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Phase 2 Trial of Pembrolizumab in Relapsed and Refractory Gray-Zone Lymphoma (GZL), Primary Central Nervous System Lymphoma (PCNSL), and other Extranodal Diffuse Large B-cell Lymphomas

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Commercial Agents: Pembrolizumab

PRÉCIS

Background:

- Gray-zone lymphomas (GZL) are rare, aggressive lymphomas that share clinical and biological features of diffuse large B-cell lymphoma (DLBCL) and Hodgkin lymphoma
- Standard upfront therapy for GZL is dose-intensive chemotherapy, though disease is often resistant; consolidative radiation therapy reserved for patients who are relapsed or refractory, and patients who fail radiation therapy have a poor prognosis
- Primary central nervous system lymphoma (PCNSL), primary testicular lymphoma (PTL), primary breast lymphoma (PBL), primary cutaneous DLBCL, leg-type, and intravascular B-cell lymphoma (IVBCL) are rare, aggressive extranodal subsets of DLBCL that usually have gene expression signatures of activated B-cell (ABC) DLBCL
- ABC-DLBCL has cure rates below 40% after standard therapy, and is associated with late recurrences, often involving the CNS where treatment options are limited by chemotherapy resistance and an inability of many agents to cross the blood-brain barrier
- Molecular biology studies of GZL and extranodal DLBCL have identified potentially targetable genetic features involving the programmed death-1 (PD-1) signaling pathway
- A high proportion of GZL, PCNSL, and PTL cases have copy number alterations or chromosomal rearrangements involving the PD-1 ligands, PD-L1 and PD-L2
- Pembrolizumab, a humanized IgG4 monoclonal antibody that targets the PD-1 receptor, is a rational therapeutic target for patients with relapsed and refractory GZL, PCNSL, PTL, and other extranodal DLBCL

Objectives:

- To determine the best overall response rate of pembrolizumab in patients with relapsed and refractory GZL and extranodal DLBCL

Eligibility:

- Confirmed diagnosis of B-cell lymphoma, relapsed from or refractory to prior:
    - Cohort 1: B-cell lymphoma, unclassifiable, with features intermediate between diffuse large B-cell lymphoma and classical Hodgkin lymphoma (i.e., Gray-zone lymphoma or GZL)
    - Cohort 2: Extranodal diffuse large B-cell lymphoma involving one or more of the specified extranodal sites (i.e., extranodal DLBCL)
- Adequate bone marrow and organ function defined
- Age greater than or equal to 18 years

Design:

- Phase 2 study of patients with relapsed and refractory GZL and extranodal DLBCL
- Patients will be treated with pembrolizumab 200 mg (flat dose) IV every 3 weeks provided they have clinical benefit and no unacceptable toxicity; patients who achieve a complete response (CR) will have the option stop after 1 year of therapy.
- All responding patients (CR, PR, or SD with clinical benefit) who subsequently relapse or progress within 1 year after discontinuation of study drug are eligible for re-treatment.
- At least 20 evaluable patients each with GZL and DLBCL will be evaluated on this protocol for the primary endpoint (overall accrual ceiling of 52 patients)

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STATEMENT OF COMPLIANCE

The trial will be carried out in accordance with International Conference on Harmonisation Good Clinical Practice (ICH GCP) and the following:

- United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, 21 CFR Part 312, and/or 21 CFR Part 812)

National Institutes of Health (NIH)-funded investigators and clinical trial site staff who are responsible for the conduct, management, or oversight of NIH-funded clinical trials have completed Human Subjects Protection and ICH GCP Training.

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the Institutional Review Board (IRB) for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. In addition, all changes to the consent form will be IRB-approved; an IRB determination will be made regarding whether a new consent needs to be obtained from participants who provided consent, using a previously approved consent form.

1 INTRODUCTION

1.1 STUDY OBJECTIVES

1.1.1 Primary Objective

To determine the best overall response rate of pembrolizumab in patients with relapsed/refractory B-cell lymphoma, unclassifiable, with features intermediate between diffuse large B-cell lymphoma and classical Hodgkin lymphoma (heretofore referred to as gray-zone lymphomas (GZL) and extranodaldiffuse large B-cell lymphomas (DLBCL) that involve 1 or more extranodal sites (heretofore referred to as extranodal DLBCL) according to the International Working Group (IWG) response criteria and the International PCNSL workshop response criteria

1.1.2 Secondary Objectives

- To determine the toxicity profile of pembrolizumab in patients with GZL and extranodal DLBCL
- To determine the best overall response rate according to the 5-point Lugano classification for interpreting FDG-PET scans
- To estimate the duration of response for patients who respond to pembrolizumab
- To estimate the progression-free survival (PFS) of patients with GZL and extranodal DLBCL treated with pembrolizumab
- To estimate the event-free survival (EFS) of patients with GZL and extranodal DLBCL treated with pembrolizumab
- To estimate the overall survival (OS) of patients with GZL and extranodal DLBCL treated with pembrolizumab

1.1.3 Exploratory Objectives

- To compare the extent of PD-L1 expression in tumor biopsies for pembrolizumab responders versus non-responders
- To compare PD-L1 and PD-L2 genetic alterations in responders versus non-responders

- To identify a baseline molecular profile that predicts clinical response or resistance to pembrolizumab
- To identify changes in the molecular profile at the time of progression that suggest mechanisms of pembrolizumab resistance
- To characterize the host immune response in the peripheral blood and cerebrospinal fluid (CSF) following treatment with pembrolizumab
- To identify potential biomarkers in tissue and the peripheral blood that predict response or toxicity to pembrolizumab
- To identify T-cell and B-cell clones in the peripheral blood that correlate with response to pembrolizumab and can be used for monitoring disease

1.2 BACKGROUND AND RATIONALE

1.2.1 Trial Design Summary

This study will evaluate pembrolizumab in 2 different cohorts of patients: one cohort of gray-zone lymphomas (GZL) and a second cohort of extranodal DLBCL that includes primary CNS lymphoma (PCNSL), primary testicular lymphoma (PTL), primary breast lymphoma (PBL), primary cutaneous DLBCL, leg-type, and intravascular B-cell lymphoma (IVBCL)

1.2.2 Gray-Zone Lymphomas

Gray zone lymphomas (GZL) are a rare heterogeneous group of aggressive B-cell lymphomas first recognized in the World Health Organization (WHO) classification of lymphoid neoplasms in 2008 as a B-cell lymphoma, unclassifiable, with features intermediate between diffuse large B-cell lymphoma (DLBCL) and classical Hodgkin lymphoma (cHL). Most cases present in the mediastinum of young patients and are known as mediastinal gray zone lymphomas (MGZL)[2-4]. The indeterminate pathobiology of MGZL has led to uncertainty about its optimal therapeutic approach[5]. A recent prospective study looked at the outcome of MGZL following treatment with the dose-adjusted, infusional regimen of etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin, and rituximab (DA-EPOCH-R) and reported a 5-year event-free survival (EFS) of 62% and a 5-year overall survival (OS) of 74%.[6] Although this regimen cures the majority of patients with MGZL, these results were inferior to the results in primary mediastinal B-cell lymphoma (PMBL) where DA-EPOCH-R resulted in 5-year EFS and OS of 93% and 97%, respectively[6]. Further, patients with MGZL were more likely to require consolidative radiotherapy to the mediastinum suggesting more intrinsic chemotherapy resistance. Patients with GZL who are refractory to radiation therapy have a grave prognosis and constitute an unmet clinical need[7]. Other GZL are less commonly encountered with clinical outcomes less well described.

Recent studies have investigated the underlying molecular biology of MGZL and other GZLs[4]. Over 60% of MGZL cases have amplification or copy number alterations involving a region of chromosome 9p24 that encodes critical genes in the PD-1 pathway such as *PD-L1, PD-L2* and *JAK2*[8-10]. These genetic aberrations result in overexpression of PD-1 and its ligands, suggesting that PD-1 signaling is important for tumor survival. Blocking the PD-1 pathway may result in both direct anti-tumor effects related to PD-1 signaling as well as restoration of the immune anti-tumor response by enhancing T-cell and NK-cell function[11]. Based on these hypotheses, we have recently treated two patients with refractory MGZL with pembrolizumab, and both patients achieved a complete response to therapy (authors' unpublished data, accepted for publication). Both of these patients had genetic alterations of 9p24.1, suggesting a disease-specific, genetically

determined dependence on PD-1 for survival. These cases provide early evidence for further testing of pembrolizumab in a larger cohort of patients with relapsed and refractory MGZL.

1.2.3 Primary Central Nervous System Lymphoma (PCNSL)

Primary CNS lymphoma (PCNSL) is a rare disease representing less than 3% of all non-Hodgkin lymphomas[12]. The term encompasses all aggressive lymphomas that arise in the brain parenchyma, spinal cord, eyes, cranial nerves and meninges. PCNSL spreads outside the CNS in fewer than 5% of cases. Most cases of PCNSL are diffuse large B-cell lymphomas (DLBCL). The incidence of PNCSL has been increasing; particularly in immunocompetent hosts and in patients over the age of 65 years[12]. PCNSL also occurs in patients who are HIV-positive, but this entity is virtually always associated with EBV and is a biologically distinct disease from those in immunocompetent patients.

Compared to patients with systemic DLBCL, the outcome for patients with PCNSL is poor as late recurrences are common[13]. The standard treatment approach to PCNSL differs significantly from systemic DLBCL because many chemotherapy agents, such as anthracyclines, do not adequately penetrate the blood-brain barrier. While radiotherapy (XRT) can overcome this limitation, remissions are of only short duration. Further, XRT is associated with significant acute and delayed neurotoxicity that limits its use in patients over the age of 60 years. High dose methotrexate (HD-MTX), an agent with good CNS penetration, has formed the backbone of systemic therapy for PCNSL, but produces a progression-free survival of only 7 months as a single agent[14]. The combination of HD-MTX with XRT improves the remission rate, but is associated with late relapses and treatment-associated neurotoxicity limits the use of combined modality therapy in many patients[15,16].

Combination immunochemotherapy platforms have been developed with the goal of applying dose intensive regimens that induce remissions without the need for radiation therapy. The various systemic agents that have been added to HD-MTX include rituximab, high-dose cytarabine, etoposide, thiotepa and temozolomide[17-19]. Although such combination regimens are effective at inducing remissions in the majority of patients, late relapses are common and fewer than 30% of patients are cured with this standard approach[13].

Recent studies have focused on the development of targeted agents in PCNSL on the basis of its underlying molecular biology. PCNSL tumors commonly have a gene expression signature and share many molecular features that resemble the ABC subtype of systemic DLBCL[20,21]. As a whole, the ABC subtype of DLBCL has a poorer prognosis than other subtypes, is associated with late relapses, and commonly involves the CNS[22]. Sequencing-based approaches have shown that the genomic landscape of PCNSL is enriched for mutations in the B-cell receptor (BCR) signaling and MYD88 pathway[23-28]. Published results from 7 studies of *CD79B* and *MYD88* sequences in tumors from patients with PCNSL demonstrate that 76% of cases have either a *MYD88* L265P mutation or a mutation in the ITAM motif of *CD79B*, including 37% of cases that have both mutations[23-28]. Ibrutinib is an oral inhibitor of Bruton's tyrosine kinase (BTK) and is particularly active in systemic ABC DLBCLs suggesting that it would be highly effective in PCNSL[29]. Indeed, recent studies have shown that ibrutinib monotherapy results in clinical remissions in a high number of patients, but of only short duration as a single agent.[30-32] Lenalidomide is another novel agent with single agent activity in ABC DLBCL that is under clinical development in PCNSL.[33] Similar to ibrutinib, single agent lenalidomide demonstrates clinical responses in PCNSL, but they tend to be of brief duration.

Additional targetable genetic features of PCNSL have also recently been reported by Chapuy and colleagues[27]. Using an integrative approach, they characterized the recurrent somatic mutations, chromosomal rearrangements, and copy number alterations in PCNSL. The authors identified a unique set of abnormalities in PCNSL characterized by genomic instability, abnormal signaling through the Toll-like receptor (TLR) pathway; often in combination with activation of the BCR pathway, and upregulation of PD-1 ligands. Copy gains of 9p24.1, which includes the genes for programmed death-ligands 1 and 2 (*PDL1* and *PDL2*) were found in more than 50% of cases of PCNSL. Since PD-1 inhibitors have demonstrated the ability to induce clinical responses in a variety of aggressive B-cell lymphomas, these pre-clinical data provide strong rationale to test anti-PD-1 therapy in relapsed cases of PCNSL[34-37]. Indeed, a recent report of 4 patients with relapsed and refractory PCNSL showed that targeting the PD-1 pathway can induce remissions in patients with relapsed and refractory PCNSL without unexpected toxicities[38]. Further testing of PD-1 inhibitors in patients with relapsed and refractory PCNSL is clearly warranted and a multi-center study is currently underway with nivolumab [NCT02857426].

1.2.4 Primary Testicular Lymphoma (PTL) and other extranodal ABC lymphomas

Additional rare extranodal forms of DLBCL share a biologic link to PCNSL and are included in this study. These lymphomas have clinical similarities to PCNSL including frequent involvement of immune-privileged sites and a propensity to remain confined within the involved organ until late stages of disease. The specified extranodal forms of DLBCL include primary testicular lymphoma (PTL), primary breast lymphoma (PBL), intravascular B-cell lymphoma (IVLBCL), and primary cutaneous diffuse large B-cell lymphoma, leg-type. All of these lymphomas are predominantly of the ABC subtype and harbor frequent mutations of *CD79B* and *MYD88*[39-46]. Additional evidence suggesting a biologic link among these tumors is a common pattern of disease spread. Many of these extranodal ABC lymphomas either involve the CNS at diagnosis or at the time of recurrence.[47]

A biologic link between PCNSL and PTL has recently been demonstrated with comprehensive molecular characterization. Chapuy et al. characterized PTL tumors on the basis of recurrent mutations, chromosomal rearrangements, and copy number alterations[27]. The authors found that both PCNSL and PTL share remarkably similar combinations of genetic features including frequent alterations of 9p24.1, *PD-L1*, and *PD-L2*. Indeed, these authors have anecdotally reported that PD-1 pathway blockade was effective in a case of relapsed PTL, and a multicenter study is underway testing PD-1 inhibitors in relapsed and refractory PCNSL and PTL [NCT02857426]. The other extranodal DLBCL subsets included in this study are hypothesized to have similar molecular biology since they are almost exclusively of the ABC subtype and share common clinical behavior. Given the low incidence of these tumors and strong rationale for potential benefit, they are included in this study in the same cohort as PCNSL and PTL.

1.2.5 Programmed cell death pathway (PD-1) as a therapeutic target

Immune surveillance plays a key regulatory role in the development of many lymphomas, and GZL and the extranodal DLBCL subtypes included in this protocol are hypothesized to have acquired tolerogenic mechanisms that permit them to evade an effective immune response. Programmed Cell Death-1 (PD-1; CD279) is a cell surface signaling molecule that delivers inhibitory signals that regulate the balance between T cell activation and tolerance by interacting with its ligands, PD-L1 (CD274; B7-H1) and PD-L2 (B7-DC/CD273). PD-1 is primarily expressed on activated T cells, B cells, and myeloid cells.[48] PD-1expression can also be detected on memory T-cell subsets with variable levels. Upon ligand binding to PD-1, T-cell activation is down-

regulated in both murine and human systems. The interaction of PD-1 on tumor specific cytotoxic T cells with its ligands PD-L1 and PD-L2 causes a decrease in the ability of these cells to proliferate and exert cytotoxic effects, increases their apoptotic rate and alters the functional characteristics of the cells to produce a tolerogenic phenotype. Inhibition of the interaction between PD-1 and its ligands promotes immune responses and antigen-specific T-cell responses to both foreign antigens as well as self-antigens. Since these responses are variable and dependent upon various host genetic factors, PD-1 deficiency or inhibition is not accompanied by a universal loss of tolerance to self-antigens.

PD-L1 expression may be a mechanism by which tumors can directly engage PD-1 to evade an effective anti-tumor immune response. PD-L1 expression by malignant tumor cells is a marker of poor prognosis in aggressive lymphomas such as diffuse large B-cell lymphoma (DLBCL).[49] Other cells in the tumor microenvironment of these tumors such as T cells, dendritic cells, and monocytes are also positive for PD-L1 and have the potential to interact with tumor specific T cells that express PD-1.[49] Blocking PD-1 may reverse the inactivation of tumor-specific effector T-cells at the tumor site, as well as activate anti-tumor responses that are limited by PD-L1 expression on host cytotoxic cells.

The host's adaptive immune response to inhibitors of the PD-1 axis has not been completely characterized and is a research priority. Pre-clinical studies in mice with chronic viral infections established that a subset of exhausted CD8 T-cells can be rescued with inhibition of the PD-L1/PD-1 axis and can be functionally restored.[50] In lung cancer, increases in the peripheral blood of $CD8^+$ T-cells with an effector phenotype have been observed after PD-1 inhibition.[51] These increases tend to occur early and are associated with clinical response. Predictive biomarkers that identify specific T-cell sub-populations still capable of being restored have not been established, however.

1.2.6 Pembrolizumab

Pembrolizumab is a potent and highly selective humanized monoclonal antibody (mAb) of the IgG4/kappa isotype designed to directly block the interaction between PD-1 and its ligands, PD-L1 and PD-L2. Keytruda™ (pembrolizumab) has been approved in the United Stated for the treatment of patients with metastatic melanoma, metastatic non-small cell lung cancer, recurrent or metastatic head and neck squamous cell carcinoma, and recurrent and refractory classical Hodgkin lymphoma.

1.2.6.1 Rationale for dosing

An open-label Phase I trial has been conducted to evaluate the safety and clinical activity of single agent pembrolizumab. The dose escalation portion of this trial evaluated three dose levels, 1 mg/kg, 3 mg/kg, and 10 mg/kg, administered every 2 weeks (Q2W) in subjects with advanced solid tumors. All of three dose levels were well tolerated and no dose-limiting toxicities were observed. This first in human study of pembrolizumab showed evidence of target engagement and objective evidence of tumor size reduction at all dose levels (1 mg/kg, 3 mg/kg and 10 mg/kg Q2W). No MTD has been identified to date. 10.0 mg/kg Q2W, the highest dose tested in this phase 1 study, will be the dose and schedule utilized in this protocol to test for initial tumor activity. Recent data from other clinical studies within the pembrolizumab program has shown that a lower dose of pembrolizumab and a less frequent schedule may be sufficient for target engagement and clinical activity.

A population pharmacokinetic analysis has been performed using serum concentration time data from 476 patients. Within the resulting population PK model, clearance and volume parameters of

pembrolizumab were found to be dependent on body weight. The relationship between clearance and body weight, with an allometric exponent of 0.59, is within the range observed for other antibodies and would support both body weight normalized dosing or a fixed dose across all body weights. Pembrolizumab has been found to have a wide therapeutic range based on the melanoma indication. The differences in exposure for a 200 mg fixed dose regimen relative to a 2 mg/kg Q3W body weight based regimen are anticipated to remain well within the established exposure margins of 0.5 – 5.0 for pembrolizumab in the melanoma indication. The exposure margins are based on the notion of similar efficacy and safety in melanoma at 10 mg/kg Q3W vs. the proposed dose regimen of 2 mg/kg Q3W (i.e. 5-fold higher dose and exposure). The population PK evaluation revealed that there was no significant impact of tumor burden on exposure. In addition, exposure was similar between the NSCLC and melanoma indications. Therefore, there are no anticipated changes in exposure between different indication settings. In this study the planned dose of pembrolizumab will be 200mg every 3 weeks until confirmed disease progression or unacceptable toxicity, with an option for a treatment interruption in cases of response and retreatment upon progression.

1.2.6.2 Efficacy of Pembrolizumab in Classical Hodgkin lymphoma

A phase I study of pembrolizumab in patients with relapsed/refractory hematologic malignancies (KEYNOTE-13) is ongoing [NCT01953692]. Patients are treated with 10mg/m^2 of pembrolizumab every 2 weeks until disease progression unless or excessive toxicity. Responses were assessed at week 12 and every 8 weeks thereafter. Since patients with classical Hodgkin lymphoma (cHL) frequently exhibit genetic alterations in the PD-1 pathway, this cohort was assessed independently. A total of 31 patients with cHL with relapsed or refractory disease were included in this analysis. All patients had been previously treated with brentuximab vedotin and 71% and undergone autologous stem cell transplantation. The overall response rate to pembrolizumab monotherapy was 65% (90% CI, 48% to 79%) with the majority of responses lasting longer than 6 months. Further, 5 patients (16%) had a complete response (CR) at 12 weeks.

Given the promising response rate in cHL, a multi-center phase II study (KEYNOTE-087) has recently been completed testing the response rate of pembrolizumab monotherapy in patients with relapsed and refractory cHL[52]. In this study, three cohorts of cHL patients were included for a total of 210 patients. The ORR of the entire group was 69% (95% CI, 62.3% to 75.2%) and the CR rate was 22.4% (95% CI, 16.9% to 28.6%). Patients received a median of 13 treatment cycles and many patients had responses lasting longer than 6 months. This study led to accelerated FDA approval of pembrolizumab for relapsed and refractory cHL.

1.2.6.3 Adverse event profile of Pembrolizumab in Lymphoid Malignancies

All patients treated with PD-1 inhibitors require monitoring for the development of immune-related complications including, but not limited to, diarrhea, pneumonitis, and rash. Given that this study will include patients with tumors involving the CNS, special concern for immune-related complications within the CNS will be implemented. Overall, in the phase 1 study of pembrolizumab in cHL, there were no serious adverse events (SAEs) or grade 3-4 AEs related to treatment[34]. Overall, 5 patients experienced a grade 3 drug-related AE. The most common drug-related AEs were grade 1-2 respiratory events (20%) and thyroid disorders (20%). One patient discontinued study treatment because of an AE (grade 2 pneumonitis), and 3 patients ended therapy after progressive disease (PD). In the phase II study in patients with cHL, the safety profile was as expected. The most common treatment-related AEs were hypothyroidism (12.4% and pyrexia (10.5%), while the most common grade 3-4 treatment-related AEs were neutropenia (2.4%),

dyspnea (1%), and diarrhea (1%). In conclusion, pembrolizumab therapy appears to be safe, tolerable, and associated with clinical benefit in patients with heavily pretreated cHL.

1.2.7 Pharmacodynamics/Biomarkers

Predictive biomarkers within baseline tumor tissue or in the peripheral blood are a research priority shared across all immuno-oncology studies. The identification of reliable biomarkers that can predict either response or toxicity may enhance individualized treatment decisions. The expression of PD-L1 by immunohistochemistry in malignant and surrounding inflammatory cells has been demonstrated as a predictor of response to PD-1 inhibitors in various studies. In lymphoma, however, the expression of PD-1 is present on both malignant cells as well as non-malignant cells in the tumor microenvironment. Further, expression of PD-1 is expected in the majority of cases, so simply the presence or absence may not predict for response. Therefore, localization of PD-1 staining will be assessed on this study as well as longitudinal sampling on optional biopsies taken during therapy and at the time of progression.

Currently, there is an incomplete understanding of the molecular pathways that are susceptible to inhibition of PD-1. A molecular profile may exist that identify patients likely (or unlikely) to respond to PD-1 inhibition. In a study of patients with relapsed Hodgkin lymphoma, pre-treatment tumor specimens from multiple patients revealed copy-number gains in PD-L1 and PD-L2 and increased expression of these ligands.[37] In patients with lung cancer, the number of non-synonymous mutations in the pre-treatment biopsy specimen predicted likelihood of response to PD-1 inhibitor.[53] In melanoma, the absence of PTEN expression has been associated with a lack of clinical response to PD-1 inhibitors[54]. A comprehensive molecular profile will be used on baseline and sequential tumor samples and utilize DNA/RNA sequencing as well as copy number alterations as part of the exploratory analysis to identify genetic profiles of tumors that are likeliest to respond to pembrolizumab.

Another research priority is to identify potential biomarkers in the peripheral blood and CSF that correlate with response or toxicity. A recent study demonstrated that PD-1 inhibitors result in an increase in the number of $CD8^{+}Ki\text{-}67^{+}PD\text{-}1^{+}$ effector T-cells in the peripheral blood shortly after initiation of therapy in patients with lung cancer[51]. We will use multi-parameter flow cytometry for T-cell and NK-cell subsets and monitor the peripheral blood for an early host adaptive immune response (6 weeks), a “rebound effect” (18 weeks), at 1 years, and 2 years. In addition, we will assess the host immune response at the time of disease progression. In the case of patients with PCNSL, these tests will also be performed longitudinally in the CSF and correlated with response. Tissue biopsy specimens and peripheral blood samples obtained while on pembrolizumab therapy may identify other potential biomarkers that predict response and/or help elucidate the mechanisms of treatment resistance at the cellular level.

2 ELIGIBILITY ASSESSMENT AND ENROLLMENT

2.1 ELIGIBILITY CRITERIA

2.1.1 Inclusion Criteria

2.1.1.1 Patients must have a diagnosis of B-cell lymphoma confirmed by Laboratory of Pathology, NCI, that is relapsed from or refractory to prior therapy as follows:

- Cohort 1: B-cell lymphoma, unclassifiable, with features intermediate between diffuse large B-cell lymphoma and classical Hodgkin lymphoma (i.e., Gray-zone lymphoma or GZL)
- Cohort 2: Extranodal diffuse large B-cell lymphoma involving one or more of the specified extranodal sites (i.e., extranodal DLBCL). The following subtypes are included (they do not have to be confirmed as non-GCB subtype for study entry):
  - Primary CNS lymphoma (PCNSL)
  - Primary testicular lymphoma (PTL)
  - Primary breast lymphoma (PBL)
  - Primary cutaneous DLBCL, leg-type
  - Intravascular large B-cell lymphoma (IVBCL)
  - Diffuse large B-cell, NOS, activated B-cell type, involving 1 or more extranodal site

NOTE: For GZL, diagnosis will be in accordance with the 2016 World Health Organization classification of lymphoid malignancies.[1] Patients diagnosed with other extranodal DLBCL subtypes or that are not otherwise specified (NOS) must involved at least 1 extranodal site and must be considered non-GCB by local immunohistochemistry algorithms. Cases that are non-GCB by the Hans criteria are considered eligible as well as cases of DLBCL that are both CD10+ and MUM1+.

2.1.1.2 Evaluable disease by clinical exam (i.e., palpable lymphadenopathy, measurable skin lesions, etc.), laboratory assessment (i.e., lymphoma involvement of bone marrow or peripheral blood by morphology, cytology or flow cytometry), and/or imaging (measurable lymph nodes or masses on CT or MRI and/or evaluable FDG-avid lesions on PET)

2.1.1.3 Adequate tumor tissue (archival or fresh) must be available for correlative studies. **NOTE:** Tumor tissue may be from any previously collected tissue and adequacy is at the discretion of the Principal Investigator. If prior tissue is not available, patient must be willing to undergo baseline tumor biopsy.

2.1.1.4 Be ≥18 years of age on day of signing informed consent

2.1.1.5 Adequate performance status (PS) as follows (see APPENDIX A):

- Patients ≥ 18 years must have ECOG PS 0-1 and Karnofsky ≥ 60%.

NOTE: Patients ≥ 18 years with an ECOG PS of 2 and Karnofsky ≥ 60 will be considered eligible at the discretion of the Principal Investigator if decreased ECOG performance status is felt to be related to residual neurologic deficits caused by CNS disease involvement that are not progressive or anticipated to cause clinical management problems during study participation.

2.1.1.6 Adequate organ function as evidenced by the following laboratory parameters (unless related to lymphoma infiltration at the discretion of the investigator):

• Absolute neutrophil count (ANC)	≥ 750 /mcL
• Platelets	≥ 50,000 / mcL (transfusions not permitted)
• Hemoglobin	≥ 9 g/dL (transfusions permitted)
• Serum creatinine **OR** Measured or calculated creatinine clearance (GFR can also be used in place of creatinine or CrCl)	Adults: ≤ 1.5 X upper limit of normal (ULN) Children age ≥14: ≤ 1.5 mg/dL **OR** ≥ 30 mL for subject with creatinine levels > 1.5 X institutional ULN (CrCl should be calculated per institutional standard)
• Serum total bilirubin	≤ 1.5 X ULN **OR** Direct bilirubin ≤ ULN for patients with total bilirubin levels > 1.5 ULN
• AST (SGOT) and ALT (SGPT)	≤ 3 X ULN (≤ 5 X ULN if liver involvement)

2.1.1.7 The effects of pembrolizumab on the developing human fetus are unknown. For this reason, the following measures apply:

- Women of childbearing potential must have a negative serum or urine pregnancy test within 72 hours prior to the first dose of pembrolizumab.
- Men and women of childbearing potential (WOCBP) who are sexually active must agree to adequate contraception (hormonal or barrier method of birth control; abstinence) prior to study entry, for the duration of study participation, and for at least 120 days after the last dose of pembrolizumab as outlined in Section **4.3.2** and **4.3.3**. Should a woman become pregnant or suspect she is pregnant while she or her partner is participating in this study, she should inform her treating physician immediately.
- Participants must not be planning to conceive or father children within the projected duration of the trial, starting with the pre-screening/screening visit through 120 days after the last dose of pembrolizumab.
- WOCBP is defined as any female who has experienced menarche and who has not undergone successful surgical sterilization or who is not postmenopausal. **NOTE:** See Section **4.3.2** for definitions.

2.1.1.8 Ability of patient or Legally Authorized Representative (LAR) to understand and the willingness to sign a written informed consent document

2.1.2 Exclusion Criteria

2.1.2.1 Patients with DLBCL who best fit the criteria of EBV+ DLBCL, NOS are not eligible

2.1.2.2 Current or prior anti-cancer treatment prior to the first dose of pembrolizumab as defined below:

- Chemotherapy, targeted small molecule therapy, or other anti-cancer treatment not otherwise specified below within 2 weeks
- Radiation therapy within 2 weeks
- Anti-cancer monoclonal antibody (mAb) treatment within 4 weeks

- Use of an investigational agent (e.g., biologic, drug, or other) within 4 weeks
- Allogeneic stem cell transplant within 100 days
- Prior therapy with an anti-PD-1, anti-PD-L1, or anti-PD-L2 agent at any time

2.1.2.3 No current use of systemic corticosteroids at physiologic doses > 10 mg/day of dexamethasone or equivalent are permitted. Patients receiving current systemic steroids must be on a stable steroid dose (i.e., ≤ 10 mg/day of dexamethasone or equivalent at the same dose for at least 7 days). Patients who recently discontinued systemic steroids must have completed them at least 7 days prior to entry.

2.1.2.4 Uncontrolled intercurrent illness including, but not limited to the following that may limit interpretation of results or that could increase risk to the patient at the discretion of the investigator:

- Active autoimmune disease that has required systemic treatment in the past 2 years (i.e., with use of disease modifying agents, corticosteroids or immunosuppressive drugs). **NOTE:** Replacement therapy (e.g., thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency, etc.) is not considered a form of systemic treatment.
- History of (non-infectious) pneumonitis that required steroids, evidence of interstitial lung disease or active, non-infectious pneumonitis.
- Clinically significant history of liver disease, including viral or other hepatitis, current alcohol abuse, or cirrhosis; as well as active infection with HBV or HCV:
    - Patients with occult or prior HBV infection (defined as positive total hepatitis B core antibody [HBcAb] and negative HBsAg) may be included if HBV DNA is undetectable.
    - Subjects who are positive for HCV antibody must be negative for HCV by polymerase chain reaction (PCR) to be eligible for study participation.
- Uncontrolled and/or symptomatic thyroid disease
- Active graft-vs-host disease (GVHD) requiring treatment or any history of ≥ grade II acute GVHD
- Seizure activity within the past 4 weeks
- Known mental or physical illness that would interfere with cooperation with the requirements of the trial or confound the results or interpretation of the results of the trial and, in the opinion of the treating investigator, would make the patient inappropriate for entry into the study.

2.1.2.5 Because there is an unknown but potential risk for adverse events in nursing infants secondary to treatment of the mother with pembrolizumab, breastfeeding must be discontinued if the mother is treated with pembrolizumab

2.1.2.6 Received a live vaccine within 30 days of planned start of study therapy. **NOTE:** Seasonal influenza vaccines for injection are generally inactivated flu vaccines and are

allowed; however intranasal influenza vaccines (e.g., Flu-Mist®) are live attenuated vaccines, and are not allowed.

2.1.2.7 History of allergic reactions attributed to compounds of similar chemical or biologic composition to pembrolizumab unless felt to be in the best interests of the patient in the opinion of the investigator

2.1.2.8 Known additional malignancy that requires active systemic treatment

2.1.3 Recruitment Strategies

This protocol may be abstracted into a plain language announcement posted on NIH websites and NIH Social Media platforms. Study participants will be recruited from the population of patients screened in the lymphoid malignancies clinic of the National Institutes of Health. These will include both referrals from outside physicians as well as patient self-referrals.

2.2 SCREENING EVALUATION

Note: Screening evaluation testing/procedures are conducted under the separate screening protocol, 01-C-0129 (Eligibility Screening and Tissue Procurement for the NIH Intramural Research Program Clinical Protocols).

NOTE: Assessments and procedures to confirm study eligibility should be completed within 28 days prior to registration confirmation/verification (unless otherwise noted).

2.2.1 Clinical Evaluations

- Disease history, including: diagnosis, treatment (e.g., systemic treatments, radiation and surgeries), status, and significant prior/ongoing side effects and symptoms
- Complete medical history, including: all active conditions considered to be clinically significant by the treating investigator
- Physical examination, including: height (screening only), weight, vital signs (i.e., temperature, pulse, respiratory rate, and blood pressure); review of concomitant medications and symptoms/side effects; and, assessment of performance status

2.2.2 Laboratory Evaluations

NOTE: Results from outside NIH are accepted.

- CBC with differential
- Chemistry panels (as noted) or specific analyte required for eligibility, including: Creatinine (i.e., or Acute Care Panel); ALT, AST, total and direct (if required) bilirubin (i.e., or Hepatic Panel); and, 24-hour urine creatinine clearance (if needed to measure CrCl in cases where serum creatinine >1.5mg/dl)
- Thyroid function tests, including: thyroid stimulating hormone (TSH), total triiodothyronine (T3), free thyroxine (T4)
- Hepatitis B surface antigen (HBsAg), Hepatitis B core antibody, Hepatitis C antibody (HCV) [qualitative]) (3 months)
- Urine and/or serum HCG in women of childbearing potential (within 3 days prior to initiation of study therapy)

2.2.3 Imaging Studies

NOTE: Results from NIH only.

- CT chest, abdomen and pelvis
- MRI of brain (required in patients with PCNSL; as clinically indicated in other patients – i.e., known or suspected involvement of CNS)

2.2.4 Other Procedures

- Pathologic review/confirmation of diagnosis by Laboratory of Pathology, NCI (no time limit). A tissue sample is required for this evaluation; if archival sample is not available, a fresh tumor biopsy will be obtained. If a biopsy procedure is attempted, but tissue is not able to be obtained for any reason (e.g., safety reasons), patient may still be eligible for enrollment at the discretion of the Principal Investigator.

2.3 PARTICIPANT REGISTRATION AND STATUS UPDATE PROCEDURES

Registration and status updates (e.g., when a participant is taken off protocol therapy and when a participant is taken off-study) will take place per CCR SOP ADCR-2, CCR Participant Registration & Status Updates found here.

2.4 TREATMENT ASSIGNMENT PROCEDURES

2.4.1 Cohorts

Number	Name	Description
1	Gray-zone lymphoma	B-cell lymphoma, unclassifiable, with features intermediate between diffuse large B-cell lymphoma and classical Hodgkin lymphoma (so-called GZL)
2	Extranodal diffuse large B-cell lymphoma	Extranodal DLBCL that involves one or more extranodal sites

2.4.2 Arms

Number	Name	Description
1	Experimental: Pembrolizumab	Administered intravenously (IV) at a fixed dose of 200 mg every 3 weeks until disease progression or unacceptable toxicity; if ongoing clinical benefit after 24 months, option for treatment interruption and retreatment upon relapse

2.4.3 Treatment Assignment and Randomization/Blinding

Patients are assigned to a group/cohort based upon diagnosis; treatment assignment is single arm, open-label and non-randomized (i.e., subjects in Cohorts 1 and 2 directly assigned to Arm 1).

2.5 BASELINE EVALUATION

The following should be performed within 28 days prior to the first dose of pembrolizumab unless other noted; tests performed as part of screening do not need to be repeated if they were performed within the specified window prior to the first dose of pembrolizumab.

2.5.1 Clinical Evaluations

- Medical history (interim)
- Physical examination, including weight, and vital signs (i.e., temperature, pulse, respiratory rate, and blood pressure); review of concomitant medications and symptoms/side effects; and, assessment of performance status (within 14 days)

2.5.2 Laboratory Evaluations

NOTE: Results from outside NIH are accepted.

- Required within 3 days:
  - Urine and/or serum HCG in WOCBP
- Required within 14 days:
  - CBC with differential
  - Chemistry panels, including: Acute Care Panel (sodium, potassium, chloride, CO_2, glucose, BUN, creatinine), Mineral Panel (serum calcium, phosphate, magnesium and albumin), Hepatic Panel (alkaline phosphatase, ALT, AST, total and direct bilirubin), and 24-hour urine creatinine clearance (if needed measure CrCl if serum creatinine >1.5mg/dl)
  - Others: LDH, Uric acid, Total protein
  - Coagulation panel, including: PT/INR and aPTT
  - Thyroid function tests, including: thyroid stimulating hormone (TSH), total triiodothyronine (T3), free thyroxine (T4)
  - Urinalysis (with microscopic examination if abnormal)
- Required within 28 days:
  - HIV antibody (within 3 months allowed)
  - Lymphocyte Phenotype: T, B and NK cell subsets
  - Quantitative serum immunoglobulin (IG) levels
  - Anti-Nuclear Antibody (ANA)

2.5.3 Imaging Studies

- CT chest, abdomen and pelvis
- MRI of brain (required in patients with PCNSL; as clinically indicated in other patients)
- 18F-FDG PET/CT

NOTE: Results from NIH only. Other body areas may be imaged if clinically indicated.

2.5.4 Other Procedures

- Flow cytometry will be performed on peripheral blood for both diagnostic and staging purposes (only NIH results accepted; NCI Laboratory of Pathology)
- Bone marrow aspiration and biopsy, if clinically indicated (within 3 months)
- Lumbar puncture (LP) for cytology and flow cytometry; required in patients with PCNSL and if clinically indicated in other patients (within 3 months)
- Ophthalmologic evaluation (in patients with PCNSL)

2.5.5 Research Correlates

NOTE: See Section **5** for additional information. The following sample types will be collected for correlative research studies:

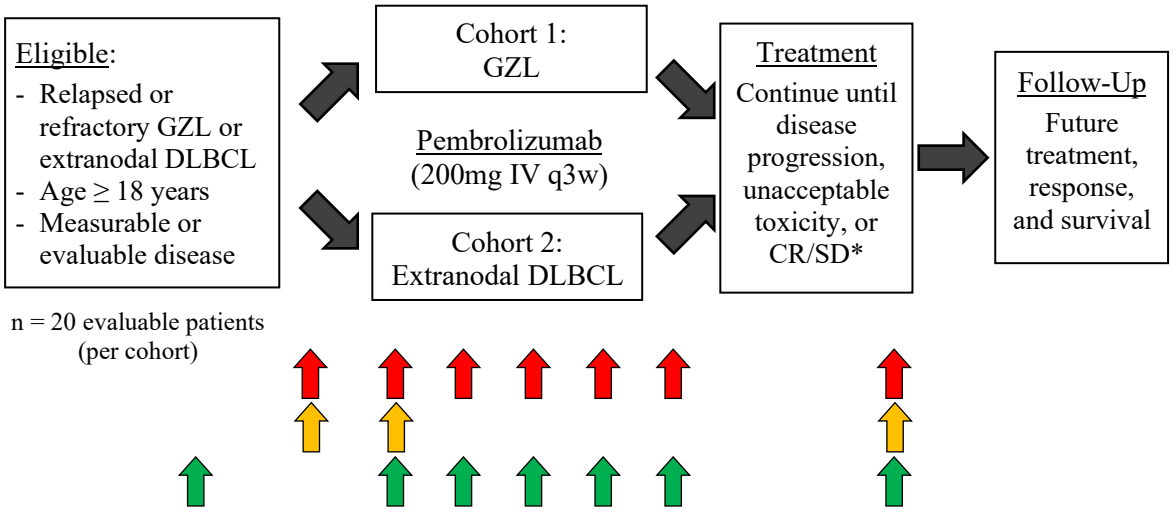
- Required: Blood samples and tumor tissue (archival or fresh). Cheek swabs or saliva samples (preferred) may be obtained as a source of germline DNA instead of blood.

- Optional: Tumor biopsy is required for study entry if archival tissue is not available or adequate; otherwise, this is optional.
- Select patients: CSF samples (i.e., patients with Ommaya or planned procedure)

3 STUDY IMPLEMENTATION

3.1 STUDY DESIGN

This is a non-randomized, open-label, single arm, single institution phase 2 study of pembrolizumab in patients with relapsed or refractory GZL or extranodal DLBCL (including PCNSL). The patients with GZL and extranodal DLBCL will be enrolled into two (2) separate, disease-specific cohorts.



Bloods for correlates collected prior to treatment, after cycles 2 and 6, and at approximately months 9, 12, 18, and every 6 months thereafter.

Tissue for correlates collected prior to treatment (archival or fresh); with optional fresh tumor biopsy at baseline, after 2 cycles, and at disease progression.

Disease evaluations will be performed prior to treatment and after initiation of treatment at the same time points at correlate blood sample collection.

3.2 DRUG ADMINISTRATION

Each cycle of treatment is 21 days or 3 weeks. The minimum window between cycles due to scheduling or other administrative reasons is 18 days (i.e., 21 days -3 days).

All patients will receive single-agent pembrolizumab at a fixed dose of 200 milligrams (mg) administered via intravenous (IV) infusion every 21 days (3 weeks). Dosing of pembrolizumab is fixed; not based upon subject weight. Infusions may be done peripherally or via central venous access device, etc.

Pembrolizumab will be administered as a 30-minute infusion. Every effort should be made to target the infusion timing as close to 30 minutes as possible; however, a preferred window of -5/+10 minutes to account for variability of infusion pumps is permitted (i.e., anticipated infusion window of 25-40 minutes).

Treatment will be on an outpatient basis; however, at the investigator's discretion (e.g., for additional monitoring, patient social reasons, etc.), patients may be treated on an inpatient basis. Any cases of planned hospitalization are not considered reportable serious adverse events per Section 7.

No premedications are required; however, may be used in specific patients at treating investigator discretion or as directed per toxicity management.

NOTE: The FDA-approved labeling contains additional specific instructions for the preparation of pembrolizumab infusion fluid and administration of infusion solution.

3.3 DOSE MODIFICATIONS

Adverse events (both non-serious [AEs] and serious [SAEs]) associated with pembrolizumab exposure may represent an immunologic etiology. These adverse events may occur shortly after the first dose or several months after the last dose of treatment.

Pembrolizumab must be withheld for all drug-related toxicities and severe or life-threatening AEs as per below. See Section **3.3.1** for immune-related event supportive care guidelines, including use of corticosteroids.

For any other, non-immune related AEs/SAEs, the treating investigator may use discretion with regards to dose holds, modifications, and supportive care. **NOTE: S**ee Section **3.3.3** for guidelines and management specific to infusion reaction/infusion-related toxicity,

Dosing interruptions are permitted in the case of medical and/or surgical events or logistical reasons not related to study therapy (e.g., elective surgery, unrelated medical events, patient vacation, and/or holidays). Patients should be placed back on study therapy within 3 weeks of the scheduled interruption, whenever possible. The reason for interruption should be documented in the medical/research records. These interruptions will not be considered protocol deviations.

3.3.1 Immune-Related Toxicity Management

Patients should receive appropriate supportive care measures as deemed necessary by the treating investigator. Suggested supportive care measures for the management of adverse events with potential immunologic etiology are outlined below (i.e., immune-related adverse events or irAEs). Where appropriate, these guidelines include the use of oral or intravenous 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 the event is determined not to be related, the investigator does not need to follow the treatment guidance (as outlined below). Refer to Section **3.3** for dose modification.

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

3.3.2 Immune-Related Adverse Events

General Instructions:

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

Immune-related AEs	Toxicity grade or conditions (CTCAEv4.0)	Action taken to pembrolizumab	irAE management with corticosteroid and/or other therapies	Monitor and follow-up
Pneumonitis	Grade 2	Withhold	• Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper	• Monitor participants for signs and symptoms of pneumonitis • Evaluate participants with suspected pneumonitis with radiographic imaging and initiate corticosteroid treatment • Add prophylactic antibiotics for opportunistic infections
	Grade 3 or 4, or recurrent Grade 2	Permanently discontinue		
Diarrhea/ Colitis	Grade 2 or 3	Withhold	• Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper	• Monitor participants for signs and symptoms of enterocolitis (ie, diarrhea, abdominal pain, blood or mucus in stool with or without fever) and of bowel perforation (ie, peritoneal signs and ileus). • Participants with ≥ Grade 2 diarrhea suspecting colitis should consider GI consultation and performing endoscopy to rule out colitis. • Participants with diarrhea/colitis should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion.
	Grade 4	Permanently discontinue		
AST/ ALT elevation or	Grade 2	Withhold	• Administer corticosteroids (initial dose of 0.5- 1 mg/kg prednisone or equivalent) followed by taper	• Monitor with liver function tests (consider weekly or more frequently until liver

Immune-related AEs	Toxicity grade or conditions (CTCAEv4.0)	Action taken to pembrolizumab	irAE management with corticosteroid and/or other therapies	Monitor and follow-up
Increased bilirubin	Grade 3 or 4	Permanently discontinue	• Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper	enzyme value returned to baseline or is stable
Type 1 diabetes mellitus (T1DM) or Hyperglycemia	Newly onset T1DM or Grade 3 or 4 hyperglycemia associated with evidence of β-cell failure	Withhold	• Initiate insulin replacement therapy for participants with T1DM • Administer anti-hyperglycemic in participants with hyperglycemia	• Monitor participants for hyperglycemia or other signs and symptoms of diabetes.
Hypophysitis	Grade 2	Withhold	• Administer corticosteroids and initiate hormonal replacements as clinically indicated.	• Monitor for signs and symptoms of hypophysitis (including hypopituitarism and adrenal insufficiency)
	Grade 3 or 4	Withhold or permanently discontinue[1]		
Hyperthyroidism	Grade 2	Continue	• Treat with non-selective beta-blockers (eg, propranolol) or thionamides as appropriate	• Monitor for signs and symptoms of thyroid disorders.
	Grade 3 or 4	Withhold or permanently discontinue[1]		
Hypothyroidism	Grade 2-4	Continue	• Initiate thyroid replacement hormones (eg, levothyroxine or liothyroinine) per standard of care	• Monitor for signs and symptoms of thyroid disorders.
Nephritis and Renal dysfunction	Grade 2	Withhold	• Administer corticosteroids (prednisone 1-2 mg/kg or equivalent) followed by taper.	• Monitor changes of renal function
	Grade 3 or 4	Permanently discontinue		
Myocarditis	Grade 1 or 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		

Immune-related AEs	Toxicity grade or conditions (CTCAEv4.0)	Action taken to pembrolizumab	irAE management with corticosteroid and/or other therapies	Monitor and follow-up
All other immune-related AEs	Intolerable/ persistent Grade 2	Withhold	• Based on type and severity of AE administer corticosteroids **NOTE:** Events that require discontinuation include and not limited to: Gullain-Barre Syndrome, encephalitis.	• Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 3	Withhold or discontinue based on the type of event.		
	Grade 4 or recurrent Grade 3	Permanently discontinue		
1. Withhold or permanently discontinue pembrolizumab is at the discretion of the investigator or treating physician. **NOTE:** For participants with Grade 3 or 4 immune-related endocrinopathy where withhold of pembrolizumab is required, pembrolizumab may be resumed when AE resolves to ≤ Grade 2 and is controlled with hormonal replacement therapy or achieved metabolic control (in case of T1DM).				

3.3.3 Management of Infusion Reactions

Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion. The table below shows treatment guidelines for patients who experience an infusion reaction associated with administration of pembrolizumab:

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 subject is deemed medically stable in the opinion of the investigator.	None
Grade 2 Requires infusion interruption but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDS, narcotics, IV fluids); prophylactic medications indicated for < =24 hrs	**Stop Infusion and monitor symptoms.** 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 subject is deemed medically stable in the opinion of the investigator. If symptoms resolve within one hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (e.g., from 100 mL/hr to 50 mL/hr). Otherwise dosing will be held until symptoms resolve and the subject should be premedicated for the next scheduled dose. **Patients who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further trial treatment administration.**	Subject may be premedicated 1.5h (± 30 minutes) prior to infusion of pembrolizumab (PEMBROLIZUMAB) with: Diphenhydramine 50 mg po (or equivalent dose of antihistamine). Acetaminophen 500-1000 mg po (or equivalent dose of antipyretic).
Grades 3 or 4 Grade 3: Prolonged (i.e., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (e.g., 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: IV fluids Antihistamines NSAIDS Acetaminophen Narcotics Oxygen Pressors Corticosteroids Epinephrine Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator. Hospitalization may be indicated. **Subject is permanently discontinued from further trial treatment administration.**	No subsequent dosing
Appropriate resuscitation equipment should be available in the room and a physician readily available during the period of drug administration.		

3.4 ON STUDY EVALUATIONS

Upon confirmation of eligibility and successful registration, and following completion of the Screening/Baseline visit, patients will begin treatment with pembrolizumab. Patients must

maintain eligibility for any assessments/tests repeated post-registration and prior to administration of the first dose of pembrolizumab.

After Cycle 1, pre-dose assessments may be performed up to 3 days prior to Day 1 of a cycle (7 days for imaging), except where otherwise noted. The results from all procedures/tests must be reviewed prior to initiation of each cycle of treatment for consideration of dose modifications.

Pembrolizumab will continue until disease progression absent clinical benefit, unacceptable treatment-related toxicity, or other reasons outlined in Section **3.10.1**.

Refer to the Study Calendar (Section **3.8**) for all tests and procedures to be conducted during screening/baseline, on study/during treatment, and upon discontinuation of treatment and during follow-up.

In summary, the following will be done at follow-up visits per the Study Calendar:

3.4.1 Clinical Evaluations

- Medical history (interim)
- Physical examination, including weight and vital signs; review of concomitant medications and symptoms/side effects; and, assessment of performance status

3.4.2 Laboratory Evaluations

- CBC with differential
- Chemistries, including: acute care, mineral, and hepatic panels
- Others: LDH, uric acid, and total protein
- Thyroid function tests, including: TSH, total T3, free thyroxine (T4)
- Lymphocyte Phenotype: T, B and NK cell subsets
- Quantitative serum immunoglobulin (IG) levels
- Urinalysis

3.4.3 Imaging Studies

NOTE: Results from NIH only. These are done at the following time points during treatment (see Study Calendar for windows): after cycles 2 and 6, and months 9, 12, 18, and every 6 months thereafter during treatment.

- CT chest, abdomen and pelvis; and/or MRI of brain (in patients with PCNSL or those with known or suspected involvement of CNS)

3.4.4 Other Procedures

The following will be done as clinically indicated, including if required to confirm response or progression:

- Flow cytometry will be performed on peripheral blood (only NIH results accepted; NCI Laboratory of Pathology)
- Bone marrow aspiration and biopsy
- Lumbar puncture (LP) for cytology and flow cytometry (in patients with PCNSL)
- Ophthalmologic evaluation (in patients with PCNSL)

3.4.5 Research Samples

NOTE: See Section **5** for additional information.

- Required: Blood samples
- Optional: Tumor biopsy at the first disease re-evaluation time point (i.e., after 2 cycles) and at disease progression
- Select patients only: CSF samples (i.e., in patients with Ommaya or planned routine procedure)

3.5 TREATMENT CONSIDERATIONS/EXCEPTIONS

3.5.1 Treatment Beyond Progression ("Pseudo-progression")

A minority of patients treated with immunotherapy may derive clinical benefit despite initial evidence of progressive (PD). Patients suspected to have PD by response criteria will be permitted to continue pembrolizumab treatment beyond confirmed PD as measured by the appropriate evaluation criteria as long as they meet all of the following criteria as determined by the investigator:

- Investigator assessed clinical benefit
- Subject is tolerating pembrolizumab
- Stable performance status
- Absence of other signs and symptoms indicating disease progression
- Absence of evidence to suggest that other or alternative medical intervention or treatment is needed to treat the disease

Patients that meet the above criteria should have repeat radiographic evaluation within 6 weeks of initial investigator-assessed progression to determine whether there has been a decrease in the tumor size or continued PD.

3.5.2 Discontinuation of Study Therapy

3.5.2.1 Post-24 Months of Treatment

Discontinuation of treatment may be considered for patients who have completed 24 months of uninterrupted treatment with pembrolizumab or 35 administrations of study medication, whichever is later (24 months of study medication is calculated from the date of first dose). Patients who stop pembrolizumab after 24 months may be eligible for up to one year of additional treatment with pembrolizumab via the Second Course Phase at the discretion of the investigator if no cancer treatment was administered since the last dose of pembrolizumab, the subject meets the safety parameters listed in the Inclusion/Exclusion criteria, and the trial is open. Patients will resume therapy at the same dose and schedule at the time of initial discontinuation. Additional details are provided in Section **3.5.3**.

3.5.2.2 Post-Complete Response (CR)

Discontinuation of treatment may be considered for patients who have attained a confirmed CR that have been treated for at least 1 year with pembrolizumab and had at least two treatments with pembrolizumab beyond the date when the initial CR was declared. Patients who then experience disease relapse may be eligible for additional treatment with pembrolizumab via the Second Course Phase at the discretion of the investigator if no cancer treatment was administered since the last dose of pembrolizumab, the subject meets the safety parameters listed in the Inclusion/Exclusion criteria, and the trial is open. Patients will resume therapy at the same dose and schedule at the time of initial discontinuation. Additional details are provided in Section **3.5.3**.

3.5.2.3 Discontinuation Evaluations

When a subject discontinues, all applicable activities scheduled for the End of Treatment Visit should be performed at the time of discontinuation (see **Study Calendar**). Any adverse events which are present at the time of discontinuation should be followed in accordance with the safety requirements outlined in Section **7**.

3.5.3 Second Course Phase (Retreatment Period)

Patients who stop pembrolizumab with SD or better may be eligible for up to one year of additional pembrolizumab therapy if they relapse or progress after stopping study treatment. This retreatment is termed the Second Course Phase of this study and is only available if the study remains open and the subject meets the following conditions:

- **Either**
  - Stopped initial treatment with pembrolizumab after attaining an investigator-determined confirmed CR, and
    - Was treated for at least 1 year with pembrolizumab before discontinuing therapy
    - Received at least two treatments with pembrolizumab beyond the date when the initial CR was declared

    OR
  - Had SD, PR or CR and stopped pembrolizumab treatment after 24 months of study therapy for reasons other than disease progression or intolerability

AND

- Experienced an investigator-determined confirmed radiographic disease progression or relapse after stopping their initial treatment with pembrolizumab
- Did not receive any anti-cancer treatment since the last dose of pembrolizumab
- Has a performance status of 0-2 on the ECOG Performance Scale
- Demonstrates adequate organ function as detailed in Section **2.1.1.6**
- Female subject of childbearing potential should have a negative serum or urine pregnancy test within 72 hours prior to receiving retreatment with study medication.
- Female subject of childbearing potential should be willing to use 2 methods of birth control or be surgically sterile, or abstain from heterosexual activity for the course of the study through 120 days after the last dose of study medication (Section **4.3.2** and **4.3.3**). Patients of child bearing potential are those who have not been surgically sterilized or have been free from menses for > 1 year.
- Male subject should agree to use an adequate method of contraception starting with the first dose of study therapy through 120 days after the last dose of study therapy.
- Does not have a history or current evidence of any condition, therapy, or laboratory abnormality that might interfere with the subject's participation for the full duration of the trial or is not in the best interest of the subject to participate, in the opinion of the treating investigator.

Patients who restart treatment will be retreated at the same dose and dose interval as when they last received pembrolizumab. Treatment will be administered for up to one additional year.

Additionally, the same treatment and testing schedule should be followed at the discretion of the investigator (see Section **3.8**).

After discontinuing the Second Course/Retreatment Phase, patients should return to the site for a Safety Follow-up Visit (Section **3.7.1**) and then proceed to the Follow-Up Period of the study (Sections **3.7.2** and **3.7.3**).

3.6 TREATMENT DISCONTINUATION/POST-TREATMENT EVALUATIONS

Taking into account required 30-Day Safety and Follow-Up requirements below (Section **3.7**), the following will be performed at the end of treatment (and at disease progression, if subject discontinues treatment for a reason other than progression) within 30 days of the last dose of trial treatment (and prior to the start of new anti-cancer therapy).

In absence of progression or new anti-cancer therapy, follow-up will continue at the following time points, unless otherwise noted: every 3 months (+/- 2 weeks) for first year after completion of therapy, every 6 months for years 2-5 (+/- 4 weeks), and then annually thereafter (+/- 6 weeks) at the discretion of the investigator. Other assessments should be performed as clinically indicated; see Study Calendar (Section **3.8**) for additional information.

Upon disease progression or initiation of other anti-cancer therapy, contact will be for survival only until the subject is off study; unless otherwise clinically indicated.

3.6.1 Clinical Evaluations

- Medical history (interim)
- Physical examination, including weight and vital signs; review of concomitant medications and symptoms/side effects; and, assessment of performance status

3.6.2 Laboratory Evaluations

- CBC with differential
- Chemistries, including: acute care, mineral, and hepatic panels
- Others: LDH, uric acid, and total protein
- Thyroid function tests, including: TSH, total T3, free thyroxine (T4)
- Lymphocyte Phenotype: T, B and NK cell subsets
- Quantitative serum immunoglobulin (IG) levels

3.6.3 Imaging Studies

NOTE: Results from NIH only until disease progression. See Section **3.7.2** for imaging time points.

- CT chest, abdomen and pelvis; and/or MRI of brain (in patients with PCNSL and those with known or suspected involvement of CNS)
- 18F-FDG PET/CT (at disease progression if clinically indicated)

3.6.4 Other Procedures

The following will be done as clinically, including if required to confirm response or progression:

- Flow cytometry will be performed on peripheral blood (only NIH results accepted; NCI Laboratory of Pathology)
- Bone marrow aspiration and biopsy

- Lumbar puncture (LP) for cytology and flow cytometry (in patients with PCNSL)
- Ophthalmologic evaluation (in patients with PCNSL)

3.6.5 Research Samples

NOTE: See Section **5** for additional information.

- Required: Blood samples
- Optional: Tumor biopsy (at disease progression)
- Select patients only: CSF samples (i.e., in patients with Ommaya or planned routine procedure) (at disease progression)

3.7 FOLLOW-UP EVALUATIONS

The investigator or qualified designee will review all new anti-neoplastic therapy initiated after the last dose of trial treatment. If a subject initiates a new anti-cancer therapy within 30 days after the last dose of trial treatment, the 30-day Safety Follow-up visit must occur before the first dose of the new therapy.

Once new anti-cancer therapy has been initiated the subject will move into survival follow-up.

3.7.1 30-Day Safety Follow-Up Visit

The mandatory Safety Follow-Up Visit should be conducted approximately 30 days after the last dose of trial treatment or before the initiation of a new anti-cancer treatment, whichever comes first. All AEs that occur prior to the Safety Follow-Up Visit should be recorded. Patients with an AE of Grade > 1 will be followed until the resolution of the AE to Grade 0-1 or until the beginning of a new anti-neoplastic therapy, whichever occurs first. SAEs that occur within 90 days of the end of treatment and before initiation of a new anti-cancer treatment should also be followed and recorded. Patients who are eligible for retreatment with pembrolizumab (as described in Section **3.5.3**) may have up to two safety follow-up visits, one after the Treatment Period and one after the Second Course Phase.

3.7.2 Follow-Up Visits – Prior to Disease Progression

Patients who discontinue trial treatment for a reason other than disease progression will move into the Follow-Up Phase and should be assessed approximately every 3 months clinically and every 6 months by radiologic imaging to monitor disease status (see Section **3.6** for full information and Study Calendar, Section **3.8**). Every effort should be made to collect information regarding disease status until the start of new anti-neoplastic therapy, disease progression, death, end of the study or if the subject begins retreatment with pembrolizumab as detailed in Section **3.5.3**. Information regarding post-study anti-neoplastic treatment will be collected if new treatment is initiated.

Patients who are eligible to receive retreatment with pembrolizumab according to the criteria in Section **3.5.3** will move from the follow-up phase to the Second Course Phase when they experience disease progression.

3.7.3 Follow-Up Visits – Survival/Post-Disease Progression

Once a subject experiences confirmed disease progression or starts a new anti-cancer therapy, the subject moves into the survival follow-up phase and should be contacted approximately every 12 weeks to assess for survival status until death, withdrawal of consent, or the end of the study, whichever occurs first (see **Study Calendar**).

3.8 STUDY CALENDAR

Procedure	Screening	Baseline	Treatment Cycles				Disease Evaluations	End of Treatment	Post-Treatment Follow-Up		
			1	2	3+ odd	4+ even			Safety	Follow-Up (Prior to PD)	Survival (Post-PD)
Scheduling Window (Days):	-28 to -1[1]		-14[2]	-3	-3	-3	During-Treatment[3]	Treatment discon./PD[4]	30-90 days[5]	Every 3, 6, or 12 months[6]	Every 3 months[7]
Physical Exam (including, history, vitals, weight, and height [screening only]); ECOG/Lansky PS	X	X	X	X	X	X		X		X	
Confirmation of Diagnosis	X										
CBC with Differential	X	X	X	X	X	X		X		X	
Chemistry Panels (i.e., Acute care and Hepatic)	X	X	X	X	X	X		X		X	
Mineral Panel, LDH, Uric Acid, Total Protein		X	X	X	X	X		X		X	
PT/INR and aPTT		X	X								
Thyroid Function (i.e., TSH, T3, T4)	X	X	X		X			X		X	
Urinalysis		X			X						
Pregnancy Test (urine/serum; WOCBP)	X	X	X								
Hepatitis B and C Testing	X										
HIV Antibody Testing		X									
TBNK and Quant. IG Panel		X			X			X		X	
Anti-Nuclear Antibody (ANA)		X									
Tumor Imaging: CT Scans, Brain MRI[8]	X	X					X	X		X	
^{18}F-FDG-PET/CT Scan		X						X (PD)[9]			
Peripheral Blood Flow Cytometry[10]		X					X			X	
Bone Marrow Aspiration/Biopsy[11]		X									
Lumbar Puncture[12]		X									
Ophthalmologic Evaluation (PCNSL patients)[13]		X	X								
Symptoms/Adverse Events Assessment, Concomitant Medication Review	X	X	X …….…… X					X	X		
Research Tissues (archival/fresh biopsy)[14]		X		X				X (PD)			
Research Bloods, Saliva/Buccal, CSF Samples[15]		X	X	X		X(C6)	X	X			
Survival Status											X

NOTE: Additional assessments may be done as clinically indicated.

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[1] Screening and Baseline evaluations should be performed within 28 days prior to enrollment and dosing, respectively, with the following exceptions: Confirmation of diagnosis (no time limit); HIV antibody, Hepatitis B surface antigen and Hepatitis C antibody (within 3 months). **NOTE:** Any screening tests performed within the specified time frame for baseline do not need to be repeated.

[2] Within 14 days prior to dosing on C1D1, with the following exceptions: Pregnancy test (within 72 hours of dosing; must be negative).

[3] To be done after cycles 2 and 6, and months 9, 12, 18, and every 6 months during treatment; or, as otherwise clinically indicated.

[4] To be done within 30 days (+7 days) after treatment discontinuation (i.e., may coincide with the safety follow-up visit). If treatment is discontinued for a reason other than disease progression, assessments should be repeated at the time of progression. If subject to initiate new anti-cancer therapy assessments should occur before the first dose of the new therapy.

[5] Serious adverse events (SAEs) that occur within 90 days of the last dose of treatment and before initiation of new anti-cancer treatment must also be followed and recorded (see Section **3.7.1**).

[6] Follow-up to occur about every 3 months (+/- 2 weeks) for first 12 months, every 6 months for years 2-5 (+/- 4 weeks), and then annually (+/- 6 weeks) until disease progression or initiation of new anti-cancer therapy. See Sections **3.7.2** and **3.7.3** for special procedures on imaging.

[7] After disease progression or initiation of new anti-cancer therapy, contact for survival about every 3 months (+/- 4 weeks). See Section **3.7**.

[8] CT scans (preferred) of chest, abdomen and pelvis at baseline; may be adjusted to assess known sites of disease, as needed (e.g., other sites of disease and/or other modalities such as MRI). MRI of brain (required in patients with PCNSL at baseline); as clinically indicated in other patients at baseline and as clinically indicated in follow-up. Scans performed after cycles 2 and 6, at 9, 12, 18 months and every 6 months thereafter during treatment.

[9] 18F-FDG PET/CT (at disease progression if clinically indicated)

[10] Peripheral blood flow cytometry for diagnostic and staging purposes; repeat in follow-up to confirm response or progression, or as clinically indicated.

[11] Bone marrow aspiration/biopsy (within 3 months prior to starting treatment) if clinically indicated; repeat in follow-up to confirm response or progression.

[12] LP for cytology and flow cytometry required within 3 months prior to start of study therapy in patients with PCNSL and as clinically indicated in other patients; repeat in follow-up to confirm response or progression.

[13] Opthalmalogic evaluation required at baseline in patients with PCNSL; repeat in follow-up to confirm response or progression.

[14] If adequate archival tissue at baseline, fresh tumor biopsy is optional. Optional "on-treatment" tumor biopsies will be performed at the first disease re-evaluation time point (i.e., after 2 cycles) and at disease progression in all subjects (see Section **5**).

[15] Samples for correlative research blood, saliva (preferred)/buccal swabs, and cerebrospinal fluid (CSF) samples to be collected as indicated in Section **5**.

3.9 COST AND COMPENSATION

3.9.1 Costs

NIH does not bill health insurance companies or participants for any research or related clinical care that participants receive at the NIH Clinical Center. If some tests and procedures performed outside the NIH Clinical Center, participants may have to pay for these costs if they are not covered by insurance company. Medicines that are not part of the study treatment will not be provided or paid for by the NIH Clinical Center.

3.9.2 Compensation

Participants will not be compensated on this study.

3.9.3 Reimbursement

The NCI will cover the costs of some expenses associated with protocol participation. Some of these costs may be paid directly by the NIH and some may be reimbursed to the participant/guardian as appropriate. The amount and form of these payments are determined by the NCI Travel and Lodging Reimbursement Policy.

3.10 CRITERIA FOR REMOVAL FROM PROTOCOL THERAPY AND OFF STUDY CRITERIA

Prior to documenting removal from study, effort must be made to have all patients complete a safety visit approximately 30 days following the last dose of study therapy. Additional safety visits and follow-up will continue as per Section **3.6**.

3.10.1 Criteria for Removal from Protocol Therapy

- Completed 24 months or more of uninterrupted treatment with pembrolizumab without disease progression per Section **3.5.2.1** at the discretion of the treating investigator/subject. **NOTE:** Patients may be eligible for up to one year of additional study treatment if they progress after stopping study treatment provided they meet the requirements detailed in Section **3.5.3**.
- Achieved a complete response (CR) and completed at least 1 year of treatment with pembrolizumab per Section **3.5.2.2** at the discretion of the treating investigator/subject. **NOTE:** Patients may be eligible for up to one year of additional study treatment if they progress after stopping study treatment provided they meet the requirements detailed in Section **3.5.3**.
- Confirmed radiographic disease progression
    - A subject may be granted an exception to continue on treatment with confirmed radiographic progression if clinically stable or clinically improved, please see Section **3.5.1**.
- Unacceptable toxicity as listed in Section **3.3.2**.
- Intercurrent illness that prevents further administration of treatment
- Requirement for use of prohibited therapies as listed in Section **4.2**
- Pregnancy
- Subject's requests to be withdrawn from protocol therapy
- Noncompliance with trial treatment or procedure requirements
- Investigator's decision to withdraw the subject
- Study is cancelled for any reason

3.10.2 Off-Study Criteria

- Completion of study follow-up period
- Subject requests to be withdrawn from study
- Subject is lost to follow-up
- Death
- Study is cancelled for any reason

4 CONCOMITANT MEDICATIONS/MEASURES

Medications or vaccinations specifically prohibited in the exclusion criteria are not allowed during the ongoing trial. If there is a clinical indication for one of these or other medications or vaccinations specifically prohibited during the trial, discontinuation from trial therapy or vaccination may be required. The investigator should discuss any questions regarding this with the Merck Clinical team. The final decision on any supportive therapy or vaccination rests with the investigator and/or the subject's primary physician.

4.1 ACCEPTABLE MEDICATIONS

All treatments that the investigator considers necessary for a subject's welfare may be administered at the discretion of the investigator in keeping with the community standards of medical care. All concomitant medication will be recorded on the case report form (CRF) including all prescription, over-the-counter (OTC), herbal supplements, and IV medications and fluids. If changes occur during the trial period, documentation of drug dosage, frequency, route, and date may also be included on the CRF.

All concomitant medications received within 28 days before the first dose of trial treatment and until 30 days after the last dose of trial treatment or until start of next treatment, whichever occurs first, should be recorded. Concomitant medications administered after 30 days after the last dose of trial treatment should also be recorded for SAEs and ECIs (Section 7).

4.2 PROHIBITED MEDICATIONS

Patients are prohibited from receiving the following therapies during the Screening and Treatment Phase (including retreatment for post-complete response relapse) of this trial:

- Antineoplastic systemic chemotherapy or biological therapy
- Immunotherapy not specified in this protocol
- Chemotherapy not specified in this protocol
- Investigational agents other than pembrolizumab
- Radiation therapy
    - **NOTE:** Radiation therapy to a symptomatic solitary lesion or to the brain may be allowed at the investigator's discretion.
- Live vaccines within 30 days prior to the first dose of trial treatment and while participating in the trial. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, varicella/zoster, yellow fever, rabies, BCG, and typhoid vaccine.
- Systemic glucocorticoids for any purpose other than to modulate symptoms from an event of clinical interest of suspected immunologic etiology are generally not allowed. For subjects who are on stable doses of steroids (i.e., ≤ 10 mg/day of dexamethasone or

equivalent) at study entry, the investigator should try to taper/discontinue dosing after initiation of therapy, if appropriate. Other exceptions include the use of physiologic doses of corticosteroids and steroid use for acute issues (e.g., for up to 2 weeks unless otherwise felt to be clinically necessary in the opinion of the PI to continue for longer) after consultation with the PI.

Patients who, in the assessment by the investigator, require the use of any of the aforementioned treatments for clinical management should be removed from the trial. Patients may receive other medications that the investigator deems to be medically necessary.

The Exclusion Criteria describes other medications which are prohibited in this trial.

There are no prohibited therapies during the Post-Treatment Follow-up Phase.

4.3 OTHER CONSIDERATIONS

4.3.1 Diet

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

4.3.2 Contraception

Pembrolizumab may have adverse effects on a fetus in utero. Furthermore, it is not known if pembrolizumab has transient adverse effects on the composition of sperm.

For this trial, male patients will be considered to be of non-reproductive potential if they have azoospermia (whether due to having had a vasectomy or due to an underlying medical condition).

Female patients will be considered of non-reproductive potential if they are either:

1. Postmenopausal (defined as at least 12 months with no menses without an alternative medical cause; in women < 45 years of age a high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a post-menopausal state in women not using hormonal contraception or hormonal replacement therapy. In the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.); **OR**
2. have had a hysterectomy and/or bilateral oophorectomy, bilateral salpingectomy or bilateral tubal ligation/occlusion, at least 6 weeks prior to screening; **OR**
3. has a congenital or acquired condition that prevents childbearing.

Female and male patients of reproductive potential must agree to avoid becoming pregnant or impregnating a partner, respectively, while receiving study drug and for 120 days after the last dose of study drug by complying with one of the following:

1. practice abstinence[†] from heterosexual activity; **OR**
2. use (or have their partner use) acceptable contraception during heterosexual activity.

4.3.3 Acceptable methods of contraception are[‡]:

4.3.3.1 Single method

Use of one of the following is acceptable:

- intrauterine device (IUD)
- vasectomy of a female subject's male partner
- contraceptive rod implanted into the skin

4.3.3.2 Combination method

Requires use of two of the following:

- diaphragm with spermicide (cannot be used in conjunction with cervical cap/spermicide)
- cervical cap with spermicide (nulliparous women only)
- contraceptive sponge (nulliparous women only)
- male condom or female condom (cannot be used together)
- hormonal contraceptive: oral contraceptive pill (estrogen/progestin pill or progestin-only pill), contraceptive skin patch, vaginal contraceptive ring, or subcutaneous contraceptive injection

†Abstinence (relative to heterosexual activity) can be used as the sole method of contraception if it is consistently employed as the subject's preferred and usual lifestyle and if considered acceptable by local regulatory agencies and ERCs/IRBs. Periodic abstinence (e.g., calendar, ovulation, sympto-thermal, post-ovulation methods, etc.) and withdrawal are not acceptable methods of contraception.

‡If a contraceptive method listed above is restricted by local regulations/guidelines, then it does not qualify as an acceptable method of contraception for patients participating at sites in this country/region.

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

4.3.4 Use in Pregnancy

If a subject inadvertently becomes pregnant while on treatment with pembrolizumab, the subject will immediately be removed from the study treatment. The site will contact the subject at least monthly and document the subject's status until the pregnancy has been completed or terminated. The outcome of the pregnancy will be reported to Merck without delay and within 2 working days to Merck if the outcome is a serious adverse experience (e.g., death, abortion, congenital anomaly, or other disabling or life-threatening complication to the mother or newborn).

The study investigator will make every effort to obtain permission to follow the outcome of the pregnancy and report the condition of the fetus or newborn to Merck. If a male subject impregnates his female partner the study personnel at the site must be informed immediately and the pregnancy reported to Merck and followed as described above and in Section 8.1.4.3.

4.3.5 Use in Nursing Women

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

5 CORRELATIVE STUDIES

5.1 SUMMARY

The signaling pathways immediately disrupted by PD-1 blockade as well as the compensatory pathways that emerge with PD-1 blockade are poorly understood. The magnitude and duration of PD-1 blockade is expected to correlate with clinical benefit. Understanding the biology of the

tumor microenvironment both pre-/post-treatment will be critical for evaluating the role that pembrolizumab plays in modulating the immune system and its response to PD-1 blockade. Molecular profiling of malignant cells and the tumor microenvironment in the tissue may be a biologic correlate of tumor response.

Research Samples Calendar:

Sample	Collection Details*	Time Points										Supervising Laboratory/ Investigator
		Baseline	Post-Cycles		On Treatment Months					Discon.	PD	
			2	6	9	12	18	24	q6			
Blood Samples												
PBMCs, Protein, DNA/ RNA, Immune Markers	• 3 x 8-10 mL CPTs (sodium citrate)	X	X	X		X		X		X	X	Trepel
	• 1 x 2.5-3 mL PAXgene tube	X	X	X		X		X		X	X	
Circulating Tumor Cells (CTCs)	• 1-2 x 7-10 mL K_2EDTA tube	X	X	X		X		X		X	X	
Cytokines	• 1 x 8-10 mL SST	X	X	X	X	X	X	X	X	X	X	Figg
ctDNA	• 1 x 10 mL Streck/BCT tube	X	X	X	X	X	X	X	X	X	X	
Tissue Samples												
Archival and/or Fresh Tissue Biopsy	• FFPE (block or slides); biopsy is required if archival is not adequate or unavailable • Excision (single or multiple nodes) or core (4-6 passes); placed in formalin/FFPE and media, as appropriate	X	(X)								(X)	Figg/ NCI LP
Other Samples												
Germline DNA	• Blood, Buccal swab, or Saliva (preferred)	X										Figg
CSF samples *(if Ommaya or planned procedure)*: Immune Markers	• 1 x 3mL K_2EDTA tubes or sterile syringe	X	X	X							X	Trepel
	• 1 x 3mL K_2EDTA tubes or sterile syringe	X	X	X	X	X	X	X	X	X	X	Figg

(X) = Optional

*Tubes/media may be adjusted at the time of collection based upon materials available or to ensure the best samples are collected for planned analyses.

#Subjects who discontinue treatment for a reason other than disease progression and who do not start new treatment should continue to have study bloods collected at the scheduled time points.

^Samples for the Trepel lab may be expanded to include the same/additional time points as samples going to the Figg lab if future effort/funding allow.

5.2 SAMPLE COLLECTION AND PROCESSING

5.2.1 Summary

The planned analyses described below may be done on leftover and/or shared sample portions from the respective laboratories, as needed. In addition to the prospectively collected samples below, leftover portions of samples sent for routine laboratory testing (e.g., plasma from CBC/hematologies) may also be retrieved for research tests prior to being discarded. The planned prospective analyses are identified below; laboratories may share resources or collaborate on analyses, if appropropriate (e.g., isolation/analysis of DNA is not prospectively planned by the Trepel lab, yet may be incorporated if needed during the planned analyses).

Portions of all samples may be banked for future research analyses; prospective consent will be obtained during the informed consent process.

The blood drawing limits for research purposes are as follows:

- For adult subjects: The amount of blood that may be drawn from adult patients for research purposes shall not exceed 10.5 mL/kg or 550 mL, whichever is smaller, over any eight-week period.

5.2.2 Blood Samples – Trepel Lab

Upon subject scheduling and immediately after sample collection, contact the Trepel Lab, Developmental Therapeutics Branch, NCI for pick-up: Jane Trepel: trepel@helix.nih.gov; Min-Jung Lee: leemin@mail.nih.gov; Akira Yuno: akira.yuno@nih.gov; and, Sunmin Lee: lees@pop.nci.nih.gov; and/or 240-760-6330.

5.2.2.1 Peripheral Blood Mononuclear Cells (PBMCs)

- Collect blood in Cell Preparation Tubes with sodium citrate (e.g., blue/black speckled top); gently invert tubes 8-10 times immediately after collection.
- PBMCs will be isolated per routine laboratory techniques.

5.2.2.2 RNA Sequencing

- Collect blood in PAXgene RNA tubes; gently invert tubes 8-10 times immediately after collection.
- RNA will be isolated per routine laboratory techniques.

5.2.2.3 Circulating Tumor Cells (CTCs)

- Collect blood in K_2EDTA tubes; gently invert tubes 8-10 times immediately after collection.
- Cells will be enumerated and plasma will be isolated per routine laboratory techniques.

5.2.3 Blood Samples – Figg Lab

For questions, please contact Dr. Figg's Blood Processing Core (BPC) at 240-760-6180; additionally, for pre-notification of planned samples (at least 24 hours in advance, the Friday before is preferred) email (NCIBloodcore@mail.nih.gov). After sample collection, please page 102-11964 for immediate pick-up. For any questions regarding sample processing, you may contact by e-mail NCIBloodcore@mail.nih.gov.

5.2.3.1 Cytokines and serum banking

- Collect blood in Serum Separator Tubes (e.g., red/gray or red/yellow speckled top); gently invert the tubes 8-10 times immediately after collection and allow the blood to clot by at room temperature for approximately 30 minutes.
- Serum will be isolated and frozen at -80ºC until analysis (e.g., centrifuged at 1200 x g for 5 minutes at 4ºC; serum transferred/frozen in aliquots of 1.5-2 mL each).

5.2.3.2 Cell-free DNA (cfDNA)/Circulating Tumor DNA (ctDNA) and plasma banking

- Collect blood in cell-free DNA (e.g., Streck BCT/collection tubes) and K_2EDTA tubes; gently invert the tubes 8-10 times immediately after collection.
- Plasma will be isolated and frozen at -80ºC until analysis (e.g., centrifuged at 1800 x g for 10 minutes at room temperature; plasma transferred/frozen in aliquots of 1.5-2 mL each). Tissue Samples

5.2.4 Tissue Samples

5.2.4.1 Archival tissue

Archival block(s) or slides (i.e., at least 15 unstained slides, 5-microns) is required at baseline; these may also be required in follow-up in case of future routine procedures or in case additional tissue is needed even in the event of optional tumor biopsy.

5.2.4.2 Lymph node excision or core needle biopsy procedure

Lymph node excision or core needle biopsy will be performed per routine standard of care, by Surgery Consultants or Interventional Radiology, as appropriate. A procedure-specific consent form will be signed by the patient prior to the procedure. Every attempt will be made to perform excisional lymph node biopsies to obtain the best quality tissue for translational investigation. Consideration of alternative biopsy methods (e.g., core needle biopsy) will only be made if follow-up excisional biopsy is not possible/safe or patient is unwilling to undergo repeat excisional lymph node biopsy.

In the event that a surgical biopsy procedure is performed, more than one lymph node and at more than one anatomic site may be collected, provided the additional procedures are not unacceptable risk to the patient. In the event of core needle biopsy, these are obtained typically by using a 16-18G needle at the discretion of the provider performing the procedure. Conscious sedation may be used, if warranted, and the use and risks are acceptable to the patient.

Potential site(s) of biopsy include, but are not limited to: bone marrow lesions, bony lesions, extramedullary disease/masses, and lymph nodes. The type of procedure to be done and manner in which it will proceed (e.g., excision/core, single vs. multiple sites of biopsy) will be discussed with the patient prior to the biopsy procedure. The patient will be reminded that all sampling for research is voluntary.

5.2.4.3 Sample handling/processing

When performed, excisions or core biopsies will be placed in sterile collection/core cylinder tubes (e.g., formalin); gently invert/inspect tubes with media 8-10 times immediately after collection to ensure the core(s) is completed immersed in the media.

Tissue samples will be handled/processed as below prior to planned analyses, as appropriate:

- Any required routine review for histopathologic confirmation of diagnosis and/or grade will occur per standard of care (e.g., H&E, immunohistochemistry), if required.
- Formalin samples will be fixed and paraffin-embedded per routine techniques.

5.2.5 Other Samples

5.2.5.1 Germline DNA

Germline DNA will be collected by blood, buccal swab, and/or saliva samples (preferred). These will ideally be collected at baseline; however, may be collected at any point on study based on supplies. Standardized, commercial collection kits or tubes will be used (e.g., 1, 5-10 mL K_2EDTA tube for blood; Isohelix SK-1 for buccal swabs; Salviette/Oragene® for saliva). In the case of buccal swabs, two (2) samples may be collected in order to ensure adequate DNA collection.

The samples will be processed and DNA extracted/isolated per kit instructions and established techniques. These will also be handled by Dr. Figg's lab (see Section **5.2.3** for contact information).

5.2.5.2 Cerebrospinal fluid (CSF)

- Collect CSF in K_2EDTA tubes or sterile syringes; gently invert tubes 8-10 times immediately after collection.
- Samples will be processed per routine laboratory techniques. These will be handled by both (i.e., one tube each) Dr. Figg's and Trepel's labs (see above for contact information).

5.3 BIOMARKER AND RESEARCH METHODS

The technology platforms that are able to interrogate genomic structure and function are constantly in flux; therefore, the exact nature of the methodologies that will be employed will be assessed at the time that the samples are collected and ready for analysis.

The following are technologies that are currently in use for each planned analysis:

5.3.1 Molecular Profiling

Immunohistochemical (IHC) analyses will take part in tumor tissue samples, including but not necessarily limited to CD3, CD4, CD8, CD20, CD45RO, CD57, CD68, FOZP3, Granzyme B, LAG3, PD-1/PD-L1 (H-score), CD14, CD33, CD163 and/or CD206. FISH probe for 9p.24 amplification will be done on all available pre-treatment FFPE specimens.

5.3.2 Immune Subset Analysis

Peripheral blood mononuclear cells (PBMC) will be assessed using multiparameter flow cytometry for immune subsets including but not necessarily limited to CD8+ T-cells, CD4+Foxp3- T-cells, Tregs, T_{ex}, Th1, Th2 and Th17+ CD4+ T-cells, monocyte subsets, MDSC subsets. Assessment will include functional markers, i.e. PD-1, Tim-3, CTLA-4, PD-L1, HLA-DR, Ki67 and/or CD40.

5.3.3 Peripheral Blood Metabolism Gene Expression

Peripheral metabolic transcriptional signature will be evaluated using the NanoString nCounter® platform (NanoString Technologies, Seattle, WA). We will use the nCounter 180 gene cancer metabolism panel, built in collaboration with the Urologic Oncology Branch. Peripheral blood will

be collected in a PAXgene tube (PreAnalytix; 2.5 cc peripheral blood per tube) per the manufacturer's instructions. RNA will be isolated using the PAXgene Blood RNA Kit according to the manufacturer's instructions.

5.3.4 Circulating Tumor Cells (CTCs)

CTCs will be isolated and evaluated per established techniques in the Trepel laboratory (e.g., flow-based analysis). As analysis is primarily exploratory, technique(s) may be adjusted over the course of the study to determine the best methods for analysis.

5.3.5 DNA/RNA Sequencing

Genomic DNA and total RNA will be extracted from tumor samples using a Qiagen All-prep kit. For individual target genes that are recurrently mutated in DLBCL (CARD11, CD79B, MYD88, EZH2), classical Sanger sequencing will be performed on PCR amplicons, using primers surrounding the known sites of mutation. To broadly assess mutations, next generation sequencing (e.g., on an Illumina HiSeq 2000 platform) will be employed, using a paired end sequencing strategy of libraries constructed from tumor DNA. DNA will either be sequenced in its entirety from a whole genome library or will be first enriched for exonic sequences using the Agilent Sure Select system, aiming for 30X or 100X average coverage per base, respectively. The sequence fragments will be mapped back to the genome using the BWA algorithm. Of sequences overlapping a particular base pair in the genome, the percent mutant calls greater that 20% with a minimum of 25X coverage will be considered as an arbitrary threshold for single nucleotide variants (SNVs). SNVs that are not present in the matched normal sample will be considered candidate somatic mutations.

A related technology, RNA-Seq, utilizes RNA from the tumor specimen to create a cDNA library for high-throughput sequencing. RNA-seq will be performed using Illumina kits followed by high-throughput sequencing on an Illumina HighSeq 2000 machine. The cutoffs for coverage and percent mutant calls mentioned above will also be used to identify putative SNVs. RNA sequencing will also be used to read out digital gene expression across the genome as described.

5.3.6 DNA Copy Number Analysis

Array comparative genomic hybridization (e.g., on Agilent 240K or Affy SNP 6.0 microarrays) will be used to assess DNA copy number alterations as described, in tumor DNA to yield somatically acquired regions of copy number gain and loss.

5.3.7 Other Analyses

Other analyses include the following:

- Cell analysis and histological (e.g., H&E), immunohistochemical review and analysis per standard and established research techniques (e.g., PD-1/PD-L1 expression [Dako], FISH for 9p24 amplicon, and other IHC analyses in blood and tissue).
- Cytokine analysis (e.g., IL-6, IL-10, interferon beta, TNF-alpha)
- cfDNA/ctDNA for liquid genotyping as a non-invasive dynamic monitoring of disease as well as monitoring for individual molecular aberrations that herald progression or disease transformation; specifically, amplification and sequencing of the VDJ segment of the immunoglobulin receptor is planned

5.3.8 Future Use

Any blood, tissue, or other (e.g., CSF) products or portions leftover from other analyses will be stored for future research.

5.4 SAMPLE STORAGE, TRACKING AND DISPOSITION

5.4.1 General

Samples will be ordered in CRIS and tracked through a Clinical Trial Data Management system. Should a CRIS screen not be available, the CRIS downtime procedures will be followed. Samples will not be sent outside NIH without appropriate approvals and/or agreements, if required.

All specimens obtained in the protocol are used as defined in the protocol. Any specimens that are remaining at the completion of the protocol will be stored in the conditions described below. The study will remain open so long as sample or data analysis continues. Samples from consenting patients will be stored until they are no longer of scientific value or if a subject withdraws consent for their continued use, at which time they will be destroyed.

If the patient withdraws consent his/her data will be excluded from future distributions, but data that have already been distributed for approved research use will not be able to be retrieved.

The PI will record any loss or unanticipated destruction of samples as a deviation. Reporting will be per the requirements of Section **7.2.1.**

5.4.2 Developmental Therapeutics Branch (Trepel Lab)

Under the direction of Dr. Trepel, all samples processed by the Developmental Therapeutics Branch Laboratory will be uniquely barcoded, with data entered using a secure computerized database and backup hardcopy process per standard laboratory practice.

Samples are stored in labeled boxes in secured freezers (i.e., -20ºC to -80ºC, or other, as appropriate) according to stability requirements; these freezers are located onsite. Access to stored clinical samples is restricted and limited to research personnel for approved analyses only (as per the IRB approved protocol).

Upon completion of planned analyses by the Trepel lab, leftover samples may be stored for future analyses at the Clinical Support Laboratory, Leidos Biomedical Research, Inc.in Frederick, MD (see below).

5.4.3 Clinical Pharmacology Program (Figg Lab)

5.4.3.1 Sample Data Collection

All samples sent to the Blood Processing Core (BPC) of the Clinical Pharmacology Program under the direction of Dr. Figg will be barcoded, with data entered and stored in the Labmatrixutilized by the BPC. This is a secure program, with access to Labmatrix limited to defined Figg lab personnel, who are issued individual user accounts. Installation of Labmatrix is limited to computers specified by Dr. Figg. These computers all have a password restricted login screen. All Figg lab personnel with access to patient information annually complete the NIH online Protection of Human Subjects course.

Labmatrix creates a unique barcode ID for every sample and sample box, which cannot be traced back to patients without Labmatrix access. The data recorded for each sample includes the patient ID, name, trial name/protocol number, time drawn, cycle time point, dose, material type, as well as box and freezer location. Patient demographics associated with the clinical center patient number are provided in the system. For each sample, there are notes associated with the processing method (delay in sample processing, storage conditions on the ward, etc.).

5.4.3.2 Sample Storage

Barcoded samples are stored in barcoded boxes in a locked freezers at appropriate temperatures (e.g., -20ºC to -80ºC) according to stability requirements. These freezers are located onsite in the BPC and offsite at NCI Frederick Central Repository Services in Frederick, MD. Visitors to the laboratory are required to be accompanied by laboratory staff at all times.

Access to stored clinical samples is restricted. Samples will be stored until requested by a researcher named on the protocol. All requests are monitored and tracked in Labmatrix. All researchers are required to sign a form stating that the samples are only to be used for research purposes associated with this trial (as per the IRB approved protocol) and that any unused samples must be returned to the BPC. It is the responsibility of the NCI Principal Investigator to ensure that the samples requested are being used in a manner consistent with IRB approval.

Sample barcodes are linked to patient demographics and limited clinical information. This information will only be provided to investigators listed on this protocol, via registered use of the Labmatrix. It is critical that the sample remains linked to patient information such as race, age, dates of diagnosis and death, and histological information about the tumor, in order to correlate genotype with these variables.

5.4.4 Hematopathology Section of Laboratory of Pathology (Tissue samples)

Archival and/or freshly collected and processed tumor tissue may be stored in the Hematopathology Section of Laboratory of Pathology until ready for planned and/or future research assays if the patient has agreed to allowing specimens to be used in future research studies. IRB approval will be obtained before using any samples to conduct studies that are not described within this protocol. Samples will be stored under conditions appropriate to the type of sample and processing (e.g., ambient or frozen).

Tissue that is given to the technician will be assigned an accession number (HP#) in the HP Case Log book; sample tracking also takes place with a FileMaker Pro data base called HP Patient Information and Specimen Inventory. A Patient background sheet may be filled out and filed with any accompanying paperwork, with final reports and any supplemental reports that follow added as completed.

5.5 SAMPLES FOR GENETIC/GENOMIC ANALYSIS

5.5.1 Description of the scope of genetic/genomic analysis

The research correlates for this study are expected to include DNA/RNA sequencing of tumors, including circulating tumor (ct) DNA. In addition, whole exome sequencing may include evaluation for known lymphoma mutations. For any genetic studies performed, the results will be deposited in a database such as dbGaP per NIH requirements. Although there is controlled access to such a database, such a submission carries theoretical risks of revealing the identity of the subject. This is discussed in the consent.

5.5.2 Description of how privacy and confidentiality of medical information/biological specimens will be maximized

Confidentiality for genetic samples will be maintained as described (Section **5.2.1**). In addition, a Certificate of Confidentiality has been obtained for this study.

5.5.3 Management of Results

Subjects will be contacted if a clinically actionable gene variant is discovered. Clinically actionable findings for this study are defined as disorders appearing in the American College of Medical Genetics and Genomics recommendations for the return of incidental findings that is current at the time of primary analysis. (A list of current guidelines is maintained on the CCR intranet: https://ccrod.cancer.gov/confluence/display/CCRCRO/Incidental+Findings+Lists).

5.5.4 Genetic Counseling

Subjects will be contacted with a request to provide a blood sample to be sent to a CLIA certified laboratory. If the research findings are verified in the CLIA certified lab, the subject will be offered the opportunity to come to NIH to have genetic education and counseling to explain this result; at the time of any such event(s), these activities will be funded by the NCI/CCR in consideration of the specific circumstances. If the subject does not want to come to NIH, a referral to a local genetic healthcare provider will be provided (at their expense).

This is the only time during the course of the study that incidental findings will be returned. No interrogations regarding clinically actionable findings will be made after the primary analysis.

6 DATA COLLECTION AND EVALUATION

6.1 DATA COLLECTION

The PI will be responsible for overseeing entry of data into an in-house password protected electronic system (C3D) and ensuring data accuracy, consistency and timeliness. The Principal Investigator, associate investigators/research nurses and/or a contracted data manager will assist with the data management efforts. Primary and final analyzed data will have identifiers so that research data can be attributed to an individual human subject participant.

All adverse events, including clinically significant abnormal findings on laboratory evaluations, regardless of severity, will be followed until return to baseline or stabilization of event.

Document AEs from the first study intervention, Study Day 1, through 30 days after the last dose of the study treatment

Adverse events that are serious need to be recorded through 90 days. Beyond or, for SAEs, 30 days after the last intervention, only adverse events which are serious and related to the study intervention need to be recorded.

End of study procedures: Data will be stored according to HHS, FDA regulations, and NIH Intramural Records Retention Schedule as applicable.

Loss or destruction of data: Should we become aware that a major breach in our plan to protect subject confidentiality and trial data has occurred, this will be reported expeditiously per requirements in section **7.2.1**.

6.1.1 Data Collection /Recording Exceptions

6.1.1.1 Abnormal Laboratory Values

An abnormal laboratory value will be considered an AE if the laboratory abnormality is characterized by any of the following:

- Results in discontinuation from the study
- Is associated with clinical signs or symptoms

- Requires treatment or any other therapeutic intervention
- Is associated with death or another serious adverse event, including hospitalization
- Is judged by the Investigator to be of significant clinical impact
- If any abnormal laboratory result is considered clinically significant, the investigator will provide details about the action taken with respect to the test drug and about the patient's outcome.

6.1.1.2 Hospitalizations

Any cases of planned or prolonged hospitalization are not considered reportable serious adverse events if for the following reasons:

- Technical, practical, or social reasons, in absence of an AE
- Routine treatment or monitoring of the studied indication not associated with any deterioration in condition, including scheduled therapy or standard procedure for the target disease of the study, and those required to allow efficacy measurement for the study
- Diagnostic or elective surgical procedures for preexisting conditions or a procedure that is planned (e.g., planned prior to starting of treatment on study)
- Closer monitoring and/or prophylaxis of TLS at any cycle
- Emergency outpatient treatment or observation that does not result in admission, unless fulfilling other seriousness criteria

6.2 DATA SHARING PLANS

6.2.1 Human Data Sharing Plan

What data will be shared?

I will share human data generated in this research for future research as follows:

_X_ Coded, linked data in an NIH-funded or approved public repository.

_X_ Coded, linked data in BTRIS (automatic for activities in the Clinical Center)

_X_ Identified or coded, linked data with approved outside collaborators under appropriate agreements.

How and where will the data be shared?

Data will be shared through:

_X_ An NIH-funded or approved public repository. Insert name or names: ClinicalTrials.gov, dbGaP.

_X_ BTRIS (automatic for activities in the Clinical Center)

_X_ Publication and/or public presentations.

When will the data be shared?

_X_ Before publication.

_X_ At the time of publication or shortly thereafter.

6.2.2 Genomic Data Sharing Plan

Unlinked genomic data will be deposited in public genomic databases such as dbGaP in compliance with the NIH Genomic Data Sharing Policy.

6.3 RESPONSE CRITERIA

Response rate of pembrolizumab in patients with relapsed/refractory gray-zone lymphomas (GZL) and extranodal diffuse large B-cell lymphomas (DLBCL) will be assessed according to the International Working Group (IWG) response criteria and the International PCNSL workshop response criteria. In addition, we will also look at overall response rate according to the 5-point Lugano classification for interpreting FDG-PET scans.

When appropriate, for patients with disease involvement of the bone marrow at baseline, repeat assessment will be done to confirm response.

6.3.1 Response Criteria for Lymphoma Lymphoma – GZL and DLBCL (not PCNSL)

The following will be used to assess response in subjects with GZL and extranodal ABC, with the exception of PCNSL (see Section **6.3.2**).

6.3.1.1 International Working Group (IWG) response criteria

The International Working Group (IWG) response criteria will be used (Cheson et al.):

Response Category	Physical Examination	Lymph Nodes	Lymph Node Masses	Bone Marrow
CR	Normal	< 1 cm	< 1 cm	Normal
CRu	Normal	> 1 cm	> 75% decrease	Indeterminate
PR	Normal	Normal	Normal	Positive
	Normal	≥50% decrease	≥50% decrease	Irrelevant
	Decrease in liver/spleen	≥50% decrease	≥50% decrease	Irrelevant
Progression	Enlarging liver/spleen; new sites	New or increased > 50%	New or increased > 50%	Reappearance

6.3.1.2 The Five-Point Scale (5-PS) Deauville criteria

The five-point scale (5-PS) has been validated for use at interim staging and at the end of treatment and was adopted as the preferred reporting method at the First International Workshop on PET in Lymphoma in Deauville, France (i.e., Deauville criteria), and in several international trials.

The 5-PS scores the most intense uptake in a site of initial disease:

1. if present, as follows:no uptake or no residual uptake (when used at interim)
2. slight uptake, but below blood pool (mediastinum)
3. uptake above mediastinal, but below or equal to uptake in the liver
4. uptake slightly to moderately higher than liver
5. markedly increased uptake or any new lesion (on response evaluation)

6.3.1.3 Lugano Classification of Response

Lugano classification of response criteria with PET (Cheson et al., 2014).

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†	• Target nodes/nodal masses must regress to ≤1.5 cm in LDi • No extralymphatic sites of disease
	NOTE: *It is recognized that in Waldeyer's ring or extranodal sites with high physiologic uptake or with activation within spleen or marrow (e.g., 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.*	
Nonmeasured lesions	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 measureable nodes and extranodal sites *When a lesion is too small to measure on CT, assign 5 mm x 5 mm as the default valve; when no longer visible, 0 x 0 mm. For a node >5 mm x 5 mm, but smaller than normal, use actual measurement for calculation.*
Nonmeasured lesions	Not applicable	Absent/normal, regressed, but no increase
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 form baseline	Not applicable

Response and Site	PET-CT Based Response	CT-Based Response
Progressive disease	**Progressive metabolic disease**	**Progressive disease** *Requires at least 1 of the following:*
Individual target nodes/nodal masses	Score 4 or 5 with an increase in intensity of uptake from baseline; *and/or*	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: o 0.5 cm for lesions ≤2 cm o 1.0 cm for lesions >2 cm
Extranodal lesions	New FDG-avid foci consistent with lymphoma at interim or end of treatment assessment	• In the setting of splenomegaly, the splenic length must increase by >50% of the extent of its prior increase beyond baseline (e.g., 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
Nonmeasured lesions	None	New or clear progression of preexisting nonmeasured lesions
New lesions	New FDG-avid foci consistent with lymphoma rather than another etiology (e.g., 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 trails involving PET where de-escalation is investigated, it may be preferable to consider a score of 3 as inadequate response (to avoid under treatment). Measured dominant lesions: Up to 6 of the largest dominant nodes, nodal masses, and extranodal lesions selected to be clearly measurable in 2 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, and 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 of 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.

6.3.2 Response Criteria for Lymphoma – PCNSL

The following response criteria as per the CNS lymphoma working group (Abrey et al. JCO 2005) will be used for subjects on study with PCNSL:

Response	Brain Imaging	Corticosteroid dose	Eye examination	CSF cytology
CR	No contrast enhancement	None	Normal	Negative
CRu	No contrast enhancement	Any	Normal	Negative
	Minimal abnormality	Any	Minor RPE abnormality	Negative
PR	50% decrease in enhancing tumor	Irrelevant	Minor RPE abnormality or normal	Negative
	No contrast enhancement	Irrelevant	Decrease in vitreous cells or retinal infiltrate	Persistent or suspicious
PD	25% increase in lesion	Irrelevant	Recurrent or new ocular disease	Recurrent or positive
	Any new site of disease: CNS or systemic			
Abbreviations: CR, complete response; CRu, unconfirmed complete response; RPE, retinal pigment epithelium; PR, partial response; PD, progressive disease				

6.3.3 Best Overall Response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started). The patient's best response assignment will depend on the achievement of both measurement and confirmation criteria.

6.3.4 Duration of Response

The duration of response (DOR) is measured from the time measurement criteria are met for CR or PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since the treatment started), death, or, in the absence of PD, date of last assessment.

6.3.5 Progression-Free Survival

Progression-free survival (PFS) is defined as the duration of time from the date of study enrollment until time of disease relapse, disease progression, or death, whichever occurs first.

6.3.6 Event-Free Survival

Event-free survival (EFS) is defined as the duration of time from the date of study enrollment until time of disease relapse, disease progression, alternative therapy for lymphoma given (such as radiation), or death, whichever occurs first.

6.3.7 Other

Evaluable for toxicity: All patients who receive at least 1 dose of pembrolizumab will be evaluable for toxicity.

Evaluable for objective response: Only those patients who have measurable or evaluable disease present at baseline, have received at least two doses of therapy, and have had their disease re-evaluated with radiographic imaging will be considered evaluable for response. These patients will have their response classified according to the definitions stated below. (NOTE: Patients who exhibit objective disease progression prior to the end of cycle 1 will also be considered evaluable.)

6.4 TOXICITY CRITERIA

The following adverse event management guidelines are intended to ensure the safety of each patient while on the study. The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 4.0. A copy of the CTCAE version 4.0 can be downloaded from the CTEP web site (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_40).

7 NIH REPORTING /DATA AND SAFETY MONITORING PLAN

7.1 DEFINITIONS

7.1.1 Adverse Event

Please refer to definitions provided in Policy 801: Reporting Research Events found here.

7.2 OHSRP OFFICE OF COMPLIANCE AND TRAINING / IRB REPORTING

7.2.1 Expedited Reporting

Please refer to the reporting requirements in Policy 801: Reporting Research Events and Policy 802 Non-Compliance Human Subjects Research found here.

7.2.2 IRB Requirements for PI Reporting at Continuing Review

Please refer to the reporting requirements in Policy 801: Reporting Research Events found here.

7.3 NCI CLINICAL DIRECTOR REPORTING

Problems expeditiously reported to the OHSRP in iRIS will also be reported to the NCI Clinical Director. A separate submission is not necessary as reports in iRIS will be available to the Clinical Director.

In addition to those reports, all deaths that occur within 30 days after receiving a research intervention should be reported via email to the Clinical Director unless they are due to progressive disease.

To report these deaths, please send an email describing the circumstances of the death to Dr. Dahut at NCICCRQA@mail.nih.gov within one business day of learning of the death.

7.4 NIH REQUIRED DATA AND SAFETY MONITORING PLAN

7.4.1 Principal Investigator/Research Team

The clinical research team will meet on a regular basis (i.e., approximately weekly) when patients are being actively treated on the trial to discuss each patient. Decisions about trial continuation will be made based on the efficacy data from prior patients at appropriate time points per the statistical plan.

All data will be collected in a timely manner and reviewed by the principal investigator or a lead associate investigator. Events meeting requirements for expedited reporting as described in section **7.2.1** will be submitted within the appropriate timelines.

The principal investigator will review adverse event and response data on each patient to ensure safety and data accuracy. The principal investigator will personally conduct or supervise the investigation and provide appropriate delegation of responsibilities to other members of the research staff.

8 SPONSOR PROTOCOL/SAFETY REPORTING

8.1 SAFETY REPORTING CRITERIA TO THE PHARMACEUTICAL COLLABORATORS

8.1.1 General Information and Summary

Merck is providing pembrolizumab for participants in this clinical trial. As part of the agreement, information about the trial, including adverse events will be shared with them.

Unless otherwise agreed to with Merck, Merck-provided/-specific forms will be used to report events to Merck during the course of this study. These will be provided to the Principal Investigator and study team, and maintained in the regulatory files.

8.1.2 Reporting Timeframes/Requirements

For the purposes of reporting:

- From the time that the consent form is signed but before initiation of treatment:
    - All adverse events that occur must be reported if they cause the subject to be excluded from the trial, or are the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, or a procedure.
    - Any serious adverse event, or follow up to a serious adverse event, including death due to any cause other than progression of the cancer under study that occurs to any subject must be reported within 2 working days to Merck Global Safety if it causes the subject to be excluded from the trial, or is the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, or a procedure.

      NOTE: These same reporting requirements and windows apply to Events of Clinical Interest (see Section **8.1.4**).
- From the time after treatment allocation through 90 days following cessation of treatment, or 30 days following cessation of treatment if the subject initiates new anticancer therapy, whichever is earlier:
    - Any serious adverse event, or follow up to a serious adverse event, including death due to any cause other than progression of the cancer under study, whether or not related to the Merck product, must be reported within 2 working days to Merck Global Safety.
    - Additionally, any serious adverse event, considered by an investigator who is a qualified physician to be related to Merck product that is brought to the attention of the investigator at any time following consent through the end of the specified safety follow-up period specified in the paragraph above, or at any time outside of

the time period specified in the previous paragraph also must be reported immediately to Merck Global Safety.

NOTE: These same reporting requirements and windows apply to Events of Clinical Interest (see Section **8.1.4**).

All patients with serious adverse events must be followed up for outcome.

SAE reports and any other relevant safety information are to be forwarded to the Merck Global Safety facsimile number: +1-215-993-1220. See **APPENDIX B** for the specific criteria and categories of information that require documentation and reporting to Merck with each event.

8.1.3 Serious Adverse Events

In addition to the serious adverse events listed in Section **7.1.1** , the following are also required to be reported as "serious" events to Merck:

- Is a new cancer (that is not a condition of the study)
- Is associated with an overdose (see additional information in Section **8.1.4.1**)

8.1.4 Reporting Requirements for Events of Clinical Interest

Selected non-serious and serious adverse events are also known as Events of Clinical Interest (ECI) and must be reported within 2 working days to Merck Global Safety. (Attn: Worldwide Product Safety; FAX 215 993-1220).

All ECI reporting time frames are indicated above in Section **8.1.2**.

8.1.4.1 Overdose of a Merck Product

For purposes of this trial, an overdose of pembrolizumab will be defined as any dose of 1,000 mg or greater (≥5 times the indicated dose) and is a reportable event of special interest. No specific information is available on the treatment of overdose of pembrolizumab. Appropriate supportive treatment should be provided if clinically indicated. In the event of overdose, the subject should be observed closely for signs of toxicity. Appropriate supportive treatment should be provided if clinically indicated.

If an adverse event(s) is associated with ("results from") the overdose of a Merck product, the adverse event(s) is reported as a serious adverse event, even if no other seriousness criteria are met.

If a dose of Merck's product meeting the protocol definition of overdose is taken without any associated clinical symptoms or abnormal laboratory results, the overdose is reported as a non-serious Event of Clinical Interest (ECI), using the terminology "accidental or intentional overdose without adverse effect."

8.1.4.2 Liver Function Tests (LFTs)

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, are also to be reported as events of clinical interest to Merck in an expedited fashion. **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.

8.1.4.3 Reporting of Pregnancy and Lactation to Merck

Although pregnancy and lactation are not considered adverse events, it is the responsibility of investigators or their designees to report any pregnancy or lactation in a subject (spontaneously reported to them) that occurs during the trial.

Pregnancies and lactations that occur from the time of treatment allocation through 120 days following cessation of pembrolizumab, or 30 days following cessation of treatment if the subject initiates new anticancer therapy, whichever is earlier, must be reported by the investigator. All reported pregnancies must be followed to the completion/termination of the pregnancy. Pregnancy outcomes of spontaneous abortion, missed abortion, benign hydatidiform mole, blighted ovum, fetal death, intrauterine death, miscarriage and stillbirth must be reported as serious events (Important Medical Events). If the pregnancy continues to term, the outcome (health of infant) must also be reported.

Such events must be reported within 2 working days to Merck Global Safety. (Attn: Worldwide Product Safety; FAX 215 993-1220)

8.1.5 Protocol-Specific Exceptions to Serious Adverse Event Reporting

Efficacy endpoints as outlined in this section will not be reported to Merck as described in Section **8.1.2**, unless there is evidence suggesting a causal relationship between the drug and the event. Any such event will be submitted to Merck Global Safety within 2 working days either by electronic or paper media.

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

The PI will monitor unblinded aggregated efficacy endpoint events and safety data to ensure the safety of the patients in the trial. Any suspected endpoint which upon review is not progression of the cancer under study will be forwarded to Merck Global Safety as a SAE within 2 working days of determination that the event is not progression of the cancer under study.

In addition, hospitalization related to convenience (e.g., transportation issues etc.) will not be considered a SAE or a Protocol Deviation.

9 STATISTICAL CONSIDERATIONS

9.1 STATISTICAL HYPOTHESIS

- Primary Endpoint:
    - Overall response rate (ORR); this will be assessed at up to 24 months.
- Secondary Endpoints:
    - Type, grade, and frequency of toxicities
    - Duration of response
    - Progression-free survival (PFS)
    - Event-free survival (EFS)
    - Overall survival (OS)

    NOTE: Each of the above will be assessed definitively when 24 months have passed since the last patient has been enrolled.

9.2 SAMPLE SIZE DETERMINATION

The trial will be conducted in two cohorts using a single stage design for evaluating efficacy in each cohort since modestly high clinical response rates are expected in both cohorts.

In the GZL cohort, results from a prior study indicate that 3 of 3 patients had a complete response when treated with (authors data, manuscript accepted for publication). With 20 evaluable patients, there would be 91% power to rule out 50% and be consistent with 80% who may be able to experience a clinical response, using an exact binomial test with a 0.10 one-sided significance level. As an illustration, if 20 evaluable patients are enrolled, 14 of 20 (70.0%) who experience a clinical response would have an associated one-sided lower 90% confidence interval bound of 53.3%, and simultaneously an associated one-sided upper 90% confidence interval bound of 83.4%. This demonstrates that 14 responses in 20 patients would be a desirable result based on the parameters selected.

In the PCNSL and extranodal DLBCL cohort, newly published results in 5 patients suggest the overall response rate will be moderately high.[38] With 20 evaluable patients, there would be 88% power to rule out 40% and be consistent with 70% who may be able to experience a clinical response, using an exact binomial test with a 0.10 one-sided significance level. As an illustration, if 20 evaluable patients are enrolled, 12 of 20 (60.0%) who experience a clinical response would have an associated one-sided lower 90% confidence interval bound of 43.3%, and simultaneously an associated one-sided upper 90% confidence interval bound of 75.1%. This demonstrates that 12 responses in 20 patients would be a desirable result based on the parameters selected.

Within the PCNSL and extranodal DLBCL cohort, the goal will be to enroll a total of 10 PCNSL patients and 10 extranodal DLBCL patients. By doing so, at the conclusion of the trial, there will potentially be adequate patients to make an approximate estimate of the response rate for each group, which could provide information that may guide future development in these patient subsets. While 20 patients may be needed for evaluation per cohort, in order to allow for a small number of inevaluable patients, we intend to initiate treatment in 48 eligible subjects. In order to also account for ineligible patients (i.e., screen failures who do not initiate treatment), the accrual ceiling will be set at 52 patients. If 18-20 patients may be accrued onto this trial per year, accrual should be completed within 2 to 2.5 years.

9.3 POPULATIONS FOR ANALYSES

All patients who receive at least 2 doses of pembrolizumab, and who have both a baseline and follow-up scan at the appropriate time to assess response will be considered evaluable and included in the analyses.

9.4 STATISTICAL ANALYSES

9.4.1 General Approach

The response rate will be determined and reported along with a 95% confidence interval. Other time-to-event outcomes will be reported using Kaplan-Meier curves.

9.4.2 Analysis of the Primary Endpoints

The ORR in each cohort will be determined and reported along with a 95% confidence interval.

9.4.3 Analysis of the Secondary Endpoints

The duration of response (DOR; beginning at the date clinical response is first identified), overall survival (OS), event free survival (EFS), and progression free survival (PFS) will be estimated for each of the two types of lymphoma individually using Kaplan-Meier curves with appropriate confidence intervals reported.

9.4.4 Safety Analyses

The type, grade and frequency of toxicities will be reported.

9.4.5 Planned Interim Analyses

No interim analyses are planned because of the single stage design of the trial.

9.4.6 Sub-Group Analyses

None.

9.4.7 Tabulation of Individual Participant Data

None.

9.4.8 Exploratory Analyses

The exploratory objectives such as seeking to identify potential biomarkers or T-cell and B-cell clones in peripheral blood which are associated with response, will be assessed using descriptive statistics as well as non-parametric methods such as exact Wilcoxon rank sum tests. The analyses will be done without formal adjustment for multiple comparisons, but in the context of the number of tests performed.

10 COLLABORATIVE AGREEMENTS

10.1 CLINICAL TRIAL AGREEMENT

There will be a CTA between the National Cancer Institute and Merck, Inc. (CTA #01043-17) A CRADA is also being discussed and will be added in an amendment, if finalized.

11 HUMAN SUBJECTS PROTECTIONS

11.1 RATIONALE FOR SUBJECT SELECTION

Gray-zone lymphomas (GZL) affect all races and genders, but certain subsets such as mediastinal gray-zone lymphomas occur preferentially in young adults with a slight male predominance. Extranodal DBCL and other ABC-like subtypes of DLBCL including PCNSL are more likely to occur in older patients. Across both cohorts, we anticipate an even gender distribution. This trial is directed at assessing a novel therapy using single agent pembrolizumab in patients with either previously treated GZL and patients with previously treated extranodal DLBCL. Pregnant or nursing mothers are excluded because of the potential teratogenic effects of therapy.

11.2 PARTICIPATION OF CHILDREN

The original intent was for the study to include participation of children. Specifically, that subjects who are at least 14 years old will be included because mediastinal gray zone lymphomas do occasionally affect younger age subjects and because there is no adequate treatment at this time. The age cut-off is based on the rarity of this disease in younger children.

However, given the difficulty in recruitment and decision to close the study to accrualearly, and that no children were enrolled to the study prior to the decision to close, children were ultimately not included. Due to required protocol updates at the request of the NIH IRBO (made in early 2021), the study was revised to note enrollment and inclusion of only adults in the study.

11.3 Participation of Subjects Unable to Give Consent

Adults who are unable to consent are included in this protocol because the protocol offers a prospect of direct benefit and should therefore exclude participants only when scientifically necessary or participants with this condition are at risk of losing capacity at least temporarily and enrollment might be compromised without their involvement.

In addition, re-consent on this protocol may be necessary and there is a possibility that subjects could become decisionally impaired. For this reason and because there is a prospect of direct benefit from research participation (Section **11.4**), all subjects ≥ age 18 will be offered the opportunity to fill in their wishes for research and care, and assign a substitute decision maker on the "NIH Advance Directive for Health Care and Medical Research Participation" form so that another person can make decisions about their medical care in the event that they become incapacitated or cognitively impaired during the course of the study.

NOTE: The PI or AI will contact the NIH Ability to Consent Assessment Team (ACAT) for evaluation to assess ongoing capacity of the subjects and to identify an LAR, as needed. Please see section **11.5** for consent procedure.

11.4 Evaluation of Benefits and Risks/Discomforts

Patients may obtain direct benefit from treatment with pembrolizumab. The most common adverse reactions (≥10%) observed in clinical trials were rash, fatigue, nausea, diarrhea, cough, pruritus, dyspnea, musculoskeletal pain, decreased appetite, headache, vomiting, asthenia, pyrexia, back pain, anemia, peripheral edema and constipation. Although the potential for serious adverse events exists for these patients, the incidence of them is decidedly lower and management algorithms have been developed. The potential toxicity of pembrolizumab is reasonable in relation to the potential benefit to this group of patients who have few treatment options. The risks associated with research procedures (i.e., research blood and tissue collection, including planned analyses and risks associated with genetic research) are described in detail in the informed consent document.

11.4.1 Risks

11.4.1.1 Imaging

In addition to the radiation risks discussed below, scans often use a contrast agent and may include the risks of an allergic reaction to the contrast. Participants might experience hives, itching, headache, difficulty breathing, increased heartrate and swelling.

11.4.1.2 CT and PET scans

CT and PET scans often use a contrast agent. There is a small risk of having a reaction to the contrast and most often include nausea, pain in the vein where the contrast is given, headache, metallic and/ or bitter taste in the mouth and a warm, flushing feeling. Rarely, some people have more severe allergic reactions to the contrast which may include skins rashes, shortness of breath, wheezing or low blood pressure.

11.4.1.3 MRI

People are at risk for injury from the MRI magnet if they have some kinds of metal in their body. People with fear of confined spaces may become anxious during an MRI. Those with back

problems may have back pain or discomfort from lying in the scanner. The noise from the scanner is loud enough to damage hearing, especially in people who already have hearing loss.

There are no known long-term risks of MRI scans.

11.4.1.4 Gadolinium enhanced MRI (Required in patients with PCNSL)
During part of the MRI patient will receive gadolinium, a contrast agent, through an intravenous (IV) catheter (small tube). It will be done for research purposes.

The risks of an IV catheter include bleeding, infection, or inflammation of the skin and vein with pain and swelling. Participants undergoing gadolinium enhanced MRIs may also be at risk for kidney damage.

Most of the gadolinium contrast is eliminated in the urine. However, recent studies have found very small amounts of residual gadolinium in the body, including the brain and bone, by imaging and at autopsy. Macrocyclic gadolinium-containing contrast agents are substantially less likely to leave gadolinium behind than linear agents. There is presently no evidence that the retained gadolinium is associated with any adverse effects or other health risks. Participants undergoing gadolinium enhanced MRIs may also be at risk for kidney damage.

11.4.1.5 Radiation Exposure
The procedures for performing the CT and ^{18}F-FDG PET/CT scans will follow clinical policies, no special procedures apply to these additional assessments for research purposes. In summary, subjects may receive additional radiation exposure from up to five (5) additional CT scans of the chest, abdomen, and pelvis and two (2) additional ^{18}F-FDG PET/CT scans maximum in an annual period.

The total additional radiation dose for research purposes will be approximately 7.9 rem. This amount is more than would be expected from everyday background radiation. Being exposed to excess radiation can increase the risk of cancer.

11.4.1.6 Blood sampling
Side effects of blood draws include pain and bruising, lightheadedness, and rarely, fainting.

11.4.1.7 Bone marrow aspirate and/or biopsy
Bone marrow biopsy is minimally invasive and is typically a very safe procedure. Usually hipbone is numbed with anesthesia. Using a needle, the solid and liquid portion of bone marrow is taken out. This procedure causes some pain. Very rarely, infection or bleeding may occur at the needle site.

11.4.1.8 Biopsy (optional)

All care will be taken to minimize risks that may be incurred by tumor sampling. However, there are procedure-related risks (such as bleeding, infection, and injury) that will be explained fully during informed consent

11.4.1.9 Urine collection
There is no physical risk involved with urine collection.

11.4.1.10 Lumbar puncture
Risks of lumbar puncture include headache, dizziness, infection, back discomfort, minor radicular numbness and brainstem herniation.

11.4.1.11 Opthalmalogic evaluation

There are no anticipated long-term physical risks expected with the eye exams planned in patients in PCNSL.

11.5 Consent Process and Documentation

The informed consent document will be provided to the participant or consent designee(s) as applicable for review prior to consenting. A designated study investigator will carefully explain the procedures and tests involved in this study, and the associated risks, discomforts and benefits. In order to minimize potential coercion, as much time as is needed to review the document will be given, including an opportunity to discuss it with friends, family members and/or other advisors, and to ask questions of any designated study investigator. A signed informed consent document will be obtained prior to entry onto the study.

The initial consent process as well as re-consent, when required, may take place in person or remotely (e.g., via telephone or other NIH approved remote platforms) per discretion of the designated study investigator and with the agreement of the participant/consent designee(s). Whether in person or remote, the privacy of the subject will be maintained. Consenting investigators (and participant/consent designee, when in person) will be located in a private area (e.g., clinic consult room). When consent is conducted remotely, the participant/consent designee will be informed of the private nature of the discussion and will be encouraged to relocate to a more private setting if needed.

11.5.1 Consent Process for Adults Who Lack Capacity to Consent to Research Participation

For participants addressed in section **11.3**, an LAR will be identified consistent with Policy 403 and informed consent obtained from the LAR, as described in Section **11.5**.

11.6 Inclusion of Women and Minorities

Both men and women and members of all races are eligible for this trial.

12 REGULATORY AND OPERATIONAL CONSIDERATIONS

12.1 Study Discontinuation and Closure

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to study participants, investigator, funding agency, and regulatory authorities. If the study is prematurely terminated or suspended, the Principal Investigator (PI) will promptly inform study participants, the Institutional Review Board (IRB), and sponsor and will provide the reason(s) for the termination or suspension. Study participants will be contacted, as applicable, and be informed of changes to study visit schedule.

Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants
- Demonstration of efficacy that would warrant stopping
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable
- Determination that the primary endpoint has been met
- Determination of futility

Study may resume once concerns about safety, protocol compliance, and data quality are addressed, and satisfy the sponsor and IRB.

12.2 QUALITY ASSURANCE AND QUALITY CONTROL

The clinical site will perform internal quality management of study conduct, data and biological specimen collection, documentation and completion. An individualized quality management plan will be developed to describe the site's quality management.

Quality control (QC) procedures will be implemented beginning with the data entry system and data QC checks that will be run on the database will be generated. Any missing data or data anomalies will be communicated to the site(s) for clarification/resolution.

Following written Standard Operating Procedures (SOPs), the monitors will verify that the clinical trial is conducted and data are generated and biological specimens are collected, documented (recorded), and reported in compliance with the protocol, International Conference on Harmonisation Good Clinical Practice (ICH GCP), and applicable regulatory requirements (e.g., Good Laboratory Practices (GLP), Good Manufacturing Practices (GMP)).

The investigational site will provide direct access to all trial related sites, source data/documents, and reports for the purpose of monitoring and auditing by the sponsor, and inspection by local and regulatory authorities.

12.3 CONFLICT OF INTEREST POLICY

The independence of this study from any actual or perceived influence, such as by the pharmaceutical industry, is critical. Therefore, any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the design and conduct of this trial. The study leadership in conjunction with the National Cancer Institute has established policies and procedures for all study group members to disclose all conflicts of interest and will establish a mechanism for the management of all reported dualities of interest.

12.4 CONFIDENTIALITY AND PRIVACY

Participant confidentiality and privacy is strictly held in trust by the participating investigators, their staff, and the sponsor(s). This confidentiality is extended to cover testing of biological samples and genetic tests in addition to the clinical information relating to participants. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor.

All research activities will be conducted in as private a setting as possible.

The study monitor, other authorized representatives of the sponsor, representatives of the Institutional Review Board (IRB), and/or regulatory agencies may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the participants in this study. The clinical study site will permit access to such records.

The study participant's contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by the reviewing IRB, Institutional policies, or sponsor requirements.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be stored at the NCI CCR. This will not include the participant's contact or identifying information. Rather, individual participants and their research data will be identified by a unique study identification number. The study data entry and study management systems used by the clinical site(s) and by NCI CCR research staff will be secured and password protected. At the end of the study, all study databases will be archived at the NIH.

To further protect the privacy of study participants, a Certificate of Confidentiality has been issued by the National Institutes of Health (NIH). This certificate protects identifiable research information from forced disclosure. It allows the investigator and others who have access to research records to refuse to disclose identifying information on research participation in any civil, criminal, administrative, legislative, or other proceeding, whether at the federal, state, or local level. By protecting researchers and institutions from being compelled to disclose information that would identify research participants, Certificates of Confidentiality help achieve the research objectives and promote participation in studies by helping assure confidentiality and privacy to participants.

13 PHARMACEUTICAL INFORMATION

This clinical investigation of a marketed drug is exempt from the IND requirements because all of the criteria for an exemption in 21CFR 312.2(b) are met:

- The drug product is lawfully marketed in the United States.
- The investigation is not intended to be reported to FDA as a well-controlled study in support of a new indication and there is no intent to use it to support any other significant change in the labeling of the drug.
- In the case of a prescription drug, the investigation is not intended to support a significant change in the advertising for the drug.
- The investigation does not involve a route of administration, dose, patient population, or other factor that significantly increases the risk (or decreases the acceptability of the risk) associated with the use of the drug product.
- The investigation is conducted in compliance with the requirements for review by an IRB (21 CFR part 56) and with the requirements for informed consent (21 CFR part 50).
- The investigation is conducted in compliance with the requirements of 21 CFR 312.7, i.e., the drug may not be represented as safe or effective, nor may it be commercially distributed, for the purposes for which it is under investigation.

13.1 PEMBROLIZUMAB

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 investigational product in accordance with the approved, marketed product label and information, this clinical protocol, and any applicable laws and regulations. It has been confirmed with Merck prior to activation that commercial drug lots (i.e., not research/investigational lots) will be provided for this clinical trial.

A summary of protocol-specific information is included here:

13.1.1 Source

Pembrolizumab will be supplied by Merck, Inc. for use by subjects in this clinical trial.

13.1.2 Toxicity

Please refer to the Package Insert for pembrolizumab (KEYTRUDA®) for toxicity information.

13.1.3 Formulation and Preparation

Clinical supplies will be affixed with a clinical label in accordance with regulatory requirements. The formulations to be supplied are as follows:

Product Name & Potency	**Dosage Form**
Pembrolizumab 50 mg	Lyophilized Powder for Injection
Pembrolizumab 100 mg/ 4mL	Solution for Injection

Preparation for infusion should follow current clinical practice for marketed pembrolizumab.

NOTE: This trial is open-label; therefore, the subject and the trial site personnel are not blinded to treatment. Drug identity (name, strength) is included in the label text; random code/disclosure envelopes or lists are not provided.

13.1.4 Stability and Storage

Clinical supplies must be stored in a secure, limited-access location under the storage conditions specified on the label. Receipt and dispensing of trial supplies must be recorded by an authorized person at the trial site.

Clinical supplies may not be used for any purpose other than that stated in the protocol.

13.1.5 Administration procedures

Pembrolizumab should be administered per the FDA-approved labeling instructions as is applicable for the commercial lots of drug being supplied for this study.

13.1.6 Returns and Reconciliation

The investigator is responsible for keeping accurate records of the clinical supplies received from Merck or designee, the amount dispensed and the amount remaining at the conclusion of the trial.

Upon completion or termination of the study, all unused and/or partially used investigational product will be destroyed at the site per institutional policy. It is the investigator's responsibility to arrange for disposal of all empty containers, provided that procedures for proper disposal have been established according to applicable federal, state, local and institutional guidelines and procedures, and provided that appropriate records of disposal are kept.

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15 APPENDIX A: PERFORMANCE STATUS CRITERIA

ECOG Performance Status Scale		**Karnofsky Performance Scale**	
Grade	Descriptions	Percent	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.	100	Normal, no complaints, no evidence of disease.
		90	Able to carry on normal activity; minor signs or symptoms of disease.
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).	80	Normal activity with effort; some signs or symptoms of disease.
		70	Cares for self, unable to carry on normal activity or to do active 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.	60	Requires occasional assistance, but is able to care for most of his/her needs.
		50	Requires considerable assistance and frequent medical care.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.	40	Disabled, requires special care and assistance.
		30	Severely disabled, hospitalization indicated. Death not imminent.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.	20	Very sick, hospitalization indicated. Death not imminent.
		10	Moribund, fatal processes progressing rapidly.
5	Dead.	0	Dead.

16 APPENDIX B: MERCK ADVERSE EVENT DOCUMENTATION REQUIREMENTS

The following information should be considered for each reportable event to Merck:

V4.0 CTCAE Grading	**Grade 1**	**Mild; asymptomatic or mid 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 or hospitalization indicated; disabling; limiting self-care ADL.**
	Grade 4	**Life threatening consequences; urgent intervention indicated.**
	Grade 5	**Death related to AE**
Seriousness	A serious adverse event is any adverse event occurring at any dose or during any use of Merck product that:	
	†**Results in death**; or	
	†**Is life threatening; or** places the subject, in the view of the investigator, at immediate risk of death from the event as it occurred (Note: This does not include an adverse event that, had it occurred in a more severe form, might have caused death.); or	
	†**Results in a persistent or significant disability/incapacity** (substantial disruption of one's ability to conduct normal life functions); or	
	†**Results in or prolongs an existing inpatient hospitalization** (hospitalization is defined as an inpatient admission, regardless of length of stay, even if the hospitalization is a precautionary measure for continued observation. (Note: Hospitalization for an elective procedure to treat a pre-existing condition that has not worsened is not a serious adverse event. A pre-existing condition is a clinical condition that is diagnosed prior to the use of a Merck product and is documented in the patient's medical history.); or	
	†**Is a congenital anomaly/birth defect** (in offspring of subject taking the product regardless of time to diagnosis); or	
	Is a new **cancer** (that is not a condition of the study) **(**although not serious per ICH definition, is reportable to Merck within 2 working days to meet certain local requirements); or	
	Is an overdose (whether accidental or intentional). Any adverse event associated with an overdose is considered a serious adverse event for collection purposes. An overdose that is not associated with an adverse event is considered a non-serious event of clinical interest and must be reported to Merck within 2 working days.	
	Other important medical events that may not result in death, not be life threatening, or not require hospitalization may be considered a serious adverse event when, based upon appropriate medical judgment, the event may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed previously (designated above by a †).	
Duration	Record the start and stop dates of the adverse event. If less than 1 day, indicate the appropriate length of time and units	
Action taken	Did the adverse event cause Merck product to be discontinued?	

<table>
<tr><td>Relationship to Merck Product</td><td colspan="2">Did Merck product cause the adverse event? The determination of the likelihood that Merck product caused the adverse event will be provided by an investigator who is a qualified physician. The investigator's signed/dated initials on the source document or worksheet that supports the causality noted on the AE form, ensures that a medically qualified assessment of causality was done. This initialed document must be retained for the required regulatory time frame. The criteria below are intended as reference guidelines to assist the investigator in assessing the likelihood of a relationship between the test drug and the adverse event based upon the available information.
The following components are to be used to assess the relationship between Merck product and the AE; the greater the correlation with the components and their respective elements (in number and/or intensity), the more likely Merck product caused the adverse event (AE):</td></tr>
<tr><td></td><td>Exposure</td><td>Is there evidence that the subject was actually exposed to Merck product such as: reliable history, acceptable compliance assessment (pill count, diary, etc.), expected pharmacologic effect, or measurement of drug/metabolite in bodily specimen?</td></tr>
<tr><td></td><td>Time Course</td><td>Did the AE follow in a reasonable temporal sequence from administration of Merck product?
Is the time of onset of the AE compatible with a drug-induced effect (applies to trials with investigational medicinal product)?</td></tr>
<tr><td></td><td>Likely Cause</td><td>Is the AE not reasonably explained by another etiology such as underlying disease, other drug(s)/vaccine(s), or other host or environmental factors</td></tr>
<tr><td></td><td colspan="2">The following components are to be used to assess the relationship between the test drug and the AE: (continued)</td></tr>
<tr><td></td><td>Dechallenge</td><td>Was Merck product discontinued or dose/exposure/frequency reduced?
If yes, did the AE resolve or improve?
If yes, this is a positive dechallenge. If no, this is a negative dechallenge.
(Note: This criterion is not applicable if: (1) the AE resulted in death or permanent disability; (2) the AE resolved/improved despite continuation of the study drug; or (3) the trial is a single-dose drug trial); or (4) study drug is only used one time.)</td></tr>
<tr><td></td><td>Rechallenge</td><td>Was the subject re-exposed to Merck product in this study?
If yes, did the AE recur or worsen?
If yes, this is a positive rechallenge. If no, this is a negative rechallenge.
(Note: This criterion is not applicable if: (1) the initial AE resulted in death or permanent disability, or (2) the trial is a single-dose drug trial); or (3) study drug is used only one time).
NOTE: IF A RECHALLENGE IS PLANNED FOR AN ADVERSE EVENT WHICH WAS SERIOUS AND WHICH MAY HAVE BEEN CAUSED BY MERCK PRODUCT, OR IF REEXPOSURE TO MERCK PRODUCT POSES ADDITIONAL POTENTIAL SIGNIFICANT RISK TO THE SUBJECT, THEN THE RECHALLENGE MUST BE APPROVED IN ADVANCE BY THE PI AS PER DOSE MODIFICATION GUIDELINES IN THE PROTOCOL.</td></tr>
<tr><td></td><td>Consistency with Trial Treatment Profile</td><td>Is the clinical/pathological presentation of the AE consistent with previous knowledge regarding Merck product or drug class pharmacology or toxicology?</td></tr>
<tr><td colspan="3">The assessment of relationship will be reported on the case report forms /worksheets by an investigator who is a qualified physician according to his/her best clinical judgment, including consideration of the above elements.</td></tr>
<tr><td colspan="2">Record one of the following</td><td>Use the following scale of criteria as guidance (not all criteria must be present to be indicative of Merck product relationship).</td></tr>
<tr><td colspan="2">Yes, there is a reasonable possibility of Merck product relationship.</td><td>There is evidence of exposure to Merck product. The temporal sequence of the AE onset relative to the administration of Merck product is reasonable. The AE is more likely explained by Merck product than by another cause.</td></tr>
<tr><td colspan="2">No, there is not a reasonable possibility of Merck product relationship</td><td>Subject did not receive the Merck product OR temporal sequence of the AE onset relative to administration of Merck product is not reasonable OR the AE is more likely explained by another cause than the Merck product. (Also entered for a subject with overdose without an associated AE.)</td></tr>
</table>