Official Protocol Title:	A Phase 2, Open-label, Single-arm Study to Evaluate the Safety and Efficacy of Pembrolizumab in Participants with Recurrent or Metastatic Cutaneous Squamous Cell Carcinoma (R/M cSCC)
NCT number:	NCT03284424
Document Date:	10-Feb-2023

Title Page

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Protocol Title: A Phase 2, Open-label, Single-arm Study to Evaluate the Safety and Efficacy of Pembrolizumab in Participants with Recurrent or Metastatic Cutaneous Squamous Cell Carcinoma (R/M cSCC)

Protocol Number: 629-06

Compound Number: MK-3475

Sponsor Name and Legal Registered Address:

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

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

Regulatory Agency Identifying Number(s):

IND NUMBER: 134,760

EudraCT NUMBER: 2017-000594-37

Approval Date: 10 February 2023

Sponsor Signatory

Typed Name: Date
Title:

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

Investigator Signatory

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

Typed Name: Date
Title:

DOCUMENT HISTORY

Document	Date of Issue	Overall Rationale
3475-629-06	10-FEB-2023	To add language to allow participants to continue in a pembrolizumab extension study.
3475-629-05	21-JUN-2022	Merck Sharp & Dohme Corp. underwent an entity name and address change to Merck Sharp & Dohme LLC, Rahway, NJ, USA. This conversion resulted only in an entity name change and update to the address.
3475-629-04	03-JUN-2021	To update the dose modification and toxicity management guidelines for immune-related adverse events (irAEs) and incorporate updates from Protocol Clarification Letter (PCL) #3.
3475-629-03	25-SEP-2018	To add a cohort of 50 participants with locally advanced unresectable cSCC.
3475-629-02	08-FEB-2018	To add German-specific requirements to the study in response to a request from the German regulatory agency.
3475-629-01	27-MAR-2018	To add inclusion of 1L participants to the study.
3475-629-00	21-APR-2017	To test the clinical activity of pembrolizumab in participants with unresectable and/or metastatic cSCC.

PROTOCOL AMENDMENT SUMMARY OF CHANGES

Amendment 06

Overall Rationale for the Amendment:

To add language to allow participants to continue in a pembrolizumab extension study.

Summary of Changes Table:

Section # and Name	Description of Change	Brief Rationale
5.3 Beginning and End of Study Definition	Added that upon study completion, participants are discontinued and may be enrolled in a pembrolizumab extension study, if available.	To allow participants to continue in a pembrolizumab extension study.
7.7 Concomitant Therapy	Clarified that live attenuated vaccines are not permitted during the study. Added that licensed COVID-19 vaccines are allowed, but investigational vaccines are not allowed.	To clarify which vaccines are permitted.
9.8 Future Biomedical Research Sample Collection	Deleted list of samples and replaced with "Leftover samples listed in Section 9.9."	To reduce ambiguity and eliminate a source of confusion.

Section # and Name	Description of Change	Brief Rationale
9.9 Biomarkers	Changed “Tissue Collection” to “Tumor Tissue.”	To reduce ambiguity and eliminate a source of confusion. “Tumor tissue” represents all tumor collections (archival tissue, newly obtained, biopsies, etc.).
Throughout Document	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. Synopsis

Protocol Title:

A Phase 2, Open-Label, Single Arm Study to Evaluate the Safety and Efficacy of Pembrolizumab in Participants with Recurrent or Metastatic Cutaneous Squamous Cell Carcinoma

Short Title:

Phase 2 Study of Pembrolizumab in Participants With Recurrent or Metastatic Cutaneous Squamous Cell Carcinoma

Objectives/Hypothesis and Endpoints:

In male/female participants aged 18 years or older with R/M cSCC or LA unresectable cSCC.

Objective/Hypothesis	Endpoint
Primary	
(1) To estimate the objective response rate (ORR) per RECIST 1.1 as assessed by blinded independent central review (BICR).	(1) Objective response: defined as complete response (CR) or partial response (PR).
Secondary	
(1) To evaluate the duration of response (DOR) per RECIST 1.1 as assessed by BICR.	(1) DOR: for participants who demonstrate CR or PR, DOR is defined as the time from first documented evidence of CR or PR until disease progression or death due to any cause, whichever occurs first.
(2) To evaluate the disease control rate (DCR) per RECIST 1.1 as assessed by BICR	(2) Disease control: defined as CR or PR or stable disease (SD) for at least 12 weeks.

(3) To evaluate the progression-free survival (PFS) per RECIST 1.1 as assessed by BICR.	(3) PFS: defined as the time from first day of study treatment to the first documented disease progression or death due to any cause, whichever occurs first. Note: A new primary low-risk cSCC lesion is not considered as a PFS event.
(4) To evaluate the overall survival (OS) of the participants.	(4) OS: defined as the time from first day of study treatment to death due to any cause.
(5) To determine the safety and tolerability of pembrolizumab in study participants with R/M cSCC.	(5) Adverse events (AEs). Study drug discontinuations due to AEs.

Overall Design:

Trial Phase	Phase 2
Clinical Indication	Recurrent or metastatic (R/M) cutaneous squamous cell carcinoma (cSCC) or locally advanced (LA) unresectable cSCC.
Population	Participants with cSCC not amenable to surgery and/or radiation and/or systemic therapies
Trial Type	Interventional
Type of Design	Single arm, nonrandomized
Type of Control	No treatment control
Trial Blinding	Unblinded Open-label
Estimated Duration of Trial	The Sponsor estimates that the trial will require approximately 54 months from the time the first participant (or their legally acceptable representative) provides documented informed consent until the last participant's last study-related contact.

Number of Participants:

Up to approximately 150 participants will be enrolled.

Treatment Groups and Duration:

Treatment Groups	Pembrolizumab 200 mg every 3 weeks (Q3W)
Duration of Participation	Each participant will participate in the trial from the time the participant provides documented informed consent form (ICF) through the final protocol-specified contact. After a screening phase of 28 days, each participant will be assigned to receive trial treatment until disease progression is assessed by the site per Response Evaluation Criteria in Solid Tumors (RECIST) 1.1*, unacceptable adverse event(s) (AE[s]), intercurrent illness that prevents further administration of treatment, investigator's decision to discontinue the participant from study treatment, administrative reasons requiring cessation of treatment, or until the participant has received 35 administrations of pembrolizumab (approximately 2 years). Participants who stop trial treatment after receiving 35 administrations of pembrolizumab for reasons other than disease progression or intolerability, or participants who attain a CR and stop trial treatment may be eligible for up to 17 additional administrations of pembrolizumab (approximately 1 year) upon experiencing disease progression (Section 5.1 and 7.2.2). * For participants without RECIST 1.1 measurable disease on CT or MRI scans that were deemed eligible by digital photography, a tissue biopsy is required within 30 days of investigator determined CR for central pathology review and confirmation of a CR. For participants considered to have obtained CR prior to the release of Amendment 03, a biopsy will be required within 30 days of Protocol Amendment 03 approval in the respective country. After the end of treatment, each participant will be followed for the occurrence of AEs and spontaneously reported pregnancy as described under Section 9.3.6 Participants who discontinue for reasons other than disease progression will have post-treatment follow-up for disease status until disease progression is assessed by the site per RECIST 1.1, initiating a non-trial cancer treatment, withdrawing consent, or becoming lost to follow-up. All participants will be followed by telephone for OS until death, withdrawal of consent, or the end of the study.

A list of abbreviations used in this document can be found in Appendix 1.

2. Schedule of Activities (SoA)

2.1 Schedule of Activities – Recurrent/Metastatic cSCC

Schedule of Activities – R/M cSCC																
Trial Period	**Screening**	**Treatment Cycle[a]**										**EOT**	**Post-Treatment**			**Notes:**
Treatment Cycle/Title	**Screening (Visit 1)**	**1**			**2**			**3**	**4**	**5**	**6 to 35**	**Discon**	**Safety**	**FU***	**Survival**	**Treatment cycles are 3 weeks. Cycles will be repeated up to 35 infusions or until protocol specific criteria to discontinue treatment is met.** *For participants who discontinue study therapy without documented disease progression by imaging assessment, every effort should be made to continue monitoring their disease status as per protocol.
Scheduled Window (Days)	**- 28 to - 1**		**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**At time of discon**	**30D post discon (± 14)**	**Q6W post discon (± 14)**	**Q12W (± 14)**	
Day of visit		**D1**	**D8**	**D15**	**D1**	**D8**	**D15**	**D1**	**D1**	**D1**	**D1**					
Administrative Procedures																
Informed Consent	X															Additional consent is required at disease progression.
Informed Consent for Future Biomedical Research	X															
Participant Identification Card	X	X														At D1 the participants allocation number is added to the participant identification card
Inclusion/ Exclusion Criteria	X															
Demographics and Medical History	X															
Prior/ Concomitant Medication Review	X	X	X	X	X	X	X	X	X	X	X	X	X			Record all medications taken within 28 days of the Screening Visit and enter new medications started during the trial.

Schedule of Activities – R/M cSCC																
Trial Period	**Screening**	**Treatment Cycle[a]**										**EOT**	**Post-Treatment**			**Notes:**
Treatment Cycle/Title	**Screening (Visit 1)**	**1**			**2**			**3**	**4**	**5**	**6 to 35**	**Discon**	**Safety**	**FU[*]**	**Survival**	**Treatment cycles are 3 weeks.** **Cycles will be repeated up to 35 infusions or until protocol specific criteria to discontinue treatment is met.** *For participants who discontinue study therapy without documented disease progression by imaging assessment, every effort should be made to continue monitoring their disease status as per protocol.
Scheduled Window (Days)	**- 28 to - 1**		**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**At time of discon**	**30D post discon (± 14)**	**Q6W post discon (± 14)**	**Q12W (± 14)**	
Day of visit		**D1**	**D8**	**D15**	**D1**	**D8**	**D15**	**D1**	**D1**	**D1**	**D1**					
Pembrolizumab Administration		X			X			X	X	X	X					Treatment 1, Cycle 1 must be given within 3 days after treatment allocation. Study drug to be administered on D1 of each cycle after all procedures/ assessments have been completed.
Post-study Anticancer Therapy Status												X	X	X	X	
Survival Status		<- ->													X*	*Survival FU begins after investigator determined progression or start of next line anticancer treatment. By telephone contact every 12 weeks (84 ± 7 days) until death, withdrawal of consent, becoming lost to follow-up, or the end of the study, whichever occurs first. In addition, upon Sponsor request, participants may be contacted for survival status at any time during the course of the study.
Clinical Procedure/Assessments																
Review Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X	X	X		Record all AEs and ECIs occurring within 30 days after last dose of study treatment and SAEs for 90 days after the end of treatment or 30 days after end of treatment if the participant initiates new anticancer therapy (whichever is earlier). Report treatment related SAEs regardless of when they occur.

Schedule of Activities – R/M cSCC																
Trial Period	**Screening**	**Treatment Cycle[a]**										**EOT**	**Post-Treatment**			**Notes:**
Treatment Cycle/Title	**Screening (Visit 1)**	**1**			**2**			**3**	**4**	**5**	**6 to 35**	**Discon**	**Safety**	**FU[*]**	**Survival**	**Treatment cycles are 3 weeks.** **Cycles will be repeated up to 35 infusions or until protocol specific criteria to discontinue treatment is met.** *For participants who discontinue study therapy without documented disease progression by imaging assessment, every effort should be made to continue monitoring their disease status as per protocol.
Scheduled Window (Days)	**- 28 to - 1**		**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**At time of discon**	**30D post discon (± 14)**	**Q6W post discon (± 14)**	**Q12W (± 14)**	
Day of visit		**D1**	**D8**	**D15**	**D1**	**D8**	**D15**	**D1**	**D1**	**D1**	**D1**					
12-lead ECG (Local)	X															
Full Physical Examination and Height*	X											X				To be performed by the investigator or qualified designee. *Height will be measured at Screening only.
Directed Physical Examination		X	X	X	X	X	X	X	X	X	X					
Vital Signs	X	X	X	X	X	X	X	X	X	X	X	X	X			Prior to dosing assess and record BP, pulse, temperature, and weight.
ECOG Performance Status	X	X	X	X	X	X	X	X	X	X	X	X	X			Must be performed prior to each dose of trial treatment where ECOG is collected.
Laboratory Procedures/Assessments: analysis performed by LOCAL laboratory																
Serum or Urine Pregnancy Test (if applicable)	X	X			X			X	X	X	X	X	X			Serum or urine pregnancy test must occur 72 hours prior to administration of trial treatment. Monthly pregnancy tests are required for participants enrolled from German sites. For all other countries, monthly pregnancy testing should be conducted as per local regulations where applicable.
HIV/HBV/HCV serology	X															Testing is required at screening for participants enrolled from German sites. All other countries should follow local regulations where applicable

Schedule of Activities – R/M cSCC																
Trial Period	**Screening**	**Treatment Cycle[a]**										**EOT**	**Post-Treatment**			**Notes:**
Treatment Cycle/Title	**Screening (Visit 1)**	**1**			**2**			**3**	**4**	**5**	**6 to 35**	**Discon**	**Safety**	**FU***	**Survival**	**Treatment cycles are 3 weeks.** **Cycles will be repeated up to 35 infusions or until protocol specific criteria to discontinue treatment is met.** *For participants who discontinue study therapy without documented disease progression by imaging assessment, every effort should be made to continue monitoring their disease status as per protocol.
Scheduled Window (Days)	**- 28 to - 1**		**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**At time of discon**	**30D post discon (± 14)**	**Q6W post discon (± 14)**	**Q12W (± 14)**	
Day of visit		**D1**	**D8**	**D15**	**D1**	**D8**	**D15**	**D1**	**D1**	**D1**	**D1**					
PT/INR and aPTT	X															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	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, lab samples can be collected up to 72 hours prior to the scheduled time point. See Section 9.5.4. Total T3 or free T3 are acceptable as well as FT4 and TSH * D8 and D15 are required safety visits for the first 2 pembrolizumab infusions. Collection of Day 8 and Day 15 laboratory samples of Cycles 1 and 2 are optional at the discretion of the investigator. ‡ To be repeated every 2 cycles after Cycle 6. †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	X	X	X	X†			
Urinalysis	X															
T3, FT4, and TSH	X				X				X		X‡		X†			

Schedule of Activities – R/M cSCC																
Trial Period	**Screening**	**Treatment Cycle[a]**										**EOT**	**Post-Treatment**			**Notes:**
Treatment Cycle/Title	**Screening (Visit 1)**	**1**			**2**			**3**	**4**	**5**	**6 to 35**	**Discon**	**Safety**	**FU***	**Survival**	**Treatment cycles are 3 weeks. Cycles will be repeated up to 35 infusions or until protocol specific criteria to discontinue treatment is met.** *For participants who discontinue study therapy without documented disease progression by imaging assessment, every effort should be made to continue monitoring their disease status as per protocol.
Scheduled Window (Days)	**- 28 to - 1**		**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**At time of discon**	**30D post discon (± 14)**	**Q6W post discon (± 14)**	**Q12W (± 14)**	
Day of visit		**D1**	**D8**	**D15**	**D1**	**D8**	**D15**	**D1**	**D1**	**D1**	**D1**					
Laboratory Procedures/Assessments: analysis performed by CENTRAL laboratory																
Pharmacokinetic Samples		X			X				X		X					Predose drawn within 24 hrs before pembrolizumab infusion at C1, 2, 4, 6, 8 and Q4C thereafter, until discon of study drug or participants starts new anti-cancer therapy. Post-dose will be drawn within 30 minutes after pembrolizumab infusion at C1
Blood for Genetic Analysis		X														This sample should be drawn for planned analysis of the association between genetic variants in DNA and drug response. This sample will not be collected at that site if there is either a local law or regulation prohibiting collection, or if the IRB/IEC does not approve the collection of the sample for these purposes. If the sample is collected, leftover extracted DNA will be stored for future biomedical research if the participant (or their legally acceptable representative) provides documented informed consent for FBR. If the planned genetic analyses are not approved, but FBR is approved and consent is given, this sample will be collected for the purpose of FBR.

Schedule of Activities – R/M cSCC																
Trial Period	**Screening**	**Treatment Cycle[a]**										**EOT**	**Post-Treatment**			**Notes:**
Treatment Cycle/Title	**Screening (Visit 1)**	**1**			**2**			**3**	**4**	**5**	**6 to 35**	**Discon**	**Safety**	**FU***	**Survival**	**Treatment cycles are 3 weeks.** **Cycles will be repeated up to 35 infusions or until protocol specific criteria to discontinue treatment is met.** *For participants who discontinue study therapy without documented disease progression by imaging assessment, every effort should be made to continue monitoring their disease status as per protocol.
Scheduled Window (Days)	**- 28 to - 1**		**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**At time of discon**	**30D post discon (± 14)**	**Q6W post discon (± 14)**	**Q12W (± 14)**	
Day of visit		**D1**	**D8**	**D15**	**D1**	**D8**	**D15**	**D1**	**D1**	**D1**	**D1**					
Blood for RNA Analyses		X			X					X		X				Samples will be collected on Day 1 of Cycles 1, 2, 5 and at EOT/discontinuation.
Blood for Plasma Biomarker Analysis		X			X							X				Samples will be collected on Day 1 of Cycles 1, 2, and at EOT/discontinuation.
Blood for Serum Biomarker Analyses		X			X							X				

Schedule of Activities – R/M cSCC																
Trial Period	**Screening**	**Treatment Cycle[a]**										**EOT**	**Post-Treatment**			**Notes:**
Treatment Cycle/Title	**Screening (Visit 1)**	**1**			**2**			**3**	**4**	**5**	**6 to 35**	**Discon**	**Safety**	**FU***	**Survival**	**Treatment cycles are 3 weeks. Cycles will be repeated up to 35 infusions or until protocol specific criteria to discontinue treatment is met.** *For participants who discontinue study therapy without documented disease progression by imaging assessment, every effort should be made to continue monitoring their disease status as per protocol.
Scheduled Window (Days)	**- 28 to - 1**		**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**At time of discon**	**30D post discon (± 14)**	**Q6W post discon (± 14)**	**Q12W (± 14)**	
Day of visit		**D1**	**D8**	**D15**	**D1**	**D8**	**D15**	**D1**	**D1**	**D1**	**D1**					
Efficacy Measurements																
Tumor Imaging	X							X		X	X‡	X*		X		Initial tumor imaging, including any digital photography, will be performed within 28 days prior to the date of treatment allocation and must be sent to the central vendor. The first on-study imaging assessment should be performed at 6 weeks (42 days + 7 days) from the date of treatment allocation. ‡Subsequent tumor imaging should be performed every 6 weeks (±7 days) until Year 1, thereafter ever 9 weeks(±7 days), or more frequently if clinically indicated. For all imaging, the clock will start from the date of treatment allocation. Pelvic imaging is not required during the study with the exception of the primary involvement of the pelvis and lower extremities. *For participants who discontinue study treatment, tumor imaging should be performed at the time of treatment discontinuation (±4 week window). If previous imaging was obtained within 4 weeks prior to the date of discontinuation, then imaging at treatment discontinuation is not required and the participant should continue with the protocol specified tumor imaging time points. For participants who discontinue study treatment due to documented disease progression, this is the final required tumor imaging if the Investigator elects not to implement irRECIST.
Digital Photography; cutaneous lesions	X							X		X	X‡	X*		X		

Schedule of Activities – R/M cSCC																
Trial Period	**Screening**	**Treatment Cycle[a]**										**EOT**	**Post-Treatment**			**Notes:**
Treatment Cycle/Title	**Screening (Visit 1)**	**1**			**2**			**3**	**4**	**5**	**6 to 35**	**Discon**	**Safety**	**FU***	**Survival**	**Treatment cycles are 3 weeks.** **Cycles will be repeated up to 35 infusions or until protocol specific criteria to discontinue treatment is met.** *For participants who discontinue study therapy without documented disease progression by imaging assessment, every effort should be made to continue monitoring their disease status as per protocol.
Scheduled Window (Days)	**- 28 to - 1**		**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**At time of discon**	**30D post discon (± 14)**	**Q6W post discon (± 14)**	**Q12W (± 14)**	
Day of visit		**D1**	**D8**	**D15**	**D1**	**D8**	**D15**	**D1**	**D1**	**D1**	**D1**					
Tumor Tissue Collection																
Tissue Collection	X	------If clinically indicated*------														Screening for biomarker analysis only (Section 9.7.1). *For participants deemed eligible via digital photography only. Participants considered to have obtained a CR require biopsy within 30 days of initial confirmation. For participants considered to have obtained CR prior to the release of Amendment 03, a biopsy will be required within 30 days of Protocol Amendment 03 approval in the respective country. All samples to be submitted for central pathology review.
Patient Reported Outcomes																
EuroQol EQ-5D		X			X			X		X		X	X			Questionnaires will be administered prior to dosing at Cycle 1, Cycle 2, Cycle 3, and every 2 cycles (ie, every 6 weeks) through Year 1, then every 3 cycles (ie., every 9 weeks) after Year 1 until End of Treatment, and at the 30-day Safety Follow-up Visit.
EORTC QLQ-C30		X			X			X		X		X	X			

AE = adverse events; aPTT = activated partial thromboplastin time; BP = blood pressure; C1D1= cycle one day one; CBC= complete blood count; D = day(s); discon = discontinuation; DNA = deoxyribonucleic acid; ECG = electrocardiogram; ECI = events of clinical interest; ECOG = Eastern Cooperative Oncology Group; EORTC QLQ-C30 = European Organization for Research and Treatment of Cancer; EOT = End of treatment; EuroQol EQ-5D = European Quality of Life; FBR = future biomedical research; FNA = fine needle aspirate; FT4 = free thyroxine; FU = Follow-up; HBV = Hepatitis B virus; HCV = Hepatitis C virus; HIV = Human Immunodeficiency Virus; IEC = Independent Ethics Committee; IRB = Institutional Review Board; INR = international normalized ratio; PD-L1 = Programmed Death Ligand 1; PT = prothrombin time; PTT = partial thromboplastin time; Q = every; RNA = ribonucleic acid; SAE = serious adverse event; T3 = triiodothyronine; TSH = thyroid-stimulating hormone; W = weeks.

2.2 Schedule of Activities – Locally Advanced Unresectable cSCC

Schedule of Activities – LA unresectable cSCC												
Trial Period	**Screening**	**Treatment Cycle[a]**						**EOT**	**Post-Treatment**			**Notes:** **Cycles will be repeated up to 35 infusions or until protocol specific criteria to discontinue treatment is met**
Treatment Cycle/Title	**Screening (Visit 1)**	**1**	**2**	**3**	**4**	**5**	**6 to 35**	**Discon**	**Safety**	**FU[b]**	**Survival**	
Scheduled Window (Days)	**- 28 to - 1**		**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**At time of discon**	**30D post discon (± 14)**	**Q6W post discon (± 14)**	**Q12W (± 14)**	
Day of visit		**D1**	**D1**	**D1**	**D1**	**D1**	**D1**					
Administrative Procedures												
Informed Consent	X											Additional consent is required at disease progression.
Informed Consent for Future Biomedical Research	X											
Participant Identification Card	X	X										At D1 the participants allocation number is added to the participant identification card
Inclusion/ Exclusion Criteria	X											
Demographics and Medical History	X											
Prior/Concomitant Medication Review	X	X	X	X	X	X	X	X	X			Record all medications taken within 28 days of the Screening Visit and enter new medications started during the trial.
Pembrolizumab Administration		X	X	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.
Post-study Anticancer Therapy Status								X	X	X	X	

Schedule of Activities – LA unresectable cSCC												
Trial Period	**Screening**	**Treatment Cycle[a]**						**EOT**	**Post-Treatment**			**Notes:** **Cycles will be repeated up to 35 infusions or until protocol specific criteria to discontinue treatment is met**
Treatment Cycle/Title	**Screening (Visit 1)**	**1**	**2**	**3**	**4**	**5**	**6 to 35**	**Discon**	**Safety**	**FU[b]**	**Survival**	
Scheduled Window (Days)	**- 28 to - 1**		**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**At time of discon**	**30D post discon (± 14)**	**Q6W post discon (± 14)**	**Q12W (± 14)**	
Day of visit		**D1**	**D1**	**D1**	**D1**	**D1**	**D1**					
Survival Status		<----------					---------->				X*	* Survival FU begins after investigator determined progression or start of next line anticancer treatment. By telephone contact every 12 weeks (84 ± 7 days) for survival until death, withdrawal of consent, becoming lost to follow-up, or the end of the study, whichever occurs first. In addition, upon Sponsor request, participants may be contacted for survival status at any time during the course of the study.
Clinical Procedure/Assessments												
Review Adverse Events	X	X	X	X	X	X	X	X	X	X		Record all AEs and ECIs occurring within 30 days after last dose of study treatment and SAEs for 90 days after the end of treatment or 30 days after end of treatment if the participant initiates new anticancer therapy (whichever is earlier). Report treatment related SAEs regardless of when they occur.
12-lead ECG (Local)	X											
Full Physical Examination and Height*	X							X				To be performed by the investigator or qualified designee. *Height will be measured at Screening only.
Directed Physical Examination		X	X	X	X	X	X					
Vital Signs	X	X	X	X	X	X	X	X	X			Prior to dosing assess and record BP, pulse, temperature, and weight. Height at screening only.
ECOG Performance Status	X	X	X	X	X	X	X	X	X			Must be performed prior to each dose of trial treatment where ECOG is collected.

Schedule of Activities – LA unresectable cSCC												
Trial Period	**Screening**	**Treatment Cycle[a]**						**EOT**	**Post-Treatment**			
Treatment Cycle/Title	**Screening (Visit 1)**	**1**	**2**	**3**	**4**	**5**	**6 to 35**	**Discon**	**Safety**	**FU[b]**	**Survival**	**Notes:**
Scheduled Window (Days)	**- 28 to - 1**		**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**At time of discon**	**30D post discon (± 14)**	**Q6W post discon (± 14)**	**Q12W (± 14)**	**Cycles will be repeated up to 35 infusions or until protocol specific criteria to discontinue treatment is met**
Day of visit		**D1**	**D1**	**D1**	**D1**	**D1**	**D1**					
Laboratory Procedures/Assessments: analysis performed by LOCAL laboratory												
Serum or Urine Pregnancy Test (if applicable)	X	X	X	X	X	X	X	X	X			Serum or urine pregnancy test must occur 72 hours prior to administration of trial treatment. Monthly pregnancy tests are required for participants enrolled from German sites. For all other countries, monthly pregnancy testing should be conducted as per local regulations where applicable.
HIV/HBV/HCV serology	X											Testing is required at screening for participants enrolled from German sites. All other countries should follow local regulations where applicable.
PT/INR and aPTT	X											Screening -within 10 days prior to the start of study treatment. Samples to be taken prior to study drug administration. After Cycle 1, lab samples can be collected up to 72 hours prior to the scheduled time point. See Section 9.5.4. 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. Total T3 or free T3 are acceptable as well as FT4 and TSH ‡ To be repeated every 2 cycles after Cycle 6. †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.
CBC with Differential	X		X	X	X	X	X	X	X†			
Chemistry Panel	X		X	X	X	X	X	X	X†			
Urinalysis	X											
T3, FT4, and TSH	X		X		X		X‡		X†			

Schedule of Activities – LA unresectable cSCC												
Trial Period	**Screening**	**Treatment Cycle[a]**						**EOT**	**Post-Treatment**			
Treatment Cycle/Title	**Screening (Visit 1)**	**1**	**2**	**3**	**4**	**5**	**6 to 35**	**Discon**	**Safety**	**FU[b]**	**Survival**	**Notes:**
Scheduled Window (Days)	**- 28 to - 1**		**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**At time of discon**	**30D post discon (± 14)**	**Q6W post discon (± 14)**	**Q12W (± 14)**	**Cycles will be repeated up to 35 infusions or until protocol specific criteria to discontinue treatment is met**
Day of visit		**D1**	**D1**	**D1**	**D1**	**D1**	**D1**					
Laboratory Procedures/Assessments: analysis performed by CENTRAL laboratory												
Pharmacokinetic Samples		X*	X		X		X					Predose drawn within 24 hrs before pembrolizumab infusion at C1, 2, 4, 6, 8 and Q4C thereafter, until discon of SD or participants starts new anti-cancer therapy. *Post-dose will be drawn within 30 minutes after pembrolizumab infusion at C1
Blood for Genetic Analysis		X										This sample should be drawn for planned analysis of the association between genetic variants in DNA and drug response. This sample will not be collected at that site if there is either a local law or regulation prohibiting collection, or if the IRB/IEC does not approve the collection of the sample for these purposes. If the sample is collected, leftover extracted DNA will be stored for future biomedical research if the participant (or their legally accepted representative) provides documented informed consent for FBR. If the planned genetic analyses are not approved, but FBR is approved and consent is given, this sample will be collected for the purpose of FBR.
Blood for RNA Analyses		X	X			X		X				Samples will be collected at on Day 1 of Cycles 1, 2, 5 and at EOT/ discontinuation
Blood for Plasma Biomarker Analysis		X	X					X				Samples will be collected at on Day 1 of Cycles 1, 2, and at EOT/discontinuation.
Blood for Serum Biomarker Analyses		X	X					X				

Schedule of Activities – LA unresectable cSCC												
Trial Period	**Screening**	**Treatment Cycle[a]**						**EOT**	**Post-Treatment**			**Notes:** **Cycles will be repeated up to 35 infusions or until protocol specific criteria to discontinue treatment is met**
Treatment Cycle/Title	**Screening (Visit 1)**	**1**	**2**	**3**	**4**	**5**	**6 to 35**	**Discon**	**Safety**	**FU[b]**	**Survival**	
Scheduled Window (Days)	**- 28 to - 1**		**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**At time of discon**	**30D post discon (± 14)**	**Q6W post discon (± 14)**	**Q12W (± 14)**	
Day of visit		**D1**	**D1**	**D1**	**D1**	**D1**	**D1**					
Efficacy Measurements												
Tumor Imaging	X			X		X	X‡	X*		X		Initial tumor imaging, including any digital photography, will be performed within 28 days prior to the date of treatment allocation and must be sent to the central vendor. The first on-study imaging assessment should be performed at 6 weeks (42 days + 7 days) from the date of treatment allocation. ‡Subsequent tumor imaging should be performed every 6 weeks (±7 days) until Year 1, thereafter ever 9 weeks (±7 days), or more frequently if clinically indicated. For all imaging, the clock will start from the date of treatment allocation. Pelvic imaging is not required during the study with the exception of the primary involvement of the pelvis and lower extremities. *For participants who discontinue study treatment, tumor imaging should be performed at the time of treatment discontinuation (±4 week window). If previous imaging was obtained within 4 weeks prior to the date of discontinuation, then imaging at treatment discontinuation is not required and the participant should continue with the protocol specified tumor imaging time points. For participants who discontinue study treatment due to documented disease progression, this is the final required tumor imaging if the Investigator elects not to implement irRECIST.
Digital Photography; cutaneous lesions	X			X		X	X‡	X*		X		
Tumor Tissue Collection												
Tissue Collection	X	------If clinically indicated*------										Screening for biomarker analysis only (Section 9.7.1). *For participants deemed eligible via digital photography only. Participants considered to have obtained a CR require biopsy within 30 days of initial confirmation. All samples to be submitted for central pathology review.

Schedule of Activities – LA unresectable cSCC												
Trial Period	**Screening**	**Treatment Cycle[a]**						**EOT**	**Post-Treatment**			**Notes:** **Cycles will be repeated up to 35 infusions or until protocol specific criteria to discontinue treatment is met**
Treatment Cycle/Title	**Screening (Visit 1)**	**1**	**2**	**3**	**4**	**5**	**6 to 35**	**Discon**	**Safety**	**FU[b]**	**Survival**	
Scheduled Window (Days)	**- 28 to - 1**		**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**At time of discon**	**30D post discon (± 14)**	**Q6W post discon (± 14)**	**Q12W (± 14)**	
Day of visit		**D1**	**D1**	**D1**	**D1**	**D1**	**D1**					
Patient Reported Outcomes												
EuroQol EQ-5D		X	X	X		X		X	X			Questionnaires will be administered by trained site personnel on D1 of Cycles 1, 2, 3, and then every 2 cycles (ie, every 6 weeks) until Year 1, thereafter every 3 cycles (ie, every 9 weeks) after until EOT/discontinuation, and at the 30-day Safety Follow-up Visit. It is strongly recommended that PROs are completed by participants prior to all procedures/assessments, and in the following order: EQ-5D then EORTC QLQ-C30.
EORTC QLQ-C30		X	X	X		X		X	X			

AE = adverse events; aPTT = activated partial thromboplastin time; BP = blood pressure; C1D1= cycle one day one; CBC= complete blood count; D = days; discon = discontinuation; DNA = deoxyribonucleic acid; ECI = events of clinical interest; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; EORTC QLQ-C30 = European Organization for Research and Treatment of Cancer; EOT = End of treatment; EuroQol EQ-5D = European Quality of Life; FBR = future biomedical research; FNA = fine needle aspirate; FT4 = free thyroxine; FU = Follow-up; HBV = Hepatitis B virus; HCV = Hepatitis C virus; HIV = Human Immunodeficiency Virus; IEC = Independent Ethics Committee; IRB = Institutional Review Board; INR = international normalized ratio; PD-L1 = Programmed Death Ligand 1; PT = prothrombin time; PTT = partial thromboplastin time; Q = every; RNA = ribonucleic acid; SAE = serious adverse event; T3 = triiodothyronine; TSH = thyroid-stimulating hormone; W = weeks.

2.3 Second Course Phase (Retreatment) for Pembrolizumab (MK-3475)

Trial Period:	**Treatment Cycles (3-week Cycles)**						**EOT**	**Post-Treatment**			**Notes:**
Treatment Cycle/Title:	**1**	**2**	**3**	**4**	**5**	**6 to 17**	**Discon**	**Safety FU**	**FU Visits**	**Survival FU**	**Cycles will be repeated up to 17 infusions or until protocol specific criteria to discontinue treatment is met**
Scheduling Window (Days):	**+ 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**At time of discon**	**30D post discon (± 14)**	**Q6W post discon (± 14)**	**Q12W (± 14)**	
Administrative Procedures											
Eligibility Criteria	X										Participants who either a) attain a CR and discontinue treatment or b) discontinue treatment after 24 months on pembrolizumab for reasons other than disease progression or intolerability may restart trial treatment if they meet the criteria provided in the protocol
Concomitant Medication Review	X	X	X	X	X	X	X	X			Enter new medications started during the trial through the Safety Follow-up Visit.
Pembrolizumab Administration	X	X	X	X	X	X					
Post-study Anti-cancer Therapy Status									X	X	
Survival Status	<----------								---------->	X	*Survival FU begins after investigator determined progression or start of next line anticancer treatment. By telephone contact every 12 weeks (84 ± 7 days) until death, withdrawal of consent, becoming lost to follow-up, or the end of the study, whichever occurs first. In addition, upon Sponsor request, participants may be contacted for survival status at any time during the course of the study.
Clinical Procedures/Assessments											
Review Adverse Events	X	X	X	X	X	X	X	X	X		Record all AEs and ECIs occurring within 30 days after last dose of study treatment and SAEs for 90 days after the end of treatment or 30 days after end of treatment if the participant initiates new anticancer therapy (whichever is earlier). Report treatment related SAEs regardless of when they occur.
Full Physical Examination	X						X				
Directed Physical Examination		X	X	X	X	X					

Trial Period:	**Treatment Cycles (3-week Cycles)**						**EOT**	**Post-Treatment**			**Notes:** **Cycles will be repeated up to 17 infusions or until protocol specific criteria to discontinue treatment is met**
Treatment Cycle/Title:	**1**	**2**	**3**	**4**	**5**	**6 to 17**	**Discon**	**Safety FU**	**FU Visits**	**Survival FU**	
Scheduling Window (Days):	**+ 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**At time of discon**	**30D post discon (± 14)**	**Q6W post discon (± 14)**	**Q12W (± 14)**	
Vital Signs	X	X	X	X	X	X	X	X			Prior to dosing assess and record BP, pulse, temperature, and weight.
ECOG Performance Status	X	X	X	X	X	X	X	X			Must be performed prior to each dose of trial treatment where ECOG is collected.
Laboratory Procedures/Assessments: analysis performed by LOCAL laboratory											
Serum or Urine Pregnancy Test (if applicable)	X	X	X	X	X	X	X	X			Serum or urine pregnancy test must occur 72 hours prior to administration of trial treatment. Monthly pregnancy tests are required for participants enrolled from German sites. For all other countries, monthly pregnancy testing should be conducted as per local regulations where applicable.
PT/INR and aPTT	X*										*Laboratory tests for determining eligibility for retreatment are to be performed within 10 days prior to the first retreatment dose of pembrolizumab. After Cycle 1, lab samples can be collected up to 72 hours prior to the scheduled time point. †Unresolved labs that are drug-related AEs should be followed until resolution. Labs do not need to be repeated after the end of trial treatment if labs are within normal range. Urinalysis required at Cycle 1 only. Total T3 or free T3 are acceptable as well as FT4, and TSH. Thyroid panel will continue to be collected every other cycle after cycle 5 See Section 9.5.4
CBC with Differential	X*	X	X	X	X	X	X	X†			
Chemistry Panel	X*	X	X	X	X	X	X	X†			
Urinalysis[a]	X*										
T3, FT4, and TSH	X		X		X			X†			

Trial Period:	**Treatment Cycles (3-week Cycles)**						**EOT**	**Post-Treatment**			**Notes:** **Cycles will be repeated up to 17 infusions or until protocol specific criteria to discontinue treatment is met**
Treatment Cycle/Title:	**1**	**2**	**3**	**4**	**5**	**6 to 17**	**Discon**	**Safety FU**	**FU Visits**	**Survival FU**	
Scheduling Window (Days):	**+ 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**At time of discon**	**30D post discon (± 14)**	**Q6W post discon (± 14)**	**Q12W (± 14)**	
Efficacy Measurements											
Tumor Imaging	X		X		X		X		X		Tumor imaging, including any digital photography, must be performed within 28 days prior to restarting treatment with pembrolizumab. Imaging should be performed at 6 weeks (42 days + 7 days) from the first dose of trial treatment and continue every 6 weeks (42 ± 7 days) or more frequently if clinically indicated. The processes for image collection and transmission to the central vendor are in the Site Imaging Manual. Pelvic imaging is not required during the second course imaging schedule with exception of the primary involvement of pelvis and lower extremities. For participants who discontinue study treatment, tumor imaging should be performed at the time of treatment discontinuation (±4 week window). If previous imaging was obtained within 4 weeks prior to the date of discontinuation, then imaging at treatment discontinuation is not required and the participant should continue with the protocol specified tumor imaging time points. For participants who discontinue study treatment due to documented disease progression, this is the final required tumor imaging if the Investigator elects not to implement irRECIST.
Digital Photography: cutaneous lesions	X		X		X		X		X		

AE = adverse events; aPTT = activated partial thromboplastin time; BP = blood pressure; CR = complete response; D = day(s); Discon/discon = discontinuation; ECI = events of clinical interest; ECOG = Eastern Cooperative Oncology Group; EOT = End of treatment; FT4 = free thyroxine; FU = Follow-up; INR = international normalized ratio; PT = prothrombin time; PTT = partial thromboplastin time; Q = every; SAE = serious adverse event; T3 = triiodothyronine; TSH = thyroid- stimulating hormone; W = weeks.

3. Introduction

Pembrolizumab (trade name KEYTRUDA®) is a potent and highly selective humanized monoclonal antibody (mAb) of the immunoglobulin G4 (IgG4) / kappa isotype designed to directly block the interaction between Programmed Cell Death 1 (PD-1) receptor and its ligands, Programmed Death Ligand 1 (PD-L1), and Programmed Death Ligand 2 (PD-L2).

For more detail on specific indications, please refer to the Pembrolizumab Investigator's Brochure (IB).

3.1 Study Rationale

Due to the paucity of clinical trial data in the unresectable and/or metastatic cutaneous squamous cell carcinoma (cSCC) population, there is no current standard of care treatment for these participants. Therefore, since there are no clear standard of care recommendations and no approved treatments for this population, we propose to test the clinical activity of pembrolizumab in a single arm Phase 2 study for unresectable and/or metastatic cSCC, a disease with limited treatment options and a significant unmet clinical need.

3.2 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 intravenous (IV) immunotherapy for various malignancies. KEYTRUDA® (pembrolizumab) is indicated for the treatment of patients across a number of indications because of its mechanism of action to bind the PD-1 receptor on the T-cell. For more details on specific indications refer to the IB.

3.2.1 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 (TILs) 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 (Tregs) 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 immunoglobulin (Ig) superfamily member related to cluster of differentiation 28 (CD28) and cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4) that has been shown to negatively regulate antigen receptor signaling upon engagement of its ligands (PD-L1 and/or PD-L2) [Greenwald, R. J., et al 2005] [Okazaki, T., et al 2001].

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

Evidence of Clinical Efficacy of Pembrolizumab in Head and Neck Squamous Cell Carcinoma

Evidence of both clinical efficacy and safety has been reported in studies evaluating pembrolizumab in head and neck squamous cell carcinoma (HNSCC). Participants with incurably recurrent and/or metastatic (R/M) HNSCC whose tumor tissues contained at least 1% of tumor cells or stroma that were PD-L1 positive by immunohistochemistry (IHC), were enrolled onto the KEYNOTE 012 trial, a Phase 1b global, multi-cohort clinical trial utilizing pembrolizumab at 10 mg/kg intravenously every 2 weeks. Of the 60 participants enrolled, approximately 38% (n=23) were human papilloma virus (HPV) positive. Approximately 63% (n=38) of participants had been treated with both platinum and cetuximab based therapies prior to enrolling on study, and 70% (n=42 of 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% (n=8 of 45 evaluable for response; 95% confidence interval [CI] 8%to 32%) with a median time to response of 8 weeks (95% CI 7 to 17 weeks) and a median duration of response (DOR) of 53 weeks (95% CI 13 weeks to not reached). Median progression-free survival (PFS) and overall survival (OS) were 2 (95% CI 2 to 4 months) and 13 (95% CI 5 months to not reached) months, respectively. Pembrolizumab was well tolerated with the overall proportion of patients with drug related adverse events (AEs) of any grade being 63% (n=38), with the most common events being fatigue, pruritus, nausea, decreased appetite, and rash. Approximately 17% (n = 10 of 60) of participants experienced Grade 3 or 4 drug-related AEs, and 27 participants (45%) experienced a serious adverse event (SAE) [Seiwert, T. Y., et al 2016].

Further support for the efficacy and safety of pembrolizumab in HNSCC has been provided by a separate report of the larger expansion cohort of the KEYNOTE 012 trial [Chow, L. Q., et al 2016]. This Phase 1b, multi-center, clinical trial enrolled a cohort of incurably R/M HNSCC irrespective of PD-L1 biomarker tumor status and treated these participants with pembrolizumab at the fixed dose of 200 mg every 3 weeks. Of the 132 participants enrolled, 125 participants had tumors that had at least 1% of PD-L1 positivity by IHC in either tumors cells or their associated infiltrating immune cells, 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, objective response rate (ORR) was found to be 18% (95% CI, 12 % to 26%) by independent review, with a median time to response of 2 months (range, 2 to 11 months), and a median duration of response that was not reached (range, ≥ 2 to ≥ 11 months). Progression-free survival 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 as described above, ORR was further confirmed at 22%.

The safety profile of pembrolizumab remained consistent utilizing the fixed dose of 200 mg every 3 weeks, with approximately 62% (n=82) participants experiencing treatment-related AEs, and 12 participants (9%) who experienced a Grade 3 or 4 treatment-related AE. Thus, both the safety and efficacy of pembrolizumab for R/M HNSCC have been described. Additionally, the activity or checkpoint inhibitors for R/M HNSCC have been confirmed as a class of agents [Ferris, R. L., 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 to 150 per 100,000 persons per year in the US [Vandergriff, T., et al 2010], and is expected to increase as much as 2% to 4% per year. 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 to 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]. Because of the daily exposure of the head and neck region to the ionizing ultraviolet (UV) rays of the sun, the head and neck region is one of the most common anatomic regions for cSCC to develop. Due to its ability to metastasize, 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 locally advanced (LA)/high-risk cSCC annually [Jennings, L. 2010] [Brantsch, K. D., et al 2008].

Locally Advanced (LA) high-risk cSCC

LA high-risk cSCC is defined as cSCC that has high-risk features, including regional nodal disease, and has no distant metastasis. High-risk features of cSCC defined per National Comprehensive Cancer Network (NCCN) Guidelines for Squamous Cell Skin Cancer [National Comprehensive Cancer Network 2017] 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]. The majority of patients with cSCC are successfully treated with surgical resection of the primary site. Patients with high-risk features are at risk for local recurrence and regional metastasis and these patients have significantly worse outcomes compared to those cured by initial surgery.

The Association Between Ultraviolet Light and cSCC

In contrast to basal cell carcinoma (BCC), the development of cSCC has been found to be due to multi-step carcinogenic events that accumulate over a lifetime of outdoor UV exposure, commonly associated with chronic occupational sun exposure [World Health Organization 1992] [International Agency for Research on Cancer 2007]. The typical pattern of UV-B induced mutations (C>T transitions), as well as a high frequency of double base (CC>TT) transitions, have been found to occur commonly within the p53gene 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]. Of interest, as reviewed by Boukamp, both alleles can be affected with each allele carrying a different and mostly UV-type specific mutation [Boukamp, P. 2005].

Karyotypic complexity and cytogenetic heterogeneity, most commonly affecting chromosomes 3, 8, 5, 9, and 11 have also been implicated in the initiation, maintenance, and propagation of this disease [Boukamp, P. 2005]. Ultraviolet-A rays that directly induce deoxyribonucleic acid (DNA) damage by inducing double-strand DNA breaks that generate genomic instability occur throughout the initiation and development of cSCC. Thus, while the 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. It is hypothesized that in this setting of loss of p53 mediated protective tumor suppression, with time, continued repetitive UV exposure may lead to an increase in the number and complexity of chromosomal and cytogenetic aberrations. The accumulation of these karyotypic and chromosomal aberrations ultimately results in a cumulative high mutational burden within cSCC.

More recently, Pickering and colleagues attempted to characterize a somatic mutation gene signature of cSCC that might be implicated in the propagation of the disease by restricting whole exome sequencing of cSCC tissue specimens to those obtained from patients with clinically aggressive disease. Similar to HNSCC, the mutational landscape was dominated by tumor suppressor genes. Potential novel candidate driver genes were also described (eg, NOTCH2, PARD3, and RASA1). Importantly, the mutation frequency seen in this analysis, was one of the highest reported, with a total of 108,034 mutations in 16,588 genes. This mutation frequency was noted to be more than four times higher than the mutation frequency for melanoma, as well as higher than the rate of several other squamous cell malignancies, including HNSCC [Pickering, C. R., et al 2014].

The Role of HPV Infection and cSCC

Human papilloma viruses replicate exclusively in keratinocytes, are dependent upon keratinocyte differentiation to complete their life cycle [Cardoso, J. C. 2011] [Aldabagh, B., et al 2013] [Doorbar, J. 2005], and have been historically implicated in the development of the common wart (verrucae vulgaris). Subsequent initial evidence for a role for cutaneous HPVs in the pathogenesis of skin malignancies came from the identification of HPV 5 and 8 from patients with epidermodysplasia verruciformis (EV), the rare autosomal recessive condition characterized by diffuse wart-like lesions over broad areas of the skin associated with a 30% to 50% lifetime risk of progression to invasive cSCC [Cardoso, J. C. 2011]. Since then, more than 200 different types of the papillomaviridae family have been identified, with approximately 90% of HPV viruses being encompassed by the alpha, beta, and gamma genotypes [Bzhalava, D., et al 2014] [Aldabagh, B., et al 2013]. The alpha HPV genotypes are associated with mucosal malignancies such as HNSCC, cervical, and anogenital cancers (ie, HPV 16, 18, 31, 33, 45). However, the beta genotypes are associated with cutaneous non-melanoma malignancies that include cSCC and BCC.

Evidence for HPV involvement in the pathogenesis of cSCC includes the products of the early expressed genes, the viral proteins E6 and E7. E6 binds to and mediates the degradation of the p53 tumor suppressor gene, while E7 has been shown to activate telomerase and inactivate the retinoblastoma protein, thus preventing cell cycle inhibition. Therefore, E6 and E7 may act synergistically to facilitate the accumulation of UV-mediated DNA damage. Additionally, there is evidence of a dose-response relationship between HPV and cSCC, as the risk of development of cSCC has been demonstrated to increase 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 beta 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. One study using serial skin sampling, showed that HPV DNA from topical skin infection was higher from sun-exposed areas (forehead and back of hand) compared to non-sun-exposed areas (buttocks) [Aldabagh, B., et al 2013].

Ultraviolet light and HPV can interact to alter the body's local immunity at sun exposed or sunburned sites. Increased numbers of HPV DNA species were found in plucked eyebrow samples from participants reporting a history of prior sunburns, without any association between HPV seropositivity and lifetime sun exposure [Termorshuizen, F., et al 2004]. Additional evidence from Cestari et al. demonstrated an altered local T-cell and cell-mediated response in the UV-radiated skin, thus increasing susceptibility to HPV infection in that area [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, 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.

Merkel Cell Carcinoma and Responsiveness to Pembrolizumab

Similar to cSCC, the rare neuroendocrine Merkel cell carcinoma (MCC) particularly affecting older Caucasian patients is another UV exposure and virally based skin cancer [Cassler, N. M., et al 2016]. Merkel cells are thought to arise from epidermal stem cells, which can also give rise to keratinocytes [Cassler, N. M., et al 2016]. A highly aggressive cancer, MCC or primary cutaneous neuroendocrine carcinoma, has been found to be caused by 2 independent mechanisms of carcinogenesis – the UV light associated signature of mutations associated with increased genomic instability and a high mutational burden, as well as the Merkel cell polyomavirus (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. The MCPyV is a double-stranded nonenveloped DNA virus ubiquitous in the general population from early childhood, and usually clinically asymptomatic without evidence of detectable viremia [Chang, Y. 2012]. However, in the elderly and immunosuppressed, where mechanisms of immune surveillance are decreased, 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].

Using whole exome sequencing and next-generation sequencing, the approximately 20% of MCC that are MCPyV negative, have been found to have a high mutation burden resulting in single nucleotide variants that can be as high as over 1000 per-exome with frequent mutations in the p53 and Rb genes [Goh, G., et al 2016] [Harms, P. W., et al 2015]. This high mutation burden displayed the distinctive UV signature (C > T, CC>TT) similar to other cancers, including cSCC, also resulting in increased genetic instability. Of note, virus negative MCC were also shown to harbor more tumor neoantigens than either melanomas or non-small cell lung cancer. Moreover, when correlated with PD-L1 expression, MCPyV negative tumors that were PD-L1 positive by IHC were found to have a significantly increased mutational burden compared with PD-L1 negative tumors [Wong, S. Q., et al 2015]. In contrast, MCPyV positive MCC harbor very few single nucleotide variants (median 12.5 SSNVs/tumor), but may initiate tumorigenesis by causing mutational inactivation within tumor suppressor genes such as the p53 and RB1 genes and NOTCH signaling pathway.

In possibly the largest correlation of PD-L1 expression with survival in MCC, evaluating 67 MCC specimens from 49 patients, consistent with multiple reports of the prevalence of the MCPyV in MCC, 78% were found to be virus positive. Of virus positive specimens, 50% were PD-L1 positive with the virus co-localizing with the visualized moderate-to-severe immune infiltrate in a so-called “adaptive immunity” pattern, and associated with an improvement in OS. This was in contrast to MCPyV negative specimens, which were all negative for PD-L1 expression and had very little associated infiltrating immune cells and a worse survival prognosis. Based on this, it was postulated that checkpoint inhibitor therapy may play a therapeutic role in the treatment of MCPyV positive MCC with the role for MCPyV negative MCC less clear [Lipson, E. J., et al 2013].

The first prospective clinical trial evidence for a role for checkpoint inhibitor therapy may have come from the Phase 1 study of pembrolizumab, in which the 1 of the 2 participants with a complete response (CR) were MCC (the other tumor type being metastatic melanoma). PD-L1 status was untested in these 2 participants, but these results served to confirm the potential clinical utility of checkpoint inhibitors [Patnaik, A., et al 2015].

This initial evidence was subsequently confirmed in a multicenter Phase 2 noncontrolled clinical trial of participants with advanced MCC not amenable to curative therapy, who had received no prior systemic therapy and were all treated with pembrolizumab for a maximum of 2 years of continuous treatment, or until a CR was achieved, progressive disease (PD), or unacceptable toxicity. Of the 26 evaluable patients with Stage IIIB or IV MCC, based on central radiology review, 14 had a confirmed response (4 with CR and 10 with partial response [PR]) for an ORR of 56% (95% CI, 35 to 76 patients). An additional one patient had an unconfirmed response and was continued on treatment at the time of reporting, and another one patient (4%) had stable disease (SD). 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. Importantly, clinically relevant responses were seen 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 IHC on tumor cells) was more frequent in virus positive tumors than virus negative tumors (71% versus 25%, P=0.049), but, was not required for clinical activity of pembrolizumab. Additionally, pembrolizumab was reported to be well tolerated in this population (median age = 68 years [range 57-91 years]) with drug-related Grade 3 or 4 AEs occurring in 15% of patients [Nghiem, P. T., et al 2016]. These results have been subsequently confirmed with other checkpoint inhibitors [Kaufman, H. L., et al 2016].

HPV Positive HNSCC and Responsiveness to Pembrolizumab

Further evidence supporting the robust response of checkpoint inhibitors to the dichotomous biologies of mutational burden as well as viral etiology within a single tumor type comes from HNSCC. In the aforementioned KEYNOTE 012 clinical trial of R/M HNSCC, in which all tumors were PD-L1 positive by trial design, similar clinical efficacy was seen in either HPV positive or negative disease (25% ORR, range 7-52, and 14% ORR, range 4-32, respectively). In the KEYNOTE 012 expansion cohort that enrolled participants whose tumors were both PD-L1 positive or negative, response rates were 21% and 27% in HPV

positive and HPV negative, respectively [Seiwert, T. Y., et al 2015]. Thus, similar to MCC, evidence of broad clinical activity was seen regardless of viral etiology.

Current Therapies for Incurably R/M cSCC

Due to the overall low prevalence of incurably R/M cSCC, no randomized clinical systemic therapy trials have been conducted in this malignancy, and evidence based clinical treatment guidelines are sparse. Although the overall incidence of this skin cancer is increasing worldwide, the overall majority will be cured with local measures such as surgery and/or radiotherapy. Metastasis occurs in only about 5% of participants, making it challenging to conduct large, randomized trials.

For early-stage low-risk disease, surgery, with or without adjuvant radiotherapy, is commonly employed for the treatment of unresectable disease or localized disease with high risk features. In patients with incurably R/M cSCC, no clear consensus regarding treatment guidelines exist due to the paucity of robust clinical trial data. National Comprehensive Cancer Network (NCCN) guidelines have stated that "cisplatin either as a single agent or combined with 5-FU [5-fluorouracil] has occasionally produced useful responses, but data supporting efficacy are limited." European consensus guidelines acknowledge the potential clinical utility of platinum- based treatment regimens, as well as 5-fluorouracil (5-FU)-based treatment while noting that no established standard regimen exists based on clinical trial evidence [Garbe, C., et al 2012]. German guidelines from the German Cancer Society and the German Society of Dermatology note that there "is insufficient evidence-based data on systemic treatment of metastasized cSCC"; however, outside of clinical trial participation, polychemotherapy with cisplatin in combination with 5-FU, or 5-FU monotherapy, or cetuximab can be considered**.** Globally, there are no treatment recommendations from any consensus group for second line therapy(ies), thus making the need for well-studied treatments for all unresectable and/or metastatic cSCC an unmet clinical need.

One of the only studies acknowledged by the NCCN guidelines is the prospective Phase 2, single-arm, single institution clinical trial conducted at M.D. Anderson Cancer Center testing the combination regimen of interferon alpha, cis-retinoic acid, and cisplatin that enrolled 39 participants from 1993 to 1999 with unresectable and/or distant metastatic disease. Of the 35 participants who were assessable for response, the overall ORR was 34% (17% CR and 17% PR), and included 1 of 11 participants with metastatic disease who experienced a CR. There is no consensus recommendation regarding the use of this regimen in advanced cSCC as it is not recommended by the European consensus guidelines.

Below in Table 1 is a summary of prospective single-arm trials of chemotherapy conducted for unresectable and/or distant metastatic disease, all in the first line setting, all conducted from approximately 15 to 30 years ago.

Table 1 Prospective Single-arm Clinical Trials of Chemotherapy for Unresectable and/or Metastatic cSCC

Regimen	Line	Study Phase	N	ORR	Year Reported
Cis/Dox	1st	2	3[a]	67%	1985
Cis/5-FU/Bleomycin	1st	2	14	84%	1990
Cis/5-FU	1st	2	7	86%	1991
Oral 5-FU	1st	2	14	14%	2000
Ifn2/13-cRA	1st	2	32	68%	1992

[a]This clinical trial enrolled participants with either cSCC or Basal Cell Carcinoma. Three of the 11 participants enrolled had cSCC.

Cis = cisplatin; 13-cRA = 13-cis retinoic acid; cSCC = cutaneous squamous cell carcinoma; Dox = Doxorubicin; 5-FU = fluorouracil; Ifn2 = interferon; ORR = objective response rate.

Source: [Guthrie, T. H., et al 1985] [Khansur, T. 1991]

More recently, because of the epithelial origin of cSCC, epithelial growth factor inhibitors have been investigated for the treatment of advanced cSCC with modest results. Below in Table 2 are the results of 2 single-arm Phase 2 trials assessing these agents in incurably R/M cSCC.

Table 2 Prospective Single-arm Clinical Trials for Incurable Unresectable and/or Metastatic cSCC

Regimen	Line	Study Phase	N	ORR	Year Reported
Cetuximab	1st	2	36	28%	2011
Panitumumab	1st/2nd	2	16	31%	2014
cSCC = cutaneous squamous cell carcinoma; ORR = objective response rate					

Source: [Foote, M. C., et al 2014]

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. Ultraviolet 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 this malignancy a likely candidate to benefit from checkpoint inhibitor therapy. In malignancies with dichotomous etiologies such as MCC and HNSCC, checkpoint inhibitor 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 (MK-3475) in unresectable and/or metastatic cSCC, a disease population with limited treatment options and a significant unmet clinical need.

Immunosuppression has long been associated with increased risk of cSCC. Participants with prior allogeneic transplantation on 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 control participants. However, several recent case reports of allograft rejection following treatment of 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 clinical trial.

Inclusion of First-line (1L) Participants in the Study:

There are regional differences when it comes to recommended standard of care guidelines for R/M cSCC. However, widely accepted treatment practice guidelines recommend using either platinum based chemotherapy (as monotherapy or in combination with 5-FU) or epidermal growth factor inhibitors such as cetuximab. They specifically note that "cisplatin either as a single agent or combined with 5-FU has occasionally produced useful responses, but data supporting efficacy are limited" [National Comprehensive Cancer Network 2017]. There are no prospective Phase 3 studies available, and the supporting data for cytotoxic based treatments come from a limited number of smaller single arm Phase 2 trials (Table 1 on current therapies for incurable R/M cSCC section summarizes 1L chemotherapy studies). One such platinum based Phase 2 study, tested the combination of cisplatin with interferon alpha and cis-retinoic acid therapies in 39 patients with R/M cSCC. Of the 35 patients who were assessable for response, the ORR was 34% [Shin, D. M., et al 2002]. More recently, because of the epithelial origin of cSCC, epithelial growth factor (EGFR) inhibitors have been investigated for the treatment of advanced cSCC with modest results (Table 2 on current therapies for incurable R/M cSCC section summarizes EGFR inhibitor based studies). In a Phase 2 study of cetuximab as first line therapy for patients with unresectable cSCC, Maubec et al. reported an ORR of approximately 28%, with a median PFS of 4.1 months and mean OS of 8.1 months (median OS not reached) [Maubec, E., et al 2011].

Recent prospective 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 local/regionally advanced or metastatic cSCC. In a Phase 1 open-label study (NCT02383212), patients with metastatic cSCC, including 1L metastatic patients (n=10) were treated for up to 48 weeks with cemiplimab (3 mg/kg every 2 weeks [Q2W]). Results presented by Owonikoko et al [Owonikoko, T. K., et al 2018] at the American Society of Clinical Oncology (ASCO) 2018 revealed an ORR, based on RECIST 1.1 by independent central review, of 60% (95% CI: 26.2 to 87.8) and a disease control rate (DCR) of 80% (95% CI: 44.4 to 97.5) in the metastatic population. Primary analysis of the ongoing pivotal Phase 2 study (NCT02760498) of cemiplimab (REGN2810) in 59 patients with metastatic cSCC reported an 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 [Rischin, D., et al 2018]. Based on these encouraging data demonstrating efficacy of an anti-PD-1 mAb in the 1L metastatic cSCC setting, the addition of 1L R/M patients to be treated with pembrolizumab monotherapy is

justified by the Sponsor, and this scientifically, peer reviewed data justified the inclusion of the 1L R/M population in the KEYNOTE-629 study.

Current Therapies for LA Unresectable cSCC

Currently, there is no widely accepted systemic therapy standard of care therapy for LA unresectable cSCC [National Comprehensive Cancer Network 2017]. Yet these subjects have a substantial risk of disease-specific death, and endure significant morbidity associated with disease recurrence. In a retrospective study of 55 patients, treated at 2 tertiary referral centers between 1997 and 2006 with T3 and T4 disease of the trunk and extremities (according to the 2002 AJCC staging guidelines), the overall cancer-specific survival at 5 years was 49.7%; and no patients with T4 nor lymph node metastasis were alive at 5 years [de Lima Vazquez, V., et al 2011].

Although the standard of care for LA high-risk disease is surgical resection and radiotherapy, patients with LA cSCC, who are often older and less tolerant of chemotherapy, considered medically unfit or not amenable for surgical resection (due to disease with extensive local involvement and/or invasion) and have a poor prognosis [Samstein, R. M., et al 2014]. Although, these patients might receive modest benefit from radiation therapy, newer treatment modalities, including checkpoint inhibitor therapy, can be considered. Recent Phase 1 data on cemiplimab (REGN2810), provides evidence of clinical activity of anti-PD-1 inhibitors in patients with unresectable locally and/or regionally advanced cSCC. In study NCT02383212 (discussed above) cemiplimab administered to 16 patients with unresectable LA cSCC demonstrated an ORR of 43.8% [Owonikoko, T. K., et al 2018]. Based on the encouraging evidence of clinical activity for the checkpoint inhibitor therapeutic class, we hypothesize that pembrolizumab would be able to provide substantial clinical benefit for this group of patients with an unmet medical need. Therefore, we propose to study pembrolizumab in a similar LA population by adding a single arm cohort of participants with LA unresectable cSCC to study KEYNOTE-629.

3.3 Benefit/Risk Assessment

Participants in clinical trials generally cannot expect to receive direct benefit from treatment during participation, as clinical trials are designed to provide information about the safety and effectiveness of an investigational medicine.

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

4. Objectives/Hypotheses and Endpoints

All objectives and hypotheses apply to male/female participants aged 18 years or older with R/M cSCC and LA unresectable cSCC.

Objective/Hypothesis	Endpoint
Primary	
(1) To estimate the ORR per Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 as assessed by blinded independent central review (BICR).	(1) Objective response: defined as CR or PR.
Secondary	
(1) To evaluate the DOR per RECIST 1.1 as assessed by BICR.	(1) DOR: for participants who demonstrate CR or PR, DOR is defined as the time from first documented evidence of CR or PR until disease progression or death due to any cause, whichever occurs first.
(2) To evaluate the DCR per RECIST 1.1 as assessed by BICR.	(2) Disease control: defined as CR or PR or SD for at least 12 weeks.
(3) To evaluate the PFS per RECIST 1.1 as assessed by BICR.	(3) PFS: defined as the time from first day of study treatment to the first documented disease progression or death due to any cause, whichever occurs first. Note: A new primary low-risk cSCC lesion is not considered as a PFS event.
(4) To evaluate the OS of the participants.	(4) OS: defined as the time from first day of study treatment to death due to any cause.
(5) To determine the safety and tolerability of pembrolizumab in study participants with R/M cSCC.	(5) AEs. Study drug discontinuations due to AEs.
Tertiary/Exploratory	
(1) To evaluate ORR, DOR, DCR, and PFS using immune-related RECIST (irRECIST) as assessed by BICR.	(1) ORR, DOR, DCR, and PFS.
(2) To identify molecular (genomic, metabolic, and/or proteomic) biomarkers that may be indicative of clinical response/resistance, safety, pharmacodynamic activity, and/or the mechanism of action of MK-3475 and other treatments.	(2) Germline genetic variation, genetic (DNA) mutations from tumor, tumor and blood ribonucleic acid (RNA) variation, proteomics and IHC, and other blood-derived biomarkers

Objective/Hypothesis	Endpoint
(3) To investigate the relationship between pembrolizumab treatment and the checkpoint inhibitor pathway including but not limited to PD-L1 and/or PD-L2, utilizing newly obtained or archival tumor tissue and blood, including serum and plasma.	(3) PD-L1 and/or PD-L2 checkpoint inhibition pathway at baseline and post-baseline time points.
(4) To evaluate pharmacokinetic (PK) exposure	(4) PK exposure
(5) To evaluate changes from baseline in health-related quality of life using the EORTC QLQ-C30 and characterize utilities using EuroQol EQ-5D.	(5) Changes from baseline in patient-reported outcome (PRO) assessments at post-baseline time points

5. Study Design

5.1 Overall Design

This is a multi-site, open-label, non-randomized, single-arm Phase 2 study of pembrolizumab therapy in Male/Female participants aged 18 years or older with R/M cSCC and LA unresectable cSCC.

All participants must obtain baseline radiographic evidence showing measurable disease assessed by blinded independent central review (BICR) based on RECIST 1.1 before enrollment into this study. Up to approximately 150 study participants will be enrolled in this study; 100 with R/M cSCC and 50 with LA unresectable cSCC. It is at the discretion of the Sponsor to stop the study or terminate the study earlier due to futility of accrual.

All participants will receive a 200 mg dose of pembrolizumab by IV administration every 3 weeks (Q3W). Participants will be evaluated at 6 weeks (42 days + 7 days) and then every 6 weeks (42 days ± 7 days) with radiologic/photographic imaging to assess response to study treatment. After 12 months, radiographic/photographic imaging will be conducted every 9 weeks (63 days ± 7 days). Note: For participants deemed eligible for enrollment by digital photography, upon investigator-determined CR, a biopsy is required within 30 days of CR for confirmation of CR by central pathology (see Section 9.2.1.8). The primary efficacy endpoint will be evaluated by ORR assessed by BICR per RECIST 1.1. Secondary objectives include evaluation of safety, DCR, DOR, and PFS per RECIST 1.1 assessed by BICR, and OS of the study participants.

Exploratory endpoints will also be evaluated by ORR, DOR, DCR and PFS based on irRECIST as assessed by BICR. Exploratory endpoints also will include PROs as measured by EuroQol EQ-5D and EORTC QLQ-C30 questionnaires and exploratory biomarker assessment.

Participants will be monitored carefully for the development of AEs and for clinical and/or radiographic evidence of PD according to RECIST 1.1. Adverse events will be monitored throughout the study and graded in severity according to the guidelines outlined in the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE), Version 4.0. However, central review based on irRECIST (See Section 5.4.1), may be used by the investigator for treatment decisions to account for tumor response patterns seen with pembrolizumab (eg, tumor pseudoprogression). In participants who have initial evidence of radiological PD by RECIST 1.1, it will be at the discretion of the investigator whether or not to continue a participant on study treatment until repeat imaging is obtained. This clinical judgment decision should be based on the participant's overall clinical condition, including performance status, clinical symptoms, and laboratory data. Participants may continue to receive study treatment until tumor assessment is repeated ≥4 weeks later in order to confirm PD by irRECIST per the independent central radiologic review's assessment.

Participants may receive pembrolizumab study treatment for up to 35 cycles and no more than 24 months of treatment after C1D1. Participants will continue treatment until documented PD, 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, participant completes 35 administrations of pembrolizumab (no more than 24 months of treatment), or cessation due to administrative reasons, at which point they will be discontinued from treatment but continue to be monitored in the study except when the subject withdrawals consent resulting in discontinuation from the study. Participants will be treated thereafter at the discretion of the physician.

Note: Participants who discontinue pembrolizumab after 35 administrations may be eligible for up to 17 administrations (approximately one year) of additional study treatment if they progress after discontinuing study treatment provided they meet additional criteria. Participants who discontinue study treatment before receiving 35 administrations of pembrolizumab for reasons other than PD or intolerability, or who attain a CR and discontinue study treatment, may also be eligible for up to 17 administrations (approximately 12 months of retreatment [Second Course Phase] after experiencing PD). The decision to begin the second course will be at the discretion of the investigator, provided that the participant meets the criteria for treatment, and the study is ongoing (See Section 6.1 and 6.2).

After the End of Treatment (EoT), each study participant will be followed for 30 days for AE and event of clinical interest (ECI) monitoring and 90 days for SAE monitoring. Study participants who discontinue treatment for reasons other than PD will have post-treatment follow-up of disease status until PD, initiating a non-study cancer treatment, withdrawing

consent, or becoming lost to follow-up. All study participants will be followed by telephone contact every 12 weeks (84 ± 7 days) for survival until death, withdrawal of consent, becoming 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 course of the study. For example, survival status may be requested prior to the final analysis. All subjects 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.

The trial will be conducted in conformance with Good Clinical Practices (GCPs).

Specific procedures to be performed during the trial, as well as their prescribed times and associated visit windows, are outlined in the Trial SoA - Section 2. Details of each procedure are provided in Section 9 – Study Assessments and Procedures.

5.1.1 Study Diagram

The study design is depicted in Figure 1.

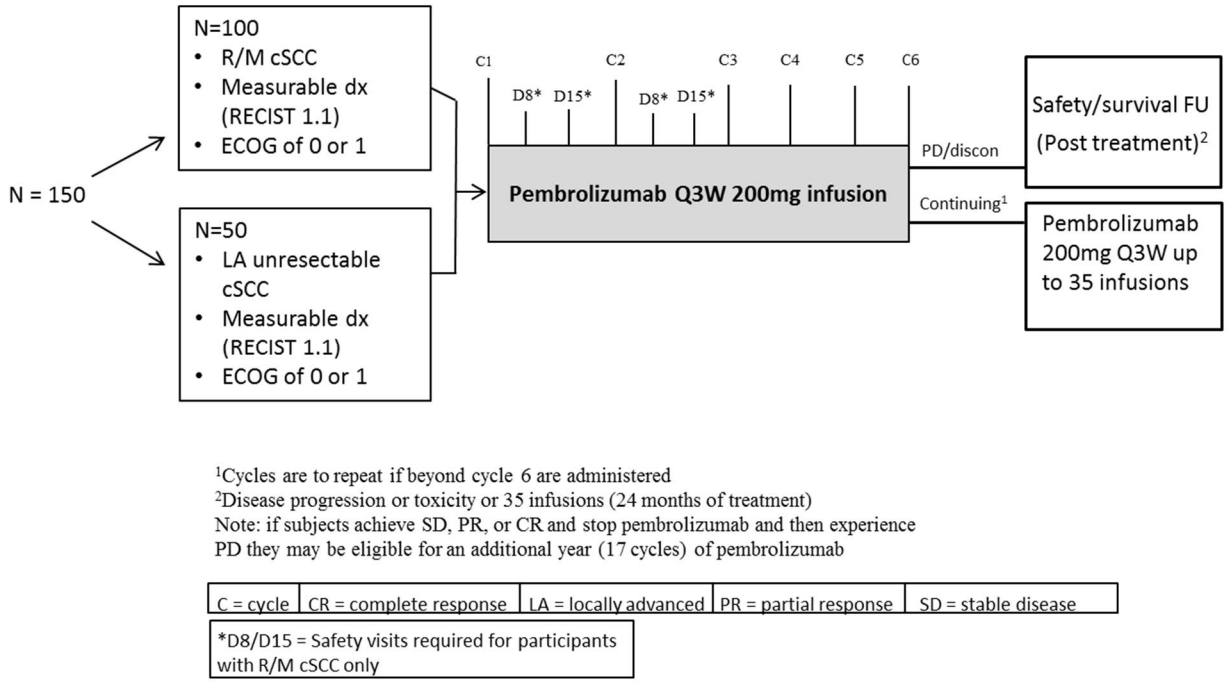

Figure 1 Trial Design

5.2 Number of Participants

Up to approximately 100 study participants with incurably recurrent and/or metastatic cSCC and 50 participants with LA unresectable cSCC will be allocated.

5.3 Beginning and End of Study Definition

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

Upon study completion, participants are discontinued and may be enrolled in a pembrolizumab extension study, if available.

5.3.1 Clinical Criteria for Early Trial Termination

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

5.4 Scientific Rationale for Study Design

This Phase 2 study will evaluate the efficacious advantage of pembrolizumab in participants with R/M cSCC or LA unresectable cSCC.

5.4.1 Rationale for Endpoints

5.4.1.1 Primary Efficacy Endpoints

This study will use ORR based on RECIST 1.1 criteria as assessed by a BICR as the primary endpoint. Objective response rate is an acceptable measure of clinical benefit for a late stage study that demonstrates safety and efficacy of a new antineoplastic therapy, especially if the magnitude of the effect is large and the therapy has an acceptable risk/benefit profile.

The use of a BICR and RECIST 1.1 to assess ORR is typically considered acceptable by regulatory authorities. In addition, the final determination of radiologic progression will be based on the central assessment of progression, rather than a local site investigator/radiology assessment. Real time determination of radiologic progression as determined by central review will be communicated to the site.

5.4.1.2 Secondary Efficacy Endpoints

Duration of response, DCR, and PFS based on RECIST 1.1 and assessed by BICR, and OS are commonly accepted endpoints by both regulatory authorities and the oncology community.

Note: A new primary low-risk cSCC is not considered a PFS event (see Section 9.2.1.6). The occurrence of a new primary low-risk cSCC lesion 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 systemic therapy. The use of pembrolizumab will be focused on that of life-threatening disease, which would be the case for recurrent/metastatic cSCC.

Overall survival has been recognized as the gold standard for the demonstration of benefit of an antineoplastic therapy in randomized clinical studies.

5.4.1.3 Exploratory Efficacy Endpoints

5.4.1.3.1 Immune-related RECIST

RECIST 1.1 will be adapted to account for the unique tumor response characteristics seen following the treatment of pembrolizumab. Immunotherapeutic agents such as pembrolizumab may produce antitumor effects by potentiating endogenous cancer-specific immune responses. The response patterns seen with such an approach may extend beyond the typical time course of responses seen with cytotoxic agents, and participants may manifest a clinical response after an initial increase in tumor burden or even the appearance of new lesions. Standard RECIST 1.1 may, therefore, not provide an accurate response assessment of immunotherapeutic agents such as pembrolizumab.

Based on an analysis of participants with melanoma enrolled in the KEYNOTE-001 trial, 7% of evaluable participants experienced delayed or early tumor pseudo-progression. Of note, participants who had PD by RECIST 1.1, but not by irRECIST, had longer OS than participants with PD by both criteria. Additionally, the data suggest that RECIST 1.1 may underestimate the benefit of pembrolizumab in approximately 15% of participants. These findings support the need to apply a modification to RECIST 1.1 that takes into account the unique patterns of atypical response in immunotherapy and enables treatment beyond initial radiographic progression.

The irRECIST assessment is based on RECIST 1.1 and is adapted to account for the unique tumor response seen with immunotherapeutics as described in Nishino et al., CCR 2013 [Nishino, M., et al 2013]. The assessment of unidimensional target lesions and response categories per irRECIST are identical to RECIST 1.1. However, MSD has implemented an adaptation related to new lesions, non-target lesions, and tumor burden assessment in order to confirm radiographic progression. Immune-related RECIST will be used by local site investigators to assess tumor response and progression, and to make treatment decisions, as well as used by the central imaging vendor in support of the PFS, ORR, DCR, and DOR endpoint. For further information on irRECIST, see Section 9.2.1.6.

5.4.1.4 Rationale for Patient-reported Outcomes

Changes in health-related quality of life (HRQoL) measured using patient-reported outcome (PRO) assessments can provide important information on clinical benefit and are accepted clinical endpoints by health authorities. Participants will provide information regarding their HRQoL using the EORTC QLQ-C30 PRO instrument. Health utilities will be evaluated

using the EuroQol-5D (EQ-5D) PRO instrument. These PRO assessments are not pure efficacy or safety endpoints because they are affected by both disease progression and treatment tolerability.

EORTC QLQ-C30

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

EuroQol EQ-5D

The EuroQol-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 [Aaronson, N. K., et al 1993]. 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 his or her general state of health at the time of the assessment. This instrument has been used extensively in cancer studies and published results from these studies support its validity and reliability [Pickard, A. S., et al 2007].

5.4.1.5 Rationale for Safety Endpoints

Safety parameters commonly used for evaluating investigational systemic anticancer treatments are included as safety endpoints including, but not limited to, the incidence of, causality, and outcome of AEs/SAEs, and changes in vital signs and laboratory values. Adverse events will be assessed as defined by CTCAE, Version 4.0.

5.4.1.6 Pharmacokinetic Endpoints

Pharmacokinetics of pembrolizumab will be explored per existing modeling analysis plan (MAP).

5.4.1.7 Planned Exploratory Biomarker Research

Cancer immunotherapies represent an important and novel class of anti-tumor agents. However, the mechanism of action of these exciting new therapies is not completely understood and much remains to be learned regarding how best to leverage these new drugs in treating patients. Thus, to aid future patients, it is important to investigate the determinants of response or resistance to cancer immunotherapy, as well as determinants of AEs in the course of our clinical trials. These efforts will identify novel predictive/PD biomarkers and generate information that will better guide single-agent and combination therapy with

immune-oncology drugs. To identify novel biomarkers, biospecimens (ie, 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:

5.4.1.7.1 Germline Genetic Analyses

Germline (blood) genetic analyses (eg, single nucleotic polymorphism [SNP] analyses, whole exome sequencing, whole genome sequencing): This research will evaluate whether genetic variation within a clinical trial population correlates with response to the treatment(s) under evaluation. If genetic variation is found to predict efficacy or AEs, the data might inform optimal use of therapies in the patient population. Furthermore, it is important to evaluate germline DNA variation across the genome in order to interpret tumor-specific DNA mutations.

5.4.1.7.2 Tumor Genetic Analyses

Genetic (DNA) analyses from tumor: The application of new technologies, such as next generation sequencing, has provided scientists the opportunity to identify tumor-specific DNA changes (ie, mutations, methylation status, microsatellite instability). Key molecular changes of interest to immune-oncology drug development include the mutational burden of tumors and the clonality of T-cells in the tumor microenvironment. Increased mutational burden (sometimes referred to as a ”hyper-mutated” state) may generate neo-antigen presentation in the tumor microenvironment. To conduct this type of research, it is important to identify tumor-specific mutations that occur across all genes in the tumor genome. Thus, genome-wide approaches may be used for this effort. Note that in order to understand tumor-specific mutations it is necessary to compare the tumor genome with the germline genome. Microsatellite instability may also be evaluated as this is an important biomarker for some cancers (ie, colorectal cancer).

5.4.1.7.3 Tumor and Blood RNA Analyses

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

5.4.1.7.4 Proteomic Biomarkers and IHC

Proteomics and IHC using blood or tumor: Tumor and blood samples from this trial may undergo proteomic analyses (eg, PD-L1 IHC). PD-L1 protein level in tumor sections, assessed by IHC, has been shown to correlate with response to pembrolizumab in patients

with non-small cell lung cancer (NSCLC), and an in vitro diagnostic (IVD) device has been developed for use with pembrolizumab in NSCLC. Preliminary data indicates that this association may also be true in additional cancer types (ie, triple negative breast cancer, head and neck, and gastric). Additional tumor or blood-derived proteins may also correlate with response to pembrolizumab. Therefore, tumor tissue may be participant to proteomic analyses using a variety of platforms that could include but are not limited to immunoassays and liquid chromatography/mass spectrometry. This approach could identify novel protein biomarkers that could aid in patient selection for pembrolizumab (MK-3475) therapy.

5.4.1.7.5 Other Blood Derived Biomarkers

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

5.4.1.8 Future Biomedical Research

The Sponsor will conduct Future Biomedical Research on specimens consented for future biomedical research during this clinical trial. This research may include genetic analyses (DNA), gene expression profiling (RNA), proteomics, metabolomics (serum, plasma) and/or the measurement of other analytes, depending on which specimens are consented for future biomedical research.

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

5.5 Justification for Dose

5.5.1 Rationale for Pembrolizumab Dose

The planned dose of pembrolizumab for this trial is 200 mg every 3 weeks (Q3W). Based on the totality of data generated in the KEYTRUDA® development program, 200 mg Q3W is the appropriate dose of pembrolizumab across all indications and regardless of tumor type. As outlined below, this dose is justified by:

- Clinical data from eight randomized studies demonstrating flat dose- and exposure-efficacy relationships from 2 mg/kg Q3W to 10 mg/kg every two weeks (Q2W)

- Clinical data showing meaningful improvement in benefit-risk including overall survival at 200 mg Q3W across multiple indications

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

Among the eight randomized dose-comparison studies, a total of 2262 subjects were enrolled with melanoma and non-small cell lung cancer (NSCLC), covering different disease settings (treatment naïve, previously treated, PD-L1 enriched and all-comers) and different treatment settings (monotherapy and in combination with chemotherapy). Five studies compared 2 mg/kg Q3W versus 10 mg/kg Q3W (KN001 B2, KN001 D, KN002, KN010 and KN021), and three studies compared 10 mg/kg Q3W versus 10 mg/kg Q2W (KN001 B3, KN001 F2 and KN006). All of these studies demonstrated flat dose- and exposure-response relationships across the doses studied representing an approximate 5 to 7.5 fold difference in exposure. The 2 mg/kg (or 200 mg fixed-dose) Q3W provided similar responses to the highest doses studied. Subsequently, flat dose-/exposure-response relationships were also observed in other tumor types including head and neck cancer, bladder cancer, gastric cancer and classical Hodgkin Lymphoma, confirming 200 mg Q3W as the appropriate dose independent of the tumor type. These findings are consistent with the mechanism of action of pembrolizumab, which acts by interaction with immune cells, and not via direct binding to cancer cells.

Additionally, pharmacology data clearly show target saturation at 200 mg Q3W. First, PK data in KN001 evaluating target-mediated drug disposition (TMDD) conclusively demonstrated saturation of PD-1 in systemic circulation at doses much lower than 200 mg Q3W. Secondly, a PBPK analysis was conducted to predict tumor PD-1 saturation over a wide range of tumor penetration and PD-1 expression. This evaluation concluded that pembrolizumab at 200 mg Q3W achieves full PD-1 saturation in both blood and tumor.

Finally, population PK analysis of pembrolizumab, which characterized the influence of body weight and other subject covariates on exposure, has shown that the fixed-dosing provides similar control of PK variability as weight based dosing, with considerable overlap in the distribution of exposures from the 200 mg Q3W fixed dose and 2 mg/kg Q3W dose. Supported by these PK characteristics, and given that fixed-dose has advantages of reduced dosing complexity and reduced potential of dosing errors, the 200 mg Q3W fixed-dose was selected for evaluation across all pembrolizumab protocols.

6. Study Population

Male/Female participants with R/M cSCC or LA unresectable cSCC ≥ 18 years of age will be enrolled in this trial.

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

6.1 Inclusion Criteria

Participants are eligible to be included in the study only if all of the following criteria apply:

Type of Participant and Disease Characteristics

1. R/M disease cohort only – All participants must have cSCC that is either metastatic, defined as disseminated disease, and/or unresectable disease that is not curable by surgery or radiation.

2. Participants must have histologically confirmed cSCC as the primary site of malignancy (metastatic skin involvement from another 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 (hairbearing) 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.

   Note: Participants who have squamous cell parotid metastases and have been treated previously for cSCC are permitted.

3. LA disease cohort only – Participants must be ineligible for surgical resection. Contraindications for surgical resection:

   - cSCC that has recurred in the same location after 2 or more surgical procedures and not amenable to curative resection.

   - cSCC with significant local invasion that prevents total resection.

   - cSCC in anatomically challenging locations for which surgery is not feasible and may result in severe dysfunction and disfigurement (eg, nose, ear, eye resections, or limb amputation.

4. LA disease cohort only – Participants who received prior radiation therapy(RT) to index site or must be deemed to be not eligible for RT.

   Contraindications (Ineligibility) for RT:

   - cSCC in anatomically challenging locations for which RT would be associated with unacceptable toxicity risk.

   - Patients who have previously received maximum recommended cumulative dose of RT at the index site for cSCC.

5. LA disease cohort only – Participants who received prior systemic therapy for curative intent are eligible regardless of regimen.

6. R/M disease cohort only – Participants must have metastatic disease, defined as disseminated disease distant to the initial/primary site of diagnosis, and/or must have locally recurrent disease that has been previously treated (with either surgery or radiotherapy) and is not curable by either surgery or radiotherapy.

   Note: There is no requirement for prior chemotherapy and/or biological systemic treatment for incurably recurrent and/or metastatic disease

   Note: There is no limit to the number of prior systemic therapies that a participant may have received in order to meet eligibility for this trial.

7. Participants must have measurable disease based on RECIST 1.1 as assessed by the central imaging vendor. Lesions situated in a previously irradiated area are considered measurable if progression has been demonstrated in such lesions.

   Note: The site investigator must confirm the participant has measurable disease per RECIST 1.1 prior to submitting to the central vendor.

8. Participants must have an Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 1 within 10 days prior to the start of treatment.

9. Participants must have adequate organ function as defined in the following table (Table 3). Specimens must be collected within 10 days prior to the start of treatment.

Table 3 Adequate Organ Function Laboratory Values

System	Laboratory Value
Hematological	
Absolute neutrophil count (ANC)	≥ 1500 cells/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 g/dL or ≥5.6 mmol/L. Participants are eligible if levels are reached after blood transfusion.
Renal	
[a]Measured or calculated creatinine clearance (GFR can also be used in place of creatinine or CrCl)	≤1.5 × ULN **OR** ≥45 mL/min for participants with creatinine levels >1.5 × institutional ULN
Hepatic	
[b]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 (≤5 x ULN for participants with liver metastases)
Coagulation	
[c]International normalized ratio (INR) **OR** PT and aPTT	≤1.5 × ULN unless participant is receiving anticoagulant therapy as long as prothrombin time (PT) or activated partial thromboplastin time (aPTT) is within therapeutic range of intended use of anticoagulants

[a] Creatinine clearance should be calculated per institutional standard.

[b] For participants with Gilbert's disease, total bilirubin may be >1.5 × ULN; however, direct bilirubin must be normal.

[c] Partial thromboplastin time (PTT) may be performed if the local laboratory is unable to perform aPTT.

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.

10. Participants must have a tissue sample adequate for PD-L1 testing as determined by central laboratory testing prior to trial allocation. This tissue sample may be obtained from either a newly obtained core or excisional biopsy, or a prior archival tissue specimen.

    Note: Participants from whom PD-L1 testing cannot be performed due to infeasibility of testing of the tissue sample will not be eligible.

    Note: Submit an evaluable sample for analysis. If submitting unstained cut slides, freshly cut slides should be submitted to the testing laboratory within 14 days from when the slides are cut. See Section 9.7 – Pharmacodynamics for an explanation.

11. Participants must have a life expectancy of greater than 3 months.

Demographics

12. Be at least 18 years of age on the day of signing the informed consent.

Female participants:

13. Female participants of childbearing potential must have a negative urine or serum pregnancy test within 72 hours prior to receiving the first dose of trial medication. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required.

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

14. A female participant is eligible to participate if she is not pregnant (see Appendix 5), not breastfeeding, and at least one of the following conditions applies:
    a.) Not a woman of childbearing potential (WOCBP) as defined in Appendix 5
    OR
    b.) A WOCBP who agrees to use an adequate method of contraception as detailed in Appendix 5 of this protocol, during the treatment period and for at least 120 days after the last dose of study treatment. Note: Abstinence is acceptable if this is the usual lifestyle and preferred contraception for the participant.

Informed Consent

15. The participant (or legally acceptable representative if applicable) must be willing and able to provide documented informed consent for the trial. The participant may also provide consent for Future Biomedical Research. However the participant may participate in the main trial without participating in Future Biomedical Research.

6.2 Exclusion Criteria

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

Medical Conditions

1. Participant has cSCC that can be cured with surgical resection, radiotherapy, or with a combination of surgery and radiotherapy.
2. Participant has any other histologic type of skin cancer other than invasive squamous cell carcinoma as the primary disease under study, eg, basal cell carcinoma that has not been definitively treated with surgery or radiation, Bowen's disease, MCC, melanoma.
3. Participants with any prior allogeneic solid organ or bone marrow transplantations are excluded.

Prior/Concomitant Therapy

4. Participant has received prior therapy with an anti-PD-1, anti-PD-L1, or anti-PD-L2 agent or with an agent directed to another stimulatory or co-inhibitory T-cell receptor (eg, CTLA-4, OX-40, CD137).
5. Participant has received prior systemic anti-cancer therapy including investigational agents within 4 weeks prior to allocation.

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

   Note: If a participant received major surgery, they must have recovered adequately from the toxicity and/or complications from the intervention prior to starting trial treatment.
6. Participant has received prior radiotherapy within 2 weeks of start of trial treatment. Participants must have recovered from all radiation-related toxicities, not require corticosteroids, and not have had radiation pneumonitis. A 1-week washout is permitted for palliative radiation (≤2 weeks of radiotherapy) to non-central nervous system (CNS) disease.
7. Participant has received a live vaccine within 30 days prior to the first dose of trial drug. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, varicella/zoster (chicken pox), yellow fever, rabies, Bacillus Calmette-Guérin (BCG), and typhoid vaccine. Seasonal influenza vaccines for injection are generally killed-virus vaccines and are allowed; however, intranasal influenza vaccines (eg, FluMist®) are live- attenuated vaccines and are not allowed.

Prior/Concurrent Clinical Study Experience

8. Participant is currently participating in or has participated in a trial of an investigational agent or has used an investigational device within 4 weeks prior to the first dose of trial treatment.

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

Diagnostic assessments

9. Participant has a diagnosis of immunodeficiency or is receiving systemic steroid therapy (in dosing exceeding 10 mg daily of prednisone equivalent) or any other form of immunosuppressive therapy within 7 days prior the first dose of trial drug.
10. Participant has a diagnosis and/or has been treated for additional malignancy within the past 5 years prior to allocation.

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

    Note: Participants with 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 (PSA) (≤ 10 ng/ml) either treated with definitive intent or untreated in active surveillance that has been stable for the past year prior to trial allocation.
11. Participant has known active CNS metastases and/or carcinomatous meningitis. Participants with previously treated brain metastases may participate provided they are radiologically stable, ie, without evidence of progression for at least 4 weeks by repeat imaging (note that the repeat imaging should be performed during study screening), clinically stable, and without requirement of steroid treatment for at least 7 days prior to first dose of trial treatment.
12. Has severe hypersensitivity (≥Grade 3) to pembrolizumab and/or any of its excipients.
13. Participant has an active autoimmune disease that has required systemic treatment in the past 2 years (eg, with use of disease-modifying agents, anticoagulants, corticosteroids or immunosuppressive drugs). Replacement therapy (eg, thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency) is not considered a form of systemic treatment and is allowed.
14. Participant has a history of (noninfectious) pneumonitis that required steroids or has current pneumonitis.
15. Participant has an active infection requiring systemic therapy.
16. Participant has a known history of human immunodeficiency virus (HIV) infection.

    Note: No HIV testing is required unless mandated by a local health authority.

    Note: for participants enrolled from German sites, HIV testing is required as part of the screening procedures

17. Participant has a known history of Hepatitis B (defined as Hepatitis B surface antigen [HBsAg] reactive) or known active Hepatitis C virus (defined as HCV RNA [qualitative] is detected) infection.

    Note: No testing for Hepatitis B or Hepatitis C is required unless mandated by a local health authority.

    Note: for participants enrolled from German sites, Hepatitis B and C testing is required as part of the screening procedures

18. Participant has a history or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the trial, interfere with the participant's participation for the full duration of the trial, or is not in the best interest of the participant to participate, in the opinion of the treating investigator.
19. Participant has a known psychiatric or substance abuse disorder that would interfere with the participant's ability to cooperate with the requirements of the trial.

Other Exclusions

20. Participant is pregnant or breastfeeding or expecting to conceive or father children within the projected duration of the trial, starting with the screening visit through 120 days after the last dose of trial treatment.

6.3 Lifestyle Restrictions

There are no lifestyle restrictions.

6.3.1 Meals and Dietary Restrictions

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

6.3.2 Caffeine, Alcohol, and Tobacco

Caffeine, alcohol and tobacco restrictions are not applicable in this study protocol.

6.3.3 Activity

There are no limitations on activity during the participation of this trial.

6.3.4 Contraception

Pembrolizumab may have adverse effects on a fetus in utero. Refer to Appendix 5 for approved methods of contraception. For this trial, male participants will be considered to be of non-reproductive potential if they have azoospermia (whether due to having had a vasectomy or due to an underlying medical condition).

Participants should be informed that taking the trial medication may involve unknown risks to the fetus (unborn baby) if pregnancy were to occur during the trial. In order to participate in the trial, participants of childbearing potential must adhere to the contraception requirement (Appendix 5) from the day of trial medication initiation (or 14 days prior to the initiation of trial medication for oral contraception) throughout the trial period up to 120 days after the last dose of trial 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 trial.

6.3.5 Pregnancy

If a participant inadvertently becomes pregnant while on treatment with pembrolizumab, the participant will be immediately discontinued from trial treatment. The site will contact the participant at least monthly and document the participant's status until the pregnancy has been completed or terminated. The outcome of the pregnancy will be reported to the Sponsor without delay and within 24 hours if the outcome is a serious adverse experience (eg, death, abortion, congenital anomaly, or other disabling or life-threatening complication to the mother or newborn). The trial investigator will make every effort to obtain permission to follow the outcome of the pregnancy and report the condition of the fetus or newborn to the Sponsor. If a male participant impregnates his female partner, the trial personnel at the site must be informed immediately and the pregnancy must be reported to the Sponsor and followed as described in Section 9.3.6.

6.3.6 Use in Nursing Women

It is unknown whether pembrolizumab is excreted in human milk. Since many drugs are excreted in human milk, and because of the potential for serious adverse reactions in the nursing infant, participants who are breastfeeding are not eligible for enrollment.

6.4 Screen Failures

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

6.5 Participant Replacement Strategy

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

7. Treatments

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

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

7.1 Treatments Administered

The treatments to be used in this trial are outlined below in Table 4.

Table 4 Trial Treatments

Drug	Dose/ Potency	Dose Frequency	Route of Administration	Regimen/ Treatment Period	Use
Pembrolizumab (MK-3475)	200 mg	Q3W	Intravenous (IV) infusion	Day 1 of each cycle (3 week cycles)	Experimental
Q3W = every 3 weeks All study treatments will be administered on an outpatient basis. Pembrolizumab will be provided centrally by the Sponsor. For Cycle 1, Day 1, study treatment should be given on the day of treatment allocation, but up to 3 days after treatment allocation/randomization is permitted. For all subsequent cycles, +/- 3 days of Day 1 are permitted.					

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

All supplies indicated in Table 5 will be provided per the 'Sourcing' row depending upon local country operational requirements. Every attempt should be made to source these supplies from a single lot/batch number. The trial site is responsible for recording the lot number, manufacturer, and expiry date for any locally purchased product as per local guidelines unless otherwise instructed by the Sponsor.

Refer to section 9.1.8 for details regarding administration of the study treatment.

The study treatment to be used in this trial is outlined below in Table 5.

Table 5 Study Treatment(s)

Study Treatment Name:	Pembrolizumab (MK-3475)
Dosage Formulation:	Solution for intravenous (IV) infusion
Unit Dose Strength(s):	25 mg/mL (100 mg/4 mL)
Dosage Level(s):	200 mg dose per cycle/infusion
Route of Administration:	IV infusion
Sourcing:	Provided centrally by the Sponsor

7.2 Dose Modification (Escalation/Titration/Other)

7.2.1 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. Based on the severity of irAEs, withhold or permanently discontinue pembrolizumab and administer corticosteroids.

Dose Modification and Toxicity Management Guidelines for irAEs associated with pembrolizumab monotherapy, coformulations, or IO combinations are provided in Table 6.

Table 6 Dose Modification and Toxicity Management Guidelines for Immune-related Adverse Events Associated with Pembrolizumab Monotherapy, Coformulations or IO Combinations

General instructions:

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

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

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

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

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

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

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

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

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

Pembrolizumab may cause severe or life threatening infusion-reactions including severe hypersensitivity or anaphylaxis. Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion. Dose modification and toxicity management guidelines on pembrolizumab associated infusion reaction are provided in Table 7.

Table 7 Pembrolizumab Infusion Reaction Dose modification and Treatment Guidelines

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

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

Other allowed dose interruption for pembrolizumab

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

7.2.2 Second Course Phase (Retreatment) for Pembrolizumab (MK-3475)

All participants who stop study treatment with SD or better may be eligible for up to an additional 17 cycles (approximately 1 year) of pembrolizumab treatment if they progress after stopping trial treatment from the initial treatment phase. This retreatment is termed the Second Course Phase of this trial and is only available if the trial remains open and the participant meets the following conditions:

Either

- Stopped initial treatment with trial treatment after attaining an investigator-determined confirmed CR based on RECIST 1.1, and
    - Was treated with at least 8 cycles of trial treatment before discontinuing treatment, and

- Received at least 2 treatments with pembrolizumab beyond the date when the initial CR was declared.

OR

- Had SD, PR, or CR and stopped trial treatment after completion of 35 administrations (approximately 2 years) of trial treatment for reasons other than disease progression or intolerability

AND

- Experienced an investigator-determined radiographic/cutaneous disease progression by RECIST 1.1 after stopping initial treatment, and
  - No new anticancer treatment was administered after the last dose of trial treatment, and
  - The participant meets all of the safety parameters listed in the inclusion criteria and none of the safety parameters listed in the exclusion criteria, and
  - The trial is ongoing.

An objective response or disease progression that occurs during the Second Course Phase for a participant will not be counted as an event for the primary analysis of either endpoint in this trial.

7.2.3 Pembrolizumab (MK-3475) Administration

Trial treatment of pembrolizumab (MK-3475) should be administered on Day 1 of each cycle after all procedures/assessments have been completed as detailed in Section 2 - Schedule of Activities. In general, the window for each visit is ± 3 days unless otherwise noted.

All trial treatments will be administered on an outpatient basis.

Pembrolizumab (MK-3475) will be administered as a 30-minute IV infusion every 3 weeks. Sites should make every effort to target infusion timing to be as close to 30 minutes as possible. However, given the variability of infusion pumps from site to site, a window of - 5 minutes and + 10 minutes is permitted (ie, infusion time is 30 minutes: - 5 minutes/+ 10 minutes).

The Pharmacy Manual contains specific instructions for the preparation of the pembrolizumab (MK-3475) infusion fluid and administration of infusion solution.

7.3 Method of Treatment Assignment

Treatment allocation will occur centrally using an interactive voice response system/ integrated web response system (IVRS/IWRS).

7.3.1 Stratification

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

7.4 Blinding

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

7.5 Preparation/Handling/Storage/Accountability

7.5.1 Dose Preparation

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

7.5.2 Handling, Storage, and Accountability

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

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

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

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

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

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

7.6 Treatment Compliance

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

Refer to Section 7.2.1 for dose modification and toxicity management for irAEs associated with pembrolizumab and for other allowed dose interruptions of pembrolizumab.

7.7 Concomitant Therapy

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

Listed below are concomitant medications/therapies that are prohibited during the course of the trial:

- Surgical intervention to a target lesion

  Note: During study treatment surgical intervention to the disease under study is prohibited. This restriction applies to all skin lesions including actinic keratosis, target or non-target lesions. If a lesion is biopsied (not completely resected) and the histology is identified as different then cSCC, the case must be discussed between the investigator and Sponsor; if the biopsy result of a lesion biopsy confirms cSCC, this would be considered progressive disease leading to possible early discontinuation of study treatment.

- Antineoplastic systemic chemotherapy or biological therapy

- Immunotherapy not specified in this protocol (other than denosumab for bone metastasis)

- Chemotherapy not specified in this protocol

- Investigational agents other than pembrolizumab

- Radiation therapy

  Note: Radiation therapy to a symptomatic solitary nontarget lesion or to the brain may be allowed at the investigator's discretion.

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

  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.

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

- Systemic glucocorticoids for any purpose other than to modulate symptoms from an AE that is suspected to have an immunologic etiology. The use of physiologic doses of corticosteroids may be approved after consultation with the Sponsor.

  Note: Use of prophylactic corticosteroids to avoid allergic reactions (eg, IV contrast dye or transfusions) is permitted.

  Note: The use of intermittent inhaled steroids or intranasal or local injection of corticosteroids is permitted.

Participants who, in the assessment of the investigator, require the use of any of the aforementioned treatments for clinical management should be discontinued from study treatment, but continue to be followed in the trial.

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 medication will be recorded on the electronic case report form (eCRF) including all prescription, over-the-counter (OTC) products, herbal supplements, and IV medications and fluids. If changes occur during the trial 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 trial treatment and up to 30 days after the last dose of trial treatment should be recorded. All concomitant medications administered during SAEs or ECIs are to be recorded. SAEs and ECIs are defined in Section 9.3.

7.7.1 Rescue Medications & 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 7.2 [Table 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. Refer to Table 6 in Section 7.2 for guidelines regarding dose modification and supportive care.

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

7.8 Treatment After the End of the Study

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

7.9 Clinical Supplies Disclosure

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

8. Discontinuation/Withdrawal Criteria

8.1 Discontinuation of Study Treatment

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

As certain data on clinical events beyond study treatment discontinuation may be important to the study, they must be collected through the participant's last scheduled follow-up, even if the participant has discontinued study treatment. Therefore, all participants who discontinue study treatment prior to completion of the protocol-specified treatment period will still continue to participate in the study as specified in Section 2 – Schedule of Activities and Section 9.10.3 – Discontinued Participants Continuing to be Monitored in the Study.

Participants may discontinue study treatment at any time for any reason or be dropped from the study treatment at the discretion of the investigator should any untoward effect occur. In addition, a participant may be discontinued from study treatment by the investigator or the Sponsor if study treatment is inappropriate, the trial plan is violated, or for administrative and/or other safety reasons. Specific details regarding procedures to be performed at study treatment discontinuation are provided in Section 9.1.9 – Withdrawal/Discontinuation.

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

- The participant or participant's legally acceptable representative requests to discontinue study treatment.
- The participant has a medical condition or personal circumstance which, in the opinion of the investigator and/or Sponsor, placed the participant at unnecessary risk from continued administration of study treatment.
- The participant has a confirmed positive serum pregnancy test.
- Confirmed radiographic disease progression outlined in Section 9.2.1.6 (after obtaining informed consent addendum and Sponsor communication, the investigator may elect to continue treatment beyond disease progression)
- Any progression or recurrence of any malignancy, or any occurrence of another malignancy that requires active treatment
- Any study intervention-related toxicity specified as a reason for permanent discontinuation as defined in the guidelines for dose modification due to AEs in Section 7.2
- Discontinuation of treatment may be considered for participants who have attained a confirmed CR and have been treated for at least 8 cycles (at least 24 weeks), receiving at least 2 doses of pembrolizumab beyond the date when the initial CR was declared. These participants may be eligible for second course treatment described in Section 7.2.2.
- Completion of 35 treatments (approximately 2 years) with pembrolizumab
- Note: The number of treatments is calculated starting with the first dose. Participants who stop pembrolizumab after receiving 35 doses may be eligible for retreatment if they progress after stopping trial treatment, provided they meet the requirements detailed in Section 7.2.2. Subjects may be retreated in the Second Course Phase (Retreatment) for up to an additional 17 cycles (approximately 1 year).

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

Participants may be allowed to begin study treatment again if deemed medically appropriate.

8.2 Withdrawal From the Study

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

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

Specific details regarding procedures to be performed at the time of withdrawal from the study, as well as specific details regarding withdrawal from Future Biomedical Research are outlined in Section 9.1.9 – Withdrawal/Discontinuation. 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 8.3.

8.3 Lost to Follow Up

1. 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:

2. 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.

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

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

9. Study Assessments and Procedures

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

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

3. 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.

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

9.1 Administrative and General Procedures

9.1.1 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 trial or Future Biomedical Research. If there are changes to the participant's status during the trial (eg, health or age of majority requirements), the investigator or medically qualified designee must ensure the appropriate documented informed consent is in place.

9.1.1.1 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 trial protocol number, trial protocol title, dated signature, and agreement of the participant (or his/her legally acceptable representative) and of the person conducting the consent 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 trial.

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 trial. The communication of this information will be provided and documented via a revised consent form or addendum to the original consent form that captures the 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 trial and the trial population are to be included in the trial informed consent form.

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

9.1.1.2 Consent and Collection of Specimens for Future Biomedical Research

The investigator or medically qualified designee will explain the future biomedical research 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 future biomedical research. A copy of the informed consent will be given to the participant before performing any procedure related to future biomedical research.

9.1.2 Inclusion/Exclusion Criteria

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

9.1.3 Participant Identification Card

All participants will be given a Participant Identification Card identifying them as participants in a research trial. The card will contain trial 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 treatment allocation/randomization, site personnel will add the treatment/randomization number to the Participant Identification Card.

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

9.1.4 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 significant. Details regarding the disease for which the participant has enrolled in this trial will be recorded separately and not listed as medical history.

9.1.4.1 Cutaneous Squamous Cell Carcinoma

The investigator or qualified designee will obtain information regarding the participant's cSCC. This information will include, but is not limited to, the presentation at primary diagnosis, date and stage at primary diagnosis, date of and stage at most recent recurrence, and location of metastases at screening (if applicable).

9.1.5 Prior and Concomitant Medications Review

9.1.5.1 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 the first dose of trial treatment. Prior treatment for other cancers will also be recorded as a prior medication.

9.1.5.2 Concomitant Medications

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

9.1.6 Assignment of Screening Number

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

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

Specific details on the screening visit requirements (screening/rescreening) are provided in Section 9.10.1.

9.1.7 Assignment of Treatment/Randomization Number

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

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

9.1.8 Treatment Administration

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

Administration of trial medication will be monitored by the investigator and/or institution staff. The total volume of pembrolizumab infused will be compared to the total volume prepared to determine compliance with each dose of pembrolizumab administered.

9.1.8.1 Timing of Dose Administration

Not applicable.

9.1.9 Withdrawal/Discontinuation

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

When a participant withdraws from participation in the study, all applicable activities scheduled for the final study visit should be performed at the time of withdrawal. Any adverse events which are present at the time of withdrawal should be followed in accordance with the safety requirements outlined in Section 9.3 - Adverse Events, Serious Adverse Events and Other Reportable Safety Events.

9.1.9.1 Withdrawal From Future Biomedical Research

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

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

9.1.10 Participant Blinding/Unblinding

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

9.1.11 Calibration of Equipment

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

9.2 Efficacy Assessments

9.2.1 Tumor Imaging and Assessment of Disease

The process for image collection and transmission to the central imaging vendor can be found in the Site Imaging Manual (SIM). Tumor imaging should be acquired by computed tomography (CT, strongly preferred). Magnetic resonance imaging (MRI) should be used when CT is contraindicated or for imaging in the brain. The same imaging technique regarding modality and use of contrast should be used in a participant throughout the trial to optimize the visualization of existing and new tumor burden. Baseline imaging should include head, neck, chest, abdomen, and pelvis; imaging of the affected extremities is required for those participants with disease in the extremities at baseline. Please refer to the SIM for further guidance on required imaging at scheduled assessments.

Note: imaging of the pelvis is not required after the baseline image is obtained with the exception of the primary involvement of the pelvis and lower extremities.

Expedited confirmation of measurable disease based on RECIST 1.1 by the central imaging vendor at screening will be used to determine participant eligibility. Confirmation of measurable disease by the central imaging vendor per RECIST 1.1 is required prior to participant enrollment. Although RECIST 1.1 references a maximum of 5 target lesions in total and 2 per organ, MSD allows a maximum of 10 target lesions in total and 5 per organ. For participants with no RECIST 1.1 measurable disease visualized by CT or MRI, participants with cutaneous lesions will be considered to have RECIST 1.1 measurable disease when the lesion is superficial and ≥ 10 mm in diameter when assessed using calipers.

All scheduled images for all study participants from the sites will be submitted to the central imaging vendor. In addition, additional imaging (including other modalities) that are obtained at an unscheduled time point to determine disease progression, as well as imaging obtained for other reasons but captures radiologic progression, should be submitted to the central imaging vendor as well. Image submission requirements include imaging acquired at off-site facilities while participant is on trial.

9.2.1.1 Initial Tumor Imaging

Initial tumor imaging including any digital photography at screening must be performed within 28 days prior to the date of treatment allocation. The site study team must review screening images to confirm the participant has measurable disease per RECIST 1.1 prior to submitting to the central vendor. The screening images must be submitted to the central imaging vendor for confirmation of measurable disease per RECIST 1.1 for eligibility prior to randomization.

Scans performed as part of routine clinical management are acceptable for use as screening tumor imaging if they are of diagnostic quality, performed within 28 days prior to the date of randomization, and can be assessed by the central imaging vendor.

Participants with previously treated brain metastases may participate provided they have stable brain metastases, ie, without evidence of progression by imaging [confirmed by MRI if MRI was used at prior imaging, or confirmed by CT imaging if CT was used at prior imaging] for at least 4 weeks prior to the first dose of trial treatment. Any neurologic symptoms must have returned to baseline and participants must have no evidence of new or enlarging brain metastases, and have not used steroids for brain metastases for at least 7 days prior to trial initiation as per local site assessment. This exception does not include carcinomatous meningitis, as participants with carcinomatous meningitis are excluded regardless of clinical stability.

9.2.1.2 Tumor Imaging During the Trial

The first on-study imaging assessment should be performed at 6 weeks (42 days + 7 days) from the date of treatment allocation. Subsequent tumor imaging should be performed every 6 weeks (42 days ± 7 days) or more frequently if clinically indicated through Year 1. After 1 year, participants who remain on treatment will have imaging performed every 9 weeks (63 days ± 7 days). Imaging timing should follow calendar days and should not be adjusted for delays in cycle starts. Imaging should continue to be performed until disease progression (unless site principal investigator [PI] elects to continue treatment and follow irRECIST), the start of new anti-cancer treatment, withdrawal of consent, death, or notification by the Sponsor, whichever occurs first. Following first radiographic indication of disease progression, participant management should shift to irRECIST and disease progression should be confirmed at least 4 weeks after the first scan indicating PD in clinically stable participants. All supplemental imaging must be submitted to the central imaging vendor.

Per RECIST 1.1*, PR and CR should be confirmed by a repeat tumor imaging assessment obtained 4 weeks or longer from the date the response was first documented. The tumor imaging performed to confirm a response should be performed at the earliest 4 weeks after the first indication of response, or at the next scheduled scan. Participants who obtain a confirmation scan do not need to undergo the next scheduled tumor imaging if it is ≤4 weeks later; tumor imaging may resume at the subsequent scheduled imaging time point. *For participants who were deemed eligible via digital photography and who have obtained a CR, a biopsy is required to be submitted for central pathology review to confirm CR within 30 days of initial confirmation. For participants who have obtained a CR prior to the release of Amendment 03, a biopsy is required within 30 days of protocol Amendment 03 approval in their respective countries for submission to central pathology review (see Section 9.2.1.8).

Per irRECIST (Section 9.2.1.6.), disease progression should be confirmed by the site at least 4 weeks after site-assessed first radiologic evidence of PD in clinically stable participants. Participants who have unconfirmed disease progression may continue on treatment at the discretion of the site investigator until progression is confirmed by the site, provided they have met the conditions detailed in Section 9.2.1.6. Participants who obtain a confirmation scan do not need to undergo the next scheduled tumor imaging if it is ≤ 4 weeks later; tumor imaging may resume at the subsequent scheduled imaging time point if clinically stable. Participants who have confirmed disease progression as assessed by the site will discontinue trial treatment. Exceptions are detailed in Section 9.2.1.6.

9.2.1.3 End of Treatment and Follow-up Tumor Imaging

For participants who discontinue study treatment, tumor imaging should be performed at the time of treatment discontinuation (±4 week window). If previous imaging was obtained within 4 weeks prior to the date of discontinuation, then imaging at treatment discontinuation is not required and the participant should continue with the protocol specified tumor imaging time points. For participants who discontinue study treatment due to documented disease progression, this is the final required tumor imaging if the Investigator elects not to implement irRECIST.

In participants who discontinue trial treatment without documented disease progression, every effort should be made to continue monitoring their disease status by tumor imaging using the same imaging schedule used while on treatment (every 6 weeks in Year 1 or 9 weeks after Year 1) to monitor disease status until the start of new anti-cancer treatment, disease progression, death, or the end of the trial, whichever occurs first.

9.2.1.4 Second Course (Retreatment) Tumor Imaging

Tumor imaging including any digital photography must be performed within 28 days prior to restarting treatment with pembrolizumab. Local reading (investigator assessment with site radiology reading) will be used to determine eligibility. Imaging should be submitted to the central imaging vendor for retrospective review.

Note: imaging of the pelvis is not required prior to restarting treatment with pembrolizumab with the exception of the primary involvement of the pelvis and lower extremities during the initial treatment phase.

The first on trial imaging assessment should be performed at 6 weeks (42 days + 7 days) after the restart of treatment. Subsequent tumor imaging should be performed every 6 weeks (42 days ± 7 days) or more frequently if clinically indicated.

If tumor imaging shows initial PD per RECIST 1.1, tumor assessment should be repeated ≥ 4 weeks later in order to confirm PD with the option of continuing treatment while awaiting radiologic confirmation of progression. Participants who obtain a confirmation scan do not need to undergo scheduled tumor imaging if it is 4 weeks later and may wait until the next scheduled imaging time point if clinically stable.

Imaging should continue to be performed until disease progression, the start of new anti-cancer treatment, withdrawal of consent, death, or notification by the Sponsor, whichever occurs first. Disease progression may be confirmed at least 4 weeks after the first tumor imaging indicating PD in clinically stable participants. Additional irRECIST details are described in Section 9.2.1.6.

In participants who discontinue trial treatment, tumor imaging 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. In participants who discontinue trial treatment due to documented disease progression, this is the final required tumor imaging.

In participants who discontinue trial treatment without documented disease progression, every effort should be made to continue monitoring their disease status by radiologic imaging every 6 weeks (42 days ± 7 days) until either the start of a new anti-cancer treatment, disease progression, death, or the end of the trial, whichever occurs first.

9.2.1.5 RECIST 1.1 Assessment of Disease

RECIST 1.1 will be used by BICR 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 trial therapy). Although RECIST 1.1 references a maximum of 5 target lesions in total and 2 per organ, the Sponsor allows a maximum of 10 target lesions in total and 5 per organ, if clinically relevant to enable a broader sampling of tumor burden.

9.2.1.6 irRECIST Assessment of Disease

Immune-related RECIST is RECIST 1.1 adapted as described below to account for the unique tumor response seen with immunotherapeutic drugs. Immune-related RECIST will be used by the site investigator/local radiology reviewers to confirm tumor response and progression, and make treatment decisions. This data will be collected in the clinical database.

When feasible, participants treated with pembrolizumab should not be discontinued until progression is confirmed by the local site investigator/radiology assessment. 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. Participants that are deemed clinically unstable are not required to have repeat tumor imaging for confirmation of PD. Tumor flare includes any of the following scenarios:

- Worsening of existing target lesion(s)
- Worsening of existing non-target lesion(s)
- Development of new lesion(s)

In participants treated with pembrolizumab who have shown initial evidence of radiological PD by RECIST 1.1 as assessed by the site, it is at the discretion of the PI whether to continue a participant on trial medication until repeat imaging is obtained (using irRECIST for participant management) (Table 8 and Figure 2). This clinical judgment decision by the site investigator should be based on the participant's overall clinical condition, including performance status, clinical symptoms, and laboratory data. Participants may receive trial

medication and the tumor assessment should be repeated ≥ 4 weeks later in order to confirm PD by irRECIST per site assessment. Clinical stability is defined as the following:

- Absence of symptoms and signs indicating clinically significant progression of disease, including worsening of laboratory values
- No decline in ECOG performance status
- Absence of rapid progression of disease
- Absence of progressive tumor at critical anatomical sites (eg, cord compression) requiring urgent alternative medical intervention

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

In determining whether or not the tumor burden has increased or decreased per irRECIST, the local site investigator should consider all target and non-target lesions, as well as any incremental new lesion(s).

Disease progression will be considered to be "not confirmed" at repeat imaging if ALL of the following occur (as assessed by irRECIST):

- Target lesion sum of diameters is <20% or <5 mm absolute increase compared to nadir
- Non-target disease resulting in initial PD is stable or qualitatively improved
- New lesion resulting in initial PD is stable or qualitatively improved
- No incremental new lesion(s) since last evaluation
- No incremental new non-target lesion progression since last evaluation

If repeat imaging does not confirm PD per irRECIST as assessed by the local site investigator and the participant continues to be clinically stable, treatment may continue and follow the regular imaging schedule.

Disease progression will be considered to be "confirmed" at repeat imaging if ANY of the following occur (as assessed by irRECIST):

- Target lesion sum of diameters remains ≥20% and at least 5 mm absolute increase compared to nadir
- Non-target disease resulting in initial PD is qualitatively worse
- New lesion resulting in initial PD is qualitatively worse
- Additional new lesion(s) since last evaluation
- Additional new non-target lesion progression since last evaluation

If repeat imaging confirms PD due to any of the scenarios listed above, participants will be discontinued from trial therapy.

NOTE: If a participant has confirmed radiographic progression (ie, 2 scans at least 4 weeks apart demonstrating PD) per irRECIST, but the participant is achieving a clinically meaningful benefit, and there is no further increase in the tumor burden at the confirmatory tumor imaging, an exception to continue treatment may be considered following consultation with the Sponsor. In this case, if treatment is continued, tumor imaging should continue to be performed following the intervals as outlined in Section 2.0 and be submitted to the central imaging vendor.

Note: A new primary low-risk cSCC lesion is not considered as a PFS event. A new primary low-risk 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 Medical Monitor is required where there is uncertainty of new primary cSCC lesion vs 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 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, <2mm in thickness and no perineural, lymphatic, or vascular involvement.

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

Additional details about irRECIST are provided in the MSD TIP Sheet for RECIST 1.1 and irRECIST.

Table 8 Imaging and Treatment After First Radiologic Evidence of Progressive Disease

	Clinically Stable		**Clinically Unstable**	
	Imaging	**Treatment**	**Imaging**	**Treatment**
First radiologic evidence of PD by RECIST 1.1	Repeat imaging at ≥4 weeks at site to confirm PD	May continue trial treatment at the local site investigator's discretion while awaiting confirmatory tumor imaging by site by irRECIST	Repeat imaging at≥4 weeks to confirm PD per physician discretion only	Discontinue treatment
Repeat tumor imaging confirms PD by irRECIST at the local site	No additional imaging required	Discontinue treatment (exception is possible upon consultation with Sponsor)	No additional imaging required	Not applicable
Repeat tumor imaging shows SD, PR, or CR by irRECIST at the local site	Continue regularly scheduled imaging assessments	Continue trial treatment at the local site investigator's discretion	Continue regularly scheduled imaging assessments	May restart trial treatment if condition has improved and/or clinically stable per investigator's discretion. Next tumor image should occur according to the regular imaging schedule.

CR = complete response; irRECIST = immune-related response evaluation criteria in solid tumors; PD = progressive disease; PR = partial response; RECIST = response evaluation criteria in solid tumors; SD = stable disease

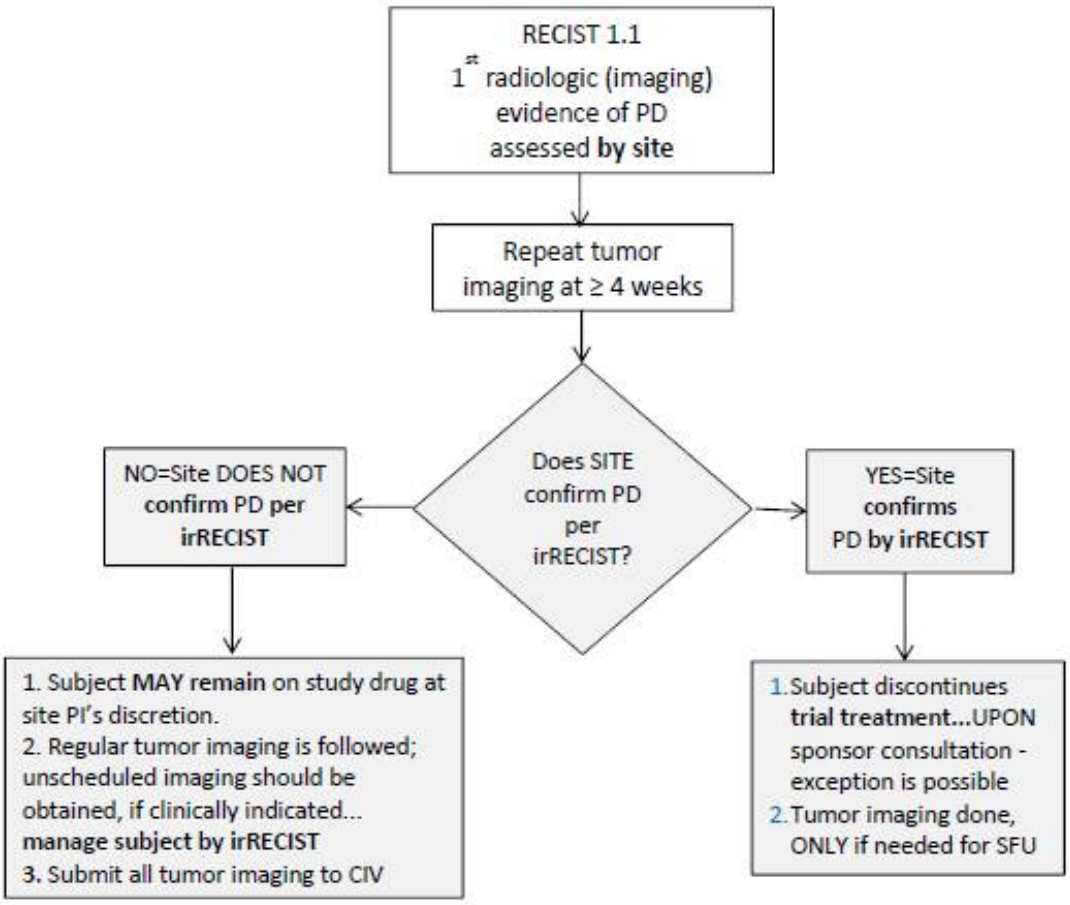

Figure 2 Imaging and Treatment for Clinically Stable Participants After First Radiologic Evidence of PD Assessed by the Site

9.2.1.7 Photography for Cutaneous Lesions

For participants without RECIST 1.1 measurable disease on CT or MRI scans, digital photographs documenting RECIST 1.1 measurable cutaneous lesions must be obtained if the cutaneous lesion is included as part of the target lesions assessment according to RECIST 1.1. Target cutaneous lesions are defined as superficial lesions which are ≥ 10 mm diameter as assessed using calibers. Any target 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. Any malignant cutaneous lesion < 10 mm in diameter can be followed as non-target disease. Copies of the color digital photograph must be forwarded to the central imaging vendor for assessment. The timing for capturing cutaneous lesion photographs must follow the same schedule as the imaging scans. The requirements de-identifying and transmitting the digital photographs to the central imaging vendor are located in the SIM.

9.2.1.8 Tumor Tissue Collection and Assessment of Disease Recurrence

For participants without RECIST 1.1 measurable disease on CT or MRI scans that were deemed eligible by digital photography only (see Section 9.2.1.7), a tissue biopsy is required within 30 days of investigator-determined CR and submitted for central pathology review and confirmation of the absence of disease. For participants considered to have obtained CR prior to the release of Amendment 03, a biopsy is required within 30 days of Protocol Amendment 03 approval in their respective countries.

The study pathologists will send the representative specimens (slides) for central pathology review, as detailed in the Vendor Manual. The Vendor Manual will outline the standard guidelines for pathological evaluation of specimens. A summary note will be provided to the study pathologist that includes a general overview of the study.

Communication from surgeon to local pathologist should follow local practice and institutional guidelines. Detailed instructions for tissue collection, processing and shipment are provided in the Vendor Manual.

In the absence of biopsy confirmed CR, response assessment will be considered as PR; stable disease is not considered a response.

9.2.2 Quality of Life Assessments

9.2.2.1 Patient Reported Outcomes

The EuroQol EQ-5D and EORTC QLQ-C30 questionnaires will be administered by trained site personnel and completed electronically by participants in the following order: EuroQol EQ-5D first, then EORTC QLQ-C30. The questionnaires should be administered prior to dosing at Cycle 1, Cycle 2, Cycle 3, every 2 cycles (ie, every 6 weeks) through Year 1, then every 3 cycles (ie., every 9 weeks) after Year 1 until End of Treatment, and at the 30-day Safety Follow-up Visit.

It is best practice and strongly recommended that electronic patient-reported outcomes (ePROs) are administered to randomized participants prior to 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.

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

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

Progression of the cancer under study is not considered an adverse event as described in Section 9.3.5 – Disease-Related Events and/or Disease-Related Outcomes Not Qualifying as AEs or SAEs, and Appendix 4.

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

The investigator, who is a qualified physician, and any designees are responsible for detecting, assessing, documenting, and reporting events that meet the definition of an AE or SAE as well as other reportable safety events. Investigators remain responsible for following up AE, SAEs and other reportable safety events for outcome according to Section 9.3.3.

9.3.1 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 treatment allocation/randomization, must be reported by the investigator if the participant is receiving placebo run-in or other run-in treatment, if the event causes the participant to be excluded from the trial, or is the result of a protocol-specified intervention, including, but not limited to washout or discontinuation of usual therapy, diet, or a procedure.

- All AEs from the time of treatment allocation/randomization through 30 days following cessation of study treatment must be reported by the investigator.
- All AEs meeting serious criteria, from the time of treatment allocation/randomization through 90 days following cessation of study treatment, or 30 days following cessation of study treatment if the participant initiates new anticancer therapy, whichever is earlier must be reported by the investigator.
- All pregnancies and exposure during breastfeeding, from the time of treatment allocation/randomization through 120 days following cessation of study treatment, or 30 days following cessation of study treatment if the participant initiates new anticancer therapy must be reported by the investigator.
- Additionally, any SAE brought to the attention of an investigator at any time outside of the time period specified above must be reported immediately to the Sponsor if the event is considered to be drug-related.

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

All initial and follow-up AEs, SAEs and other reportable safety events will be recorded and reported to the sponsor or designee within the timeframes as indicated in Table 9.

Table 9 Reporting Time Periods and Timeframes for Adverse Events and Other Reportable Safety Events

Type of Event		Reporting Time Period: Consent to Randomization/ Allocation	Reporting Time Period: Randomization/ Allocation through Protocol-Specified Follow-up Period	Reporting Time Period: After the Protocol Specified Follow-up Period		Timeframe to Report Event and Follow-up Information to SPONSOR:
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

9.3.2 Method of Detecting AE, SAE and Other Reportable Safety Events

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

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

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All AE, SAE and other reportable safety events including pregnancy and exposure during breastfeeding, ECI, 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 8.3). In addition, the investigator will make every attempt to follow all non-serious AEs that occur in randomized participants for outcome. Further information on follow-up procedures is given in Appendix 4.

9.3.4 Regulatory Reporting Requirements for SAE

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

2. The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study treatment under clinical investigation. All Adverse Events will be reported to regulatory authorities, IRB/IECs and investigators in accordance with all applicable global laws and regulations, i.e., per ICH Topic E6 (R1) Guidelines for Good Clinical Practice.

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

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

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

Progression of the cancer under study is not considered a reportable event.

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

9.3.6 Pregnancy and Exposure During Breastfeeding

Although pregnancy and infant exposure during breastfeeding are not considered adverse events, any pregnancy or infant exposure during breastfeeding in a participant (spontaneously reported to the investigator or their designee), including the pregnancy of a male participant's female partner, that occurs during the trial are reportable to the Sponsor.

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

9.3.7 Events of Clinical Interest (ECI)

Selected non-serious and serious adverse events are also known as Events of Clinical Interest (ECI) and must be reported to the Sponsor.

Events of clinical interest for this trial include:

1. an overdose of Sponsor's product, as defined in Section 9.4 – Treatment of Overdose, that is not associated with clinical symptoms or abnormal laboratory results.

2. an elevated AST or ALT lab value that is greater than or equal to 3X the upper limit of normal and an elevated total bilirubin lab value that is greater than or equal to 2X the upper limit of normal and, at the same time, an alkaline phosphatase lab value that is less than 2X the upper limit of normal, as determined by way of protocol-specified laboratory testing or unscheduled laboratory testing.*

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

9.4 Treatment of Overdose

For purposes of this trial, an overdose will be defined as any dose exceeding the prescribed dose for pembrolizumab (MK-3475) by ≥1000 mg (5 times the dose) and as any dose >20% over the prescribed dose for the standard treatments. No specific information is available on the treatment of overdose of pembrolizumab (MK-3475). In the event of overdose, pembrolizumab (MK-3475) should be discontinued and the participant should be observed closely for signs of toxicity. Appropriate supportive treatment should be provided if clinically indicated.

9.5 Safety

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

9.5.1 Physical Examinations

The investigator or qualified designee will perform a complete physical exam during the Screening Period. Clinically significant abnormal findings should be recorded as medical history. The time points for full physical exams are described in Section 2. After the first dose of trial treatment, new clinically significant abnormal findings should be recorded as AEs.

For cycles that do not require a full physical exam as defined in Section 2, the investigator or qualified designee will perform a directed physical exam prior to the administration of the trial treatment. New clinically significant abnormal findings should be recorded as AEs. Investigators should pay special attention to clinical signs related to previous serious illnesses.

9.5.2 Vital Signs

Prior to dosing vital signs will be measured after 5 minutes rest and will include temperature, systolic and diastolic blood pressure, weight, height (screening only), and pulse.

9.5.3 Electrocardiograms

A standard 12-lead electrocardiogram (ECG) will be performed using local standard procedures once at screening. Clinically significant abnormal findings should be recorded as medical history. Additional time points may be performed as clinically necessary.

9.5.4 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.

1. The investigator 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.

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

3. If laboratory values from non-protocol 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).

4. For any laboratory tests with values considered clinically significantly abnormal during participation in the study or within 14 days after the last dose of study treatment, every attempt should be made to perform repeat assessments until the values return to normal or baseline or if a new baseline is established as determined by the investigator.

Details regarding specific laboratory procedures/assessments to be performed in this trial are provided below and Appendix 2. The total amount of blood/tissue to be drawn/collected over the course of the trial (from pretrial to post-trial visits), including approximate blood/tissue volumes drawn/collected by visit and by sample type per participant can be found in the Trial Manual. Refer to the Schedule of Activities (Section 2) for the timing of laboratory assessments.

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

Laboratory tests for screening should be performed within 10 days prior to the first dose of trial treatment. (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 trial treatment). Participants eligible for trial retreatment should have imaging performed within 21 days and laboratory tests performed within 10 days prior to the first dose of trial treatment in the Second Course Phase. After Cycle 1, in both the Initial Treatment Phase and the Second Course Phase, predose laboratory safety tests can be conducted up to 72 hours prior to dosing unless otherwise noted on the flow charts. Urinalysis is only required at the screening visit. During the Second Course Phase thyroid laboratory assessments will continue to be collected every other cycle after Cycle 5.

Laboratory test results must be reviewed by the investigator or qualified designee and found to be acceptable prior to administration of each dose of trial 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.

9.5.4.2 Pregnancy Test

All women who are being considered for participation in the trial, and who are not surgically sterilized or postmenopausal, must be tested for pregnancy within 72 hours of the initial trial treatment, EOT and 30 days post-treatment. If a urine test is positive or not evaluable, a serum test will be required. Participants must be excluded from participation in the event of a positive result during screening. In the event of a positive or borderline-positive test result during the study, the participant must be taken off treatment but continue to be followed (See Appendix 5).

Note: for participants enrolled from German sites, monthly pregnancy testing is required while on study therapy.

9.5.5 Performance Assessments

9.5.5.1 Eastern Cooperative Oncology Group Performance Scale

The investigator or qualified designee will assess ECOG status (Table 10) at screening, prior to the administration of each dose of trial treatment, at all on treatment visits, and during the follow-up period as specified in the Schedule of Activities (Section 2).

Table 10 Eastern Cooperative Oncology Group Performance Status

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

Source: [Oken, M. M., et al 1982]
http://www.ecog-acrin.org/resources/ecog-performance-status

9.6 Pharmacokinetics

To evaluate the exposure of pembrolizumab in this indication, PK sample collections are currently planned as shown in the Schedule of Activities (Section 2). Blood samples for PK collected may only be stored. Further analysis may be performed if required. If ongoing PK sampling is deemed to be unnecessary by the Sponsor, it may be reduced or discontinued.

9.6.1 Blood Collection for PK

PK sampling of pembrolizumab will be obtained from all participants. All predose (trough) PK samples should be drawn within 24 hours before infusion of pembrolizumab at Cycles 1, 2, 4, 6, 8 and every 4 cycles thereafter, until discontinuation of study drug (or until the participant starts new anti-cancer therapy). Post-dose peak PK samples will be drawn within 30 minutes after the end of pembrolizumab infusion at Cycle 1.

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

9.7 Pharmacodynamics

9.7.1 Tumor Tissue Collection

Tissue for biomarker analysis should be obtained from an archival tissue sample or newly obtained core or excisional biopsy of a tumor lesion not previously irradiated. An archived tumor tissue sample must be <5 years old. This tissue should come from the site of metastasis, if available. Informed consent for the study must be taken prior to collection of a fresh biopsy. 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. Details regarding time points for collection of tumor tissue are outlined in the SoA – Section 2. Include a copy of the local pathology report with the tissue for biomarker analysis.

For a tumor biopsy to be considered newly obtained (fresh biopsy) the sample from a core or excisional biopsy must be obtained from the subject during the screening period.

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

9.8 Future Biomedical Research Sample Collection

The following specimens are to be obtained as part of Future Biomedical Research:

- Leftover samples listed in Section 9.9

9.9 Biomarkers

Collection of samples for other biomarker research is also part of this study. The following samples for biomarker research are required and will be collected from all participants in this study as specified in the SoA (Section 2):

- Blood for genetic analysis
- Blood for RNA analyses
- Blood for plasma biomarker analyses

- Blood for serum biomarker analyses
- Tumor tissue

9.9.1 Planned Genetic Analysis Sample Collection

Sample collection, storage and shipment instructions for Planned Genetic Analysis samples will be provided in the Procedures Manual. Procedures Manual Samples should be collected for planned analysis of associations between genetic variants in germline/tumor DNA and drug response. If a documented law or regulation prohibits (or local IRB/Independent Ethics Committee [IEC] does not approve) sample collection for these purposes, then such samples should not be collected at the corresponding sites. Leftover DNA extracted from planned genetic analysis samples will be stored for future biomedical research only if participant provides documented informed consent for Future Biomedical Research.

9.10 Visit Requirements

Visit requirements are outlined in Section 2 – Schedule of Activities (SoA). Specific procedure-related details are provided above in Section 9 – Study Assessments and Procedures.

9.10.1 Screening

Within 28 days prior to treatment allocation/randomization, potential participants will be evaluated to determine that they fulfill the entry requirements as set forth in Section 6.0 Visit requirements are outlined in the SoA (Section 2). Screening procedures may be repeated after consultation with the Sponsor.

Participants may be rescreened after consultation with the Sponsor. Rescreening should include all screening procedures listed in the protocol SoA, including consent review. Rescreen procedures cannot be conducted the day prior to treatment allocation/randomization if there are Day -1 procedures planned per protocol.

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 prior to the first dose of trial treatment except for the following:

- Evaluation of ECOG is to be performed within 10 days prior to the first dose of trial treatment.
- For women of reproductive potential, a urine or serum pregnancy test will be performed within 72 hours prior to the first dose of trial treatment. If urine pregnancy results cannot be confirmed as negative, a serum pregnancy test will be required (performed by the local trial site laboratory).

Participants may be rescreened after initially failing to meet the inclusion/exclusion criteria.

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

9.10.2 Treatment Period Visits

Visit requirements are outlined in the Section 2 – Schedule of Activities. Specific procedure-related details are provided in Section 9.1

9.10.3 Discontinued Participants Continuing to be Monitored in the Study

Participants who discontinue study treatment for a reason other than disease progression will be considered as on study and should continue with regularly scheduled assessments including collecting participant information on the start of new anticancer therapy, disease progression, and death.

9.10.4 Post-treatment Visit

9.10.4.1 Safety Follow-up Visit

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

Participants who are eligible for retreatment with pembrolizumab may have up to 2 Safety Follow-up Visits, 1 after the Initial Treatment Period and 1 after the Second Course Treatment.

9.10.4.2 Follow-up Visits

Participants who discontinue trial treatment for a reason other than disease progression will move into the Follow-up phase and should be assessed every 6 weeks (Q6W) in Year 1 and every 9 weeks (Q9W) after Year 1 to monitor disease status. Every effort should be made to collect information regarding disease status until the start of new anti-cancer therapy, disease progression, death, end of trial (or if the participant begins retreatment with pembrolizumab as detailed in [Section 7.2]). Information regarding post-trial anti-cancer treatment will be collected if new treatment is initiated.

Participants who are eligible to receive retreatment with pembrolizumab according to the criteria in Section 7 will move from the Follow-up Phase to the Second Course Phase when they experience disease progression. Details are provided in the Schedule of Activities (Section 2) for retreatment with pembrolizumab.

9.10.4.3 Survival Follow-up Assessments

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

9.10.4.4 Post-Study

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

9.10.4.5 Survival Status

To ensure current and complete survival data is available at the time of database locks, updated survival status may be requested during the course of the study by the Sponsor. For example, updated survival status may be requested prior to but not limited to an external Data Monitoring Committee (eDMC) review, interim and/or final analysis. Upon Sponsor notification, all participants who do not/will not have a scheduled study visit or study contact during the Sponsor defined time period will be contacted for their survival status (excluding participants that have a previously recorded death event in the collection tool).

10. Statistical Analysis Plan

This section outlines the statistical analysis strategy and procedures for the study. If, after the study has begun, changes are made to primary and/or key secondary hypotheses, or the statistical methods related to those hypotheses, then the protocol will be amended (consistent with 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 a supplemental Statistical Analysis Plan (sSAP) and referenced in the Clinical Study Report (CSR) for the study. A separate PK analysis plan as well as biomarker analysis plan will be provided. Post-hoc exploratory analyses will be clearly identified in the CSR. The PRO analysis plan will also be included in the sSAP.

10.1 Statistical Analysis Plan Summary

Key elements of the statistical analysis plan are summarized below; the comprehensive plan is provided in Sections 10.2-10.12.

Study Design Overview	Phase 2 trial of pembrolizumab in R/M cSCC or LA unresectable cSCC (KEYNOTE-629)
Treatment Assignment	Single-arm, open-label
Analysis Populations	Efficacy: All Participants as Treated (APaT) Safety: All Participants as Treated (APaT)
Primary Endpoint(s)	ORR per RECIST 1.1 assessed by BICR
Secondary Endpoints	1. DOR per RECIST 1.1 assessed by BICR 2. DCR per RECIST 1.1 assessed by BICR 3. PFS per RECIST 1.1 assessed by BICR 4. OS
Statistical Methods for Key Efficacy Analyses	The estimate of the ORR, along with its 95% CI based on the Clopper-Pearson method [Clopper, C. J. and Pearson, E. S. 1934], will be provided.
Statistical Methods for Key Safety Analyses	Counts, percentages and the corresponding 95% confidence intervals (CIs) of participants with AEs will be provided
Interim Analyses	Periodic data monitoring will be performed by the sponsor.
Multiplicity	No multiplicity adjustment will be applied.
Sample Size and Power	The planned sample size is up to approximately 100 participants with R/M cSCC and 50 participants with LA unresectable cSCC. Section 10.9 provides the precision of the ORR estimates.

10.2 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.

This trial is being conducted as a non-randomized, open-label study, ie, participants, investigators, and Sponsor personnel will be aware of participant treatment assignments after each participant is enrolled and treatment is assigned.

The clinical biostatistics department will generate the allocation schedule(s) for study treatment assignment.

10.3 Hypotheses/Estimation

Objectives and hypotheses of the study are stated in Section 4.

10.4 Analysis Endpoints

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

10.4.1 Efficacy Endpoints

The definitions of ORR, DOR, DCR, and PFS below apply to the endpoints based on RECIST 1.1 as well as the endpoints based on irRECIST. Per RECIST 1.1, PR and CR should be confirmed by a repeat tumor imaging assessment obtained 4 weeks or longer from the date the response was first documented.

Objective Response Rate (ORR): proportion of participants in the analysis population who have CR or PR.

Duration of Response (DOR): for participants who demonstrate CR or PR, DOR is defined as the time from first documented evidence of CR or PR until disease progression or death due to any cause, whichever occurs first.

Disease Control Rate (DCR): DCR is defined as the proportion of participants in the analysis population who have CR or PR or SD for at least 12 weeks.

Progression-free Survival (PFS): time from the date of the first dose of study medication to the first documented disease progression or death due to any cause.

Overall Survival (OS): time from the date of the first dose of study medication to death due to any cause.

10.4.2 Safety Endpoints

Safety will be assessed by reported adverse experiences using CTCAE, Version 4.0. The attribution to study treatment, time of onset, duration of the event, its resolution, and any concomitant medications administered will be recorded. Adverse events will be analyzed including but not limited to all AEs, SAEs, fatal AEs, and laboratory changes. Consider referring to Section 5.4.1.5 and Section 9.5 for the initial description of safety measures.

10.5 Analysis Populations

10.5.1 Efficacy Analysis Population

The All Participants as Treated (APaT) population will be used for the analysis of ORR, DCR, PFS, and OS. The APaT population consists of all allocated participants who received at least one dose of study treatment.

The analysis population for DOR consists of all responders.

10.5.2 Safety Analysis Population

The APaT population will be used for the analysis of safety data in this study. The APaT population consists of all allocated participants who received at least one dose of study treatment.

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

10.6 Statistical Methods

10.6.1 Statistical Methods for Efficacy Analyses

This section describes the statistical methods that address the primary and secondary objectives. Methods related to exploratory objectives will be described in the supplemental SAP. Analyses will be performed by cohort (R/M cSCC participants versus LA unresectable cSCC participants).

10.6.1.1 Statistical Methods for Primary Efficacy Endpoint

The primary endpoint is ORR per RECIST 1.1 assessed by BICR. The point estimate and 95% CI will be provided using exact binomial method proposed by Clopper and Pearson (1934) [Clopper, C. J. and Pearson, E. S. 1934]. Participants in the primary analysis population (APaT) without ORR data will be counted as non-responders.

10.6.1.2 Statistical Methods for Secondary Efficacy Endpoints

Duration of Response (DOR)

For DOR, Kaplan-Meier (KM) curves and median estimates from the KM curves will be provided. Censoring rules for DOR are summarized in Table 11.

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

Table 11 Censoring Rules for DOR

Situation	Date of progression or censoring	Outcome
No progression or death, no new anti-cancer therapy initiated	Last adequate assessment	Censor (non-event)
No progression or death, new anti-cancer therapy initiated	Last adequate assessment before new anti-cancer therapy initiated	Censor (non-event)
Death or progression after ≥ 2 consecutive missed adequate disease assessments or after new anti-cancer therapy, if any	Earlier date of last adequate assessment prior to ≥ 2 missed adequate disease assessments and new anti-cancer therapy, if any	Censor (non-event)
Death or progression after ≤1 missed adequate disease assessments and before new anti-cancer therapy, if any	Death or progression	End of response (event)

NOTE: Participants are considered to have an ongoing response if censored, alive, have not progressed, have not started a new anti-cancer therapy, and have not been determined to be lost to follow-up.

Disease Control Rate (DCR)

The same method used to analyze ORR will be used to analyze DCR.

Progression-Free Survival (PFS)

The non-parametric Kaplan-Meier method will be used to estimate the PFS curve. Since disease progression is assessed periodically, progressive disease (PD) can occur any time in the time interval between the last assessment where PD was not documented and the assessment when PD is documented. The true date of disease progression will be approximated by the date of the first assessment at which PD is objectively documented per RECIST 1.1 by BICR. Death is always considered as a confirmed PD event. Subjects who do not experience a PFS event will be censored at the last disease assessment.

Overall Survival (OS)

The non-parametric Kaplan-Meier method will be used to estimate the OS curve.

10.6.1.3 Summary of Efficacy Analysis Methods

The efficacy endpoints, analysis population, and statistical methods (including missing data handling) that will be employed for the efficacy analyses are presented in Table 12.

Table 12 Summary of Analysis Strategy for Efficacy Endpoints

Endpoint	Statistical Method	Analysis Population	Missing data approach
Primary Endpoint			
ORR • RECIST 1.1, BICR	Exact method based on binomial distribution	APaT	Participants with missing data are considered non-responders
Secondary Endpoints			
DOR • RECIST 1.1, BICR	Summary statistics using Kaplan-Meier method	Responders in APaT population	Censored at last assessment date
DCR • RECIST 1.1, BICR	Exact method based on binomial distribution	APaT	Participants with missing data are considered as disease not under control
PFS • RECIST 1.1, BICR	Summary statistics using Kaplan-Meier method	APaT	Censored at last assessment date
OS	Summary statistics using Kaplan-Meier method	APaT	Censored at last date the participant was known to be alive

APaT = All Participants as Treated; BICR = Blinded independent central review; DCR = Disease control rate; DOR = Duration of response; ORR = Overall response rate; OS = overall survival; PFS = Progression-free survival; RECIST = Response Evaluation Criteria In Solid Tumors.

NOTE: Analyses per irRECIST are considered supportive.

10.6.2 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. Counts, percentages, and the corresponding 95% CIs of participants with AEs will be provided. Analyses will be performed by cohort (R/M cSCC participants versus LA unresectable cSCC participants).

10.6.3 Summaries of Baseline Characteristics, Demographics, and Other Analyses

The number and percentage of participants screened, allocated, the primary reasons for screening failure, and the primary reason for discontinuation will be displayed. Demographic variables (such as age and gender) and baseline characteristics will be summarized either by descriptive statistics or categorical tables.

10.7 Interim Analyses

Periodic data monitoring will be performed by the sponsor. The timing of interim analyses and the final analysis will be documented in the sSAP. The sSAP will also be updated as the trial evolves. Participants will continue to be followed after the final analysis until the overall trial ends.

10.8 Multiplicity

No multiplicity adjustment will be applied.

10.9 Sample Size and Power Calculations

10.9.1 Sample Size and Power for Efficacy Analyses

In this study, up to approximately 100 participants with R/M cSCC and 50 participants with LA unresectable cSCC will be allocated to receive pembrolizumab 200 mg Q3W. With expected ORR to be at least 30% for R/M cSCC participants, the study has >95% power to have the lower bound of the 95% CI >15%. Table 13 shows the two-sided 95% CI for ORR with 100 R/M cSCC participants for different objective response rates. With expected ORR to be at least 40% for LA unresectable cSCC participants, the study has 84.4% power to have the lower bound of the 95% CI >20%. Table 14 shows the two-sided 95% CI for ORR with 50 LA unresectable cSCC participants for different objective response rates. The calculations are based on the exact binomial method by Clopper and Pearson (1934) [Clopper, C. J. and Pearson, E. S. 1934].

Table 13 Two-sided 95% CI for ORR with 100 R/M cSCC Participants

Number of Responders	ORR Estimate (%)	95% CI† of ORR (%)	Probability that Lower Bound of 95% CI > 15%
20	20	(12.7, 29.2)	26.1%
25	25	(16.9, 34.7)	71.4%
30	30	(21.2, 40.0)\	95.2%
35	35	(25.7, 45.2)	99.7%
40	40	(30.3, 50.3)	>99.9%
45	45	(35.0, 55.3)	>99.9%
50	50	(39.8, 60.2)	>99.9%
55	55	(44.7, 65.0)	>99.9%
60	60	(49.7, 69.7)	>99.9%

† Based on the two-tailed exact CI of a binomial proportion (Clopper and Pearson, 1934).

CI = Confidence interval; cSCC=cutaneous squamous cell carcinoma; ORR = Objective response rate. CI = Confidence interval; R/M=recurrent/metastatic

Table 14 Two-sided 95% CI for ORR with 50 LA Unresectable cSCC Participants

Number of Responders	ORR Estimate (%)	95% CI† of ORR (%)	Probability that Lower Bound of 95% CI > 20%
20	40	(26.4, 54.8)	84.4%
23	46	(31.8, 60.7)	96.9%
25	50	(35.5, 64.5)	99.2%
28	56	(41.3, 70.0)	>99.9%
30	60	(45.2, 73.6)	>99.9%
33	66	(51.2, 78.8)	>99.9%
35	70	(55.4, 82.1)	>99.9%

† Based on the two-tailed exact CI of a binomial proportion (Clopper and Pearson, 1934).

CI = Confidence interval; cSCC=cutaneous squamous cell carcinoma; LA=locally advanced; ORR = Objective response rate.

10.9.2 Sample Size and Power for Safety Analyses

The estimate of and the 95% CI for the percentage of participants experiencing AEs given various hypothetical observed number of participants experiencing AEs are provided in Table 15 for 100 R/M cSCC participants and in Table 16 for 50 LA unresectable cSCC participants. These calculations are based on the exact binomial method by Clopper and Pearson (1934) [Clopper, C. J. and Pearson, E. S. 1934].

Table 15 Estimate of and 95% CI for Incidence of Participants Experiencing AEs With 100 R/M cSCC Participants

Hypothetical Number of Participants With AEs	Estimate of Incidence (%)	95% CI† (%)
70	70	(60.0, 78.8)
75	75	(65.3, 83.1)
80	80	(70.8, 87.3)
85	85	(76.5, 91.4)
90	90	(82.4, 95.1)
95	95	(88.7, 98.4)

† Based on the two-tailed exact CI of a binomial proportion (Clopper and Pearson, 1934).

AE=adverse event; cSCC=cutaneous squamous cell carcinoma; CI=confidence interval; R/M=recurrent/metastatic.

Table 16 Estimate of and 95% CI for Incidence of Participants Experiencing AEs With 50 LA Unresectable cSCC Participants

Hypothetical Number of Participants With AEs	Estimate of Incidence (%)	95% CI[†] (%)
35	70	(55.4, 82.1)
38	75	(61.8, 86.9)
40	80	(66.3, 90.0)
43	85	(73.3, 94.2)
45	90	(78.2, 96.7)
48	95	(86.3, 99.5)

[†] Based on the two-tailed exact confidence interval of a binomial proportion (Clopper and Pearson, 1934).
AE=adverse event; cSCC=cutaneous squamous cell carcinoma; CI=confidence interval; LA=locally advanced.

10.10 Subgroup Analyses

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

- Age category (<65 versus ≥65 years)
- Sex (female versus male)
- Race (white versus all others)
- Region (North America versus European Union versus Rest of the World)

10.11 Compliance (Medication Adherence)

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

10.12 Extent of Exposure

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

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12. Appendices

12.1 Appendix 1: Abbreviations and Trademarks

Abbreviation/Term	Definition
2L	Second line
ADA	Anti-drug antibody
ADL	Activities of daily living
AE	Adverse event
ALT	alanine aminotransferase
AMA	American Medical Association
ANC	absolute neutrophil count
APaT	All Participants as Treated
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
β-HCG	beta human chorionic gonadotropin
BCC	Basal cell carcinoma
BCG	Bacillus Calmette-Guérin
BICR	Blinded independent central review
BUN	blood urea nitrogen
CAC	Clinical Adjudication Committee
CD3ζ	CD3 zeta
CFR	Code of Federal Regulations
CI	confidence interval
cHL	classical Hodgkin lymphoma
CNS	Central nervous system
CONSORT	Consolidated Standards of Reporting Trials
COVID-19	coronavirus disease caused by severe acute respiratory syndrome coronavirus 2
CR	complete response
CrCl	Calculated creatinine clearance
CRF	case report form
cSCC	Cutaneous squamous cell carcinoma
CSR	Clinical study report
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTFG	Clinical Trial Facilitation Group
CTLA-4	cytotoxic T-lymphocyte-associated antigen-4
CTR	Clinical Trials Register
DCR	Disease control rate
DILI	drug-induced liver injury
DNA	deoxyribonucleic acid
DOR	duration of response
ECI	Event of clinical interest
ECG	electrocardiogram

Abbreviation/Term	Definition
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EDC	electronic data capture
ELISA	Enzyme-linked immunosorbent assay
EMA	European Medicines Agency
EOC	Executive Oversight Committee
EORTC	European Organization for Research and Treatment of Cancer
EoT	End of Treatment
ePRO	electronic patient-reported outcome
ERC	Ethics Review Committee
ERCs	European Research Councils
EU	European Union
EuroQol	European Quality of Life
EV	Epidermodysplasia verruciformis
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act
FNA	fine needle aspirate
FSH	Follicle stimulating hormone
FT4	free thyroxine
GCP	Good Clinical Practice
GFR	glomerular filtration rate
HBsAg	Hepatitis B surface antigen
HCV	Hepatitis C virus
HIV	human immunodeficiency virus
HNSCC	Head and neck squamous cell carcinoma
HPV	human papillomavirus
HRT	Hormonal replacement therapy
IB	Investigator's Brochure
IA(s)	interim analysis(ses)
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
Ig	Immunoglobulin
IgV	Ig-variable–type
IHC	immunohistochemistry
INR	international normalized ratio
irAE	immune-related adverse event
IRB	Institutional Review Board
irRECIST	immune-related RECIST
IUD	Intrauterine device
IUS	Intrauterine hormone-releasing system
IV	intravenous

Abbreviation/Term	Definition
IVD	In vitro diagnostic
IVRS	interactive voice response system
IWRS	integrated web response system
KM	Kaplan-Meier
LA	locally advanced
mAb	monoclonal antibody
MCC	Merkel cell carcinoma
MCPyV	Merkel cell polyomavirus
MRI	magnetic resonance imaging
mRNA	Messenger RNA
NCI	National Cancer Institute
NSAID	nonsteroidal anti-inflammatory drug
ORR	objective response rate
OS	overall survival
OTC	over-the-counter
PCL	Protocol Clarification Letter
PD	progressive disease
PD-1	Programmed Cell Death 1
PD-L1	Programmed Death Ligand 1
PD-L2	Programmed Death Ligand 2
PFS	progression-free survival
PI	Principal investigator
PK	pharmacokinetic
PKCθ	Protein kinase C-theta
PR	partial response
PRO	Patient reported outcome
PSA	Prostate-specific antigen
PT	prothrombin time
PTT	partial thromboplastin time
Q3W	every 3 weeks
Q6W	Every 6 weeks
Q12W	Every 12 weeks
RBC	red blood cell
RECIST	Response Evaluation Criteria in Solid Tumors
R/M	Recurrent and/or metastatic
RNA	ribonucleic acid
RT	radiation therapy
SAC	Scientific Advisory Committee
SAE	serious adverse event
SD	stable disease
SGOT	serum glutamic oxaloacetic transaminase
SGPT	serum glutamic pyruvic transaminase
SIM	Site Imaging Manual

Abbreviation/Term	Definition
SNP	Single nucleotic polymorphism
SoA	Schedule of Activities
sSAP	Supplemental Statistical Analysis Plan
SUSAR	Suspected unexpected serious adverse reactions
Treg	Regulatory T-cell
T1DM	type 1 diabetes mellitus
T3	triiodothyronine
TIL	tumor-infiltrating lymphocyte
TSH	thyroid-stimulating hormone
ULN	upper limit of normal
UV	Ultraviolet
WBC	white blood cell
WOCB	Woman of childbearing potential
ZAP70	Zeta-chain–associated protein kinase

12.2 Appendix 2: Clinical Laboratory Tests

- The tests detailed in Table 17 will be performed by the local laboratory.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 6.1 and 6.2 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 17 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
Coagulation[a] (screening)	PT (INR)	aPTT[b]		
Chemistry	Blood Urea Nitrogen (BUN)[c]	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)
		Carbon dioxide or bicarbonate	Chloride	Phosphorous
	Creatinine	Sodium	Alanine aminotransferase (ALT)/Serum glutamic-pyruvic transaminase (SGPT)	Total protein
	Glucose (nonfasting)	Calcium	Alkaline phosphatase	Urea[c]
Routine urinalysis[d]	• Specific gravity • Glucose, protein, blood (by dipstick) • Microscopic examination (if blood or protein is abnormal)			

Laboratory Assessments	Parameters
Other screening tests	• Follicle-stimulating hormone and estradiol (as needed in women of non-childbearing potential only) • Total T3 or free T3, FT4, and TSH[e] • Serum or urine beta-human chorionic gonadotropin (β-HCG) pregnancy test (as needed for women of childbearing potential) • HIV/HBV/HCV Serology

aPTT = activated partial thromboplastin time; FT4 = free thyroxine; INR = international normalized ratio; MCH = mean corpuscular hemoglobin; MCV = mean corpuscular volume; PT = prothrombin time; RBC = red blood cell; T3 = total triiodothyronine; TSH = thyroid stimulating hormone; WBC = white blood cell.

a Any participant receiving anticoagulant therapy should have coagulation tests monitored closely throughout the trial.
b PTT may be performed if the local laboratory is unable to perform aPTT.
c Blood Urea Nitrogen is preferred; if not available, urea may be tested.
d Urinalysis required at screening only
e If the local laboratory is unable to perform these tests, the site should submit the sample to the central laboratory for testing.
NOTE: Additional details are provided in the Procedures Manual.

Investigators must document their review of each laboratory safety report.

12.3 Appendix 3: Study Governance Considerations

Code of Conduct for Clinical Trials

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

Code of Conduct for Interventional Clinical Trials

I. Introduction

A. Purpose

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

B. Scope

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

II. Scientific Issues

A. Trial Conduct

1. Trial Design

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

The design (i.e., participant population, duration, statistical power) must be adequate to address the specific purpose of the trial 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 (or individuals acting on behalf of MSD) 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 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 potential fraud, scientific/research misconduct, privacy incidents/breaches or Clinical Trial-related Significant Quality Issues are reported, such matters are investigated. When necessary, appropriate corrective and/or preventative actions are defined and regulatory authorities and/or ethics review committees are notified.

B. Publication and Authorship

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

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

III. Participant Protection

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

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

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

B. Safety

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

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

C. Confidentiality

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

D. Genomic Research

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

IV. Financial Considerations

A. Payments to Investigators

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

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

B. Clinical Research Funding

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

C. Funding for Travel and Other Requests

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

V. Investigator Commitment

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

Financial Disclosure

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

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

Data Protection

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

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

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

Confidentiality of Data

By signing this protocol, the investigator affirms to the Sponsor that information furnished to the investigator by the Sponsor will be maintained in confidence, and such information will be divulged to the institutional review board, ethics review committee (IRB/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 trial will be considered confidential by the investigator, except to the extent that it is included in a publication as provided in the Publications section of this protocol.

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 trial documents in order to verify worksheet/case report form data. By signing the consent form, the participant agrees to this process. If trial documents will be photocopied during the process of verifying worksheet/case report form information, the participant will be identified by unique code only; full names/initials will be masked prior to transmission to the Sponsor.

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

Confidentiality of IRB/IEC Information

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

Publication Policy

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

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

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

Compliance with Trial Registration and Results Posting Requirements

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

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

Compliance With Law, Audit and Debarment

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

The Code of Conduct, a collection of goals and considerations that govern the ethical and scientific conduct of clinical investigations sponsored by MSD, is provided in this appendix under the MSD 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 trial reimbursed to the investigator by the Sponsor.

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

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

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.

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

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.

Source Documents

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

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

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 trial site, the Sponsor will promptly notify that trial site's IRB/IEC.

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

Definition of AE

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

Events <u>Meeting</u> 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, or are considered clinically significant in the medical and scientific judgment of the investigator. • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. • New conditions detected or diagnosed after study treatment administration even though it may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study treatment or a concomitant medication. • For all reports of overdose (whether accidental or intentional) with an associated adverse event, 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). Note: Progression of the cancer under study is not a reportable event. Refer to Section 9.3.5 for additional details.

Events NOT Meeting the AE Definition
● Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE. ● Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital). ● Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen. ● Surgery planned prior to informed consent to treat a pre-existing condition that has not worsened. ● Refer to section 9.3.5 for protocol specific exceptions

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

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

e. Is a congenital anomaly/birth defect

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

f. Other important medical events:

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

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

Additional Events reported in the same manner as SAE

Additional Events which require reporting in the same manner as SAE

- In addition to the above criteria, adverse events meeting either of the below criteria, although not serious per ICH definition, are reportable to the Sponsor in the same timeframe as SAEs to meet certain local requirements. Therefore, these events are considered serious by the Sponsor for collection purposes.
  - Is a new cancer (that is not a condition of the study);
  - Is associated with an overdose.

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 Adverse Event case report forms/worksheets at each examination.
- It is **not** acceptable for the investigator to send photocopies of the participant's medical records to the Sponsor in lieu of completion of the AE CRF page.
- There may be instances when copies of medical records for certain cases are requested by the Sponsor. In this case, all participant identifiers, with the exception of the participant number, will be blinded on the copies of the medical records before submission to the Sponsor.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity

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

Assessment of Causality

- Did the Sponsor's product cause the adverse event?
  - The determination of the likelihood that the Sponsor's product caused the adverse event 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 adverse event based upon the available information
  - **The following components are to be used to assess the relationship between the Sponsor's product and the AE;** the greater the correlation with the components and their respective elements (in number and/or intensity), the more likely the Sponsor's product caused the adverse event:
    - **Exposure:** Is there evidence that the participant was actually exposed to the Sponsor's product such as: reliable history, acceptable compliance assessment (pill count, diary, etc.), expected pharmacologic effect, or measurement of drug/metabolite in bodily specimen?
    - **Time Course:** Did the AE follow in a reasonable temporal sequence from administration of the Sponsor's product? Is the time of onset of the AE compatible with a drug-induced effect (applies to trials with investigational medicinal product)?

- **Likely Cause:** Is the AE not reasonably explained by another etiology such as underlying disease, other drug(s)/vaccine(s), or other host or environmental factors
- **Dechallenge:** Was the Sponsor's product discontinued or dose/exposure/frequency reduced?
  - If yes, did the AE resolve or improve?
    - If yes, this is a positive dechallenge.
  - If no, this is a negative dechallenge.

  (Note: This criterion is not applicable if: (1) the AE resulted in death or permanent disability; (2) the AE resolved/improved despite continuation of the Sponsor's product; (3) the trial is a single-dose drug trial); or (4) Sponsor's product(s) is/are only used one time.)
- **Rechallenge:** Was the participant re-exposed to the Sponsor's product in this trial?
  - If yes, did the AE recur or worsen?
    - If yes, this is a positive rechallenge.
  - If no, this is a negative rechallenge.

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

NOTE: IF A RECHALLENGE IS PLANNED FOR AN ADVERSE EVENT WHICH WAS SERIOUS AND WHICH MAY HAVE BEEN CAUSED BY THE SPONSOR'S PRODUCT, OR IF RE-EXPOSURE TO THE SPONSOR'S PRODUCT POSES ADDITIONAL POTENTIAL SIGNIFICANT RISK TO THE PARTICIPANT THEN THE RECHALLENGE MUST BE APPROVED IN ADVANCE BY THE SPONSOR CLINICAL DIRECTOR AS PER DOSE MODIFICATION GUIDELINES IN THE PROTOCOL, AND IF REQUIRED, THE INSTITUTIONAL REVIEW BOARD/INDEPENDENT ETHICS COMMITTEE.

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

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

- Use the following scale of criteria as guidance (not all criteria must be present to be indicative of a Sponsor's product relationship).
  - Yes, there is a reasonable possibility of Sponsor's product relationship: There is evidence of exposure to the Sponsor's product. The temporal sequence of the AE onset relative to the administration of the Sponsor's product is reasonable. The AE is more likely explained by the Sponsor's product than by another cause.
  - No, there is not a reasonable possibility of Sponsor's product relationship: Participant did not receive the Sponsor's product OR temporal sequence of the AE onset relative to administration of the Sponsor's product is not reasonable OR the AE is more likely explained by another cause than the Sponsor's product. (Also entered for a participant with overdose without an associated AE.)
- For each AE/SAE, the investigator must document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to the Sponsor. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the Sponsor.
- The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements

Follow-up of AE and SAE

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

Reporting of AE, SAE, and Other Reportable Safety Events to the Sponsor

AE, SAE, and Other Reportable Safety Event Reporting to Sponsor via Electronic Data Collection Tool

- The primary mechanism for reporting to the Sponsor will be the electronic data collection (EDC) tool.
  - Electronic reporting procedures can be found in the EDC data entry guidelines (or equivalent).

- If the electronic system is unavailable for more than 24 hours, then the site will use the paper AE Reporting form.
    - Reference section 9.3.1 – Time Period and Frequency for Collecting AE and SAE and Other Reportable Safety Event Information 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 electronic data collection 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 electronic data collection tool has been taken off-line, then the site can report this information on a paper SAE form or by telephone (see next section).
- Contacts for SAE reporting can be found in the Investigator Trial File Binder (or equivalent).

SAE Reporting to the Sponsor via Paper CRF

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

12.5 Appendix 5: Contraceptive Guidance and Pregnancy Testing

Woman of Childbearing Potential (WOCBP)

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

Women in the following categories are not considered WOCBP:

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

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

Highly Effective Contraception Requirements

Female Participants:

Female participants of childbearing potential are eligible to participate if they agree to use a highly effective method of contraception consistently and correctly as described in Table 18 during the protocol-defined time frame in Section 6.1.

Table 18 Highly Effective Contraception Methods

Highly Effective Contraceptive Methods That Are User Dependent [a] *Failure rate of <1% per year when used consistently and correctly.*
● Combined (estrogen- and progestogen- containing) hormonal contraception [b] ○ Oral ○ Intravaginal ○ Transdermal ○ Injectable
● Progestogen-only hormonal contraception [b] ○ Oral ○ Injectable
Highly Effective Methods That Have Low User Dependency *Failure rate of <1% per year when used consistently and correctly.*
● Progestogen- only contraceptive implant [b] ● Intrauterine hormone-releasing system (IUS) ● Intrauterine device (IUD) ● Bilateral tubal occlusion
● **Vasectomized partner** A vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.
● **Sexual abstinence** Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatment. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.)
Notes: Use should be consistent with local regulations regarding the use of contraceptive methods for participants of clinical studies. a) Typical use failure rates are higher than perfect-use failure rates (ie, when used consistently and correctly). If a contraceptive method listed is restricted by local regulations/guidelines, then it does not qualify as an acceptable method of contraception for participants participating at sites in this country/region. b) If locally required, in accordance with Clinical Trial Facilitation Group (CTFG) guidelines, acceptable hormonal contraceptives are limited to those which inhibit ovulation. Note: The following are not acceptable methods of contraception: • Periodic abstinence (calendar, sympothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea method (LAM). • Male condom with cap, diaphragm, or sponge with spermicide. • Male and female condom should not be used together (due to risk of failure with friction).

Pregnancy Testing

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

Following initiation of treatment additional pregnancy testing will be performed at EOT and 30 days, after the last dose of study treatment and as required locally.

Pregnancy testing will be performed whenever an expected menstrual cycle is missed or when pregnancy is otherwise suspected.

Monthly pregnancy testing should be conducted as per local regulations where applicable. Pregnancy testing (urine or serum as required by local regulations) should be conducted at the end of relevant systemic exposure.

Note: for participants enrolled from German sites, monthly pregnancy testing is required while on study therapy.

Female participants of childbearing/reproductive potential must have a negative urine or serum pregnancy test within 72 hours prior to randomization. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required.

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

12.6 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 trial as outlined in Section 9.8 – Future Biomedical Research Sample Collection will be used in various experiments to understand:

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

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

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

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

a. Participants for Enrollment

All participants enrolled in the clinical trial will be considered for enrollment in the Future Biomedical Research.

b. Informed Consent

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

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

c. eCRF Documentation for Future Biomedical Research Specimens

Documentation of participant consent for Future Biomedical Research will be captured in the electronic Case Report Forms (eCRFs). Any specimens for which such an informed consent cannot be verified will be destroyed.

d. Future Biomedical Research Specimen(s)

Collection of specimens for Future Biomedical Research will be performed as outlined in the trial flow chart. In general, if additional blood specimens are being collected for Future Biomedical Research, these will usually be obtained at a time when the participant is having blood drawn for other trial 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 participant' clinical information with future test results. In fact little or no research can be conducted without connecting the clinical trial data to the specimen. The clinical data allow specific analyses to be conducted. Knowing participant characteristics like gender, age, medical history and treatment outcomes are critical to understanding clinical context of analytical results.

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

At the clinical trial site, unique codes will be placed on the Future Biomedical Research specimens. This code is a random number which does not contain any personally

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

5. Biorepository Specimen Usage[3,4]

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

6. Withdrawal From Future Biomedical Research[3,4]

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

In the event that the medical records for the main trial are no longer available (eg, if the investigator is no longer required by regulatory authorities to retain the main trial records) or the specimens have been completely anonymized, there will no longer be a link between the 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 main study. Specimens may be stored for longer if a regulatory or governmental authority has active questions that are being answered. In this special circumstance, specimens will be stored until these questions have been adequately addressed.

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

8. Data Security[3,4]

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

9. Reporting of Future Biomedical Research Data to 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 trials 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. No additional risks to the participant have been identified as no additional specimens are being collected for Future Biomedical Research (i.e., only leftover samples are being retained).

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

12. Questions

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

13. References

1. National Cancer Institute: http://www.cancer.gov/dictionary/?searchTxt=biomarker

2. International Conference on Harmonization: DEFINITIONS FOR GENOMIC BIOMARKERS, PHARMACOGENOMICS, PHARMACOGENETICS, GENOMIC DATA AND SAMPLE CODING CATEGORIES - E15; http://www.ich.org/LOB/media/MEDIA3383.pdf

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

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