Official Protocol Title:	A Phase 3, Randomized, Double-blind, Placebo-controlled Study to Evaluate Pembrolizumab Versus Placebo as Adjuvant Therapy Following Surgery and Radiation in Participants with High-risk Locally Advanced Cutaneous Squamous Cell Carcinoma (LA cSCC) (KEYNOTE-630).
NCT number:	NCT03833167
Document Date:	12-DEC-2024

TITLE PAGE

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Protocol Title: A Phase 3, Randomized, Double-blind, Placebo-controlled Study to Evaluate Pembrolizumab Versus Placebo as Adjuvant Therapy Following Surgery and Radiation in Participants with High-risk Locally Advanced Cutaneous Squamous Cell Carcinoma (LA cSCC) (KEYNOTE-630)

Protocol Number: 630-10

Compound Number: MK-3475

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

Legal Registered Address:

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

Regulatory Agency Identifying Number(s):

NCT	03833167
EU CT	2022-500395-57-00
EudraCT	2018-001974-76
JAPIC-CT	Not applicable
WHO	Not applicable
UTN	Not applicable
IND	134760

Approval Date: 12 December 2024

Sponsor Signatory

Typed Name: Title:	Date

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

Investigator Signatory

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

Typed Name: Title:	Date

DOCUMENT HISTORY

Document	Date of Issue	Overall Rationale
Amendment 10	12-DEC-2024	This amendment addresses a change in strategy to stop the study based on the recommendation of eDMC after review of the results from the prespecified efficacy IA (data cutoff 28-JUN-2024). At this IA, pembrolizumab did not cross the boundary for statistical significance in RFS by investigator assessment compared to placebo. OS was not formally tested, but the HR point estimate did not favor pembrolizumab versus placebo. The risk/benefit profile did not support continuation of the study.
Amendment 9	02-NOV-2023	To update the statistical analysis strategy accounting for slower enrollment and faster RFS accumulation in the study
Amendment 8	28-JUN-2022	Include an iCRO to collect and hold images and add the collection of standard of care images during the Survival Follow-up Phase for participants who have not experienced a Recurrence-free Survival event
Amendment 7	09-AUG-2021	To correct inadvertent changes to contraception requirements table in Appendix 5 and make pregnancy testing required prior to every cycle to align with feedback from regulatory agencies
Amendment 6	10-JUN-2021	To harmonize the presentation of safety information across all Food and Drug Administration (FDA)-approved programmed cell death 1/ ligand 1 (PD-1/L1) antibody prescribing information; to roll country-specific requirements into the Country-specific Requirements Appendix; for inclusion criteria clarification; removal of reference to a substudy for future biomedical research
Amendment 5/ Ireland-specific amendment	24-JAN-2020	Health authority request
Amendment 4/ Italy-specific amendment	04-NOV-2019	Health authority request
Amendment 3/ UK-specific amendment	25-JUL-2019	Change in eligibility for cross-over/retreatment participants

Document	Date of Issue	Overall Rationale
Amendment 2	25-JUL-2019	Change in eligibility for cross-over/retreatment participants
Amendment 1/ UK-specific amendment	30-JAN-2019	Clarify Screening exclusion, test requirements and dose modification guidelines for immune-related adverse events associated with pembrolizumab as required by the regulatory agency in the UK
Original Protocol	20-NOV-2018	Not applicable

PROTOCOL AMENDMENT SUMMARY OF CHANGES

Amendment: 10

Overall Rationale for the Amendment:

This amendment addresses a change in strategy to stop the study based on the recommendation of eDMC after review of the results from the prespecified efficacy IA (data cutoff 28-JUN-2024). At this IA, pembrolizumab did not cross the boundary for statistical significance in RFS by investigator assessment compared to placebo. OS was not formally tested, but the HR point estimate did not favor pembrolizumab versus placebo. The risk/benefit profile did not support continuation of the study.

Summary of Changes Table

Section Number and Name	Description of Change	Brief Rationale
Primary Reason for Amendment		
Section 1.1, Synopsis	Overall Design: Added a note (in alignment with the study-specific investigator letter dated 29-AUG-2024) to provide information regarding the results of the prespecified IA reviewed by eDMC and subsequent decision of the Sponsor to discontinue the study, and which analyses will or will not be conducted going forward. It also includes instructions for discontinuation of study intervention and a high-level summary of the modified protocol study procedures to be implemented as a result of the decision to discontinue the study.	To address a change in strategy to stop the study based on the results of the prespecified efficacy IA and incorporate instructions for discontinuation of study intervention, appropriate measures for follow-up of ongoing study participants, and the plan for end of study analysis going forward.

Section Number and Name	Description of Change	Brief Rationale
Additional Changes		
Section 1.1, Synopsis	Duration of Participation: Added information on extension study giving ongoing study participants an option to transition into an extension study on study discontinuation.	To transition ongoing study participants into a pembrolizumab extension study, if available, prior to close out of this study.
Section 4.1, Overall Design	Added a note (in alignment with the study-specific investigator letter dated 29-AUG-2024) to provide information regarding the results of the prespecified IA reviewed by eDMC and subsequent decision of the Sponsor to discontinue the study, and which analyses will or will not be conducted going forward. It also includes instructions for discontinuation of study intervention and a high-level summary of the modified protocol study procedures to be implemented as a result of the decision to discontinue the study.	Refer to the rationale for primary reason for amendment.
	Added information on extension study giving ongoing study participants an option to transition into an extension study on study discontinuation.	To transition ongoing study participants into a pembrolizumab extension study, if available, prior to close out of this study.
Section 1.3, Schedule of Activities	Added a note to indicate the changes to the schedule of activities for participants who are still on the study.	Refer to the rationale for primary reason for amendment.
Section 6.3.3, Blinding	Added text to indicate the study was unblinded after the efficacy IA.	Refer to the rationale for primary reason for amendment.
Section 8.2.1, Tumor Imaging and Assessment of Disease	Added text to indicate that scans will no longer be sent to the iCRO and digital photography of cutaneous lesions is no longer required.	Refer to the rationale for primary reason for amendment.
Section 8.2.1.7.2, iRECIST Assessment of Disease	Added text to indicate that scans will no longer be sent to the iCRO.	Refer to the rationale for primary reason for amendment.
Section 8.2.1.8, Photography for Cutaneous Lesions	Added text to indicate that digital photography of cutaneous lesions is no longer required.	Refer to the rationale for primary reason for amendment.
Section 8.2.2, Survival	Added text to indicate that scans will no longer be sent to the iCRO.	Refer to the rationale for primary reason for amendment.
Section 8.2.3, Patient Reported Outcomes	Added text to indicate that ePRO assessments will be discontinued.	Refer to the rationale for primary reason for amendment.

Section Number and Name	Description of Change	Brief Rationale
Section 8.11.4, Participants Discontinued From Study Intervention but Continuing to be Monitored in the Study	Added text to indicate the changes to the assessments/procedures for participants who are still on the study.	Refer to the rationale for primary reason for amendment.
Section 9, Statistical Analysis Plan	Added a note to provide information regarding the results of the prespecified IA reviewed by eDMC and subsequent decision of the Sponsor to discontinue the study and to clarify the scope of analyses to be performed subsequent to the decision to discontinue the study.	Refer to the rationale for primary reason for amendment.
Section 9.1, Statistical Analysis Plan Summary	Added text to clarify the scope of analyses to be performed subsequent to the decision to discontinue the study.	Refer to the rationale for primary reason for amendment.
	Updated participant randomization status and added the final number of participants randomized in the study and the total sample size.	The study is being discontinued and no additional participants will be randomized.
Section 9.2, Responsibility for Analyses/In-house Blinding	Added text to indicate the study was unblinded after efficacy IA.	Refer to the rationale for primary reason for amendment.
Section 9.6, Statistical Methods	Added a note to clarify the scope of analyses to be performed subsequent to the decision to discontinue the study.	Refer to the rationale for primary reason for amendment.
Section 9.7, Interim Analyses	Added a note to clarify that the prespecified final analysis described in the SAP will not be performed.	Refer to the rationale for primary reason for amendment.
Section 9.7.2, Safety Interim Analyses	Added text to clarify that safety monitoring will continue per protocol and safety analysis will be performed at the end of the study.	Refer to the rationale for primary reason for amendment.
Section 9.8, Multiplicity	Added a note to clarify that the prespecified final efficacy analysis involving hypothesis testing will not be performed and therefore, no multiplicity adjustment will be needed.	Refer to the rationale for primary reason for amendment.
Section 9.9, Sample Size and Power Calculations	Added final randomization numbers and noted that the power calculations are not applicable because no statistical testing will be performed.	Refer to the rationale for primary reason for amendment.
Throughout	Minor administrative, formatting, grammatical, and/or typographical changes were made throughout the document.	To ensure clarity and accurate interpretation of the intent of the protocol.

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1 PROTOCOL SUMMARY

1.1 Synopsis

Protocol Title: A Phase 3, Randomized, Double-blind, Placebo-controlled Study to Evaluate Pembrolizumab Versus Placebo as Adjuvant Therapy Following Surgery and Radiation in Participants with High-risk Locally Advanced Cutaneous Squamous Cell Carcinoma (LA cSCC) (KEYNOTE-630)

Short Title: Pembrolizumab as adjuvant therapy for resectable high-risk LA cSCC

Acronym: KEYNOTE-630

Hypotheses, Objectives, and Endpoints:

Hypotheses are aligned with objectives in the Objectives and Endpoints table.

In male/female participants aged 18 years or older with resectable high-risk LA cSCC after surgery and RT:

Primary Objective	**Primary Endpoint**
Objective: To compare the recurrence-free survival (RFS), as assessed by the investigator and confirmed by biopsy, in individuals who receive pembrolizumab with individuals who receive placebo as adjuvant therapy. Hypothesis (H1): Pembrolizumab as adjuvant therapy is superior to placebo with respect to RFS as assessed by the investigator	-RFS: defined as the time from the date of randomization to the date of first record of the following events: -Local or regional recurrence of the index lesion -Distant metastasis -Death due to any cause Note: A new low risk primary cSCC is not considered as a RFS event
Secondary Objectives	**Secondary Endpoints**
Objective: To compare overall survival (OS) in individuals who receive pembrolizumab with individuals who receive placebo as adjuvant therapy. Hypothesis (H2): Pembrolizumab as adjuvant therapy is superior to placebo with respect to OS.	OS: defined as time from randomization to death due to any cause
To compare mean change from baseline in health-related quality of life (HRQoL) scores from the European Organisation for Research and Treatment of Cancer (EORTC) QoL Questionnaire (QLQ) C30, in individuals who receive pembrolizumab with individuals who receive placebo as adjuvant therapy.	-EORTC QLQ-C30 global health status/QoL scales -EORTC QLQ-C30 physical functioning scale
Objective: To determine the safety and tolerability of pembrolizumab as adjuvant therapy.	-Adverse events (AEs) -Study drug discontinuations due to AEs

Overall Design:

Study Phase	Phase 3
Primary Purpose	Treatment
Indication	Squamous cell carcinoma of skin
Population	Participants with high-risk LA cSCC eligible for adjuvant treatment following surgery and RT with curative intent
Study Type	Interventional
Intervention Model	Parallel This is a multi site study.
Type of Control	Placebo
Study Blinding	Double-blind
Blinding Roles	Investigator, Participant, Sponsor
Estimated Duration of Study	The Sponsor estimates that the study will require approximately 8 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.

NOTE: This study will be discontinued based on the results of the prespecified IA of efficacy and safety data (data cutoff 28-JUN-2024) reviewed by eDMC on 21-AUG-2024. At this IA, pembrolizumab did not cross the boundary for statistical significance in RFS by investigator assessment compared to placebo. Although not formally tested based on multiplicity strategy, the OS point estimate did not favor pembrolizumab versus placebo. The eDMC recommended that the study should be stopped for futility as the benefit/risk profile did not support continuing the study. The EOC reviewed the data and accepted the eDMC's recommendation. Based on these data and the recommendation of the eDMC, the study was unblinded on 22-AUG-2024. The prespecified final efficacy analysis of the study described in the SAP will not be performed. Efficacy and safety analyses will be performed at the end of the study; there will be no further planned analyses for ePRO endpoints.

In alignment with the study-specific investigator letter dated 29-AUG-2024, all participants should discontinue study treatment (pembrolizumab/placebo). On a case-by-case basis, the investigators may contact the Sponsor for the consideration of continuing pembrolizumab treatment if they assess a participant is deriving clinical benefit. All ongoing participants should undergo study procedures as specified in this amendment (Amendment 10).

As of Amendment 10, ePRO assessments are no longer required. Participants should continue tumor imaging and investigator assessment of the tumor scans per protocol;

however, scans no longer need to be submitted to the iCRO and digital photography of cutaneous lesions is not required.

Number of Participants:

Approximately 430 participants will be randomized in the study.

Intervention Groups and Duration:

Arm Name	Intervention Name	Unit Dose Strength(s)	Dosage Level(s)	Route of Administration	Regimen/ Treatment Period	Use
Pembrolizumab	Pembrolizumab	25 mg/mL	400 mg	IV Infusion	Q6W; Day 1 of each 42-day cycle for up to 9 cycles (approximately 1 year)	Test Product
Placebo	Placebo	N/A	N/A	IV Infusion	Q6W; Day 1 of each 42-day cycle for up to 9 cycles (approximately 1 year)	Placebo

IV=intravenous; N/A=not applicable; Q6W=every 6 weeks

Following surgical resection and RT, participants will be randomized to receive either:

- Pembrolizumab (Pembrolizumab group) - 400 mg fixed dose, intravenously (IV) every 6 weeks (Q6W) for up to 9 cycles, or
- Placebo (Control group)

After first biopsy proven disease recurrence: if clinically indicated (and with Sponsor approval) participants may cross over to or receive retreatment with pembrolizumab 400 mg IV Q6W for up to 18 cycles; for participants that received pembrolizumab in the Adjuvant Treatment Phase, any retreatment will be a minimum of 6 months after completing all 9 cycles in the Adjuvant Treatment Phase.

Other current or former names or aliases for study intervention are as follows: KEYTRUDA®, MK-3475.

Total Number of Intervention Groups/Arms	2
Duration of Participation	Each participant will participate in the study from the time that the participant provides documented informed consent through the final protocol-specified contact. After a screening phase of up to 28 days, each participant will be assigned to receive study adjuvant treatment until new high-risk primary cSCC or biopsy proven* disease recurrence, start of new anticancer treatment, unacceptable AE(s) toxicity, intercurrent illness that prevents further administration of treatment, investigator's decision to discontinue the participant, participant withdrawal of consent, pregnancy of the participant, administrative reasons requiring cessation of treatment, or until the participant has received 9 administrations of pembrolizumab (approximately 1 year). Upon first biopsy proven* disease recurrence, treatment will be unblinded. If clinically indicated (and with Sponsor approval), participants may cross over to or receive open-label retreatment with pembrolizumab until disease progression as assessed by the investigator per Response Evaluation Criteria in Solid Tumors 1.1 (RECIST 1.1)/modified RECIST 1.1 for immune-based therapeutics (iRECIST), start of new systemic anticancer therapy, unacceptable AE(s) toxicity, intercurrent illness that prevents further administration of treatment, investigator's decision to discontinue the participant, noncompliance with study treatment or procedure requirements, participant withdrawal of consent, pregnancy of the participant, administrative reasons requiring cessation of treatment, or until the participant has received 18 administrations of pembrolizumab (approximately 2 years); for participants that received pembrolizumab in the Adjuvant Treatment Phase, any retreatment will be a minimum of 6 months

	after completing all 9 cycles (approximately 1 year) in the Adjuvant Treatment Phase. The decision to retreat will be at the discretion of the investigator (after approval from the Sponsor) if they meet the criteria for cross-over/retreatment and the study is ongoing. After the end of treatment, each participant will be followed for the occurrence of AEs and spontaneously reported pregnancy as described under Section 8.4. Participants who discontinue study adjuvant treatment for reasons other than a new high-risk primary cSCC or disease recurrence will have Study Adjuvant follow-up for disease status monitoring until a new high-risk primary cSCC or biopsy proven* disease recurrence, withdrawal of consent, pregnancy, death, or lost to followup. Participants who discontinue study treatment in cross-over/retreatment for reasons other than disease progression will have Safety and Survival Follow-up. All participants will be followed by telephone for OS until death, withdrawal of consent, or the end of the study. * Tissue biopsy is required for the confirmation of disease recurrence. Only if a biopsy cannot be performed due to feasibility, such as location of recurrence (ie, bone lesion), and upon Sponsor consultation, can radiographic imaging be used to confirm disease recurrence. On study discontinuation, all ongoing participants will be discontinued and may be enrolled in an extension study, if available. In the extension study, participants who experience disease recurrence per SOC clinical assessment may be considered eligible for cross-over/retreatment upon consultation with the Sponsor.

Study Governance Committees:

Executive Oversight Committee	Yes
Data Monitoring Committee	Yes
Clinical Adjudication Committee	No
Scientific Advisory Committee	Yes

Study governance considerations are outlined in Appendix 1.

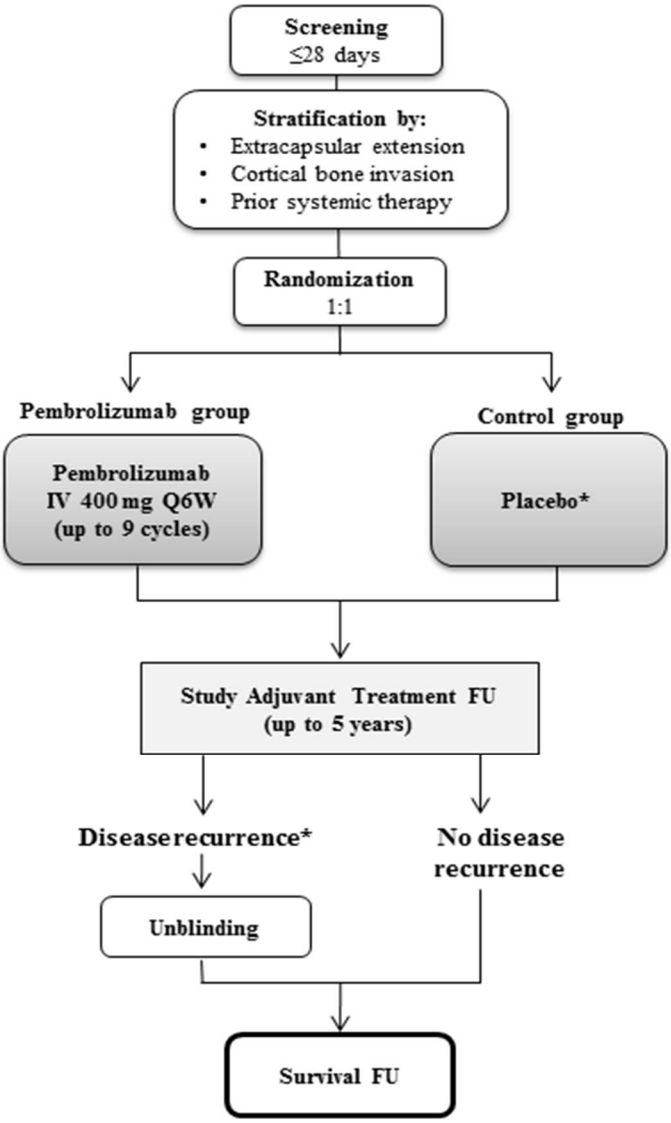
Study Accepts Healthy Participants: No

A list of abbreviations is in Appendix 9.

1.2 Schema

The study design is depicted in Figure 1.

Figure 1 Study Design



* Upon biopsy proven disease recurrence, and with Sponsor approval, treatment will be unblinded; if clinically indicated, participants may cross over to (within 12 weeks of biopsy proven recurrence) or receive retreatment (if biopsy proven disease recurrence occurs more than 6 months after completing 1 year of study adjuvant therapy) with open-label pembrolizumab 400 mg IV Q6W.

FU=follow-up; IV=intravenous; Q6W=every 6 weeks

1.3 Schedule of Activities

Details of each procedure outlined in the Schedule of Activities are provided in Section 8. Refer to Appendix 7 for country-specific requirements.

NOTE: As of Amendment 10, participants who are still on the study will no longer require ePRO assessments to be performed. For all ongoing participants, tumor imaging and investigator assessments of tumor scans should continue per protocol. Digital photography of cutaneous lesions is not required and tumor scans no longer need to be submitted to the iCRO.

The full SoA tables below are retained for reference.

1.3.1 Adjuvant Treatment Phase

Trial Period	**Screening**	**Treatment Cycle**						**EOT**	**Notes:** Cycles will be repeated up to 9 infusions or until protocol-specific criteria to discontinue treatment is met. Participants that complete or discontinue study treatment for reasons other than a new high-risk primary cSCC or disease recurrence will have a Safety FU and then proceed to Adjuvant FU (Section 1.3.2). Participants that discontinue study treatment due to a new high-risk primary cSCC or disease recurrence will have a Safety FU and then proceed directly to Survival FU (Section 1.3.2) or cross-over, if eligible (Section 1.3.3).
Treatment Cycle/Title		**1**		**2**		**3**	**4 to 9**	**Discon**	
Scheduled Window (days)	**-28 to -1**	**+3**	**±3**	**±3**	**±3**	**±3**	**±3**	**At time of treatment discon**	
Day of visit		**D1**	**D22**	**D1**	**D22**	**D1**	**D1**		
Administrative Procedures									
Informed Consent	X								Additional consent is required at disease recurrence.
Informed Consent for Future Biomedical Research	X								Optional, the participant may participate in the study without participating in FBR.
Inclusion/ Exclusion Criteria	X								
Participant Identification Card	X	X							Add the allocation or randomization number at the time of allocation or randomization.
Demographics and Medical History	X								

Trial Period	**Screening**	**Treatment Cycle**						**EOT**	**Notes:** Cycles will be repeated up to 9 infusions or until protocol-specific criteria to discontinue treatment is met. Participants that complete or discontinue study treatment for reasons other than a new high-risk primary cSCC or disease recurrence will have a Safety FU and then proceed to Adjuvant FU (Section 1.3.2). Participants that discontinue study treatment due to a new high-risk primary cSCC or disease recurrence will have a Safety FU and then proceed directly to Survival FU (Section 1.3.2) or cross-over, if eligible (Section 1.3.3).
Treatment Cycle/Title		**1**		**2**		**3**	**4 to 9**	**Discon**	
Scheduled Window (days)	**-28 to -1**	**+3**	**±3**	**±3**	**±3**	**±3**	**±3**	**At time of treatment discon**	
Day of visit		**D1**	**D22**	**D1**	**D22**	**D1**	**D1**		
Prior/Concomitant Medication Review	X	X	X	X	X	X	X	X	Prior medications – Record all medications taken within 28 days of first dose. Concomitant medications – Enter new medications started during the study through the Safety Follow-up visit.
Post-study Anticancer Therapy Status								X	
Treatment Randomization via IRT		X							Site personnel will access the IRT after screening and determine if the participant is eligible for randomization.
Study Intervention Administration		X		X		X	X		Treatment 1, Cycle 1 must be given within 3 days after treatment randomization via IRT. Study drug to be administered on D1 of each cycle after all procedures/ assessments have been completed.
Unblinding - for Participants with Disease Recurrence Only								X*	*Upon biopsy-confirmed disease recurrence participants will be unblinded (see Section 8.1.10); if clinically indicated (and with Sponsor approval) participants may cross over to or receive retreatment with pembrolizumab (see Section 8.1.8). Participants that complete study treatment or discontinue for reasons other than disease recurrence will not be unblinded.
Vital Status		←					→		Upon Sponsor request, participants may be contacted for survival status at any time during the study.

Trial Period	**Screening**	**Treatment Cycle**						**EOT**	**Notes:** Cycles will be repeated up to 9 infusions or until protocol-specific criteria to discontinue treatment is met. Participants that complete or discontinue study treatment for reasons other than a new high-risk primary cSCC or disease recurrence will have a Safety FU and then proceed to Adjuvant FU (Section 1.3.2). Participants that discontinue study treatment due to a new high-risk primary cSCC or disease recurrence will have a Safety FU and then proceed directly to Survival FU (Section 1.3.2) or cross-over, if eligible (Section 1.3.3).
Treatment Cycle/Title		**1**		**2**		**3**	**4 to 9**	**Discon**	
Scheduled Window (days)	**-28 to -1**	**+3**	**±3**	**±3**	**±3**	**±3**	**±3**	**At time of treatment discon**	
Day of visit		**D1**	**D22**	**D1**	**D22**	**D1**	**D1**		
Efficacy Procedures									
Tumor Imaging - CT/MRI - Head and Neck, Chest, Abdomen, Pelvis and Extremities (if indicated)	X	--If clinically indicated‡--					X‡ Q12W	X*	Baseline imaging will be performed within 28 days prior to the date of randomization. ‡ The first on-study imaging assessment should be performed at 12 weeks (±7 days) from the date of randomization; subsequent tumor imaging (to include disease involved areas and associated draining lymph node regions) every 12 weeks (84 days ±7days) until end of Year 2, or more frequently if clinically indicated. For all imaging, the clock will start from the date of treatment allocation. * In participants who discontinue study therapy, imaging should be performed at the time of treatment discontinuation (ie, date of discontinuation ±4 weeks). If previous scan/ was obtained within 4 weeks prior to the date of discontinuation, then a scan at treatment discontinuation does not need to be performed. Continuation of imaging/biopsies is required for participants who have not yet experienced a new high-risk primary cSCC or disease recurrence.
Digital Photography: Cutaneous Lesions		------If Clinically Indicated------							At time of disease recurrence (see Section 8.2.1.8).
Biopsy		------If Clinically Indicated------							Details of any biopsy-confirmed disease recurrence to be inserted into the eCRF. Sponsor consultation is required if a biopsy cannot be performed due to feasibility.

Trial Period	**Screening**	**Treatment Cycle**						**EOT**	**Notes:** Cycles will be repeated up to 9 infusions or until protocol-specific criteria to discontinue treatment is met. Participants that complete or discontinue study treatment for reasons other than a new high-risk primary cSCC or disease recurrence will have a Safety FU and then proceed to Adjuvant FU (Section 1.3.2). Participants that discontinue study treatment due to a new high-risk primary cSCC or disease recurrence will have a Safety FU and then proceed directly to Survival FU (Section 1.3.2) or cross-over, if eligible (Section 1.3.3).
Treatment Cycle/Title		**1**		**2**		**3**	**4 to 9**	**Discon**	
Scheduled Window (days)	**-28 to -1**	**+3**	**±3**	**±3**	**±3**	**±3**	**±3**	**At time of treatment discon**	
Day of visit		**D1**	**D22**	**D1**	**D22**	**D1**	**D1**		
EORTC QLQ-C30		X		X		X	X‡ Q12W	X*	PROs are to be administered by trained site personnel on D1 of C1, C2, C3 and then every 2 cycles (ie, every 12 weeks)‡ until end of Year 2. It is strongly recommended that PROs are completed by participants prior to all procedures/assessments, and in the following order: EORTC QLQ-C30, Skindex-16, and then EQ-5D. If the participant does not complete the PROs for any reason, the Miss Mode form must be completed to capture the reason the assessment was not performed. *In participants who discontinue study therapy, PROs should be administered at the time of treatment discontinuation (ie, date of discontinuation ±4 weeks). If previous PROs were obtained within 4 weeks prior to the date of discontinuation, then administration of PROs at treatment discontinuation does not need to be performed.
Skindex-16		X		X		X	X‡ Q12W	X*	
EuroQol EQ-5D		X		X		X	X‡ Q12W	X*	
Safety Procedures									
Full Physical Examination and Height*	X							X	To be performed by the investigator or medically qualified designee. Follow NCCN cSCC 2018 guidelines: To include a history and physical exam that includes a complete skin and lymph node exam. *Height will be measured at Screening only.

Trial Period	**Screening**	**Treatment Cycle**						**EOT**	**Notes:** Cycles will be repeated up to 9 infusions or until protocol-specific criteria to discontinue treatment is met. Participants that complete or discontinue study treatment for reasons other than a new high-risk primary cSCC or disease recurrence will have a Safety FU and then proceed to Adjuvant FU (Section 1.3.2). Participants that discontinue study treatment due to a new high-risk primary cSCC or disease recurrence will have a Safety FU and then proceed directly to Survival FU (Section 1.3.2) or cross-over, if eligible (Section 1.3.3).
Treatment Cycle/Title		**1**		**2**		**3**	**4 to 9**	**Discon**	
Scheduled Window (days)	**-28 to -1**	**+3**	**±3**	**±3**	**±3**	**±3**	**±3**	**At time of treatment discon**	
Day of visit		**D1**	**D22**	**D1**	**D22**	**D1**	**D1**		
Directed Physical Examination		X	X	X	X	X	X		To be performed by the investigator or medically qualified designee. Follow NCCN cSCC 2018 guidelines: To include a history and physical exam that includes a complete skin and lymph node exam.
Weight and Vital Signs	X	X	X	X	X	X	X	X	Vital signs to be collected include: temperature, resting pulse, resting respiratory rate, blood pressure.
12-lead ECG (local)	X								
Urine or Serum β-hCG Pregnancy Test (POCBP only) – as per local SOP	X	X		X		X	X		The protocol requires pregnancy testing within 72 hours prior to administration of each dose of study treatment. Refer to Appendix 7 for country-specific requirements for Germany, Ireland, Italy, Norway, and the UK.
HIV, Hepatitis B and C Screen (testing optional per site SOP)	X								Testing is required where mandated by the local health authority. For Germany-and UK-specific requirements see Appendix 7.
Coagulation Tests (PT/INR and aPTT/PTT)	X	--If Clinically Indicated-							Screening - within 10 days prior to the start of study treatment. Samples to be taken prior to study drug administration. Any participant receiving anticoagulant therapy should have coagulation tests monitored closely throughout the study. PTT may be performed if the local laboratory is unable to perform aPTT.

Trial Period	**Screening**	**Treatment Cycle**						**EOT**	**Notes:** Cycles will be repeated up to 9 infusions or until protocol-specific criteria to discontinue treatment is met. Participants that complete or discontinue study treatment for reasons other than a new high-risk primary cSCC or disease recurrence will have a Safety FU and then proceed to Adjuvant FU (Section 1.3.2). Participants that discontinue study treatment due to a new high-risk primary cSCC or disease recurrence will have a Safety FU and then proceed directly to Survival FU (Section 1.3.2) or cross-over, if eligible (Section 1.3.3).
Treatment Cycle/Title		**1**		**2**		**3**	**4 to 9**	**Discon**	
Scheduled Window (days)	**-28 to -1**	**+3**	**±3**	**±3**	**±3**	**±3**	**±3**	**At time of treatment discon**	
Day of visit		**D1**	**D22**	**D1**	**D22**	**D1**	**D1**		
CBC With Differential	X	X[§]	X	X	X	X	X	X	Screening - within 10 days prior to the start of study treatment. Samples to be taken prior to study drug administration. After Cycle 1, samples can be collected up to 72 hours prior to the scheduled time point. [§]Optional - CBC and Chemistry labs are not required at C1D1 if they were collected during screening and within 10 days of first dose. * In case of elevated TSH add free T3 and free T4. ‡ To be repeated every 2 cycles. Unresolved abnormal labs that are drug-related AEs should be followed until resolution. Labs do not need to be repeated after the EOT if labs are within normal range.
Chemistry Panel	X	X[§]	X	X	X	X	X	X	
Urinalysis	X								
Thyroid Function (TSH)*, T3, FT4	X			X			X[‡]	X	
ECOG Performance Status	X	X	X	X	X	X	X	X	Screening - ECOG is to be performed within 10 days prior to the first dose of study therapy. Must be performed prior to each dose of study treatment where ECOG is collected.
AE/SAE Review	X	----------Continuous Reporting----------							Record all AEs and ECIs occurring within 30 days after EOT and SAEs for 90 days after the EOT or 30 days after EOT if the participant initiates new anticancer therapy (whichever is earlier). Report treatment-related SAEs regardless of when they occur.
Pharmacodynamics/ Biomarkers									
Blood for Genetic Analysis		X							See Section 8.8 for details
Blood for RNA Analyses		X		X		X	X*	X	* Cycle 5 only
Blood for Plasma Biomarker Analysis		X		X		X	X*	X	* Cycle 5 only

Trial Period	**Screening**	**Treatment Cycle**						**EOT**	**Notes:** Cycles will be repeated up to 9 infusions or until protocol-specific criteria to discontinue treatment is met. Participants that complete or discontinue study treatment for reasons other than a new high-risk primary cSCC or disease recurrence will have a Safety FU and then proceed to Adjuvant FU (Section 1.3.2). Participants that discontinue study treatment due to a new high-risk primary cSCC or disease recurrence will have a Safety FU and then proceed directly to Survival FU (Section 1.3.2) or cross-over, if eligible (Section 1.3.3).
Treatment Cycle/Title		**1**		**2**		**3**	**4 to 9**	**Discon**	
Scheduled Window (days)	**-28 to -1**	**+3**	**±3**	**±3**	**±3**	**±3**	**±3**	**At time of treatment discon**	
Day of visit		**D1**	**D22**	**D1**	**D22**	**D1**	**D1**		
Blood for Serum Biomarker Analyses		X		X		X	X*	X	* Cycle 5 only
Blood for ctDNA		X						X*	*Collected at end of treatment or disease recurrence (whichever comes first).
Tumor Tissue Sample Collection									
Tissue Collection for Biomarker Analysis (tested centrally)	X	(x)							Baseline tumor tissue for biomarker analysis from a newly obtained core or excisional biopsy (FNA not adequate) or prior archival tissue specimen must be provided to the central vendor for PD-L1 biomarker testing. (x) Optional - biopsy may be collected at recurrence if participant consents.

AE=adverse event; aPTT=activated partial thromboplastin time; β-hCG=β-human chorionic gonadotropin; C=cycle; CBC=complete blood count; cSCC=cutaneous squamous cell carcinoma; ctDNA=circulating tumor DNA; CT=computed tomography; D=day; ECG=electrocardiogram; ECI=event of clinical interest; ECOG=Eastern Cooperative Oncology Group; eCRF=electronic case report form; EORTC=European Organisation for Research and Treatment of Cancer; EOT=End of Treatment; EQ-5D=EuroQol-5 Dimensions; FBR=Future Biomedical Research; FNA=fine needle aspirate; FT4=free thyroxine; FU=follow-up; HIV=human immunodeficiency virus; INR=international normalized ratio; IRT=Interactive Response Technology; MRI=magnetic resonance imaging; NCCN=National Comprehensive Cancer Network; PD L1=Programmed Death Ligand 1; POCBP=participants of childbearing potential; PRO=patient-reported outcome; PT=prothrombin time; PTT=partial thromboplastin time; Q12W=every 12 weeks; QLQ-C30=Quality of Life Questionnaire-C30; RNA=ribonucleic acid; SAE=serious adverse event; SOP=standard operating procedure; T3=triiodothyronine; TSH=thyroid-stimulating hormone; UK=United Kingdom.

1.3.2 Follow-up Phase

Trial Period	**Follow-up Phase**				
Visit Number/Title	**Safety FU**	**Study Adjuvant FU‡**			**Survival FU**
Treatment Cycle/Day		**Up to Year 1***	**Years 1-2**	**Years 3-5**	
Scheduling Window Days (unless noted)	**30 days from last dose ±14**	**Q12W ±7**	**Q12W ±7**	**Q6M ±14**	**Q12W ±14**
Administrative Procedures					
Prior/Concomitant Medication Review	X	←	—	→	
Unblinding- for participants with disease recurrence only.		←	—	→	
Post-study Anticancer Therapy Status		←	—	→	X
Vital Status		←	—	→	X

Notes:
A participant may discontinue from study treatment for any reason other than a new high-risk primary cSCC or disease recurrence but will remain in the study for Study Adjuvant follow-up for disease recurrence (Section 8.11.3.3) unless consent is withdrawn.
Participants that discontinue study treatment due to a new high-risk primary cSCC or disease recurrence will have Safety FU then proceed directly to Survival FU or cross-over/retreatment if eligible (Section 1.3.3).
Participants that complete adjuvant treatment or discontinue study treatment for reasons other than a new high-risk primary cSCC or disease recurrence will enter Safety FU then proceed to Adjuvant FU.
*For participants that discontinue before Year 1.
‡ More frequent FU is permitted based on risk and per treating physician discretion. When clinically indicated additional diagnostic evaluation, including imaging, can be performed by treating physician discretion.

Upon biopsy-confirmed disease recurrence participants will be unblinded (see Section 8.1.10); if clinically indicated (and with Sponsor approval) participants may cross over to or receive retreatment with pembrolizumab (see Section 8.1.8). Participants that discontinue FU for reasons other than disease recurrence will not be unblinded.

By telephone contact in Survival FU.
The Sponsor may request survival status to be assessed at additional time points during the study.

Trial Period	**Follow-up Phase**					**Notes:** A participant may discontinue from study treatment for any reason other than a new high-risk primary cSCC or disease recurrence but will remain in the study for Study Adjuvant follow-up for disease recurrence (Section 8.11.3.3) unless consent is withdrawn. Participants that discontinue study treatment due to a new high-risk primary cSCC or disease recurrence will have Safety FU then proceed directly to Survival FU or cross-over/retreatment if eligible (Section 1.3.3). Participants that complete adjuvant treatment or discontinue study treatment for reasons other than a new high-risk primary cSCC or disease recurrence will enter Safety FU then proceed to Adjuvant FU. *For participants that discontinue before Year 1. ‡ More frequent FU is permitted based on risk and per treating physician discretion. When clinically indicated additional diagnostic evaluation, including imaging, can be performed by treating physician discretion.
Visit Number/Title	**Safety FU**	**Study Adjuvant FU‡**			**Survival FU**	
Treatment Cycle/Day		**Up to Year 1***	**Years 1-2**	**Years 3-5**		
Scheduling Window Days (unless noted)	**30 days from last dose ±14**	**Q12W ±7**	**Q12W ±7**	**Q6M ±14**	**Q12W ±14**	
Efficacy Procedures						
Tumor Imaging		X	X	X		For all imaging, the clock will start from the date of treatment allocation. Follow-up tumor imaging (to include disease involved areas and associated draining lymph node regions) will be performed every 12 weeks (±7 days) until end of Year 2, then every 6 months (±14 days) until end of Year 5, or more frequently if clinically indicated. Imaging timing should follow calendar days and should not be recalculated based on the date of previous scans. In participants who discontinue study therapy without documented disease recurrence, every effort should be made to continue monitoring their disease status by radiologic imaging as outlined in Section 8.2.1.3. Continuation of imaging/biopsies is required for participants who have not yet experienced an RFS event. Additionally, imaging assessment/biopsies performed as part of standard of care to evaluate disease status for participants in Survival FU who have not yet experienced a new high-risk primary cSCC or disease recurrence should be collected during Survival FU. All available images should be submitted to the iCRO and recorded in the applicable eCRF (see Section 8.2.2).
Digital Photography: Cutaneous Lesions		---If Clinically Indicated----				At time of disease recurrence (see Section 8.2.1.8).
Biopsy		-If Clinically Indicated-				Details of any biopsy-confirmed disease recurrence to be inserted into the eCRF. Sponsor consultation is required if a biopsy cannot be performed due to feasibility.

Trial Period	**Follow-up Phase**					**Notes:** A participant may discontinue from study treatment for any reason other than a new high-risk primary cSCC or disease recurrence but will remain in the study for Study Adjuvant follow-up for disease recurrence (Section 8.11.3.3) unless consent is withdrawn. Participants that discontinue study treatment due to a new high-risk primary cSCC or disease recurrence will have Safety FU then proceed directly to Survival FU or cross-over/retreatment if eligible (Section 1.3.3). Participants that complete adjuvant treatment or discontinue study treatment for reasons other than a new high-risk primary cSCC or disease recurrence will enter Safety FU then proceed to Adjuvant FU. *For participants that discontinue before Year 1. ‡ More frequent FU is permitted based on risk and per treating physician discretion. When clinically indicated additional diagnostic evaluation, including imaging, can be performed by treating physician discretion.
Visit Number/Title	**Safety FU**	**Study Adjuvant FU‡**			**Survival FU**	
Treatment Cycle/Day		**Up to Year 1***	**Years 1-2**	**Years 3-5**		
Scheduling Window Days (unless noted)	**30 days from last dose ±14**	**Q12W ±7**	**Q12W ±7**	**Q6M ±14**	**Q12W ±14**	
EORTC QLQ-C30	X	X	X	X		To be administered at safety FU, and every 12 weeks (±7 days) until end of Year 2, then every 6 months (±14 days) until end of Year 5. PROs are to be administered by trained site personnel. It is strongly recommended that PROs are completed by participants prior to all procedures/assessments, and in the following order: EORTC QLQ-C30, Skindex-16, and then EQ-5D. If the participant does not complete the PROs for any reason, the Miss Mode form must be completed to capture the reason the assessment was not performed.
Skindex-16	X	X	X	X		
EuroQol EQ-5D	X	X	X	X		
Safety Procedures						
Directed Physical Examination	X	X	X	X		Follow NCCN cSCC 2018 guidelines for FU: include a history and physical exam that includes a complete skin and lymph node exam every 12 weeks until Year 2, every 6 months until Year 5.
Weight and Vital Signs	X	----If Clinically Indicated------				Vital signs to be collected include temperature, resting pulse, resting respiratory rate, blood pressure.
Urine or Serum β-hCG Pregnancy Test (POCBP only)	X					Pregnancy testing should be performed approximately 120 days after last dose of pembrolizumab.
CBC With Differential	X	----If Clinically Indicated------				
Chemistry Panel	X	----If Clinically Indicated------				
Coagulation Tests (PT/INR and aPTT/PTT)	X	----If Clinically Indicated------				PTT may be performed if the local laboratory is unable to perform aPTT.

Trial Period	**Follow-up Phase**					**Notes:** A participant may discontinue from study treatment for any reason other than a new high-risk primary cSCC or disease recurrence but will remain in the study for Study Adjuvant follow-up for disease recurrence (Section 8.11.3.3) unless consent is withdrawn. Participants that discontinue study treatment due to a new high-risk primary cSCC or disease recurrence will have Safety FU then proceed directly to Survival FU or cross-over/retreatment if eligible (Section 1.3.3). Participants that complete adjuvant treatment or discontinue study treatment for reasons other than a new high-risk primary cSCC or disease recurrence will enter Safety FU then proceed to Adjuvant FU. *For participants that discontinue before Year 1. ‡ More frequent FU is permitted based on risk and per treating physician discretion. When clinically indicated additional diagnostic evaluation, including imaging, can be performed by treating physician discretion.
Visit Number/Title	**Safety FU**	**Study Adjuvant FU‡**			**Survival FU**	
Treatment Cycle/Day		**Up to Year 1***	**Years 1-2**	**Years 3-5**		
Scheduling Window Days (unless noted)	**30 days from last dose ±14**	**Q12W ±7**	**Q12W ±7**	**Q6M ±14**	**Q12W ±14**	
Thyroid Function (TSH)	X	----If Clinically Indicated------				TSH; in case of elevated TSH add free T3 and free T4.
ECOG Performance Status	X	X	X	X		
AE/SAE Review	X	--Continuous Reporting--				All AEs occurring up until 30 days following EOT and SAEs occurring up until 90 days following EOT or 30 days if the participant initiates new anticancer therapy, whichever is earlier should be reported. Treatment-related toxicity may be collected for up to 5 years.

AE=adverse event; aPTT=activated partial thromboplastin time; β-hCG=β-human chorionic gonadotropin; C=cycle; cSCC=cutaneous squamous cell carcinoma; D=day; ECOG=Eastern Cooperative Oncology Group; eCRF=electronic case report form; EORTC=European Organisation for Research and Treatment of Cancer; EOT=End of Treatment; EQ-5D=EuroQol-5 Dimensions; FT4=free thyroxine; FU=follow-up; iCRO = Imaging Contract Research Organization; INR=international normalized ratio; NCCN=National Comprehensive Cancer Network; POCBP=participants of childbearing potential; PRO=patient-reported outcome; PT=prothrombin time; PTT=partial thromboplastin time; Q6M=every 6 months; Q12M=every 12 months; Q12W=every 12 weeks; Q8W=every 8 weeks; QLQ-C30=Quality of Life Questionnaire-C30; RFS = Recurrence-free Survival; SAE=serious adverse event; SoC=standard of care; SOP=standard operating procedure; T3=triiodothyronine; TSH=thyroid-stimulating hormone.

1.3.3 Cross-over / Retreatment

Only applicable for participants that have confirmation of disease recurrence and qualify for cross-over to or retreatment with up to 18 cycles of pembrolizumab (Section 8.1.8.1.2).

For participants eligible for cross-over only, tests performed at the Adjuvant Treatment Phase EOT/Safety FU visits do not need to be repeated at screening if performed within the screening window.

Trial Period	**Screening**	**Treatment Cycle**						**EOT**	**Safety FU**	**Survival FU**	**Notes:** Cycles will be repeated up to 18 infusions or until protocol-specific criteria to discontinue treatment is met. Participants that complete cross-over/retreatment or discontinue study treatment for any reason will have Safety FU then proceed directly to Survival FU.
Treatment Cycle/Title		**1**		**2**		**3**	**4 to 18**	**Discon**			
Scheduled Window (days)	**-28 to -1**	**+3**	**±3**	**±3**	**±3**	**±3**	**±3**	**At time of treatment discontinuatio**	**30 days from last dose ±14 days**	**Q12W ±14**	
Day of visit		**D1**	**D22**	**D1**	**D22**	**D1**	**D1**				
Administrative Procedures											
Informed Consent	X										Separate consent required for cross-over/retreatment Additional consent is required at disease progression.
Concomitant Medication Review	X	X	X	X	X	X	X	X	X		Concomitant medications – Enter new medications started since Adjuvant treatment EOT visit through the cross-over/retreatment Safety FU.
Post-study Anticancer Therapy Status	X	X	X	X	X	X	X	X	X	X	Enter anticancer therapy started since Adjuvant treatment EOT visit through cross-over/retreatment survival FU. By telephone contact in Survival FU.
Vital Status		←					→			X	Survival FU begins after end of cross-over/retreatment for whatever reason. In addition, upon Sponsor request, participants may be contacted for survival status at any time during the course of the study.

Trial Period	**Screening**	**Treatment Cycle**						**EOT**	**Safety FU**	**Survival FU**	**Notes:** Cycles will be repeated up to 18 infusions or until protocol-specific criteria to discontinue treatment is met. Participants that complete cross-over/retreatment or discontinue study treatment for any reason will have Safety FU then proceed directly to Survival FU.
Treatment Cycle/Title		**1**		**2**		**3**	**4 to 18**	**Discon**			
Scheduled Window (days)	**-28 to -1**	**+3**	**±3**	**±3**	**±3**	**±3**	**±3**	**At time of treatment discontinuatio**	**30 days from last dose ±14 days**	**Q12W ±14**	
Day of visit		**D1**	**D22**	**D1**	**D22**	**D1**	**D1**				
Pembrolizumab Administration		X		X		X	X				For Cross-over (participants originally assigned to placebo) - Treatment 1, Cycle 1 must be given within 12 weeks after confirmed disease recurrence. Pembrolizumab to be administered on D1 of each cycle after all procedures/ assessments have been completed.
Efficacy Procedures											
Tumor Imaging and RECIST 1.1/iRECIST assessment	X					X	X‡ Q12W	X*			Baseline imaging/digital photography should be performed within 28 days before starting study treatment with pembrolizumab. If the recurrence scan falls outside of this window, a new scan is required at baseline. The first on-treatment imaging assessment should be performed at 12 weeks (±7 days) from the date of the first dose of pembrolizumab in cross-over/retreatment. ‡Subsequent tumor imaging should be performed every 12 weeks (84 days ±7 days) until Year 2, or more frequently if clinically indicated. The visit window for imaging/photography is ±7 days. * In participants who discontinue study therapy, imaging/digital photography should be performed at the time of treatment discontinuation (ie, date of discontinuation ±4 weeks). If previous scan/digital photograph was obtained within 4 weeks prior to the date of discontinuation, then a scan/digital photograph at treatment discontinuation does not need to be performed.
Digital Photography: Cutaneous Lesions	X					X	X‡ Q12W	X*			

Trial Period	**Screening**	**Treatment Cycle**						**EOT**	**Safety FU**	**Survival FU**	**Notes:** Cycles will be repeated up to 18 infusions or until protocol-specific criteria to discontinue treatment is met. Participants that complete cross-over/retreatment or discontinue study treatment for any reason will have Safety FU then proceed directly to Survival FU.
Treatment Cycle/Title		**1**		**2**		**3**	**4 to 18**	**Discon**			
Scheduled Window (days)	**-28 to -1**	**+3**	**±3**	**±3**	**±3**	**±3**	**±3**	**At time of treatment discontinuatio**	**30 days from last dose ±14 days**	**Q12W ±14**	
Day of visit		**D1**	**D22**	**D1**	**D22**	**D1**	**D1**				
EORTC QLQ-C30		X		X		X	X‡ Q12W	X*	X		PROs are to be administered by trained site personnel on D1 of C1, C2, C3 and then every 2 cycles (ie, every 12 weeks)‡ until Year 2. It is strongly recommended that PROs are completed by participants prior to all procedures/assessments, and in the following order: QLQ-C30, Skindex-16, and then EQ-5D EORTC. If the participant does not complete the PROs for any reason, the Miss Mode form must be completed to capture the reason the assessment was not performed. *In participants who discontinue study therapy, PROs should be administered at the time of treatment discontinuation (ie, date of discontinuation ± 4 weeks). If previous PROs were obtained within 4 weeks prior to the date of discontinuation, then administration of PROs at treatment discontinuation does not need to be performed.
Skindex-16		X		X		X	X‡ Q12W	X*	X		
EuroQol EQ-5D		X		X		X	X‡ Q12W	X*	X		
Safety Procedures											
Full Physical Examination	X							X			To be performed by the investigator or medically qualified designee.
Directed Physical Examination		X	X	X	X	X	X		X		
Weight and Vital Signs	X	X	X	X	X	X	X	X	X		Vital signs to be collected include: temperature, resting pulse, resting respiratory rate, blood pressure.

Trial Period	**Screening**	**Treatment Cycle**						**EOT**	**Safety FU**	**Survival FU**	**Notes:** Cycles will be repeated up to 18 infusions or until protocol-specific criteria to discontinue treatment is met. Participants that complete cross-over/retreatment or discontinue study treatment for any reason will have Safety FU then proceed directly to Survival FU.
Treatment Cycle/Title		**1**		**2**		**3**	**4 to 18**	**Discon**			
Scheduled Window (days)	**-28 to -1**	**+3**	**±3**	**±3**	**±3**	**±3**	**±3**	**At time of treatment discontinuatio**	**30 days from last dose ±14 days**	**Q12W ±14**	
Day of visit		**D1**	**D22**	**D1**	**D22**	**D1**	**D1**				
Urine or Serum β-hCG Pregnancy Test (POCBP only) – as per local SOP	X	X		X		X	X		X		The protocol requires pregnancy testing within 72 hours prior to administration of each dose of pembrolizumab. Refer to Appendix 7 for country-specific requirements for Germany, Ireland, Italy, Norway, and the UK.
Coagulation Tests (PT/INR and aPTT/PTT)	X	----If Clinically Indicated----									Screening - within 10 days prior to the start of study treatment. Samples to be taken prior to pembrolizumab administration. Any participant receiving anticoagulant therapy should have coagulation tests monitored closely throughout the study. PTT may be performed if the local laboratory is unable to perform aPTT.
CBC With Differential	X	X[§]	X	X	X	X	X	X	X		Screening - within 10 days prior to the start of study treatment. Samples to be taken prior to study drug administration. After Cycle 1, samples can be collected up to 72 hours prior to the scheduled time point. [§] Optional - CBC and Chemistry labs are not required at C1D1 if they were collected during screening and within 10 days of first dose. * In case of elevated TSH add free T3 and free T4. [‡] To be repeated every 2 cycles.
Chemistry Panel	X	X[§]	X	X	X	X	X	X	X		
Urinalysis	X										
Thyroid Function (TSH)*, T3, FT4	X			X			X‡	X	X		
ECOG Performance Status	X	X	X	X	X	X	X	X	X		Screening - ECOG is to be performed within 10 days prior to the first dose of pembrolizumab. Must be performed prior to each dose of pembrolizumab where ECOG is collected.

Trial Period	**Screening**	**Treatment Cycle**						**EOT**	**Safety FU**	**Survival FU**	**Notes:** Cycles will be repeated up to 18 infusions or until protocol-specific criteria to discontinue treatment is met. Participants that complete cross-over/retreatment or discontinue study treatment for any reason will have Safety FU then proceed directly to Survival FU.
Treatment Cycle/Title		**1**		**2**		**3**	**4 to 18**	**Discon**			
Scheduled Window (days)	**-28 to -1**	**+3**	**±3**	**±3**	**±3**	**±3**	**±3**	**At time of treatment discontinuatio**	**30 days from last dose ±14 days**	**Q12W ±14**	
Day of visit		**D1**	**D22**	**D1**	**D22**	**D1**	**D1**				
AE/SAE Review	X	----------Continuous Reporting----------									Record all AEs and ECIs occurring within 30 days after last dose of study treatment and SAEs for 90 days after the EOT or 30 days after EOT if the participant initiates new anticancer therapy (whichever is earlier). Report treatment-related SAEs regardless of when they occur.

AE=adverse event; aPTT=activated partial thromboplastin time; β-hCG=β-human chorionic gonadotropin; C=cycle; CBC=complete blood count; D=day; ECI=event of clinical interest; ECOG=Eastern Cooperative Oncology Group; EORTC=European Organisation for Research and Treatment of Cancer; EOT=End of Treatment; EQ-5D=EuroQol-5 Dimensions; FT4=free thyroxine; FU=follow-up; INR=international normalized ratio; POCBP=participants of childbearing potential; PRO=patient-reported outcome; PT=prothrombin time; PTT=partial thromboplastin time; Q12W=every 12 weeks; QLQ-C30=Quality of Life Questionnaire-C30; SAE=serious adverse event; SOP=standard operating procedure; T3=triiodothyronine; TSH=thyroid-stimulating hormone; UK=United Kingdom.

2 INTRODUCTION

This study will assess the safety and efficacy of pembrolizumab adjuvant therapy in participants with resectable high-risk LA cSCC following surgical resection with curative intent and RT.

2.1 Study Rationale

Pembrolizumab has demonstrated durable clinical activity in participants with R/M HNSCC and is currently approved in the US and in several global locations for the treatment of R/M HNSCC with disease progression on or after platinum-containing chemotherapy. Approximately 80% of cSCC involves the head and neck region. Although, HNSCC and cSCC are biologically different cancers, they clinically behave very similarly. Therefore, it is proposed that treatment with pembrolizumab will also work for cSCC.

Cutaneous squamous cell carcinoma is the second most frequent skin cancer. Most patients with cSCC are successfully treated with surgical treatment of the primary site. However, a minority of patients are at risk for local recurrence and regional metastasis [Burton, K. A., et al 2016]. With the incidence of cSCC continuing to rise, and because R/M cSCC has a potentially devastating impact on patients, the development of adjuvant treatment strategies to eradicate early micrometastatic disease following SoC (detailed in Section 2.2.1) and thus decrease the rate of recurrence without compromising the QoL [Kang, S. Y. 2016] for patients identified as at high-risk of recurrence and/or metastasis would have an important clinical significance. We propose to evaluate the efficacy and safety of pembrolizumab as adjuvant therapy in a randomized, double-blind, placebo-controlled, Phase 3 study for resectable high-risk LA cSCC.

2.2 Background

Pembrolizumab is a potent humanized IgG4 mAb with high specificity of binding to the PD-1 receptor, thus inhibiting its interaction with PD-L1 and PD-L2. 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 several indications. For more details on specific indications refer to the IB.

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 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 CTLA-4 that has been shown to negatively regulate antigen receptor signaling on engagement of its ligands (PD-L1 and/or PD-L2) [Greenwald, R. J., et al 2005] [Okazaki, T., et al 2001].

The structure of murine PD-1 has been resolved [Zhang, X., et al 2004]. PD-1 and its family members are type I transmembrane glycoproteins containing an IgV–type domain responsible for ligand binding and a cytoplasmic tail responsible for the binding of signaling molecules. The cytoplasmic tail of PD-1 contains 2 tyrosine-based signaling motifs, an immunoreceptor tyrosine-based inhibition motif, and an immunoreceptor tyrosine-based switch motif. After T-cell stimulation, PD-1 recruits the tyrosine phosphatases, SHP-1 and SHP-2, to the immunoreceptor tyrosine-based switch motif within its cytoplasmic tail, leading to the dephosphorylation of effector molecules such as CD3ζ, PKCθ, and ZAP70, which are involved in the CD3 T-cell signaling cascade [Okazaki, T., et al 2001] [Chemnitz, J. M., et al 2004] [Sheppard, K-A, et al 2004] [Riley, J. L. 2009]. The mechanism by which PD-1 down-modulates T-cell responses is similar to, but distinct from, that of CTLA-4, because both molecules regulate an overlapping set of signaling proteins [Parry, R. V., et al 2005] [Francisco, L. M., et al 2010]. As a consequence, the PD-1/PD-L1 pathway is an attractive target for therapeutic intervention in patients with solid tumors.

The Association Between Ultraviolet Light and cSCC

Exposure to solar ionizing UV rays is the major risk factor for cSCC. The head and neck region is one of the most common anatomical regions for cSCCs to develop because of its daily exposure to solar ionizing UV rays. Development of cSCC involves multi-step carcinogenic events that accumulate over time with UV exposure [World Health Organization 1992] [International Agency for Research on Cancer 2007]. A pattern of UV-B induced mutations (typically cytosine [C]>thymine [T] and/or CC>TT transitions) occur commonly within the p53 gene and are thought to be an early event in the carcinogenic process [Lawrence, M. S., et al 2013] [Davoli, T., et al 2013] [Boukamp, P. 2005]. Ultraviolet-A rays that directly induce DNA damage by inducing double-strand DNA breaks and generating genomic instability occur throughout the initiation and development of cSCC. Therefore, while UV-B dependent mutational inactivation of p53 may be an early carcinogenic event resulting in loss of protection of chromosomal integrity, with continued sun exposure, repetitive UV-A exposure propagates genomic and karyotypic instability by inducing DNA damage that is not efficiently repaired. The accumulation of these karyotypic and chromosomal aberrations ultimately results in a cumulative high mutational burden within cSCC.

The Role of Human Papillomavirus Infection and cSCC

HPV, which replicate exclusively in keratinocytes [Cardoso, J. C. 2011] [Aldabagh, B., et al 2013] [Doorbar, J. 2005], have been implicated in the pathogenesis of cSCC by facilitating the accumulation of UV mediated DNA damage. There is evidence of a dose-response relationship between HPV and cSCC; the risk of development of cSCC increases with increasing numbers of infection with HPV genus β-species [Farzan, S. F., et al 2013]. Although there seems to be consensus for a role for β-HPVs in the initiation of cSCC, the role in the maintenance and propagation of the disease is less clear as a greater number of HPV types are present in premalignant lesions, and the number and frequency of HPV types decrease in advanced/metastatic lesions [Hampras, S. S., et al 2016] [Toll, A., et al 2014] [Aldabagh, B., et al 2013]. Although there is no consensus regarding the specific HPV species involved in cSCC, HPV local infection can vary depending on anatomic location; HPV DNA from topical skin infection was higher from sun exposed areas compared to non-sun exposed areas [Aldabagh, B., et al 2013]. Ultraviolet light and HPV can interact to alter the body's local immunity at sun exposed or sunburned sites [Halprin, K. M., et al 1981] [Cestari, T. F., et al 1995]. Although the immune response to HPV infection is both antibody- and cell-mediated, a functional T-cell response is the major mechanism of immunity against HPV [Aldabagh, B., et al 2013]. Thus, UV light exposure is hypothesized to promote localized HPV infection through localized cutaneous immunosuppression.

In other malignancies, high mutation burden has been associated with clinical benefit from pembrolizumab therapy [Le, D. T., et al 2017]. Highly mutated tumors are more likely to express immunogenic tumor neoantigens that attract effector T-cells, which can be unleashed by blockade of the PD-1 immune checkpoint. Furthermore, immunosuppression, usually associated with organ transplantation, elevates the risk of developing cSCC by over 100-fold [Pickering, C. R., et al 2014], suggesting the important of the adaptive cellular immune system in the surveillance and eradication of cSCC.

Evidence for Efficacy of PD-l Immune Checkpoint Inhibitors in cSCC

Initial evidence of a role for checkpoint inhibitor therapy in cSCC comes from early studies of pembrolizumab that included participants with MCC.

Similar to cSCC, the rare neuroendocrine MCC is an aggressive skin cancer linked to UV light exposure, resulting in distinctive UV associated mutations with the distinctive signature (C>T, CC>TT) similar to cSCC, associated with increased genomic instability, and MCPyV infection [Cassler, N. M., et al 2016]. Approximately 80% of MCC can be directly linked to the clonal integration of the MCPyV into the host genome. While ubiquitous in the general population from early childhood, and usually clinically asymptomatic [Chang, Y. 2012], in the elderly and immunosuppressed, where mechanisms of immune surveillance are decreased, MCPyV disease progression has been correlated with increasing detectable viremia [Chang, Y. 2012] [Pastrana, D. V., et al 2009] [Tolstov, Y. L., et al 2009], [Touze, A., et al 2011].

In a Phase 2, multicenter uncontrolled study, treatment naïve participants with advanced MCC not amenable to curative therapy, received pembrolizumab 2 mg/kg of body weight

every 3 weeks (Q3W) for up to 2 years. Of the 26 evaluable participants with Stage IIIB or IV MCC, 14 had a confirmed response (4 with CR and 10 with PR) for an ORR of 56% (95% CI: 35 to 76). With a median follow-up of 33 weeks (range, 7 to 53 weeks), the DOR ranged from at least 2.2 months to at least 9.7 months. Clinically relevant responses were reported in both MCPyV positive and negative participants with response rates of 62% and 44%, respectively. PD-L1 expression (defined as at least 1% staining by immunohistochemistry [IHC] on tumor cells) was more frequent in virus positive tumors than virus negative tumors (71% versus 25%, p=0.049), but as not required for clinical activity of pembrolizumab [Nghiem, P. T., et al 2016].

Clinical Efficacy of Pembrolizumab in HNSCC

Evidence of both clinical efficacy and safety of pembrolizumab has been reported in studies evaluating pembrolizumab in HNSCC, as detailed in the IB.

In KN012, a Phase 1b global, multi-cohort study, participants with incurable R/M HNSCC, whose tumor tissues contained at least 1% of tumor cells or stroma that were PD-L1 positive by IHC, were treated with IV pembrolizumab 10 mg/kg Q2W. Of 60 participants enrolled, approximately 38% (23/60) were HPV-positive. Approximately 63% (38/60) of participants had been treated with both platinum and cetuximab based therapies prior to enrolling on study, and 70% (42/60) had at least 2 or more prior lines of treatment for R/M disease prior to study entry. In this heavily pretreated population, the proportion of participants with an overall response by central imaging review was 18% (8/45 evaluable for response; 95% CI: 8% to 32%) with similar clinical efficacy in HPV-positive or negative disease (25% ORR, range 7-52, and 14% ORR, range 4-32, respectively). The median DOR was 53 weeks (95% CI: 13 weeks to not reached) and median PFS and OS were 2 (95% CI: 2 to 4 months) and 13 (95% CI: 5 months to not reached) months, respectively [Seiwert, T. Y., et al 2016].

In the KN012 expansion cohort, 132 participants with incurably R/M HNSCC, irrespective of PD-L1 or HPV status, received a fixed dose of pembrolizumab at 200 mg Q3W. PD-L1 positive disease was reported in 125 participants, 28 (21%) were HPV positive, and approximately 57% of participants had been treated with at least 2 or more lines of therapy for R/M HNSCC. After a median follow-up duration of 9 months, ORR was 18% (95% CI: 12 % to 26%) by BICR, with a median time to response of 2 months (range, 2 to 11 months), and a median DOR that was not reached (range, >2 to >11 months). PFS and OS were 2 months (95% CI: 2.0 to 2.2 months) and 8 months (95% CI: 6 to 10 months), respectively. For participants whose tumors expressed at least 1% of PD-L1 positivity, ORR was further confirmed at 22%. Irrespective of PD-L1 status, response rates were 32% and 14% in participants that were HPV-positive and HPV-negative, respectively [Chow, L. Q., et al 2016]. Thus, similar to MCC, evidence of broad clinical activity was seen regardless of viral etiology. Of note, the consistent ORR of 14% observed in participants with HPV-negative disease in both KN012 HNSCC cohorts, suggests that patients with non–HPV-associated R/M cSCC may also benefit from pembrolizumab. The safety profile of pembrolizumab remained consistent utilizing the fixed dose of 200 mg Q3W [Chow, L. Q., et al 2016].

Cutaneous Squamous Cell Carcinoma

Cutaneous squamous cell carcinoma is the second most frequent non-melanoma skin cancer, representing approximately 20% of all non-melanoma skin cancers and 20% of all skin cancer deaths. cSCC is diagnosed at a rate of 100-150 per 100,000 persons in the United States [Vandergriff, T., et al 2010] and is expected to increase as much as 2% to 4% per year [Burton, K. A., et al 2016]. The age-adjusted incidence rates of cSCC in Europe is generally lower, with Northern European countries, such as Norway, Finland, and Denmark, reporting rates 10 per 100,000 person-years, and the UK, Ireland and Germany reporting 20-30 cSCC cases per 100,000 person-years [Lomas, A., et al 2012] [Vandergriff, T., et al 2010] [Eisemann, N., et al 2014]. It is estimated that over 3.3 million persons with non-melanoma skin cancers or keratinocyte carcinoma were treated in the US in 2012, with ~38% of those cases being invasive cSCCs [Rogers, H. W., et al 2015]. Due to its ability to metastasize to distant regions, when not cured by local therapy, cSCC ultimately results in death with mortality rates that exceed 70% [Burton, K. A., et al 2016]. The rate of local recurrence and regional metastasis may be as high as 20% in tertiary care centers [Moore, B. A., et al 2005]. Patients with regional metastasis have 3-year disease-free survival (DFS) rate of 56%. While 5-year OS ranges from 25% to 35%, 10-year OS appears to be less than 20% [Johnson, T. M., et al 1992] [Kraus, D. H., et al 1998] [Kwa, R. E., et al 1992]. cSCC carries a low but significant risk of metastasis and death. A US study of 974 cSCC patients at Brigham and Women's Hospital reported a risk of nodal metastasis of 3.4% [Karia, P. S., et al 2014], and approximately 3,000 deaths are attributed to LA/high-risk cSCC annually [Jennings, L. 2010] [Brantsch, K. D., et al 2008].

Locally advanced high-risk cSCC is defined as a cSCC that has high-risk features, including regional nodal disease, and has no distant metastasis. High-risk features of cSCC defined per NCCN eSCC guidelines [National Comprehensive Cancer Network 2017] and include depth of invasion, histologic features, anatomical location, horizontal size, perineural involvement, tumor recurrence, incomplete excision, multiple tumors, patient characteristics, and genetic/molecular markers [Burton, K. A., et al 2016] [National Comprehensive Cancer Network 2017]. Clinically, the initial lesions of a cSCC tumor can be present as a painless plaque-like or verrucous tumor that can ultimately progress to being large, necrotic, and infected. Tumors can also present with paresthesia or lymphadenopathy depending on the location involved.

The majority of patients with cSCC are successfully treated with surgical treatment of the primary site. Some patients are at risk for local recurrence and regional metastasis and these patients have significantly worse outcomes compared to those cured by initial surgery.

Current Therapies for Resectable High-Risk LA cSCC

The current SoC for resectable high-risk LA cSCC, as recommended by NCCN cSCC 2018 guidelines (evidence category 2A - low-level evidence) [National Comprehensive Cancer Network 2017], consists of surgical resection of the primary tumor and the involved lymph nodes, followed by adjuvant RT based on the presence of involved lymph nodes and/or high-risk features for recurrent/metastatic disease [Porceddu, S. V., et al 2015] [Porceddu, S. V. 2015a]. While the majority of patients are cured with local surgical excision, approximately

20% of patients develop local recurrence and regional metastasis [Moore, B. A., et al 2005]. The majority of recurrences tend to occur within 2 years of the initial primary diagnosis [Porceddu, S. V. 2015a]. The presence of primary disease with high-risk features increases the risk for regional nodal metastatic disease and predicts for inferior survival.

Results from the first Phase 3, randomized study (Trans Tasman Radiation Oncology Group 05.01), comparing adjuvant RT (60 to 70 Gy) to concurrent chemoradiotherapy in 310 patients with high-risk cSCC, showed freedom from locoregional relapse was high following surgery and post-operative RT (83% [95% CI: 77 to 90%]) and the addition of concurrent chemotherapy (carboplatin) did not improve freedom from locoregional relapse. The 5-year DFS and OS was similar between the treatment arms (67% [95% CI: 60% to 76%] and 76% [95% CI: 69% to 84%], respectively, for RT alone; 73% [95% CI: 66% to 81%] and 79% [95 % CI: 72% to 86%], respectively, for RT plus carboplatin) [Porceddu, S. V., et al 2017].

Similar to MCC, where 2 distinct causes of carcinogenesis have been identified, UV light and viral infection, cSCC has also been long considered to be an immunogenic cancer. UV light associated with a high mutation burden, karyotypic and chromosomal instability, and increased neoantigens, as well as chronic HPV infection with T-cell dysfunction, make cSCC a likely candidate to benefit from checkpoint inhibitor therapy. In malignancies with dichotomous etiologies such as MCC and HNSCC, pembrolizumab therapy has provided similar benefit for each dichotomous subpopulation and has proven to be an important clinical treatment advance for diseases with limited treatment options. Therefore, we propose to test the clinical activity of pembrolizumab as adjuvant therapy in resectable high-risk LA cSCC following SoC surgery and RT.

Recent data on cemiplimab (REGN2810), a human anti-PD-1 mAb, provides evidence that PD 1 inhibitors, could provide a well-tolerated, effective, and durable response in patients with LA or metastatic cSCC. In a Phase 1 open-labeled study (NCT02383212), populations of patients with unresectable LA or metastatic cSCC were treated for up to 48 weeks with cemiplimab (3 mg/kg Q2W). Final results from 26 patients were represented by Owonikoko et al [Owonikoko, T. K., et al 2018] at the ASCO 2018. The ORR, based on RECIST 1.1 by independent central review, for the LA population (n=16) was 43.8% (95% CI: 19.8 to 70.1 [CR, n=0; PR, n=7]) and the durable DCR was 56.3% (11/16, 95% CI: 29.9 to 80.2). In the preliminary results, 81% (17/21) of evaluated tumors were positive (≥1%) for tumor expression of PD-L1 by IHC and there was no apparent association between PD L1 IHC results and objective response [Papadopoulos, K., et al 2017].

2.2.2 Preclinical and Clinical Studies

Details of preclinical and clinical studies are provided in the IB. Two clinical studies (KN012 and KN055) formed the basis of approval for pembrolizumab in the treatment of R/M HNSCC.

Clinical studies with pembrolizumab have demonstrated efficacy in participants with advanced melanoma, non–small cell lung cancer, gastric cancer, HNC, bladder cancer, Hodgkin’s lymphoma, and MSI high cancers.

2.2.3 Ongoing Clinical Studies

There is an expansive ongoing research program of clinical studies evaluating pembrolizumab in patients with a number of hematological and solid malignancies, including HNC. For study details please refer to the IB.

KEYNOTE-629 (KN629)

KN629 is an ongoing Phase 2, open-label, single arm study of pembrolizumab in participants with R/M cSCC or LA unresectable cSCC. Approximately 150 participants with cSCC not amenable to surgery and/or radiation and/or systemic therapies are planned to be enrolled to examine the efficacy and safety of pembrolizumab 200 mg Q3W for up to 35 cycles. The primary endpoint of the study is the ORR per RECIST 1.1 as assessed by BICR; secondary endpoints include DOR, DCR, PFS per RECIST 1.1 as assessed by BICR, OS and safety. Enrollment has started and is ongoing.

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.

In this clinical study, participants who have received SoC become eligible for the study and will be randomized to receive either pembrolizumab or placebo control. The benefit of pembrolizumab as adjuvant therapy in this specific patient population is unknown.

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 HYPOTHESES, OBJECTIVES, AND ENDPOINTS

Hypotheses are aligned with objectives in the Objectives and Endpoints table.

In male/female participants aged 18 years or older with resectable high-risk LA cSCC after surgery and RT:

Primary Objective	**Primary Endpoint**
Objective: To compare the recurrence-free survival (RFS), as assessed by the investigator and confirmed by biopsy, in individuals who receive pembrolizumab with individuals who receive placebo as adjuvant therapy. Hypothesis (H1): Pembrolizumab as adjuvant therapy is superior to placebo with respect to RFS as assessed by the investigator	-RFS: defined as the time from the date of randomization to the date of first record of the following events: -Local or regional recurrence of the index lesion -Distant metastasis -Death due to any cause Note: A new low risk primary cSCC is not considered as a RFS event
Secondary Objectives	**Secondary Endpoints**
Objective: To compare overall survival (OS) in individuals who receive pembrolizumab with individuals who receive placebo as adjuvant therapy. Hypothesis (H2): Pembrolizumab as adjuvant therapy is superior to placebo with respect to OS.	OS: defined as time from randomization to death due to any cause
To compare mean change from baseline in health-related quality of life (HRQoL) scores from the European Organisation for Research and Treatment of Cancer (EORTC) QoL Questionnaire (QLQ) C30, in individuals who receive pembrolizumab with individuals who receive placebo as adjuvant therapy.	-EORTC QLQ-C30 global health status/QoL scales -EORTC QLQ-C30 physical functioning scale
Objective: To determine the safety and tolerability of pembrolizumab as adjuvant therapy.	-Adverse events (AEs) -Study drug discontinuations due to AEs

Tertiary/Exploratory Objectives	Tertiary/Exploratory Endpoints
CCI [redacted]	

The study is considered to have met its primary objective if pembrolizumab is superior to placebo as adjuvant therapy with respect to RFS CCI [redacted].

4 STUDY DESIGN

4.1 Overall Design

NOTE: This study will be discontinued based on the results of the prespecified IA of efficacy and safety data (data cutoff 28-JUN-2024) reviewed by eDMC on 21-AUG-2024. At this IA, pembrolizumab did not cross the boundary for statistical significance in RFS by investigator assessment compared to placebo. Although not formally tested based on the prespecified multiplicity strategy, the OS point estimate did not favor pembrolizumab versus placebo. The eDMC recommended that the study should be stopped for futility as the benefit/risk profile did not support continuing the study. The EOC reviewed the data and accepted the eDMC's recommendation. Based on these data and the recommendation of the eDMC, the study was unblinded on 22-AUG-2024. The prespecified final efficacy analysis of the study described in the SAP will not be performed. Efficacy and safety analyses will be performed at the end of the study; there will be no further planned analyses for ePRO endpoints.

In alignment with the study-specific investigator letter dated 29-AUG-2024, all participants should discontinue study treatment (pembrolizumab/placebo). On a case-by-case basis, the investigators may contact the Sponsor for the consideration of continuing pembrolizumab treatment if they assess a participant is deriving clinical benefit. All ongoing participants should undergo study procedures as specified in this amendment (Amendment 10).

As of Amendment 10, ePRO assessments are no longer required. All ongoing participants should continue tumor imaging and investigator assessment of the tumor scans per protocol; however, scans no longer need to be submitted to the iCRO and digital photography of cutaneous lesions is not required.

On study discontinuation, all ongoing participants will be discontinued and may be enrolled in an extension study, if available. In the extension study, participants who experience disease recurrence per SOC clinical assessment may be considered eligible for cross-over/retreatment upon consultation with the Sponsor.

Original protocol text included below in this section has been retained for reference.

This is a Phase 3, randomized, double-blind, placebo-controlled, multisite study to evaluate the efficacy and safety of pembrolizumab as adjuvant therapy in participants with high-risk LA cSCC. The study will be conducted in conformance with GCP.

Participants with high-risk LA cSCC (as defined in the inclusion criteria) that have undergone surgery with curative intent and adjuvant RT (last dose of RT ≥4 weeks and ≤16 weeks from randomization) may be screened and randomized for this study. Participants must be tumor-free as assessed by the investigator via radiological imaging of the head, neck, chest, abdomen, pelvis, and extremities (if disease involvement). All participants must provide a tissue specimen from either the resected tumor or archival FFPE tumor biopsy assessed as adequate for PD-L1 determination by IHC by a central laboratory.

Approximately 430 participants will be randomized in a 1:1 ratio to receive either pembrolizumab 400 mg Q6W (up to 9 cycles) or placebo (see Figure 1). Study

randomization will start at a minimum of 4 weeks and maximum of 16 weeks after the last dose of RT and when participants have recovered adequately from the morbidity and/or complications from RT. Participants will be stratified by CCI [redacted] (see Section 6.3.2).

Participants will have baseline imaging performed at screening and subsequently every 12 weeks (± 7 days) until Year 2, then every 6 months (± 14 days) until the end of Year 5 from the date of treatment allocation, or more frequently if clinically indicated, until a documented new high-risk primary cSCC tumor occurs or disease recurrence, death, pregnancy, or the end of the study, whichever occurs first. The primary efficacy endpoint will be evaluated by RFS as assessed by the investigator and confirmed by biopsy. Secondary objectives include evaluation of OS of the study participants, HRQoL, and safety.

In the Adjuvant Treatment Phase, participants will continue study treatment until: a new high-risk primary cSCC tumor occurs or biopsy proven disease recurrence, the start of any new anticancer treatment, unacceptable AE(s) toxicity, intercurrent illness that prevents further administration of treatment, investigator's decision to discontinue treatment, participant withdrawal of consent, pregnancy of the participant, administrative reasons requiring cessation of treatment, or the participant completes 9 administrations of study drug (approximately 1 year of treatment). Participants discontinued from treatment will continue to be monitored in the study except when the participant withdraws consent resulting in discontinuation from the study. Participants who withdraw consent will be treated thereafter at the discretion of the physician.

Upon first biopsy proven disease recurrence (Sections 8.2.1.5 and 8.2.1.6), and with Sponsor approval, study treatment will be unblinded (Section 8.1.10). Tissue biopsy is required for the confirmation of disease recurrence; only if a biopsy cannot be performed due to feasibility, such as location of recurrence (ie, bone lesion), and upon Sponsor consultation, can radiographic imaging be used to confirm disease recurrence.

Following documented disease recurrence, if the participant is not eligible for surgical resection, the participant may cross-over to or receive retreatment with open-label pembrolizumab 400 mg IV Q6W for up to 18 cycles (approximately 2 years). Participants assigned to placebo who experience biopsy proven disease recurrence before the end of Year 5, and who wish to continue study treatment after discussion with the investigator, must start cross-over treatment within 12 weeks of biopsy proven recurrence; participants assigned to pembrolizumab are eligible for retreatment if biopsy proven disease recurrence occurs before the end of Year 5 and more than 6 months after completing 9 cycles (approximately 1 year) of study adjuvant therapy, if clinically indicated and after approval from the Sponsor. Section 8.1.8.1.2 provides cross-over/retreatment criteria and guidance. Participants in the Cross-over/Retreatment Phase will continue study cross-over/retreatment until: documented disease progression as assessed by the investigator per response evaluation criteria in solid tumors (RECIST 1.1)/ modified RECIST 1.1 for immune-based therapeutics (iRECIST), the start of a new systemic anticancer treatment, unacceptable AE(s) toxicity, intercurrent illness that prevents further administration of treatment, investigator's decision to discontinue treatment, participant withdrawal of consent, pregnancy of the participant, noncompliance

with study treatment or procedure requirements, administrative reasons requiring cessation of treatment, or the participant completes 18 administrations of study drug (approximately 2 years of treatment), or cessation due to administrative reasons. Participants that discontinue study treatment in the Cross-over/Retreatment Phase will have Safety FU and enter Survival Follow-up and be treated thereafter at the discretion of the physician.

Participants will be monitored carefully for the development of AEs and for clinical and/or radiographic evidence of disease recurrence (or progression for participants receiving cross-over/retreatment) as assessed by the investigator and confirmed by biopsy. AEs will be monitored throughout the study and graded in severity according to the guidelines outlined in the NCI CTCAE Version 4.0.

A safety follow-up visit will be conducted at 30 days (± 14 days) after the last dose of study treatment (see Section 8.11.3.2 and Section 8.4) for participants who receive study treatment and for those with Early Discontinuations. All participants will be followed by telephone contact every 12 weeks for OS until death, withdrawal of consent, lost to follow-up, or the end of the study, whichever occurs first. The Sponsor may request survival status to be assessed at additional time points during the study. For example, survival status may be requested prior to the final analysis. All participants who are in the Survival Follow-up Phase and not known to have died prior to the request for these additional survival status time points will be contacted at that time.

This study will use an independent, eDMC and an EOC to monitor safety and efficacy (Appendix 1). There will be 1 formal IA for efficacy (see Section 9.7).

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

4.2 Scientific Rationale for Study Design

Cutaneous squamous cell carcinoma has long been considered to be an immunogenic cancer. Immune checkpoints that regulate the immune response have led to the development of strategies that can be positively exploited to impact T-cell activity and generate clinically relevant antitumor activity.

Until 2017, there was no prospective data for anti-PD1 therapy in the cSCC LA setting. Data from ASCO 2017 and ASCO-Society for Immunotherapy of Cancer 2018 on cemiplimab (REGN2810), a human anti-PD-1 mAb, provides evidence that PD-1 inhibitors could provide a well-tolerated, effective, and durable response in patients with LA or metastatic cSCC (see Section 2.2.1 for more details). In a Phase 1 open-labeled study (NCT02383212) patients with unresectable locally and/or regionally advanced cSCC were treated for up to 48 weeks with cemiplimab (REGN2810). Final results revealed an ORR of 43.8% (95% CI: 19.8 to 70.1) and DCR of 56.3% (95% CI: 29.9 to 80.2) in the LA population [Owonikoko, T. K., et al 2018].

In a recent press release, Regeneron announced positive results from an ongoing pivotal Phase 2 study of cemiplimab (REGN2810) in 82 patients with advanced cSCC [Regeneron Pharmaceuticals, Inc. 2017]. Data from the primary analysis presented at ASCO 2018 from the metastatic population (n=59) reported ORR of 47.5% (95% CI: 34.3 to 60.9) and DCR of 61.0% (95% CI: 47.4 to 73.5), as determined by independent review; the median DOR had not yet been reached at the data cutoff point [Rischin, D., et al 2018]. Results for the LA population are yet to be published. Further Phase 2 data for pembrolizumab in the LA setting will be provided in KN629 (see Section 2.2.3); the Sponsor plans to include a cohort with LA cSCC whose disease is not eligible for surgery.

This Phase 3 study will evaluate the efficacious advantage of pembrolizumab adjuvant therapy in participants with resectable high-risk LA cSCC (as defined in Section 5.1 – Inclusion Criteria). Upon study entry, all participants will have undergone surgical resection with curative intent and RT. The specific treatment must comply with ASTRO and RCR guidelines for adjuvant RT of high-risk LA cSCC [Likhacheva, A., et al 2020] [The Royal College of Radiologists 2019]. The study is a randomized, double-blind, placebo-controlled design, which will provide controlled data in this population for which limited data are available. The placebo control is necessary to ensure double blinding since the presence/absence of extra infusions would identify treatment assignment. The placebo control also allows statistical isolation of the true effect associated with pembrolizumab therapy from the placebo effect.

Participants will be stratified by extracapsular extension (yes vs. no), cortical bone invasion (yes vs. no), and prior systemic therapy (yes vs. no) (see Section 6.3.2); extracapsular extension and cortical bone invasion are poor prognostic factors for cSCC and the effect of prior systemic therapy on the adjuvant setting for cSCC is unknown; stratification will allow the latter to be explored.

The primary objective of the study is to compare RFS of pembrolizumab versus placebo, while ensuring access to pembrolizumab for all participants entering the study by allowing cross-over after first recurrence. Upon disease recurrence, participants will move from having LA disease to R/M disease for which treatment options are limited and mortality rates exceed 70% [Burton, K. A., et al 2016]. Upon biopsy proven disease recurrence, and with Sponsor approval, study treatment will be unblinded (see Section 8.1.10.2). If the participant is not eligible for surgical resection participants may cross over to or receive retreatment with pembrolizumab 400 mg IV Q6W for up to 18 cycles. Participants randomized to placebo must start cross-over treatment within 12 weeks of disease recurrence. Participants assigned to pembrolizumab are eligible for retreatment if biopsy proven disease recurrence occurs before Year 5 and more than 6 months after completing 9 cycles (1 year) of study adjuvant therapy; participants that experience recurrence earlier than this could indicate pembrolizumab refractory disease and would not be eligible for retreatment. A treatment duration of up to 18 cycles is consistent with the total dosage in Phase 2 KN629 study in participants with R/M cSCC.

Immunosuppression has long been associated with increased risk of cSCC. Participants with prior allogeneic transplantation or chronic immunosuppression have been found to be up to 65 times as likely to develop the risk of developing an invasive cSCC compared to

age-matched controls. However, several case reports of allograft rejection following anti-PD-1 therapy have recently been described [Spain, L., et al 2016]. Although there is evidence of robust clinical response in allograft organ recipients, including PR and CR, the potential risk for allograft rejection may not justify the potential therapeutic benefit. Therefore, participants with a history of prior solid organ or allogeneic bone marrow transplant will be excluded in this study.

4.2.1 Rationale for Endpoints

4.2.1.1 Efficacy Endpoints

4.2.1.1.1 Recurrence-free Survival

This study will use RFS, as assessed by the investigator, as the primary endpoint. RFS is considered an appropriate clinical endpoint for adjuvant studies that will evaluate the study treatment's impact on disease recurrence and is a common clinical surrogate endpoint to in adjuvant settings in which patients are expected to experience cancer symptoms upon recurrence (eg, adjuvant breast cancer hormonal therapy, adjuvant colon cancer, and adjuvant cytotoxic breast cancer therapy). Additionally, given the morbidity and mortality associated with recurrent high-risk LA cSCC, RFS of the baseline index lesion represents a clinically significant endpoint for patients with this disease. See Section 9.4 for the primary and secondary endpoint definitions. Images will be assessed by local site investigator; the final determination of radiologic recurrence will be confirmed by biopsy.

Note: A new high-risk primary cSCC is considered an RFS event; however, a new low risk primary cSCC is not considered as an RFS event (see Section 8.2.1.5). The occurrence of a new low risk primary cSCC that can be surgically removed without the need for additional radiotherapy and/or systemic therapy would not threaten OS and would not be expected to require a clinical need for pembrolizumab. The use of pembrolizumab will be focused to prevent debilitating morbidity and recurrence of life-threatening disease, which would be the case for recurrence of high-risk LA cSCC.

4.2.1.1.2 Overall Survival

OS has been recognized as the gold standard for the demonstration of superiority of a new antineoplastic therapy in randomized clinical studies. In this study, OS will be measured as a secondary endpoint. The OS endpoint may be potentially confounded by subsequent therapy, thus limiting its utility as a primary endpoint. In this study, participants randomized to placebo can cross over and receive pembrolizumab upon disease recurrence. The OS endpoint for this disease can be heterogeneous given the variability of salvage procedures, which is highly center and expertise dependent, and this variability may have an impact on the OS endpoint. Further complicating the OS endpoint is that patients who survive more than 3 years have an OS impact mainly driven by participant comorbidities and second primaries, rather than by disease recurrence. For all the reasons stated above, RFS is the primary endpoint and OS will be a secondary endpoint.

4.2.1.2 Safety Endpoints

Safety parameters frequently used for evaluating investigational-systemic anticancer treatments are included as safety endpoints including, but not limited to, the incidence of, causality, and outcome of AEs/SAEs, and changes in vital signs and laboratory values. AEs will be assessed as defined by CTCAE, Version [4.0]. The severity (as CTCAE grade), attribution to drug, time-of-onset, duration, resolution, and any concomitant medications administered will be recorded.

4.2.1.3 Patient-reported Outcomes

The study will incorporate HRQoL measures as secondary and exploratory endpoints. Participants will provide information regarding their HRQoL using the EORTC QLQ-C30 and Skindex-16 PRO instruments. Health utilities will be evaluated using the EQ-5D PRO instrument. The EORTC QLQ-C30, Skindex-16, and EQ-5D PROs are not pure efficacy or safety endpoints because they are affected by both disease recurrence and treatment tolerability.

4.2.1.3.1 EORTC QLQ-C30

The EORTC QLQ-C30 is the most widely used cancer specific HRQoL instrument, which contains 30 items and measures 5 functioning 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 HRQoL in oncology studies [Aaronson, N. K., et al 1993] and has been psychometrically validated in the NMSC population (N=172) [Muller, K., et al 2017].

4.2.1.3.2 Skindex-16

Skindex-16 is a 16-item instrument that is broadly used for dermatology skin conditions to measure the extent that patients are bothered by their skin condition, in terms of skin symptoms, feelings, and effects on function. Scores vary from 0 (best QoL) to 100 (worst QoL), and responses are analyzed into 3 domains, including symptoms (4 items: itching, burning/stinging, hurting, irritated), emotions (7 items: persistence/recurrence, worry, appearance, frustration, embarrassment, being annoyed, feeling depressed), and functioning (5 items: interaction with others, desire to be with people, affection, daily activities, ability to work) [Chren, M. M. 2012]. The original Skindex-61 instrument was developed in a cohort of N=201 dermatology patients inclusive of N=35 NMSC patients; the reduced Skindex-29 instrument was developed in a cohort of N=685 dermatology patients including N=136 NMSC patients [Chren, M. M., et al 1997], and the subsequent refinement into the Skindex-16 was psychometrically validated in a cohort of N=386 dermatology patients including N=84 NMSC patients [Chren, M. M., et al 2001]. The Skindex-16 has been used to assess disease-related HRQoL in NMSC patients including patients with cSCC, where it was able to detect changes in disease-related HRQoL following surgical treatment [Chren, M. M., et al 2007] [Chen, T., et al 2007]. The instrument has also been incorporated in a study of

systemic therapy for the treatment of unresectable LA basal cell carcinoma [Grob, J. J., et al 2016].

4.2.1.3.3 EuroQOL EQ-5D

The EQ-5D 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. and de Charro, F. 2001]. The 5 health state dimensions in the EQ-5D 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 also includes a graded (0 to 100) vertical visual analog scale on which the participant rates their 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 Planned Exploratory Biomarker Research

The mechanism of action of many antitumor agents is not completely understood and much remains to be learned regarding how best to leverage new drugs in treating patients. Thus, to aid future patients, it is important to investigate the determinants of response or resistance to cancer treatments. These efforts may identify novel predictive/pharmacodynamic biomarkers and generate information that may better guide single-agent and combination therapy with antineoplastic drugs. To identify novel biomarkers, biospecimens (eg, blood components, tumor material, etc) 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 the following:

Germline 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, the data might inform optimal use of therapies in the patient population. Furthermore, it is important to evaluate germline DNA variation across the genome to interpret tumor-specific DNA mutations. Finally, MSI may be evaluated as this is an important biomarker for some cancers (ie, colorectal cancer).

Genetic (DNA) tumor analyses

The application of new technologies, such as next generation sequencing, has provided scientists the opportunity to identify important tumor-specific DNA changes (eg, mutations, methylation status, microsatellite instability, etc). Key molecular changes of interest to oncology drug development may also include the mutational burden of tumors and the clonality of T-cells in the tumor microenvironment. Microsatellite instability may also be evaluated as this is an important biomarker for some cancers (eg, colorectal cancer). Genome-wide approaches may be used for this effort. Note that to understand tumor-specific mutations, it is necessary to compare the tumor genome with the germline genome. Circulating tumor DNA may also be evaluated from biospecimens (eg, blood, urine, etc).

Tumor and/or blood RNA analyses

Both genome-wide and targeted mRNA expression profiling and sequencing in tumor tissue and/or in blood may be performed to define gene signatures that might correlate to clinical response to treatment with antitumor therapies. Specific gene sets (eg, those capturing interferon-gamma transcriptional pathways) may be evaluated and new signatures may be identified. Expression of individual genes may also be evaluated. MicroRNA profiling may also be pursued as well as exosomal profiling. Circulating tumor RNA may also be evaluated from biospecimens (eg, blood, urine, etc).

Immunohistochemical (IHC) and/or proteomic analyses using tumor

Tumor samples from this study may undergo histopathological (eg, PD-L1 IHC), proteomic, and/or immunological analyses. These approaches could identify novel protein biomarkers that could aid in patient selection for antitumor therapy.

Other biomarkers

In addition to expression on the tumor tissue, tumor-derived proteins can be shed from tumor and released into the blood. Assays such as ELISA may be used to measure such proteins in serum and/or plasma. Correlation of expression with response to therapy may identify new approaches for predictive biomarkers in blood, representing a major advance from today's reliance on assessing tumor biomarkers.

Other molecular changes of interest may include the subtype of T-cells in the tumor microenvironment. The T-cell repertoire from tumor tissue and blood components may be evaluated. Furthermore, when applicable, cell populations may be also separated by either flow cytometry or mass cytometry-based sorting. These approaches may be used to quantify cell- and/or tissue-based analytes to further elucidate mechanism of action and/or assess disease-related parameters.

4.2.1.5 Future Biomedical Research

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

Such research is for biomarker testing to address emergent questions not described elsewhere in the protocol and will only be conducted on specimens from appropriately consented participants. The objective of collecting/retaining specimens for FBR is to explore and identify biomarkers that inform the scientific understanding of diseases and/or their therapeutic treatments. The overarching goal is to use such information to develop safer, more effective drugs/vaccines, and/or to ensure that participants receive the correct dose of the correct drug/vaccine at the correct time. The details of FBR research are presented in Appendix 6.

4.3 Justification for Dose

Maximum Dose/Exposure for This Study

In the Adjuvant Treatment Phase, participants may receive pembrolizumab 400 mg Q6W for up to 9 cycles in total. A 400 mg Q6W dosing regimen of pembrolizumab is expected to have a similar benefit-risk profile as 200 mg Q3W, in all treatment settings in which 200 mg Q3W pembrolizumab is currently appropriate [Lala, M., et al 2020]. Specifically, the dosing regimen of 400 mg Q6W for pembrolizumab is considered adequate based on modeling and simulation analyses, given the following rationale:

- PK simulations demonstrating that in terms of pembrolizumab exposures:
  - C_{av} (or AUC) at 400 mg Q6W is similar to the approved 200 mg Q3W dose, thus bridging efficacy between dosing regimens.
  - C_{min} at 400 mg Q6W are generally within the range of those achieved with 2 mg/kg or 200 mg Q3W in the majority (>99%) of patients.
  - C_{max} at 400 mg Q6W are well below the C_{max} for the highest clinically tested dose of 10 mg/kg Q2W, supporting that the safety profile for 400 mg Q6W should be comparable to the established safety profile of pembrolizumab.
- E-R for pembrolizumab has been shown to be flat across indications, and OS predictions in melanoma and NSCLC show that efficacy at 400 mg Q6W is expected to be similar to 200 mg or 2 mg/kg Q3W, given the similar exposures; thus, 400 mg Q6W is expected to be efficacious across indications.

The safety, efficacy, and PK profile of the pembrolizumab 400 mg Q6W dose regimen are objectives of the ongoing KEYNOTE-555 study.

The optimal duration of treatment with immune checkpoint inhibitors has yet to be defined; only Phase 1 data is available for anti-PD-1 or anti-PD-L1 immune checkpoints inhibitors in LA cSCC. For breast cancer, treatment modalities such as human epidermal growth factor receptor 2 directed therapy (trastuzumab) the optimal treatment duration is 1 year; increasing treatment duration to 2 years was not associated with additional benefit for trastuzumab in this indication, even though patients with advanced disease might receive treatment for a longer time [Piccart-Gebhart, M. J., et al 2005]. Based on this experience and in the absence of additional data for immune checkpoint inhibitors, this study will evaluate pembrolizumab adjuvant therapy for up to 1 year (9 cycles); the same duration therapy was used in a study of pembrolizumab adjuvant therapy in resected Stage III melanoma [Eggermont, A. M. M., et al 2018].

After first documented disease recurrence, if clinically indicated and with Sponsor approval, participants may cross over to or receive retreatment with pembrolizumab 400 mg IV Q6W for up to 18 cycles; for participants that received pembrolizumab in the Adjuvant Treatment Phase, any retreatment will be a minimum of 6 months after the last dose in the Adjuvant Treatment Phase. A treatment duration of up to 18 cycles is consistent with the total dosage in Phase 2 KN629 study of R/M cSCC.

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 (Section 7.3), or the last participant on active treatment is consented in the extension study. For purposes of analysis and reporting, the overall study ends when the Sponsor receives the last laboratory test result or at the time of final contact with the last participant, whichever comes last.

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

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 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 as described in Appendix 1.10.

5 STUDY POPULATION

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

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

5.1 Inclusion Criteria

An individual is eligible for inclusion in the study if the individual meets all of the following criteria:

Type of Participant and Disease Characteristics

1. Participant must have histologically confirmed cSCC as the primary site of malignancy (metastatic skin involvement from another type of primary cancer or from an unknown primary cancer is not permitted).

   Note: Participants for whom the primary site of squamous cell carcinoma was anogenital area (penis, scrotum, vulva, perianal region) are not eligible. Participants with tumors arising on cutaneous non-glabrous (hair-bearing) lip with extension onto vermillion (dry red lip) may be eligible after communication and approval from the clinical director. Participants for whom the primary site is the nose may be eligible after communication and approval from the clinical director if the primary site is skin, not nasal mucosa with outward extension to skin.

2. Participant must have undergone complete macroscopic resection of all known cSCC disease with or without microscopic positive margins. For those participants with residual microscopic positive margin involvement, confirmation that additional re-excision is not possible must be provided. Surgery may consist of 1 or a combination of the following:
   a. Resection of the primary lesion (Note: If a primary lesion is present, it must be completely resected as above)
   b. Any type of neck dissection(s)
   c. Any type of parotidectomy (superficial, total, partial)
3. Participant must have histologically confirmed LA cSCC with a high-risk feature(s) as the primary site of malignancy (metastatic skin involvement from another primary cancer or from an unknown primary cancer is not permitted) [National Comprehensive Cancer Network 2017]. High-risk features include at least 1 of the following:
   a. Histologically involved nodal disease with the following features:
      - Extracapsular extension with either at least 1 lymph node >2 cm in greatest diameter or ≥2 lymph nodes involved.

b. Any index tumor with ≥2 of the following high-risk features:
   - Tumor ≥4 cm with a depth >6 mm or invasion beyond subcutaneous fat
   - Multifocal perineural invasion for nerves of <0.1 mm diameter (3 or more foci) or any involved nerve ≥0.1 mm diameter
   - Poor differentiation and/or sarcomatoid and/or spindle cell histology
   - Recurrent disease (any cSCC that recurs within 3 years in the previously surgically or topically treated area)
   - Satellite lesions (satellitosis) and/or in-transit metastases
   - Lymphatic or vascular involvement

c. Any gross cortical bone invasion or skull base invasion and/or skull base foramen invasion.

4. Participant must have completed adjuvant RT for LA cSCC with last dose of RT ≥4 weeks and ≤16 weeks from randomization.
5. Participants who received an adequate post op dose of RT (either hypofractionated or conventional) are eligible. This includes all participants with a BED EQD2 >48 Gy. Examples of commonly used acceptable regimens include doses of 30-35Gy in 5fx; 40Gy/10 fx; 40-45Gy/15fx; 50-55Gy/20fx; 45-50Gy/25fx; 50.4Gy/28fx; 54Gy/30fx; 60-66Gy/30-33fx; the specific treatment must comply with ASTRO and RCR guidelines for adjuvant RT of high-risk LA cSCC [Likhacheva, A., et al 2020] [The Royal College of Radiologists 2019].
6. Participant is disease-free as assessed by the investigator with complete radiographic staging assessment ≤28 days from randomization**.**

Demographics

7. Participant is male or female and at least 18 years of age at the time of signing the informed consent.

Female Participants

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

- A female participant is eligible to participate if she is not pregnant or breastfeeding, and at least one of the following conditions applies:
  - Is not a POCBP
    - OR
  - Is a POCBP 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 5 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 POCBP must have a negative highly sensitive pregnancy test (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 5.
  - 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.
  - Abstains from breastfeeding during the study intervention period and for at least 120 days after study intervention.
  - If the contraception requirements in the local label for any of the study interventions is more stringent than the requirements above, the local label requirements are to be followed.

Refer to Appendix 7 for country-specific requirements.

Informed Consent

9. Participant (or legally acceptable representative, if applicable) provides documented informed consent for the study. The participant may also provide consent for future biomedical research. However, the participant may participate in the main study without participating in future biomedical research.

   Note: Eligible participants must provide additional informed consent for participation in post-study cross-over/retreatment.

Additional Categories

10. Participant provides a tumor tissue sample adequate for PD-L1 testing as determined by central laboratory testing. This tissue sample may be obtained from either the surgical resection, or a prior archival tissue specimen not previously irradiated. FFPE tissue blocks are preferred to slides.

    Note: Participants from whom PD-L1 testing cannot be performed due to infeasibility of testing of the tissue sample will not be eligible. Participants will not be excluded if tissue was initially thought to be adequate but a PD-L1 result was unable to be reported for whatever reason.

    Note: Central pathological review for PD-L1 will not be performed before randomization.

11. Participant has a life expectancy of greater than 3 months.
12. Participant has an ECOG performance status of 0 or 1 performed within 10 days prior to treatment initiation.
13. Participant has adequate organ function as defined in the following table (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 without granulocyte colony-stimulating factor (G-CSF) support within 2 weeks prior to the first dose of study treatment
Platelets	≥100 000/µL
Hemoglobin	≥9.0 g/dL or ≥5.6 mmol/L[a] Participants are eligible if levels are reached after blood transfusion.
Renal	
Creatinine OR Measured or calculated[b] creatinine clearance (CrCl; glomerular filtration rate [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)	≤2.5 × ULN
Coagulation	
International normalized ratio (INR) OR prothrombin time (PT) Activated partial thromboplastin time (aPTT)[c]	≤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); CrCl=creatinine clearance; GFR=glomerular filtration rate; ULN=upper limit of normal.

[a] Criteria must be met without erythropoietin dependency.

[b] Cockcroft Gault calculation of CrCl preferred, but CrCl can be calculated per institutional standard.

[c] PTT may be performed if the local laboratory is unable to perform aPTT.

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

The participant must be excluded from the study if the participant meets any of the following criteria:

Medical Conditions

1. Has macroscopic residual cSCC after surgery and/or recurrence with active cSCC disease before randomization.
2. Has any other histologic type of skin cancer other than invasive cSCC, eg, basal cell carcinoma that has not been definitively treated with surgery or radiation, Bowen's disease, MCC, melanoma.

3. A POCBP who has a positive urine pregnancy test within 72 hours before the first dose of study treatment (see Appendix 5). If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test is required. In such cases, the participant must be excluded from participation if the serum pregnancy result is positive.

   Note: If 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 treatment.

   Refer to Appendix 7 for country-specific requirements.

Prior/Concomitant Therapy

4. Has received prior therapy with an anti-PD-1, anti-PD-L1, or anti-PD-L2 agent or with an agent directed to another costimulatory or coinhibitory T-cell receptor (eg, CTLA-4, OX-40, CD137).
5. Has received prior systemic anticancer therapy including investigational agents for cSCC within 4 weeks before the start of study intervention.

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

   Note: If participant received major surgery, they must have recovered adequately from the toxicity and/or complications from the intervention prior to starting study treatment.
6. Participant must have recovered from all radiation-related toxicities and not have had radiation pneumonitis.
7. Has received a live or live-attenuated vaccine within 30 days prior to the first dose of study treatment. Administration of killed vaccines are allowed.

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

Prior/Concurrent Clinical Study Experience

8. Has received an investigational agent or has used an investigational device within 4 weeks prior to the first dose of study treatment.

Diagnostic Assessments

9. 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 to the first dose of study drug.
10. Known additional malignancy that is progressing or has required active treatment within the past 2 years.

    Note: Participants with basal cell carcinoma of the skin, squamous cell carcinoma of the skin or carcinoma in situ, excluding carcinoma in situ of the bladder, that have undergone potentially curative therapy are not excluded. Other exceptions may be considered with Sponsor consultation.

Note: Participants with low risk early-stage prostate cancer defined as below are not excluded: Stage T1c or T2a with a Gleason score ≤6 and a prostate-specific antigen (≤10 ng/ml) either treated with definitive intent or untreated in active surveillance that has been stable for the past year prior to study allocation. Early stage asymptomatic CLL without prior treatment and without any of the risk features (unmutated IGHV, lymphocytes >15,000μL, palpable lymph nodes) will be eligible for the study [Condoluci, A., et al 2020].

11. Has known active central nervous system metastases and/or carcinomatous meningitis.
12. Has severe hypersensitivity (≥ Grade 3) to pembrolizumab and/or any of its excipients (refer to the Investigator's Brochure for a list of excipients).

    Refer to Appendix 7 for UK-specific requirements.
13. Has an active autoimmune disease that has required systemic treatment in past 2 years except replacement therapy (eg, thyroxine, insulin, or physiologic corticosteroid).
14. Has a history of (noninfectious) pneumonitis/interstitial lung disease that required steroids or has current pneumonitis/interstitial lung disease.
15. Has an active infection requiring systemic therapy.
16. Has a known history of human immunodeficiency virus (HIV) infection. No HIV testing is required unless mandated by local health authority.

    Refer to Appendix 7 for Germany and UK-specific requirements.
17. Has a known history of hepatitis B (defined as hepatitis B surface antigen [HBsAg] reactive) or known active hepatitis C virus (HCV; defined as HCV RNA [qualitative] is detected) infection.

    Note: No testing for hepatitis B and hepatitis C is required unless mandated by local health authority.

    Refer to Appendix 7 for Germany and UK-specific requirements.
18. Has a history or current evidence of any condition, therapy, or laboratory abnormality, or other circumstances that might confound the results of the study, interfere with the participant's participation for the full duration of the study such that it is not in the best interest of the participant to participate, in the opinion of the treating investigator.
19. 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

20. Is pregnant or breastfeeding or expecting to conceive or father children within the projected duration of the study, starting with the screening visit through 120 days after the last dose of study treatment.
21. Has had an allogeneic tissue/solid organ transplant.

5.3 Lifestyle Considerations

There are no lifestyle restrictions.

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

There are no activity restrictions during participation in this study. As part of SoC, participants will receive repetitive education throughout the study regarding sun avoidance and protection.

5.3.4 Contraception

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

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

5.4 Screen Failures

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

5.5 Participant Replacement Strategy

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

6 STUDY INTERVENTION

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

Clinical supplies (study intervention(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 Study Intervention(s) Administered

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

Table 2 Study Interventions

Arm Name	Arm Type	Intervention Name	Intervention Type	Dose Formulation	Unit Dose Strength(s)	Dosage Level(s)	Route of Administration	Regimen/ Treatment Period	Use	IMP or NIMP/AxMP	Sourcing
Pembrolizumab	Experimental	Pembrolizumab	Biological/Vaccine	Solution	25 mg/mL	400 mg	IV Infusion	Q6W; Day 1 of each 42-day cycle for up to 9 cycles (approximately 1 year)	Test Product	IMP	Provided centrally by the Sponsor
Placebo	Placebo Comparator	Placebo	Drug	Solution	N/A	N/A	IV Infusion	Q6W; Day 1 of each 42-day cycle for up to 9 cycles (approximately 1 year)	Placebo	IMP	Locally by the site

AxMP=auxiliary medical product; IMP=investigational medicinal product; IV=intravenous; N/A=not applicable; NIMP=noninvestigational medicinal product; pembro=pembrolizumab; Q6W=every 6 weeks.
The classification of IMP and NIMP/AxMP in this table is based on guidance issued by the European Commission and applies to countries in the European Economic Area. Country differences with respect to the definition/classification of IMP or NIMP/AxMP may exist. In these circumstances, local legislation is followed.

All study interventions will be administered on an outpatient basis.

All products indicated in Table 2 will be provided centrally by the Sponsor or locally by the study site, subsidiary, or designee, depending on local country operational or regulatory requirements.

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

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

6.1.1 Treatment

Following surgical resection and RT, participants will be randomized to receive either:

- Pembrolizumab (Pembrolizumab group) - 400 mg fixed dose, IV Q6W for up to 9 cycles,

or

- Placebo (Control group)

After first biopsy proven disease recurrence: if clinically indicated (and with Sponsor approval) participants may cross over to or receive retreatment with pembrolizumab 400 mg IV Q6W for up to 18 cycles; for participants that received pembrolizumab in the Adjuvant Treatment Phase, any retreatment will be a minimum of 6 months after completing all 9 cycles in the Adjuvant Treatment Phase.

6.1.2 Medical Devices

Not applicable.

6.2 Preparation/Handling/Storage/Accountability

6.2.1 Dose Preparation

Details on preparation and administration of pembrolizumab and placebo 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 intervention received, and any discrepancies are reported and resolved before use of the study intervention.

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

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

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

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

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

6.3 Measures to Minimize Bias: Randomization and Blinding

6.3.1 Intervention Assignment

Intervention allocation/randomization will occur centrally using an IRT system. There are 2 study intervention arms. Participants will be assigned randomly in a 1:1 ratio to pembrolizumab (pembrolizumab group) and placebo (control group), respectively.

6.3.2 Stratification

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

- Extracapsular extension (yes vs. no)
- Cortical bone invasion (yes vs. no)
- Prior systemic therapy (yes vs. no)

6.3.3 Blinding

In this study a double-blinding technique will be used. Pembrolizumab will be provided as open-label supplies. Therefore, an unblinded pharmacist or medically qualified study personnel will be used for blinding supplies. Pembrolizumab and placebo will be prepared and/or dispensed in a blinded fashion by an unblinded pharmacist or qualified study-site

personnel. The participant, the investigator, and Sponsor personnel or delegate(s) who are involved in the study intervention administration or clinical evaluation of the participants are unaware of the intervention assignments.

Upon disease recurrence, the investigator will request authorization via an SCF for official unblinding and consideration to proceed to cross-over/retreatment. Cross-over/retreatment is open-label; therefore, the Sponsor, site personnel, study staff, investigator, participant, and study teams associated with the conduct of the study will know the treatment administered. See Section 8.1.10 for details of the method for unblinding a participant.

After efficacy IA, the study was unblinded on 22-AUG-2024. Original protocol text in this section has been retained for reference.

6.4 Study Intervention Compliance

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

Interruptions from the protocol-specified treatment plan for more than 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.

If there are interruptions in the study intervention schedule or infusion/injection was stopped, the details of and reason for any interruption or infusion/injection cessation of study intervention will be documented in the participant's medical record.

Refer to Section 6.6.1 for Dose Modification and Toxicity Management Guidelines for irAEs associated with pembrolizumab monotherapy, coformulations, or IO combinations and for other allowed dose interruptions.

6.5 Concomitant Therapy

If there is a clinical indication for any medications or vaccinations prohibited, the investigator must discuss any questions regarding this with the Sponsor's Clinical Director. The final decision on any supportive therapy or vaccination rests with the investigator and/or the participant's primary physician. However, the decision to continue the participant on study intervention requires the mutual agreement of the investigator and the Sponsor.

The following medications and vaccinations are prohibited during the study:

- Surgical intervention to skin lesions.
  Note: Surgical intervention to skin lesion(s), without consultation with the Sponsor, is not permitted during the Adjuvant Treatment Phase.

- Live or live-attenuated vaccines within 30 days before the first dose of study intervention and while participating in the study.
  Note: Any licensed COVID-19 vaccine (including for Emergency Use) in a particular country is allowed in the study as long as they are mRNA vaccines, replication-incompetent adenoviral vaccines, or inactivated vaccines. These vaccines will be treated just as any other concomitant therapy.
- Systemic glucocorticoids except when used for the following purposes:
  - To modulate symptoms of an AE that is suspected to have an immunologic etiology
  - For the prevention of emesis
  - To premedicate for IV contrast allergies
  - To treat asthma or COPD exacerbations (only short-term oral or IV use in doses >10 mg/day prednisone equivalent)
  - For chronic systemic replacement not to exceed 10 mg/day prednisone equivalent
- Other glucocorticoid use except when used for the following purposes:
  - For topical use or ocular use
  - Intraarticular joint use
  - For inhalation in the management of asthma or COPD

If the investigator determines that a participant requires any of the following prohibited medications and vaccinations for any reason during the study, study intervention must be discontinued:

- Systemic antineoplastic chemotherapy, immunotherapy, or biological therapy not specified in this protocol
- Investigational agents other than those specified in this protocol
- Radiation therapy
  Note: RT is not permitted during the Adjuvant Treatment Phase. After determination of eligibility for cross-over/retreatment, participants may undergo sequential RT after consultation with the Sponsor.
- Investigational vaccines (ie, those not licensed or approved for Emergency Use) are not allowed.

All treatments that the investigator considers necessary for a participant's welfare may be administered at the discretion of the investigator in keeping with the community standards of medical care. All concomitant medications will be recorded on the eCRF including all prescriptions, 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 intervention and up to 30 days after the last dose of study intervention should be recorded.

All concomitant medications administered during SAEs or ECIs are to be recorded. SAEs and ECIs are defined in Section 8.4.

6.5.1 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.

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

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

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

6.6 Dose Modification (Escalation/Titration/Other)

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

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

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

Dose Modification and Toxicity Management Guidelines for irAEs Associated With Pembrolizumab Monotherapy, Coformulations, or IO Combinations are provided in Table 3.

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

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

irAEs	Toxicity Grade (CTCAE Version 4.0)	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 (CTCAE Version 4.0)	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 (CTCAE Version 4.0)	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 Monotherapy, Coformulations, or IO Combinations

Pembrolizumab monotherapy, coformulations, or IO combinations 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 monotherapy, coformulations, or IO combinations associated infusion reactions are provided in Table 4.

Table 4 Pembrolizumab Monotherapy, Coformulations, or IO Combinations – Infusion Reaction Dose Modification and Treatment Guidelines

NCI CTCAE Grade	Treatment	Premedication at Subsequent Dosing
Grade 1 Mild reaction; infusion interruption not indicated; intervention not indicated	Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator	None
Grade 2 Requires therapy or infusion interruption but responds promptly to symptomatic treatment (eg, antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for ≤24 h	Stop Infusion Additional appropriate medical therapy may include but is not limited to: IV fluids Antihistamines NSAIDs Acetaminophen Narcotics Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator. If symptoms resolve within 1 hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (eg, from 100 mL/h to 50 mL/h). Otherwise, dosing will be held until symptoms resolve and the participant should be premedicated for the next scheduled dose. Participants who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further study intervention.	Participant may be premedicated 1.5 h (±30 min) prior to infusion of study intervention with: Diphenhydramine 50 mg po (or equivalent dose of antihistamine). Acetaminophen 500 to 1000 mg po (or equivalent dose of analgesic).

NCI CTCAE Grade	Treatment	Premedication at Subsequent Dosing
Grades 3 or 4 Grade 3: Prolonged (ie, not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms after initial improvement; hospitalization indicated for other clinical sequelae (eg, renal impairment, pulmonary infiltrates) Grade 4: Life-threatening; pressor or ventilatory support indicated	Stop Infusion. Additional appropriate medical therapy may include but is not limited to: Epinephrine** IV fluids Antihistamines NSAIDs Acetaminophen Narcotics Oxygen Pressors Corticosteroids Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator. Hospitalization may be indicated. **In cases of anaphylaxis, epinephrine should be used immediately. Participant is permanently discontinued from further study intervention.	No subsequent dosing
CTCAE=Common Terminology Criteria for Adverse Events; h=hour; IV=intravenous; NCI=National Cancer Institute; NSAIDs=nonsteroidal anti-inflammatory drugs. Note: Appropriate resuscitation equipment should be available at the bedside and a physician readily available during the period of drug administration. For further information, please refer to the CTCAE v4.0 at http://ctep.cancer.gov		

Other Allowed Dose Interruption for Pembrolizumab Monotherapy, Coformulations, or IO Combinations

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

6.6.2 Cross-over/Retreatment

Upon biopsy proven disease recurrence, participants may be eligible for up to an additional 18 cycles (approximately 2 years) of pembrolizumab treatment. Cross-over/retreatment is optional, at the discretion of the investigator after approval from the Sponsor, and is only available if the study remains open and the participant meets conditions detailed in Section 8.1.8.1.2.

6.7 Intervention After the End of the Study

The study is complete upon consent of the last active treatment participant for an extension study using pembrolizumab monotherapy, if available.

All study-related procedures and data collection as defined per protocol will be terminated at study completion. In addition, survival follow-up will be stopped upon study completion as defined in Section 4.4.

6.8 Clinical Supplies Disclosure

The adjuvant treatment phase of the study is blinded but supplies are provided open-label; therefore, an unblinded pharmacist or qualified study site personnel will be used to blind supplies. Study treatment identity (name, strength or potency) is included in the label text; random code/disclosure envelopes or lists are not provided.

The emergency unblinding call center will use the intervention/randomization schedule for the study to unblind participants and to unmask study intervention identity for study adjuvant treatment. The emergency unblinding call center should only be used in cases of emergency (see Section 8.1.10.1). If the emergency unblinding call center is not available for a given site in this study, the central electronic intervention allocation/randomization system (IRT) should be used to unblind participants and to unmask study intervention identity. The Sponsor will not provide random code/disclosure envelopes or lists with the clinical supplies.

See Section 8.1.10 for a description of the method of unblinding a participant during the study, should such action be warranted.

6.9 Standard Policies

Not applicable.

7 DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT WITHDRAWAL

7.1 Discontinuation of Study Intervention

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

As certain data on clinical events beyond study intervention discontinuation may be important to the study, they must be collected through the participant's last scheduled follow-up, even if the participant has discontinued study intervention. Therefore, all participants who discontinue study intervention before completion of the protocol-specified treatment periods will still continue to be monitored in this study and participate in the study visits and procedures as specified in Section 1.3 and Section 8.11.4 unless the participant has withdrawn from the study as outlined in Section 7.2.

Participants may discontinue study intervention at any time for any reason or be discontinued from the study intervention at the discretion of the investigator should any untoward effect occur. In addition, a participant may be discontinued from study intervention by the investigator or the Sponsor if study intervention is inappropriate, the study plan is violated, or for administrative and/or other safety reasons.

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

- The participant or participant's legally acceptable representative requests to discontinue study intervention.
- Any prolonged interruption of study intervention beyond the permitted periods, for irAE management or other allowed dose interruptions, as noted in Section 6.6.1, require Sponsor consultation prior to restarting treatment. If treatment will not be restarted, the participant will continue to be monitored in the study and the reason for discontinuation of study intervention will be recorded in the medical record.
- The participant has a medical condition or personal circumstance which, in the opinion of the investigator and/or Sponsor, placed the participant at unnecessary risk from continued administration of study intervention.
- The participant has a confirmed positive urine or serum pregnancy test.
- Biopsy-confirmed disease recurrence as outlined in Section 8.2.1.6 (exception if the participant moves into Cross-over/Retreatment).
- Any progression or recurrence of malignancy, or any occurrence of another malignancy that requires active treatment.
- Any study intervention-related toxicity specified as a reason for permanent discontinuation as defined in the guidelines for dose modification due to AEs in Section 6.6.
- Recurrent Grade 2 pneumonitis.

- Use of prohibited concomitant medication (see Section 6.5).
- Completion of 9 cycles of study treatment (approximately 1 year).

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

Participants may be allowed to begin study treatment again if deemed medically appropriate (see Section 8.1.8.1.2).

7.2 Participant Withdrawal From the Study

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

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

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

7.3 Lost to Follow-up

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

- The site must attempt to contact the participant and reschedule the missed visit. If the participant is contacted, the participant should be counseled on the importance of maintaining the protocol-specified visit schedule.
- The investigator or designee must make every effort to regain contact with the participant at each missed visit (eg, telephone calls and/or a certified letter to the participant's last known mailing address or locally equivalent methods). These contact attempts should be documented in the participant's medical record.

8 STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarized in the SoA.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- The investigator is responsible for ensuring that procedures are conducted by appropriately qualified (by education, training, and experience) staff. Delegation of study-site personnel responsibilities will be documented in the Investigator Trial File Binder (or equivalent).
- All study-related medical decisions must be made by an investigator who is a qualified physician.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the participant's routine clinical management (eg, blood count) and obtained before providing documented informed consent may be used for screening or baseline purposes provided the procedures meet the protocol-specified criteria and were performed within the time frame defined in the SoA.
- Additional evaluations/testing may be deemed necessary by the investigator and or the Sponsor for reasons related to participant safety. In some cases, such evaluation/testing may be potentially sensitive in nature (eg, HIV, hepatitis C), and thus local regulations may require that additional informed consent be obtained from the participant. In these cases, such evaluations/testing will be performed in accordance with those regulations.
- The maximum amount of blood collected from each participant over the duration of the study, including any extra assessments that may be required, are detailed in the Vendor Manual.
- Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

8.1 Administrative and General Procedures

8.1.1 Informed Consent

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

8.1.1.1 General Informed Consent

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

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

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

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

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

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

8.1.1.2 Consent and Collection of Specimens for Future Biomedical Research

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

8.1.2 Inclusion/Exclusion Criteria

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

The investigator must ensure that eligibility criteria are met for all participants that experience disease recurrence and enter cross-over/retreatment before the start of pembrolizumab treatment. Cross-over/retreatment eligibility criteria are detailed in Section 8.1.8.1.2.

8.1.3 Participant Identification Card

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

The participant's ID card will be updated if they enter cross-over/retreatment.

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

8.1.4 Medical History

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

If a medical condition is diagnosed at the time of screening due to the physical examination, laboratory tests, radiologic assessment, other assessment, and/or a combination of these evaluations, the medical condition is to be recorded as a baseline condition along with the participant's other medical history unless due to any protocol-specified intervention (eg, procedure, washout, or run-in treatment including placebo run-in).

8.1.4.1 Disease Details

Details regarding participants cSCC status at baseline must be thoroughly evaluated by the investigator or qualified designee and recorded in the appropriate eCRF including: date of initial diagnosis, stage at diagnosis, tumor grade, primary tumor location and type (ie, single lesion, multifocal), tumor, node, and metastasis staging at baseline. Prior to entry in the study, all participants will have undergone surgical resection; details regarding date of surgery, type of surgery, etc. will be recorded in the appropriate eCRF. Refer to Sections 5.1 and 5.2 to ensure participant's disease status meets the relevant inclusion and exclusion criteria for study entry.

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. Treatment for the disease for which the participant

has enrolled in this study will be recorded separately and not listed as a prior medication. Prior treatment for other cancers will be recorded as a prior medication.

8.1.5.2 Concomitant Medications

The investigator or qualified designee will record medication, if any, taken by the participant during the study through the Safety Follow-up Visit. All medications related to reportable AEs, SAEs, and ECIs should be recorded as defined in Appendix 3.

8.1.5.3 Post-study Anticancer Therapy Status

The investigator or qualified designee will record anticancer therapy medication, if any, taken by the participant after discontinuing from study adjuvant treatment and through study follow up. For participants that enter cross-over/retreatment, the investigator or qualified designee will record anticancer therapy (including RT and surgical intervention) if any, received by the participant, from the study adjuvant phase End of Treatment visit and through Survival Follow-up.

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 before randomization. Each participant will be assigned only 1 screening number. Screening numbers must not be reused for different participants.

Any individual who is screened multiple times will retain the original screening number assigned at the initial Screening Visit. Specific details on the screening/rescreening visit requirements are in Section 8.11.1.

8.1.7 Assignment of Treatment/Randomization Number

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

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

8.1.8 Study Intervention Administration

Study intervention(s) will be administered by the investigator and/or an appropriately qualified designee according to the specifications within the pharmacy manual.

Interruptions from the protocol-specified treatment plan for greater than 12 weeks between pembrolizumab/placebo doses require consultation between the investigator and the Sponsor and written documentation of the collaborative decision on participant management.

Study intervention should begin within 3 days of randomization. Thereafter, study treatment may be administered up to 3 days before or after the scheduled Day 1 of each cycle (eg, due to administrative reasons) after Cycle 1.

8.1.8.1 Timing of Dose Administration

The dose and schedule modifications of pembrolizumab are provided in Section 6.6 – Dose Modification (Escalation/Titration/Other).

8.1.8.1.1 Adjuvant Treatment with Pembrolizumab/Placebo

Study treatment will be administered on Day 1 of each 6-week dosing cycle after all procedures and assessments are completed according to the SoA (Section 1.3). Each cycle is 42 days.

Participants will be administered pembrolizumab 400 mg or placebo using a 30-minute IV infusion. Sites should make every effort to target infusion timing to be as close to 30 minutes as possible. However, given the variability of infusion pumps from site to site, a window between −5 minutes and +10 minutes is permitted (ie, infusion time is 30 minutes −5 min / +10 min).

Participants can receive study treatment at a minimum of 4 weeks (± 3 days) and a maximum of 16 weeks (± 3 days) after the last dose of RT and once they have recovered adequately from the morbidity and/or complications from RT, as determined by the investigator.

Participants may receive up to 9 cycles of study treatment in total. If an interruption occurs, the participant should restart study treatment as soon as medically appropriate with the subsequent cycle and should not skip cycles. The participant, after an interruption, may restart treatment cycles without delay from the original 6-week interval schedule, but all future doses should be recalculated in 6-week intervals. Participants should be administered all planned 9 cycles, which could extend beyond the 1-year timeframe of the study.

The Pharmacy Manual contains specific instructions for the pharmacist for the preparation of the pembrolizumab and placebo infusions and administration of infusion solutions.

8.1.8.1.2 Cross-over/Retreatment with Pembrolizumab

Upon documented disease recurrence, adjuvant treatment will be unblinded as per Section 8.1.10. The primary objective of the study is to compare RFS of pembrolizumab versus placebo, while ensuring access to pembrolizumab for all patients entering the study.

Next Line of Treatment – Cross-over

Participants assigned to placebo in the Adjuvant Treatment Phase who experience biopsy proven disease recurrence may be eligible for up to 18 cycles (approximately 2 years) of pembrolizumab 400 mg Q6W treatment. Cross-over is optional, at the discretion of the investigator after approval from the Sponsor, and is only available if the study remains open and the participant meets the following conditions:

- Stopped study treatment after attaining an investigator-determined disease recurrence confirmed by histology.

AND

- The participant is not eligible for surgical resection, and
- Upon unblinding at the time of verified disease recurrence, is found to have received placebo, and
- No new systemic anticancer treatment was administered after the last dose of study treatment, and
- Biopsy proven recurrence occurred before the end of Year 5 and ≤12 weeks before the start of Cross-over Treatment, and
- The participant meets all of the safety parameters listed in the inclusion criteria (criteria 11 to 13) and none of the safety parameters listed in the exclusion criteria (criteria 3, 7, and 9 to 21), and
- The study is ongoing.

A disease progression that occurs during the Cross-over Phase for a participant will not be counted as an event for the primary analysis of endpoints in this study.

Next Line of Treatment – Pembrolizumab Retreatment

Participants may be considered for retreatment with pembrolizumab after biopsy proven disease recurrence >6 months after completing 1 year of adjuvant pembrolizumab treatment. Participants may be retreated with up to an additional 18 cycles (approximately 2 years) of pembrolizumab 400 mg IV Q6W. Retreatment is optional and at the discretion of the investigator after approval from the Sponsor. This retreatment is only available if the study remains open and the participant meets the following conditions:

- Attaining an investigator-determined disease recurrence confirmation by histology before the end of Year 5 and >6 months after last dose of treatment in the Adjuvant Treatment Phase, and
- The participant is not eligible for surgical resection, and
- Completion of 9 cycles of adjuvant treatment before disease recurrence, and

- Upon unblinding at the time of verified disease recurrence, is found to have received pembrolizumab, and
- No new systemic anticancer treatment was administered after the last dose of study treatment, and
- The participant meets all of the safety parameters listed in the inclusion criteria (criteria 11 to 13) and none of the safety parameters listed in the exclusion criteria (criteria 3, 7, and 9 to 21), and
- The study is ongoing.

For both cross-over and retreatment pembrolizumab will be administered at a dose of 400 mg using a 30-minute IV infusion. Sites should make every effort to target infusion timing to be as close to 30 minutes as possible. However, given the variability of infusion pumps from site to site, a window between −5 minutes and +10 minutes is permitted (ie, infusion time is 30 minutes −5 min / +10 min).

Participants may receive up to 18 cycles of pembrolizumab in total. If an interruption occurs, the participant should restart pembrolizumab as soon as medically appropriate with the subsequent cycle and should not skip cycles. The participant, after an interruption, may restart pembrolizumab cycles without delay from the original 6-week interval schedule, but all future doses should be recalculated in 6-week intervals. Participants should be administered all planned 18 cycles, which could extend beyond the 2-year treatment timeframe of the study.

8.1.9 Discontinuation and Withdrawal

Participants who discontinue study intervention before completion of the study Adjuvant Treatment period should be encouraged to continue to be followed for all remaining study visits.

Participants who withdraw from the study should be encouraged to complete all applicable activities scheduled for the End of Treatment Visit at the time of withdrawal. Any AEs that are present at the time of withdrawal should be followed in accordance with the safety requirements outlined in Section 8.4.

8.1.9.1 Withdrawal From Future Biomedical Research

Participants may withdraw their consent for FBR. Participants may withdraw consent at any time by contacting the study investigator. If medical records for the study are still available, the investigator will contact the Sponsor using the designated mailbox (clinical.specimen.management@MSD.com). Subsequently, the participant's consent for FBR will be withdrawn. A letter will be sent from the Sponsor to the investigator confirming the withdrawal. It is the responsibility of the investigator to inform the participant of completion of withdrawal. Any analyses in progress at the time of request for withdrawal or already performed before 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.

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

8.1.10 Participant Blinding/Unblinding

8.1.10.1 Emergency Unblinding

STUDY INTERVENTION IDENTIFICATION INFORMATION IS TO BE UNMASKED 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 intervention 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. Before contacting the emergency unblinding call center to request unblinding of a participant's intervention assignment, the investigator who is a qualified physician should make reasonable attempts to enter the intensity/toxicity grade of the AEs observed, the relation to study intervention, the reason thereof, etc, in the medical record. If it is not possible to record this assessment in the medical record before the unblinding, the unblinding should not be delayed.

Participants whose treatment assignment has been unblinded by the investigator or medically qualified designee and/or nonstudy treating physician may be allowed to continue study intervention and should continue to be monitored in the study.

Additionally, the investigator or medically qualified designee must go into the IRT system and perform the unblind in the IRT system to update drug disposition. If the emergency unblinding call center is not available for a given site in this study, the IRT system should be used for emergency unblinding if this is required for participant safety.

If unblinding has occurred, in response to events other than biopsy-proved disease recurrence (See Section 8.1.10.2), the circumstances around the unblinding (eg, date, reason and person performing the unblinding) must be documented promptly, and the Sponsor Clinical Director notified as soon as possible. Only the principal investigator or delegate and the respective participant's code should be unblinded. Other study site personnel and Sponsor personnel directly associated with the conduct of the study should not be unblinded.

At the end of the study, random code/disclosure envelopes or lists and unblinding logs are to be returned to the Sponsor or designee.

8.1.10.2 Unblinding by Investigator After First Disease Recurrence

Upon biopsy/confirmed disease recurrence, the investigator will request authorization for official non-emergency unblinding. If the participant is determined to be ineligible for surgical resection, a request for consideration to proceed to cross-over or retreatment will also be submitted. Non-emergency unblinding may occur on an individual basis and only after consultation with and approval of Sponsor Clinical Director via an SCF. Every effort should be made not to unblind the participant unless necessary.

The emergency unblinding methods described in Section 8.1.10.1 should not be used in this process.

Upon biopsy-confirmed disease recurrence, every effort will 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.

After unblinding is complete, the site will assess participant eligibility for Cross-over/Retreatment by reviewing all qualifications per protocol Sections 8.1.8.1.2, 5.1, and 5.2. If a participant fulfills the eligibility criteria, the site will access the recurrence phase module in IRT and request treatment assignment in Cross-over or Retreatment.

After biopsy proven disease recurrence, the study participant, investigator, site personnel, Sponsor personnel, study teams associated with the conduct of the study will become unblinded in order to continue monitoring each participant in the study.

8.1.11 Domiciling

At the discretion of the investigator, participants will report to the CRU the evening before the scheduled day of study intervention administration for each treatment period and remain in the unit until 24 hours postdose. At the discretion of the investigator, participants may be requested to remain in the CRU longer.

8.1.12 Calibration of Equipment

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

8.1.13 Tumor Tissue for Biomarker Status

Details regarding time points for collection of tumor tissue are outlined in the SoA (Section 1.3). Include a copy of the local pathology report with the tissue for biomarker analysis.

In accordance with the study inclusion criteria, participants are required to provide baseline tumor tissue from new or archived FFPE tissue specimens for PD-L1 assessment.

Tissue biopsy is required for confirmation of disease recurrence (Section 8.2.1.6); Sponsor consultation is required if a biopsy cannot be performed due to feasibility, such as location of recurrence (ie, bone lesion). If the participant provides documented informed consent for Future Biomedical Research, any leftover tissue that would ordinarily be discarded at the end of the main study will be retained for Future Biomedical Research.

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

PD-L1 testing

Archived tumor specimens will be tested centrally for characterization of PD-L1 status and translational research. The tissue sample must be assessed as adequate for PD-L1 testing as determined by central laboratory testing before randomization but central review of PD-L1 does not need to be completed before randomization.

This specimen may be the diagnostic sample for participants with a new diagnosis of LA cSCC or the surgical excised sample.

8.2 Efficacy Assessments

8.2.1 Tumor Imaging 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.

The process for scan acquisition can be found in the SIM. At screening, tumor scans (head, neck, chest, abdomen, and pelvis; scans of the affected extremities are required for those participants with disease in the extremities at baseline) are strongly preferred to be acquired by CT. For the head, neck, abdomen, pelvis, and extremities, contrast-enhanced MRI may be used when CT with iodinated contrast is contraindicated, or when mandated by local practice. On-study scans should cover affected site of the disease under study, along with associated draining lymph nodes (see Section 8.2.1.5). The same scan technique should be used in a participant throughout the study to optimize the reproducibility of the assessment of disease recurrence based on scans (See SIM). 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.

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

All scheduled scans for all randomized study participants will be submitted to the iCRO. Also, additional scans (CT, MRI, or FDG-PET) that are obtained at an unscheduled time point for any reason should be submitted to the iCRO if they show disease progression.

Note: As of Amendment 10, all ongoing participants should continue tumor imaging and investigator assessment of the scans per protocol; however, scans no longer need to be submitted to the iCRO and digital photography of cutaneous lesions is not required.

8.2.1.1 Initial Tumor Scans

Initial tumor scans at Screening must be performed within 28 days prior to the date of randomization and should include the anatomical sites detailed in Section 8.2.1. During screening, tumor scans of the site of the disease after surgical resection and RT will be considered as baseline scans.

Tumor scans performed as part of routine clinical management is acceptable for use as screening tumor scans if it is of diagnostic quality and performed within 28 days prior to the date of randomization.

Brain scans are required to rule out radiographically detectable brain metastases. MRI is preferred; however, CT scans will be acceptable, if MRI is medically contraindicated or CT is mandated by local practice.

8.2.1.2 Tumor Scans During the Study

The first on-study scans (to include disease involved areas and associated draining lymph node regions, see Table 5) should be performed at 12 weeks (± 7 days) from the date of randomization. Subsequent tumor scans should be performed every 12 weeks (84 days ± 7 days) or more frequently if clinically indicated, during treatment. Scan timing should follow calendar days and should not be adjusted for delays in cycle starts. Scans are to be performed until disease recurrence is identified by the investigator/site radiologist, pregnancy, withdrawal of consent, or death, whichever occurs first.

Table 5 Required Scans

Affected disease site	Scans Required to cover Affected Sites and Associated Draining Lymph Nodes
Skin of the Head and Neck (including scalp)	Head and Neck (occipital, parotid, cervical, perifacial, and supraclavicular), Chest
Skin of the Back/Torso/Upper Chest	Neck, Chest (axillary, supraclavicular, and posterior cervical)
Skin of the Lower Abdomen/Buttock/Groin	Chest Abdomen, Pelvis (inguino-femoral, internal iliac, and external iliac)
Pelvis	Chest, Abdomen, Pelvis (inguino-femoral, internal iliac, and external iliac)
Skin of the Upper Extremities	Involved Extremity and Chest (axillary, supraclavicular, and posterior cervical)
Skin of the Lower Extremities	Involved Extremity, Chest, Abdomen, Pelvis (inguino-femoral, internal iliac, and external iliac)

8.2.1.3 End-of-treatment and Follow-up Tumor Scans

For participants who complete or discontinue study treatment, tumor scans should be performed at the time of treatment discontinuation (±4-week window). If previous scans were obtained within 4 weeks prior to the date of discontinuation, then scans at treatment discontinuation is not mandatory. Tumor scans (to include disease involved areas and associated draining lymph node regions, see Table 5) should be performed at end of treatment (±4 weeks). For participants who discontinue study treatment due to biopsy proven disease recurrence, these are the final required tumor scans.

For participants who complete or discontinue study treatment without documented disease progression, every effort should be made to continue monitoring disease status by tumor scans every 12 weeks (±7 days) until Year 2, then every 6 months (±14 days) until the end of Year 5, until new high risk primary cSCC/biopsy proven disease recurrence, pregnancy, death, withdrawal of consent, or the end of the study, whichever occurs first.

8.2.1.4 Cross-over/Retreatment Tumor Scans

Tumor scans must be performed within 28 days prior to starting study treatment with pembrolizumab. If the recurrence scan falls outside of this window, a new scan is required at baseline.

The first on-study scans should be performed at 12 weeks (84 days ±7 days) after the restart of pembrolizumab treatment. Subsequent tumor scans should be performed every 12 weeks (84 days ±7 days) until end of year 2, or more frequently, if clinically indicated from the date of the first dose of pembrolizumab in cross-over/retreatment.

Per iRECIST (Section 8.2.1.7.2), if tumor scans show initial PD per RECIST 1.1, tumor assessment should be repeated 4 to 8 weeks later to confirm PD with the option of continuing treatment while awaiting radiologic confirmation of progression in clinically stable participants. Participants who obtain confirmatory scans do not need to undergo scheduled tumor scans if it is less than 4 weeks later and may wait until the next scheduled scan time point, if clinically stable.

Scans should continue to be performed until disease progression, the start of a new systemic anticancer treatment, withdrawal of consent, pregnancy, death, or notification by the Sponsor, whichever occurs first. In clinically stable participants, disease progression may be confirmed by the investigator using iRECIST 4 to 8 weeks after the first tumor scans indicating PD.

For participants who discontinue cross-over/retreatment study therapy, tumor scans should be performed at the time of treatment discontinuation (± 4-week window). If a previous scan was obtained within 4 weeks prior to the date of discontinuation, then a scan at treatment discontinuation is not mandatory. These are the final required tumor scans.

8.2.1.5 Assessment of Disease Recurrence

8.2.1.5.1 Criteria for Determination of Disease Recurrence

Recurrence is defined as cancer that has recurred (come back), usually after a period of time during which the cancer could not be detected. The cancer may come back to the same place as the original (primary) tumor or to another place in the body (https://www.cancer.gov/publications/dictionaries/cancer-terms/def/recurrence).

Local cutaneous recurrence: Recurrence that has recurred at or near the same place as the original (primary) tumor, usually after a period of time during which the cancer could not be detected (https://www.cancer.gov/publications/dictionaries/cancer-terms/def/locally-recurrent-cancer). Its neoplastic nature must be confirmed either by histology/cytology.

Regional lymphatic and nodal recurrences: The neoplastic nature of the regional recurrences should be confirmed by histology/cytology.

- In-Transit Metastases: The American Joint Committee on Cancer defines in-transit metastases as any skin or subcutaneous metastases that are more than 2 cm from the primary lesion but are not beyond the regional nodal basin.
- Regional Nodal Recurrences: Regional nodal failure in a previously dissected basin is usually found at the periphery of the prior surgical procedure.

Distant metastases: cancer that has spread from the original (primary) tumor to distant organs or distant lymph nodes (https://www.cancer.gov/publications/dictionaries/cancer-terms/def/distant-cancer).

Note: A new high risk primary cSCC is considered an RFS event; however, a new low risk primary cSCC is not considered as an RFS event. A new low risk primary cSCC should be in an anatomically separate site to the original (Index) cSCC site. A new lesion(s) in close proximity (≤5 cm from the index lesion) to the index cSCC lesion site should be considered a recurrence unless the lesion originates from the epidermis and is completely contained within the dermis with epidermal connection and contains no “high risk” features (outlined below). Discussion with the Sponsor Clinical Director is required where there is uncertainty of new primary cSCC lesion versus recurrence of a lesion. If the new lesion does not originate from the epidermis and is confined to the dermis without epidermal connection or invading

subcutaneous fat tissue, the lesion will be considered as “in-transit metastasis” and will be deemed as an event.

For a lesion to be considered “low risk” per NCCN cSCC Guidelines [National Comprehensive Cancer Network 2017], the histopathology report needs to confirm the following: well or moderately differentiated lesion, no adenoid, adenosquamous, desmoplastic or metaplastic subtypes, <2 mm in thickness, and no perineural, lymphatic or vascular involvement.

Discussion with the Sponsor Clinical Director is required if these criteria are not met, and the investigator assesses the new lesion as consistent with a new primary cSCC.

In the Adjuvant Treatment Phase, tumor scans (to include disease involved areas and associated draining lymph node regions, see Table 5) will be performed with assessments based on disease recurrence. If indicated, biopsy confirmation of recurrent lesion/s will be performed (see Section 8.2.1.6). Confirmation of radiographic disease recurrence by cytology/histology is mandatory; only if a biopsy cannot be performed due to feasibility, such as location of recurrence (ie, bone lesion), and upon Sponsor consultation, can radiographic imaging be used alone to confirm disease recurrence.

If scans are performed after screening and disease recurrence is assessed, this will be an RFS event. However, the participant may be allowed to stay on study until a biopsy recurrence, if clinically stable upon consultation with Sponsor.

Clinical stability is defined as the following:

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

Any participant deemed **clinically unstable** should be discontinued from study treatment at site-assessed first radiologic/histologic evidence of recurrence.

8.2.1.5.2 Date of Recurrence

The first date when recurrence was observed is taken into account, regardless of the method of assessment. Therefore, recurrence will be declared for any lesion when:

- Only pathology was performed, and recurrence confirmed (in solitary or in doubtful lesions, cutaneous, subcutaneous, or lymph node lesions).
- Both pathology and imaging were done, and recurrence confirmed. In this case, whatever examination came first; its date is considered to be the date of recurrence.
- Only imaging was performed, and disease recurrence confirmed.

Note: Sponsor consultation is required if a biopsy cannot be obtained.

8.2.1.6 Tumor Tissue Collection and Assessment of Disease Recurrence

A core biopsy or punch biopsy (fine needle aspirate is not acceptable) will be collected at the time of suspected disease recurrence. Communication from surgeon to local pathologist should follow local practice and institutional guidelines. Pathology results will be entered to eCRF.

Representative specimens of tumor tissue collected will be submitted to the central laboratory for translational research, for participants who agree to participate, as specified in Section 4.2.1.4 – Planned Exploratory Biomarker Research. Any leftover tissue will be archived for FBR if the participant has signed the optional informed consent for FBR as specified in Section 4.2.1.5 – Future Biomedical Research.

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

8.2.1.7 Assessment of Disease Progression (Cross-over/Retreatment Phase Only)

8.2.1.7.1 RECIST 1.1 Assessment of Disease

For participants that start cross-over/retreatment, RECIST 1.1 will be used by investigators 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.

8.2.1.7.2 iRECIST Assessment of Disease

iRECIST is based on RECIST 1.1 but adapted to account for the unique tumor response seen with immunotherapeutic drugs. iRECIST will be used by 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, according to the rules outlined in Appendix 8. 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

- 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. Scans must be sent to the iCRO.

Note: As of Amendment 10, scans are no longer required to be submitted to the iCRO.

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) as defined in Appendix 8, 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.

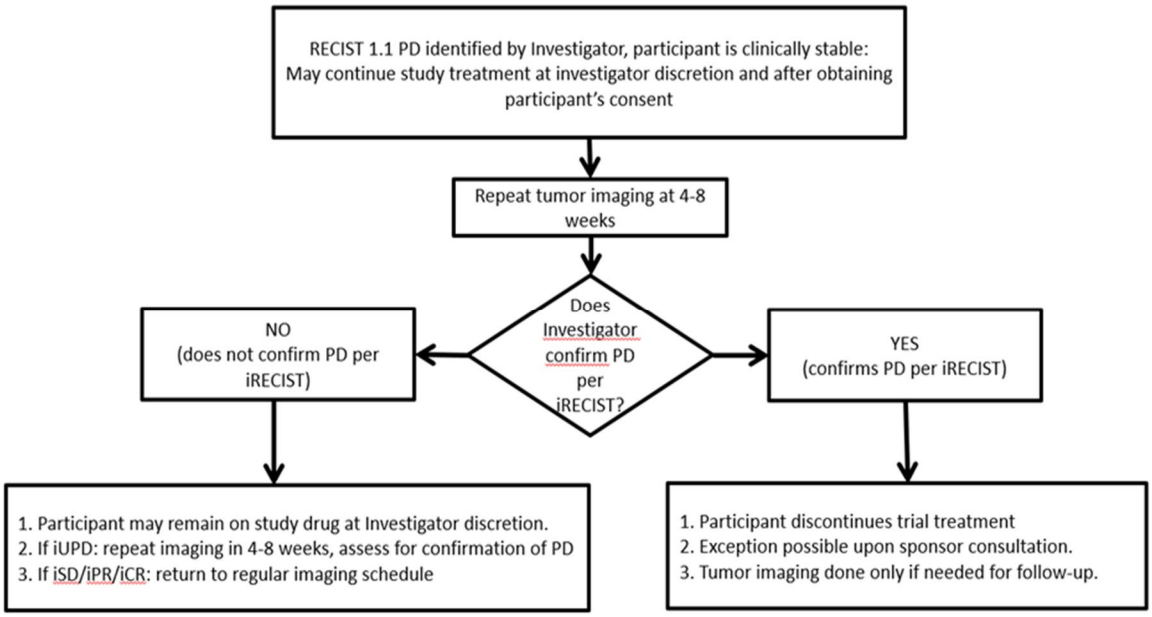
A description of the adaptations and iRECIST process is provided in Appendix 8, with additional details in the iRECIST publication [Seymour, L., et al 2017]. A summary of imaging and treatment requirements after first radiologic evidence of progression is provided in Table 6 and illustrated in Figure 2.

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 per investigator assessment	Repeat imaging at 4 to 8 weeks to confirm PD	May continue study treatment at the assessment of the investigator and after the participant's consent	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.

Figure 2 Imaging and Treatment for Clinically Stable Participants Treated with Pembrolizumab after First Radiologic Evidence of PD Assessed by the Investigator



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.

8.2.1.8 Photography for Cutaneous Lesions

Initial digital photography is required at the time of disease recurrence. Digital color photography should include the initial site of tumor prior to surgery and RT target areas. Any recurrent skin lesion must be followed using color photography, which includes a ruler to estimate lesion size. Specific guidance on how to acquire digital photographs of skin lesions will be provided in the SIM. The timing for capturing cutaneous lesion photographs must follow the same schedule as the imaging scans. All photography is required to be sent to the iCRO.

As of Amendment 10, digital photography for cutaneous lesions is no longer required.

8.2.2 Survival

RFS and OS data will be collected from the time of randomization throughout the study. Definitions of the survival endpoints are provided in Section 9.4 and censoring rules are presented in Section 9.6.1.

At the time of obtaining survival status, evidence of a new high risk primary cSCC or disease recurrence confirmed by biopsy and/or surgery (eg, biopsy and surgery pathology reports) will also be collected for participants in Survival Follow-up who have not yet experienced a new high risk primary cSCC or disease recurrence, if available, and maintained in source documentation and recorded in the database, as appropriate. Additionally, imaging

assessment performed as a part of standard of care to evaluate for disease status for participants in Survival Follow-up who have not yet experienced a new high risk primary cSCC or disease recurrence, should be collected during Survival Follow-up. All available images must be submitted to the iCRO and recorded in the database.

Note: As of Amendment 10, scans are no longer required to be submitted to the iCRO.

8.2.3 Patient-reported Outcomes

The EQ-5D-5L and EORTC QLQ-C30 questionnaires will be administered by trained site personnel and completed electronically by participants in the following order: EORTC QLQ-C30 first, CCI [redacted]. Details regarding time points for administering the questionnaires are outlined in the SoA (Section 1.3).

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

Note: As of Amendment 10, ePRO assessments will be discontinued.

8.3 Safety Assessments

Details regarding specific safety procedures/assessments to be performed in this study are provided below.

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

8.3.1 Physical Examinations

8.3.1.1 Full Physical Examination

The investigator or qualified designee will perform a complete physical examination 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; height will be measure at Screening only. After the first dose of study intervention, new clinically significant abnormal findings should be recorded as AEs.

8.3.1.2 Directed Physical Examination

For visits that do not require a full physical examination as defined in Section 1.3, the investigator or medically qualified designee (consistent with local requirements) will perform a directed physical examination to include a complete skin and lymph node examination as per NCCN cSCC 2018 guidelines [National Comprehensive Cancer Network 2017] prior to the administration of study treatment. New clinically significant abnormal findings should be recorded as AEs.

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

8.3.2 Vital Signs

The investigator or qualified designee will take weight and vital signs at Screening and as specified in the SoA (Section 1.3). Vital signs will be measured after 5 minutes of rest and will include temperature, systolic and diastolic blood pressure, respiratory rate, and pulse. Vital signs should be measured prior to administration of each dose of study treatment.

8.3.3 Electrocardiograms

A standard 12-lead ECG will be obtained and reviewed by an investigator or medically qualified designee (consistent with local requirements) as outlined in the SoA once at Screening. Clinically significant abnormal findings should be recorded as medical history. Additional time points may be performed as clinically necessary.

8.3.4 Clinical Safety Laboratory Assessments

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

- The investigator or medically qualified designee (consistent with local requirements) must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the CRF. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.
- All protocol-required laboratory assessments, as defined in Appendix 2, must be conducted in accordance with the laboratory manual and the SoA.
- If laboratory values from nonprotocol-specified laboratory assessments performed at the institution's local laboratory require a change in study participant management or are considered clinically significant by the investigator (eg, SAE or AE or dose modification), then the results must be recorded in the appropriate CRF (eg, SLAB).
- For any laboratory tests with values considered clinically significantly abnormal during participation In the study or within 30 days after the last dose of study intervention, every attempt should be made to perform repeat assessments until the values return to normal or baseline or if a new baseline is established as determined by the investigator.

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

Details regarding specific laboratory 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 Vendor Manual. Refer to the SoA (Section 1.3) for the timing of laboratory assessments.

Laboratory tests for screening should be performed within 10 days prior to the first dose of study medication. (If the screening labs are collected outside 10 days from treatment allocation, then the Day 1 screening labs will be collected and reviewed before the start of study treatment). After Cycle 1, lab samples can be collected up to 72 hours prior to the scheduled time point. Participants eligible for cross-over treatment should have imaging performed within 28 days and laboratory tests performed within 10 days prior to the first dose of study treatment in the Cross-over Phase.

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

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

8.3.4.2 Pregnancy Testing

- Pregnancy testing:
  - Pregnancy testing requirements for study inclusion are described in Section 5.1.
  - Pregnancy testing (urine and/or serum) should be conducted as per SoA at every protocol cycle.
  - Pregnancy testing (urine and/or serum) should be conducted at the end of relevant systemic exposure. The length of time required to continue pregnancy testing for each study intervention is:
    - MK-3475: 120 days
  - Additional serum or urine pregnancy tests may be performed, as determined necessary by the investigator or required by local regulation, to establish the absence of pregnancy at any time during the participant's participation in the study.

Refer to Appendix 7 for country-specific requirements.

8.3.4.3 HIV, HBV, and HCV Serology

Screening tests are only required if mandated by local regulations. Refer to Appendix 7 for country-specific requirements. HIV, HBV, and HCV serology will be conducted on participants per local regulations and site standard operating procedures. Active hepatitis B is defined as a known positive HBsAg result. Active hepatitis C is defined by a known positive hepatitis C Ab antibody result and known quantitative HCV RNA results greater than the lower limits of detection of the assay.

8.3.5 Performance Assessments

8.3.5.1 Eastern Cooperative Oncology Group Performance Status

The investigator or qualified designee will assess ECOG status (see http://ecog-acrin.org/resources/ecog-performance-status) at screening, before the administration of each dose of study intervention and during the follow-up period as specified in the SoA (Section 1.3).

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

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

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

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

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

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

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

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

All AEs, SAEs, and other reportable safety events that occur after the participant provides documented informed consent, but before intervention allocation/randomization, must be reported by the investigator if the participant is receiving placebo run-in or other run-in treatment, if the event cause the participant to be excluded from the study, or is the result of a

protocol-specified intervention, including, but not limited to washout or discontinuation of usual therapy, diet, or a procedure.

- All AEs from the time of intervention allocation/randomization through 30 days after cessation of study intervention must be reported by the investigator.
- All AEs meeting serious criteria, from the time of intervention allocation/randomization through 90 days after cessation of study intervention or 30 days after cessation of study intervention if the participant initiates new anticancer therapy, whichever is earlier, must be reported by the investigator.
- All pregnancies and exposure during breastfeeding, from the time of intervention allocation/randomization through the time required to eliminate systemic exposure after cessation of study intervention as described in Sections 5.1 and 8.3.4.2, or 30 days after cessation of study intervention if the participant initiates new anticancer therapy must be reported by the investigator.
- Additionally, any SAE brought to the attention of an investigator at any time outside the time specified above must be reported immediately to the Sponsor if the event is considered related to study intervention.

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

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

Exception: A positive pregnancy test at the time of initial screening is not a reportable event unless the participant has received study intervention.

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

Type of Event	Time Period			Time Frame to Report Event and Follow-up Information to Sponsor
	Consent to Randomization/ Allocation	**Randomization/ Allocation Through Protocol-specified Follow-up Period**	**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: - due to intervention - causes exclusion	Report all	Previously reported – Follow to completion/ termination; report outcome	Within 24 hours of learning of event
Event of Clinical Interest (require regulatory reporting)	Report if: - due to intervention - causes exclusion	Report – potential DILI – require regulatory reporting	Not required	Within 24 hours of learning of event
Event of Clinical Interest (Do not require regulatory reporting)	Report if: - due to intervention - causes exclusion	Report – non-DILI ECIs and those not requiring regulatory reporting	Not required	Within 5 calendar days of learning of event

DILI=drug-induced liver injury; ECI=event of clinical interest; NSAE=nonserious adverse event; SAE=serious adverse event.

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

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

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

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All AEs, SAEs, and other reportable safety events, including pregnancy and exposure during breastfeeding, ECIs, cancer, and overdose will be

followed until resolution, stabilization, until the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3). In addition, the investigator will make every attempt to follow all nonserious AEs that occur in randomized participants for outcome. Further information on follow-up procedures is given in Appendix 3.

8.4.4 Regulatory Reporting Requirements for SAE

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

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

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

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

8.4.5 Pregnancy and Exposure During Breastfeeding

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

All reported pregnancies must be followed to the completion/termination of the pregnancy.

Any pregnancy complication will be reported as an AE or SAE.

The medical reason (example: maternal health or fetal disease) for an elective termination of a pregnancy will be reported as an AE or SAE. Prenatal testing showing fetus will be born with severe abnormalities/congenital anomalies that leads to an elective termination of a pregnancy will be reported as an SAE for the fetus.

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

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

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

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

The Sponsor will ensure that unblinded aggregated efficacy endpoint events and safety data are monitored to safeguard the participants in the study.

Any suspected endpoint that upon review is not recurrence of the cancer under study will be forwarded to Global Pharmacovigilance as an SAE within 24 hours of determination that the event is not recurrence of the cancer under study.

8.4.7 Events of Clinical Interest

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

Events of clinical interest for this study include:

- An overdose of Sponsor's product, as defined in Section 8.5, that is not associated with clinical symptoms or abnormal laboratory results.
- An elevated AST or ALT laboratory value that is greater than or equal to 3× the ULN and an elevated total bilirubin laboratory value that is greater than or equal to 2× the ULN and, at the same time, an alkaline phosphatase laboratory value that is less than 2× the ULN, as determined by way of protocol-specified laboratory testing or unscheduled laboratory testing.*
  *Note: These criteria are based on available regulatory guidance documents. The purpose of the criteria is to specify a threshold of abnormal hepatic tests that may require an additional evaluation for an underlying etiology. The study-site guidance for assessment and follow up of these criteria can be found in the Investigator Study File Binder (or equivalent).

  It may also be appropriate to conduct additional evaluation for an underlying etiology in the setting of abnormalities of liver blood tests including AST, ALT, bilirubin, and alkaline phosphatase that do not meet the criteria noted above. In these cases, the decision to proceed with additional evaluation will be made through consultation between the study investigators and the Sponsor Clinical Director. However, abnormalities of liver blood tests that do not meet the criteria noted above are not ECIs for this study.

8.5 Treatment of Overdose

For this study, an overdose of pembrolizumab will be defined as any dose of 1000 mg or greater.

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

8.6 Pharmacokinetics

PK parameters will not be evaluated in this study.

8.7 Pharmacodynamics

Pharmacodynamic parameters will not be evaluated in this study.

8.8 Biomarkers

CCI [redacted]

8.8.1 Planned Genetic Analysis Sample Collection

CCI [redacted]

CCI [redacted]

8.9 Future Biomedical Research Sample Collection

If the participant provides documented informed consent for FBR, the following specimens will be obtained as part of FBR:

Biomarker samples listed in Section 8.8.

8.10 Medical Resource Utilization and Health Economics

All-cause hospitalizations and emergency department visits must be reported in the eCRF from the time of treatment allocation/randomization through 90 days after cessation of study intervention or 30 days after cessation of study intervention 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 in Section 8.

8.11.1 Screening

Documented informed consent must be provided before performing any protocol-specific procedure. Results of a test performed before the participant signing consent as part of routine clinical management are acceptable in lieu of a screening test if performed within the specified time frame.

Screening procedures are to be completed within 28 days before the first dose of study intervention. Except for the following:

- Laboratory tests are to be performed within 10 days prior to the first dose of study intervention. An exception is hepatitis testing, which may be done up to 28 days prior to the first dose of study intervention.
- Evaluation of ECOG is to be performed within 10 days prior to the first dose of study treatment.
- For women of reproductive potential, a urine or serum pregnancy test will be performed within 72 hours prior to the first dose of study treatment. If urine pregnancy results cannot be confirmed as negative, a serum pregnancy test will be required (performed by the local study site laboratory).

Refer to Appendix 7 for Germany and UK-specific requirements.

- Archival tumor sample collection is not required to be obtained within 28 days prior to the first dose of study treatment. The tumor sample must be collected within the past 5 years prior to randomization.

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

8.11.2 Adjuvant Treatment Period Visits

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

The Adjuvant Treatment Phase is expected to start at a range of 4 to 16 weeks after the last dose of RT. If performed outside of this window, Sponsor consultation will be required. At the start of the study, participants will be advised by the investigator regarding the use of sun protection and self-examination of skin and lymph nodes, as per NCCN cSCC 2018 guidelines [National Comprehensive Cancer Network 2017].

8.11.3 Posttreatment Visit

Post-treatment visit requirements are outlined in the SoA (Section 1.3.2).

8.11.3.1 End of Treatment Visit

The End of Treatment visit should occur at the time study treatment is completed or discontinued for any reason. Participants who are eligible for cross-over/retreatment with pembrolizumab may have 2 End of Treatment visits, 1 after the initial Adjuvant Treatment Period and 1 after cross-over/retreatment.

Participants who discontinue study treatment for a reason other than a new high risk primary cSCC or disease recurrence will still be considered on study and should continue with regularly scheduled assessments (see Section 8.11.4), including collecting participant information on the start of new anticancer therapy, a new high risk primary cSCC or disease recurrence, and death. If the End of Treatment visit occurs 30 days from the last dose of study treatment, at the same time as the mandatory 30-Day Safety Follow-up visit, the End of Treatment visit procedures and any additional Safety Follow-up procedures can be combined into a single visit.

Participants who discontinue study treatment due to disease recurrence will be unblinded. Participants in the placebo group will be offered to cross over and receive pembrolizumab, if cross-over eligibility criteria are met (Section 8.1.8.1.2).

8.11.3.2 Safety Follow-up Visit

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

Participants who are eligible for cross-over/retreatment with pembrolizumab may have 2 Safety Follow-up visits, 1 after the initial Adjuvant Treatment Period and 1 after cross over/retreatment.

8.11.3.3 Study Adjuvant Follow-up Visits

Participants who complete study adjuvant treatment or discontinue study adjuvant treatment for a reason other than a new high risk primary cSCC or disease recurrence will move into the Study Adjuvant Follow-up Phase and should be assessed in office every 12 weeks (±7 days) until end of Year 2 (measured from time of randomization), then every 6 months until the end of Year 5, to monitor disease status. After Year 5, participants will move into Survival Follow-up. Any additional tests/investigations or imaging assessments for recurrent disease or safety will be at the discretion of participant's treating physician per local SoC. Every effort should be made to collect information regarding disease status until a new high risk primary cSCC or disease recurrence, death, or end of study. Information regarding post-study anticancer treatment will be collected if new treatment is initiated.

Participants who discontinue Study Adjuvant Follow-up Phase early, have entered Survival Follow-up, and have not experienced a new high risk primary cSCC or disease recurrence, will be requested to have standard of care imaging assessments/biopsy performed to evaluate disease status. All imaging assessments must be uploaded to the iCRO.

Details are provided in the SoA (Section 1.3.3) for cross-over/retreatment with pembrolizumab.

For a participant who dies during the Follow-up period, date and cause of death should be recorded in the appropriate eCRF.

Participants in Study Adjuvant Follow-up will be followed for treatment-related toxicities for up to Year 5 and should be recorded.

8.11.3.4 Survival Follow-up Contacts

Participant survival follow-up status will be assessed approximately every 12 weeks to assess for survival status until death, withdrawal of consent, or the end of the study, whichever occurs first.

The first survival follow-up assessment should be scheduled as described below:

- For participants who discontinue treatment intervention and who will not enter Adjuvant Follow-up, 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 Adjuvant Follow-up, the first survival follow-up contact will be scheduled 12 weeks after the last Adjuvant Follow-up assessment follow-up visit has been performed.

8.11.4 Participants Discontinued From Study Intervention but Continuing to be Monitored in the Study

Participants who discontinue study treatment for reasons other than a new high risk primary cSCC or disease recurrence will enter Safety and Study Adjuvant Follow-up and undergo all assessments at the scheduled time points per the SoA (Section 1.3) as described in Sections 8.11.3.2, 8.11.3.3, and 8.11.3.4.

As of Amendment 10, ePRO assessments will no longer be required. Digital photography of cutaneous lesions is not required and tumor scans no longer need to be submitted to the iCRO.

Participants that discontinue study treatment due to a new high risk primary cSCC or disease recurrence will have Safety Follow-up and then proceed directly to Survival Follow-up as described in Section 8.11.3.4. Participants who discontinue study treatment because of the start of new anticancer treatment will enter Safety Follow-up and then proceed directly to Adjuvant Follow-up as described in Section 8.11.3.3.

8.11.5 Vital Status

To ensure current and complete survival information (vital status) is available at the time of database locks, updated vital status may be requested during the study by the Sponsor. For example, updated vital status may be requested before but not limited to, an eDMC review, CCI [redacted]. Upon Sponsor notification, all participants who do not/will not have a scheduled study visit or study contact during the Sponsor-defined period will be contacted for their vital status.

9 STATISTICAL ANALYSIS PLAN

As of Amendment 10, the SAP is amended as follows:

NOTE: Based on the data from the interim efficacy and safety analysis for KN630 (data cutoff 28-JUN-2024) reviewed by eDMC on 21-AUG-2024, the study will be discontinued. Pembrolizumab did not cross the boundary for statistical significance in RFS by investigator assessment compared to placebo. OS point estimate did not favor pembrolizumab versus placebo, although not formally tested based on the prespecified multiplicity strategy. The eDMC recommended that the study should be stopped for futility as the risk/benefit profile did not support continuing the trial. Based upon these data and the recommendation of the eDMC, the study was unblinded on 22-AUG-2024. The prespecified final efficacy analysis of the study described in the SAP will not be performed. Efficacy and safety analyses will be performed at the end of the study; there will be no further planned analyses for ePRO endpoints.

This section outlines the statistical analysis strategy and procedures for the study. The study has been unblinded as of 22-AUG-2024. Changes made to primary and/or key secondary hypotheses, or the statistical methods related to those hypotheses that occurred prior to Amendment 10 were documented in previous protocol amendments (consistent with ICH Guideline E-9). Changes to exploratory or other non-confirmatory analyses made after the protocol has been finalized, but prior to the conduct of any analysis, will be documented in an sSAP and referenced in the CSR for the study. The PRO analysis plan will also be included in the sSAP. CCI [redacted]

9.1 Statistical Analysis Plan Summary

Key elements of the statistical analysis plan are summarized below; the comprehensive plan is provided in Sections 9.2 through 9.12. As of Amendment 10, the prespecified final efficacy analysis of the study described in the SAP will not be performed. Efficacy and safety analyses will be performed at the end of the study; there will be no further planned analyses of ePRO endpoints. The SAP summary has been updated accordingly.

Study Design Overview	A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate Pembrolizumab versus Placebo as Adjuvant Therapy Following Surgery and Radiation of High-Risk Locally Advanced Cutaneous Squamous Cell Carcinoma (LA cSCC).
Treatment Assignment	As of Amendment 10, 450 participants have been randomized 1:1 into pembrolizumab group and control group and no additional participants will be randomized. • Pembrolizumab Group: Pembrolizumab 400 mg Q6W • Control Group: placebo This study will be conducted as a double-blind study. Stratification factors are as follows: • Extracapsular extension (yes vs. no) • Cortical bone invasion (yes vs. no) • Prior systemic therapy (yes vs. no)

Analysis Populations	Efficacy: Intention-to-Treat (ITT) Safety: All Participants as Treated (APaT) PRO: Full Analysis Set (FAS)
Primary Endpoint(s)	Recurrence-free Survival (RFS)
Key Secondary Endpoints	Overall Survival (OS)
Statistical Methods for Key Efficacy Analyses	The primary hypothesis for RFS will be evaluated by comparing pembrolizumab to placebo using a stratified log-rank test. Estimation of the hazard ratio (HR) will be done using a stratified Cox regression model. Event rates over time will be estimated within each treatment group using the Kaplan-Meier method. The same method for the analysis of RFS will be applied to the key secondary hypothesis for OS.
Statistical Methods for Key Safety Analyses	For specific AEs that meet predefined threshold rules, point estimates and 95% CIs for the differences between treatment groups in the percentages of participants with events will be provided using the Miettinen and Nurminen (M&N) method [Miettinen, O. and Nurminen, M. 1985].
Interim Analyses	CCI [redacted]
Multiplicity	
Sample Size and Power	

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.

After efficacy IA, the study was unblinded on 22-AUG-2024.

This study will be conducted as a double-blind study under in-house blinding procedures. 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. The investigator will request authorization for official unblinding upon disease recurrence and consideration to proceed to cross-over to or receive retreatment with pembrolizumab.

The Clinical Biostatistics department will generate the randomized allocation schedule(s) for study treatment assignment. Randomization will be implemented in an IRT.

The investigator will be blinded to participant-level biomarker results.

CCI [redacted]

9.3 Hypotheses/Estimation

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

9.4 Analysis Endpoints

Primary and secondary efficacy, safety and PRO endpoints that will be evaluated for within- and/or between-treatment differences are listed below. CCI [redacted]

9.4.1 Efficacy Endpoints

Primary

Recurrence-free survival (RFS): the time from the date of randomization to the date of first of the following events:

- Local or regional recurrence of the index lesion
- Distant metastasis
- Death due to any cause

For disease recurrence, the assessment will be based on investigator assessment with biopsy confirmation. Only if a biopsy cannot be performed due to feasibility, disease recurrence will be based on radiographic imaging only. In addition, a second new low risk primary cSCC is not considered as an RFS event. However, a new high risk primary cSCC is considered an RFS event.

Secondary

Overall survival (OS): the time from randomization to death due to any cause.

9.4.2 Safety Endpoints

Safety measurements are described in Section 4.2.1.2 and Section 8.

9.4.3 PRO Endpoints

The following main PRO endpoint will be evaluated as described in Section 4.2.1.3:

- Global health status/ QoL scales from EORTC QLQ-C30.
- Physical function scale from EORTC QLQ-C30.

CCI [redacted]

9.5 Analysis Populations

9.5.1 Efficacy Analysis Population

CCI [redacted]

9.5.2 Safety Analysis Population

CCI [redacted]

[redacted]

9.5.3 PRO Analysis Population

CCI [redacted]

9.6 Statistical Methods

NOTE: As of Amendment 10, the prespecified final efficacy analysis of the study described in the SAP will not be performed. Efficacy and safety analyses will be performed at the end of the study; there will be no further planned analyses of ePRO endpoints. Original protocol text that is contained in this section has been retained for reference. For the efficacy analyses to be performed at the end of study, there will be no formal comparisons between treatment arms. Nominal p-values will be provided.

9.6.1 Statistical Methods for Efficacy Analyses

This section describes the statistical methods that address the primary and secondary objectives. CCI

CCI

9.6.1.1 Recurrence-free Survival

The non-parametric 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 PH model with Efron's method of tie handling will be used to assess the magnitude of the treatment difference (ie, HR) between the treatment group and placebo group. The HR and its 95% CI from the Cox model with Efron's method of tie handling and with a single treatment covariate will be reported. The stratification factors used for randomization (see Section 6.3.2) will be applied to both the stratified log-rank test and the stratified Cox model. In the event that there are small number of events in one or more strata, for the purpose of analysis, strata will be combined to ensure sufficient number of events in each stratum. CCI

Since disease recurrence is assessed periodically, recurrence can occur any time in the time interval between the last assessment where recurrence was not documented and the assessment when recurrence is first documented. The true date of recurrence will be approximated by the date of the first assessment at which recurrence is objectively documented. Death is always considered as an event. Participants who do not experience a recurrence event will be censored at the last disease assessment.

CCI

CCI [redacted]

Table 8 Censoring Rules for Primary and Sensitivity Analyses of RFS

CCI [redacted]

9.6.1.2 Overall Survival

The non-parametric 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 PH 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 Cox model with a single treatment covariate will be reported. The stratification factors used for randomization (see Section 6.3.2) will be applied to both the stratified log-rank test and the stratified Cox model. CCI [redacted]

CCI [redacted]

CCI [redacted]

9.6.1.3 Summary of Efficacy Analysis Methods

A summary of the primary analysis strategy for the primary and secondary efficacy endpoints is provided in Table 9.

Table 9 Efficacy Analysis Methods for Primary and Secondary Efficacy Endpoints

Endpoint/Variable (Description, Time Point)	Statistical Method	Analysis Population	Missing Data Approach
Primary Analyses:			
RFS (investigator assessment with biopsy confirmation)	Testing: stratified Log-rank test Estimation: stratified Cox model with Efron's tie handling method	ITT	Censored according to rules in Table 8.
Secondary Analyses:			
OS	Testing: stratified Log-rank test Estimation: stratified Cox model with Efron's tie handling method	ITT	Censored at last date when participant was known to be alive
RFS=recurrence-free survival; ITT=intent-to-treat; OS=overall survival			

9.6.2 Statistical Methods for Safety Analyses

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

The overall safety evaluation will include a summary by treatment group of the number and percentage of participants with at least one AE, drug-related AE, serious AE, serious drug-related AE, Grade 3-5 AE, drug-related Grade 3-5 AE, discontinuation from study intervention due to an AE, and an AE resulting in death.

The number and percentage of participants with specific AEs will also be provided. Point estimate and 95% CIs for the difference between treatment groups in the percentage of participants with specific AEs will be provided for AEs that occur in at least CCI [redacted] of participants in any treatment group. The threshold of at least CCI [redacted] of participants was chosen because the population enrolled in this study is in critical condition and usually experiences various AEs of similar types regardless of treatment; events reported less frequently than CCI [redacted] of participants would obscure the assessment of the overall safety profile and add little to the interpretation of potentially meaningful treatment differences. In addition, difference in the percentage of participants with specific Grade 3-5 AEs CCI [redacted] and SAEs CCI [redacted] will also be

summarized by point estimate and 95% CI. Rainfall plots with point estimates and 95% CIs will be displayed for specific AEs, specific Grade 3-5 AEs, and specific SAEs that meet the corresponding predefined threshold rules.

CIs for between treatment group differences will be provided using the M&N method [Miettinen, O. and Nurminen, M. 1985]. Because many 95% CIs may be provided without adjustment for multiplicity, the CIs should be regarded as helpful descriptive measures for the review of the safety profile and not as a formal method for assessing the statistical significance of the between-group differences.

The number and percentage of participants with laboratory toxicity grade increased from baseline will be summarized by the post-baseline maximum toxicity grade per CTCAE Version 4.0 for each gradable laboratory test.

For continuous safety measures, such as change from baseline in laboratory and vital signs, summary statistics for baseline, on-treatment, and change from baseline values will be provided.

Assessment of Safety Topics of Special Interest

AEs that are immune-mediated or potentially immune-mediated are considered safety topics of special interest (AEOSI) in this study. These events have been characterized consistently throughout the pembrolizumab clinical development program. Point estimates and 95% CIs for between-group difference is not expected to add value to the safety evaluation, and hence only number and percentage of participants with such pembrolizumab AEOSI will be provided, as well as the number and percentage of participants with corticosteroids administration to treat an AEOSI. Summary statistics will be provided for the analysis of time from first dose to the onset of an AEOSI. Table 10 summarizes the analysis strategy for safety endpoints in this study.

Table 10 Analysis Strategy for Safety Parameters

Analysis Part	Safety Endpoint	Descriptive Statistics	95% between-group CI (Graphical display)
Overall Safety Assessment	Specific AEs [redacted]	X	X
	Specific Grade 3-5 AE [redacted]	X	X
	Specific serious AE [redacted]	X	X
	Any AE	X	
	Any Grade 3-5 AE	X	
	Any serious AE	X	
	Any drug-related AE	X	
	Any serious and drug-related AE	X	
	Any Grade 3-5 and drug-related AE	X	
	Discontinuation of study treatment due to AE	X	
	Interruption of study treatment due to AE	X	
	AE that resulted in death	X	
	Laboratory toxicity grade increase from baseline	X	
	Change from baseline results (vital signs)	X	
Assessment of safety topics of special interest	Pembrolizumab AEOSI	X	

AE=adverse event; AEOSI=adverse event of special interest; CI=confidence interval

9.6.3 Statistical Methods for PRO Analyses

To assess the treatment effects on the PRO score changes from baseline in the global health status/QoL and physical function outcomes, a constrained longitudinal data analysis model will be applied, with the PRO score as the response variable, and treatment, time, stratification factors, the treatment by time interaction as covariates. The differences in the least square mean change from baseline will be evaluated. The long-term treatment effect on PRO score change from baseline will be primarily evaluated and compared in both treatment arms at 1 year adjuvant follow-up, and each year during the study adjuvant follow-up phase.

9.6.4 Summaries of Baseline Characteristics and Demographics

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

9.7 CCI [redacted]

CCI [redacted]

9.7.1 CCI [redacted]

CCI [redacted]

9.7.2 CCI [redacted]

CCI [redacted]

9.8 CCI [redacted]

CCI [redacted]

9.8.1 CCI [redacted]

CCI [redacted]

CCI

[redacted]

CCI [redacted]

9.9 Sample Size and Power Calculations

This study is well-powered for the primary efficacy endpoint for comparisons. Enrollment of 430 participants is assumed to occur over 58 months.

NOTE: As of Amendment 10, the study randomized 450 participants in a 1:1 ratio into the pembrolizumab and placebo arms. Because no statistical testing will be performed, the power calculations are not applicable.

Recurrence-free Survival

The RFS hypothesis testing strategy was designed fo CCI [redacted]

CCI [redacted]

Overall Survival

At α = 0.025 (one-sided), the final OS hypothesis test yields CCI [redacted] power to detect a HR of CCI [redacted]. The duration of OS in the placebo group is assumed to follow CCI [redacted]

Power and CCI [redacted] for RFS and OS were performed using the CCI [redacted].

9.10 Subgroup Analyses

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

CCI [redacted]

The consistency of the treatment effect will be assessed descriptively via summary statistics by category for the classification variables listed above. In addition, a Forest plot will be produced, which provides the estimated point estimates and CIs for the treatment effect across the categories of subgroups listed above. If the number of participants in a category of a subgroup variable is less than 10%, the subgroup analysis will not be performed for this category of the subgroup variable, and this subgroup variable will not be displayed in the forest plot. The subgroup analyses will be conducted using the unstratified analysis based on the corresponding analysis method for RFS and OS.

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

Extent of exposure for a participant is defined as number of cycles in which the participant receives the study treatment infusion. Summary statistics will be provided on Extent of Exposure for APaT population.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

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

10.1.1 Code of Conduct for Interventional Clinical Trials

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

Code of Conduct for Interventional Clinical Trials

I. Introduction

A. Purpose

MSD, through its subsidiaries, conducts clinical trials worldwide to evaluate the safety and effectiveness of our products. As such, we are committed to designing, implementing, conducting, analyzing and reporting these trials in compliance with the highest ethical and scientific standards. Protection of participants in clinical trials is the overriding concern in the design of clinical trials. In all cases, MSD clinical trials will be conducted in compliance with local and/or national regulations (eg, 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 (eg, contract research organizations, collaborative research efforts). This Code is not intended to apply to trials that are observational in nature, or which are retrospective. Further, this Code does not apply to investigator-initiated trials, which are not under the full control of MSD.

II. Scientific Issues

A. Trial Conduct

1. Trial Design

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

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

2. Site Selection

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

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

3. Site Monitoring/Scientific Integrity

Investigative trial sites are monitored to assess compliance with the trial protocol and 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 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 (eg, 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, frequently known as a financial disclosure form, provided by the Sponsor. The investigator/subinvestigator(s) also consent to the transmission of this information to the Sponsor in the United States for these purposes. This may involve the transmission of information to countries that do not have laws protecting personal data.

10.1.3 Data Protection

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

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

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

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

10.1.3.1 Confidentiality of Data

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

10.1.3.2 Confidentiality of Participant Records

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

This study was developed in collaboration with an 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 EOC is comprised of members of Sponsor Senior Management. The EOC will receive and decide on any recommendations made by the eDMC or Steering Committee regarding the study.

10.1.4.3 External Data Monitoring Committee

To supplement the routine study monitoring outlined in this protocol, an external DMC will monitor the [redacted] 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. [redacted]

Specific details regarding composition, responsibilities, and governance, including the roles and responsibilities of the various members and the external collaborating organization 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 ICMJE authorship requirements.

10.1.6 Compliance with Study Registration and Results Posting Requirements

Under the terms of the FDAAA of 2007 and the EMA clinical trials Regulation 536/2014, the Sponsor of the study is solely responsible for determining whether the study and its results are subject to the requirements for submission to http://www.clinicaltrials.gov, www.clinicaltrialsregister.eu, https://euclinicaltrials.eu, or other local registries. MSD, as Sponsor of this study, will review this protocol and submit the information necessary to fulfill these requirements. MSD entries are not limited to FDAAA or the EMA clinical trials Regulation 536/2014 mandated trials. Information posted will allow participants to identify potentially appropriate studies for their disease conditions and pursue participation by calling a central contact number for further information on appropriate study locations and study-site contact information.

By signing this protocol, the investigator acknowledges that the statutory obligations under FDAAA, the EMA clinical trials Regulation 536/2014, or other locally mandated registries are that of the Sponsor and agrees not to submit any information about this study or its results to those registries.

10.1.7 Compliance with Law, Audit, and Debarment

By signing this protocol, the investigator agrees to conduct the study in an efficient and diligent manner and in conformance with this protocol, generally accepted standards of GCP (eg, ICH GCP: Consolidated Guideline and other generally accepted standards of GCP), and all applicable federal, state, and local laws, rules, and regulations relating to the conduct of the clinical study.

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

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

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

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

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

10.1.8 Data Quality Assurance

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

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

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

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

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

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

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

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

10.1.9 Source Documents

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

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

10.1.10 Study and Site Closure

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

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

10.2 Appendix 2: Clinical Laboratory Tests

- The tests detailed in Table 15 will be performed by the local laboratory.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Sections 5.1 and 5.2 of the protocol.
- Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.

Table 15 Protocol-required Safety Laboratory Assessments

Laboratory Assessments	**Parameters**			
Hematology	Platelet Count RBC Count Hemoglobin Hematocrit	RBC Indices: MCV MCH		WBC count with Differential: Neutrophils Lymphocytes Monocytes Eosinophils Basophils
Chemistry	Blood Urea Nitrogen (BUN)[a]	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)
	Creatinine	A measure of CO_2 or bicarbonate[b]	Chloride	Phosphorous
	Creatinine clearance (CrCl)[c] or GFR	Sodium	Alanine Aminotransferase (ALT)/ Serum Glutamic-Pyruvic Transaminase (SGPT)	Total Protein
	Glucose (fasting or nonfasting, as per local SOP)	Calcium[d]	Alkaline phosphatase	Magnesium
	Albumin			
Coagulation tests (Screening)[e]	Prothrombin (PT) or International normalized ratio (INR)		Activated partial thromboplastin time (aPTT)[f]	
Routine Urinalysis	• Specific gravity • pH, glucose, protein, blood, ketones, [bilirubin, urobilinogen, nitrite, leukocyte esterase] by dipstick • Microscopic examination (if blood or protein is abnormal)			

Laboratory Assessments	Parameters
Other Screening Tests	• Follicle-stimulating hormone and estradiol (as needed in POCBP only) • Serum or urine β-human chorionic gonadotropin (β-hCG) pregnancy test (as needed for POCBP. Refer to Section 8.3.4.2) • Note: Refer to Appendix 7 for country-specific requirements • Serology (HIV antibody, hepatitis B surface antigen [HBsAg], and hepatitis C virus antibody) is not required unless mandated by local health authority. Note: For countries that mandate testing at screening see Appendix 7 – Country-specific Requirements. If required, testing will be conducted per local regulations and site SOPs. • Total free triiodothyronine (T3)[g] • Free thyroxine (FT4)[g] • Thyroid-stimulating hormone (TSH)

NOTES:
BUN=blood urea nitrogen; CrCl=creatinine clearance; GFR=glomerular filtration rate; HIV=human immunodeficiency virus; MCH=mean corpuscular hemoglobin; MCV=mean corpuscular volume; RBC=red blood cell; ULN=upper limit of normal; WBC=white blood cell

a. BUN is preferred; if not available, urea may be tested.
b. Performed if available as SoC in your region. The carbon dioxide may be either a measurement of CO_2 or bicarbonate as an electrolyte.
c. CrCl should be calculated per institutional standard.
d Corrected calcium should be checked for participants with hypoalbuminemia.
e. Any participant receiving anticoagulant therapy should have coagulation tests monitored closely throughout the study.
f. PTT may be performed if the local lab is unable to perform aPTT.
g. In case of elevated TSH, add free T3 and free T4. Free T3 if available as SoC in your region. If not available locally, thyroid function testing can be performed by the central laboratory

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

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

10.3.1 Definitions of Medication Error, Misuse, and Abuse

Medication Error

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

Misuse

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

Abuse

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

10.3.2 Definition of AE

AE definition

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

Events meeting the AE definition

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator.
- Exacerbation of a chronic or intermittent preexisting condition including either an increase in frequency and/or intensity of the condition.

- New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication.
- For all reports of overdose (whether accidental or intentional) with an associated AE, the AE term should reflect the clinical symptoms or abnormal test result. An overdose without any associated clinical symptoms or abnormal laboratory results is reported using the terminology "accidental or intentional overdose without adverse effect."
- Any new cancer (that is not a condition of the study). Progression of the cancer under study is not a reportable event. Refer to Section 8.4.6 for additional details.

Events NOT meeting the AE definition

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

10.3.3 Definition of SAE

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

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

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

c. Requires inpatient hospitalization or prolongation of existing hospitalization
   - Hospitalization is defined as an inpatient admission, regardless of length of stay, even if the hospitalization is a precautionary measure for continued observation. (Note: Hospitalization for an elective procedure to treat a 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 participant's medical history.

d. Results in persistent or significant disability/incapacity
   - The term disability means a substantial disruption of a person's ability to conduct normal life functions.
   - This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) that may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect
   - In offspring of participant taking the product regardless of time to diagnosis.

f. Other important medical events
   - Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent 1 of the other outcomes listed in the above definition. These events should usually be considered serious.
   - Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

10.3.4 Additional Events Reported in the Same Manner as SAE

Additional events that require reporting in the same manner as SAE

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

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

10.3.5 Recording AE and SAE

AE and SAE recording

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

Assessment of intensity/toxicity

- An event is defined as "serious" when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, not when it is rated as severe.
- The investigator will make an assessment of intensity for each AE and SAE (and other reportable safety event) according to the NCI CTCAE, version 4.0. Any AE that changes CTCAE grade over the course of a given episode will have each change of grade recorded on the AE CRFs/worksheets.
  - Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
  - Grade 2: Moderate; minimal, local, or noninvasive intervention indicated; limiting age-appropriate instrumental ADL.
  - Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL.
  - Grade 4: Life-threatening consequences; urgent intervention indicated.
  - Grade 5: Death related to AE.

Assessment of causality

- Did the study intervention cause the AE?
- The determination of the likelihood that the study intervention 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 study intervention and the AE; the greater the correlation with the components and their respective elements (in number and/or intensity), the more likely the study intervention caused the AE:**
  - **Exposure:** Is there evidence that the participant was actually exposed to the study intervention 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 study intervention? Is the time of onset of the AE compatible with a drug-induced effect (applies to studies with IMP)?
  - **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 study intervention 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 study intervention; (3) the study is a single-dose drug study; or (4) study intervention (s) is/are only used 1 time.)
  - **Rechallenge:** Was the participant reexposed to the study intervention 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; (2) the study is a single-dose drug study; or (3) study intervention (s) is/are used only 1 time.)

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

- **Consistency with study intervention profile:** Is the clinical/pathological presentation of the AE consistent with previous knowledge regarding the study intervention or drug class pharmacology or toxicology?
- The assessment of relationship will be reported on the case report forms/worksheets by an investigator who is a qualified physician according to their 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 study intervention relationship).
  - Yes, there is a reasonable possibility of study intervention relationship:
    - There is evidence of exposure to the study intervention. The temporal sequence of the AE onset relative to the administration of the study intervention is reasonable. The AE is more likely explained by the study intervention than by another cause.
  - No, there is not a reasonable possibility of study intervention relationship:
    - Participant did not receive the study intervention OR temporal sequence of the AE onset relative to administration of the study intervention is not reasonable OR the AE is more likely explained by another cause than the study intervention. (Also entered for a participant with overdose without an associated AE.)
- The investigator must review and provide an assessment of causality for each AE/SAE and document this in the medical notes.
- 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 their opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is 1 of the criteria used when determining regulatory reporting requirements.
- For studies in which multiple agents are administered as part of a combination regimen, the investigator may attribute each AE causality to the combination regimen or to a single agent of the combination. In general, causality attribution should be assigned to the combination regimen (ie, to all agents in the regimen). However, causality attribution may be assigned to a single agent if in the investigator's opinion, there is sufficient data to support full attribution of the AE to the single agent.

Follow-up of AE and SAE

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

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

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

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

SAE reporting to the Sponsor via paper CRF

- If the EDC tool is not operational, facsimile transmission or secure 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 Study File Binder (or equivalent).

10.4 Appendix 4: Medical Device and Drug–Device Combination Products: Product Quality Complaints/Malfunctions: Definitions, Recording, and Follow-up

Not Applicable

10.5 Appendix 5: Contraceptive Guidance

10.5.1 Definitions

Participants of Childbearing Potential (POCBP)

A participant assigned female sex at birth is considered fertile following menarche and capable of becoming pregnant until becoming postmenopausal unless permanently sterile (see below):

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

Participants assigned female sex at birth who are in the following categories are not capable of becoming pregnant and, therefore, not considered POCBP:

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

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

  Note: Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.
- Postmenopausal
  - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
    - A high FSH level in the postmenopausal range may be used to confirm a postmenopausal state in participants assigned female sex at birth who are not using hormonal contraception or HRT. However, in the absence of 12 months of amenorrhea, confirmation with 2 FSH measurements in the postmenopausal range is required.
  - Participants assigned female sex at birth who are on HRT and whose menopausal status is in doubt will be required to use one of the nonhormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

10.5.2 Contraceptive Requirements

Contraceptives allowed during the study include:
Highly Effective Contraceptive Methods That Have Low User Dependency[a] *Failure rate of <1% per year when used consistently and correctly.*
• Progestogen-only subdermal contraceptive implant[b] • IUS[c] • Nonhormonal IUD • Bilateral tubal occlusion
• Azoospermic partner (vasectomized or secondary to medical cause) – All sexual partner(s) of the POCBP must be azoospermic. The participant must provide verbal confirmation of partner azoospermia during Medical History. If not, an additional highly effective method of contraception should be used. A spermatogenesis cycle is approximately 90 days.
Highly Effective Contraceptive Methods That Are User Dependent *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
Sexual Abstinence • Sexual abstinence is considered a highly effective method only if defined as refraining from penile-vaginal intercourse with a partner capable of producing sperm, during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.
[a] Typical use failure rates are higher than perfect-use failure rates (ie, when used consistently and correctly). [b] If locally required, in accordance with CTFG guidelines, acceptable contraceptives are limited to those which inhibit ovulation. [c] IUS is a progestin-releasing IUD. Note: • Tubal occlusion includes tubal ligation

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

1. Definitions

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

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

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

d. DNA: Deoxyribonucleic acid.

e. RNA: Ribonucleic acid.

2. Scope of Future Biomedical Research[3, 4]

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

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

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

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

3. Summary of Procedures for Future Biomedical Research[3, 4]

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[3, 4]

In order to optimize the research that can be conducted with future biomedical research specimens, it is critical to link participants' 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 sex, age, medical history, and intervention outcomes is 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 that 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[3, 4]

Specimens obtained for the Sponsor will be used for analyses using good scientific practices. Analyses using 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[3, 4]

Participants may withdraw their consent for FBR and ask that their biospecimens not be used for FBR. Participants may withdraw consent at any time by contacting the study investigator. If medical records for the study are still available, the investigator will contact the Sponsor using the designated mailbox (clinical.specimen.management@MSD.com). Subsequently, the participant's specimens will be flagged in the biorepository and restricted to study use only. If specimens were collected from study participants specifically for FBR, 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 before 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.

If the medical records for the study are no longer available (eg, if the investigator is no longer required by regulatory authorities to retain the 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[3, 4]

Future biomedical research specimens will be stored in the biorepository for potential analysis for up to 20 years from the end of the 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 used 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[3, 4]

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[3, 4]

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[3, 4]

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[3, 4]

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

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

12. Questions

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

13. References

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

10.7 Appendix 7: Country-specific Requirements

10.7.1 France

Patients should be permanently discontinued from study treatment if any of the following AEs occur:

- Steven-Johnson Syndrome
- Toxic-epidermal necrolysis
- Recurrent Grade 3 Colitis

Table 3 Dose modification and toxicity management guidelines for immune-related AEs associated with pembrolizumab

General instructions:
1. Corticosteroid taper should be initiated upon AE improving to Grade 1 or less and continue to taper over at least 4 weeks.
2. For situations where pembrolizumab has been withheld, pembrolizumab can be resumed after AE has been reduced to Grade 1 or 0 and corticosteroid has been tapered. Pembrolizumab must be permanently discontinued if AE does not resolve within 12 weeks of last dose or corticosteroids cannot be reduced to ≤10 mg prednisone or equivalent per day within 12 weeks.
3. For severe and life-threatening irAEs, IV corticosteroid should be initiated first followed by oral steroid. Other immunosuppressive treatment should be initiated if irAEs cannot be controlled by corticosteroids.

Immune-related AEs	**Toxicity grade or conditions (CTCAE Version 4.0)**	**Action taken to pembrolizumab**	**irAE management with corticosteroid and/or other therapies**	**Monitor and follow-up**
Diarrhea / Colitis	Grade 4 or recurrent Grade 3	Permanently discontinue	• 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 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.
Skin Reactions	Grade 3 or suspected Stevens-Johnson Syndrome or Toxic-epidermal necrolysis	Withhold	• Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper	
	Grade 4 or confirmed Stevens-Johnson Syndrome or Toxic-epidermal necrolysis	Permanently discontinue		

Relates to section:

6.6.1 Dose Modification

10.7.2 Germany

1. Monthly pregnancy testing is required throughout study treatment and at end of treatment for women of childbearing potential.

Urine β-hCG or serum pregnancy test (as needed for POCBP)

Relates to sections:

1.3 Schedule of Activities (1.3.1, 1.3.2, and 1.3.3)
8.3.4.2 Pregnancy testing
Appendix 2: Clinical Laboratory Tests
Appendix 5: Contraceptive Guidance and Pregnancy Testing

2. Has a known history of HIV infection. HIV testing is required at Screening for participants enrolled from German sites.

Relates to sections:

1.3 Schedule of Activities (1.3.1)
5.2 Exclusion Criterion #16
8.3.4.3 HIV, HBV, and HCV Serology
Appendix 2: Clinical Laboratory Tests

3. Has a known history of hepatitis B (defined as HBsAg reactive) or known active HCV (defined as HCV RNA [qualitative] is detected) infection. Testing is required at Screening for participants enrolled from German sites.

Relates to sections:

1.3 Schedule of Activities (1.3.1)
5.2 Exclusion Criterion #17
8.3.4.3 HIV, HBV, and HCV Serology
Appendix 2: Clinical Laboratory Tests

Throughout

Persons of legal age, who are incapable of comprehending the nature, significance, and implications of the clinical study and of determining their will, are excluded from the study at German sites; therefore, all references to a participant's "legally acceptable representative" in the protocol are not applicable for participants in Germany.

10.7.3 Ireland

Monthly pregnancy testing throughout study treatment and at end of treatment is required for women of childbearing potential.

Relates to sections:

1.3 Schedule of Activities
8.3.4.2 Pregnancy testing
Appendix 2: Clinical Laboratory Tests
Appendix 5: Contraceptive Guidance and Pregnancy Testing

10.7.4 Italy

1. Monthly pregnancy testing throughout study treatment and at end of treatment is required for women of childbearing potential.

Relates to sections:

1.3 Schedule of Activities
8.3.4.2 Pregnancy testing
Appendix 2: Clinical Laboratory Tests
Appendix 5: Contraceptive Guidance and Pregnancy Testing

2. Patients should be permanently discontinued from study treatment if any of the following AEs occur:

- Steven-Johnson Syndrome
- Toxic-epidermal necrolysis
- Recurrent Grade 3 Colitis

Table 3 Dose modification and toxicity management guidelines for immune-related AEs associated with pembrolizumab.

General instructions:
1. Corticosteroid taper should be initiated upon AE improving to Grade 1 or less and continue to taper over at least 4 weeks.
2. For situations where pembrolizumab has been withheld, pembrolizumab can be resumed after AE has been reduced to Grade 1 or 0 and corticosteroid has been tapered. Pembrolizumab must be permanently discontinued if AE does not resolve within 12 weeks of last dose or corticosteroids cannot be reduced to ≤10 mg prednisone or equivalent per day within 12 weeks.
3. For severe and life-threatening irAEs, IV corticosteroid should be initiated first followed by oral steroid. Other immunosuppressive treatment should be initiated if irAEs cannot be controlled by corticosteroids.

Immune-related AEs	**Toxicity grade or conditions (CTCAE Version 4.0)**	**Action taken to pembrolizumab**	**irAE management with corticosteroid and/or other therapies**	**Monitor and follow-up**
Diarrhea / Colitis	Grade 4 or recurrent Grade 3	Permanently discontinue	• 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 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.
Skin Reactions	Grade 3 or suspected Stevens-Johnson Syndrome or Toxic-epidermal necrolysis	Withhold	• Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper	
	Grade 4 or confirmed Stevens-Johnson Syndrome or Toxic-epidermal necrolysis	Permanently discontinue		

Relates to section:

- 6.6.1 Dose Modification

10.7.5 Norway

Monthly pregnancy testing throughout study treatment and until 4 months after the last administration of study treatment is required for women of childbearing potential.

Relates to sections:

1.3 Schedule of Activities
8.3.4.2 Pregnancy testing
Appendix 2: Clinical Laboratory Tests
Appendix 5: Contraceptive Guidance and Pregnancy Testing

10.7.6 United Kingdom

1. Monthly pregnancy testing throughout study treatment and at end of treatment is required for women of childbearing potential.

Relates to sections:

1.3 Schedule of Activities (1.3.1 and 1.3.3)
8.3.4.2 Pregnancy testing
Appendix 2: Clinical Laboratory Tests
Appendix 5: Contraceptive Guidance and Pregnancy Testing

2. Serum pregnancy testing is required at Screening for women of childbearing potential.

Relates to sections:

1.3 Schedule of Activities (1.3.1, 1.3.3)
5.2 Exclusion Criterion #3
8.3.4.2 Pregnancy Testing
8.11.1 Screening
Appendix 2: Clinical Laboratory Tests
Appendix 5: Contraceptive Guidance and Pregnancy Testing

3. Has a known history of HIV infection. HIV testing is required at Screening for participants enrolled from UK sites.

Relates to sections:

1.3 Schedule of Activities (1.3.1)
5.2 Exclusion Criterion #16
8.3.4.3 HIV, HBV, and HCV Serology
Appendix 2: Clinical Laboratory Tests

4. Has a known history of hepatitis B (defined as HBsAg reactive) or known active HCV (defined as HCV RNA [qualitative] is detected) infection. Testing is required at Screening for participants enrolled from UK sites.

Relates to sections:

1.3 Schedule of Activities (1.3.1)
5.2 Exclusion Criterion #17
8.3.4.3 HIV, HBV, and HCV Serology
Appendix 2: Clinical Laboratory Tests

5. Participants enrolled from UK sites are excluded from the study if they have had hypersensitivity to pembrolizumab and/or any of its excipients.

Relates to sections:

5.2 Exclusion Criterion #12

6. Patients should be permanently discontinued from study treatment if any of the following AEs occur:

- Steven-Johnson Syndrome
- Toxic-epidermal necrolysis
- Recurrent Grade 3 Colitis

Table 3 Dose modification and toxicity management guidelines for immune-related AEs associated with pembrolizumab

General instructions:
1. Corticosteroid taper should be initiated upon AE improving to Grade 1 or less and continue to taper over at least 4 weeks.
2. For situations where pembrolizumab has been withheld, pembrolizumab can be resumed after AE has been reduced to Grade 1 or 0 and corticosteroid has been tapered. Pembrolizumab must be permanently discontinued if AE does not resolve within 12 weeks of last dose or corticosteroids cannot be reduced to ≤10 mg prednisone or equivalent per day within 12 weeks.
3. For severe and life-threatening irAEs, IV corticosteroid should be initiated first followed by oral steroid. Other immunosuppressive treatment should be initiated if irAEs cannot be controlled by corticosteroids.

Immune-related AEs	**Toxicity grade or conditions (CTCAE Version 4.0)**	**Action taken to pembrolizumab**	**irAE management with corticosteroid and/or other therapies**	**Monitor and follow-up**
Diarrhea / Colitis	Grade 4 or recurrent Grade 3	Permanently discontinue	• 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 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.
Skin Reactions	Grade 3 or suspected Stevens-Johnson Syndrome or Toxic-epidermal necrolysis	Withhold	• Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper	
	Grade 4 or confirmed Stevens-Johnson Syndrome or Toxic-epidermal necrolysis	Permanently discontinue		

Relates to section:

6.6.1 Dose Modification

10.8 Appendix 8: Description of the iRECIST Process for Assessment of Disease Progression

Assessment at Screening and Prior to RECIST 1.1 Progression

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 4 to 8 weeks later is obtained using iRECIST for participant management (see Table 6 and Figure 2). This 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
- 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 non-target 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 non-target lesions identified at baseline by RECIST 1.1 will be assessed as usual.

New lesions will be classified as measurable or non-measurable, 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 – Non-target.

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 iUPD at the previous visit 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 non-target 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 non-target 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 trial, either before or after an instance of pseudo-progression.
- Non-target lesions

  - If non-target lesions have never shown unequivocal progression, their doing so for the first time results in iUPD.
  - If non-target lesions have shown previous unequivocal progression, and this progression has not resolved, iUPD results from any significant further growth of non-target 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 non-target 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].

10.9 Appendix 9: Abbreviations

Abbreviation	Expanded Term
ADL	activities of daily living
AE	adverse event
ALT	alanine aminotransferase
APaT	all participants as treated
aPTT	activated partial thromboplastin time
ASCO	American Society of Clinical Oncology
AST	aspartame aminotransferase
ASTRO	American Society for Radiation Oncology
AUC	area under the curve
BCG	Bacillus Calmette–Guérin
BICR	blinded independent central review
C	cytosine
C_{av}	average concentration over the dosing interval
CD	cluster of differentiation
CI	confidence interval
CLL	chronic lymphocytic leukemia
C_{min}	trough concentration
C_{max}	peak concentration
CONSORT	Consolidated Standards of Reporting Trials
COPD	chronic obstructive pulmonary disease
CPS	combined positive score
CR	complete response
CRF	case report form
CSR	clinical study report
cSSC	cutaneous squamous cell carcinoma
CT	computed tomography
CTCAE	common terminology criteria for adverse events
ctDNA	circulating tumor DNA
CTFG	Clinical Trial Facilitation Group

Abbreviation	Expanded Term
CTLA-4	cytotoxic T-lymphocyte-associated protein 4
DCR	disease control rate
DFS	disease-free survival
DMC	Data Monitoring Committee
DNA	deoxyribonucleic acid
DOR	duration of response
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
EEA	European Economic Area
ELISA	enzyme-linked immunosorbent assay
EMA	European Medicines Agency
EOC	Executive Oversight Committee
EORTC	European Organisation for Research and Treatment of Cancer
ePRO	electronic patient-reported outcome
EQ-5D	EuroQol-5 Dimensions
E-R	exposure-response
EU CT	European Union Clinical Trial
FA	final analysis
FAS	full analysis set
FBR	future biomedical research
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act
FDG-PET	fluorodeoxyglucose positive emission tomography
FFPE	formalin-fixed paraffin-embedded
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice

Abbreviation	Expanded Term
H1/H2	hypothesis 1/2
HBsAg	hepatitis B surface antigen
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HNC	head and neck cancer
HNSCC	head and neck squamous cell carcinoma
HPV	human papillomavirus
HR	hazard ratio
HRQoL	health-related quality of life
HRT	hormone replacement therapy
IA	interim analysis
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Conference on Harmonisation
iCPD	confirmed progressive disease
iCRO	Imaging Contract Research Organization
IEC	Independent Ethics Committee
Ig	immunoglobulin
IGHV	immunoglobulin heavy chain
IHC	immunohistochemistry
IMP	investigational medicinal product
IND	Investigational New Drug
IO	immuno-oncology
irAE	immune-related adverse event
IRB	Institutional Review Board
iRECIST	modified RECIST 1.1 for immune-based therapeutics
IRT	interactive response technology
ITT	intent-to treat
IUD	intrauterine device
iUPD	unconfirmed progressive disease

Abbreviation	Expanded Term
IUS	intrauterine hormone-releasing system
IV	intravenous(ly)
KN012/KN069	KEYNOTE-012/KEYNOTE-069
LA	locally advanced
mAb	monoclonal antibody
MCC	Merkel cell carcinoma
MCPyV	Merkel cell polyomavirus
MRI	magnetic resonance imaging
MSI	microsatellite instability
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NMSC	non-melanoma skin cancer
NSCLC	non–small cell lung cancer
ORR	objective response rate
OS	overall survival
PD	progressive disease / pharmacodynamic
PD-1	programmed cell death 1
PD-L1	programmed death ligand 1
PD-L2	programmed death ligand 2
PFS	progression-free survival
PH	proportional hazard
PK	pharmacokinetic
po	per os (orally)
POCBP	participants of childbearing potential
PR	partial response
PRO	patient-reported outcome
Q2W	every 2 weeks
Q3W	every 3 weeks
Q6W	every 6 weeks
QLQ-C30	quality of life questionnaire-C30

Abbreviation	Expanded Term
QoL	quality of life
R/M	recurrent/metastatic
RCR	Royal College of Radiologists
RECIST	response evaluation criteria in solid tumors
RFS	recurrence-free survival
RNA	ribonucleic acid
RT	radiotherapy
SAC	Scientific Advisory Committee
SAE	serious adverse event
SCF	sponsor consultation form
SHP	src homology region 2 domain-containing
SIM	site imaging manual
SoA	schedule of activities
SoC	standard of care
sSAP	supplemental statistical analysis plan
SUSAR	suspected unexpected serious adverse reaction
T	thymine
T-regs	regulatory T cells
UK	United Kingdom
ULN	upper limit of normal
US	United States
UV	ultraviolet
β-hCG	β-human chorionic gonadotropin

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