Official Protocol Title:	A Phase 3 Open-label, Single Arm Study to Evaluate the Safety and Efficacy of Pembrolizumab (MK-3475) as First-line Therapy in Participants With Advanced Merkel Cell Carcinoma (KEYNOTE-913)
NCT number:	NCT03783078
Document Date:	01-JUL-2022

Title Page

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Protocol Title: A Phase 3 Open-label, Single Arm Study to Evaluate the Safety and Efficacy of Pembrolizumab (MK-3475) as First-line Therapy in Participants With Advanced Merkel Cell Carcinoma (KEYNOTE-913)

Protocol Number: 913-03

Compound Number: MK-3475

Sponsor Name:

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

Legal Registered Address:

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P.O. Box 2000

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Regulatory Agency Identifying Number(s):

IND	127548
EudraCT	2018-002601-57

Approval Date: 01 July 2022

Sponsor Signatory

Typed Name: Date
Title:

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

Investigator Signatory

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

Typed Name: Date
Title:

DOCUMENT HISTORY

Document	Date of Issue	Overall Rationale
Amendment 3	01-JUL-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.
Amendment 2	08-JUN-2021	To harmonize the presentation of safety information across all FDA-approved PD-1/L1 antibody prescribing information and to update imaging frequency.
Amendment 1	25-SEP-2020	Country-specific change, procedural updates, clarification of ORR, and removal of substudy references for Future Biomedical Research.
Original Protocol	25-SEP-2018	Not applicable

PROTOCOL AMENDMENT SUMMARY OF CHANGES

Amendment: 03

Overall Rationale for the Amendments:

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

Summary of Changes Table:

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

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1 PROTOCOL SUMMARY

1.1 Synopsis

Protocol Title: A Phase 3 Open-label, Single Arm Study to Evaluate the Safety and Efficacy of Pembrolizumab (MK-3475) as First-line Therapy in Participants With Advanced Merkel Cell Carcinoma (KEYNOTE-913)

Short Title: Pembrolizumab (MK-3475) as First-line Therapy for Advanced Merkel Cell Carcinoma

Acronym: KEYNOTE-913

Hypotheses, Objectives, and Endpoints:

There are no hypotheses for this study.

In participants at least 12 years of age with advanced Merkel cell carcinoma (MCC):

Primary Objectives	Primary Endpoints
- Objective: To assess the objective response rate (ORR), as assessed by blinded independent central review (BICR) per Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST 1.1) modified to follow a maximum of 10 target lesions and a maximum of 5 target lesions per organ, following administration of pembrolizumab	- Objective response (OR): Complete response (CR) or partial response (PR)
Secondary Objectives	Secondary Endpoints
- Objective: To assess duration of response (DOR), as assessed by BICR per RECIST 1.1 modified to follow a maximum of 10 target lesions and a maximum of 5 target lesions per organ, following administration of pembrolizumab	- DOR: For participants who demonstrate confirmed CR or PR, the time from first documented evidence of CR or PR until disease progression or death from any cause, whichever occurs first
- Objective: To assess the progression-free survival (PFS), as assessed by BICR per RECIST 1.1 modified to follow a maximum of 10 target lesions and a maximum of 5 target lesions per organ, following administration of pembrolizumab	- PFS: The time from the first day of study treatment to the first documented disease progression per RECIST 1.1 by BICR or death due to any cause, whichever occurs first

- Objective: To assess overall survival (OS) following administration of pembrolizumab	- OS: The time from the first day of study treatment to death due to any cause
- Objective: To assess safety and tolerability of treatment with pembrolizumab	- Adverse events (AEs)

Overall Design:

Study Phase	Phase 3
Primary Purpose	Treatment
Indication	Treatment of unresectable Stage III and Stage IV MCC
Population	Participants with no prior systemic therapy for advanced MCC (prior adjuvant therapy is permitted)
Study Type	Interventional
Intervention Model	Single Group This is a multi-site study
Type of Control	No Treatment Control
Study Blinding	Unblinded Open-label
Masking	No Masking
Estimated Duration of Study	The Sponsor estimates that the study will require approximately 13 years from the time the first participant signs the informed consent/assent until the last participant's last study-related telephone call or visit.

Number of Participants:

Approximately 50 participants will be allocated to study intervention.

Intervention Groups and Duration:

Intervention Groups

Intervention Group Name	Drug	Dose Strength	Dose Frequency	Route of Admin.	Regimen/ Treatment Period	Use
Pembrolizumab	Pembrolizumab (MK-3475)	200 mg (adult participants) or 2 mg/kg (up to 200 mg; pediatric participants) on Day 1 of each cycle	Q3W	IV	Up to 35 administrations (approximately 2 years)	Experimental

IV=intravenous; Q3W=every 3 weeks

Total Number

1 intervention group

Duration of Participation

Each participant will participate in the study from the time the participant provides documented informed consent through the final protocol-specified contact.

After a screening phase of up to 28 days, each participant will be assigned to receive study intervention until disease progression is radiographically documented, confirmed by the site per modified Response Evaluation Criteria in Solid Tumors 1.1 for immune-based therapeutics (iRECIST) when clinically appropriate, unacceptable adverse event(s) (AEs), pregnancy, intercurrent illness that prevents further administration of treatment, investigator's decision to discontinue the participant, administrative reasons requiring cessation of treatment, or until the participant has received 35 administrations of pembrolizumab (approximately 2 years).

After the end of treatment, each participant will be followed for the occurrence of AEs and spontaneously reported pregnancy as described under Section 8.4.

Participants who discontinue for reasons other than radiographic disease progression will have post-treatment follow-up imaging for disease status until disease progression is documented radiographically per RECIST 1.1, and when clinically appropriate, confirmed by the site per iRECIST, the start of a new anticancer treatment, withdrawal of consent, pregnancy, death, or loss to follow-up. All participants will be followed by telephone for overall survival until death, withdrawal of consent, or the end of the study.

Once the participant has achieved the study objective or the study has ended, the participant is discontinued from this study and will be enrolled in an extension study to continue protocol-defined assessments and treatment.

Study Governance Committees:

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

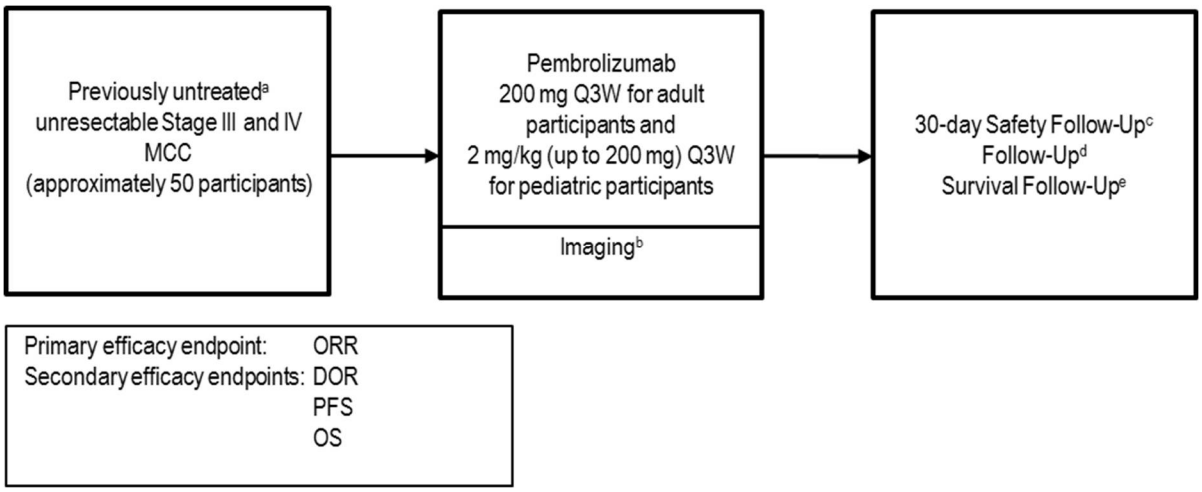
Study Accepts Healthy Volunteers: No

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

1.2 Schema

The study design is depicted in Figure 1.

Figure 1 KEYNOTE-913 Study Design



BICR=blinded independent central review; C1D1=Cycle 1 Day 1; DOR=duration of response; ORR=objective response rate; OS=overall survival; PFS=progression-free survival; Q3W=every 3 weeks; Q12W=every 12 weeks; Q24W=every 24 weeks; RECIST=Response Evaluation Criteria In Solid Tumors

a Prior adjuvant therapy may be allowed as detailed in Section 5.1, inclusion criterion #2.

b Imaging to be performed Q12W or sooner if clinically indicated after C1D1 (±7 days) until Week 54 of study intervention, Q24W thereafter or sooner if clinically indicated, or more frequently if required by local standard of care, until disease progression per RECIST 1.1.

c If End of Treatment visit occurs >30 days after last dose of study intervention, a Safety Follow-up Visit is not required.

d For participants discontinuing for reasons other than disease progression, tumor imaging should continue to be performed as if on study intervention (ie, Q12W until Week 54 after C1D1 (±7 days), Q24W thereafter or sooner if clinically indicated, or more frequently if required by local standard of care, until disease progression per RECIST 1.1).

e Participants in Survival Follow-up will be contacted approximately Q12W or sooner to assess for survival status or death, withdrawal of consent, or the end of study, whichever occurs first.

1.3 Schedule of Activities (SoA)

Procedures and activities are outlined in Table 1.

Table 1 Study Schedule of Activities

Study Period	**Screening Phase**	**Intervention Phase (Q3W)**			**End of Treatment**	**Post-treatment Follow-up**			**Notes**
Treatment Cycle		1	2	3 and onwards	Discontinu-ation	Safety Follow-up[a]	Follow-up[b]	Survival Follow-up	Procedures should occur predose on Day 1 of each cycle unless otherwise noted. Post-treatment Period: Refer to Section 8.12.3.
Scheduled Timing	-28 to -1				At time of d/c	30 days post last dose		~Q12W (telephone)	
Window (days):		+ 3	± 3	± 3		+ 7	± 7	± 7	
Administrative Procedures									
Informed Consent/Assent	X								Consent/assent form can be signed at any time prior to any protocol-specific screening procedures being performed. Additional consent/assent is required at disease progression.
Informed Consent/Assent for Future Biomedical Research	X								Participation in future biomedical research is not mandatory for participation in this study.
Inclusion/Exclusion Criteria	X								
Participant Identification Card	X								
Medical/Surgical History and Demographics	X								Significant medical/surgical history will be captured for last 10 years.
Staging	X								At initial diagnosis and at study entry.

Study Period	**Screening Phase**	**Intervention Phase (Q3W)**			**End of Treatment**	**Post-treatment Follow-up**			**Notes**
Treatment Cycle		1	2	3 and onwards	Discontinu-ation	Safety Follow-up[a]	Follow-up[b]	Survival Follow-up	Procedures should occur predose on Day 1 of each cycle unless otherwise noted. Post-treatment Period: Refer to Section 8.12.3.
Scheduled Timing	-28 to -1				At time of d/c	30 days post last dose		~Q12W (telephone)	
Window (days):		+ 3	± 3	± 3		+ 7	± 7	± 7	
Prior and Concomitant Medication Review	X	X	X	X	X	X	X		Record all prior medications taken within 28 days before C1D1. Enter new medications started during the study through the post-treatment Safety Follow-up. Record concomitant medications beyond 30 days after treatment discontinuation if related to SAE or ECI.
Study Intervention									
Intervention Allocation		X							Participants will be allocated on C1D1 (-3 days) after confirmation of eligibility.
Pembrolizumab (MK-3475) Administration		X	X	X					Pembrolizumab 200 mg Q3W for adult participants or 2 mg/kg (up to 200 mg) Q3W for pediatric participants.
Poststudy Anticancer Therapy						X	X	X	All anticancer therapy will be recorded until time of death or termination of Survival Follow-up. If a clinic visit is not feasible, follow-up information may be obtained via telephone or e-mail.

Study Period	**Screening Phase**	**Intervention Phase (Q3W)**			**End of Treatment**	**Post-treatment Follow-up**			**Notes**
Treatment Cycle		1	2	3 and onwards	Discontinu-ation	Safety Follow-up[a]	Follow-up[b]	Survival Follow-up	Procedures should occur predose on Day 1 of each cycle unless otherwise noted. Post-treatment Period: Refer to Section 8.12.3.
Scheduled Timing	-28 to -1				At time of d/c	30 days post last dose		~Q12W (telephone)	
Window (days):		+ 3	± 3	± 3		+ 7	± 7	± 7	
Survival Status		<----------						X	After investigator-determined PD or start of new anticancer treatment. In addition, upon Sponsor request, participants may be contacted for survival status at any time during the course of the study (unless this information is not allowed to be provided due to confidentiality).
Efficacy Procedures									
Tumor Imaging (CT/MRI; Chest, Abdomen, and Pelvis)	X	<----------[c]			X[d]		X		Prior scans performed within the screening period but before signing informed consent may be used if consistent with protocol requirements per SIM. All imaging visits have a scheduling window of ±7 days. Imaging to be performed Q12W or sooner if clinically indicated from the date of C1D1 until Week 54 of study treatment, Q24W or sooner if clinically indicated thereafter, or more frequently if required by local standard of care until disease progression per RECIST 1.1.

Study Period	**Screening Phase**	**Intervention Phase (Q3W)**			**End of Treatment**	**Post-treatment Follow-up**			**Notes**
Treatment Cycle		1	2	3 and onwards	Discontinu-ation	Safety Follow-up[a]	Follow-up[b]	Survival Follow-up	Procedures should occur predose on Day 1 of each cycle unless otherwise noted. Post-treatment Period: Refer to Section 8.12.3.
Scheduled Timing	-28 to -1				At time of d/c	30 days post last dose		~Q12W (telephone)	
Window (days):		+ 3	± 3	± 3		+ 7	± 7	± 7	
Safety Procedures									
Height	X	X	X	X	X				Pediatric height to be measured at every visit. Adult height measured at Screening only.
Weight	X	X	X	X	X				To be measured at every visit.
Full Physical Examination	X								Within 7 days prior to C1D1.
Directed Physical Examination		X	X	X		X			A symptom-directed physical examination may be performed at any time during the study, as clinically indicated.
Vital Signs (resting BP, pulse rate, respiratory rate, temperature)	X	X	X	X	X	X			BP and pulse rate will be measured after the participant has been resting for 5 minutes.
12-lead ECG	X								Single 12-lead ECG. After the participants has been recumbent for 5 minutes.
ECOG Performance Status (or Lansky scale)	X	X	X	X		X			Within 3 days prior to C1D1. Thereafter, prior to dosing at treatment visits. Lansky scale to be used instead of ECOG in pediatric participants ≤16 years old.

Study Period	**Screening Phase**	**Intervention Phase (Q3W)**			**End of Treatment**	**Post-treatment Follow-up**			**Notes**
Treatment Cycle		1	2	3 and onwards	Discontinu-ation	Safety Follow-up[a]	Follow-up[b]	Survival Follow-up	Procedures should occur predose on Day 1 of each cycle unless otherwise noted. Post-treatment Period: Refer to Section 8.12.3.
Scheduled Timing	-28 to -1				At time of d/c	30 days post last dose		~Q12W (telephone)	
Window (days):		+ 3	± 3	± 3		+ 7	± 7	± 7	
AE/SAE Review	X	X	<----------					---------->	AEs: monitored up to 30 days after last dose. SAEs and pregnancy: monitored up to 90 and 120 days after last dose, respectively, or 30 days after last dose if participant starts a new anticancer therapy, whichever is sooner.
Laboratory Procedures (LOCAL laboratory)									
Pregnancy Test – Serum or Urine (WOCBP only)	X		X	X	X	X	X		Refer to Appendix 5. Within 72 hours prior to C1D1, then repeat prior to each cycle of treatment and as required by local guidelines up to 120 days after last dose of study intervention or the start of a new anticancer therapy, whichever comes first.
HIV, hepatitis B and C screen (per local regulations)	X								Not required unless mandated by local health authority.
PT/INR and aPTT	X								Within 3 days prior to C1D1. Repeat as needed for participants on warfarin-based anticoagulation therapy.

Study Period	**Screening Phase**	**Intervention Phase (Q3W)**			**End of Treatment**	**Post-treatment Follow-up**			**Notes**
Treatment Cycle		1	2	3 and onwards	Discontinu-ation	Safety Follow-up[a]	Follow-up[b]	Survival Follow-up	Procedures should occur predose on Day 1 of each cycle unless otherwise noted. Post-treatment Period: Refer to Section 8.12.3.
Scheduled Timing	-28 to -1				At time of d/c	30 days post last dose		~Q12W (telephone)	
Window (days):		+ 3	± 3	± 3		+ 7	± 7	± 7	
T3 (or Free T3), Free T4, and TSH	X		X	X	X				Within 10 days prior to C1D1. Then within 1 day prior to Day 1 of every other cycle starting from Cycle 2 (eg, Cycle 2, 4, 6, 8, etc.) and at EOT. Free T3 is acceptable where T3 cannot be determined.
Hematology	X		X	X	X	X			Blood for hematology and chemistry panel should be collected within 3 days prior to C1D1 and then within 1 day prior to Day 1 of every cycle. Urine for urinalysis should be collected within 3 days prior to C1D1 and then within 1 day prior to Day 1 of every 4 cycles starting from Cycle 4 (eg, Cycle 4, 8, 12, 16, etc.). Every effort should be made to collect samples at the same time of day.
Chemistry Panel	X		X	X	X	X			
Urinalysis	X			X	X	X			
Laboratory Procedures (CENTRAL laboratory)									
Blood for Future Biomedical Research		X							

AE=adverse event; aPTT=activated partial thromboplastin time; BP=blood pressure; C=Cycle; C1D1=Cycle 1 Day 1; CR=complete response; CT=computed tomography; D=Day; ECG=electrocardiogram; ECI=Event of Clinical Interest; ECOG=Eastern Cooperative Oncology Group; EOT=End of Treatment; HIV=human immunodeficiency virus; INR=international normalized ratio; MRI=magnetic resonance imaging; PD=progressive disease; PT=prothrombin time; Q3W=every 3 weeks; Q12W=every 12 weeks; Q24W=every 24 weeks; RECIST=Response Evaluation Criteria In Solid Tumors; SAE=serious adverse event; SIM=Site Imaging Manual; T3=triiodothyronine; T4=thyroxine; TSH=thyroid stimulating hormone; WOCBP=women of childbearing potential.

a If the EOT visit occurs ≥ 30 days after the last dose of study intervention, a Safety Follow-up Visit is not required. In this situation, all procedures required at the 30-day Safety Visit and EOT are performed once and entered into the EOT visit only.

b In the Follow-up Phase, participants should be assessed Q12W until Week 54 after C1D1 (±7 days); Q24W thereafter or sooner if clinically indicated, or more frequently if required by local standard of care, until disease progression per RECIST 1.1, to monitor disease status.

c The same imaging technique regarding modality and the use of contrast should be used in a participant throughout the study to optimize the visualization of existing and new tumor burden. Imaging of any anatomy that shows disease either at Screening or in subsequent evaluations will be required and should be submitted to the imaging contract research organization (iCRO).

d Participants who attain an investigator-determined CR and stop study intervention with pembrolizumab will have a Safety Follow-up Visit and move to the Follow-up Visits per SoA. Imaging at EOT is not required if the previous tumor imaging assessment was within 4 weeks prior to EOT visit. On-study brain or bone scans should be performed if clinically indicated or to confirm CR (if other lesions indicate CR and brain or bone lesions existed at baseline).

2 INTRODUCTION

2.1 Study Rationale

The current study is a postmarketing requirement designed to continue to evaluate the safety and efficacy of pembrolizumab in adult and pediatric participants with previously untreated advanced Merkel cell carcinoma (MCC).

2.2 Background

Pembrolizumab is a potent humanized immunoglobulin G4 (IgG4) monoclonal antibody (mAb) with high specificity of binding to the programmed cell death 1 (PD-1) receptor, thus inhibiting its interaction with programmed cell death ligand 1 (PD-L1) and programmed cell death ligand 2 (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 advanced malignancies.

KEYTRUDA® (pembrolizumab) is indicated for the treatment of patients across a number of indications. For more details on specific indications refer to the Investigator's Brochure (IB).

2.2.1 Pharmaceutical and Therapeutic Background

2.2.1.1 Pembrolizumab

The importance of intact immune surveillance function in controlling outgrowth of neoplastic transformations has been known for decades [Disis, M. L. 2010]. Accumulating evidence shows a correlation between tumor-infiltrating lymphocytes in cancer tissue and favorable prognosis in various malignancies. In particular, the presence of CD8+ T-cells and the ratio of CD8+ effector T-cells/FoxP3+ regulatory T-cells (T-regs) correlates with improved prognosis and long-term survival in solid malignancies, such as ovarian, colorectal, and pancreatic cancer; hepatocellular carcinoma; malignant melanoma; and renal cell carcinoma. Tumor-infiltrating lymphocytes can be expanded ex vivo and reinfused, inducing durable objective tumor responses in cancers such as melanoma [Dudley, M. E., et al 2005] [Hunder, N. N., et al 2008].

The PD-1 receptor-ligand interaction is a major pathway hijacked by tumors to suppress immune control. The normal function of PD-1, expressed on the cell surface of activated T-cells under healthy conditions, is to down-modulate unwanted or excessive immune responses, including autoimmune reactions. PD-1 (encoded by the gene *Pdcd1*) is an immunoglobulin (Ig) superfamily member related to cluster of differentiation 28 (CD28) and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) that has been shown to negatively regulate antigen receptor signaling upon engagement of its ligands (PD-L1 and/or PD-L2) [Greenwald, R. J., et al 2005] [Okazaki, T., et al 2001].

The structure of murine PD-1 has been resolved [Zhang, X., et al 2004]. PD-1 and its family members are type I transmembrane glycoproteins containing an Ig-variable–type (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 MCC.

2.2.1.2 Merkel Cell Carcinoma: Epidemiology and Current Therapeutic Options

Merkel cell carcinoma (MCC) is a rare, aggressive skin cancer causally associated with exposure to ultraviolet light and/or Merkel cell polyoma virus (MCPyV) [Nghiem, P., et al 2017] [Iyer, J. G., et al 2014] [Hodgson, N. C. 2005]. Incidence rates of MCC have risen worldwide, including Australia, China, France, Germany, Sweden, and the United States (US). During 2000-2013, the number of MCC reported cases in the US increased 95%. In 2013, the US incidence rate was 0.5 to 0.7 cases/100,000 person-years, corresponding to 2488 diagnoses per year. This number is expected to increase to >3000 diagnoses per year by 2025 [Paulson, K. G., et al 2018]. This increasing incidence is partly due to improved detection methods [Moll, I. 1992] but may also be due to the higher prevalence of known risk factors for MCC, including chronic T-cell immune suppression [Penn, I.First, M. R. 1999] [Engels, E. A., et al 2002] and extensive exposure to ultraviolet light [Heath, M., et al 2008].

Merkel cell carcinoma is most frequently diagnosed in people older than 50 years of age (median age from 54 to 78.5 years across publications) and is extremely rare in the pediatric population. It occurs 8 times more commonly in whites than blacks and is more frequent in men than in women [Nghiem, P., et al 2017] [Iyer, J. G., et al 2014] [Hodgson, N. C. 2005] [Paulson, K. G., et al 2018]. Head and neck, limbs and extremities are common primary tumor sites, and liver, skin, lymph nodes and lung are common sites of metastases [Nghiem, P., et al 2017]. Merkel cell carcinoma has a propensity for locoregional recurrence and early microscopic spread to nodes and distant sites, making it challenging to control with local therapy alone [National Comprehensive Cancer Network 2018]. Approximately 19% to 24% of patients present with regional nodal metastasis (Stage III disease) and 5% of patients with distant metastasis (Stage IV disease) at diagnosis [Ramahi, E., et al 2013] [Becker, J. C. 2010].

Approximately 48% of the patients with local or regional disease ultimately develop recurrent disease. Studies have shown that among patients who experienced recurrence, the median time between diagnosis of the primary tumor and recurrence is 9 months [Allen, P. J., et al 2005] [Santamaria-Barria, J. A. 2013]. When MCC becomes metastatic or develops an unresectable recurrence, the prognosis is poor and the intention of systemic therapy is palliative.

Recommended treatment options for advanced MCC are based on treatments for small cell lung carcinoma due to the similar neuroendocrine properties [National Comprehensive Cancer Network 2018] [Lebbe, C., et al 2015]. In patients with advanced unresectable or metastatic MCC, systemic cytotoxic chemotherapy has been the mainstay of therapy before the development of anti-PD-1 (or anti-PD-L1) agents and remains the benchmark against which new therapies such as pembrolizumab are to be considered. Frequently used regimens include a platinum agent ± etoposide phosphate, cyclophosphamide, doxorubicin (or epirubicin), and vincristine (CAV), and topotecan [National Comprehensive Cancer Network 2018] [Lebbe, C., et al 2015]. However, there are no randomized controlled studies that have evaluated the efficacy of one regimen over another [National Comprehensive Cancer Network 2018] [Tai, P. T., et al 2000]. Retrospective studies assessing patients with distant metastases have shown objective responses in approximately 52% to 61% of the patients in the first-line and in 23% of the patients in the second-line setting [Iyer, J. G., et al 2014] [Tai, P. T., et al 2000] [Satpute, S. R. 2014] [Voog, E., et al 1999] [Sharma, D., et al 1991]. Irrespective of the line of therapy, responses to chemotherapy are not durable and only last up to a median of 6 months [Iyer, J. G., et al 2014] [Tai, P. T., et al 2000] [Satpute, S. R. 2014]. Median progression-free survival (PFS) with chemotherapy has been reported to be short regardless of the line of therapy; 3.1 months in the first-line setting and 2 months in the second-line setting, and median overall survival (OS) ranged from 9 to 9.5 months [Iyer, J. G., et al 2014] [Satpute, S. R. 2014]. There are no specific recommendations for the management of pediatric MCC patients [National Comprehensive Cancer Network 2018]. Based on these data, for adult and pediatric patients with advanced unresectable or metastatic MCC, standard of care chemotherapy agents has limited clinical benefit and there is a considerable need for effective therapies in this disease with a poor prognosis.

Agents targeting the PD-1 pathway, including pembrolizumab, avelumab (Bavencio™), and nivolumab (Opdivo™), may address this unmet need. The National Comprehensive Cancer Network (NCCN) guidelines previously recommended only chemotherapeutic treatments such as cisplatin/carboplatin with or without etoposide; topotecan or CAV [National Comprehensive Cancer Network 2016] or participation in clinical studies for patients with metastatic MCC. Use of immunotherapy such as pembrolizumab was added for the first time to the NCCN Version 1.2017 dated 03-OCT-2016 [National Comprehensive Cancer Network (NCCN) 2017], based on published data from Study P017/CITN-09/KEYNOTE-017 [Nghiem, P. T., et al 2016] demonstrating both a high response rate and durability of responses with pembrolizumab, as described in Section 2.2.1.3. On 23-MAR-2017, the Food and Drug Administration (FDA) granted accelerated approval to avelumab for the treatment of adult and pediatric patients 12 years and older with metastatic MCC, including those who have not received prior chemotherapy. The approval of avelumab was based on a single-arm study and a total of 88 patients with previously treated MCC. The objective response rate (ORR) was 33% by central review [Center for Drug Evaluation and Research 2016]. With a median follow-up of 16.4 months, median time to response was 6.1 weeks and median duration of response (DOR) was not reached [Kaufman, H. L., et al 2017]. First-line data with avelumab has recently shown a confirmed objective response rate of 62.1% (95% CI: 42, 79) in 29 patients with advanced MCC who have at least 3 months of follow-up [D'Angelo, S. P., et al 2018]. Data presented with nivolumab, with a primary endpoint of

ORR, confirms the observations that anti-PD-1/L1 agents produce a high rate of response in patients with MCC [Topalian, S. L., et al 2017].

2.2.1.3 Ongoing Clinical Studies in the Merkel Cell Carcinoma Indication

Study P017/CITN-09/KEYNOTE-017 is an ongoing multicenter, single-arm study of pembrolizumab in patients with advanced unresectable or metastatic MCC who have not been previously treated with systemic cytotoxic therapy for their advanced disease. Participants are administered a dose of pembrolizumab at 2 mg/kg Q3W. Participants continue to receive up to 2 years of study intervention unless they experience disease progression, unacceptable adverse events (AEs), intercurrent illness that prevents further administration of study intervention, investigator's decision to withdraw the participant, participant withdrawal of consent, or administrative reasons requiring cessation of study intervention. Participants who achieve a complete response (CR) are allowed to discontinue treatment after 6 months of therapy provided the patient has received at least 2 cycles of pembrolizumab past the confirmation of CR.

The primary endpoint of ORR in Study P017/CITN-09/KEYNOTE-017 is measured according to Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 by investigator assessment. The secondary endpoints are PFS, DOR, and OS. The protocol was initially designed to enroll approximately 26 participants. The protocol was subsequently amended in January 2016 to enroll an additional 24 participants for a total of 50 participants. Preliminary results based on investigator assessment have been described in a publication [Nghiem, P. T., et al 2016] and were the basis for the 2017 NCCN guidelines incorporating the use of pembrolizumab in patients with advanced MCC [National Comprehensive Cancer Network (NCCN) 2017].

Results of Study P017/CITN-09/KEYNOTE-017 based on a data cutoff of 06-FEB-2018 are summarized below. Among all 50 participants, the majority of participants were ≥65 years, and 34 participants (68%) were male. The majority of participants (86%) had Stage IV MCC at study entry. A total of 84% (42 of 50) and 70% of participants (35 of 50) had received previous surgery or radiation therapy as local or locoregional treatment for their disease stage at presentation, respectively. Fourteen percent of participants (7 of 50) received prior drug therapy for their local or locoregional disease. According to blinded independent central review (BICR), 28 participants had a confirmed response (CR = 12, partial response [PR] = 16), representing an ORR by BICR of 56% (95% CI: 41, 70). Five participants (10%) had a best overall response (BOR) of stable disease (SD) and 16 participants (32%) had progressive disease (PD). The median time to response was 2.8 months and median DOR had not been reached at the time of data cutoff. Among patients with a confirmed response by BICR (n=28), the minimum duration of follow-up from first treatment to death or data cutoff is approximately 8.6 months, and the median duration of follow-up is 24.2 months. Of 28 responses, 26 occurred by approximately 3 months on treatment (first on-study scan), and 20 responses remain ongoing at the time of the data cutoff. Progression-free survival was defined as the time from first treatment to the first documented evidence of PD per RECIST 1.1 or death due to any cause, whichever occurred first. Median PFS for all participants was 16.8 months at the time of the analysis, and Kaplan-Meier estimates of PFS rates at 12, 16, 18, and 24 months were 52%, 52%, 48%, and 48%, respectively. Overall

survival was defined as the time from first treatment to death due to any cause. Median OS was not reached at the time of the data cutoff. Kaplan-Meier estimates of OS rates at 12, 18, and 24 months were 72%, 69%, and 69%, respectively. The safety of pembrolizumab in patients with MCC is generally consistent with the established safety profile of pembrolizumab.

The current protocol is intended as a confirmatory study for P017/CITN-09/KEYNOTE-017.

2.2.2 Preclinical and Clinical Studies

Refer to the IB for preclinical and clinical study data for pembrolizumab.

2.3 Benefit/Risk Assessment

As discussed in Section 2.2.1.2, there is an unmet need for effective treatments for advanced unresectable or metastatic MCC, which currently has a poor prognosis. Beneficial effects of several agents targeting the PD-1 pathway have been observed in patients with metastatic MCC, and use of immunotherapy for advanced MCC was recently added to the NCCN guidelines [National Comprehensive Cancer Network (NCCN) 2017] [National Comprehensive Cancer Network 2018]. A significantly positive benefit/risk ratio was reported for pembrolizumab in P017/CITN-09/KEYNOTE-017, a single-arm monotherapy study in participants with advanced unresectable or metastatic MCC who have not been previously treated with systemic cytotoxic therapy for their advanced disease [Nghiem, P. T., et al 2016]. The existing data suggest that PD-1 blockade is an effective therapeutic strategy and the current protocol is intended as a confirmatory study for P017/CITN-09/KEYNOTE-017.

Based on pembrolizumab data from other indications and from data in MCC patients treated with pembrolizumab as well as with other agents in the class, a favorable benefit/risk profile is anticipated. No unexpected risks have been reported in MCC with other immune checkpoint inhibitors.

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

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

3 HYPOTHESES, OBJECTIVES, AND ENDPOINTS

There are no hypotheses for this study.

In participants at least 12 years of age with advanced Merkel cell carcinoma (MCC):

Objectives	Endpoints
Primary	
• Objective: To assess the objective response rate (ORR), as assessed by blinded independent central review (BICR) per Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST 1.1) modified to follow a maximum of 10 target lesions and a maximum of 5 target lesions per organ, following administration of pembrolizumab	• Objective response (OR): Complete response (CR) or partial response (PR)
Secondary	
• Objective: To assess duration of response (DOR), as assessed by BICR per RECIST 1.1 modified to follow a maximum of 10 target lesions and a maximum of 5 target lesions per organ, following administration of pembrolizumab	• DOR: For participants who demonstrate confirmed CR or PR, the time from first documented evidence of CR or PR until disease progression or death from any cause, whichever occurs first
• Objective: To assess the progression-free survival (PFS), as assessed by BICR per RECIST 1.1 modified to follow a maximum of 10 target lesions and a maximum of 5 target lesions per organ, following administration of pembrolizumab	• PFS: The time from the first day of study treatment to the first documented disease progression per RECIST 1.1 by BICR or death due to any cause, whichever occurs first
• Objective: To assess overall survival (OS) following administration of pembrolizumab	• OS: The time from the first day of study treatment to death due to any cause
• Objective: To assess safety and tolerability of treatment with pembrolizumab	• Adverse events (AEs) • Study intervention discontinuation due to AEs

Objectives	Endpoints
Tertiary/Exploratory	
• To assess ORR, DOR, and PFS, as assessed by the investigator using modified RECIST 1.1 for immune-based therapeutics (iRECIST), following administration of pembrolizumab	• PFS using iRECIST • DOR using iRECIST • OR using iRECIST

4 STUDY DESIGN

4.1 Overall Design

This is a single-arm, open-label, multicenter, efficacy and safety study of pembrolizumab in adult and pediatric patients with previously untreated advanced MCC.

Approximately 50 participants will be enrolled into the study.

Study intervention administration will begin on Day 1 of each 3-week dosing cycle. Study intervention should begin on the day of allocation or as close as possible to the date on which the participant is allocated/assigned.

Participants will have baseline imaging performed at Screening and the first on-study imaging will be done at Week 12 (± 7 days) after C1D1. Subsequently, imaging will be performed Q12W (± 7 days) or sooner if clinically indicated until Week 54 (±7 days) of study intervention, independent of any treatment delays, Q24W thereafter or sooner if clinically indicated or more frequently if required by local standard of care. Pembrolizumab administration will continue until confirmed PD, unacceptable AE(s), pregnancy, intercurrent illness that prevents further administration of treatment, investigator's decision to discontinue the participant, administrative reasons requiring cessation of treatment, or until the participant has received 35 administrations of pembrolizumab (approximately 2 years). Participants who attain an investigator-determined confirmed CR may consider stopping study intervention after receiving at least 8 study intervention administrations in total and at least 2 additional administrations of study intervention beyond the date when the initial CR was declared.

Participants will be permitted to continue study intervention beyond RECIST 1.1-defined PD as long as the treating investigator considers that the participant may experience clinical benefit with continued treatment, and the participant is tolerating study intervention as per iRECIST. Treatment beyond disease progression per iRECIST may be permitted upon Sponsor consultation and approval.

The primary endpoint of ORR (the proportion of participants with OR) will be assessed by BICR per RECIST 1.1 criteria. Safety and tolerability will be assessed by clinical review of all relevant parameters including AEs, laboratory tests, vital signs, and electrocardiogram

(ECG) measurements, as appropriate. Adverse events will be monitored throughout the study and graded in severity according to the guidelines outlined in the NCI Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0.

After the end of treatment, each participant will have a 30-day follow-up safety assessment for AE monitoring (refer to Section 8.4.1 for time periods for reporting of serious adverse events [SAEs] and pregnancy). Participants who discontinue treatment for reasons other than PD will have post-treatment follow-up imaging for disease status until PD, the start of a new anticancer treatment, withdrawal of consent/assent, pregnancy, death, or loss to follow-up. All participants will be contacted approximately every 12 weeks, or more often as needed, for OS until death, withdrawal of consent/assent, or the end of the study, whichever comes first.

No interim analyses will be performed in this study. Further details on the Statistical Analysis Plan are provided in Section 9.

NOTE: Country-specific protocol operational items are described in Appendix 7.

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

4.2 Scientific Rationale for Study Design

If the safety profile is acceptable and pembrolizumab shows robust ORR and durable responses per RECIST 1.1 by BICR, this study will support the postmarketing requirement for the accelerated approval of pembrolizumab in patients with advanced MCC.

This Phase 3 study is designed to evaluate the efficacy and safety of pembrolizumab in participants with advanced MCC. Treatment will be open-label.

There are no randomized controlled studies in MCC that have evaluated the efficacy of 1 chemotherapeutic regimen over another [National Comprehensive Cancer Network 2018] [Tai, P. T., et al 2000] or of chemotherapy over immunotherapy [D'Angelo, S. P., et al 2018] [Nghiem, P. T., et al 2016]. The NCCN panel recognized MCC as a rare disease that precludes robust randomized studies.

4.2.1 Rationale for Endpoints

4.2.1.1 Efficacy Endpoints

This study will use ORR, defined as the proportion of participants who have best response as CR or PR. Responses are based on RECIST 1.1 criteria as assessed by blinded independent central review (BICR) as the primary endpoint. Objective response rate (ORR) is an acceptable measure of clinical benefit for a late stage study that demonstrates superiority of a new antineoplastic therapy, especially if the magnitude of the effect is large and the therapy has an acceptable risk/benefit profile. The use of BICR and RECIST 1.1 to assess ORR is

typically considered acceptable by regulatory authorities. Images will be submitted to an imaging CRO (iCRO) and read by independent central review blinded to treatment assignment to minimize bias in the response assessments.

Secondary efficacy endpoints include DOR, PFS, and OS.

Duration of response (DOR) as assessed by BICR per RECIST 1.1 criteria is a commonly accepted endpoint by both regulatory authorities and the oncology community to assess durability of responses to oncology treatments.

In this study, PFS is to be assessed by BICR per RECIST 1.1 criteria. The use of BICR and RECIST 1.1 to assess PFS is typically considered acceptable by regulatory authorities. Images will be submitted to an iCRO and read by independent central review blinded to treatment assignment to minimize bias in the response assessments. In addition, the final determination of radiologic progression will be based on the central assessment of progression, rather than a local site investigator/radiology assessment.

Overall survival (OS) is the gold standard for a “hard endpoint” in clinical studies in the area of oncology.

4.2.1.1.1 RECIST 1.1

RECIST 1.1 will be used by the BICR when assessing images for efficacy measures and by the local site when determining eligibility Section 8.2.1.4. Although traditional RECIST 1.1 references a maximum of 5 target lesions in total and 2 per organ, this protocol has implemented a modification to RECIST 1.1 to allow a maximum of 10 target lesions in total and 5 per organ.

4.2.1.1.2 RECIST 1.1 for Immune-based Therapeutics (iRECIST)

RECIST 1.1 will be adapted to account for the unique tumor response characteristics seen following treatment with pembrolizumab Section 8.2.1.5. 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 patients treated with pembrolizumab may manifest a clinical response after an initial increase in tumor burden or even the appearance of new lesions. Thus, standard RECIST 1.1 may not provide an accurate response assessment of immunotherapeutic agents such as pembrolizumab. Based on an analysis of participants with melanoma enrolled in KEYNOTE-001 (KN001), 7% of evaluable participants experienced delayed or early tumor pseudo-progression. Of note, participants who had progressive disease (PD) by RECIST 1.1 but not by the immune-related response criteria [Wolchok, J. D., et al 2009] had longer overall survival than participants with PD by both criteria [Hodi, F. S., et al 2014]. 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 responses in immunotherapy and enables treatment beyond initial radiographic progression, if the participant is clinically stable.

Modified RECIST 1.1 for immune-based therapeutics (iRECIST) assessment has been developed and published by the RECIST Working Group, with input from leading experts from industry and academia, along with participation from the US Food and Drug Administration and the European Medicines Agency [Seymour, L., et al 2017]. The unidimensional measurement of target lesions, qualitative assessment of nontarget lesions, and response categories are identical to RECIST 1.1, until progression is seen by RECIST 1.1. However, if a participant is clinically stable, additional imaging may be performed to confirm radiographic progression. iRECIST will be used by investigators to assess tumor response and progression and make treatment decisions when applicable: as well as for exploratory efficacy analyses when specified.

4.2.1.2 Safety Endpoints

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

4.2.1.3 Pharmacokinetic Endpoints

No pharmacokinetic endpoints are planned for this study.

4.2.1.4 Pharmacodynamic Endpoints

No pharmacodynamic endpoints are planned for this study.

4.2.1.5 Future Biomedical Research

The Sponsor will conduct FBR on DNA specimens for which consent was provided during this clinical study.

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

4.2.2 Rationale for the Use of Comparator/Placebo

Not applicable.

4.3 Justification for Dose

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

- Clinical data from 8 randomized studies in melanoma and NSCLC indications demonstrating flat dose- and exposure-efficacy relationships from 2 mg/kg Q3W to 10 mg/kg Q2W representing an approximate 5- to 7.5-fold exposure range (refer to IB, Section 5.2.2)

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

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

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

To date, pembrolizumab (2 mg/kg Q3W) has been evaluated in 85 pediatric participants (aged 1 to 18 years) with advanced melanoma, PD-L1 positive advanced, relapsed, or refractory solid tumors, or lymphoma. The exposures in pediatric participants following the 2 mg/kg Q3W regimen were found to be similar to that observed in adult participants. Pediatric data has also been incorporated in an integrated population PK analysis, which confirmed that a pembrolizumab dose of 2 mg/kg Q3W (up to a maximum of 200 mg Q3W) in pediatric participants renders exposures similar to adults. Based on these results, the pediatric dose for evaluation in this study is 2 mg/kg Q3W (up to a maximum of 200 mg Q3W).

4.3.1 Maximum Dose/Exposure for This Study

The maximum dose/exposure of pembrolizumab allowed in this study is 200 mg Q3W in adult participants (or 2 mg/kg [up to 200 mg] Q3W in pediatric participants) for 35 administrations (approximately 2 years).

4.4 Beginning and End of Study Definition

The overall study begins when the first participant (or their legally acceptable representative) provides documented informed consent/assent. The overall study ends when the last participant completes the last study-related contact, withdraws consent/assent, 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.

4.4.1 Clinical Criteria for Early Study Termination

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

5 STUDY POPULATION

Participants with advanced MCC who are at least 12 years old will be enrolled in this study.

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

5.1 Inclusion Criteria

To be eligible for inclusion in this study, the participant must:

1. Have histologically confirmed diagnosis of locoregional MCC that has recurred following standard locoregional therapy with surgery and/or radiation therapy and is not amenable to local therapy or metastatic MCC (Stage IV) as per American Joint Committee on Cancer (AJCC) 8th edition guidelines.

2. Have been untreated for advanced or metastatic disease except as follows:

    a. Prior intratumoral therapy will be permitted.

    b. Prior adjuvant or neoadjuvant therapy containing systemic chemotherapy will be permitted if treatment concluded at least 3 months prior to C1D1.

    c. Prior adjuvant or neoadjuvant therapy containing anti-PD-1/L1 or anti-CTLA-4 therapy will not be permitted.

3. Have at least 1 measurable lesion by computed tomography (CT) or magnetic resonance imaging (MRI) per RECIST 1.1 criteria as determined by the local site investigator/radiology assessment. Measurable disease will be verified by BICR prior to treatment allocation. Lesions situated in a previously irradiated area are considered measurable if progression has been demonstrated in such lesions.
   Note: Cutaneous lesions and other superficial lesions are not considered measurable lesions for the purposes of this protocol but may be considered as non-target lesions.

4. Toxic effect(s) of the most recent prior therapy have resolved to Grade 1 or less (except alopecia). If participant received major surgery or radiation therapy of >30 Gy, they must have recovered from the toxicity and/or complications from the intervention.

Demographics

5. Be male or female and at least 12 years of age, at the time of signing the informed consent/assent.

Male Participants

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

Female Participants

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

- A female participant is eligible to participate if she is not pregnant or breastfeeding, and at least one of the following conditions applies:
  - Is not a woman of childbearing potential (WOCBP)
  - OR
  - Is a WOCBP and using a contraceptive method that is highly effective (with a failure rate of <1% per year), with low user dependency, or be abstinent from heterosexual intercourse as their preferred and usual lifestyle (abstinent on a long term and persistent basis), as described in Appendix 5 during the intervention period and for at least 120 days (corresponding to the time needed to eliminate any study intervention) after the last dose of study intervention. The investigator should evaluate the potential for contraceptive method failure (ie, noncompliance, recently initiated) in relationship to the first dose of study intervention.
  - A WOCBP must have a negative highly sensitive pregnancy test (urine or serum as required by local regulations) within 72 hours before the first dose of study intervention.
  - If a urine test cannot be confirmed as negative (eg, an ambiguous result), a serum pregnancy test is required. In such cases, the participant must be excluded from participation if the serum pregnancy result is positive.
- Additional requirements for pregnancy testing during and after study intervention are located in Appendix 5.
- The investigator is responsible for review of medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a woman with an early undetected pregnancy.

Informed Consent

8. Participant (or legally acceptable representative if applicable) has provided documented informed consent/assent for the study and agrees to OS data collection until the study endpoints are reached. The participant may also provide consent/assent for future biomedical research; however, the participant may participate in the main study without participating in future biomedical research.

Additional Categories

9. Have an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 or Lansky Play-Performance Scale (LPS) ≥50 for pediatric participants up to and including 16 years of age (Appendix 9).

10. Have adequate organ function as defined in the following table (Table 2). Specimens must be collected within 3 days prior to C1D1.

Table 2 Adequate Organ Function Laboratory Values

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

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

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

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

[c] Participants with ALP values >3 times the ULN and known to have bone metastases can be included.

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

5.2 Exclusion Criteria

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

Medical Conditions

1. Has a known additional malignancy that is progressing or has required active treatment within the past 2 years.

   Note: Participants with basal cell carcinoma of the skin, squamous cell carcinoma of the skin, non-ulcerated primary melanoma <1 mm in depth with no nodal involvement, or carcinoma in situ (eg, breast carcinoma, cervical cancer in situ) that have undergone potentially curative therapy are not excluded.

2. 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 14 days prior to first dose of study intervention.

3. Has a diagnosis of immunodeficiency or is receiving chronic systemic steroid therapy (in dosing exceeding 10 mg daily of prednisone equivalent) or any other form of immunosuppressive therapy within 7 days prior to C1D1.

4. Has severe hypersensitivity (≥Grade 3) to pembrolizumab and/or any of its excipients.

5. Has an active autoimmune disease that has required systemic treatment in past 2 years (ie, with use of disease-modifying agents, corticosteroids or immunosuppressive drugs). Replacement therapy (eg, thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency) is not considered a form of systemic treatment and is allowed.

6. Has a history of (non-infectious) pneumonitis/interstitial lung disease that required steroids or has current pneumonitis/interstitial lung disease.

7. Has an active infection requiring systemic therapy.

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

9. 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 and Hepatitis C is required unless mandated by local health authority.

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

11. Has clinically significant cardiac disease within 6 months of C1D1, including New York Heart Association Class III or IV congestive heart failure, unstable angina, myocardial infarction, cerebral vascular accident, or cardiac arrhythmia associated with hemodynamic instability.

    Note: Medically controlled arrhythmia is permitted.

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

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

Prior/Concomitant Therapy

14. Has not received standard locoregional therapy with surgery and/or radiation therapy for the treatment of local or locoregional disease. Note: This exclusion criterion does not apply to participants who are diagnosed with unresectable or metastatic MCC.

15. 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).

16. Has received prior systemic anticancer therapy including investigational agents within 12 weeks prior to C1D1.

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

    Note: If participant received major surgery, they must have recovered adequately from the toxicity and/or complications from the intervention prior to C1D1.

17. Has received radiotherapy within 2 weeks prior to start of study intervention. Participants must have recovered from all radiation-related toxicities and not require corticosteroids.

18. Has received a live vaccine within 30 days prior to C1D1. 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

19. Is currently participating in or has participated in a study of an investigational agent or has used an investigational device within 4 weeks prior to C1D1.

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

Other Exclusions

20. Removed

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

Refer to Appendix 7 for country-specific requirements.

5.3 Lifestyle Considerations

No restrictions are required.

5.3.1 Meals and Dietary Restrictions

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

5.3.2 Pregnancy

If a participant inadvertently becomes pregnant while on treatment with pembrolizumab, the participant will be immediately discontinued from study intervention. The site will contact the participant at least monthly and document the participant's status until the pregnancy has been completed or terminated. The outcome of the pregnancy will be reported to the Sponsor without delay and within 24 hours if the outcome is a serious adverse experience (eg, death, abortion, congenital anomaly, or other disabling or life-threatening complication to the mother or newborn). The study Investigator will make every effort to obtain permission to follow the outcome of the pregnancy and report the condition of the fetus or newborn to the Sponsor. If a male participant impregnates his female partner, the study personnel at the site must be informed immediately and the pregnancy must be reported to the Sponsor and followed as described in Section 8.4.5.

5.4 Screen Failures

Screen failures are defined as participants who consent/assent to participate in the clinical study, but are not subsequently entered in the study. 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 AEs or SAEs meeting reporting requirements as outlined in the data entry guidelines.

5.5 Participant Replacement Strategy

A participant who discontinues from study intervention or withdraws consent/assent will not be replaced.

6 STUDY INTERVENTION

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

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

6.1 Study Intervention(s) Administered

The study intervention to be used in this study is outlined in Table 3.

Table 3 Study Interventions

Arm Name	Arm Type	Intervention Name	Type	Dose Formulation	Unit Dose Strength	Dosage Level(s)	Route of Administration	Regimen	Use	IMP/ NIMP	Sourcing
Pembrolizumab	Experimental	Pembrolizumab (MK-3475)	Biological/ Vaccine	Solution for Infusion	25 mg/mL vial	200 mg (adult participants) or 2 mg/kg (up to 200 mg - pediatric participants) on Day 1 of each cycle	IV Infusion	Q3W for up to 35 administrations (approximately 2 years)	Experimental	IMP	Provided centrally by the Sponsor
IMP=investigational medicinal product; IV=intravenous; NIMP=noninvestigational medicinal product; Q3W=every 3 weeks Definition Investigational Medicinal Product (IMP) and Non-Investigational Medicinal Product (NIMP) is based on guidance issued by the European Commission. Regional and/or Country differences of the definition of IMP/NIMP may exist. In these circumstances, local legislation is followed.											

All study interventions will be administered on an outpatient basis.

All products indicated in Table 3 will be provided centrally by the Sponsor or locally by the study site, subsidiary or designee, depending on local country operational or regulatory requirements .

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

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

6.1.1 Medical Devices

Not applicable.

6.2 Preparation/Handling/Storage/Accountability

6.2.1 Dose Preparation

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

6.2.2 Handling, Storage, and Accountability

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

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

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

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

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

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

6.3 Measures to Minimize Bias: Randomization and Blinding

6.3.1 Intervention Assignment

Intervention allocation will occur centrally using an interactive response technology (IRT) system. There is one study intervention arm. All participants will be assigned to pembrolizumab.

6.3.2 Stratification

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

6.3.3 Blinding

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

6.4 Study Intervention Compliance

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

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

Refer to Section 6.6.1 for dose modification and toxicity management for irAEs associated with pembrolizumab and for other allowed dose interruption of pembrolizumab.

6.5 Concomitant Therapy

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

Participants are prohibited from receiving the following therapies during the Screening and Treatment Phase of this study:

- Antineoplastic systemic chemotherapy or biological therapy

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

- Immunotherapy not specified in this protocol

- Investigational agents other than pembrolizumab

- Radiation therapy

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

- Palliative surgery of a target lesion.

  Note: Palliative surgery to treat a non-target symptomatic solitary lesion or to the brain is allowed at the investigator's discretion

If the investigator determines that a participant requires any of the aforementioned treatments for any reason, study intervention must be discontinued.

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 eCRF including all prescription, OTC products, herbal supplements, and IV medications, and fluids. If changes occur during the study period, documentation of drug dosage, frequency, route, and date should also be included on the eCRF.

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

All anticancer therapy will be recorded until time of death or termination of Survival Follow-up. If a clinic visit is not feasible, follow-up information may be obtained via telephone or e-mail.

Refer to Appendix 7 for country-specific requirements.

6.5.1 Rescue Medications and Supportive Care

Participants should receive appropriate supportive care measures as deemed necessary by the treating investigator. Suggested supportive care measures for the management of AEs with potential immunologic etiology are outlined along with the dose modification guidelines in

Section 6.6, Table 4. 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 Table 4 in Section 6.6.1 for guidelines regarding dose modification and supportive care.

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

6.6 Dose Modification (Escalation/Titration/Other)

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

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

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

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

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

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

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

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

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

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

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

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

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

Dose Modification and Toxicity Management of Infusion Reactions Related to Pembrolizumab

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

Table 5 Pembrolizumab Infusion Reaction Dose Modification and Treatment Guidelines

NCI CTCAE Grade	Treatment	Premedication at Subsequent Dosing
Grade 1 Mild reaction; infusion interruption not indicated; intervention not indicated	Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator	None
Grade 2 Requires therapy or infusion interruption but responds promptly to symptomatic treatment (eg, antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for ≤24 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 intervention.	Participant may be premedicated 1.5 h (±30 minutes) prior to infusion of study intervention 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 intervention.	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 participant's study record.

6.7 Intervention After the End of the Study

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

6.8 Clinical Supplies Disclosure

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

7 DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT WITHDRAWAL

7.1 Discontinuation of Study Intervention

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

As certain data on clinical events beyond study intervention discontinuation may be important to the study, they must be collected through the participant's last scheduled follow-up, even if the participant has discontinued study intervention. Therefore, all participants who discontinue study intervention prior to completion of the protocol-specified treatment period will still continue to participate in the study as specified in Section 1.3 (Schedule of Activities [SoA]) and Section 8.12.3.

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

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

- The participant or participant's legally acceptable representative requests to discontinue study intervention.
- Unacceptable adverse events as described in Appendix 3.
- After prolonged study intervention interruption that prohibits restarting study intervention if agreed upon with the Sponsor.
- The participant has a medical condition or personal circumstance which, in the opinion of the investigator and/or Sponsor, placed the participant at unnecessary risk from continued administration of study intervention.
- The participant has a confirmed positive serum pregnancy test.
- Prohibited concomitant medication requiring withdrawal (refer to Section 6.5).
- Recurrent Grade 3 colitis.
- Radiographic disease progression outlined in Section 8.2.1.5 (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.

- Recurrent Grade 2 pneumonitis.

- Discontinuation of treatment may be considered for participants who have attained a confirmed complete response (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.

- Completion of 35 treatments (approximately 2 years) with pembrolizumab.

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

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

7.2 Participant Withdrawal From the Study

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

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

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

7.3 Lost to Follow-up

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

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

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

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

8 STUDY ASSESSMENTS AND PROCEDURES

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

The maximum amount of blood collected from each participant in any one visit will not exceed 18.5 mL (refer to the Procedures Manual).

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

8.1 Administrative and General Procedures

8.1.1 Informed Consent/Assent

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

8.1.1.1 General Informed Consent/Assent

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

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

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

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

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

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

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

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

8.1.2 Inclusion/Exclusion Criteria

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

8.1.3 Participant Identification Card

All participants will be given a participant identification card identifying them as participants in a research study. The card will contain study site contact information (including direct telephone numbers) to be used in the event of an emergency. The investigator or qualified

designee will provide the participant with a participant identification card immediately after the participant provides documented informed consent/assent. At the time of intervention 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 healthcare provider can obtain information about study intervention in emergency situations where the investigator is not available.

8.1.4 Medical History

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

8.1.5 Prior and Concomitant Medications Review

8.1.5.1 Prior Medications

The investigator or qualified designee will review prior medication use, including any protocol-specified washout requirement, and record prior medication taken by the participant within 28 days before starting the study. Treatment for the disease for which the participant has enrolled in this study will be recorded separately and not listed as a prior medication.

8.1.5.2 Concomitant Medications

The investigator or qualified designee will record medication, if any, taken by the participant during the study through the Safety Follow-up Visit. Concomitant medications will be recorded for 30 days after the last dose (or longer if related to an SAE or ECI). Refer to Section 6.5.

8.1.6 Assignment of Screening Number

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

8.1.7 Assignment of Treatment/Randomization Number

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

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

8.1.8 Study Intervention Administration

Administration of study medication will be witnessed by the investigator and/or study staff.

Study intervention should begin within 3 days of treatment/randomization number assignment.

8.1.8.1 Timing of Dose Administration

Pembrolizumab will be administered as a 30-minute IV infusion on Day 1 of each 21-day cycle. Sites should make every effort to target infusion timing to be as close to 30 minutes as possible. However, given the variability of infusion pumps from site to site, a window of -5 minutes and +10 minutes is permitted (ie, infusion time is 30 minutes: -5 min/+10 min).

The first dose of study intervention may be administered up to 3 days after the scheduled Day 1. After C1D1, pembrolizumab may be administered up to 3 days before or after the scheduled Day 1 of each subsequent cycle due to administrative reasons.

Refer to Section 6.1 for details on study intervention administration.

Refer to Section 6.6 for information on allowed dosing interruptions.

Refer to Section 7 for criteria for discontinuation of study intervention.

8.1.9 Discontinuation and Withdrawal

Participants who discontinue study intervention prior to completion of the treatment period should be encouraged to continue to be followed for all remaining study visits as outlined in the SoA and Section 8.12.3.

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

If discontinuation occurs ≥30 days after the last dose of study intervention, a Safety Follow-up Visit (Section 8.12.3.1) is not required. In this situation, all procedures required at the 30-day Safety Visit and End of Treatment (EOT) are performed once and entered into the EOT visit only.

8.1.9.1 Withdrawal From Future Biomedical Research

A participant’s consent for Future Biomedical Research may be withdrawn by the participant or the participant’s legally acceptable representative (as appropriate). A participant’s consent may be withdrawn at any time by contacting the principal investigator for the main study. If medical records for the main study are still available, the investigator will contact the Sponsor using the designated mailbox (clinical.specimen.management@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 study data and results. No new analyses would be generated after the request is received.

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

8.1.10 Participant Blinding/Unblinding

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

8.1.11 Calibration of Equipment

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

8.2 Efficacy Assessments

8.2.1 Tumor Imaging and Assessment of Disease

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

In addition to survival, efficacy will be assessed based on evaluation of scan changes in tumor burden over time, until the participant is discontinued from the study or goes into Survival Follow-up. The process for scan collection and transmission to the iCRO can be found in the Site Imaging Manual (SIM). Tumor scans by CT are strongly preferred. For the abdomen and pelvis, contrast-enhanced MRI may be used when CT with iodinated contrast is contraindicated, or when mandated by local practice. The same scan technique should be used in a participant throughout the study to optimize the reproducibility of the assessment of existing and new tumor burden and improve the accuracy of the response assessment based on scans.

Note: for the purposes of assessing tumor scans, the term "investigator" refers to the local investigator at the site and/or the radiological reviewer at the site or at an offsite facility.

In general, scans should include the chest, abdomen, and pelvis.

Expedited confirmation of measurable disease based on RECIST 1.1 by BICR at Screening will be used to determine participant eligibility. Confirmation by the BICR that the participant's imaging shows at least 1 lesion that is appropriate for selection as a target lesion per RECIST 1.1 is required prior to participant allocation.

All scheduled imaging for all study participants will be submitted to the iCRO. In addition, imaging that is obtained at an unscheduled time point for any reason (including suspicion of progression or other clinical reason) should also be submitted to the iCRO if it shows progression, or if it is used to support a response assessment. All imaging acquired within the protocol-specified window of time around a scheduled imaging visit can be classified as pertaining to that visit. Photographs of cutaneous lesions do not need to be submitted to the iCRO.

8.2.1.1 Initial Tumor Imaging

Initial tumor scans at Screening must be performed within 28 days prior to the date of allocation. Any scans obtained after Cycle 1 Day 1 cannot be included in the screening assessment. The site must review screening scans to confirm the participant has measurable disease per RECIST 1.1. The site study team must submit screening scans to the iCRO to confirm the participant has measurable disease per RECIST 1.1 prior to allocation. Tumor scans at Screening includes CT (preferred) or MRI of the abdomen and pelvis and CT of the chest. See the SIM for additional details.

8.2.1.2 Tumor Imaging During the Study

The first on-study scan should be performed at 12 weeks (84 days ±7 days) from the date of allocation. Subsequent tumor scans should be performed every 12 weeks (84 days ±7 days) or more frequently if clinically indicated. After 54 weeks (378 days ±7 days), participants who remain on treatment will have scans performed every 24 weeks (168 days ±7 days). Scan timing should follow calendar days and should not be adjusted for delays in cycle starts. Scans are to be performed until disease progression is identified by the investigator or notification by the Sponsor, or until the start of new anticancer treatment, withdrawal of consent, or death, whichever occurs first.

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

On-study brain or bone scans should be performed if clinically indicated or to confirm CR (if other lesions indicate CR and brain or bone lesions existed at baseline).

8.2.1.3 End-of-Treatment and Follow-up Tumor Imaging

For participants who discontinue study intervention, tumor imaging should be performed at the time of treatment discontinuation (±4 week window). If previous imaging was obtained

within 4 weeks prior to the date of discontinuation, then imaging at treatment discontinuation is not mandatory. For participants who discontinue study intervention due to confirmed disease progression, this is the final required tumor imaging if the investigator elects not to implement iRECIST.

For participants who discontinue study intervention without confirmed disease progression, every effort should be made to continue monitoring disease status by tumor imaging using the same imaging schedule used while on treatment (Q12W until Week 54 after C1D1 [±7 days], Q24W thereafter or sooner or more frequently if required by local standard of care, until disease progression per RECIST 1.1) until the start of a new anticancer treatment, disease progression, pregnancy, death, withdrawal of consent, or the end of the study, whichever occurs first.

8.2.1.4 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 study intervention). Although RECIST 1.1 references a maximum of 5 target lesions in total and 2 per organ, this protocol allows a maximum of 10 target lesions in total and 5 per organ, if clinically relevant to enable a broader sampling of tumor burden.

Figure 2 illustrates the imaging flow involving verification of PD for clinically stable participants.

8.2.1.5 iRECIST Assessment of Disease

iRECIST is based on RECIST 1.1, but adapted to account for the unique tumor response seen with immunotherapeutic drugs. iRECIST will be used by the investigator to assess tumor response and progression, and make treatment decisions. When clinically stable, participants should not be discontinued until progression is confirmed by the investigator, working with local radiology, according to the rules outlined in Appendix 8. This allowance to continue treatment despite initial radiologic PD takes into account the observation that some participants can have a transient tumor flare in the first few months after the start of immunotherapy, and then experience subsequent disease response. This data will be captured in the clinical database.

Clinical stability is defined as the following:

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

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

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

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

If a participant has confirmed radiographic progression (iCPD) as defined in Appendix 8, study intervention should be discontinued; however, if the participant is achieving a clinically meaningful benefit, an exception to continue study intervention may be considered following consultation with the Sponsor. In this case, if study intervention is continued, tumor imaging should continue to be performed following the intervals as outlined in Section 8 and submitted to the iCRO.

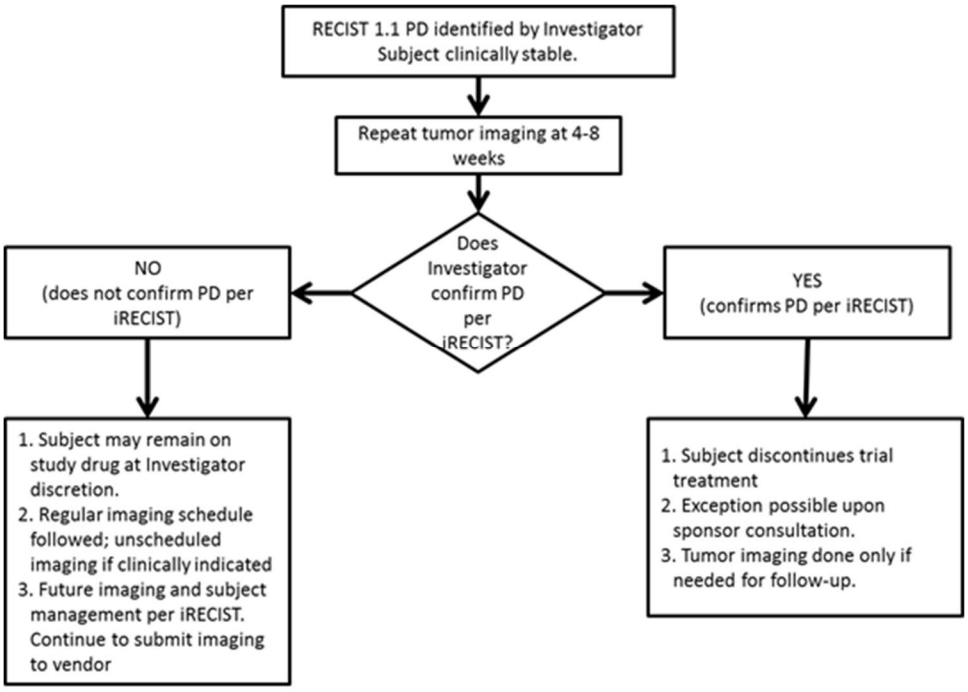
A description of the adaptations and iRECIST process is provided in Appendix 8, with additional details in the iRECIST publication [Seymour, L., et al 2017]. A summary of imaging and treatment requirements after first radiologic evidence of progression is provided in Table 6 and illustrated as a flowchart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

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

	Clinically Stable		**Clinically Unstable**	
	Imaging	**Treatment**	**Imaging**	**Treatment**
First radiologic evidence of PD by RECIST 1.1 per investigator assessment.	Repeat imaging at 4 to 8 weeks to confirm PD.	May continue study intervention at the assessment of the investigator and after the participant's consent.	Repeat imaging at 4 to 8 weeks to confirm PD per investigator's discretion only.	Discontinue treatment.
First radiologic evidence of PD by RECIST 1.1 per investigator assessment.	Repeat imaging at 4 to 8 weeks to confirm PD.	May continue study intervention at the investigator's discretion while awaiting confirmatory tumor imaging by site by iRECIST.	Repeat imaging at 4 to 8 weeks to confirm PD per investigator's discretion only.	Discontinue treatment.
Repeat tumor imaging confirms PD (iCPD) by iRECIST per investigator assessment.	No additional imaging required.	Discontinue treatment (exception is possible upon consultation with Sponsor).	No additional imaging required.	Not applicable.

	Clinically Stable		**Clinically Unstable**	
	Imaging	**Treatment**	**Imaging**	**Treatment**
Repeat tumor imaging shows iUPD by iRECIST per investigator assessment.	Repeat imaging at 4 to 8 weeks to confirm PD. May occur at next regularly scheduled imaging visit.	Continue study intervention at the investigator's discretion.	Repeat imaging at 4 to 8 weeks to confirm PD per investigator's discretion only.	Discontinue treatment.
Repeat tumor imaging shows iSD, iPR, or iCR by iRECIST per investigator assessment.	Continue regularly scheduled imaging assessments.	Continue study intervention at the investigator's discretion.	Continue regularly scheduled imaging assessments.	May restart study intervention if condition has improved and/or clinically stable per investigator's discretion. Next tumor imaging should occur according to the regular imaging schedule.
iCPD=iRECIST confirmed progressive disease; iCR=iRECIST complete response; iPR=iRECIST partial response; iRECIST=modified Response Evaluation Criteria in Solid Tumors 1.1 for immune-based therapeutics; iSD=iRECIST stable disease; iUPD=iRECIST unconfirmed progressive disease; PD=progressive disease; RECIST 1.1=Response Evaluation Criteria in Solid Tumors 1.1				

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



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

8.2.2 Patient-reported Outcomes

Not applicable.

8.3 Safety Assessments

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

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

8.3.1 Physical Examinations

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

8.3.1.1 Full Physical Examination

The investigator or medically qualified designee (consistent with local requirements) will perform a complete physical examination per institutional standards during the Screening period. Height and weight will also be measured and recorded. Clinically significant abnormal findings should be recorded as medical history. The time points for full physical examinations are described in Section 1.3 (SoA). After the first dose of study intervention, new clinically significant abnormal findings should be recorded as AEs.

In pediatric participants, height and weight will be measured at every visit. In adult participants, height will be measured at Screening only and weight will be measured at every visit.

8.3.1.2 Directed Physical Examination

For cycles that do not required a full physical examination, as defined in Section 1.3 (SoA), the investigator or medically qualified designee (consistent with local requirements) will perform a directed physical examination per institutional standard prior to the administration of the study intervention, as clinically indicated. New clinically significant abnormal findings should be recorded as AEs.

8.3.2 Vital Signs

Vital signs (body temperature [in centigrade], pulse rate [beats per minute], respiratory rate [per minute], and systolic and diastolic blood pressure [mmHg]) will be assessed by the investigator or medically qualified designee (consistent with local requirements) as specified

in Section 1.3 (SoA). Blood pressure and pulse rate will be measured after the participant has been resting for 5 minutes. All blood pressure measurements should be performed on the same arm, preferably by the same person. After the first dose of study intervention, new clinically significant abnormal findings should be recorded as AEs.

8.3.3 Electrocardiograms (ECG)

A standard 12-lead ECG will be obtained and reviewed by an investigator or medically qualified designee (consistent with local requirements) at Screening. Participants must be in the recumbent position for a period of 5 minutes prior to the ECG. Clinically significant abnormal findings should be recorded as medical history. Assessments may be repeated during the study, as clinically indicated.

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

8.3.4 Clinical Safety Laboratory Assessments

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

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

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

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

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

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

Refer to Section 1.3 (SoA) for the timing of laboratory assessments.

8.3.4.1 Laboratory Safety Evaluations (Hematology, Chemistry and Urinalysis)

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

8.3.4.2 Pregnancy Test

All women who are being considered for participation in the study, and who are not surgically sterilized or postmenopausal, must be tested for pregnancy within 72 hours prior to C1D1. If a urine test is positive or not evaluable, a serum test will be required. Participants must be excluded/discontinued from the study in the event of a positive test result. Repeated pregnancy test should be conducted according to Section 1.3 (SoA) and as required by local guidelines. Refer to Appendix 5.

8.3.5 Performance Assessments

The performance scale to be used is dependent upon age: Lansky Play-Performance Scale (LPS) for participants up to and including 16 years of age; ECOG for participants >16 years of age. The performance scale used for a given participant at baseline will be the performance scale used throughout the study.

8.3.5.1 Eastern Cooperative Oncology Group (ECOG) Performance Scale

The investigator or medically qualified designee (consistent with local requirements) will assess ECOG status (refer to Appendix 9) at the time points specified in Section 1.3 (SoA). The ECOG status must be assessed within 3 days prior to C1D1.

8.3.5.2 Lansky Play-Performance Scale (LPS)

The LPS score is a standard way of measuring the functionality of pediatric participants up to and including the age of 16 years. The LPS is rated by parents based on their child's activity over the past week. Parents fill out the assessment based on the directions on the form, and the form is re-administered over time to assess for changes in performance status. A higher score means the child is functioning better. See Appendix 9 for a description of the full scale. The LPS will be assessed as specified in Section 1.3 (SoA).

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

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

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

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

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

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

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

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

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

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

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

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

Type of Event	**Reporting Time Period: Consent to Randomization/ Allocation**	**Reporting Time Period: Randomization/ Allocation through Protocol-specified Follow-up Period**	**Reporting Time Period: After the Protocol-specified Follow-up Period**	**Time Frame to Report Event and Follow-up Information to Sponsor:**
Nonserious Adverse Event (NSAE)	Report if: - due to protocol-specified intervention - causes exclusion - participant is receiving placebo run-in or other run-in treatment	Report all	Not required	Per data entry guidelines
Serious Adverse Event (SAE) including Cancer and Overdose	Report if: - due to protocol-specified intervention - causes exclusion - participant is receiving placebo run-in or other run-in treatment	Report all	Report if: - drug/vaccine related. (Follow ongoing to outcome)	Within 24 hours of learning of event
Pregnancy/ Lactation Exposure	Report if: - due to intervention - causes exclusion	Report all	Previously reported – Follow to completion/ termination; report outcome	Within 24 hours of learning of event
Event of Clinical Interest (require regulatory reporting)	Report if: - due to intervention - causes exclusion	Report - potential drug-induced liver injury (DILI) - require regulatory reporting	Not required	Within 24 hours of learning of event
Event of Clinical Interest (do not require regulatory reporting)	Report if: - due to intervention - causes exclusion	Report - non-DILI ECIs and those not requiring regulatory reporting	Not required	Within 5 calendar days of learning of event

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

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

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

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

8.4.4 Regulatory Reporting Requirements for SAE

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

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

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

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

8.4.5 Pregnancy and Exposure During Breastfeeding

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

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

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

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

Pregnancy outcomes of ectopic pregnancy, spontaneous abortion, missed abortion, benign hydatidiform mole, blighted ovum, fetal death, intrauterine death, miscarriage, and stillbirth

must be reported as serious events (Important Medical Events). If the pregnancy continues to term, the outcome (health of infant) must also be reported.

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

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

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

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

8.4.7 Events of Clinical Interest (ECIs)

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

Events of clinical interest for this study include:

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

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

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

8.5 Treatment of Overdose

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

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

8.6 Pharmacokinetics

PK parameters will not be evaluated in this study.

8.7 Pharmacodynamics

Pharmacodynamic parameters will not be evaluated in this study.

8.8 Future Biomedical Research Sample Collection

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

- DNA for future research

8.9 Planned Genetic Analysis Sample Collection

Not applicable.

8.10 Biomarkers

Biomarkers are not evaluated in this study.

8.11 Health Economics Medical Resource Utilization and Health Economics

All-cause hospitalizations and emergency room visits must be reported in the electronic case report form (eCRF), from the time of treatment allocation through 90 days following cessation of study intervention, or 30 days following cessation of study intervention, if the participant initiates new anticancer therapy, whichever is earlier.

8.12 Visit Requirements

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

8.12.1 Screening

Documented consent/assent must be obtained prior to performing any protocol-specific procedure. Results of a test performed prior to the participant signing consent/assent 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 C1D1 except for the following:

- Laboratory tests are to be performed within 3 days prior to C1D1. Except:
  - Hepatitis and HIV testing (if mandated by the local health authority) may be done up to 28 days prior to C1D1.

- Thyroid function tests may be done up to 10 days prior to C1D1.

  Repeated laboratory evaluation to establish eligibility is not allowed unless discussed and agreed upon with the Sponsor.

- Full physical examination is to be performed within 7 days prior to C1D1.
- Evaluation of ECOG (or LPS, as appropriate) is to be performed within 3 days prior to C1D1.
- For women of reproductive potential, a urine or serum pregnancy test will be performed within 72 hours prior to C1D1. If urine pregnancy results cannot be confirmed as negative, a serum pregnancy test will be required (performed by the local study site laboratory).

Rescreening

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

8.12.2 Treatment Period

Visit requirements are outlined in Section 1.3 (SoA). Specific procedure-related details are provided in Section 8.1 through Section 8.11. Unless otherwise specified, the window for each visit is ± 3 days. Unless otherwise specified, assessments/procedures are to be performed prior to administration of study intervention.

8.12.3 Discontinued Participants Continuing to be Monitored in the Study

8.12.3.1 Safety Follow-up Visit

The mandatory Safety Follow-up Visit should be conducted approximately 30 days after the last dose of study intervention or before the initiation of a new anticancer treatment, whichever comes first. If the EOT visit occurs ≥30 days after the last dose of study intervention, a Safety Follow-up Visit is not required. In this situation, all procedures required at the 30-day Safety Visit and EOT are performed once and entered into the EOT visit only.

8.12.3.2 Follow-up Visits

Participants who discontinue study intervention for a reason other than disease progression will move into the Follow-up Phase and should be assessed Q12W until Week 54 after C1D1 (±7 days), Q24W thereafter or sooner if clinically indicated or more frequently if required by local standard of care, until disease progression per RECIST 1.1, to monitor disease status. Every effort should be made to collect information regarding disease status until the start of

new anticancer therapy, disease progression, death, end of study. Information regarding poststudy anticancer treatment will be collected if new treatment is initiated. Participants who attain an investigator-determined CR and stop study intervention with pembrolizumab will have a Safety Follow-up Visit and move to follow-up visits per Section 1.3 (SoA).

8.12.3.3 Survival Follow-up

Participants who experience confirmed disease progression and are not treated beyond confirmed disease progression or start a new anticancer therapy, will move into the Survival Follow-up Phase and should be contacted by telephone approximately every 12 weeks to assess for survival status until death, withdrawal of consent, or the end of the study, whichever occurs first.

8.12.4 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).

9 STATISTICAL ANALYSIS PLAN

This section outlines the statistical analysis strategy and procedures for the study. If, after the study has begun, changes are made to primary and/or key secondary objectives, or the statistical methods related to those objectives, 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. Post hoc exploratory analyses will be clearly identified in the CSR.

9.1 Statistical Analysis Plan Summary

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

Study Design Overview	A Phase 3 Open-label, Single Arm Study to Evaluate the Safety and Efficacy of Pembrolizumab (MK-3475) as First-line Therapy in Participants With Advanced Merkel Cell Carcinoma (KEYNOTE-913)
Treatment Assignment	Approximately 50 participants will be enrolled to treatment with pembrolizumab. This is a single-arm open-label study
Analysis Populations	Efficacy and Safety: All Participants as Treated (APaT)
Primary Endpoint	Objective Response (OR) per RECIST 1.1 by BICR

Secondary Endpoints	3. Duration of Response (DOR) per RECIST 1.1 assessed by BICR 4. Progression-free Survival (PFS) per RECIST 1.1 assessed by BICR 5. Overall Survival (OS)
Statistical Methods for Key Efficacy Analyses	Estimation of Objective Response Rate (ORR) and 95% exact binomial confidence interval (CI) for the true ORR; Estimation of PFS, OS, and DOR using the Kaplan-Meier method
Statistical Methods for Key Safety Analyses	Counts and percentages of participants with AEs
Interim Analyses	There are no planned interim analyses for this study
Multiplicity	No multiplicity adjustment is planned
Sample Size and Power	The planned sample size is approximately 50 participants. If the ORR is 56%, this sample size will produce a 95% CI for the true ORR of approximately ±15%

9.2 Responsibility for Analyses/In-house Blinding

The statistical analysis of the data obtained from this study will be the responsibility of the Clinical Biostatistics department of the Sponsor. This study is being conducted as a nonrandomized, 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.

9.3 Hypotheses/Estimation

Objectives of the study are stated in Section 3. There are no hypotheses in this study.

9.4 Analysis Endpoints

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

9.4.1 Efficacy Endpoints

9.4.1.1 Primary

Objective Response Rate (ORR) per RECIST 1.1 assessed by BICR

The ORR is defined as the percentage of participants who achieve a confirmed complete response (CR) or partial response (PR) per RECIST 1.1 as assessed by BICR. Details of the ORR analysis can be found in Section 9.6.1.1.

9.4.1.2 Secondary

Duration of Response (DOR) per RECIST 1.1 assessed by BICR

For participants who demonstrate confirmed 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. Response duration will be calculated for RECIST 1.1 based on BICR by the imaging vendor. See Section 9.6.1.2 for the definition of censoring rules for DOR.

Progression-free Survival (PFS) per RECIST 1.1 assessed by BICR

PFS is defined as the time from the first day of study treatment to the first documented disease progression per RECIST 1.1 by BICR or death due to any cause, whichever occurs first. See Section 9.6.1.3 for the definition of censoring rules for PFS.

Overall Survival (OS)

OS is defined as the time from first day of study treatment to death due to any cause. Participants without documented death at the time of the final analysis will be censored at the last known alive date. To characterize the effects on survival, the final analysis of OS will be conducted approximately 13 years after the first participant signs informed consent/assent, when it is estimated that ~70% of participants will have died.

9.4.2 Safety Endpoints

Safety measurements are described in Section 4.2.1.2.

9.5 Analysis Populations

9.5.1 Efficacy Analysis Population

The APaT population will serve as the population for the analysis of efficacy data in this study. The APaT population consists of all allocated participants who receive at least 1 dose of study treatment.

9.5.2 Safety Analysis Population

Safety analyses will be conducted in the APaT population as defined for efficacy.

At least 1 laboratory or vital sign measurement obtained subsequent to at least 1 dose of study treatment is required for inclusion in the analysis of the respective safety parameter. To assess change from baseline, a baseline measurement is also required.

9.6 Statistical Methods

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

9.6.1 Statistical Methods for Efficacy Analyses

9.6.1.1 Objective Response Rate (ORR)

ORR will be calculated as the ratio of the number of participants reported to have achieved a confirmed CR or PR verified by BICR, divided by the number of participants included in the APaT population. Participants in the APaT analysis population without ORR assessments will be counted as non-responders. A 95% exact binomial CI based on the Clopper and Pearson method will be calculated for the true ORR.

9.6.1.2 Duration of Response (DOR)

The non-parametric Kaplan-Meier method will be used to estimate the DOR survival curve. Only the subset of participants with confirmed CR or PR response verified by BICR will be included in the analysis. 95% CIs for the median response duration and point estimates at various follow-up times will be calculated. The censoring rules for the analysis of DOR are summarized in Table 8.

Table 8 Censoring Rules for Analysis of DOR

Situation	Date of Progression or Censoring	Outcome
No progression nor death, no new anticancer therapy initiated	Last adequate disease assessment	Censor (non-event)
No progression nor death, new anticancer therapy initiated	Last adequate disease assessment before new anticancer therapy initiated	Censor (non-event)
Death or progression immediately after ≥2 consecutive missed disease assessments or after new anticancer therapy, if any	Earlier date of last adequate disease assessment prior to ≥2 missed adequate disease assessments and new anticancer therapy, if any	Censor (non-event)
Death or progression after ≤1 missed disease assessments and before new anticancer therapy, if any	Progressive disease or death	End of response (Event)
DOR=duration of response Note: A missed disease assessment includes any assessment that is not obtained or is considered inadequate for evaluation of response.		

9.6.1.3 Progression-free Survival

The non-parametric Kaplan-Meier method will be used to estimate the PFS survival curve. 95% CIs for the median PFS and PFS point estimates at various follow-up times from the first day of study treatment will be calculated.

Since disease progression is assessed periodically, 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 earlier of the date of the first assessment at which PD is objectively documented per RECIST 1.1 by BICR and the date of death. Death is always considered a PD event. Participants who do not

experience a PFS event will be censored at the last disease assessment. The censoring rules for the analysis of PFS are summarized in Table 9. If a participant meets multiple criteria for censoring, the censoring criterion that occurs earliest will be applied.

Table 9 Censoring Rules for Analysis of PFS

Situation	Date of Progression or Censoring
PD or death documented after ≤1 missed disease assessment, and before new anticancer therapy, if any	Progressed at date of documented PD or death
PD or death documented immediately after ≥2 consecutive missed disease assessments or after new anticancer therapy, if any	Censored at last disease assessment prior to the earlier date of ≥2 consecutive missed disease assessment and new anticancer therapy, if any
No PD and no death; and new anticancer treatment is not initiated	Censored at last disease assessment
No PD and no death; new anticancer treatment is initiated	Censored at last disease assessment before new anticancer treatment
PD=progressive disease; PFS=progression-free survival	

9.6.1.4 Overall Survival

The non-parametric Kaplan-Meier method will be used to estimate the OS survival curve. 95% CIs for the median OS and OS point estimates at various follow-up times from the first day of study intervention will be calculated. Participants without documented death at the time of analysis will be censored at the date the participant was last known to be alive.

9.6.1.5 Analysis Strategy for Key Efficacy Endpoints

Table 10 summarizes the analysis approach for key efficacy endpoints.

Table 10 Analysis Strategy for Key Efficacy Endpoints

Endpoint	Statistical Method[a]	Analysis Population	Missing Data Approach
Primary Endpoints			
ORR per RECIST 1.1 by BICR	Estimation: Exact method based on binomial distribution (Clopper-Pearson method)	APaT	Participants without assessments are considered non-responders and conservatively included in the denominator
Key Secondary Endpoint			
DOR per RECIST 1.1 by BICR	Estimation: Summary statistics using Kaplan-Meier method	Participants in APaT population with an objective response	Non-responders are excluded from analysis; Responders are censored according to rules in Table 8

Endpoint	Statistical Method[a]	Analysis Population	Missing Data Approach
PFS per RECIST 1.1 by BICR	Estimation: Summary statistics using Kaplan-Meier method	APaT	Censoring according to Table 9
OS	Estimation: Summary statistics using Kaplan-Meier method	APaT	Censored at the last known alive date

APaT=All Patients as Treated; BICR=blinded independent central review; DOR=duration of response; ORR=objective response rate; OS=overall survival; PFS=progression-free survival; RECIST=Response Evaluation Criteria in Solid Tumors

[a] Statistical methods are described in further detail in the text.

9.6.2 Statistical Methods for Safety Analyses

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

AEs (specific terms as well as system organ class terms), consisting of the percentage of participants with any AE, any drug-related AE, any Grade 3 to 5 AE, any serious AE, any AE which is both drug-related and Grade 3 to 5, any AE which is both serious and drug-related, and who discontinued due to an AE, and death will be summarized as counts and frequencies.

Laboratory assessments and vital signs will be summarized using appropriate descriptive statistics.

9.6.3 Demographics and Baseline Characteristics

Demographic variables (eg, age, gender, race, and ethnicity), baseline characteristics, and concomitant therapies will be summarized either by descriptive statistics or categorical tables.

9.7 Interim Analyses

No interim analyses are planned in this study.

9.8 Multiplicity

No multiplicity adjustment is planned in this study.

9.9 Sample Size and Power Calculations

Approximately 50 participants will be enrolled to treatment with pembrolizumab. Table 11 provides 2-sided 95% CIs of ORR with 50 participants for different observed response rates based on the method of Clopper and Pearson. If the ORR is 56%, this sample size will produce a 95% CI for the true ORR of approximately ±15%.

Table 11 Two-sided 95% Confidence Interval of ORR With 50 Participants

Number of Observed Responders	ORR Estimate	95% CI of ORR
18	36%	(22.9%, 50.8%)
20	40%	(26.4%, 54.8%)
22	44%	(30.0%, 58.8%)
24	48%	(33.7%, 62.6%)
26	52%	(37.4%, 66.3%)
28	56%	(41.3%, 70.0%)
30	60%	(45.2%, 73.6%)
CI=confidence interval; ORR=objective response rate		

9.10 Subgroup Analyses

To determine whether the response rate is consistent across subgroups, the estimate of response rate with 95% CI for the primary endpoint will be estimated within each category of the following classification variables:

- Age category (<65 vs ≥65 years)
- Sex (female vs male)
- ECOG status (0 vs 1)
- Prior adjuvant therapy (yes vs no)

For safety endpoints, broad AE categories consisting of the percentage of participants with any AE, any drug-related AE, any Grade 3 to 5 AE, any serious AE, any AE which is both drug-related and Grade 3 to 5, any AE which is both serious and drug-related, and who discontinued due to an AE, and death will be summarized by the same subgroups of age category, sex, ECOG status, and prior adjuvant therapy.

Any specified subgroups that have less than 10 participants will be excluded from analysis.

9.11 Compliance (Medication Adherence)

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

9.12 Extent of Exposure

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

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

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

10.1.1 Code of Conduct for Clinical Trials

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

Code of Conduct for Interventional Clinical Trials

I. Introduction

A. Purpose

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

B. Scope

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

II. Scientific Issues

A. Trial Conduct

1. Trial Design

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

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

2. Site Selection

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

3. Site Monitoring/Scientific Integrity

Investigative trial sites are monitored to assess compliance with the trial protocol and general principles of Good Clinical Practice (GCP). MSD reviews clinical data for accuracy, completeness, and consistency. Data are verified versus source documentation according to standard operating procedures. Per MSD policies and procedures, if fraud, scientific/research misconduct, or serious GCP-noncompliance is suspected, the issues

are investigated. When necessary, the clinical site will be closed, the responsible regulatory authorities and ethics review committees notified.

B. Publication and Authorship

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

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

III. Participant Protection

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

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

B. Safety

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

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

C. Confidentiality

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

D. Genomic Research

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

IV. Financial Considerations

A. Payments to Investigators

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

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

B. Clinical Research Funding

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

C. Funding for Travel and Other Requests

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

V. Investigator Commitment

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

10.1.2 Financial Disclosure

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

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

10.1.3 Data Protection

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

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

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

10.1.3.1 Confidentiality of Data

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

10.1.3.2 Confidentiality of Participant Records

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

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

10.1.3.3 Confidentiality of IRB/IEC Information

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

10.1.4 Committees Structure

No committees are planned for this study.

10.1.5 Publication Policy

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

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

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

10.1.6 Compliance with Study Registration and Results Posting Requirements

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

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

10.1.7 Compliance with Law, Audit, and Debarment

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

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

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

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

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

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

10.1.8 Data Quality Assurance

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

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

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

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

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

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

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

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

10.1.9 Source Documents

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

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

10.1.10 Study and Site Closure

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

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

10.2 Appendix 2: Clinical Laboratory Tests

- The tests detailed in Table 12 will be performed by the local laboratory.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5.1 and Section 5.2 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 12 Protocol-required Safety Laboratory Assessments

Laboratory Assessments	Parameters			
Hematology	Platelet Count RBC Count Hemoglobin Hematocrit	RBC Indices: MCV[a] MCH[a] %Reticulocytes[a]	WBC count with Differential[b]: Neutrophils Lymphocytes Monocytes Eosinophils Basophils	
Chemistry	BUN[c]	Potassium	AST/SGOT	Total bilirubin (and direct bilirubin, if total bilirubin is elevated above the upper limit of normal)
	Albumin	Bicarbonate[a]	Chloride[a]	Phosphorous[a]
	Creatinine[d]	Sodium	ALT/SGPT	Total Protein[a]
	Glucose [nonfasting]	Calcium	Alkaline phosphatase	Magnesium[a]
	Lactate dehydrogenase[a]	Amylase	Lipase	
	Cholesterol[a]	Triglycerides[a]	CPK[a]	Thyroid function tests (T3 [or free T3[e]], free T4, and TSH)
	Pregnancy test[f]			
Routine Urinalysis[g]	Specific gravity pH, glucose, protein, blood, ketones, by dipstick Microscopic examination (if blood or protein is abnormal)			
Other Screening Tests	Coagulation panel (PT/INR, aPTT)[h] Serology (HIV antibody, HBsAg, and hepatitis C virus antibody), if applicable Tuberculosis test, if applicable Follicle-stimulating hormone (as needed in women of nonchildbearing potential only) Serum or urine β human chorionic gonadotropin (β hCG) pregnancy test (as needed for WOCBP)[f]			

Laboratory Assessments	Parameters

ALT=alanine aminotransferase; aPTT=activated partial thromboplastin time; AST=aspartate aminotransferase; BUN=blood urea nitrogen; CPK=creatine phosphokinase; HBsAg=hepatitis B surface antigen; HIV=human immunodeficiency virus; INR=international normalized ratio; MCH=mean cell hemoglobin; MCV=mean cell volume; PT=prothrombin time; RBC=red blood cell; SGOT=serum glutamic oxaloacetic transaminase; SGPT=serum glutamic pyruvic transaminase; T3=triiodothyronine; T4=thyroxine; TSH=thyroid stimulating hormone; WBC=white blood cell; WOCBP=women of childbearing potential
NOTES:

a. If the test is considered part of local standard of care.
b. Absolute or % acceptable per institutional standard.
c. Urea is acceptable if BUN is not available as per institutional standard.
d. Glomerular filtration rate (measured or calculated) or creatinine clearance can be used in place of creatinine at Screening only.
e. T3 is preferred over free T3. If not available, free T3 may be tested. There may be instances when sites are unable to obtain thyroid function testing results prior to the scheduled dosing; after Cycle 1, review of thyroid function test results after dosing is acceptable.
f. See Appendix 5.3.
g. If urine dipstick testing suggests a urinary tract infection, or if clinically indicated, a urine microscopy, culture, and sensitivity should be performed at the institution's laboratory.
h. PT/INR should be tested as needed for participants taking warfarin-based anticoagulation therapy.

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

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

10.3.1 Definition of AE

AE definition

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

Events meeting the AE definition

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator.
- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication.
- For all reports of overdose (whether accidental or intentional) with an associated AE, the AE term should reflect the clinical symptoms or abnormal test result. An overdose without any associated clinical symptoms or abnormal laboratory results is reported using the terminology "accidental or intentional overdose without adverse effect."
- Any new cancer (that is not a condition of the study). Progression of the cancer under study is not a reportable event. Refer to Section 8.4.6 for additional details.

Events NOT meeting the AE definition

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

10.3.2 Definition of SAE

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

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

1. Results in death
2. Is life-threatening
    - The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
3. Requires inpatient hospitalization or prolongation of existing hospitalization
    - Hospitalization is defined as an inpatient admission, regardless of length of stay, even if the hospitalization is a precautionary measure for continued observation. (Note: Hospitalization for an elective procedure to treat a pre-existing condition that has not worsened is not an SAE. A pre-existing condition is a clinical condition that is diagnosed prior to the use of an MSD product and is documented in the participant's medical history.
4. Results in persistent or significant disability/incapacity
    - The term disability means a substantial disruption of a person's ability to conduct normal life functions.
    - This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza,

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

5. Is a congenital anomaly/birth defect

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

6. Other important medical events

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

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

10.3.3 Additional Events Reported in the Same Manner as SAE

Additional events that require reporting in the same manner as SAE

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

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

10.3.4 Recording AE and SAE

AE and SAE recording

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

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

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

Assessment of intensity/toxicity

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

- The investigator will make an assessment of intensity for each AE and SAE (and other reportable safety event) according to the NCI Common Terminology for Adverse Events (CTCAE), version 4.0. Any AE that changes CTCAE grade over the course of a given episode will have each change of grade recorded on the AE CRFs/worksheets.

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

  - Grade 2: Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living (ADL).

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

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

  - Grade 5: Death related to AE.

Assessment of causality

- Did the Sponsor's product cause the AE?

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

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

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

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

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

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

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

  - If yes, did the AE resolve or improve?

  - If yes, this is a positive dechallenge.

  - If no, this is a negative dechallenge.

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

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

  - If yes, did the AE recur or worsen?

  - If yes, this is a positive rechallenge.

  - If no, this is a negative rechallenge.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Follow-up of AE and SAE

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

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

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

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

SAE reporting to the Sponsor via paper CRF

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

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

Not applicable.

10.5 Appendix 5: Contraceptive Guidance and Pregnancy Testing

10.5.1 Definitions

Women of Childbearing Potential (WOCBP)

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

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

Women in the following categories are not considered WOCBP:

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

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

  Note: Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.
- Postmenopausal female
  - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.

A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormone replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, confirmation with 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 nonhormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

10.5.2 Contraception Requirements

Female Participants

Contraceptives allowed during the study include[a]:
Highly Effective Contraceptive Methods That Have Low User Dependency *Failure rate of <1% per year when used consistently and correctly.*
• Progestogen-only subdermal contraceptive implant[b,c] • IUS[c,d] • Non-hormonal IUD • Bilateral tubal occlusion
• Azoospermic partner (vasectomized or secondary to medical cause) This is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. A spermatogenesis cycle is approximately 90 days. Note: Documentation of azoospermia for a male participant can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.
Sexual Abstinence • Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.
[a] Contraceptive use by men or women should be consistent with local regulations regarding the use of contraceptive methods for participants of clinical studies. [b] If locally required, in accordance with CTFG guidelines, acceptable contraceptive implants are limited to those which inhibit ovulation. [c] Male condoms must be used in addition to female participant hormonal contraception. [d] IUS is a progestin releasing IUD. Note: The following are not acceptable methods of contraception: - Periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and LAM. - Male condom with cap, diaphragm, or sponge with spermicide. - Male and female condom should not be used together (due to risk of failure with friction).

10.5.3 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 prior to each treatment cycle during the treatment period and prior to each cycle of treatment up to 120 days after the last dose of study intervention or the start of a new anticancer therapy, whichever comes first, and as required locally.

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

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

1. Definitions

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

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

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

d. DNA: Deoxyribonucleic acid.

e. RNA: Ribonucleic acid.

2. Scope of Future Biomedical Research

The specimens consented and/or collected in this study as outlined in Section 8.8 will be used in various experiments to understand:

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

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

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

3. Summary of Procedures for Future Biomedical Research

a. Participants for Enrollment

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

b. Informed Consent/Assent

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

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

c. eCRF Documentation for Future Biomedical Research Specimens

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

d. Future Biomedical Research Specimen(s)

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

4. Confidential Participant Information for Future Biomedical Research

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

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

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

5. Biorepository Specimen Usage

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

6. Withdrawal From Future Biomedical Research

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

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

7. Retention of Specimens

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

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

to Sponsor policies and procedures and this destruction will be documented in the biorepository database.

8. Data Security

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

9. Reporting of Future Biomedical Research Data to Participants

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

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

10. Future Biomedical Research Study Population

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

11. Risks Versus Benefits of Future Biomedical Research

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

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

12. Questions

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

13. References

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

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

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

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

10.7 Appendix 7: Country-specific Requirements

10.7.1 Germany

Section 5.2 Exclusion Criteria

Has a known history of HIV infection. HIV testing is required as mandated by local regulation.

Has a known history of Hepatitis B (defined as HBsAg reactive) or known active Hepatitis C virus (defined as HCV RNA [qualitative] is detected) infection. Testing for Hepatitis B or Hepatitis C is required at Screening.

Has a known history of active TB. Testing for TB is required at Screening.

Throughout

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

10.7.2 United Kingdom

Section 5.2 Exclusion Criteria

Has a known history of HIV infection. HIV testing is required at Screening.

Has a known history of Hepatitis B (defined as HBsAg reactive) or known active Hepatitis C virus (defined as HCV RNA [qualitative] is detected) infection. Testing for Hepatitis B or Hepatitis C is required at Screening.

Section 6.5 Concomitant Therapy

Live vaccines are prohibited through 3 months after the end of study intervention.

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

Assessment at Screening and Prior to RECIST 1.1 Progression

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

Assessment and Decision at RECIST 1.1 Progression

For participants who show evidence of radiological PD by RECIST 1.1 as determined by the investigator, the investigator will decide whether to continue a participant on study intervention until repeat imaging 4 to 8 weeks later is obtained (using iRECIST for participant management (see Table 6 and Figure 2). This decision by the investigator should be based on the participant's overall clinical condition.

Clinical stability is defined as the following:

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

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

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

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

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

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

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

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

Assessment at the Confirmatory Imaging

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

Confirmation of Progression

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

- Any of the factors that were the basis for the iUPD at the previous visit show worsening
    - For target lesions, worsening is a further increase in the sum of diameters of ≥5 mm, compared to any prior iUPD time point
    - For nontarget lesions, worsening is any significant growth in lesions overall, compared to a prior iUPD time point; this does not have to meet the “unequivocal” standard of RECIST 1.1
    - For new lesions, worsening is any of these:

An increase in the new lesion sum of diameters by ≥5 mm from a prior iUPD time point

Visible growth of new nontarget lesions

The appearance of additional new lesions

- Any new factor appears that would have triggered PD by RECIST 1.1

Persistent iUPD

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

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

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

Resolution of iUPD

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

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

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

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

Management Following the Confirmatory Imaging

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

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

Detection of Progression at Visits After Pseudo-progression Resolves

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

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

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

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

Additional details about iRECIST are provided in the iRECIST publication [Seymour, L., et al 2017].

10.9 Appendix 9: Performance Scales

Eastern Cooperative Oncology Group (ECOG) Performance Scale

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

Source: [ECOG-ACRIN Cancer Research Group 2016]

Lansky Play-Performance Scale (LPS)

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

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

10.10 Appendix 10: Abbreviations

Abbreviation	Expanded Term
AE	adverse event
AJCC	American Joint Committee on Cancer
ALT (SGPT)	alanine aminotransferase (serum glutamic pyruvic transaminase)
APaT	All Participants as Treated
aPTT	activated partial thromboplastin time
AST (SGOT)	aspartate aminotransferase (serum glutamic oxaloacetic transaminase)
BCG	Bacillus Calmette–Guérin
BICR	blinded independent central review
BOR	best overall response
C1D1	Cycle 1 Day 1
CAV	cyclophosphamide, doxorubicin (or epirubicin), and vincristine
CD28	cluster of differentiation 28
CD3ζ	cluster of differentiation 3 zeta
CNS	central nervous system
CR	complete response
CRF	Case Report Form
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTFG	Clinical Trial Facilitation Group
CTLA-4	cytotoxic T-lymphocyte-associated protein 4
DILI	drug-induced liver injury
DNA	deoxyribonucleic acid
DOR	duration of response
ECG	electrocardiogram
ECI	event of clinical interest
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic Case Report Form
EDC	electronic data collection
eDMC	external Data Monitoring Committee
EMA	European Medicines Agency
EOT	End of Treatment
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act
FSH	Follicle-stimulating hormone
GCP	Good Clinical Practice
HBsAg	Hepatitis B surface antigen
HCV	Hepatitis C virus
HIV	human immunodeficiency virus
HRT	hormone replacement therapy
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonization
iCPD	iRECIST confirmed progressive disease
iCR	iRECIST complete response
iCRO	imaging contract research organization
IEC	Independent Ethics Committee
Ig	immunoglobulin
IgG4	immunoglobulin G4
IgV-type	immunoglobulin-variable–type
IND	Investigational New Drug

Abbreviation	Expanded Term
iPR	iRECIST partial response
irAE	immune-related adverse event
IRB	Institutional Review Board
iRECIST	modified Response Evaluation Criteria in Solid Tumors 1.1 for immune-based therapeutics
IRT	interactive response technology
iSD	iRECIST stable disease
IUD	intrauterine device
iUPD	iRECIST unconfirmed progressive disease
IUS	intrauterine hormone-releasing system
IV	intravenous
LPS	Lansky Play-Performance Scale
mAb	monoclonal antibody
MCC	Merkel cell carcinoma
MCPyV	Merkel cell polyoma virus
MRI	magnetic resonance imaging
NCCN	National Comprehensive Cancer Network
OR	objective response
ORR	objective response rate
OS	overall survival
PBPK	physiologically-based pharmacokinetics
PD	progressive disease
PD-1	programmed cell death 1
PD-L1	programmed cell death ligand 1
PD-L2	programmed cell death ligand 2
PFS	progression-free survival
PK	pharmacokinetic
PKCθ	protein kinase C-theta
PR	partial response
Q2W	every 2 weeks
Q3W	every 3 weeks
Q12W	every 12 weeks
Q24W	every 24 weeks
RECIST 1.1	Response Evaluation Criteria in Solid Tumors version 1.1
RNA	ribonucleic acid
SAE	serious adverse event
SD	stable disease
SIM	Site Imaging Manual
SoA	schedule of activities
SUSAR	suspected unexpected serious adverse reaction
TB	tuberculosis
ULN	upper limit of normal
US	United States
WOCBP	woman/women of childbearing potential
ZAP70	zeta-chain-associated protein kinase

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