Official Protocol Title:	Protocol/Amendment No.: A33-03 A Phase 1 Clinical Study of Pembrolizumab (MK-3475) in Participants with Relapsed or Refractory Primary Mediastinal Large B-cell Lymphoma (rrPMBCL) (KEYNOTE-A33)
NCT number:	NCT04317066
Document Date:	28-Nov-2023

TITLE PAGE

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Protocol Title: A Phase 1 Clinical Study of Pembrolizumab (MK-3475) in Participants with Relapsed or Refractory Primary Mediastinal Large B-cell Lymphoma (rrPMBCL) (KEYNOTE-A33)

Protocol Number: A33-03

Compound Number: MK-3475

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

Legal Registered Address:

126 East Lincoln Avenue
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Regulatory Agency Identifying Number(s):

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UTN	Not applicable
IND	Not applicable

Approval Date: 28 November 2023

Sponsor Signatory

Typed Name: Title:	Date

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

Investigator Signatory

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

Typed Name: Title:	Date

DOCUMENT HISTORY

Document	Date of Issue	Overall Rationale
A33-03	28-NOV-2023	To close the study since the primary objective of this study has been achieved and additional data is not required.
A33-02	09-SEP-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. To update the dose modification and toxicity management guidelines for immune-related adverse events (irAEs).
A33-01	03-FEB-2020	To change the primary efficacy endpoint from investigator assessment to central assessment and to modify the statistical analysis.
Original Protocol	19-NOV-2019	Not applicable

PROTOCOL AMENDMENT SUMMARY OF CHANGES

Amendment:03

Overall Rationale for the Amendment:

To close the study since the primary objective of this study has been achieved and additional data is not required.

Summary of Changes Table

Section Number and Name	Description of Change	Brief Rationale
Primary Reason for Amendment		
1.1 Synopsis 4.1 Overall Design 8.9.3 Post treatment Visit	Added below sentences: After the approval of Protocol amendment 03, the study will be completed at the Safety Follow-up visit (scheduled 30 days after the last dose) or imaging assessment 120 weeks from the allocation date, of the last participant, whichever is later. If the study intervention is still ongoing at Week 120 of the last participant, further study intervention should be discontinued, and no further visits will be required after the Safety Follow-up visit which scheduled 30 days after the last dose. Participants in the Imaging Follow-up Phase or Survival Follow-up Phase will be discontinued from the study and no further visits will be required.	To close the study since the primary objective of this study has been achieved and additional data is not required.

Section Number and Name	Description of Change	Brief Rationale
Additional Changes		
Title page	Added NCT and jRCT numbers.	To provide updated information.
6.5.3 Rescue Medications and Supportive Care	Updated text from "AEs with potential immunologic etiology" to "AEs associated with study intervention" which follow dose modification guideline.	To clarify the applicable events of dose modification guidelines.
8.1.1 Informed Consent	Updated texts regarding informed consent.	Clarification.
8.1.1.1 General Informed Consent	Updated texts regarding informed consent and added that documented informed consent is required when study intervention is continued beyond disease progression.	Clarification and to obtain appropriate consent.
8.1.5.2 Concomitant Medications	Deleted "30 day".	To clarify the end of concomitant medications collection period.
8.4 Adverse Events, Serious Adverse Events, and Other Reportable Safety Events	Added "Investigators need to document if an SAE was associated with a medication error, misuse, or abuse."	To adhere the requirement of EU regulations.
8.4.7 Events of Clinical Interest	Updated text for overdose and potential DILI.	For overdose, to be consistent in terminology used throughout the document. For potential DILI, to define what potential DILI is and to align with this acronym being used in Table 5.
10.3, Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting	"Sponsor's product" is replaced by "study intervention" throughout this section.	To be consistent in terminology used throughout the document.
10.3.1 Definitions of Medication Error, Misuse, and Abuse	Added definitions of medication error, misuse, and abuse.	To adhere the requirement of EU regulations.
Throughout Document	Minor administrative, formatting, grammatical, and/or typographical changes were made throughout the document.	To ensure clarity and accurate interpretation of the intent of the protocol.
Throughout Document	After marketing approval of MK-3475 for rrPMBCL in Japan, the term of "clinical study" and "clinical trial" should be replaced with "post marketing clinical trial" and the study will be continued. All applicable laws, rules and regulations related to the conduct of the clinical trial mentioned in these sections include Japan specific local regulation, Good Post-Marketing Study Practice (GPSP) in Japan.	To adhere the requirement of Japanese regulations.

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1 PROTOCOL SUMMARY

1.1 Synopsis

Protocol Title: A Phase 1 Clinical Study of Pembrolizumab (MK-3475) in Participants with Relapsed or Refractory Primary Mediastinal Large B-cell Lymphoma (rrPMBCL) (KEYNOTE-A33)

Short Title: Phase 1 Study of MK-3475 in participants with rrPMBCL

Acronym: Not Applicable

Hypotheses, Objectives, and Endpoints:

All objectives and endpoints apply to Japanese participants with rrPMBCL:

Primary Objective	**Primary Endpoint**
To evaluate objective response using IWG Revised Response Criteria for Malignant Lymphoma (Appendix 9) as assessed by independent central review.	Objective response: complete response (CR) or partial response (PR).
To evaluate the safety and tolerability of pembrolizumab.	-Adverse event -Discontinuing study intervention due to an adverse event
Secondary Objectives	**Secondary Endpoints**
-To evaluate disease control using IWG Revised Response Criteria for Malignant Lymphoma (Appendix 9) as assessed by independent central review. -To evaluate objective response and disease control using IWG Revised Response Criteria for Malignant Lymphoma (Appendix 9) as assessed by the investigator.	-Disease control: CR, PR, or stable disease (SD). -Objective response: CR or PR.

Overall Design:

Study Phase	Phase 1
Primary Purpose	Treatment
Indication	Primary mediastinal large B-cell lymphoma
Population	Participants with rrPMBCL
Study Type	Interventional
Intervention Model	Single Group This is a multi site study.
Type of Control	No Treatment Control
Study Blinding	Unblinded open-label
Blinding Roles	No blinding
Estimated Duration of Study	The Sponsor estimates that the study will require approximately 5 years from the time the first participant (or their legally acceptable representative) provides documented informed consent until the last participant's last study-related contact.

Number of Participants:

Approximately 5 participants will be enrolled.

Intervention Groups and Duration:

Arm Name	Intervention Name	Unit Dose Strength(s)	Dosage Level(s)	Route of Administration	Regimen/ Treatment Period	Use
N/A	Pembrolizumab	25 mg/mL	200 mg	IV Infusion	Q3W; Day 1 in each cycle up to 35 cycles	Test Product

Total Number of Intervention Groups/Arms	1
Duration of Participation	Each participant will participate in the study from the time that the participant provides documented informed consent through the final protocol-specified contact. After a screening phase of 28 days, each participant will be assigned to receive study intervention until one of the conditions for discontinuation of study intervention is met. After the-end-of treatment, each participant will be followed for the occurrence of adverse events and spontaneously reported pregnancy. Participants who discontinue for reasons other than radiographic disease progression will have posttreatment follow-up imaging for disease status until any of the conditions for discontinuation of imaging are met. All participants will be followed for overall survival until death, withdrawal of consent, or the end of the study. After the approval of Protocol amendment 03, the study will be completed at the Safety Follow-up visit (scheduled 30 days after the last dose) or imaging assessment 120 weeks from the allocation date, of the last participant, whichever is later. If the study intervention is still ongoing at Week 120 of the last participant, further study intervention should be discontinued, and no further visits will be required after the Safety Follow-up visit which scheduled 30 days after the last dose. Participants in the Imaging Follow-up Phase or Survival Follow-up Phase will be discontinued from the study and no further visits will be required.

Study Governance Committees:

Executive Oversight Committee	No
Data Monitoring Committee	No
Clinical Adjudication Committee	No
Steering Committee	No

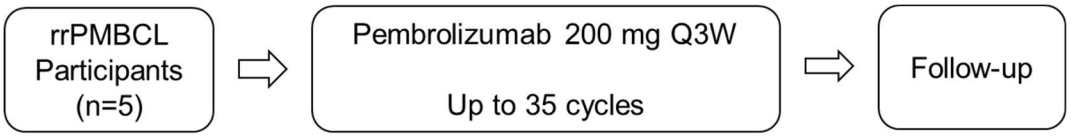
Study governance considerations are outlined in Appendix 1.

Study Accepts Healthy Participants: No

A list of abbreviations used in this document can be found in Appendix 8.

1.2 Schema

The study design is depicted in Figure 1.



Abbreviations: rrPMBCL = relapsed or refractory primary mediastinal large B-cell lymphoma, Q3W = every 3 weeks

Figure 1 Study Design

1.3 Schedule of Activities

Study Period:	Screening Phase	Treatment Phase (3-Week Cycles)				End of Treatment (EOT) / Discontinuation	Post-treatment Phase			Notes
Treatment Cycle/Title:	Screening (Visit 1)	1	2	3	4 to 35		Safety Follow-up	Imaging Follow-up	Survival Follow-up	
Treatment Days per Cycle:		1	1	1	1	At time of treatment discontinuation	30 days post last dose study medication	Every 12 weeks	Every 12 weeks	
Scheduled Window (Days):	-28 to -1	+3	±3	±3	±3		+7	±14	±14	
Administrative Procedures										
Informed Consent	X									
Participant Identification Card	X									
Inclusion/Exclusion Criteria	X									
Demographic and Medical History	X									
Prior/Concomitant Medication Review	X	X	X	X	X	X	X			
Administration of Pembrolizumab		X	X	X	X					
Post-study Anticancer Therapy Status							X	X	X	
Survival Status		←========== X==========→							X	
Safety Procedures										
Adverse Event (AE) Monitoring	X	X				X	X	X		
Full Physical Examination	X									
Directed Physical Examination		X	X	X	X	X	X			

Study Period:	Screening Phase	Treatment Phase (3-Week Cycles)				End of Treatment (EOT) / Discontinuation	Post-treatment Phase			Notes
Treatment Cycle/Title:	Screening (Visit 1)	1	2	3	4 to 35		Safety Follow-up	Imaging Follow-up	Survival Follow-up	
Treatment Days per Cycle:		1	1	1	1	At time of treatment discontinuation	30 days post last dose study medication	Every 12 weeks	Every 12 weeks	
Scheduled Window (Days):	-28 to -1	+3	±3	±3	±3		+7	±14	±14	
Vital Signs and Weight	X	X	X	X	X	X	X			VS: pulse, respiratory rate, blood pressure, temperature.
Height	X									
12-lead ECG	X									
ECOG Performance Status	X	X	X	X	X	X	X			ECOG Performance Status at screening should be performed within 7 days prior to the first dose of study intervention.
Pregnancy Test - Urine or Serum β-hCG (WOCBP only)	X					X	X			
Urinalysis	X									
PT/INR and aPTT	X									
CBC with Differential	X		X	X	X	X	X			
Comprehensive Chemistry Panel	X		X	X	X	X	X			
Thyroid Function Testing (T3, or FT3, FT4, and TSH)	X			X	X	X	X			Every 2 Cycles.

Study Period:	Screening Phase	Treatment Phase (3-Week Cycles)				End of Treatment (EOT) / Discontinuation	Post-treatment Phase			Notes
Treatment Cycle/Title:	Screening (Visit 1)	1	2	3	4 to 35		Safety Follow-up	Imaging Follow-up	Survival Follow-up	
Treatment Days per Cycle:		1	1	1	1	At time of treatment discontinuation	30 days post last dose study medication	Every 12 weeks	Every 12 weeks	
Scheduled Window (Days):	-28 to -1	+3	±3	±3	±3		+7	±14	±14	
Efficacy Procedures										
PET/CT [Neck, Chest, Abdomen, Pelvic][b]	X				X[a]	X[c]		X		Lymphoma B symptom and disease response assessments should be performed at the same time as tumor imaging; disease assessments are not to be delayed for cycle delays. a. Every 12 weeks (±7 days) from the time of allocation. b. Perform PET/CT during screening. On-study, perform disease assessments using PET/CT if PET-avid at baseline; otherwise, CT may be used. See Sections 8.2.2 and 8.2.3 for detailed information on imaging. c. In participants who discontinue study therapy, imaging should be performed at the time of treatment discontinuation (ie, date of discontinuation ± 4 weeks). If previous scan/ was obtained within 4 weeks prior to the date of discontinuation, then a scan at treatment discontinuation does not need to be performed.
Disease Response Assessment by IWG Revised Response Criteria for Malignant Lymphoma					X[a]	X[c]		X		
Disease Response Assessment by Lugano Classification					X[a]	X[c]		X		
Assessment of Lymphoma B Symptoms	X				X[a]	X[c]		X		

Study Period:	Screening Phase	Treatment Phase (3-Week Cycles)				End of Treatment (EOT) / Discontinuation	Post-treatment Phase			Notes
Treatment Cycle/Title:	Screening (Visit 1)	1	2	3	4 to 35		Safety Follow-up	Imaging Follow-up	Survival Follow-up	
Treatment Days per Cycle:		1	1	1	1	At time of treatment discontinuation	30 days post last dose study medication	Every 12 weeks	Every 12 weeks	
Scheduled Window (Days):	-28 to -1	+3	±3	±3	±3		+7	±14	±14	
Bone Marrow Biopsy and Aspirate	X				X					All participants will have bone marrow biopsy and aspirate at baseline. Subsequent bone marrow assessments will only be performed in participants who have bone marrow involvement. A bone marrow assessment should be performed to confirm CR (if participant had bone marrow involvement) and as clinically indicated.
Abbreviations: CT = computed tomography; PET = positron emission tomography; PT/INR = prothrombin time/international normalized ratio; aPTT =activated partial thromboplastin time; T3 = total triiodothyronine; FT4 = free thyroxine; TSH = thyroid stimulating hormone.										

2 INTRODUCTION

This is a Phase 1 study to evaluate the efficacy and safety of pembrolizumab in participants with rrPMBCL.

2.1 Study Rationale

Non-Hodgkin's lymphomas (NHL) are a heterogeneous group of lymphoproliferative disorders originated in B-lymphocytes, T-lymphocytes or natural killer cells. It is estimated that in 2015 around 30,000 new malignant lymphoma cases were diagnosed in Japan [National Cancer Center, Japan 2015], and the majority is diagnosed as NHL, comprise over 90% of all malignant lymphoma cases [Lymphoma Study Group of Japanese Pathologists 2000]. Diffuse Large B-Cell lymphoma (DLBCL) is the most common type of adult NHL in Japan, making up about 30 to 40% of NHL. PMBCL is a distinct subtype of NHL that histologically can be indistinguishable from DLBCL and account only for about 2.5% of all NHL cases [Jackson MW, et al 2016]. This subtype tends to occur in young adults with a median age of 35 years with a slight female predominance [Aisenberg AC 1999] [Faris JE, et al 2009] [Cazals-Hatem D, et al 1996]. Interestingly, gene expression profiling has revealed that the pattern of gene expression in PMBCL is more similar to classical Hodgkin's lymphoma than DLBCL [Rosenwald A, et al 2003] [Savage KJ, et al 2003].

The optimal therapeutic approach to PMBCL is controversial due to the limited availability of prospective studies resulted from the rarity of the disease. In the absence of randomized PMBCL clinical trials, the therapeutic approaches for PMBCL have been the same as the ones used for other subtypes of DLBCL, which is R-CHOP followed by +/- involved-field radiotherapy (IFRT) is the preferred options for front line treatment per the Japanese Society of Hematology (JSH) practical guidelines for hematological malignancies [Japanese Society of Hematology 2018].

There is currently very limited data available regarding the optimal treatment for relapsed or refractory PMBCL if there is a poor response to this first-line therapy. The prognosis in patients who either do not respond to first-line therapy or relapse is dismal with OS at 2 years of 15% [Tomassetti S, et al 2019]. The current approach is to extrapolate from modalities commonly used in the relapsed and refractory setting for other DLBCL subtypes like high-dose chemotherapy with autologous hematopoietic stem cell transplantation (auto-SCT) following front line or salvage chemotherapy regimens for auto-SCT ineligible subjects [Japanese Society of Hematology 2018]. Based on a systematic literature review of clinical outcomes in rrPMBCL in 2017 [Systematic Literature Review 2017], there is no published randomized controlled trial and only 2 single-arm clinical studies with limited size (6 and 15 each) in participants with rrPMBCL who either failed or were ineligible for auto-SCT [Zinzani PL, et al 2017] [Jacobsen ED, et al 2015]. These studies evaluated the efficacy of brentuximab vedotin (anti-CD30 antibody) and the objective response rate was not favorable (13% and 17%, respectively). The lack of randomized clinical trials as well as the limited ORR in the Phase 2 trials suggests the high unmet medical needs in rrPMBCL.

A phase 2 study (KEYNOTE-170) investigated the efficacy and safety of pembrolizumab in participants with rrPMBCL or relapsed or refractory Richter Syndrome (rrRS) in overseas.

In the rrPMBCL cohort of this study, 53 participants with rrPMBCL who have failed auto-SCT or were ineligible for auto-SCT and have failed ≥ 2 lines of prior treatments were treated with pembrolizumab 200 mg Q3W. In All Subject as Treated (ASaT) population (n=53), pembrolizumab showed ORR of 45.3% (24/53 participants; 95% CI, 31.6%-59.6%) per blinded independent central review, and median DOR was not reached (range, 1.1+ to 22.0+ months) among the participants with objective response. Pembrolizumab was generally well tolerated in the ASaT population. On Jun-2018, the United States Food and Drug Administration (US FDA) granted approval to pembrolizumab for both adult and pediatric rrPMBCL patients who have progressed after 2 or more lines of prior therapy.

Given the clinical benefit of pembrolizumab monotherapy in rrPMBCL and that there are high unmet medical needs in the treatment of rrPMBCL in Japan, we plan to conduct a multi-center, phase 1 study of pembrolizumab in Japanese participants with rrPMBCL.

2.2 Background

Refer to the IB/approved labeling for detailed background information on MK-3475 IB for detailed background information on pembrolizumab.

2.2.1 Pharmaceutical and Therapeutic Background

2.2.1.1 Pembrolizumab (MK-3475) Pharmaceutical and Therapeutic Background

Pembrolizumab is a potent humanized IgG4 mAb with high specificity of binding to the PD-1 receptor, thus inhibiting its interaction with PD-L1 and PD-L2. Based on preclinical in vitro data, pembrolizumab has high affinity and potent receptor blocking activity for PD-1. Pembrolizumab has an acceptable preclinical safety profile and is in clinical development as an IV immunotherapy for advanced malignancies. KEYTRUDA® (pembrolizumab) is indicated for the treatment of patients across a number of indications.

The importance of intact immune surveillance in controlling outgrowth of neoplastic transformation 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 (Tregs) correlates with improved prognosis and long-term survival in many solid malignancies, such as ovarian, colorectal, and pancreatic cancer; hepatocellular carcinoma; malignant melanoma; and renal cell carcinoma. Tumor-infiltrating lymphocytes can be expanded ex vivo and reinfused, inducing durable objective tumor responses in cancers such as melanoma [Dudley, M. E., et al 2005] [Hunder, N. N., et al 2008].

The PD-1 receptor-ligand interaction is a major pathway hijacked by tumors to suppress immune control. The normal function of PD-1, expressed on the cell surface of activated T cells under healthy conditions, is to down-modulate unwanted or excessive immune responses, including autoimmune reactions. PD-1 (encoded by the gene Pdcd1) is an Ig superfamily member related to CD28 and cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4) that has been shown to negatively regulate antigen receptor signaling upon

engagement of its ligands (PD-L1 and/or PD-L2) [Greenwald, R. J., et al 2005] [Okazaki, T., et al 2001].

The structure of murine PD-1 has been resolved [Zhang, X., et al 2004]. PD-1 and family members are type I transmembrane glycoproteins containing an Ig variable-type domain responsible for ligand binding and a cytoplasmic tail that is 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 (ITSM). Following T-cell stimulation, PD-1 recruits the tyrosine phosphatases SHP-1 and SHP-2 to ITSM within its cytoplasmic tail, leading to the dephosphorylation of effector molecules such as CD3 zeta, protein kinase C-theta, and zeta-chain-associated protein kinase, which are involved in the CD3 T-cell signaling cascade [Okazaki, T., et al 2001] [Chemnitz, J. M., et al 2004] [Sheppard, K-A, et al 2004] [Riley, J. L. 2009]. The mechanism by which PD-1 down modulates T-cell responses is similar to, but distinct from that of CTLA-4 as 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 rrPMBCL.

2.2.2 Preclinical and Clinical Studies

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

2.2.3 Ongoing Clinical Studies

Ongoing clinical studies with pembrolizumab are being conducted in multiple solid tumors and hematologic malignancies. In addition, multiple combinations with pembrolizumab are also being investigated. Refer to pembrolizumab IB for study details.

2.3 Benefit/Risk Assessment

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

As a result of global Phase 2 study (KEYNOTE-170), pembrolizumab treatment resulted in an ORR of 45.3%, and median DOR was not reached at the time of date cutoff (range, 1.1+ to 22.0+ months) in participants with rrPMBCL. In terms of safety, pembrolizumab was generally well tolerated in participants with rrPMBCL.

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

3 HYPOTHESES, OBJECTIVES, AND ENDPOINTS

All objectives and endpoints apply to Japanese participants with rrPMBCL:

Primary Objective	**Primary Endpoint**
To evaluate objective response using IWG Revised Response Criteria for Malignant Lymphoma (Appendix 9) as assessed by independent central review.	Objective response: complete response (CR) or partial response (PR).
To evaluate the safety and tolerability of pembrolizumab.	-Adverse event -Discontinuing study intervention due to an adverse event
Secondary Objectives	**Secondary Endpoints**
-To evaluate disease control using IWG Revised Response Criteria for Malignant Lymphoma (Appendix 9) as assessed by independent central review. -To evaluate objective response and disease control using IWG Revised Response Criteria for Malignant Lymphoma (Appendix 9) as assessed by the investigator.	-Disease control: CR, PR, or stable disease (SD). -Objective response: CR or PR.
Tertiary/Exploratory Objectives	**Tertiary/Exploratory Endpoints**
To evaluate duration of response (DOR), progression free survival (PFS) using IWG Revised Response Criteria for Malignant Lymphoma (Appendix 9) as assessed by independent central review and the investigator, and overall survival (OS).	-DOR: the time from the first documented evidence of CR or PR to the earliest date of PD or death due to any cause, whichever comes first, for individuals with a CR or PR. -PFS: the time from the first dose of study treatment to the first documented disease progression or death due to any cause, whichever occurs first. -OS: the time from the first dose of study treatment to death due to any cause.
To evaluate the objective response using the 5-point scale according to the Lugano Classification (Appendix 10) as assessed by independent central review.	Objective response: CR or PR.

4 STUDY DESIGN

4.1 Overall Design

This is a multicenter, open label, non-randomized Phase 1 study of pembrolizumab monotherapy in Japanese participants with rrPMBCL who have failed auto-SCT or relapsed after auto-SCT, or were ineligible for auto-SCT and have failed ≥ 2 lines of prior treatments or relapse after auto-SCT. This study will evaluate the efficacy and safety of pembrolizumab. This study is conducted in Japan.

The study design is shown in Figure 1. Five (5) participants will be enrolled in this study and will receive pembrolizumab 200 mg Q3W. The details about the eligible criteria are described in Sections 5.1 and 5.2.

Five (5) participants will be enrolled in this study and the anti-tumor activity at the timing of the Week 12 of the 5th evaluable participant will be reviewed by independent central review. If only <5 participants are enrolled over 1 year from the initiation of the study, the enrollment may possibly be stopped, and the efficacy/safety will be assessed based on the enrolled participants with 12 weeks follow-up data.

Participants will receive pembrolizumab 200 mg Q3W up to 35 cycles (approximately 2 years) from the first dose of the study treatment, or until disease progression is confirmed by the investigator using IWG Revised Response Criteria for Malignant Lymphoma, unacceptable AEs, investigator's decision to discontinue treatment, or other reasons requiring cessation of treatment (Section 7.1). Because of the possibility of immunotherapy-related tumor flare, participants who show initial radiographic progression, if they are clinically stable, may be continued on therapy at the discretion of the investigator. A follow-up scan should be obtained at least 4 weeks later to confirm progression.

Adverse events will be monitored throughout the study and graded in severity according to the guidelines outlined in the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) v5.0. The reporting period for adverse events is described in Section 8.4.

Participants who discontinue study treatment for reasons other than progressive disease will have post-treatment follow-up for disease status (including imaging) until disease progression is identified by the investigator, the start of new anticancer treatment, death, withdrawal of consent, or the end of the study, whichever occurs first (See Section 8.9.3). There is no re-treatment period in this study.

Participants who experience 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 (84 ±14 days) to assess for survival status until death, withdrawal of consent, or the end of the study, whichever occurs first (See Section 8.9.3).

After the approval of Protocol amendment 03, the study will be completed at the Safety Follow-up visit (scheduled 30 days after the last dose) or imaging assessment 120 weeks from the allocation date, of the last participant, whichever is later. If the study intervention is

still ongoing at Week 120 of the last participant, further study intervention should be discontinued, and no further visits will be required after the Safety Follow-up visit which scheduled 30 days after the last dose. Participants in the Imaging Follow-up Phase or Survival Follow-up Phase will be discontinued from the study and no further visits will be required.

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

4.2 Scientific Rationale for Study Design

There is currently very limited data available regarding the optimal treatment for rrPMBCL if there is a poor response to this first-line therapy. The prognosis in patients who either did not respond to first-line therapy or relapsed is poor with OS at 2 years of 15% [Tomassetti S, et al 2019]. PMBCL is very rare cancer and account only for about 2.5% of all NHL cases [Jackson MW, et al 2016]. The lack of randomized clinical trials as well as the limited ORR in the previous Phase 2 trials suggest the high unmet medical needs in rrPMBCL.

4.2.1 Rationale for Endpoints

4.2.1.1 Efficacy Endpoints

The primary efficacy objective of this study is to evaluate objective response using IWG Revised Response Criteria for Malignant Lymphoma (Appendix 9) [Cheson, B. D., et al 2007] as assessed by independent central review. Disease control as assessed by the independent central review will be evaluated as a secondary endpoint. The secondary efficacy endpoints also include objective response and disease control using IWG Revised Response Criteria for Malignant Lymphoma (Appendix 9) as assessed by the investigator. DOR, PFS and OS will be evaluated as exploratory endpoints. Objective response using the 5-point scale per the Lugano Classification (Appendix 10) [Cheson, B. D., et al 2014] will also be evaluated as an exploratory endpoint.

Objective response, disease control, DOR and PFS are acceptable measures of clinical benefit of a new antineoplastic therapy. The primary efficacy endpoint of objective response will be assessed by independent central review to minimize the bias in the response assessments. OS has been recognized as the gold standard for the demonstration of superiority of a new antineoplastic therapy in randomized clinical studies. In this study, DOR, PFS and OS will be measured as exploratory endpoint because of the small sample size.

IWG Revised Response Criteria for Malignant Lymphoma will be applied by the site as the primary measure for assessment of disease response and as a basis for all protocol guidelines related to participant status (eg, discontinuation of study intervention).

4.2.1.2 Safety Endpoints

The primary safety objective of this study is to characterize the safety and tolerability of pembrolizumab in participants with rrPMBCL. 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 5.0.

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 CCI [redacted]
- 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

4.4 Beginning and End-of-Study Definition

The overall study begins when the first participant (or their legally acceptable representative) provides documented informed consent. The overall study ends when the last participant completes the last study-related contact, withdraws consent, or is lost to follow-up (ie, the participant is unable to be contacted by the investigator). For purposes of analysis and reporting, the overall study ends when the Sponsor receives the last laboratory result or at the time of final contact with the last participant, whichever comes last.

4.4.1 Clinical Criteria for Early Study Termination

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

5 STUDY POPULATION

Male/Female participants with rrPMBCL and who are at least 18 years of ages on the day of signing informed consent 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

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

Type of Participant and Disease Characteristics

1. Have diagnosis of PMBCL, according to the World Health Organization (WHO) classification of neoplasms of the hematopoietic and lymphoid tissues (WHO Criteria, 2008 [Swedlow SH, et al 2008]) by local pathological review.
2. Have relapsed*[a] or refractory*[b] PMBCL and:
   - Have relapsed after auto-SCT or have failed to achieve a CR or PR within 60 days of auto-SCT. Subjects may have received intervening therapy after auto-SCT for relapsed or refractory disease, in which case they must have relapsed after or be refractory to their last treatment.

   OR

   - For subjects who are ineligible for auto-SCT, have received at least ≥ 2 lines of prior therapy and have failed to respond to or relapsed after their last line of treatment. For subjects who received consolidative local radiotherapy after systemic therapy, local radiotherapy will not be considered as a separate line of treatment.

   *[a] **Relapsed Disease**: progression of disease after achieving a remission to the most recent therapy

   *[b] **Refractory Disease**: failure to achieve CR or PR to the most recent therapy
3. Have been previously exposed to rituximab as part of prior lines of treatment.
4. Have radiographically measurable disease by local institutional review, defined as at least one lesion that can be accurately measured in at least two dimensions with appropriate anatomic imaging (CT scan or magnetic resonance imaging [MRI]). Minimum measurement must be > 15 mm in the longest diameter.
5. Have a performance status of 0 or 1 on the ECOG Performance Status.
   Note: evaluation of ECOG Performance Status is to be performed within 7 days prior to the first dose of study intervention.
6. Have a life expectancy of at least 3 months.
7. Demonstrate adequate organ function as defined in Table 1. Specimens must be collected within 7 days prior to the first day of study intervention.

Table 1 Adequate Organ Function Laboratory Values

System	Laboratory Value
Hematological	
Absolute neutrophil count	≥1,000/mcL
Platelets	≥75,000/mcL
Hemoglobin	≥8 g/dL or ≥5.0 mmol/L
Renal	
Serum creatinine or creatinine clearance (CrCl) (measured or calculated) [a] or Glomerular Filtration Rate (GFR) in place of CrCl	≤1.5 X ULN or ≥60 mL/min for participants with creatinine levels >1.5 X ULN
Hepatic	
Total bilirubin (serum)	≤1.5 X ULN or Direct bilirubin ≤ULN for participants with total bilirubin levels >1.5 X ULN
AST (SGOT) and ALT (SGPT)	≤2.5 X ULN or ≤5 X ULN for participants with liver metastases
Coagulation	
International Normalized Ratio (INR) or Prothrombin Time (PT) Activated Partial Thromboplastin Time (aPTT)	≤1.5 X ULN unless participant is receiving anticoagulant therapy as long as PT or aPTT is within therapeutic range of intended use of anticoagulants

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

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

Demographics

8. Is male or female, at least 18 years of age at the time of signing the informed consent.

Male Participants

9. Male participants are eligible to participate if they agree to the following during the intervention period and for at least 120 days after the last dose of study intervention:

- Refrain from donating sperm

PLUS either:

- Be abstinent from heterosexual intercourse as their preferred and usual lifestyle (abstinent on a long term and persistent basis) and agree to remain abstinent

OR

- Must agree to use contraception unless confirmed to be azoospermic (vasectomized or secondary to medical cause [Appendix 5]) as detailed below:
  - Agree to use a male condom plus partner use of an additional contraceptive method when having penile-vaginal intercourse with a WOCBP who is not currently pregnant. Note: Men with a pregnant or breastfeeding partner must agree to remain abstinent from penile-vaginal intercourse or use a male condom during each episode of penile-vaginal penetration.

- Male participants must also agree to use male condom when engaging in any activity that allows for passage of ejaculate to another person of any sex.

Female Participants

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

- Is not a WOCBP

OR

- Is a WOCBP and using a contraceptive method that is highly effective (with a failure rate of <1% per year), or be abstinent from heterosexual intercourse as their preferred and usual lifestyle (abstinent on a long term and persistent basis), as described in Appendix 5 during the intervention period and for at least 120 days after the last dose of study intervention. The investigator should evaluate the potential for contraceptive method failure (ie, noncompliance, recently initiated) in relationship to the first dose of study intervention.

- A WOCBP must have a negative highly sensitive pregnancy test (urine or serum) 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.

- Abstains from breastfeeding during the study intervention period and for at least 120 days after study intervention.

- Medical history, menstrual history, and recent sexual activity has been reviewed by the investigator to decrease the risk for inclusion of a woman with an early undetected pregnancy.

Informed Consent

The participant (or legally acceptable representative if applicable) provides written informed consent for the study.

5.2 Exclusion Criteria

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

Medical Conditions

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

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

Prior/Concomitant Therapy

2. 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).

3. Has received CAR T-cell therapy.

4. Has received a monoclonal antibody or radiation therapy within 4 weeks prior to the first dose of study intervention; has received prior chemotherapy or targeted small molecule therapy within 2 weeks prior to the first dose of study intervention; OR has not recovered (i.e., ≤ Grade 1 or at baseline) from adverse events due to a previously administered agent above.

   Note: Subjects with ≤ Grade 2 neuropathy are an exception to this criterion and may qualify for the study.

   Note: Toxicity that has not recovered to ≤ Grade 1 is allowed if it meets the inclusion requirements for laboratory parameters defined in Table 1.

5. Has had major surgery within 3 weeks prior to first dose of study intervention.

   Note: Adequate wound healing after major surgery must be assessed clinically, independent of time elapsed for eligibility.

6. Has received a live vaccine within 30 days prior to the first dose of study drug (See Section 6.5.2)

Prior/Concurrent Clinical Study Experience

7. Is currently participating in or has participated in a study of an investigational agent or has used an investigational device within 4 weeks prior to the first dose of study intervention.

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

Diagnostic Assessments

8. Has a diagnosis of immunodeficiency or is receiving chronic systemic steroid therapy (in dosing exceeding 10 mg daily of prednisone equivalent, refer to Section 6.5.2) or any other form of immunosuppressive therapy within 7 days prior the first dose of study drug.

9. Has a known additional malignancy that is progressing or has required active treatment within the past 3 years.
   Note: Participants with basal cell carcinoma of the skin, squamous cell carcinoma of the skin, or carcinoma in situ (eg, breast carcinoma, cervical cancer in situ) that have undergone potentially curative therapy are not excluded.

10. 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.

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

12. 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.

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

14. Has an active infection requiring systemic therapy.

15. Has a known history of HIV infection. No HIV testing is required unless mandated by local health authority.

16. 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.

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

17. 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.

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

Other Exclusions

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

20. Has had an allogeneic hematopoetic stem cell/solid organ transplantation within the last 5 years. (Participants who have had a transplant greater than 5 years ago are eligible as long as there are no symptoms of Graft versus Host Disease.)

5.3 Lifestyle Considerations

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.

5.4 Screen Failures

Screen failures are defined as participants who consent 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 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

If a participant discontinues from study intervention before the first on-study disease assessment, a replacement participant may be enrolled if deemed appropriate by the investigator and Sponsor. The replacement participant will be assigned a unique treatment/randomization number. The study site should contact the Sponsor for the replacement participant's treatment/randomization number.

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 provided by the Sponsor will be packaged to support enrollment and replacement participants as required. When a replacement participant is required, the Sponsor or designee needs to be contacted before dosing the replacement supplies. 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 2.

Table 2 Study Interventions

Arm Name	Arm Type	Intervention Name	Intervention Type	Dose Formulation	Unit Dose Strength(s)	Dosage Level(s)	Route of Administration	Regimen/ Treatment Period	Use	IMP/NIMP	Sourcing
N/A	Experimental	Pembrolizumab	Drug	Solution	25 mg/mL	200 mg	IV Infusion	Q3W; Day 1 in each cycle up to 35 cycles	Test Product	IMP	Central

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 supplies indicated in Table 2 will be provided per the "Sourcing" column depending upon local country operational requirements. If local sourcing, every attempt should be made to source these supplies from a single lot/batch number.

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

6.2 Preparation/Handling/Storage/Accountability

6.2.1 Dose Preparation

Details on preparation and administration of pembrolizumab 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

Participants in this study will be allocated by nonrandom assignment.

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

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

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

6.5 Concomitant Therapy

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 vaccinations specifically prohibited, discontinuation from study intervention may be required. The investigator should discuss any questions regarding this with the Sponsor's Clinical Director. The final decision on any supportive therapy or vaccinations 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.

All concomitant medications received within 28 days before the first dose of study intervention and up to 30 days after the last dose of study intervention should be recorded. All concomitant medications administered during SAEs or ECIs are to be recorded. SAEs and ECIs are defined in Section 8.4.

6.5.1 Acceptable Concomitant Medications

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. Surgery or radiotherapy for tumor control is not permitted during the study; however, radiotherapy or procedures for symptom management are allowed with sponsor approval. All concomitant medication will be recorded on the CRF including all prescription, OTC, herbal supplements, and IV medications and fluids. If changes occur during the study period, documentation of drug dosage, frequency, route, and date may also be included on the CRF.

6.5.2 Prohibited Concomitant Medications

The following medications and vaccinations are prohibited during the study:

- Antineoplastic systemic chemotherapy, biological therapy, or immunotherapy not specified in this protocol
- Investigational agents other than pembrolizumab
- Radiation therapy
    - Note: Radiation therapy to a symptomatic soft tissue lesion, bone lesions, or to the brain may be allowed after consultation with Sponsor.
    - Note: Radiation therapy is not allowed within 4 weeks prior to the first dose of study intervention.
- Live or live attenuated vaccines within 30 days prior to the first dose of study intervention and while participating in the study. Examples of live vaccines include, but are not limited to the following: measles, mumps, rubella, varicella/zoster, yellow fever, rabies, BCG, and typhoid vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed; however, intranasal influenza vaccines (eg, FluMist®) are live attenuated vaccines and are not allowed.
- Systemic glucocorticoids except when used for the following purposes:.
    - To modulate symptoms of an AE that is suspected to have an immunologic etiology
    - For the prevention of emesis
    - To premedicate for IV contrast allergies
    - To treat COPD exacerbations (only short-term oral or IV use in doses >10 mg/day prednisone equivalent)
    - For chronic systemic replacement not to exceed 10 mg/day prednisone equivalent
- Other glucocorticoid use except when used for the following purposes:
    - For topical use or ocular use
    - Intraarticular joint use
    - For inhalation in the management of asthma or chronic obstructive pulmonary disease

6.5.3 Rescue Medications and Supportive Care

Participants should receive appropriate supportive care measures as deemed necessary by the treating investigator. Suggested supportive care measures for the management of AEs associated with study intervention are outlined along with the dose modification guidelines in Section 6.6.1. Where appropriate, these guidelines include the use of oral or IV treatment with corticosteroids, as well as additional anti-inflammatory agents if symptoms do not improve with administration of corticosteroids. Note that several courses of steroid tapering may be necessary as symptoms may worsen when the steroid dose is decreased. For each disorder, attempts should be made to rule out other causes such as metastatic disease or bacterial or viral infection, which might require additional supportive care. The treatment guidelines are intended to be applied when the investigator determines the events to be related to pembrolizumab.

Note: If after the evaluation of the event, it is determined not to be related to pembrolizumab, the investigator does not need to follow the treatment guidance. Refer to Table 3 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 Dose Modification

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

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

Dose Modification and Toxicity Management Guidelines for irAEs associated with pembrolizumab monotherapy, coformulations, or IO combinations are provided in Table 3.

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

General instructions:

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

irAEs	Toxicity Grade (CTCAE v5.0)	Action With Pembrolizumab Monotherapy, Coformulations or IO Combinations	Corticosteroid and/or Other Therapies	Monitoring and Follow-up
Pneumonitis	Grade 2	Withhold	• Administer corticosteroids (initial dose of 1 to 2 mg/kg prednisone or equivalent) followed by taper • Add prophylactic antibiotics for opportunistic infections	• Monitor participants for signs and symptoms of pneumonitis • Evaluate participants with suspected pneumonitis with radiographic imaging and initiate corticosteroid treatment
	Recurrent Grade 2, Grade 3 or 4	Permanently discontinue		

irAEs	Toxicity Grade (CTCAE v5.0)	Action With Pembrolizumab Monotherapy, Coformulations or IO Combinations	Corticosteroid and/or Other Therapies	Monitoring and Follow-up
Diarrhea/Colitis	Grade 2 or 3	Withhold	• Administer corticosteroids (initial dose of 1 to 2 mg/kg prednisone or equivalent) followed by taper	• Monitor participants for signs and symptoms of enterocolitis (ie, diarrhea, abdominal pain, blood or mucus in stool with or without fever) and of bowel perforation (ie, peritoneal signs and ileus) • Participants with ≥Grade 2 diarrhea suspecting colitis should consider GI consultation and performing endoscopy to rule out colitis • Participants with diarrhea/colitis should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion
	Recurrent Grade 3 or Grade 4	Permanently discontinue		
AST or ALT Elevation or Increased Bilirubin	Grade 2 [a]	Withhold	• Administer corticosteroids (initial dose of 0.5 to 1 mg/kg prednisone or equivalent) followed by taper	• Monitor with liver function tests (consider weekly or more frequently until liver enzyme value returned to baseline or is stable)
	Grade 3 [b] or 4 [c]	Permanently discontinue	• Administer corticosteroids (initial dose of 1 to 2 mg/kg prednisone or equivalent) followed by taper	
T1DM or Hyperglycemia	New onset T1DM or Grade 3 or 4 hyperglycemia associated with evidence of β-cell failure	Withhold [d]	• Initiate insulin replacement therapy for participants with T1DM • Administer antihyperglycemic in participants with hyperglycemia	• Monitor participants for hyperglycemia or other signs and symptoms of diabetes

irAEs	Toxicity Grade (CTCAE v5.0)	Action With Pembrolizumab Monotherapy, Coformulations or IO Combinations	Corticosteroid and/or Other Therapies	Monitoring and Follow-up
Hypophysitis	Grade 2	Withhold	• Administer corticosteroids and initiate hormonal replacements as clinically indicated	• Monitor for signs and symptoms of hypophysitis (including hypopituitarism and adrenal insufficiency)
	Grade 3 or 4	Withhold or permanently discontinue [d]		
Hyperthyroidism	Grade 2	Continue	• Treat with nonselective beta-blockers (eg, propranolol) or thionamides as appropriate	• Monitor for signs and symptoms of thyroid disorders
	Grade 3 or 4	Withhold or permanently discontinue [d]		
Hypothyroidism	Grade 2, 3 or 4	Continue	• Initiate thyroid replacement hormones (eg, levothyroxine or liothyronine) per standard of care	• Monitor for signs and symptoms of thyroid disorders
Nephritis: grading according to increased creatinine or acute kidney injury	Grade 2	Withhold	• Administer corticosteroids (prednisone 1 to 2 mg/kg or equivalent) followed by taper	• Monitor changes of renal function
	Grade 3 or 4	Permanently discontinue		
Neurological Toxicities	Grade 2	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 3 or 4	Permanently discontinue		

irAEs	Toxicity Grade (CTCAE v5.0)	Action With Pembrolizumab Monotherapy, Coformulations or IO Combinations	Corticosteroid and/or Other Therapies	Monitoring and Follow-up
Myocarditis	Asymptomatic cardiac enzyme elevation with clinical suspicion of myocarditis (which was previously myocarditis Grade 1 using CTCAE v4.0)	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 2, 3 or 4	Permanently discontinue		
Exfoliative Dermatologic Conditions	Suspected SJS, TEN, or DRESS	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology or exclude other causes
	Confirmed SJS, TEN, or DRESS	Permanently discontinue		
Hematological toxicity (cHL or PMBCL only)	Grade 4	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology or exclude other causes • Can be resumed when ≤ Grade 1
All Other irAEs	Persistent Grade 2	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology or exclude other causes
	Grade 3	Withhold or discontinue based on the event [e]		
	Recurrent Grade 3 or Grade 4	Permanently discontinue		

irAEs	Toxicity Grade (CTCAE v5.0)	Action With Pembrolizumab Monotherapy, Coformulations or IO Combinations	Corticosteroid and/or Other Therapies	Monitoring and Follow-up

AE(s)=adverse event(s); ALT= alanine aminotransferase; AST=aspartate aminotransferase; cHL=classical Hodgkin lymphoma; 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; PMBCL=primary mediastinal B-cell lymphoma; SJS=Stevens-Johnson Syndrome; T1DM=type 1 diabetes mellitus; TEN=Toxic Epidermal Necrolysis; ULN=upper limit of normal.

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

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

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

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

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

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

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 4.

Table 4 Pembrolizumab Infusion Reaction Dose Modification and Treatment Guidelines

NCI CTCAE Grade	Treatment	Premedication at Subsequent Dosing
Grade 1 Mild reaction; infusion interruption not indicated; intervention not indicated	Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator	None
Grade 2 Requires therapy or infusion interruption but responds promptly to symptomatic treatment (eg, antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for ≤24 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 v5.0 (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.

6.9 Standard Policies

Not applicable.

7 DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT WITHDRAWAL

7.1 Discontinuation of Study Intervention

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

As certain data on clinical events beyond study intervention discontinuation may be important to the study, they must be collected through the participant's last scheduled follow-up, even if the participant has discontinued study intervention. Therefore, all participants who discontinue study intervention before completion of the protocol-specified treatment period will still continue to be monitored in this study and participate in the study visits and procedures as specified in Section 1.3 and Section 8.9.3 unless the participant has withdrawn from the study (Section 7.2).

Participants may discontinue study intervention at any time for any reason or be discontinued from the study intervention at the discretion of the investigator should any untoward effect occur. In addition, a participant may be discontinued from study intervention by the investigator or the Sponsor if study intervention is inappropriate, the study plan is violated, or for administrative and/or other safety reasons. Specific details regarding procedures to be performed at study intervention discontinuation are provided in Section 8.1.9 and Section 8.9.3.

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

- The participant or participant's legally acceptable representative requests to discontinue study intervention.
- Any prolonged interruption of study intervention beyond the permitted periods, for irAE management or other allowed dose interruptions, as noted in Section 6.6.1, require Sponsor consultation prior to restarting treatment. If treatment will not be restarted, the participant will continue to be monitored in the study and the reason for discontinuation of study intervention will be recorded in the medical record.
- The participant has a medical condition or personal circumstance which, in the opinion of the investigator and/or Sponsor, placed the participant at unnecessary risk from continued administration of study intervention.
- The participant has a confirmed positive serum pregnancy test.
- Radiographic disease progression outlined in Section 8.2 (exception if the Sponsor approves treatment continuation).
- Progression or recurrence of any malignancy, or occurrence of another malignancy that requires active treatment.

- Intercurrent illness other than another malignancy as noted above that prevents further administration of treatment.

- Investigator's decision to discontinue treatment.

- Completion of 35 treatments with pembrolizumab.

  Note: 35 cycles are calculated from 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.

Discontinuation from study intervention is "permanent." Once a participant is discontinued from study intervention, he/she shall not be allowed to restart study intervention.

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, 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 used for screening or baseline purposes provided the procedures meet the protocol-specified criteria and were performed within the time frame defined in the SoA.
- Additional evaluations/testing may be deemed necessary by the investigator and or the Sponsor for reasons related to participant safety. In some cases, such evaluation/testing may be potentially sensitive in nature (eg, HIV, hepatitis C), and thus local regulations may require that additional informed consent be obtained from the participant. In these cases, such evaluations/testing will be performed in accordance with those regulations.
- 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

Informed consent will adhere to IRB/IEC requirements, applicable laws and regulations, and Sponsor requirements. The ICF, any subsequent revised ICF, and any written information provided to the participant must receive the IRB/IEC's approval/favorable opinion in advance of use.

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

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

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

8.1.1.1 General Informed Consent

Specifics about the study and the study population are to be included in the ICF.

The participant (or their legally acceptable representative) should be informed in a timely manner if new information becomes available that may be relevant to the participant's willingness to continue participation in the study. The communication of this information will be provided and documented via a revised consent form or addendum to the original consent form that captures the participant's or the participant's legally acceptable representative's dated signature.

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

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. At the time of intervention allocation, site personnel will add the treatment/randomization number to the participant identification card.

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

8.1.4 Medical History

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

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

8.1.5 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 the first dose of study intervention.

8.1.5.2 Concomitant Medications

The investigator or qualified designee will record medication, if any, taken by the participant during the study through the Safety Follow-up Visit.

All medications related to reportable SAEs and ECIs should be recorded as defined in Section 8.4.

8.1.5.3 Prior Cancer Treatment

The investigator or qualified designee will review all prior cancer treatments including but not limited to systemic treatments, prior transplantation, radiation, and surgeries and record in the study database.

Prior SCT details and acute and/or chronic Graft versus Host Disease, maximum grade, and dates will be collected.

8.1.5.4 Subsequent Antineoplastic Therapy

The investigator or qualified designee will review all new antineoplastic therapy initiated after the last dose of study intervention.

Collect transplant parameters after study intervention to include the conditioning regimen, date, and type of transplant.

If a participant initiates a new antineoplastic therapy within 30 days after the last dose of study intervention, the 30-day Safety Follow-up visit must occur before the first dose of the new therapy. Once new antineoplastic therapy has been initiated, the participant will move into survival follow-up.

8.1.6 Assignment of Screening Number

All consented participants will be given a unique screening number that will be used to identify the participant for all procedures that occur before intervention allocation. Each

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

Any participant who is screened multiple times will retain the original screening number assigned at the initial screening visit. Specific details on the screening/rescreening visit requirements are provided in Section 8.9.1.

8.1.7 Assignment of Treatment/Randomization Number

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

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

8.1.8 Study Intervention Administration

Study intervention(s) will be administered by the investigator and/or study staff according to the specifications within the pharmacy manual.

8.1.8.1 Timing of Dose Administration

Dosing and schedules of the study intervention is described in Section 6.1.

First study treatment should begin within 3 days of intervention allocation. After the first cycle, study intervention may be administered ± 3 days of the scheduled dosing date for each infusion due to administrative reasons.

On Day 1 of each cycle, pembrolizumab will be administered at a dose of 200 mg using a 30-minute IV infusion. Sites should make every effort to target infusion timing to be as close to 30 minutes as possible. Given the variability of infusion pumps form site to site, a window of minus (-) 5 minutes and plus (+) 10 minutes is allowed (ie, infusion time is 30 minutes -5min/+10 min).

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

8.1.9 Discontinuation and Withdrawal

Participants who discontinue study intervention before 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 8.9.3.

Participants who withdraw from the study should be encouraged to complete all applicable activities scheduled for the final study visit at the time of withdrawal. Any AEs that are

present at the time of withdrawal should be followed in accordance with the safety requirements outlined in Section 8.4.

8.1.10 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 are 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 Criteria for Assessment of Disease

Antitumor activity of pembrolizumab will be evaluated using IWG Revised Response Criteria for Malignant Lymphoma (Appendix 9).

Lymphoma response assessment by CT/PET, based on the IWG response criteria for malignant lymphoma [Cheson, B. D., et al 2007], will be applied by the site as a basis for all protocol guidelines related participant eligibility and for participant management (eg, discontinuation of study intervention). Assessment of lymphoma B symptoms (Appendix 11) should occur with each lymphoma disease response assessment.

All scheduled imaging for all study participants will be submitted to independent central review for primary efficacy assessment. 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 independent central review if it shows progression, or if it is used to support a response assessment. A detailed description regarding tumor imaging procedures is provided in the Site Imaging Manual.

Antitumor activity of pembrolizumab will also be evaluated as part of exploratory analyses using the Lugano Classification (Appendix 10).

Refer to central review charter for independent central imaging review for both IWG response criteria and Lugano Classification.

8.2.1.1 Disease Assessment of Immunotherapeutic Agents

Immunotherapeutic agents such as pembrolizumab produce antitumor effects by potentiating endogenous cancer-specific immune responses, which may be functionally anergic. The response patterns seen with such an approach may extend beyond the typical time course of responses seen with cytotoxic agents, and can manifest a clinical response after an initial

increase in tumor burden or even the appearance of new lesions. Standard response assessment criteria may not provide a complete response assessment of immunotherapeutic agents such as pembrolizumab. Therefore, in the setting where a participant's assessment shows progressive disease, study intervention may be continued at the discretion of the investigator until the next disease response assessment provided that the participant's clinical condition is stable. However, imaging should occur at any time when there is clinical suspicion of progression.

Refer to Section 8.2.3 for confirmation assessment requirements when a participant's disease response assessment shows progressive disease.

8.2.2 Assessment of Disease and Tumor Response

Disease assessments should be performed per the frequency defined in the SoA (Section 1.3).

CT is the modality of choice for anatomic imaging, and will be the term used in this protocol when anatomic imaging is required. However, if CT with IV contrast is contraindicated, or if dictated by local practice guidelines, MRI may be performed instead.

For tumor burden assessment, CT must be of diagnostic quality. If a combination PET/CT is obtained, and the CT component is of diagnostic quality with IV contrast, that can be used. If the CT component is not of diagnostic quality, a separate diagnostic quality scan must be performed.

8.2.2.1 Initial Disease Assessment

Initial disease assessment or tumor imaging at Screening (CT and PET scans) must be performed within 28 days prior to Cycle 1 Day 1. The site study team must review screening images to confirm the participant has measurable disease per the disease-specific criteria.

Disease assessments or scans performed as part of routine clinical management are acceptable for use as the screening scan if they are of diagnostic quality and performed within 28 days prior to Cycle 1 Day 1.

CT and PET scans should be used throughout the study at time-points designated in Section 1.3-SoA. For lymphomas that are not FDG-avid at Screening, PET scans do not need to be repeated at follow-up assessments.

8.2.2.2 Disease Assessment During the Study

The first on-study imaging assessment should be performed at 12 weeks (±7 days) from the date of allocation. Subsequent tumor imaging by CT-scan should be performed every 12 weeks (±7 days) or more frequently if clinically indicated; PET scan should be performed at Week 12, Week 24, and subsequently as clinically indicated if relapse or recurrence is suspected. Imaging timing should follow calendar days and should not be adjusted for delays in cycle starts. Imaging should continue to be performed until disease progression is identified by the investigator (unless the investigator elects to continue study intervention),

the start of new anticancer treatment, death, withdrawal of consent, or the end of the study, whichever occurs first.

If PET and CT scans at Screening are positive for disease involvement of the neck, subsequent CT scans must include the neck. If PET and CT scans at Screening are negative for disease involvement in the neck, subsequent CT scans are not required to include the neck, unless enlarged lymph nodes are detected during the physical examination, or if otherwise clinically indicated, and at the discretion of the treating physician.

For participants who discontinue study intervention without documented disease progression, every effort should be made to continue monitoring their disease status by tumor imaging using the same imaging schedule used while on treatment (every 12 weeks) to monitor disease status until disease progression is identified by the investigator, the start of new anticancer treatment, death, withdrawal of consent, or the end of the study, whichever occurs first.

Response assessment by CT or PET/CT is based on IWG Revised Response Criteria for Malignant Lymphoma described in Appendix 9. If CR is documented by both CT and FDG-PET, subsequent assessments may be by CT only, with PET used only if relapse or recurrence is suspected. Assessment of lymphoma B symptoms (Appendix 11) should occur with each lymphoma disease response assessment.

8.2.3 Disease Progression Assessments

Treatment response assessments are conducted at the protocol-specified time points, but an additional assessment should occur at any time where there is clinical suspicion of progression.

If a participant has radiographic progression of disease documented at a treatment response assessment, the investigator should determine whether the participant is clinically stable. Clinical stability means:

- Absence of signs and symptoms (including worsening of laboratory values) indicating disease progression
- No decline in ECOG performance status
- Absence of rapid progression of disease
- Absence of progressive tumor at critical anatomical sites

If the participants is clinically unstable, study intervention must be discontinued. Participants who are deemed clinically unstable are not required to have repeat imaging for confirmation. However, it is requested that participants who discontinue due to clinical progression without radiographic progression undergo a tumor imaging scan if they have not had one in the prior 4 weeks.

Participants who are clinically stable may continue study intervention, at the discretion of the investigator, until the next response assessment, which should occur no later than 4 to 6 weeks after the initial determination of progression. If a participant is clinically stable and study intervention is to continue, notification to the sponsor is required and opinion of the participant to continue study intervention should be confirmed.

If, at the confirmatory assessment, the radiographic evidence of progression (enlargement of target lesions above the threshold specified in the criteria, unequivocal progression of non-target lesions, or presence of new lesions) is still present or worsening, progression is considered confirmed. These participants should be discontinued from study intervention, but the investigator, upon consultation with the Sponsor, may keep a clinically stable participant on study intervention as long as the participant is deriving clinical benefit.

If, at the confirmatory assessment, the radiographic evidence of progression is no longer present, the progression is not confirmed, and the participant may continue on treatment provided that they remain clinically stable.

8.2.4 Bone Marrow Biopsy and Aspirate

For all participants, collect bone marrow biopsy and aspirate at baseline. Bone marrow biopsy and aspirate performed as part of routine clinical management are acceptable for use as baseline data if they are performed within 28 days prior to Cycle 1 Day 1. Repeat bone marrow biopsy and aspirate as needed to confirm CR (if subject has baseline bone marrow involvement), and as clinically indicated. Local results of bone marrow biopsy and aspirate will be used for baseline and to confirm CR (or other reason).

8.3 Safety Assessments

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

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

8.3.1 Physical Examinations

8.3.1.1 Full Physical Examination

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

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

8.3.1.2 Directed Physical Examination

For cycles that do not required a full physical examination as defined in Section 1.3, the investigator or qualified designee will perform a directed physical examination as clinically indicated prior to study intervention administration. New clinically significant abnormal findings should be recorded as AEs.

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

8.3.2 Vital Signs

The investigator or qualified designee will take vital signs at the timing specified in the SoA. Vital signs include temperature, pulse, respiratory rate, weight and blood pressure. Height will be measured at Screening only.

8.3.3 Electrocardiograms

A standard 12-lead ECG will be performed using local standard procedures. The timing of ECGs is specified in the SoA. Clinically significant abnormal findings at screening should be recorded as medical history. Additional ECGs may be performed as clinically necessary. Clinically significant abnormal findings seen on all ECGs performed after the first dose of study intervention should be recorded as adverse events.

8.3.4 Clinical Safety Laboratory Assessments

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

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

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

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

Laboratory tests for screening should be performed within 7 days prior to the first dose of study intervention. After Cycle 1, predose laboratory safety tests can be conducted up to 3 days prior to dosing unless otherwise noted on the flow charts.

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

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 of Cycle 1 Day 1. 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 or borderline-positive test result. Pregnancy testing should be conducted at the end of treatment and 30 days follow-up after the last dose of study intervention.

8.3.5 Eastern Cooperative Oncology Group Performance Status

The ECOG Performance Status is standardized criteria to measure how cancer impacts level of functioning (performance status) in terms of ability to care for oneself, daily activity, and physical ability (walking, working, etc.) with grades 0 to 5.

The Investigator or qualified designee will assess ECOG Performance Status (see Appendix 12) at timing specified in the SoA.

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

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

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

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

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

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

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

All AEs, SAEs, and other reportable safety events that occur after the 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 following cessation of study intervention must be reported by the investigator.
- All AEs meeting serious criteria, from the time of intervention 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, must be reported by the investigator.
- All pregnancies and exposure during breastfeeding, from the time of intervention allocation through 120 days following cessation of study intervention, or 30 days following 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 of the time period specified above must be reported immediately to the Sponsor if the event is considered related to study intervention.

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

All initial and follow-up AEs, SAEs, and other reportable safety events will be recorded and reported to the Sponsor or designee within the time frames as indicated in Table 5.

Table 5 Reporting Time Periods and Time Frames for Adverse Events and Other Reportable Safety Events

Type of Event	**Reporting Time Period: Consent to Randomization/ Allocation**	**Reporting Time Period: Randomization/ Allocation through Protocol-specified 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: - participant has been exposed to any protocol-specified intervention (eg, procedure, washout or run-in treatment including placebo run-in) Exception: A positive pregnancy test at the time of initial screening is not a reportable event.	Report all	Previously reported – Follow to completion/ termination; report outcome	Within 24 hours of learning of event
Event of Clinical Interest (requiring regulatory reporting)	Report if: - due to intervention - causes exclusion	Report - potential drug-induced liver injury (DILI) - requiring regulatory reporting	Not required	Within 24 hours of learning of event
Event of Clinical Interest (does 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

ECI=event of clinical interest.

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. SAEs and other reportable safety events, including pregnancy and exposure during breastfeeding, ECIs, cancer, and overdose will be followed until resolution, stabilization, until the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3). The investigator will also make every attempt to follow nonserious AEs that occur in allocated participants for outcome. Further information on follow-up procedures is given in Appendix 3.

8.4.4 Regulatory Reporting Requirements for SAE

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

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

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

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

8.4.5 Pregnancy and Exposure During Breastfeeding

Although pregnancy and infant exposure during breastfeeding are not considered AEs, any pregnancy or infant exposure during breastfeeding 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 ensure that unblinded aggregated efficacy endpoint events and safety data are monitored to safeguard the participants in the study.

8.4.7 Events of Clinical Interest

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

Events of clinical interest for this study include:

1. An overdose of study intervention as defined in Section 8.5.

2. Potential DILI events defined as: 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).

3. Post-transplant complications (see Section 8.4.7.1) that occurred within 18 months from the date of the allogeneic transplant, for subject who were previously exposed to pembrolizumab.

8.4.7.1 Follow-Up Post-Allogeneic Stem Cell Transplantation

For participants who have an allogeneic SCT within 24 months of last dose of pembrolizumab, transplant parameters will be collected, and specific ECIs will be collected for 18 months from the date of the allogeneic transplant, to include graft-versus-host-disease, hepatic veno-occlusive disease or sinusoidal syndrome, febrile syndrome (a steroid-requiring febrile illness without an infectious cause), pulmonary complications, immune-mediated

AEs, critical illness, and transplant-related mortality for all grades, and regardless of relationship to study intervention.

Additional medically important AEs post-allogeneic SCT may be submitted at the investigator's discretion. If available and relevant to an event post-allogeneic SCT, concomitant medications and/or laboratory results may also be reported.

Post-allogenic SCT ECIs that occur after the normal safety follow-up period must be assessed for seriousness and causality and reported to the sponsor as follows:

- within 24 hours if serious regardless of causality or if non-serious and considered to be drug-related; and
- within 5 calendar days if non-serious and not considered to be drug-related.

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

Future biomedical research samples will not be collected in this study.

8.9 Visit Requirements

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

8.9.1 Screening

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

specified time frame. Screening procedures are to be completed within 28 days prior to the first dose of study intervention except for the following:

- Laboratory tests are to be performed within 7 days prior to the first dose of study intervention.
- Evaluation of ECOG Performance Status is to be performed within 7 days prior to the first dose of study intervention.
- For women of reproductive potential, a urine or serum pregnancy test will be performed within 72 hours prior to the first dose of study intervention. If urine pregnancy results cannot be confirmed as negative, a serum pregnancy test will be required (performed by the local study site laboratory).

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

8.9.2 Treatment Period

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

8.9.3 Post Treatment Visit

After the approval of Protocol amendment 03, the study will be completed at the Safety Follow-up visit (scheduled 30 days after the last dose) or imaging assessment 120 weeks from the allocation date, of the last participant, whichever is later. If the study intervention is still ongoing at Week 120 of the last participant, further study intervention should be discontinued, and no further visits will be required after the Safety Follow-up visit which scheduled 30 days after the last dose. Participants in the Imaging Follow-up Phase or Survival Follow-up Phase will be discontinued from the study and no further visits will be required.

8.9.3.1 Discontinuation Visit

The Discontinuation Visit should occur at the time study intervention is discontinued for any reason. If the Discontinuation Visit occurs 30 days from the last dose of study intervention, at the time of the mandatory Safety Follow-up Visit, the Discontinuation Visit procedures and any additional Safety Follow-up procedures should be performed. Visit requirements are outlined in Section 1.3. Additional details regarding participant withdrawal and discontinuation are presented in Section 7.

8.9.3.2 Safety Follow-up Visit

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

8.9.3.3 Imaging Follow-up Visits

Participants who discontinue study intervention for reasons other than verified PD should continue with imaging assessments per the protocol-defined schedule until disease progression is identified by the investigator, the start of new anticancer treatment, death, withdrawal of consent, or the end of the study, whichever occurs first.

8.9.3.4 Survival Follow-up Visits

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

The Sponsor may request survival status be assessed at additional time points during the course of the study. For example, these additional time points may be requested prior to an efficacy interim analysis, and/or final analysis. All participants who are not known to have died prior to the request for these additional survival status time points will be contacted at that time.

9 STATISTICAL ANALYSIS PLAN

This section outlines the statistical analysis strategy and procedures for the study. Changes to analyses made after the protocol has been finalized, but prior to database lock, will be documented in a supplemental SAP (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 9.2-9.12.

Study Design Overview	A Phase 1 clinical study of Pembrolizumab (MK-3475) in participants with relapsed or refractory primary mediastinal large B-cell lymphoma (rrPMBCL)
Intervention Assignment	This is a single arm, non-randomized and open label study.
Analysis Populations	Safety: All-Participants-as-Treated (APaT) Efficacy: All-Participants-as-Treated (APaT)
Primary Endpoint(s)	The primary efficacy endpoint is objective response (CR or PR) as assessed by independent central review using IWG Revised Response Criteria for Malignant Lymphoma. The safety endpoints are adverse event and discontinuing study intervention due to an adverse event.
Secondary Endpoints	Disease control (SD, CR or PR) as assessed by independent central review using IWG Revised Response Criteria for Malignant Lymphoma will be the secondary efficacy endpoint. Objective response and disease control as assessed by investigator using IWG Revised Response Criteria for Malignant Lymphoma will also be the secondary efficacy endpoints.
Statistical Methods for Efficacy/Immunogenicity/ Pharmacokinetic Analyses	ORR and DCR will be estimated together with its 95% confidence interval using an exact method based on the binomial distribution (Clopper-Pearson interval).
Statistical Methods for Safety Analyses	Adverse events will be listed and summarized by counts and frequencies. Laboratory tests, vital signs, and other safety endpoints will be summarized as appropriate.
Interim Analyses	No interim analysis will be performed.
Multiplicity	No multiplicity adjustment is planned since no formal hypothesis testing is planned.
Sample Size and Power	The sample size for this study is expected to be 5 for feasibility.

9.2 Responsibility for Analyses/In-house Blinding

The statistical analyses 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 non-randomized and open-label study, i.e., participants, investigators, and sponsor personnel will be aware of participant intervention assignment after each participant is enrolled and treatment is assigned.

9.3 Hypotheses/Estimation

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

9.4 Analysis Endpoints

9.4.1 Efficacy/Immunogenicity/Pharmacokinetics Endpoints

Objective response as assessed by independent central review using IWG Revised Response Criteria for Malignant Lymphoma will be the primary efficacy endpoint. Objective response is defined as a CR or PR. Objective response rate (ORR) is the proportion of participants in the analysis population with objective response.

Disease control defined as a response of CR, PR or SD as assessed by independent central review using IWG Revised Response Criteria for Malignant Lymphoma will be the secondary efficacy endpoint. Disease control rate (DCR) is the proportion of participants in the analysis population with disease control.

Objective response and disease control as assessed by investigator using IWG Revised Response Criteria for Malignant Lymphoma will also be the secondary endpoints.

DOR as assessed by independent central review and investigator, PFS as assessed by independent central review and investigator, OS and objective response using the 5-point scale according to the Lugano Classification as assessed by independent central review are the exploratory endpoints.

DOR is defined as the time from the first documented evidence of CR or PR to the earliest date of PD or death due to any cause, whichever comes first, for individuals with a CR or PR.

PFS is defined as the time from the first dose of study treatment to the first documented disease progression or death due to any cause, whichever occurs first.

OS is defined as the time from the first dose of study treatment to death due to any cause. Participants who do not die will be censored on the date of the last study assessment or contact.

A description of efficacy measures is provided in Section 4.2.1.1.

9.4.2 Safety Endpoints

The primary safety endpoints are adverse event and discontinuing study intervention due to an adverse event. In addition, safety and tolerability will be assessed by clinical review of all relevant parameters including AEs, laboratory tests, and vital signs.

9.5 Analysis Populations

9.5.1 Safety Analysis Populations

The All Participants as Treated (APaT) population will be used for the analysis of safety data in this study. The APaT population consists of all participants who received at least 1 dose of study intervention.

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

9.5.2 Pharmacokinetic Analysis Populations

No pharmacokinetic analysis is planned in this study.

9.5.3 Efficacy Analysis Populations

The APaT population will be used for the analysis of efficacy data in this study. The APaT population consists of all participants who received at least 1 dose of study intervention.

9.6 Statistical Methods

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

9.6.1 Statistical Methods for Efficacy Analysis

ORR and DCR will be estimated using an exact method based on the binomial distribution together with its 95% confidence interval (Clopper-Pearson interval). Table 6 summarizes the key efficacy analyses.

Table 6 Analysis Strategy for Key Efficacy Variables

Endpoint/Variable (Description, Time Point)	Statistical Method	Analysis Population	Missing Data Approach
Primary efficacy endpoint			
ORR as assessed by independent central review based on IWG Revised Response Criteria for Malignant Lymphoma	Exact method based on binomial distribution	APaT	Participants with missing data are considered non-responders
Secondary efficacy endpoints			
DCR as assessed by independent central review based on IWG Revised Response Criteria for Malignant Lymphoma	Exact method based on binomial distribution	APaT	Participants with missing data are considered non-responders
ORR as assessed by investigator based on IWG Revised Response Criteria for Malignant Lymphoma	Exact method based on binomial distribution	APaT	Participants with missing data are considered non-responders
DCR as assessed by investigator based on IWG Revised Response Criteria for Malignant Lymphoma	Exact method based on binomial distribution	APaT	Participants with missing data are considered non-responders

9.6.2 Statistical Methods for Safety Analysis

Safety and tolerability will be assessed by clinical review of all relevant parameters including AEs, SAEs, laboratory tests, vital signs, and physical examinations. Adverse events will be listed and summarized by counts and frequencies. Laboratory tests, vital signs, and other safety endpoints will be summarized as appropriate.

9.6.3 Summaries of Baseline Characteristics, Demographics, and Other Analyses

9.6.3.1 Demographic and Baseline Characteristics

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

9.6.3.2 Pharmacokinetic and Pharmacodynamic Modeling Analysis

No pharmacokinetic analysis is planned in this study.

9.7 Interim Analyses

No interim analysis will be performed.

9.8 Multiplicity

There will be no multiplicity control in this study since no formal hypothesis testing is planned.

9.9 Sample Size and Power Calculations

The sample size for this study is expected to be 5 for feasibility. Table 7 shows the ORR estimate and the 95% confidence interval (Clopper-Pearson interval) for N=5.

Table 7 Estimated ORR and 95% confidence interval (Clopper-Pearson interval).

Number of objective responses (CR/PR)	ORR (95% CI) %
0	0.0 (0.0, 52.2)
1	20.0 (0.5, 71.6)
2	40.0 (5.3, 85.3)
3	60.0 (14.7, 94.7)
4	80.0 (28.4, 99.5)
5	100.0 (47.8, 100.0)

9.10 Subgroup Analyses

No subgroup analyses will be performed.

9.11 Compliance (Medication Adherence)

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

9.12 Extent of Exposure

The extent of exposure will be summarized as duration of treatment in cycles.

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 and conduct of clinical trials. In all cases, MSD clinical trials will be conducted in compliance with local and/or national regulations (including all applicable data protection laws and regulations), and International Council for Harmonisation Good Clinical Practice (ICH-GCP), and also in accordance with the ethical principles that have their origin in the Declaration of Helsinki.

B. Scope

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

II. Scientific Issues

A. Trial Conduct

1. Trial Design

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

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

2. Site Selection

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

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

3. Site Monitoring/Scientific Integrity

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

B. Publication and Authorship

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

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

III. Participant Protection

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

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

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

B. Safety

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

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

C. Confidentiality

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

D. Genomic Research

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

IV. Financial Considerations

A. Payments to Investigators

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

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

B. Clinical Research Funding

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

C. Funding for Travel and Other Requests

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

V. Investigator Commitment

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

10.1.2 Financial Disclosure

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

The investigator/subinvestigator(s) agree, if requested by the Sponsor in accordance with 21 CFR Part 54, to provide his/her financial interests in and/or arrangements with the Sponsor to allow for the submission of complete and accurate certification and disclosure statements. The investigator/subinvestigator(s) further agree to provide this information on a Certification/Disclosure Form, frequently known as a financial disclosure form, provided by the Sponsor. The investigator/subinvestigator(s) also consent to the transmission of this

information to the Sponsor in the United States for these purposes. This may involve the transmission of information to countries that do not have laws protecting personal data.

10.1.3 Data Protection

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

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

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

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

10.1.3.1 Confidentiality of Data

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

10.1.3.2 Confidentiality of Participant Records

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

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

10.1.3.3 Confidentiality of IRB/IEC Information

The Sponsor is required to record the name and address of each IRB/IEC that reviews and approves this study. The Sponsor is also required to document that each IRB/IEC meets regulatory and ICH GCP requirements by requesting and maintaining records of the names

and qualifications of the IRB/IEC members and to make these records available for regulatory agency review upon request by those agencies.

10.1.4 Publication Policy

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

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

Authorship will be determined by mutual agreement and in line with ICMJE authorship requirements.

10.1.5 Compliance with Study Registration and Results Posting Requirements

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

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

10.1.6 Compliance with Law, Audit, and Debarment

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

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

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

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

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

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

10.1.7 Data Quality Assurance

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

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

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

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

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

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

Study monitors will perform ongoing source data review and verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the

study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

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

10.1.8 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.

10.1.9 Study and Site Closure

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

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

10.2 Appendix 2: Clinical Laboratory Tests

- The tests detailed in Table 8 will be performed by the local laboratory.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5 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.
- Pregnancy testing:
  - Pregnancy testing requirements for study inclusion are described in Section 5.1.
  - Pregnancy testing (urine or serum as required by local regulations) should be conducted at the end of treatment and 30 days follow-up after the last dose of study intervention.
  - Additional serum or urine pregnancy tests may be performed, as determined necessary by the investigator or required by local regulation, to establish the absence of pregnancy at any time during the subject's participation in the study.

Table 8 Protocol-required Safety Laboratory Assessments

Hematology	**Comprehensive Chemistry Panel**	**Urinalysis**	**Other**
Hematocrit	Albumin	Blood	Pregnancy test (serum or urine)[a]
Hemoglobin	Alkaline phosphatase	Glucose	PT/INR
Platelet count	Alanine aminotransferase	Protein	aPTT or PTT
WBC (total and differential) [c]	Aspartate aminotransferase	Specific gravity	Total T3 (or Free T3 [FT3])[b], Free T4 [FT4] and TSH
RBC	Calcium	Microscopic exam, if abnormal results are noted	
Absolute lymphocyte count	Chloride		
Absolute neutrophil count	Creatinine		
	Glucose		
	LDH		
	Magnesium		
	Phosphorus		
	Potassium		
	Sodium		
	Total bilirubin		
	Direct bilirubin (if total bilirubin is > ULN)		
	Total protein		
	Blood urea nitrogen		
	Amylase		
	Lipase		
	CRP		

[a] Perform on women of childbearing potential only at 72 hours prior to Day 1 of Cycle 1, discontinue visit, and 30-day follow-up visit.
[b] T3 is preferred; if not available, Free T3 may be tested.
[c] Report % or absolute results per standard of practice. Report the results in the same manner throughout the study.

Investigators must document their review of each laboratory safety report.

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

10.3.1 Definitions of Medication Error, Misuse, and Abuse

Medication error

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

Misuse

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

Abuse

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

10.3.2 Definition of AE

AE definition

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

Events meeting the AE definition

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

- New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication.
- For all reports of overdose (whether accidental or intentional) with an associated AE, the AE term should reflect the clinical symptoms or abnormal test result. An overdose without any associated clinical symptoms or abnormal laboratory results is reported using the terminology "accidental or intentional overdose without adverse effect."

- Any new cancer (that is not a condition of the study). Progression of the cancer under study is not a reportable event. Refer to Section 8.4.6 for additional details.

Events NOT meeting the AE definition

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

10.3.3 Definition of SAE

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

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

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

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

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

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

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

10.3.4 Additional Events Reported in the Same Manner as SAE

Additional events that require reporting in the same manner as SAE

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

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

10.3.5 Recording AE and SAE

AE and SAE recording

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

Assessment of intensity/toxicity

- An event is defined as "serious" when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, not when it is rated as severe.
- The investigator will make an assessment of intensity for each AE and SAE (and other reportable safety event) according to the NCI CTCAE, version 5.0. Any AE that changes CTCAE grade over the course of a given episode will have each change of grade recorded on the AE CRFs/worksheets.
    - Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
    - Grade 2: Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL.
    - Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL.
    - Grade 4: Life threatening consequences; urgent intervention indicated.
    - Grade 5: Death related to AE.

Assessment of causality

- Did the study intervention cause the AE?

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

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

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

  - **Time Course:** Did the AE follow in a reasonable temporal sequence from administration of the study intervention? Is the time of onset of the AE compatible with a drug-induced effect (applies to studies with 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 study intervention discontinued or dose/exposure/frequency reduced?

    - If yes, did the AE resolve or improve?

    - If yes, this is a positive dechallenge.

    - If no, this is a negative dechallenge.

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

- **Rechallenge:** Was the participant re-exposed to the study intervention in this study?
    - If yes, did the AE recur or worsen?
    - If yes, this is a positive rechallenge.
    - If no, this is a negative rechallenge.

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

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

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

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

- Use the following scale of criteria as guidance (not all criteria must be present to be indicative of a study intervention relationship).
    - Yes, there is a reasonable possibility of study intervention relationship:
        - There is evidence of exposure to the study intervention. The temporal sequence of the AE onset relative to the administration of the study intervention is reasonable. The AE is more likely explained by the study intervention than by another cause.
    - No, there is not a reasonable possibility of study intervention relationship:
        - Participant did not receive the study intervention OR temporal sequence of the AE onset relative to administration of the study intervention is not reasonable OR the AE is more likely explained by another cause than the study intervention. (Also entered for a participant with overdose without an associated AE.)

- The investigator must review and provide an assessment of causality for each AE/SAE and document this in the medical notes.

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

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

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

Follow-up of AE and SAE

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

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

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

- The primary mechanism for reporting to the Sponsor will be the EDC tool.
  - Electronic reporting procedures can be found in the EDC data entry guidelines (or equivalent).
  - If the electronic system is unavailable for more than 24 hours, then the site will use the paper AE Reporting form.
  - Reference Section 8.4.1 for reporting time requirements.
- The site will enter the SAE data into the electronic system as soon as it becomes available.
- After the study is completed at a given site, the EDC tool will be taken off-line to prevent the entry of new data or changes to existing data.

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

SAE reporting to the Sponsor via paper CRF

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

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

Not Applicable.

10.5 Appendix 5: Contraceptive Guidance

10.5.1 Definitions

Women of Childbearing Potential (WOCBP)

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

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

Women in the following categories are not considered WOCBP:

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

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

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

Male Participants

Male participants with female partners of childbearing potential are eligible to participate if they agree to 1 of the following during the protocol defined time frame in Section 5.1:

- Be abstinent from penile-vaginal intercourse as their usual and preferred lifestyle (abstinent on a long term and persistent basis) and agree to remain abstinent.

- Use a male condom plus partner use of an additional contraceptive method when having penile-vaginal intercourse with a WOCBP who is not currently pregnant.

  - The following are not acceptable methods of contraception:

    - Periodic abstinence (calendar, symptothermal, postovulation methods), withdrawal (coitus interruptus), spermicides only, and LAM.

    - Male condom with cap, diaphragm, or sponge with spermicide.

    - Male and female condom cannot be used together.

  - Note: Men with a pregnant or breastfeeding partner must agree to remain abstinent from penile-vaginal intercourse or use a male condom during each episode of penile penetration.

Female Participants

Contraceptives allowed during the study include[a]:
Highly Effective Contraceptive Methods That Have Low User Dependency[b] *Failure rate of <1% per year when used consistently and correctly.*
• Progestogen-only subdermal contraceptive implant[c] • IUS[d] • IUD • Bilateral tubal occlusion
• Azoospermic partner (vasectomized or secondary to medical cause) This is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. A spermatogenesis cycle is approximately 90 days. Note: Documentation of azoospermia can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.
Highly Effective Contraceptive Methods That Are User Dependent[b] *Failure rate of <1% per year when used consistently and correctly***.**
• Combined (estrogen- and progestogen- containing) hormonal contraception[c] - Oral - Intravaginal - Transdermal - Injectable
• Progestogen-only hormonal contraception[c] - Oral - Injectable
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. Typical use failure rates are higher than perfect-use failure rates (ie, when used consistently and correctly). c. If locally required, in accordance with CTFG guidelines, acceptable contraceptive implants are limited to those which inhibit ovulation. 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).

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

Not Applicable.

10.7 Appendix 7: Country-specific Requirements

Not Applicable.

10.8 Appendix 8: Abbreviations

Abbreviation	Expanded Term
AE	adverse event
ALT	alanine aminotransferase
APaT	All-Participants-as-Treated
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
BCG	Bacillus Calmette–Guérin
β-hCG	β-human chorionic gonadotropin
CD28	cluster of differentiation 28
CNS	central nervous system
CONSORT	Consolidated Standards of Reporting Trials
CrCl	creatinine clearance
CR	complete response/remission
CRF	Case Report Form
CRP	C-reactive protein
CSR	Clinical Study Report
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTLA-4	cytotoxic T-lymphocyte-associated protein 4
DCR	disease control rate
DILI	drug-induced liver injury
DLBCL	Diffuse Large B-Cell lymphoma
DOR	duration of response
ECG	electrocardiogram
ECI	event of clinical interest
eCRF	electronic Case Report Form
ECOG	Eastern Cooperative Oncology Group
EDC	electronic data collection
EMA	European Medicines Agency
FDG	fluorodeoxyglucose

Abbreviation	Expanded Term
FDAAA	Food and Drug Administration Amendments Act
FSH	follicle stimulating hormone
GCP	Good Clinical Practice
GFR	glomerular filtration rate
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 on Harmonization
IEC	Independent Ethics Committee
IFRT	involved-field radiotherapy
Ig	immunoglobulin
IgG4	immunoglobulin G4
IHC	immunohistochemistry
INR	international normalized ratio
irAEs	immune-related AEs
IRB	Institutional Review Board
IUD	intrauterine device
IUS	intrauterine hormone-releasing system
IV	intravenous
JSH	the Japanese Society of Hematology
LAM	lactational amenorrhoea method
LDH	lactate dehydrogenase
LDi	longest transverse diameter of a lesion
mAb	monoclonal antibody
MRI	magnetic resonance imaging
NCI	National Cancer Institute
NHL	Non-Hodgkin's lymphomas

Abbreviation	Expanded Term
ORR	objective response rate
OS	overall survival
OTC	over-the-counter
PD	disease progression
PD-1	programmed cell-death 1
PD-L1/ PD-L2	programmed cell death ligand 1/ programmed cell death ligand 2
PET	positron emission tomography
PFS	progression free survival
PK	pharmacokinetic
PPD	cross product of the LDi and perpendicular diameter
PR	partial response/remission
PT	prothrombin time
PTT	partial thromboplastin time
Q2W/ Q3W	every 2 weeks/ every 3 weeks
RBC	red blood cell
RNA	ribonucleic acid
rrPMBCL	relapsed or refractory primary mediastinal large B-cell lymphoma
SAE	serious adverse event
SAP	Statistical Analysis Plan
SCT	stem cell transplantation
SD	stable disease
SDi	shortest axis perpendicular to the LDi
SoA	schedule of activities
SPD	sum of the product of the perpendicular diameters for multiple lesions
sSAP	supplemental Statistical Analysis Plan
SUSAR	suspected unexpected serious adverse reaction
TMDD	target-mediated drug disposition
T3	total triiodothyronine
T4	total thyroxine
TSH	thyroid stimulating hormone

Abbreviation	Expanded Term
ULN	upper limit of normal
VS	vital sign
WBC	white blood cell
WHO	World Health Organization
WOCBP	woman/women of childbearing potential
5PS	5-point scale

10.9 Appendix 9: IWG Revised Response Criteria for Malignant Lymphoma

Cheson et al. Revised Response Criteria for Malignant Lymphoma. J Clin Oncol. 2007; 25:579-586.

Refer to central review charter for independent central imaging review.

Criteria for lymphoma disease assessment:

Table 2. Response Definitions for Clinical Trials

Response	Definition	Nodal Masses	Spleen, Liver	Bone Marrow
CR	Disappearance of all evidence of disease	(a) FDG-avid or PET positive prior to therapy; mass of any size permitted if PET negative (b) Variably FDG-avid or PET negative; regression to normal size on CT	Not palpable, nodules disappeared	Infiltrate cleared on repeat biopsy; if indeterminate by morphology, immunohistochemistry should be negative
PR	Regression of measuable disease and no new sites	> 50% decrease in SPD of up to 6 largest dominant masses; no increase in size of other nodes (a) FDG-avid or PET positive prior to therapy; one or more PET positive at previously involved site (b) Variably FDG-avid or PET negative; regression on CT	> 50% decrease in SPD of nodules (for single nodule in greatest transverse diameter); no increase in size of liver or spleen	Irrelevant if positive prior to therapy; cell type should be specified
SD	Failure to attain CR/PR or PD	(a) FDG-avid or PET positive prior to therapy; PET positive at prior sites of disease and no new sites on CT or PET (b) Variably FDG-avid or PET negative; no change in size of previous lesions on CT		
Relapsed disease or PD	Any new lesion or increase by > 50% of previously involved sites from nadir	Appearance of a new lesion(s) > 1.5 cm in any axis, > 50% increase in SPD of more than one node, or > 50% increase in longest diameter of a previously identifed node > 1 cm in short axis Lesions PET positive if FDG-avid lymphoma or PET positive prior to therapy	> 50% increase from nadir in the SPD of any previous lesions	New or recurrent involvement

Abbreviations: CR, complete remission; FDG, [^{18}F]fluorodeoxyglucose; PET, positron emission tomography; CT, computed tomography; PR, partial remission; SPD, sum of the product of the diameters; SD, stable disease; PD, progressive disease.

10.10 Appendix 10: Lugano Classification

Cheson BD, Fisher RI, Barrington SF, et al. Recommendations for initial evaluation, staging, and response assessment of Hodgkin and non-Hodgkin lymphoma: the Lugano classification, J Clin Oncol. 2014; Sep 20;32(27):3059-68.

Refer to central review charter for independent central imaging review.

Revised Criteria for Response Assessment

Response and Site	PET-CT Based Response	CT-Based Response
Complete	Complete metabolic response	Complete radiologic response (all of the following)
Lymph nodes and extralymphatic sites	Score 1, 2, or 3* with or without a residual mass on 5PS† It is recognized that in Waldeyer's ring or extranodal sites with high physiologic uptake or with activation within spleen or marrow (eg, with chemotherapy or myeloid colony-stimulating factors), uptake may be greater than normal mediastinum and/or liver. In this circumstance, complete metabolic response may be inferred if uptake at sites of initial involvement is no greater than surrounding normal tissue even if the tissue has high physiologic uptake.	Target nodes/nodal masses must regress to ≤ 1.5 cm in LDi No extralymphatic sites of disease
Nonmeasured lesion	Not applicable	Absent
Organ enlargement	Not applicable	Regress to normal
New lesions	None	None
Bone marrow	No evidence of FDG-avid disease in marrow	Normal by morphology; if indeterminate, IHC negative
Partial	Partial metabolic response	Partial remission (all of the following)
Lymph nodes and extralymphatic sites	Score 4 or 5† with reduced uptake compared with baseline and residual mass(es) of any size At interim, these findings suggest responding disease At end of treatment, these findings indicate residual disease	≥ 50% decrease in SPD of up to 6 target measurable nodes and extranodal sites When a lesion is too small to measure on CT, assign 5 mm × 5 mm as the default value When no longer visible, 0 × 0 mm For a node > 5 mm × 5 mm, but smaller than normal, use actual measurement for calculation
Nonmeasured lesions	Not applicable	Absent/normal, regressed, but no increase

Response and Site	PET-CT Based Response	CT-Based Response
Organ enlargement	Not applicable	Spleen must have regressed by > 50% in length beyond normal
New lesions	None	None
Bone marrow	Residual uptake higher than uptake in normal marrow but reduced compared with baseline (diffuse uptake compatible with reactive changes from chemotherapy allowed). If there are persistent focal changes in the marrow in the context of a nodal response, consideration should be given to further evaluation with MRI or biopsy or an interval scan	Not applicable
No response or stable disease	No metabolic response	Stable disease
Target nodes/nodal masses, extranodal lesions	Score 4 or 5 with no significant change in FDG uptake from baseline at interim or end of treatment	< 50% decrease from baseline in SPD of up to 6 dominant, measurable nodes and extranodal sites; no criteria for progressive disease are met
Nonmeasured lesions	Not applicable	No increase consistent with progression
Organ enlargement	Not applicable	No increase consistent with progression
New lesions	None	None
Bone marrow	No change from baseline	Not applicable
Progressive disease	Progressive metabolic disease	Progressive disease requires at least 1 of the following
Individual target nodes/nodal masses Extranodal lesions	Score 4 or 5 with an increase in intensity of uptake from baseline and/or New FDG-avid foci consistent with lymphoma at interim or end-of-treatment assessment	PPD progression An individual node/lesion must be abnormal with: LDi > 1.5 cm and Increase by ≥ 50% from PPD nadir and An increase in LDi or SDi from nadir 0.5 cm for lesions ≤ 2 cm 1.0 cm for lesions > 2 cm In the setting of splenomegaly, the splenic length must increase by > 50% of the extent of its prior increase beyond baseline (eg, a 15-cm spleen must increase to > 16 cm). If no prior splenomegaly, must increase by at least 2 cm from baseline. New or recurrent splenomegaly.

Response and Site	PET-CT Based Response	CT-Based Response
Nonmeasured lesions	None	New or clear progression of preexisting nonmeasured lesions
New lesions	New FDG-avid foci consistent with lymphoma rather than another etiology (eg, infection, inflammation). If uncertain regarding etiology of new lesions, biopsy or interval scan may be considered.	Regrowth of previously resolved lesions A new node > 1.5 cm in any axis A new extranodal site > 1.0 cm in any axis; if < 1.0 cm in any axis, its presence must be unequivocal and must be attributable to lymphoma Assessable disease of any size unequivocally attributable to lymphoma
Bone marrow	New or recurrent FDG-avid foci	New or recurrent involvement

•Abbreviations: 5PS - 5-point scale; CT - computed tomography; FDG - fluorodeoxyglucose; IHC - immunohistochemistry; LDi - longest transverse diameter of a lesion; MRI - magnetic resonance imaging; PET - positron emission tomography; PPD - cross product of the LDi and perpendicular diameter; SDi - shortest axis perpendicular to the LDi; SPD - sum of the product of the perpendicular diameters for multiple lesions.

•* A score of 3 in many patients indicates a good prognosis with standard treatment, especially if at the time of an interim scan. However, in trials involving PET where de-escalation is investigated, it may be preferable to consider a score of 3 as inadequate response (to avoid undertreatment). Measured dominant lesions: Up to six of the largest dominant nodes, nodal masses, and extranodal lesions selected to be clearly measurable in two diameters. Nodes should preferably be from disparate regions of the body and should include, where applicable, mediastinal and retroperitoneal areas. Non-nodal lesions include those in solid organs (eg, liver, spleen, kidneys, lungs), GI involvement, cutaneous lesions, or those noted on palpation. Nonmeasured lesions: Any disease not selected as measured, dominant disease and truly assessable disease should be considered not measured. These sites include any nodes, nodal masses, and extranodal sites not selected as dominant or measurable or that do not meet the requirements for measurability but are still considered abnormal, as well as truly assessable disease, which is any site of suspected disease that would be difficult to follow quantitatively with measurement, including pleural effusions, ascites, bone lesions, leptomeningeal disease, abdominal masses, and other lesions that cannot be confirmed and followed by imaging. In Waldeyer's ring or in extranodal sites (eg, GI tract, liver, bone marrow), FDG uptake may be greater than in the mediastinum with complete metabolic response, but should be no higher than surrounding normal physiologic uptake (eg, with marrow activation as a result of chemotherapy or myeloid growth factors).

•† PET 5PS: 1, no uptake above background; 2, uptake ≤ mediastinum; 3, uptake > mediastinum but ≤ liver; 4, uptake moderately > liver; 5, uptake markedly higher than liver and/or new lesions; X, new areas of uptake unlikely to be related to lymphoma

10.11 Appendix 11: Lymphoma B Symptoms and Constitutional Symptoms

Lymphoma B Symptoms:

Lymphoma B symptoms are a set of clinical criteria used in the initial diagnosis and treatment of Hodgkin Lymphoma. These criteria are used in this study as part of the initial assessment of Lymphoma disease staging and as a measure of the response to study treatment.

The criteria are as follows:

- Unexplained weight loss of more than 10% of the body weight during the 6 months before initial staging investigation;
- Unexplained, persistent, or recurrent fever with temperatures above 38°C during the previous month; and
- Recurrent drenching night sweats during the previous month.

Source: Lister TA, Crowther D, Sutcliffe, SB, et al. Report of a committee convened to discuss the evaluation and staging of participants with Hodgkin's disease: Cotswolds meeting. J Clin Oncol 1989;7:1630-1636.

Constitutional Symptoms:

Constitutional symptoms, defined as any one or more of the following disease-related symptoms or signs:

- Unintentional weight loss of 10% or more within the previous 6 months;
- Significant fatigue (ie, ECOG Performance Status 2 or worse; inability to work or perform usual activities);
- Fevers higher than 100.5°F or 38.0°C for 2 or more weeks without other evidence of infection; or
- Night sweats for more than 1 month without evidence of infection.

Source: Hallek M, Cheson BD, Catovsky D, et al. Guidelines for the diagnosis and treatment of chronic lymphocytic leukemia: a report from the International Workshop on Chronic Lymphocytic Leukemia updating the National Cancer Institute–Working Group 1996 guidelines. Blood. 2008 Jun 15; 111(12): 5446–5456.

10.12 Appendix 12: ECOG Performance Status

Grade	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.

* As published in Am. J. Clin. Oncol.: *Oken, M.M., Creech, R.H., Tormey, D.C., Horton, J., Davis, T.E., McFadden, E.T., Carbone, P.P.: Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. Am J Clin Oncol 5:649-655, 1982.* The Eastern Cooperative Oncology Group, Robert Comis M.D., Group Chair.

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