorphism, occasional mitotic figures and an associated lymphoid infiltrate may provide pathologic clues to the correct diagnosis, correlation with clinical information is, as always, essential in reaching a final diagnosis [Gershenwald, J. E., et al 2017] [Scolyer, R. A., et al 2020].

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