Official Protocol Title:	A Phase 2 Study of Pembrolizumab (MK-3475) every 6 weeks (Q6W) in Participants with Relapsed or Refractory Classical Hodgkin's Lymphoma (rrcHL) or Relapsed or Refractory Primary Mediastinal Large B-cell Lymphoma (rrPMBCL)
NCT number:	NCT04875195
Document Date:	06-June-2023

TITLE PAGE

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Protocol Title: A Phase 2 Study of Pembrolizumab (MK-3475) every 6 weeks (Q6W) in Participants with Relapsed or Refractory Classical Hodgkin's Lymphoma (rrcHL) or Relapsed or Refractory Primary Mediastinal Large B-cell Lymphoma (rrPMBCL)

Protocol Number: B68-04

Compound Number: MK-3475

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

Legal Registered Address:

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

Regulatory Agency Identifying Number(s):

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EU CT	Not applicable
EudraCT	2020-005609-20
JRCT	Not applicable
WHO	Not applicable
UTN	Not applicable
IND	118604

Approval Date: 06 June 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

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1 PROTOCOL SUMMARY

1.1 Synopsis

Protocol Title: A Phase 2 Study of Pembrolizumab (MK-3475) every 6 weeks (Q6W) in Participants with Relapsed or Refractory Classical Hodgkin's Lymphoma (rrcHL) or Relapsed or Refractory Primary Mediastinal Large B-cell Lymphoma (rrPMBCL)

Short Title: Phase 2 study of MK 3475 Q6W in rrcHL or rrPMBCL

Acronym: None

Hypotheses, Objectives, and Endpoints:

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

In male and female, programmed cell death 1 protein (PD-1) naïve, participants ≥18 years of age with either

- rrcHL who have failed to respond or relapsed after ≥1 line of multiagent therapy (can include brentuximab vedotin), or who have failed to achieve a complete response (CR) or relapsed after auto-stem cell transplantation (SCT), or are ineligible for auto-SCT,

OR

- rrPMBCL who have failed to respond or relapsed after ≥2 lines of therapy (at least 1 of the prior lines of therapy must contain a rituximab-based regimen), or who have failed to achieve a CR or relapsed after auto-SCT, or are ineligible for auto-SCT:

Primary Objective	**Primary Endpoint**
To evaluate objective response rate (ORR), by cohort, rrcHL and rrPMBCL, as assessed by the investigator according to Lugano classification criteria [Cheson, B. D., et al 2014] in individuals treated with pembrolizumab Q6W.	Participants with complete response (CR) or partial response (PR).
Secondary Objectives	**Secondary Endpoints**
To evaluate objective response rate (ORR), by cohort, rrcHL and rrPMBCL, as assessed by blinded independent central review (BICR) according to Lugano classification criteria [Cheson, B. D., et al 2014] in individuals treated with pembrolizumab Q6W.	Participants with complete response CR or PR.

To evaluate duration of response (DOR), by cohort, rrcHL and rrPMBCL, as assessed by the investigator according to Lugano classification criteria [Cheson, B. D., et al 2014] in individuals treated with pembrolizumab Q6W.	The time from first documented evidence of CR or PR until disease progression or death due to any cause, whichever occurs first.
To evaluate duration of response (DOR), by cohort, rrcHL and rrPMBCL, as assessed by BICR according to Lugano classification criteria [Cheson, B. D., et al 2014] in individuals treated with pembrolizumab Q6W.	The time from first documented evidence of CR or PR until disease progression or death due to any cause, whichever occurs first.
To evaluate the pharmacokinetic (PK) profile, immunogenicity of pembrolizumab 400 mg Q6W.	-PK parameters of pembrolizumab including AUC, C_{max} and C_{min}. -Antidrug antibody levels.
To evaluate the safety and tolerability of pembrolizumab Q6W.	-Adverse Events (AEs). -Discontinuations due to AEs.

Overall Design:

Study Phase	Phase 2
Primary Purpose	Treatment
Indication	Relapsed and/or Refractory Primary mediastinal large B-cell lymphoma, Hodgkin's lymphoma
Population	PD-1 naïve adult participants with rrcHL, who have failed to respond or relapsed after ≥1 line of multiagent therapy (with or without brentuximab vedotin), or who have failed to achieve a CR or relapsed after auto-SCT, or are ineligible for auto-SCT OR PD-1 naïve adult participants with rrPMBCL who have failed to respond or relapsed after ≥2 lines of therapy, or failed to achieve a CR or relapsed after auto-SCT, or are ineligible for auto-SCT
Study Type	Interventional

Intervention Model	Single Group This is a single group, 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 4 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 60 participants will be allocated into 2 cohorts based on baseline disease as described in Section 6.3.1.

Intervention Groups and Duration:

Arm Name	Intervention Name	Unit Dose Strength(s)	Dosage Level(s)	Route of Administration	Regimen/ Treatment Period/ Vaccination Regimen	Use
Arm 1 Cohort 1 :rrcHL Cohort 2 rrPMBCL	Pembrolizumab (MK-3475)	25 mg/mL	400 mg	IV Infusion	Day 1, then Q6W up to 18 doses (approximately 2 years)	Test Product

Other current or former name(s) or alias(es) for study intervention(s) are as follows: MK-3475.

Total Number of Intervention Groups/Arms	1 arm, 2 cohorts
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.

Study Governance Committees:

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

There are no governance committees in this study. Regulatory, ethical, and study oversight considerations are outlined in Appendix 1.

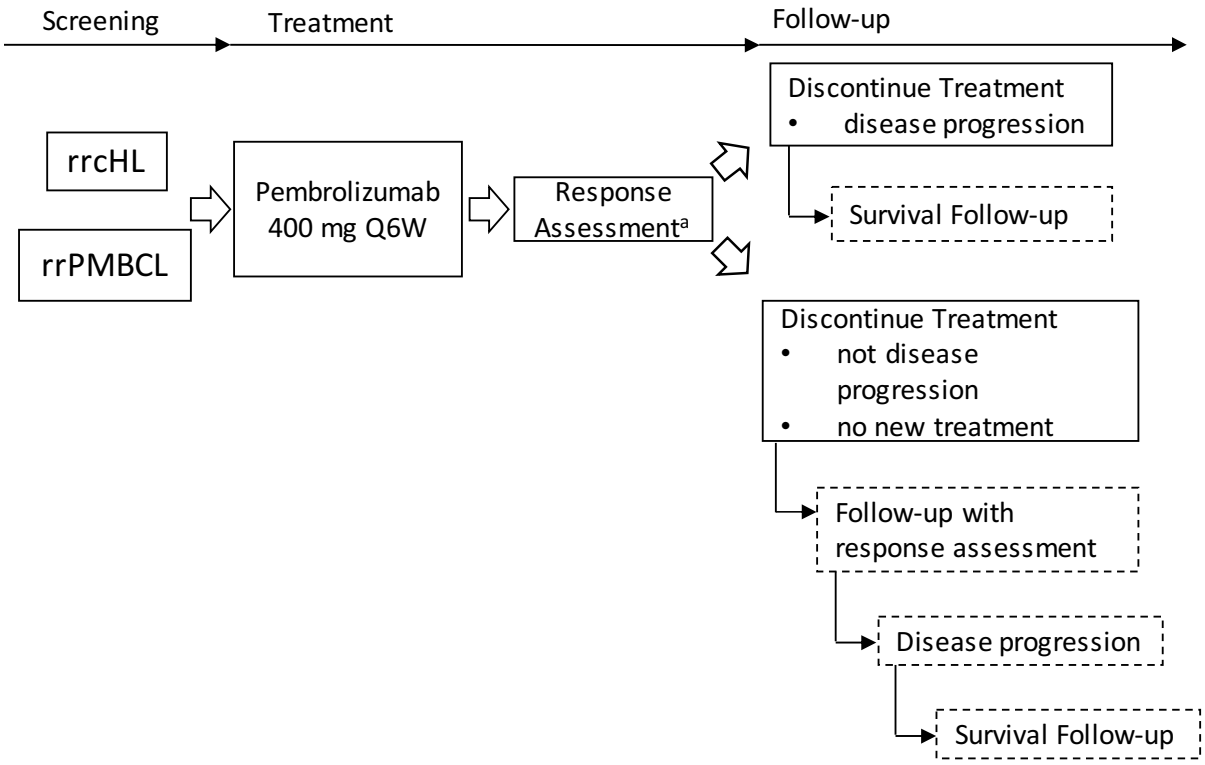
Study Accepts Healthy Participants: No

A list of abbreviations is in Appendix 9.

1.2 Schema

The study design is depicted in Figure 1.

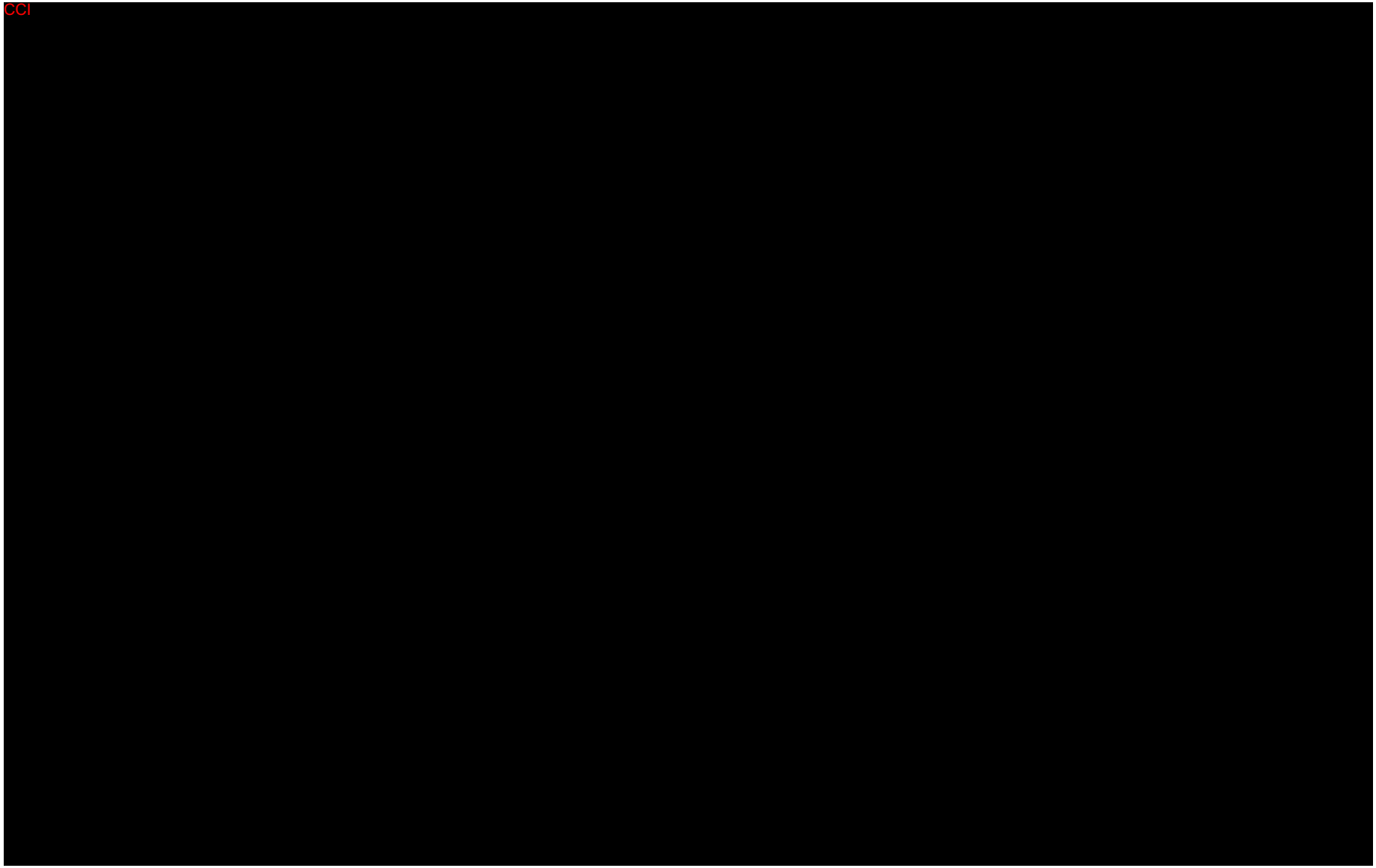
Figure 1 Study Diagram



BICR=Blinded Independent Central Review; Q6W=every 6 weeks; Q12W=every 12 weeks; rrcHL=relapsed and refractory classical Hodgkin's lymphoma; rrPMBCL=relapsed and refractory primary mediastinal B-cell lymphoma

a Imaging Q12W by investigator and BICR assessment according to Lugano classification.

1.3 Schedule of Activities



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2 INTRODUCTION

2.1 Study Rationale

On 28-APR-2020, the FDA granted accelerated approval to the additional dosing regimen of 400 mg every Q6W for pembrolizumab across all currently approved adult indications, in addition to 200 mg Q3W dosing regimen. This study is being conducted upon the request of the FDA as a post-marketing requirement to provide additional data on the efficacy and safety of pembrolizumab 400 mg Q6W dosing regimen in participants with rrcHL and rrPMBCL. The results of this study will contribute to an understanding of the safety and efficacy of pembrolizumab administered IV, in a Q6W dosing regimen in the indications rrcHL and rrPMBCL.

2.2 Background

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

2.2.1 Pharmaceutical and Therapeutic Background

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

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

The structure of murine PD-1 has been resolved [Zhang, X., et al 2004]. PD-1 and its family members are type I transmembrane glycoproteins containing an IgV–type domain responsible for ligand binding and a cytoplasmic tail responsible for the binding of signaling

molecules. The cytoplasmic tail of PD-1 contains 2 tyrosine-based signaling motifs, an immunoreceptor tyrosine-based inhibition motif, and an immunoreceptor tyrosine-based switch motif. After T-cell stimulation, PD-1 recruits the tyrosine phosphatases, SHP-1 and SHP-2, to the immunoreceptor tyrosine-based switch motif within its cytoplasmic tail, leading to the dephosphorylation of effector molecules such as CD3ζ, PKCθ, and ZAP70, which are involved in the CD3 T-cell signaling cascade [Okazaki, T., et al 2001] [Chemnitz, J. M., et al 2004] [Sheppard, K-A, et al 2004] [Riley, J. L. 2009]. The mechanism by which PD-1 down-modulates T-cell responses is similar to, but distinct from, that of CTLA-4, because both molecules regulate an overlapping set of signaling proteins [Parry, R. V., et al 2005] [Francisco, L. M., et al 2010]. As a consequence, the PD-1/PD-L1 pathway is an attractive target for therapeutic intervention in rrcHL and rrPMBCL.

2.2.2 Preclinical and Clinical Studies

Please refer to the pembrolizumab IB for descriptions of the respective preclinical and clinical evaluations.

2.2.3 Ongoing Clinical Studies

Additionally, there is an expansive ongoing research program of clinical studies evaluating pembrolizumab in participants with a number of hematological and solid malignancies, including rrcHL and rrPMBCL. For further study details, please refer to the pembrolizumab IB.

2.2.4 Information on Other Study-related Therapy

Not applicable.

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.

However, reassurance of the benefit/risk profile for the proposed study is provided by the fact that pembrolizumab has marketing approval in the US and other countries for the following:

- Treatment of adult participants with rrcHL.
- Treatment of adult participants with refractory PMBCL, or who have relapsed after 2 or more prior lines of therapy.
- Note, KEYTRUDA® is not recommended for treatment of participants with PMBCL who require urgent cytoreductive therapy.
- Dosage of 400 mg Q6W across all adult indications.

In addition, interim results (based on data cutoff date 16-JAN-2020) from KEYNOTE-204, an ongoing, randomized, open-label, Phase 3 study of IV pembrolizumab 200 mg Q3W compared with IV brentuximab vedotin 1.8 mg/kg Q3W in participants with rrcHL who have failed to respond or relapsed on at least 1 prior multiagent chemotherapy regimen, demonstrate that pembrolizumab provides a clinically meaningful and statistically significant benefit in PFS compared with brentuximab vedotin (HR = 0.65 [95% CI: 0.48, 0.88], p=0.00271). ORR and DOR findings support the PFS results.

The efficacy of a pembrolizumab 400 mg Q6W dosing regimen is expected to be similar to the initially approved 200 mg Q3W regimen in the rrcHL and rrPMBCL indications (see Section 4.3).

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

3 HYPOTHESES, OBJECTIVES, AND ENDPOINTS

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

In male and female, programmed cell death 1 protein (PD-1) naïve, participants ≥18 years of age with either

- rrcHL who have failed to respond or relapsed after ≥1 line of multiagent therapy (can include brentuximab vedotin), or who have failed to achieve a complete response (CR) or relapsed after auto-stem cell transplantation (SCT), or are ineligible for auto-SCT,

OR

- rrPMBCL who have failed to respond or relapsed after ≥2 lines of therapy (at least 1 of the prior lines of therapy must contain a rituximab-based regimen), or who have failed to achieve a CR or relapsed after auto-SCT, or are ineligible for auto-SCT:

Primary Objective	**Primary Endpoint**
To evaluate objective response rate (ORR), by cohort, rrcHL and rrPMBCL, as assessed by the investigator according to Lugano classification criteria [Cheson, B. D., et al 2014] in individuals treated with pembrolizumab Q6W.	Participants with complete response (CR) or partial response (PR).
Secondary Objectives	**Secondary Endpoints**
To evaluate objective response rate (ORR), by cohort, rrcHL and rrPMBCL, as assessed by blinded independent central review (BICR) according to Lugano classification criteria [Cheson, B. D., et al 2014] in individuals treated with pembrolizumab Q6W.	Participants with complete response CR or PR.
To evaluate duration of response (DOR), by cohort, rrcHL and rrPMBCL, as assessed by the investigator according to Lugano classification criteria [Cheson, B. D., et al 2014] in individuals treated with pembrolizumab Q6W.	The time from first documented evidence of CR or PR until disease progression or death due to any cause, whichever occurs first.

To evaluate duration of response (DOR), by cohort, rrcHL and rrPMBCL, as assessed by BICR according to Lugano classification criteria [Cheson, B. D., et al 2014] in individuals treated with pembrolizumab Q6W.	The time from first documented evidence of CR or PR until disease progression or death due to any cause, whichever occurs first.
To evaluate the pharmacokinetic (PK) profile, immunogenicity of pembrolizumab 400 mg Q6W.	-PK parameters of pembrolizumab including AUC, C_{max} and C_{min}. -Antidrug antibody levels.
To evaluate the safety and tolerability of pembrolizumab Q6W.	-Adverse Events (AEs). -Discontinuations due to AEs.
Tertiary/Exploratory Objectives	**Tertiary/Exploratory Endpoints**
CCI [redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

4 STUDY DESIGN

4.1 Overall Design

This is a Phase 2, nonrandomized, multisite, open-label study of the efficacy and safety of IV pembrolizumab 400 mg Q6W in adult participants with rrcHL or rrPMBCL. Participants should be PD-1 naïve.

Participants with rrcHL (Cohort 1) must have failed to respond or relapsed after at least 1 line of multiagent therapy (chemotherapy with or without brentuximab vedotin), or have failed to achieve CR or relapsed after an auto-SCT, or are ineligible for auto-SCT.

Participants with rrPMBCL (Cohort 2) must have failed to respond or relapsed after ≥2 lines of prior therapy, or failed to achieve a CR or relapsed after auto-SCT or are ineligible for auto-SCT. At least 1 of the prior lines of therapy must contain a rituximab-based regimen. Participants with rrPMBCL must not require urgent cytoreductive therapy.

The study design is summarized in Figure 1. The planned objectives and endpoints are detailed in Section 3.

After Screening, approximately 60 participants will receive pembrolizumab 400 mg fixed dose administered Q6W for up to 18 cycles (approximately 2 years) until documented disease progression per investigator assessment according to Lugano classification or the participant meets 1 of the discontinuation criteria (Section 7.1).

Disease will be assessed every 12 weeks using the Lugano response criteria [Cheson, B. D., et al 2014] per investigator assessment.

Participants who discontinue treatment for reasons other than disease progression will have posttreatment follow-up for disease status until disease progression, initiating a non-study cancer treatment, withdrawing consent, death, or becoming lost to follow-up. All participants will be followed for OS until death, withdrawal of consent, the end of the study, or becoming lost to follow-up, whichever comes first.

AEs will be monitored throughout the study and graded in severity according to the guidelines outlined in the NCI CTCAE 5.0. After the end-of-treatment, each participant will be followed for AE monitoring (see Section 8.4). Participants who undergo allogeneic SCT within 2 years after their last dose of study treatment will be followed for ECIs for up to 18 months post-transplant. This additional follow-up for participants undergoing an allogeneic SCT within 2 years after their last treatment is necessary to provide data for a post-marketing requirement from the FDA.

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

This is a Phase 2, nonrandomized, multisite, open-label study of the efficacy and safety of IV pembrolizumab 400 mg Q6W in adult, PD-1 naïve, participants with rrcHL or rrPMBCL.

The rationale for selected dose and dosing schedule are summarized in Section 2.1 and Section 4.3. The study includes 2 cohorts (rrcHL or rrPMBCL); enrollment into each cohort will not be controlled as the number of rrPMBCL participants could vary since this is a rare form of DLBCL.

The study is open-label as pembrolizumab is already approved for use in the rrcHL and rrPMBCL, making blinding unnecessary.

The results of this study will contribute to an understanding of the PK characteristics of pembrolizumab administered in a Q6W dosing regimen in rrcHL and rrPMBCL.

4.2.1 Rationale for Endpoints

4.2.1.1 Efficacy Endpoints

The primary endpoint for this study will be the achievement of objective response, meaning a best overall response of PR or CR, defined according to the Lugano classification [Cheson, B. D., et al 2014], as assessed by the investigator. Response assessment per Lugano includes anatomic imaging (CT), metabolic imaging (FDG-PET), and clinical information. The proportion of participants in a treatment group who achieve an objective response is called the ORR. ORR is an acceptable measure of clinical benefit for a late-stage study that demonstrates superiority of a new antineoplastic therapy, especially if the magnitude of the effect is large and the therapy has an acceptable benefit/risk profile. The Lugano classification, published in 2014, is the revised response criteria for assessing ORR in HL and NHL and recommended by the current NCCN guidelines for B-cell lymphoma [National Comprehensive Cancer Network 2019]. All images and clinical data will be assessed by the investigator.

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4.2.1.2 Safety Endpoints

A secondary objective of this study is to characterize the safety and tolerability of 400 mg pembrolizumab when administered IV Q6W.

Safety parameters frequently used for evaluating investigational-systemic anticancer treatments are included as safety endpoints including, but not limited to, the incidence of, causality, and outcome of AEs/SAEs, and changes in vital signs and laboratory values. AEs will be assessed as defined by CTCAE, Version 5.0.

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4.2.1.3 Pharmacokinetic Endpoints

An objective of this study is to characterize the PK profile of pembrolizumab after administration as an IV infusion Q6W. PK data will be analyzed after all participants complete Cycle 5. PK parameters will include AUC, Cmax, and Cmin. Results of PK analysis will be provided in a separate report added to the CSR as an appendix.

4.2.1.4 Antidrug Antibodies (ADA)

Formation of ADAs can potentially confound drug exposures at therapeutic doses and prime for subsequent infusion-related toxicity. ADA response to pembrolizumab at the beginning of each of the first 5 cycles will be determined. Any impact of presence of ADAs on exposure of pembrolizumab will be explored. Results of ADA analysis will be provided in a separate report added to the CSR as an appendix.

4.2.1.5 Pharmacodynamic Endpoints

There are no pharmacodynamic endpoints in this study.

4.2.1.6 CCI [redacted]

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4.2.1.7 CCI [redacted]

[redacted]

[redacted]

4.2.2 Rationale for the Use of Comparator/Placebo

Not applicable.

4.3 Justification for Dose

The current approved dosing regimen of pembrolizumab for an IV administration are 200 mg Q3W or 400 mg Q6W for adults.

A 400 mg Q6W dosing regimen of pembrolizumab is expected to have a similar benefit/risk profile as 200 mg Q3W, in all treatment settings in which 200 mg Q3W pembrolizumab is currently appropriate [Lala, M., et al 2020]. Specifically, the dosing regimen of 400 mg Q6W for pembrolizumab is considered adequate based on modeling and simulation analyses, given the following rationale:

- PK simulations demonstrating that in terms of pembrolizumab exposures:
  - Average concentration over the dosing interval C_{avg} (or AUC) at 400 mg Q6W is similar to the approved 200 mg Q3W dose, thus bridging efficacy between dosing regimens.
  - Trough concentrations (C_{min}) at 400 mg Q6W are generally within the range of those achieved with 2 mg/kg or 200 mg Q3W in the majority (>99%) of participants.
  - Peak concentrations (C_{max}) at 400 mg Q6W are well below the C_{max} for the highest clinically tested dose of 10 mg/kg every 2 weeks, supporting that the safety profile for 400 mg Q6W should be comparable to the established safety profile of pembrolizumab.

- Exposure-response for pembrolizumab has been shown to be flat across indications, and OS predictions in melanoma and NSCLC show that efficacy at 400 mg Q6W is expected to be similar to 200 mg or 2 mg/kg Q3W, given the similar exposures; thus, 400 mg Q6W is expected to be efficacious across indications.

4.3.1 Starting Dose for This Study

The study will use pembrolizumab at a fixed dose of 400 mg Q6W.

4.3.2 Maximum Dose Exposure for This Study

All participants may receive up to 18 infusions of pembrolizumab (approximately 2 years) or until confirmed PD, whichever comes first.

4.4 Beginning and End-of-Study Definition

The overall study begins when the first participant (or their legally acceptable representative) provides documented informed consent. The overall study ends when the last participant completes the last study-related contact, withdraws consent, or is lost to follow-up (Section 7.3). For purposes of analysis and reporting, the overall study ends when the Sponsor receives the last laboratory test result or at the time of final contact with the last participant, whichever comes last.

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

4.4.1 Clinical Criteria for Early Study Termination

The clinical study may be terminated early if the extent (incidence and/or severity) of emerging effects/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

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

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

5.1 Inclusion Criteria

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

Type of Participant and Disease Characteristics

1. Male/female participants who are at least 18 years of age on the day of documented informed consent.
2. Have a histologically confirmed diagnosis of cHL or PMBCL, according to the WHO classification of neoplasms of the hematopoietic and lymphoid tissues [Swerdlow, S. H., et al 2008].
3. Have radiographically measurable cHL or PMBCL disease as per Lugano classification with at least 1 nodal lesion (which has not been previously radiated) that is >15 mm in long axis, regardless of the length of the short axis, and/or extranodal lesion of >10 mm in long and short axis.

PMBCL-Specific Disease Characteristics:

4. 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. Participants 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 participants 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. At least 1 of the prior lines of therapy must contain a rituximab-based regimen. For participants who received consolidative local radiotherapy after systemic therapy, local radiotherapy will not be considered as a separate line of treatment.

Note: Participants should not need urgent cytoreductive therapy.

[a] **Relapsed Disease**: disease progression after achieving an overall response of PR or CR in response to the most recent therapy

[b] **Refractory Disease**: failure to achieve CR or PR to the most recent therapy.

cHL-Specific Disease Characteristics:

5. Have relapsed[a] or refractory[b] cHL and:

   - Have relapsed during their last cHL regimen after receiving at least 2 cycles of therapy or within 12 months after completing the last regimen for cHL.

   OR

   - Have received at least ≥1 line of prior multiagent therapy with/without brentuximab vedotin (excluding radiation) or auto-SCT for cHL and have failed to respond to or relapsed after their last line of treatment (for country-specific requirements see Appendix 7).

   *[a] **Relapsed Disease**: disease progression after achieving an overall response of PR or CR to the most recent therapy

   *[b] **Refractory Disease**: failure to achieve CR or PR to the most recent therapy.

Demographics

6. 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, as required by local regulations) within 24 hours for urine or within 72 hours for serum 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.

- Abstains from breastfeeding during the study intervention period and for at least 120 days after study intervention.
- Additional requirements for pregnancy testing during and after study intervention are in Section 8.3.5.
- The investigator is responsible for review of medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a woman with an early undetected pregnancy.
- Contraceptive use by women should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.

Informed Consent

7. The participant (or legally acceptable representative) has provided documented informed consent/assent for the study. The participant may also provide consent/assent for FBR. However, the participant may participate in the study without participating in FBR.

Additional Categories

8. Submit an evaluable core lymph node biopsy for biomarker analysis from an archival (>60 days) or newly obtained core or incisional (within 30 days) biopsy, which was not previously irradiated at Screening (Visit 1).

   Note: If no archival tissue is available, 2 new fresh core needle samples are required.

9. Have an ECOG Performance Status of 0 to 1 assessed within 7 days before allocation.
10. Life expectancy >3 months.
11. Have blood oxygen saturation >92%.
12. Have adequate organ function as defined in the following table (Table 2). Specimens must be collected within 7 days before the start of study intervention.

Table 2 Adequate Organ Function Laboratory Values

System	Laboratory Value
Hematological	
Absolute neutrophil count (ANC)	≥1000/µL (unless marrow involvement)
Platelets[a]	≥75 000/µL (unless marrow involvement)
Hemoglobin[a]	≥8.0 g/dL or ≥5.6 mmol/L[a] (unless marrow involvement)
Renal	
Creatinine **OR** Measured or calculated creatinine clearance (GFR can also be used in place of creatinine or CrCl)	≤1.5 × ULN **OR** ≥30 mL/min
Hepatic	
Total bilirubin	≤1.5 × ULN **OR** direct bilirubin ≤ULN for participants with total bilirubin levels >1.5 × ULN
AST (SGOT) and ALT (SGPT)	≤2.5 × ULN (≤5 × ULN for participants with liver metastases)
Coagulation	
International normalized ratio (INR) or prothrombin time (PT)	≤1.5 × ULN unless participant is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants
Activated partial thromboplastin time (aPTT)	≤1.5 × ULN unless participant is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants

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

[a] Criteria must be met without erythropoietin dependency and without packed red blood cell (pRBC) transfusion within last 2 weeks prior to first dose of study intervention.

5.2 Exclusion Criteria

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

Medical Conditions

1. Has undergone solid organ transplant at any time, or prior allogeneic hematopoietic SCT within the last 5 years. [redacted]
2. Has clinically significant (ie, active) cardiovascular disease: cerebral vascular accident/stroke (<6 months prior to enrollment), myocardial infarction (<6 months prior to enrollment), unstable angina, congestive heart failure (New York Heart Association Classification Class ≥II), or serious cardiac arrhythmia requiring medication.
3. Has pericardial effusion or clinically significant pleural effusion.
4. Has a history of a second malignancy, unless potentially curative treatment has been completed with no evidence of malignancy for 2 years.

   Note: The time requirement does not apply to participants who underwent successful definitive resection of basal cell carcinoma of the skin, squamous cell carcinoma of the skin, superficial bladder cancer, in situ cervical cancer, or other in situ cancers.

Prior/Concomitant Therapy

5. Is receiving systemic steroid therapy (in dosing exceeding 10 mg daily of prednisone equivalent) <3 days prior to the first dose of study intervention.

   Note: Participants who receive daily steroid replacement therapy are an exception. Daily prednisone at doses of 5 to 7.5 mg is an example of replacement therapy.

   Note: Equivalent hydrocortisone doses are permitted if administered as replacement therapy.
6. Has received prior monoclonal antibody within 4 weeks prior to first dose of study intervention or has not recovered (ie, ≤Grade 1 or at baseline) from AEs due to agents administered more than 4 weeks earlier.
7. Has received prior therapy with an anti-PD-1, anti-PD-L1, or anti-PD-L2 agent or with an agent directed to another stimulatory or coinhibitory T-cell receptor (eg, CTLA-4, OX 40, CD137).
8. Has received prior CAR-T therapy (for country-specific requirements see Appendix 7).
9. Has received prior systemic anticancer therapy, or radiotherapy, including investigational agents within 4 weeks prior to the first dose of study intervention.
10. Has received prior radiotherapy within 2 weeks of start of study intervention or has radiation-related toxicities, requiring corticosteroids.

    Note: Two weeks or fewer of palliative radiotherapy for non-CNS disease, with a 1-week washout, is permitted.

11. Has received a live or live-attenuated vaccine within 30 days before the first dose of study drug.

    Note: Killed vaccines are allowed (for country-specific requirements see Appendix 7). Refer to Section 6.5 for information on COVID-19 vaccines.

Prior/Concurrent Clinical Study Experience

12. Has received an investigational agent or has used an investigational device 4 weeks prior to study intervention administration.

Diagnostic Assessments

13. Has a diagnosis of immunodeficiency or is receiving chronic systemic steroid therapy (in dosing exceeding 10 mg daily of prednisone equivalent) or any other form of immunosuppressive therapy within 7 days prior the first dose of study medication.
14. Has known active CNS lymphoma involvement or active CNS involvement by lymphoma. Participants with prior CNS involvement are eligible if their CNS disease is in radiographic, cytological (for cerebrospinal fluid disease) and clinical remission.
15. Has severe hypersensitivity (≥Grade 3) to pembrolizumab and/or any of its excipients.
16. Has an active autoimmune disease that has required systemic treatment in past 2 years except replacement therapy (eg, thyroxine, insulin, or physiologic corticosteroid).
17. Has a history of (noninfectious) pneumonitis/interstitial lung disease that required steroids or has current pneumonitis/interstitial lung disease.
18. Has an active infection requiring systemic therapy.
19. Has a known history of HIV infection. No HIV testing is required unless mandated by local health authority (see Appendix 7).
20. 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 (see Appendix 7).
21. 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.
22. Has a known psychiatric or substance abuse disorder that would interfere with the participant’s ability to cooperate with the requirements of the study.

5.3 Lifestyle Considerations

No lifestyle restrictions are required.

5.3.1 Meals and Dietary Restrictions

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

5.3.2 Caffeine, Alcohol, and Tobacco Restrictions

No restrictions are required.

5.3.3 Activity Restrictions

No restrictions are necessary.

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.

Participants who fail Screening may be rescreened for eligibility after consultation between the investigator and the Sponsor and written documentation of the collaborative decision on participant management.

5.5 Participant Replacement Strategy

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

6 STUDY INTERVENTION

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

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

6.1 Study Intervention(s) Administered

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

Country-specific requirements are noted in Appendix 7.

Table 3 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/ Vaccination Regimen	Use	IMP or NIMP/ AxMP	Sourcing
Arm 1 Cohort 1 :rrcHL Cohort 2 rrPMBCL	Experimental	Pembrolizumab (MK-3475)	Biological/Vaccine	Solution	25 mg/mL	400 mg	IV Infusion	Day 1, then Q6W up to 18 doses (approximately 2 years)	Test Product	IMP	Central by Sponsor

EEA=European Economic Area; IMP=investigational medicinal product; NIMP/AxMP=noninvestigational/auxiliary medicinal product.
The classification of IMP and NIMP/AxMP in this table is based on guidance issued by the European Commission and applies to countries in the EEA. Country differences with respect to the definition/classification of IMP and NIMP/AxMP may exist. In these circumstances, local legislation is followed.

All study interventions will be administered on an outpatient basis.

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

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

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

6.1.1 Treatment

The treatment of pembrolizumab monotherapy consists of 18 treatments.

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

6.2 Preparation/Handling/Storage/Accountability

6.2.1 Dose Preparation

All participants will receive 400 mg pembrolizumab by IV infusion Q6W. Details on preparation and administration of pembrolizumab are provided in the Pharmacy Manual.

There are no specific calculations or evaluations required to be performed to administer the proper dose to each participant. The rationale for selection of doses to be used in this study is in Section 4.3.

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

Enrollment into Cohorts 1 and 2 are of equal priority. All participants will receive 400 mg IV pembrolizumab Q6W.

Intervention allocation will occur centrally using an IRT system. There are 2 cohorts of participants and 1 study intervention arm.

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.

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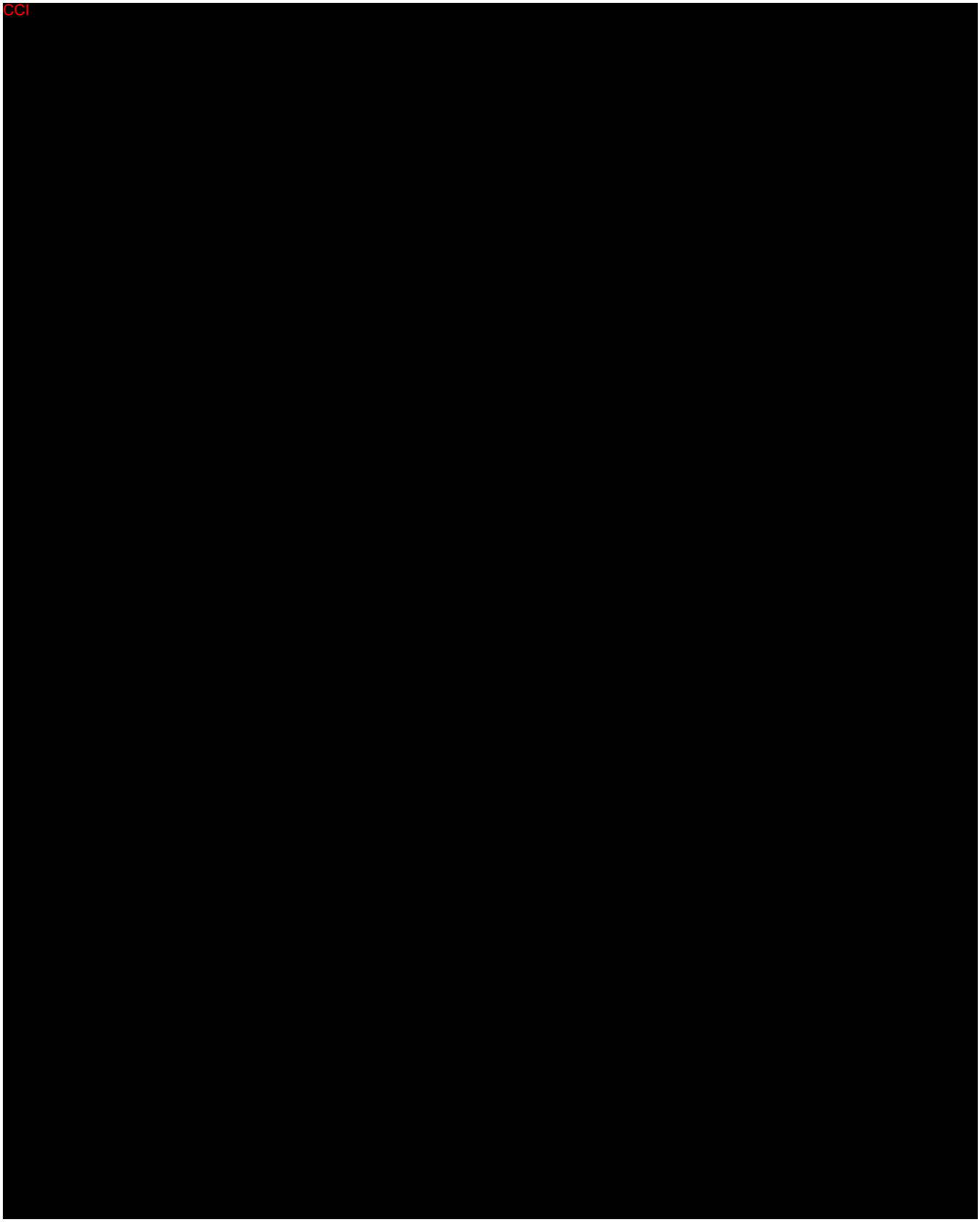

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Table 4 CCI [redacted]

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**
CCI [redacted]	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
[redacted]	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		
[redacted]	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	
[redacted]	New onset T1DM or Grade 3 or 4 hyperglycemia associated with evidence of b-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
CCI	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]		
CCI	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 CCI		
CCI	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
CCI	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		
CCI	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		
CCI	Grade 1	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 2, 3 or 4	Permanently discontinue		

irAEs	Toxicity Grade (CTCAE v5.0)	Action With Pembrolizumab Monotherapy, Coformulations or IO Combinations	Corticosteroid and/or Other Therapies	Monitoring and Follow-up
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	Grade 3	Withhold or discontinue based on the event [e]		
	CCI			

AE(s)=adverse event(s); ALT= alanine aminotransferase; AST=aspartate aminotransferase; CTCAE=Common Terminology Criteria for Adverse Events; DRESS=Drug Rash with Eosinophilia and Systemic Symptom; GI=gastrointestinal; IO=immuno-oncology; ir=immune related; IV=intravenous; SJS=Stevens-Johnson Syndrome; T1DM=type 1 diabetes mellitus; TEN=Toxic Epidermal Necrolysis; ULN=upper limit of normal.
Note: Non-irAE will be managed as appropriate, following clinical practice recommendations.
[a] 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 Monotherapy, Coformulations or IO Combinations

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

Table 5 Pembrolizumab Monotherapy, Coformulations or IO Combinations Infusion Reaction Dose Modification and Treatment Guidelines

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

NCI CTCAE Grade	Treatment	Premedication at Subsequent Dosing
Grades 3 or 4 Grade 3: Prolonged (ie, not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms after initial improvement; hospitalization indicated for other clinical sequelae (eg, renal impairment, pulmonary infiltrates) Grade 4: Life-threatening; pressor or ventilatory support indicated	Stop Infusion. Additional appropriate medical therapy may include but is not limited to: Epinephrine** IV fluids Antihistamines NSAIDs Acetaminophen Narcotics Oxygen Pressors Corticosteroids Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator. Hospitalization may be indicated. **In cases of anaphylaxis, epinephrine should be used immediately. Participant is permanently discontinued from further study drug intervention.	No subsequent dosing
IV=Intravenous; NSAIDS=Non-steroidal anti-inflammatory drugs; PO=by mouth. 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 Monotherapy, Coformulations, or IO Combinations

Pembrolizumab monotherapy, coformulations, or IO combinations may be interrupted for situations other than treatment-related AEs such as medical or surgical events and/or unforeseen circumstances not related to study intervention. However, study intervention is to be restarted within 6 weeks (42 days) of the originally scheduled dose and within 84 days of the previously administered dose, unless otherwise discussed with the Sponsor. The reason for study intervention interruption is to be documented in the participant's study record.

6.7 Intervention After the End of the Study

There is no study-specified intervention after 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.

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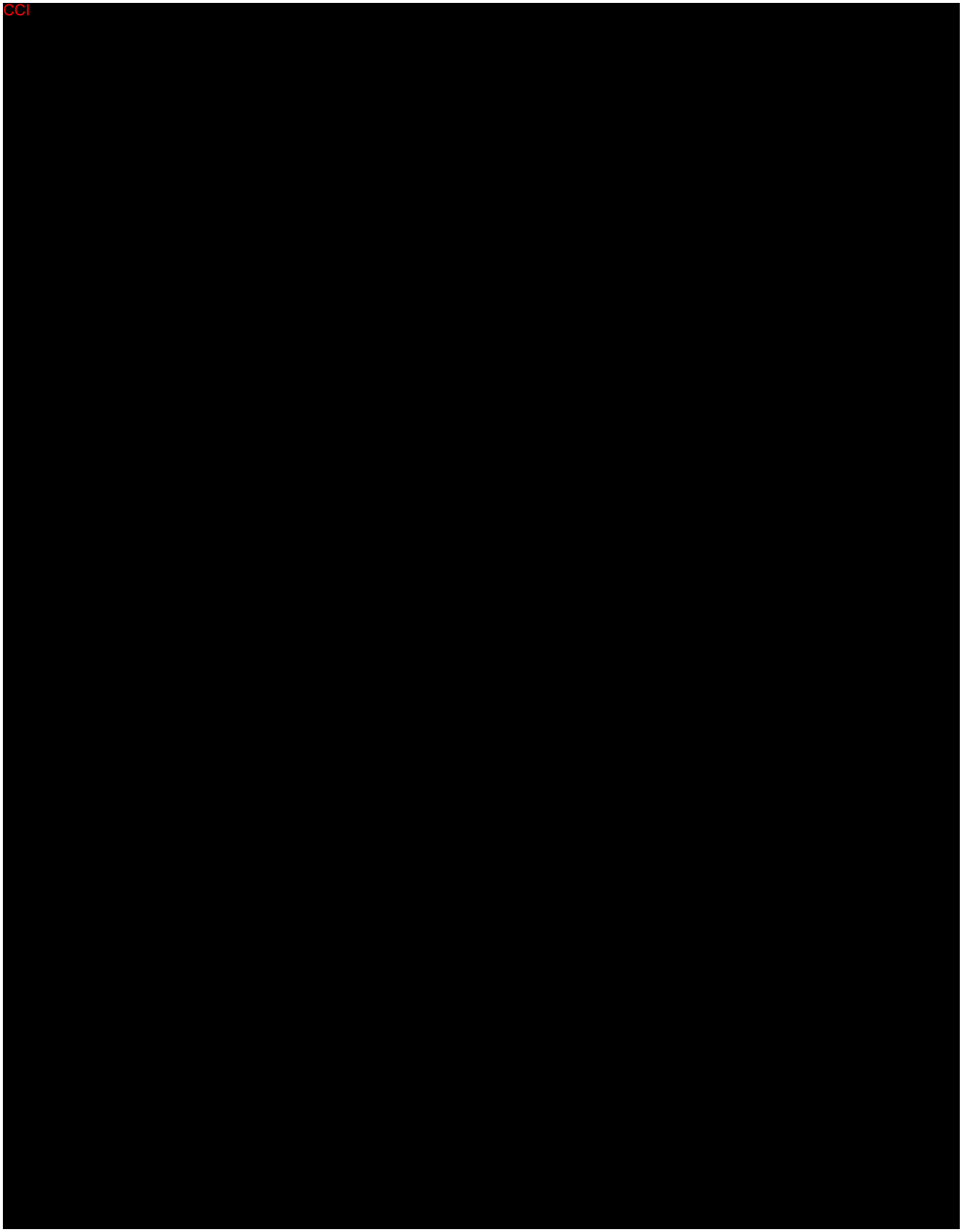

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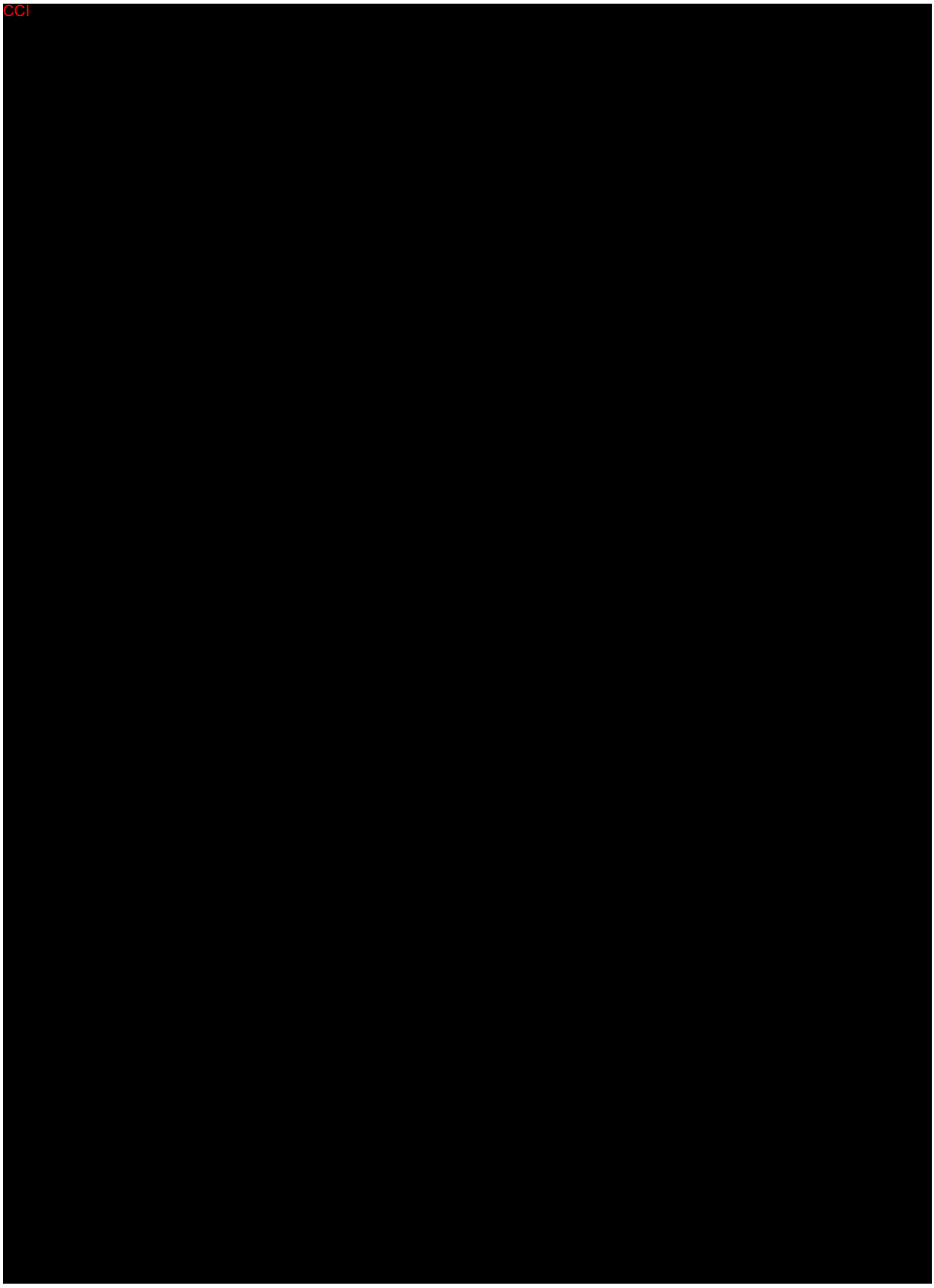
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8.2.2 Tumor Imaging and Assessment of Disease

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

In addition to survival, efficacy will be assessed based on evaluation of scan changes in tumor burden over time, until the participant is discontinued from the study or enters the Survival Follow-up. Disease response assessments may use CT/MRI and/or PET scans, laboratory studies, and physical examination. The process for scan collection (including anatomical coverage, preferred modalities, and specifics of scanning technique) can be found in the Site Imaging Manual. Tumor scans should include CT (in this protocol, the term CT is used to mean anatomic imaging that could be CT or MRI) that is of diagnostic quality and acquired with IV contrast, and metabolic imaging by PET. All participants require contrast enhanced CT or PET-CT scans of the neck, chest, abdomen, and pelvis. The Site Imaging Manual will provide alternative methods for scanning if PET-CT cannot be performed due to medical contraindication or local practice. The same type of scan should be used in a participant throughout the study to optimize the reproducibility of the assessment and improve the accuracy of the response assessment.

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

Other types of medical imaging (such as ultrasound) will not be included in response assessment.

Local assessment (investigator assessment with site radiology reading) will be used to determine participant eligibility and for participant management.

8.2.2.1 Initial Tumor Scans

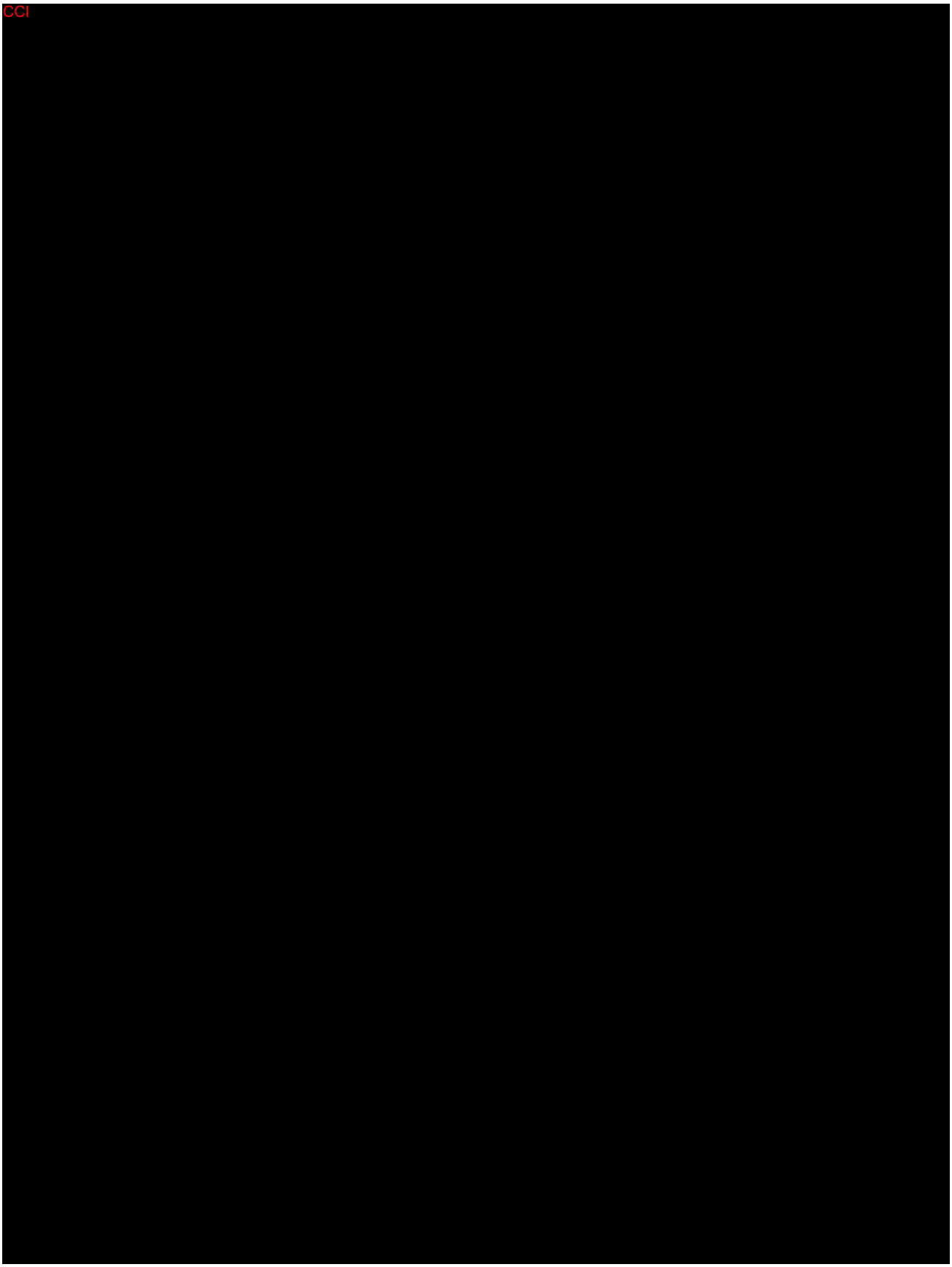
Diagnostic quality anatomic scans (typically contrast enhanced CT scan) and metabolic scans via FDG-PET must be performed during Screening.

Initial tumor scans at Screening must be performed within 28 days prior to the date of the first dose of study intervention. Any scans obtained after Cycle 1 Day 1 cannot be included in the screening assessment. The site must review screening scans to confirm the participant has measurable disease as defined in the inclusion 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 the first dose of study intervention.

8.2.2.2 Lymphoma Disease Response Assessment/Scan During the Study

After Screening, disease response assessments will occur at Week 12 (±7 days) and every 12 weeks (±7 days) thereafter as detailed in the SoA (Section 1.3, Table 1). The first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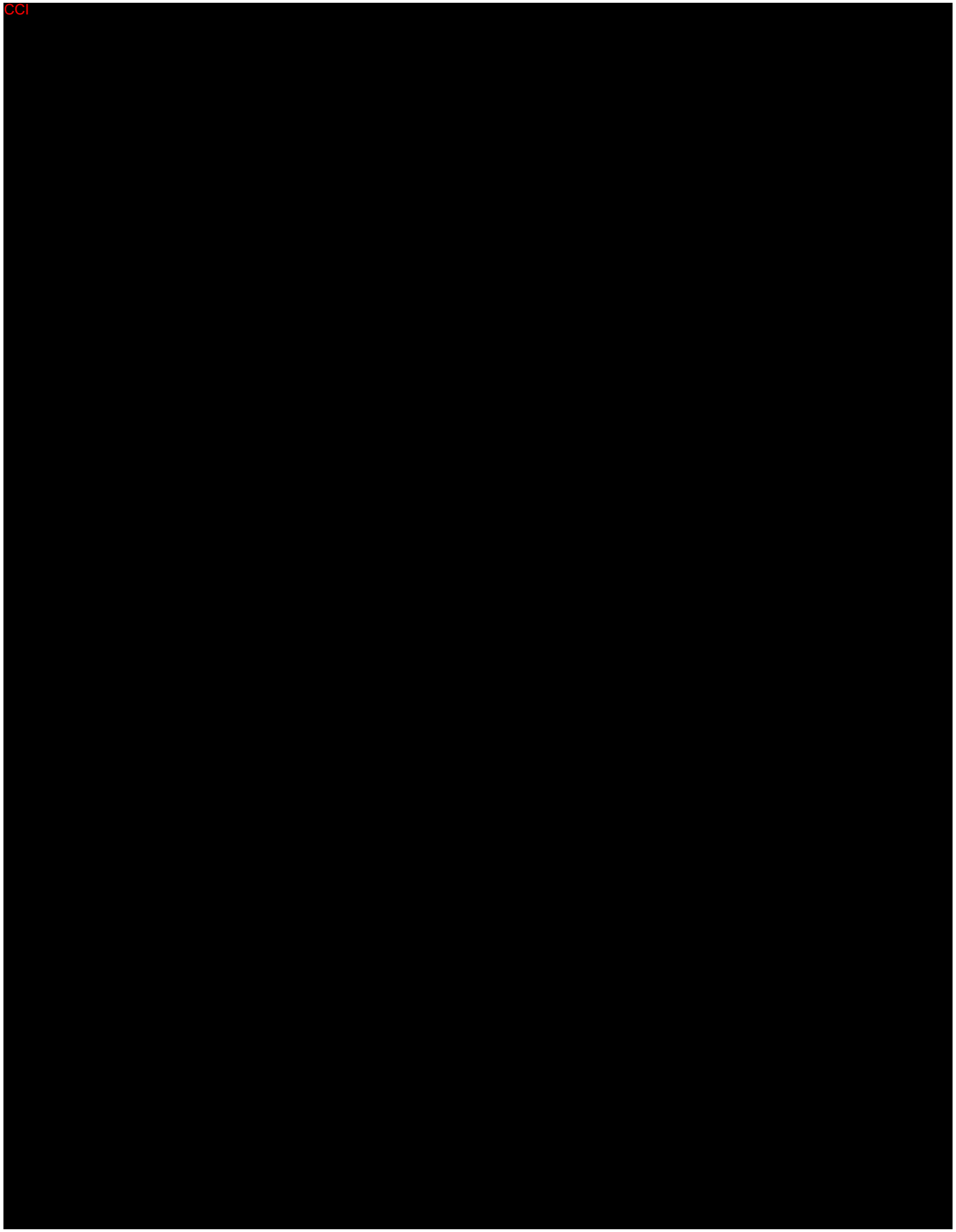

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9 STATISTICAL ANALYSIS PLAN

This section outlines the statistical analysis strategy and procedures for the study. Changes to analyses made after the protocol has been finalized will be documented in a sSAP and referenced in the CSR for the study. Post hoc exploratory analyses will be clearly identified in the CSR.

9.1 Statistical Analysis Plan Summary

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

Study Design Overview	This is a Phase 2 Study of Pembrolizumab (MK-3475) 400 mg Q6W in Participants with rrcHL or rrPMBCL.
Treatment Assignment	Participants meeting inclusion/exclusion criteria will be allocated to one of the 2 cohorts, rrcHL or rrPMBCL, and receive 400 mg of pembrolizumab Q6W. The population of each cohort, rrcHL and rrPMBCL, is defined in Section 3.
Analysis Populations	Efficacy: APaT Safety: APaT
Primary Endpoints	Objective Response per Lugano classification as assessed by Investigator.
Secondary Endpoints	Objective Response per Lugano classification as assessed by BICR. DOR per Lugano classification as assessed by Investigator. DOR per Lugano classification as assessed by BICR. AEs and study intervention discontinuations due to AEs.
Statistical Methods for Key Efficacy Analyses	The point estimate of ORR will be provided together with 95% CI using exact binomial method proposed by Clopper and Pearson (1934) [Clopper, C. J. and Pearson, E. S. 1934].
Statistical Methods for Key Safety Analyses	Summary statistics (counts, percentage, mean, standard deviation, etc.) will be provided for the safety endpoints as appropriate.

Interim Analyses	There are no planned interim analyses for this study.
Multiplicity	No multiplicity adjustment is planned as there is no hypothesis testing.
Sample Size and Power	The sample size is expected to be approximately 60 participants with no required minimum in either cohort.

9.2 Responsibility for Analyses/In-house Blinding

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

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

9.3 Hypotheses/Estimation

Objectives of the study are stated in Section 3.

9.4 Analysis Endpoints

Efficacy, safety, and PK endpoints that will be evaluated are listed below, followed by the descriptions of the derivations of selected endpoints.

9.4.1 Efficacy Endpoints

Primary

- Objective Response Rate

The ORR is defined as the proportion of participants who achieve a CR or PR per Lugano classification as assessed by investigator.

Secondary

- Objective Response Rate

The ORR is defined as the proportion of participants who achieve a CR or PR per Lugano classification as assessed by BICR.

- Duration of Response

For participants who demonstrate CR or PR, DOR is defined as the time from the first documented evidence of CR or PR until disease progression or death due to any cause, whichever occurs first. DOR will be created, separately, for investigator and BICR assessments.

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9.4.2 Safety Endpoints

The safety endpoints include AEs, SAEs, and study treatment discontinuation due to AEs. In addition, safety and tolerability will be assessed by clinical review of all relevant parameters including AEs, laboratory tests, vital signs, and ECGs. A description of safety measures is provided in Section 8.3 and 8.4.

9.4.3 Pharmacokinetic Endpoints

PK and ADA analyses will be reported in separate memos that will be attached to the CSR as an appendix. PK and ADA data will be analyzed after all participants complete Cycle 5. PK parameters, such as AUC, C_{max}, and C_{min} as well as incidence of ADA, will be summarized (see Sections 4.2.1.3, 4.2.1.4, and 8.6 for additional details).

9.5 Analysis Populations

9.5.1 Efficacy Analysis Population

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

9.5.2 Safety Analysis Population

The APaT population will be used for the analysis of safety data in this study. The APaT population consists of all allocated subjects who received at least 1 dose of study treatment.

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

9.6 Statistical Methods

This section describes the statistical methods that address the primary and secondary objectives. Methods related to the exploratory endpoints will be described in the sSAP. No formal hypothesis tests will be conducted for this study.

9.6.1 Statistical Methods for Efficacy Analysis

Efficacy (ORR, DOR, PFS and OS) will be evaluated separately in each cohort, rrcHL and rrPMBCL.

9.6.1.1 Objective Response Rate

The primary efficacy endpoint for this study is the ORR, defined as the proportion of participants who have response (CR or PR) according to Lugano classification as assessed by the investigator. Participants without response data will be considered as nonresponders. The ORR based on BICR will also be provided as supportive.

The point estimate along with 95% exact CI using exact binomial method proposed by [Clopper. J. and Pearson, E. S. 1934] will be calculated.

9.6.1.2 Duration of Response

If sample size permits, DOR will be summarized descriptively using Kaplan-Meier medians and quartiles. Only the subset of participants who show a CR or PR will be included in this analysis. Censoring rules for DOR are summarized in Table 7. DOR analysis will be conducted, separately, for investigator and BICR assessments.

For each DOR analysis, a corresponding summary of the reasons responding participants are censored will also be provided. Responding participants who are alive, have not progressed,

CCI [redacted]

Table 7 CCI [redacted]

[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]		

9.6.1.3 CCI [redacted]

[redacted]

Table 8 CCI [redacted]

[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	

9.6.1.4 CCI [redacted]

[redacted]

9.6.1.5 Analysis Strategy for Key Efficacy Variables

A summary of the primary analysis strategy for the key efficacy variables is provided in Table 9.

Table 9 Analysis Strategy for Key Efficacy Variables

Endpoint/Variable	Statistical Method	Analysis Population	Missing Data Approach
Primary Analyses			
ORR per Lugano classification by investigator assessment	Summary statistics with 95% CI using exact method based on binomial distribution	APaT	CCI
Secondary Analyses			
ORR per Lugano classification by BICR assessment	Summary statistics with 95% CI using exact method based on binomial distribution	APaT	CCI
DOR per Lugano classification by investigator assessment	Summary statistics using Kaplan-Meier method	APaT	CCI
DOR per Lugano classification by BICR assessment	Summary statistics using Kaplan-Meier method	APaT	CCI
Exploratory Analyses			
PFS per Lugano classification by investigator assessment	Summary statistics using Kaplan-Meier method	APaT	CCI
PFS per Lugano classification by BICR assessment	Summary statistics using Kaplan-Meier method	APaT	CCI
OS	Summary statistics using Kaplan-Meier method	APaT	CCI

Abbreviations: APaT=all participants as treated; DOR=duration of response; ORR=objective response rate; OS=overall survival; PFS=progression-free survival.

No formal statistical testing is planned.

9.6.2 Statistical Methods for Safety Analyses

Both cohorts, rrcHL and rrPMBCL, will be pooled for safety evaluations. Safety and tolerability will be assessed by clinical review of all relevant parameters including AEs, laboratory parameters, vital signs, and ECG measurements. The broad AE categories consisting of the percentage of participants with any AE, a drug-related AE, a serious AE, an AE, which is both drug-related and serious, a Grade 3 to 5 AE, a drug-related Grade 3 to 5 AE, and who discontinued due to an AE will be summarized. The number and percentage of participants with increased laboratory toxicity grade shift from baseline will also be provided.

9.6.3 Demographic and Baseline Characteristics

The number and percentage of participants screened and allocated and the primary reasons for screening failure and discontinuation will be displayed. Demographic variables, baseline characteristics, primary and secondary diagnoses, and prior and concomitant therapies will be summarized by descriptive statistics or categorical tables.

9.7 Interim Analyses

No interim analyses are planned for this study.

9.8 Multiplicity

No multiplicity adjustment is required because there is no hypothesis testing.

9.9 Sample Size and Power Calculations

A total of 60 participants with rrPMBCL or rrcHL are expected to be enrolled. There is no required minimum enrollment for either cohort. There are no formal hypotheses to be tested. Based on the objectives and the estimated enrollment rates, along with a range of anticipated effect sizes and associated 95% CIs (refer to Table 10 and Table 11) a sample size of 60 was chosen.

rrPMBCL: Due to rarity of the disease, low enrollment is anticipated for rrPMBCL. Table 10 provides the two-sided 95% exact CIs for ORR for a range of observed response rates (20%, 40% and 60%) for different sample sizes.

Table 10 CCI

[redacted]	[redacted]		
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[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
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[redacted]			

rrcHL: Table 11 shows the two-sided 95% exact CIs for ORR for a range of observed response rates (20%, 40% and 60%) for different sample sizes.

Table 11 CCI [redacted]

[redacted]	[redacted]		
	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]			

9.10 CCI [redacted]

[redacted]

9.11 Compliance (Medication Adherence)

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

9.12 Extent of Exposure

Extent of exposure for a participant is defined as the number of cycles and number of days for which the participant receives the study treatment. Summary statistics will be provided on the extent of exposure for the overall study treatment, by cohort, for the APaT population.

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