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TITLE: Phase II study of pembrolizumab for *PD-L1* gene-altered, relapsed/refractory DLBCL

IND NUMBER: 132029

UNIVERSITY OF CHICAGO IRB NUMBER: IRB19-0076

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PROTOCOL AMENDMENT VERSION 10

- Pembrolizumab dose modification guidelines were updated in accordance with Version 12 of the pembrolizumab MISP Protocol Template.

- All patients with prior CAR-T will now be considered eligible provided they meet the remainder of the inclusion and exclusion criteria of the study. The previous protocol versions excluded patients who relapsed within 90 days of their CAR T-cell infusion.

- The CLIA-certified cytogenetics laboratory at City of Hope is now listed as an additional site for the initial PD-L1 FISH screening.

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1.0 TRIAL SUMMARY

Abbreviated Title	Pembrolizumab for *PD-L1* gene-altered, relapsed/refractory DLBCL
Trial Phase	*II*
Clinical Indication	*PD-L1* gene-altered relapsed/refractory diffuse large B cell lymphoma (DLBCL)
Trial Type	Interventional, single-arm, biomarker-driven
Type of control	Historical (DLBCL patients enrolled on KEYNOTE-013 study)
Route of administration	Intravenous
Trial Blinding	Unblinded Open-label
Treatment Groups	1
Number of trial participants	13-29
Estimated enrollment period	2 years
Estimated duration of trial	3-4 years
Duration of Participation	Each subject will participate in the trial from the time he or she signs the Informed Consent Form (ICF) through the final protocol-specified contact. After the initial pre-screening and screening phases, eligible subjects will receive pembrolizumab treatment at a dose of 200 mg IV every 3 weeks (Q3W) for a duration of 2 years (35 cycles). Treatment with pembrolizumab will continue until documented disease progression, unacceptable adverse event(s), intercurrent illness that prevents further administration of treatment, investigator's decision to withdraw the subject, subject withdraws consent, pregnancy of the subject, noncompliance with trial treatment or procedure requirements, or administrative reasons reuiring cessation of treatment. After the end of treatment, each subject will be followed for the occurrence of adverse events and spontaneously reported pregnancy as described under section 7.2 of the protocol. Subjects who discontinue for reasons other than disease progression will have post-treatment follow-up for disease status until disease progression, initiating a non-study cancer treatment, withdrawing consent, or becoming lost to follow-up. All subjects will be followed by telephone for overall survival until death, withdrawal of consent, or the end of the study.
Estimated average length of treatment per patient	1 year

2.0 TRIAL DESIGN

2.1 Trial Design

This is a nonrandomized, unblinded, open-label, phase II study designed to investigate the efficacy of pembrolizumab in patients with relapsed/refractory diffuse large B cell lymphoma (DLBCL) that harbors genetic alterations (copy number alterations or chromosomal translocations) involving the programmed death – ligand 1 (*PD-L1*) locus. Patients having received ≥2 lines of prior systemic therapy, or ≥1 line of prior systemic therapy but are either ineligible or have refused autologous stem cell transplantation, are considered eligible. Furthermore, patients with primary refractory disease or who relapse within 12 months of initial diagnosis, are also eligible for

enrollment. Pembrolizumab will be administered at a fixed dose of 200 mg IV every 3 weeks (Q3W). A Simon two-stage design will be employed, and approximately 13-29 patients will be enrolled. Treatment with pembrolizumab will continue for up to 24 months. Reasons for discontinuing study treatment prior to 24 months include: confirmed disease progression, unacceptable adverse event(s), intercurrent illness that prevents further administration of treatment, investigator's decision to withdraw the subject, subject withdraws consent, pregnancy of the subject, noncompliance with trial treatment or procedure requirements, or administrative reason requiring cessation of treatment. Adverse events will be monitored throughout the trial, and graded in severity according to the guidelines outlined in the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. This trial will be conducted in accordance with Good Clinical Practices.

Patients will undergo an initial pre-screening phase within 28 days prior to treatment allocation. This will include a review of the patient's medical history to determine potential study eligibility, and an evaluation for the presence of *PD-L1* gene alterations utilizing fluorescent *in-situ* hybridization (FISH) on archived formalin-fixed paraffin-embedded (FFPE) tissue (ideally obtained at the time of most recent relapse). *PD-L1* FISH will be performed at The University of Chicago or at City of Hope in a CLIA-certified laboratory using a previously validated technique (see Appendix 1). Patients fulfilling pre-screening criteria will proceed to a screening phase to determine whether they meet the remainder of the study entry criteria (see Section 5.1), and will undergo a baseline evaluation, including evaluation of disease status by positron emission tomography (PET) and diagnostic computerized tomography (CT) scans (bone marrow exam will also be performed for patients with a history of prior bone marrow involvement). Patients meeting enrollment criteria will be allocated to trial treatment by non-random assignment.

Patients enrolled on this study will undergo serial peripheral blood samples for correlative analyses, and archived FFPE specimens will be collected and stored for future exploratory research. Disease response to pembrolizumab will be determined using the LYRIC response criteria (1), and will be performed at designated timepoints outlined in the Trial Flow Chart in Section 6.0, and any time disease progression is clinically suspected. Specific procedures to be performed during the trial, as well as their prescribed times and associated visit windows, are outlined in the Trial Flow Chart – Section 6.0. Details of each procedure are provided in Section 7.0 – trial procedures. After 24 months, ongoing disease re-assessments will be performed at the discretion of the treating physician. Any patient who experiences disease progression at any time will be removed from study, and alternative treatment can be pursued at the discretion of the treating physician. After the end of treatment, each subject will be followed for the occurrence of adverse events and spontaneously reported pregnancy as described in Section 7.2 of the protocol. Subjects who discontinue treatment for reasons other than disease progression will undergo post-treatment follow-up for disease status until disease progression, initiation of a non-study cancer treatment, withdrawal of consent, or becoming lost to follow-up. All subjects will be followed by telephone contact for overall survival until death, withdrawal of consent, or the end of the study, whichever comes first.

Adverse events associated with pembrolizumab often represent immune-related toxicities. These adverse events may occur shortly after the first dose or several months after the last dose of treatment. Pembrolizumab must be held for drug-related toxicities and severe or life-threatening

adverse events as per Table 3. See Section 5.2 for supportive care guidelines including use of corticosteroids.

The primary objective of this trial is to determine whether the overall response rate (ORR) of pembrolizumab is significantly higher in relapsed/refractory DLBCL patients harboring *PD-L1* gene alterations compared to the ORR of unselected relapsed/refractory DLBCL patients enrolled on KEYNOTE-013 Cohort 4D (15% ORR). Secondary objectives include analysis of additional efficacy parameters (progression-free survival (PFS), duration of response (DOR), and overall survival (OS)). Correlative studies are also planned, and will serve as exploratory analyses. These will include an in-depth analysis of the immunogenomic landscape of *PD-L1* gene-altered DLBCLs, an examination of the influence of the intestinal microbiota on endogenous anti-lymphoma immunity and on response to anti-PD-1 antibody therapy, as well as a detailed investigation of the clonal evolution of DLBCL in response to pembrolizumab through serial analysis of circulating tumor DNA (ctDNA).

If this study confirms an improved ORR in *PD-L1* gene-altered DLBCL patients compared to historical controls, then an expansion cohort may be considered if deemed appropriate by the principal investigator and study sponsor.

2.2 Trial Diagram

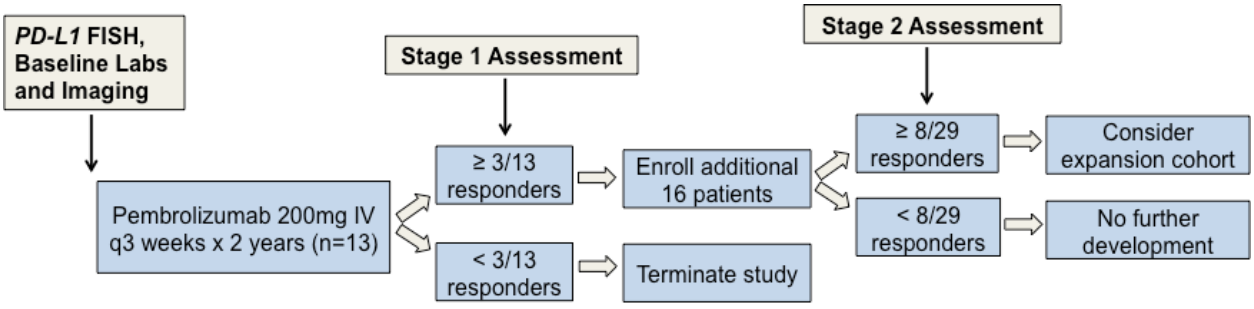

Figure 1. Trial Diagram.

3.0 OBJECTIVES & HYPOTHESES

3.1 Primary Objective & Hypothesis

(1) **Objective:** To determine whether the overall response rate (ORR) to pembrolizumab treatment is significantly higher in *PD-L1* gene-altered, relapsed/refractory DLBCL patients compared to the ORR of unselected relapsed/refractory DLBCL patients enrolled on KEYNOTE-013 Cohort 4D (15% ORR).

Hypothesis: Relapsed/refractory DLBCL patients harboring *PD-L1* gene alterations will exhibit a significantly higher ORR to pembrolizumab compared to unselected relapsed/refractory DLBCL patients enrolled onto Cohort 4D of the KEYNOTE-013 study (ORR 15%).

3.2 Secondary Objectives & Hypotheses

(1) **Objective**: To determine whether the median duration of response (DOR), median progression-free survival (PFS), and median overall survival (OS) of *PD-L1* gene-altered, relapsed/refractory DLBCL patients to pembrolizumab treatment is significantly higher in *PD-L1* gene-altered, relapsed/refractory DLBCL patients compared to unselected relapsed/refractory DLBCL patients enrolled onto Cohort 4D of the KEYNOTE-013 study.

Hypothesis: Relapsed/refractory DLBCL patients harboring *PD-L1* gene alterations will have a significantly longer DOR, PFS, and OS compared to unselected relapsed/refractory DLBCL patients enrolled on KEYNOTE-013 Cohort 4D.

3.3 Exploratory Objectives

(1) **Objective**: To compare the immune landscape of DLBCLs with and without *PD-L1* gene alterations (non-*PD-L1* gene-altered DLBCLs will consist of previously identified patient samples stored in The University of Chicago Lymphoma Biobank).

(2) **Objective**: To compare gene expression signatures of DLBCLs with and without *PD-L1* gene alterations.

(3) **Objective**: To compare genomic mutational profiles and neo-antigen load of DLBCLs with and without *PD-L1* gene alterations.

(4) **Objective**: To determine whether the degree of *PD-L1* gene alterations in DLBCL (amplified = translocated > relative copy gain > polysomy) correlates with response and survival to pembrolizumab.

(5) **Objective**: To determine the impact of PD-L1 protein expression as assessed by immunohistochemistry (IHC) (both on malignant tumor cell and within the tumor microenvironment using Dako PD-L1 IHC 22C3 pharmDx)) on the ORR to pembrolizumab treatment in patients with *PD-L1* gene-altered DLBCLs.

(6) **Objective**: To compare the intestinal microbiota diversity and composition between DLBCL patients with and without *PD-L1* gene alterations, and to determine if the composition and/or diversity of the host microbiome predicts for response to pembrolizumab in *PD-L1* gene-altered DLBCL patients.

(7) **Objective**: To identify the feasibility of monitoring clonal tumor evolution in response to pembrolizumab using ctDNA, and to determine the utility of measuring ctDNA burden in predicting clinical outcomes (PFS, DOR, OS) following pembrolizumab treatment.

4.0 BACKGROUND & RATIONALE

4.1 Background

Pembrolizumab is a potent humanized immunoglobulin G4 (IgG4) monoclonal antibody (mAb) with high specificity of binding to the programmed cell death 1 (PD-1) receptor, thus inhibiting its

interaction with programmed cell death ligand 1 (PD-L1) and programmed cell death ligand 2 (PD-L2). Based on preclinical in vitro data, pembrolizumab has high affinity and potent receptor blocking activity for PD-1. Pembrolizumab has an acceptable preclinical safety profile and is in clinical development as an intravenous (IV) immunotherapy for advanced malignancies. Keytruda® (pembrolizumab) is indicated for the treatment of patients across a number of indications because of its mechanism of action to bind the PD-1 receptor on the T cell. For more details on specific indications refer to the Investigator brochure.

4.1.1 Pharmaceutical and Therapeutic Background

The importance of intact immune surveillance function in controlling outgrowth of neoplastic transformations has been known for decades (2). Accumulating evidence shows a correlation between tumor-infiltrating lymphocytes in cancer tissue and favorable prognosis in various malignancies. In particular, the presence of CD8+ T-cells and the ratio of CD8+ effector T-cells/FoxP3+ regulatory T-cells (T-regs) correlates with improved prognosis and long-term survival in solid malignancies, such as ovarian, colorectal, and pancreatic cancer; hepatocellular carcinoma; malignant melanoma; and renal cell carcinoma. Tumor-infiltrating lymphocytes can be expanded ex vivo and reinfused, inducing durable objective tumor responses in cancers such as melanoma (3, 4).

The PD-1 receptor-ligand interaction is a major pathway hijacked by tumors to suppress immune control. The normal function of PD-1, expressed on the cell surface of activated T-cells under healthy conditions, is to down-modulate unwanted or excessive immune responses, including autoimmune reactions. PD-1 (encoded by the gene *Pdcd1*) is an immunoglobulin (Ig) superfamily member related to cluster of differentiation 28 (CD28) and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) that has been shown to negatively regulate antigen receptor signaling upon engagement of its ligands (PD-L1 and/or PD-L2) (5, 6).

The structure of murine PD-1 has been resolved (7). PD-1 and its family members are type I transmembrane glycoproteins containing an Ig-variable–type (IgV-type) domain responsible for ligand binding and a cytoplasmic tail responsible for the binding of signaling molecules. The cytoplasmic tail of PD-1 contains 2 tyrosine-based signaling motifs, an immunoreceptor tyrosine-based inhibition motif, and an immunoreceptor tyrosine-based switch motif. Following T-cell stimulation, PD-1 recruits the tyrosine phosphatases, SHP-1 and SHP-2, to the immunoreceptor tyrosine-based switch motif within its cytoplasmic tail, leading to the dephosphorylation of effector molecules such as CD3 zeta (CD3ζ), protein kinase C-theta (PKCθ), and zeta-chain-associated protein kinase (ZAP70), which are involved in the CD3 T-cell signaling cascade (6, 8-10). The mechanism by which PD-1 down-modulates T-cell responses is similar to, but distinct from, that of CTLA-4, because both molecules regulate an overlapping set of signaling proteins (11, 12). As a consequence, the PD-1/PD-L1 pathway is an attractive target for therapeutic intervention in DLBCL.

4.1.2 Preclinical and Clinical Trial Data

Refer to the Investigator's Brochure for Preclinical and Clinical data.

4.2 Rationale

4.2.1 Rationale for the Trial and Selected Population

4.2.1.1 Outcomes of Patients with Relapsed/Refractory DLBCL

Diffuse large B cell lymphoma (DLBCL) is the most common form of non-Hodgkin lymphoma (NHL) diagnosed in the United States (13). Although a majority of DLBCL patients are cured with modern chemo-immunotherapy, approximately 40% will have primary-refractory or relapsed disease (14), which is difficult to eradicate, and associated with high rates of early mortality (15). Even in the era of CD19-directed CAR T cell therapy, which is effective in this patient population, the reality remains that the majority of patients are not candidates for this aggressive therapy, or will benefit briefly from it (16). Moreover, autologous hematopoietic stem cell transplantation, another potentially curative treatment option for relapsed/refractory DLBCL, is associated with poor long-term survival, particularly in the rituximab era (17). New approaches are therefore needed to both prevent and effectively treat relapsed disease.

4.2.1.2 PD-1 Blockade Therapy in Lymphoma

PD-L1 expression on malignant cells potently down-regulates the function of PD-1 receptor-expressing tumor antigen-specific T cells (18-20). Interference with PD-1/PD-L1 interactions can "re-awaken" existing, but ineffective anti-tumor T cell responses. PD-1 blockade has demonstrated remarkable clinical efficacy in a number of solid tumors (21, 22), and has created a new paradigm for cancer treatment.

PD-1 blockade therapy has also been effective in select lymphomas, particularly classical Hodgkin lymphoma (cHL) (23-25), in which the genetic loci that encode the PD-1 ligands on chromosome 9p24.1 are commonly amplified (26, 27). In patients with relapsed/refractory cHL, treatment with PD-1 blocking antibodies has been associated with objective response rates (ORR) of 65-87% in phase 1 and 2 studies, with approximately 16-22% of patients achieving a complete remission (CR). The median duration of response (DOR) to PD-1 blockade therapy in relapsed/refractory cHL patients is encouraging at 16.6 months.

With regard to NHL, anti-PD-1 therapies have demonstrated promising activity in select aggressive B cell lymphomas. For example, there was a 41% ORR in patients with relapsed/refractory primary mediastinal B cell lymphoma (PMBL) in a phase 1b study of pembrolizumab (28). Notably, many of these patients experienced long-lasting responses. In the pivotal study, the median DOR was not reached at 11.3 months. Early reports have also demonstrated high response rates to PD-1 blockade therapy in Richter's transformation of CLL, primary CNS lymphoma, as well as gray zone lymphoma (29-31). Importantly, across all of these studies, treatment with anti-PD-1 antibodies has been generally safe, with only rare grade 3 or 4 toxicities reported. Immune-related adverse events (irAEs) do occur with PD-1 blockade therapy, but at a lower incidence and severity compared to what has been reported after treatment with the CTLA-4 blocking antibody, ipilimumab (32).

In contrast to the impressive response rates to PD-1 blockade therapy in the aforementioned lymphomas, the activity of anti-PD-1 therapy in patients with relapsed/refractory DLBCL has been

less encouraging. For example, the investigator-assessed ORR to the anti-PD-1 antibodies, nivolumab and pembrolizuamb, have ranged between 10-36% (33, 34). That said, DLBCL patients who achieve a response to PD-1 blockade therapy derive meaningful clinical benefit, with a median DOR of 11.3 months. This compares very favorably to other common agents prescribed for relapsed/refractory DLBCL, such as lenalidomide and ibrutinib, which have a median DOR of 4.6 and 4.8 months, respectively (35, 36). Therefore, PD-1 blockade remains a promising therapy in DLBCL given the potential for achieving durable responses in relapsed/refractory patients; however, the identification of reliable predictive biomarkers of response are needed in order to identify a subset of patients likely to derive meaningful benefit from treatment.

4.2.1.3 Predictive Biomarkers to PD-1 Blockade Therapy

The heterogenous nature of DLBCL was initially demonstrated through gene expression profiling, which identified 3 unique molecular disease subsets: 1) germinal center B cell-like, 2) activated peripheral blood B cell-like, and 3) unclassifiable (37). More recently, a number of large genomic analyses have identified over 150 genetic drivers of DLBCL that can be grouped into several unique clusters (38-40). Importantly, these studies demonstrate that unique biological DLBCL subsets are associated with widely disparate clinical outcomes following treatment with upfront chemo-immunotherapy, and in the relapsed disease setting, may also be associated with responsiveness to particular targeted therapies (35, 41). Whether there exists a subset of DLBCL patients that will be more responsive to PD-1 blockade therapy, however, is not known.

In solid cancers, infiltration and local activation of T cells indicates the presence of a spontaneous anti-tumor immune response, and enriches for the subset of patients benefitting from PD-1 blockade therapy (42-44). This so-called “T cell-inflamed” phenotype may also be a prerequisite for response to anti-PD-1 therapy in lymphoma, as exemplified by cHL, which is characterized by pronounced T cell infiltration and exquisite sensitivity to PD-1 blockade therapy (24, 25). cHL also universally exploits genetic immune escape mechanisms, most notably copy gains of the *PD-L1* locus on chromosome 9p24.1 (27). Importantly, from a biomarker perspective, studies have demonstrated that the degree of *PD-L1* amplification in cHL is predictive of best overall response and PFS to anti-PD-1 therapy (45). These findings prompted us to evaluate the incidence and immune landscape of *PD-L1* gene alterations (copy number alterations and translocations) in DLBCL, which revealed that *PD-L1* gene alterations occur in approximately 25% of de novo DLBCLs, and that these lymphomas are associated with heightened levels of T cells reminiscent of the “T cell-inflamed” phenotype that has been previously associated with responsiveness to PD-1 blockade in solid tumors (unpublished observation). Additionally, our retrospective analysis of relapsed/refractory DLBCL patients enrolled on the pembrolizumab, KEYNOTE-013 study revealed that the presence of *PD-L1* gene alterations was potentially associated with responsiveness to anti-PD-1 antibody therapy (unpublished observation). Collectively, these observations provide the rationale for this clinical study, which aims to prospectively validate the utility of *PD-L1* gene alterations as a predictive biomarker of response to pembrolizumab in relapsed/refractory DLBCL patients. If *PD-L1* gene alterations are confirmed to be a reliable predictive biomarker of response to pembrolizumab, this finding could expand the use of pembrolizumab to a genetically-defined subset of DLBCL patients, and would also inform the design of future clinical trials exploring the use of *PD-L1* gene alterations as a tissue agnostic genetic biomarker of responsiveness to PD-1 blockade, similar to the current use of microsatellite instability testing to identify neo-antigen high solid tumors.

4.2.2 Justification for Dose

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

- Clinical data from 8 randomized studies demonstrating flat dose- and exposure-efficacy relationships from 2 mg/kg Q3W to 10 mg/kg every 2 weeks (Q2W),
- Clinical data showing meaningful improvement in benefit-risk including overall survival at 200 mg Q3W across multiple indications, and
- Pharmacology data showing full target saturation in both systemic circulation (inferred from pharmacokinetic [PK] data) and tumor (inferred from physiologically-based PK [PBPK] analysis) at 200 mg Q3W

Among the 8 randomized dose-comparison studies, a total of 2262 participants were enrolled with melanoma and non-small cell lung cancer (NSCLC), covering different disease settings (treatment naïve, previously treated, PD-L1 enriched, and all-comers) and different treatment settings (monotherapy and in combination with chemotherapy). Five studies compared 2 mg/kg Q3W versus 10 mg/kg Q2W (KN001 Cohort B2, KN001 Cohort D, KN002, KN010, and KN021), and 3 studies compared 10 mg/kg Q3W versus 10 mg/kg Q2W (KN001 Cohort B3, KN001 Cohort F2 and KN006). All of these studies demonstrated flat dose- and exposure-response relationships across the doses studied representing an approximate 5- to 7.5-fold difference in exposure. The 2 mg/kg (or 200 mg fixed-dose) Q3W provided similar responses to the highest doses studied. Subsequently, flat dose-exposure-response relationships were also observed in other tumor types including head and neck cancer, bladder cancer, gastric cancer and classical Hodgkin Lymphoma, confirming 200 mg Q3W as the appropriate dose independent of the tumor type. These findings are consistent with the mechanism of action of pembrolizumab, which acts by interaction with immune cells, and not via direct binding to cancer cells.

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

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

4.2.3 Rationale for Endpoints

4.2.3.1 Efficacy Endpoints

The primary efficacy objective of this study is to determine if the ORR of patients with *PD-L1* gene-altered DLBCL to pembrolizumab monotherapy is higher than that of a historical cohort of unseleted DLBCL patients. Response in this study will be assessed according to LYRIC criteria (modified from Lugano response criteria) (1). If the primary hypothesis is proven correct, then a confirmatory, retrospective radiographic review of response in each patient will be performed in collaboration with an outside vendor.

The LYRIC criteria were chosen for designating response in this clinical trial because immunotherapeutic agents such as pembrolizumab mediate anti-tumor effects by potentiating endogenous cancer-specific immune responses. Responses to immunotherapeutic agents occasionally occur in a delayed fashion - often beyond the typical time frame of that expected following treatment with classical cytotoxic agents. Furthermore, in the context of checkpoint blockade immunotherapy, clinical responses can occur even after an initial increase in tumor burden is observed, or even after the appearance of new lesions on imaging studies, due to inflammation in sites of tumor activity and in areas uninvolved by malignancy. The LYRIC criteria represent the most up-to-date consensus guidelines for response assessment of lymphomas treated with immunomodulatory agents such as pembrolizumab, and were created by international experts. Importantly, the LYRIC criteria incorporate an indeterminate response category that allows for continued treatment in clinically stable/improving patients who would otherwise be deemed to have progressive disease using conventional response criteria. This is a significant addition to standard response criteria for immune-based therapies as evidenced by a recent study of PD-1 blockade in cHL, in which 61% of patients treated beyond conventional disease progression demonstrated stable or further reduced target tumor burdens (25). Therefore, patients with an indeterminate response in the current study will be able to continue treatment with pembrolizumab if deemed appropriate by the treating physician. These patients must undergo repeat imaging within 12 weeks to either confirm that an objective tumor response has occurred, or to unequivocably document disease progression. Overall, the LYRIC criteria are anticipated to allow for a more accurate assessment of the true clinical benefit from immunotherapies such as pembrolizumab, and are now recommended to be utilized as the standard response criteria for lymphoma clinical trials incorporating immunotherapies (1).

4.2.3.2 Biomarker Research

4.2.3.2.1 Utility of *PD-L1* gene alterations to predict ORR and PFS to pembrolizumab in DLBCL. The ORR of unselected relapsed/refractory DLBCL patients to PD-1 blockade is low (33). Predictive biomarkers of response are therefore needed in order for pembrolizumab to have a clinically meaningful impact in the treatment of DLBCL. Based on our preliminary data, we hypothesize that the identification and selection of patients with *PD-L1* gene-altered DLBCLs for pembrolizumab therapy will enrich for treatment responseiveness compared to what has been observed in unselected DLBCL patients. This hypothesis is based upon our findings indicating that *PD-L1* gene-altered lymphomas are associated with robust anti-tumor immune responses. In this clinical trial, the presence of *PD-L1* gene alterations will be determined using a validated fluorescent *in-situ* hybridization (FISH) assay (Appendix 1). In order to determine the utility of

PD-L1 gene alterations to predict for response to pembrolizumab, the ORR to pembrolizumab in this study will be compared to that of a historical cohort of 40 unselected DLBCL patients treated with pembrolizumab in the KEYNOTE-013 study, where the ORR was 13%. Additionally, we will determine whether a correlation exists between the degree of *PD-L1* alteration (amplification/translocation > relative copy gain > chromosome 9 polysomy) and best overall response (BOR) and PFS, as was the case in cHL patients treated with PD-1 blockade therapy (45). Finally, as our preliminary data reveal that only ~65% of *PD-L1* altered DLBCLs are PD-L1 positive by immunohistochemistry, we will compare the ORR of DLBCLs with positive PD-L1 protein expression on malignant cells as assessed by IHC versus those with absent PD-L1 staining in order to ascertain whether PD-L1 protein expression should be considered as a companion diagnostic with FISH for *PD-L1* gene alterations to improve the positive predictive value of this biomarker moving forward.

4.2.3.2.2 Effect of tumor cell intrinsic and environmental factors on responsiveness to pembrolizumab in DLBCL. Previous studies have demonstrated an impact of both tumor cell intrinsic and environmental factors, as well as other host variables, such as the intestinal microbiome, on responsiveness to anti-PD-1 therapies in a variety of solid tumor malignancies (46-48). To determine whether these features also influence responsiveness to PD-1 blockade in DLBCL, whole exome sequencing (WES) and RNA sequencing (seq) will be performed on pre-treatment biopsies, and baseline stool samples will be collected prior to commencing study therapy with pembrolizumab. WES of tumor samples will be performed through Theragen Etex, while RNA-seq, bioinformatics analysis, and microbiome analysis will all be conducted in core facilities at The University of Chicago.

4.2.3.2.3 Feasibility of utilizing circulating tumor DNA (ctDNA) to predict early response to pembrolizumab in DLBCL, and to identify genetic mechanisms that underlie acquired resistance to therapy. The quantification of ctDNA can be a sensitive marker of response to a wide array of therapies in a number of tumor types while also providing valuable prognostic information (49, 50). Furthermore, ctDNA offers a non-invasive method of serially monitoring the clonal evolution of tumors responding to a particular therapy, and may also identify mutations or other genomic alterations associated with emerging resistance. Currently, there are no data on the use of ctDNA to monitor response, clonal evoluation or resistance to anti-PD-1 therapy, and the mechanisms of acquired resistance to pembrolizumab in DLBCL are unknown. To investigate the hypothesis that serial ctDNA monitoring will provide early response information to pembrolizumab, and will identify mutations in genes critical for maintaining immune surveillance in patients developing acquired resistance to therapy, plasma will be collected for ctDNA analysis at baseline and after every 4 cycles of therapy (in parallel with disease response assessment via conventional imaging). All ctDNA analyses will be performed using a customized lymphoma panel created at the Cancer Precision Medicine Center in the Cancer Institute of Japanese Foundation for Cancer Research.

4.2.3.3 Future Biomedical Research

It is possible that Future Biomedical Research will be conducted on blood and lymph node specimens collected during this clinical trial. This research may include genetic analyses (DNA), gene expression profiling (RNA), proteomics, metabolomics (serum, plasma), and/or the measurement of other analytes.

Such research is for biomarker testing to address emergent questions not described elsewhere in the protocol (as part of the main trial). The objective of collecting specimens for Future Biomedical Research will be to explore and identify biomarkers that inform the scientific understanding of diseases and/or their therapeutic treatments. The details of Future Biomedical Research are presented in Appendix 6 – Collection and Management of Specimens for Future Biomedical Research.

4.3 Benefit/Risk

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

Effiacy and safety information in regards to pembrolizumab are provided in the current version of the IB.

5.0 METHODOLOGY

5.1 Study Population

Relapsed/refractory DLBCL patients with evidence of *PD-L1* gene alterations (copy number alterations or translocations) as determined by FISH.

5.1.1 Participant Inclusion Criteria

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

1. Male/female participants who are at least 18 years of age on the day of signing informed consent with a histologically confirmed diagnosis of DLBCL will be enrolled in this study.

   Note: Patients with high-grade B cell lymphomas not otherwised specified and those with MYC and BCL2 translocations (double hit lymphoma) are eligible, as are patients with transformed indolent lymphoma, so long as PD-L1 gene alterations are present.

2. A male participant must agree to use a contraception as detailed in Appendix 4 of this protocol during the treatment period, and for at least 120 days after the last dose of study treatment and refrain from donating sperm during this period.
3. A female participant is eligible to participate if she is not pregnant (see Appendix 4), not breastfeeding, and at least one of the following conditions applies:

   a.) Not a woman of childbearing potential (WOCBP) as defined in Appendix 4

   b.) A WOCBP who agrees to follow the contraceptive guidance in Appendix 4 during the treatment period and for at least 120 days after the last dose of study treatment.

   C.) patient must have negative pregnancy test within 72 hours of beginning treatment if WOCBP

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

5. Have measurable disease, defined as at least one lesion that can be accurately measured in at least two dimensions by CT scan. Minimum measurement must be >15 mm in the longest diameter by >10 mm in the short axis. Lesions situated in a previously irradiated area are considered measurable if radiographic progression has been demonstrated in such lesions.

6. Particpants must have available archived biopsy material (ideally to be performed shortly before enrollment at the time of most recent relapse) for *PD-L1* FISH and correlative studies. Formalin-fixed, paraffin embedded (FFPE) tissue blocks are preferred to slides.

   Note: If submitting unstained cut slides, newly cut slides should be submitted within 14 days from the date slides are cut if possible.

7. There is evidence of a *PD-L1* gene alteration within lymphoma cells as assessed by FISH. See Appendix 1 for detailed description of what constitutes the presence of a *PD-L1* gene alteration.

8. Participants must have received either:
   a. ≥ 2 lines of prior systemic therapy
   b. ≥ 1 line of prior systemic therapy with documented comborbidities that preclude eligbility for standard salvage chemotherapy and autologous stem cell transplant , or
   c. 1 line of prior therapy with documented disease relapse within 12 months of initial diagnosis.

   Note: patients having undergone prior CAR T cell therapy are eligible, as are patients having received a prior allogeneic transplantation, provided they do not meet any of the exclusionary GVHD criteria, and are at least 5 years removed from the date of their transplant.

9. Have an Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 1. Evaluation of ECOG performance status is to be performed within 14 days prior to the date of treatment allocation.

10. Have adequate organ function as defined in Table 1 within 10 days prior to the date of treatment allocation.

Table 1. Adequate Organ Function Laboratory Values

System	**Laboratory Value**
Hematological	
Absolute neutrophil count (ANC)	≥1,000/μL

Platelets	≥50,000/μL
Hemoglobin	≥8.0 g/dL[a]
Renal	
Creatinine OR Measured or calculated[b] creatinine clearance (GFR can also be used in place of creatinine or CrCl)	≤1.5 × ULN OR ≥30 mL/min for participant with creatinine levels >1.5 × institutional ULN
Hepatic	
Total bilirubin	≤1.5 ×ULN OR direct bilirubin ≤ULN for participants with total bilirubin levels >1.5 × ULN
AST (SGOT) and ALT (SGPT)	≤2.5 × ULN (≤5 × ULN for participants with liver metastases)
Coagulation	
International normalized ratio (INR) OR prothrombin time (PT)	≤1.5 × ULN unless participant is receiving anticoagulant therapy as long as PT or aPTT is within therapeutic range of intended use of anticoagulants
Activated partial thromboplastin time (aPTT)	

5.1.2 Participant Exclusion Criteria

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

1. A WOCBP who has a positive urine pregnancy test within 72 hours prior to treatment allocation (see Appendix 3). If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required.

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

2. Has received prior therapy with an anti-PD-1, anti-PD-L1, or anti-PD-L2 agent.

3. Has received chemotherapy, monoclonal antibody therapy, or targeted small molecule therapy within 4 weeks prior to the first dose of study medication. Subjects must have recovered (≤ Grade 1) from adverse events related to a previously administered agent (patients with ≤ Grade 2 neuropathy are eligible). Subjects who have previously received CAR T cell therapy are eligible.

   Note: If a participant received major surgery, he or she must have recovered adequately from complications from the intervention prior to starting study treatment.

4. Has received prior radiotherapy within 1 week of start of study treatment. Participants must have recovered from all radiation-related toxicities, not require corticosteroids, and not have had radiation pneumonitis.

5. Has a histologic diagnosis of primary mediastinal lymphoma or gray zone lymphoma.

6. Has known active CNS lymphoma and/or lymphomatous meningitis. Participants with previously treated brain metastases may participate provided they are radiologically stable, i.e. without evidence of progression for at least 4 weeks by repeat imaging (note that the repeat imaging should be performed during study screening), clinically stable and without requirement of steroid treatment for at least 14 days prior to first dose of study treatment.

7. Has received a live vaccine within 30 days prior to the first dose of study drug. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, varicella/zoster (chicken pox), yellow fever, rabies, Bacillus Calmette–Guérin (BCG), and typhoid vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed; however, intranasal influenza vaccines (eg, FluMist®) are live attenuated vaccines and are not allowed.

8. Is currently participating in or has participated in a study of an investigational agent or has used an investigational device within 4 weeks prior to the first dose of study treatment.
9. Has a diagnosis of immunodeficiency or is receiving chronic systemic steroid therapy (in dosing exceeding 10 mg daily of prednisone equivalent) or any other form of immunosuppressive therapy within 7 days prior to the first dose of study drug. Short courses of corticosteroids will be allowed for palliation of symptoms related to lymphoma, but must be discontinued within 7 days prior to the first dose of study drug.

10. Subjects having received prior allogeneic stem cell transplant, must be at least 5 years removed from the date of their transplant. The also must have no history of severe (grade 3-4) acute GVHD, and/or current > grade 1 acute GHVD. Subjects must not have active chronic GVHD that requires active immune suppression or more than 10 mg of prednisone/day or equivalent.

11. Has a history of a solid organ transplant.

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

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

14. Has 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).

Replacement therapy (eg., thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency, etc.) is not considered a form of systemic treatment.

15. Has a history of (non-infectious) pneumonitis that required steroids or has current pneumonitis.

16. Has an active infection requiring systemic therapy.

17. Has a known history of Human Immunodeficiency Virus (HIV) infection.

18. Has a known history of Hepatitis B (defined as Hepatitis B surface antigen [HBsAg] reactive) or known active Hepatitis C virus (defined as detection of HCV RNA) infection.

19. Has a known history of active TB (Bacillus Tuberculosis).

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

21. Has known psychiatric or substance abuse disorders that would interfere with cooperation with the requirements of the trial.

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

23. Patient is in need of immediate cytoreductive therapy

5.1.3 Lifestyle Restrictions

5.1.3.1 Meals and Dietary Restrictions

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

5.1.3.2 Contraception

Pembrolizumab may have adverse effects on a fetus in utero. Refer to Appendix 4 for approved methods of contraception.

For this study, male participants will be considered to be of non-reproductive potential if they have azoospermia (whether due to prior vasectomy or to an underlying medical condition).

5.1.4 Pregnancy

If a participant inadvertently becomes pregnant while on treatment with pembrolizumab, the participant will be immediately discontinued from study treatment. The site will contact the participant at least monthly and document the participant's status until the pregnancy has been completed or terminated. The outcome of the pregnancy will be reported to Merck within 2 working days if the outcome is a serious adverse experience (eg, death, abortion, congenital anomaly, or other disabling or life-threatening complication to the mother or newborn). The study Investigator will make every effort to obtain permission to follow the outcome of the pregnancy and report the condition of the fetus or newborn to Merck. If a male participant impregnates his female partner, the study personnel at the site must be informed immediately and the pregnancy must be reported to Merck and followed as described in Section 7.2.2.

5.1.5 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, participants who are breast-feeding are not eligible for enrollment.

5.2 Trial Treatments

The treatment to be used in this trial is outlined below in Table 2

Table 2. Trial Treatment

Drug	Dose/Potency	Dose Frequency	Route of Administration	Regimen/Treatment Period	Use
Pembrolizumab	200 mg	Q3W	IV infusion	Day 1 of each 3 week cycle	Experimental

Trial treatment should begin on or as close as possible to the day of allocation.

5.2.1 Timing of Dose Administration

Trial treatment should be administered on day 1 of each cycle after all procedures/assessments have been completed as detailed on the Trial Flow Chart (Section 6.0). Trial treatment may be administered up to 3 days before or after the scheduled day 1 of each cycle due to administrative reasons.

All trial treatments will be administered on an outpatient basis.

Pembrolizumab 200 mg will be administered as a 30 minute IV infusion every 3 weeks. Sites should make every effort to target infusion timing to be as close to 30 minutes as possible. However, given the variability of infusion pumps from site to site, a window of -5 minutes and +10 minutes is permitted (i.e., infusion time is 30 minutes: -5 min/+10 min).

The Pharmacy Manual contains specific instructions for the preparation of the pembrolizumab infusion fluid and administration of infusion solution.

5.2.2 Dose Modification and toxicity management for immune-related AEs associated with pembrolizumab

AEs associated with pembrolizumab exposure may represent an immunologic etiology. These immune-related AEs (irAEs) may occur shortly after the first dose or several months after the last dose of pembrolizumab treatment and may affect more than on body system simultaneously. Therefore, early recognition and initiation of treatment is critical to reduce complications. Based on existing clinical study data, most irAEs are reversible and can be managed with interruptions of pembrolizumab, administration of corticosteroids and/or other supportive care. For suspected irAEs, ensure adequate evaluation to confirm etiology or exclude other causes. Additional procedures or tests such as bronchoscopy, endoscopy, skin biopsy may be included as part of the evaluation. Based on the severity of irAEs, withhold or permanently discontinue pembrolizumab and administer corticosteroids. Dose modification and toxicity management guidelines for irAEs associated with pembrolizumab are provided in Table 3.

Table 3 Dose modification and toxicity management guidelines for immune-related AEs associated with pembrolizumab

General instructions:

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

irAEs	Toxicity Grade (CTCAE v5.0)	Action With Pembrolizumab	Corticosteroid and/or Other Therapies	Monitoring and Follow-up
Pneumonitis	Grade 2	Withhold	• Administer corticosteroids (initial dose of 1 to 2 mg/kg prednisone or equivalent) followed by taper • Add prophylactic antibiotics for opportunistic infections	• Monitor participants for signs and symptoms of pneumonitis • Evaluate participants with suspected pneumonitis with radiographic imaging and initiate corticosteroid treatment
	Recurrent Grade 2, Grade 3 or 4	Permanently discontinue		
Diarrhea/Colitis	Grade 2 or 3	Withhold	• Administer corticosteroids (initial dose of 1 to 2 mg/kg prednisone or equivalent) followed by taper	• Monitor participants for signs and symptoms of enterocolitis (ie, diarrhea, abdominal pain, blood or mucus in stool with or without fever)

irAEs	Toxicity Grade (CTCAE v5.0)	Action With Pembrolizumab	Corticosteroid and/or Other Therapies	Monitoring and Follow-up
	Recurrent Grade 3 or Grade 4	Permanently discontinue		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
AST or ALT Elevation or Increased Bilirubin	Grade 2 [a]	Withhold	• Administer corticosteroids (initial dose of 0.5 to 1 mg/kg prednisone or equivalent) followed by taper	• Monitor with liver function tests (consider weekly or more frequently until liver enzyme value returned to baseline or is stable)
	Grade 3 [b] or 4 [c]	Permanently discontinue	• Administer corticosteroids (initial dose of 1 to 2 mg/kg prednisone or equivalent) followed by taper	
T1DM or Hyperglycemia	New onset T1DM or Grade 3 or 4 hyperglycemia associated with	Withhold [d]	• Initiate insulin replacement therapy for participants with T1DM	• Monitor participants for hyperglycemia or other signs and symptoms of diabetes

irAEs	Toxicity Grade (CTCAE v5.0)	Action With Pembrolizumab	Corticosteroid and/or Other Therapies	Monitoring and Follow-up
	evidence of β-cell failure		• Administer antihyperglycemic in participants with hyperglycemia	
Hypophysitis	Grade 2	Withhold	• Administer corticosteroids and initiate hormonal replacements as clinically indicated	• Monitor for signs and symptoms of hypophysitis (including hypopituitarism and adrenal insufficiency)
	Grade 3 or 4	Withhold or permanently discontinue [d]		
Hyperthyroidism	Grade 2	Continue	• Treat with nonselective beta-blockers (eg, propranolol) or thionamides as appropriate	• Monitor for signs and symptoms of thyroid disorders
	Grade 3 or 4	Withhold or permanently discontinue [d]		
Hypothyroidism	Grade 2, 3 or 4	Continue	• Initiate thyroid replacement hormones (eg, levothyroxine or liothyronine) per standard of care	• Monitor for signs and symptoms of thyroid disorders
Nephritis: grading according to increased creatinine or acute kidney injury	Grade 2	Withhold	• Administer corticosteroids (prednisone 1 to 2 mg/kg or equivalent) followed by taper	• Monitor changes of renal function
	Grade 3 or 4	Permanently discontinue		
	Grade 2	Withhold		

irAEs	Toxicity Grade (CTCAE v5.0)	Action With Pembrolizumab	Corticosteroid and/or Other Therapies	Monitoring and Follow-up
Neurological Toxicities	Grade 3 or 4	Permanently discontinue	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology and/or exclude other causes
Myocarditis	Grade 1	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 2, 3 or 4	Permanently discontinue		
Exfoliative Dermatologic Conditions	Suspected SJS, TEN, or DRESS	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology or exclude other causes
	Confirmed SJS, TEN, or DRESS	Permanently discontinue		
All Other irAEs	Persistent Grade 2	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology or exclude other causes
	Grade 3	Withhold or discontinue based on the event [e]		
	Recurrent Grade 3 or Grade 4	Permanently discontinue		

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

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

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

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

irAEs	Toxicity Grade (CTCAE v5.0)	Action With Pembrolizumab	Corticosteroid and/or Other Therapies	Monitoring and Follow-up
[c] AST/ALT: >20.0 x ULN, if baseline normal; >20.0 x baseline, if baseline abnormal; bilirubin: >10.0 x ULN if baseline normal; >10.0 x baseline if baseline abnormal [d] The decision to withhold or permanently discontinue pembrolizumab is at the discretion of the investigator or treating physician. If control achieved or ≤ Grade 2, pembrolizumab may be resumed. [e] Events that require discontinuation include, but are not limited to: encephalitis and other clinically important irAEs (eg, vasculitis and sclerosing cholangitis).				

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

Pembrolizumab may cause severe or life threatening infusion-reactions including severe hypersensitivity or anaphylaxis. Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion. Dose modification and toxicity management guidelines on pembrolizumab associated infusion reaction are provided in Table 4.

Table 4 Pembrolizumab Infusion Reaction Dose modification and Treatment Guidelines

NCI CTCAE Grade	Treatment	Premedication at Subsequent Dosing
Grade 1 Mild reaction; infusion interruption not indicated; intervention not indicated	Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator.	None
Grade 2 Requires therapy or infusion interruption but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for ≤24 hrs	**Stop Infusion.** Additional appropriate medical therapy may include but is not limited to: IV fluids Antihistamines NSAIDs Acetaminophen Narcotics Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator. If symptoms resolve within 1 hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (e.g. from 100 mL/hr to 50 mL/hr). Otherwise dosing will be held until symptoms resolve and the participant should be premedicated for the next scheduled dose. **Participants who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further study drug treatment**	Participant may be premedicated 1.5h (± 30 minutes) prior to infusion of _____ with: Diphenhydramine 50 mg po (or equivalent dose of antihistamine). Acetaminophen 500-1000 mg po (or equivalent dose of analgesic).
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: Epinephrine** IV fluids Antihistamines NSAIDs Acetaminophen Narcotics Oxygen Pressors Corticosteroids Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator. Hospitalization may be indicated. **In cases of anaphylaxis, epinephrine should be used immediately. **Participant is permanently discontinued from further study drug treatment.**	No subsequent dosing

Appropriate resuscitation equipment should be available at the bedside and a physician readily available during the period of drug administration.
For further information, please refer to the Common Terminology Criteria for Adverse Events v4.0 (CTCAE) at http://ctep.cancer.gov

Other allowed dose interruption for pembrolizumab

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

5.2.3 Second Course *

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

Either

- Stopped initial treatment with study treatment after attaining an investigator-determined confirmed CR, and
  - Was treated with at least 8 cycles of study treatment before discontinuing treatment, and
  - Received at least 2 treatments with pembrolizumab beyond the date when the initial CR was declared

OR

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

AND

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

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

**Note: patients must have measurable disease at the start of protocol treatment to be eligible for this provision.*

5.3 Randomization or Treatment Allocation

Subjects participating in this trial will be allocated to trial treatment by non-random assignement.

5.4 Stratification

No stratification will be used in this trial.

5.5 Concomitant Medications/Vaccinations (allowed & prohibited)

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 final decision on any supportive therapy or vaccination rests with the investigator and/or the participants's primary physician.

5.5.1 Acceptable Concomitant Medications

All treatments that the investigator considers necessary for a participant's welfare may be administered at the discretion of the investigator in keeping with the 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 30 days after the last dose of trial treatment should be recorded. Concomitant medications administered after 30 days after the last dose of trial treatment should be recorded for SAEs and ECIs as defined in Section 7.2.

5.5.2 Prohibited Concomitant Medications

Parcticipants are prohibited from receiving the following therapies during the screening and treatment phase of this trial:

- Anti-neoplastic biological therapy
- Immunotherapy not specified in this protocol
- Chemotherapy
- Investigational agents other than pembrolizumab
- Radiation therapy

  - Note: Radiation therapy to a symptomatic solitary lesion may be allowed at the investigator's discretion, provided that study treatment is initiated at least 7 days after completion of all palliative radiation..

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

- Systemic glucocorticoids for any purpose other than to modulate symptoms from an immune-related adverse event, or the use of palliative glucocorticoids during the screening phase of the study (steroids however must be discontinued within 7 days of the first dose of pembrolizumab treatment). The use of physiologic doses of corticosteroids may be approved after consultation with the sponsor.

Participants who, in the assessment by the investigator, require the use of any of the aforementioned treatments for clinical management should be removed from the study. All treatments that the investigator considers necessary for a participant's welfare may be administered at the discretion of the investigator in keeping with the standards of medical care.

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

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

5.5.3 Rescue Medications & Supportive Care

Participants should receive appropriate supportive care measures as deemed necessary by the treating investigator. Suggested supportive care measures for the management of AEs with potential immunologic etiology are outlined along with the dose modification guidelines in Section 5.2.2, [Table 3]. Where appropriate, these guidelines include the use of oral or IV treatment with corticosteroids, as well as additional anti-inflammatory agents if symptoms do not improve with administration of corticosteroids. Note that several courses of steroid tapering may be necessary as symptoms may worsen when the steroid dose is decreased. For each disorder, attempts should be made to rule out other causes such as metastatic disease or bacterial or viral infection, which might require additional supportive care. The treatment guidelines are intended to be applied when the investigator determines the events to be related to pembrolizumab.

Note: If after the evaluation of the event, it is determined not to be related to pembrolizumab, the investigator does not need to follow the treatment guidance. Refer to [Table 3] in Section 5.2.2 for guidelines regarding dose modification and supportive care.

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

5.6 Participant Withdrawal/Discontinuation Criteria

Participants may discontinue study treatment at any time for any reason, and may also be discontinued from study treatment at the discretion of the investigator should any untoward effect occur. In addition, a participant may be discontinued from study treatment by the investigator or sponsor if study treatment is inappropriate, the trial plan is violated, or for administrative and/or other safety reasons. Specific details regarding procedures to be performed at study treatment discontinuation are provided in Section 7.1.4 – Other Procedures.

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

- The participant or participant's legally acceptable representative requests to discontinue study treatment
- Confirmed radiographic disease progression outlined in Section 7.1.2.6
- Any progression or recurrence of any malignancy, or any occurrence of another malignancy that requires active treatment
- Unacceptable adverse events as described in Section 5.2.2
- The participant has a medical condition or personal circumstance which, in the opinion of the investigator and/or sponsor, placed the participant at unnecessary risk from continued administration of study treatment.
- The participant has a confirmed positive serum pregnancy test
- Noncompliance with study treatment or procedure requirements
- Recurrent Grade 2 pneumonitis
- Discontinuation of treatment may be considered for participants who have attained a confirmed complete response (CR) and have been treated for at least 8 cycles (at least 24 weeks), receiving at least 2 doses of pembrolizumab beyond the date when the initial CR was declared. These participants may be eligible for second course treatment described in Section 5.2.3.
- The participant is lost to follow-up
- Completion of 35 treatments (approximately 2 years) with pembrolizumab

Note: The number of treatments is calculated starting with the first dose. Participants who stop the combination or pembrolizumab after receiving 35 doses may be eligible for retreatment if they progress after stopping study treatment provided they meet the requirements detailed in Section 5.2.3. Participants may be retreated in the Second Course Phase (Retreatment) for up to an additional 17 cycles (approximately 1 year).

- Administrative reasons

5.7 Participant Replacement Strategy

Subjects may be replaced in the trial as needed to ensure that the required number of evaluable subjects is achieved for the desiginated statistical analyses as put forth in section 8.0.

5.8 Criteria for Early Trial Termination

Early trial termination will be the result of the criteria specified below:

1. Quality or quantity of data recording is inaccurate or incomplete
2. Poor adherence to protocol and regulatory requirements
3. Incidence or severity of adverse drug reaction in this or other studies indicates a potential health hazard to participants
4. Plans to modify or discontinue the development of the study drug
5. The ORR does not meet stated hypothesis upon completion of the first phase of the study (< 3/13 responders)

In the event that Merck decides to no longer supply study drug, ample notification will be provided so that appropriate adjustments to participant treatment can be made.

6.0 TRIAL FLOW CHART

6.1 Study Flow Chart

Trial Period:	**Screening Phase**		**Treatment Cycles[a]**								**End of Treatment**	**Post-Treatment**		
Treatment Cycle/Title:	Pre-screening (Visit 1)	Main Study Screening (Visit 2)	1	2	3	4	To be repeated beyond 8 cycles: 5	6	7	8	Discon	Safety Follow-up	Follow Up Visits	Survival Follow-Up
Scheduling Window (Days):	-28 to -11	-10 to -1		± 3	± 3	± 3	± 3	± 3	± 3	± 3	At time of Discon	30 days post discon	Every 12 weeks post discon	Every 12 weeks
Administrative Procedures														
Pre-screening Consent	X													
Informed Consent		X												
Inclusion/Exclusion Criteria		X												
Demographics and Medical History		X												
Prior and Concomitant Medication Review		X	X	X	X	X	X	X	X	X	X	X		
Trial Treatment Administration			X	X	X	X	X	X	X	X				
Post-study anticancer therapy status													X	
Survival Status														X
Clinical Procedures/Assessments														
Review Adverse Events		X	X	X	X	X	X	X	X	X	X	X		
Full Physical Examination		X	X	X	X		X		X		X	X		
Directed Physical Examination						X		X		X				
Vital Signs and Weight		X	X	X	X	X	X	X	X	X	X	X		
ECOG Performance Status		X	X	X	X	X	X	X	X	X	X	X		
Laboratory Procedures/Assessments: analysis performed by LOCAL laboratory														
Pregnancy Test – Urine or Serum β-HCG[a]		X												
CBC with Differential		X	X	X	X	X	X	X	X	X	X	X		
Comprehensive Serum Chemistry Panel		X	X	X	X	X	X	X	X	X	X	X		

Trial Period:	**Screening Phase**		**Treatment Cycles[a]**								**End of Treatment**	**Post-Treatment**		
							To be repeated beyond 8 cycles							
Treatment Cycle/Title:	Pre-screening (Visit 1)	Main Study Screening (Visit 2)	1	2	3	4	5	6	7	8	Discon	Safety Follow-up	Follow Up Visits	Survival Follow-Up
Scheduling Window (Days):	-28 to -11	-10 to -1		± 3	± 3	± 3	± 3	± 3	± 3	± 3	At time of Discon	30 days post discon	Every 12 weeks post discon	Every 12 weeks
LDH		X	X	X	X	X	X	X	X	X	X			
Urinalysis		X					X				X	X		
TSH		X			X		X				X	X		
Efficacy Measurements														
Tumor Imaging and bone marrow exam[b]		X[b]				X				X	X			
Tumor Biopsies/Archival Tissue Collection/Correlative Studies Blood														
PD-L1 FISH Assessment	X													
Archival or Newly Obtained Tissue Collection		X									X[c]			
Correlative Studies Blood Collection		X		X			X				X			
Baseline Stool Collection		X												

[a] For women of reproductive potential, a urine pregnancy test will be performed within 72 hours prior to the first dose of trial treatment. If urine pregnancy results cannot be confirmed as negative, a serum pregnancy test will be required (performed by the local study site laboratory).

[b]Tumor imaging to consist of a PET scan and diagnostic CT scans of neck, chest, abdomen, and pelvis. Scans performed within 28 days of treatment allocation will be allowable. Bone marrow biopsy to also be performed at times of tumor imaging for patients with baseline involvement (this does not need to be performed for patients with clear progression on diagnostic imaging, and does not need to be repeated for patients with documented bone marrow clearance unless otherwise clinically indicated).

[c]A new biopsy will be performed whenever possible for patients developing progressive disease.

7.0 TRIAL PROCEDURES

7.1 Trial Procedures

The Trial Flow Chart - Section 6.0 summarizes the trial procedures to be performed at each visit. Individual trial procedures are described in detail below. It may be necessary to perform these procedures at unscheduled time points if deemed clinically necessary by the investigator.

Furthermore, additional evaluations/testing may be deemed necessary by the sponsor for reasons related to participant safety. In some cases, such evaluation/testing may be potentially sensitive in nature (e.g., HIV, Hepatitis C, etc.), and thus local regulations may require that additional informed consent be obtained from the participant. In these cases, such evaluations/testing will be performed in accordance with those regulations.

7.1.1 Administrative Procedures

7.1.1.1 Informed Consent

The investigator must obtain documented consent from each potential participant prior to participating in the clinical trial.

7.1.1.1.1 General Informed Consent

Consent (both pre-screening and screening consent forms) must be documented by the participant's dated signature or by the participant's legally acceptable representative's dated signature on a consent form along with the dated signature of the person conducting the consent discussion.

A copy of the signed and dated consent form should be given to the participant before participation in the trial.

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

Specifics about a trial and the trial population will be added to the consent form template at the protocol level.

The informed consent will adhere to IRB/ERC requirements, applicable laws and regulations and Sponsor requirements.

7.1.1.2 Inclusion/Exclusion Criteria

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

7.1.1.3 Medical History

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

7.1.1.4 Prior and Concomitant Medications Review

7.1.1.4.1 Prior Medications

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

7.1.1.4.2 Concomitant Medications

The investigator or qualified designee will record medication, if any, taken by the participant during the trial. All medications related to reportable SAEs and ECIs should be recorded as defined in Section 7.2.

7.1.1.5 Disease Details and Treatments

7.1.1.5.1 Disease Details

The investigator or qualified designee will obtain prior and current details regarding disease status.

7.1.1.5.2 Prior Treatment Details

The investigator or qualified designee will review all prior cancer treatments, including systemic treatments, radiation and surgeries.

7.1.1.5.3 Subsequent Anti-Cancer Therapy Status

The investigator or qualified designee will review all new anti-neoplastic therapy initiated after the last dose of trial treatment. If a participant 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 participant will move into survival follow-up.

7.1.1.6 Assignment of Screening Number

All consented subjects will be assigned a unique screening number that will be used to identify the subject for all procedures that occur prior to treatment allocation. Each subject will be assigned only one screening number. Screening numbers must not be re-used for different subjects. Any subject who is screened multiple times will retain the original screening number assigned at the initial screening visit.

7.1.1.7 Assignment of Randomization Number

All eligible subjects will be allocated, by non-random assignment, to trial treatment and will receive a unique treatment allocation number. The allocation number identifies the subject for all procedures. This unique number is termed an allocation number throughout the protocol for operational purposes. Once an allocation number is assigned to a subject, it can never be re-assigned to another subject. A subject cannot be assigned more than 1 allocation number.

7.1.1.8 Trial Compliance (Medication/Diet/Activity/Other)

Interruptions from the protocol specified treatment plan for > 12 weeks between doses of pembrolizumab due to toxicity require consultation between the investigator and the sponsor and written documentation of the collaborative decision on subject management.

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

The instructions for preparing and administering pembrolizumab will be provided in the Pharmacy Manual.

7.1.2 Clinical Procedures/Assessments

7.1.2.1 Adverse Event (AE) Monitoring

The investigator or qualified designee will assess each participant to evaluate for potential new or worsening AEs as specified in the Trial Flow Chart and more frequently if clinically indicated. Adverse experiences will be graded and recorded throughout the study and during the follow-up period according to NCI CTCAE Version 4.0 (see Appendix 2). Toxicities will be characterized in terms regarding seriousness, causality, toxicity grading, and action taken with regard to trial treatment.

Please refer to section 7.2 for detailed information regarding the assessment and recording of AEs.

7.1.2.2 Full Physical Exam

The investigator or qualified designee will perform a complete physical exam during the screening period. Clinically significant abnormal findings should be recorded as medical history. A full physical exam should be performed during screening,

7.1.2.3 Directed Physical Exam

For cycles that do not require a full physical exam per the Trial Flow Chart, the investigator or qualified designee will perform a directed physical exam as clinically indicated prior to trial treatment administration.

7.1.2.4 Vital Signs

The investigator or qualified designee will take vital signs at screening, prior to the administration of each dose of trial treatment and at treatment discontinuation as specified in the Trial Flow Chart (Section 6.0). Vital signs should include temperature, pulse, respiratory rate, weight and blood pressure. Height will be measured at screening only.

7.1.2.5 Eastern Cooperative Oncology Group (ECOG) Performance Scale

The investigator or qualified designee will assess ECOG status (Appendix 2) at screening, prior to the administration of each dose of trial treatment, and at discontinuation of trial treatment as specified in the Trial Flow Chart.

7.1.2.6 Tumor Imaging and Assessment of Disease

Tumor imaging will include positron emission tomography (PET) with combined diagnostic quality computed tomography (CT) scans throughout the study. For the abdomen and pelvis, contrast-enhanced magnetic resonance imaging (MRI) may be used when CT with iodinated contrast is contraindicated, or when local practice mandates it. The same imaging technique regarding modality, ideally the same scanner, and the use of contrast should be used in a participant throughout the study to optimize the reproducibility of the assessment of existing and new tumor burden and improve the accuracy of the assessment of response or progression based on imaging.

Local reading (investigator assessment with site radiology reading) will be used in determining subject eligibility and response. Response to pembrolizumab will be evaluated using LYRIC response criteria (1). The sponsor will also receive radiologic images if the primary efficacy endpoint of the trial is met in order to retrospectively confirm subject eligibility and treatment response through a contracted centralized vendor.

7.1.2.6.1 Initial Tumor Imaging

Initial tumor imaging performed at screening must be conducted within 28 days prior to the date of treatment allocation, and consist of both PET and diagnostic CT scans of the neck, chest, abdomen and pelvis. The site study team must review screening images to confirm the participant has measurable disease as defined in the inclusion criteria. The baseline imaging scans must also be submitted to the central imaging vendor for a retrospective analysis of this eligbility criterion if the primary efficacy objective is met.

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

7.1.2.6.2 Tumor Imaging During the Study

Imaging assessments with PET and diagnostic CT scans will be performed after every 4 cycles (12 weeks ±7 days)) of therapy. Imaging timing should follow calendar days and should not be adjusted for delays in cycle starts. During the first 2 years of the study, imaging should continue to be performed until documented disease progression, the start of new anti-cancer treatment, withdrawal of consent, death, or the end of study, whichever comes first. After 2 years on study, further imaging is to be performed at the discretion of the treating physician. See Section 7.1.2.6.4 for confirmation assessment requirements when a subject's disease response assessment shows an indeterminate response according to the LYRIC reposnse criteria.

7.1.2.6.3 End of Treatment and Follow-up Tumor Imaging

In participants who discontinue study treatment, tumor imaging should be performed at the time of treatment discontinuation (±4 week window). If previous imaging was obtained within 4 weeks prior to the date of discontinuation, then imaging at treatment discontinuation is not mandatory. In participants who discontinue study treatment due to documented disease progression, no further tumor imaging in the context of this trial is required.

In participants who discontinue study treatment without documented disease progression, every effort should be made to continue monitoring their disease status by tumor imaging using the same imaging schedule used while receiving study treatment (every 12 weeks for up to 2 years) to monitor disease status until the start of a new anticancer treatment, disease progression, pregnancy, death, withdrawal of consent, or the end of the study, whichever occurs first.

7.1.2.6.4 Confirmation Assessments

Because subjects treated with PD-1 blocking antibodies may have pseudoprogression of disease (there is progression on imaging per conventional response criteria, but the subject is clinically stable or improving), confirmation of progression should be performed in patients having an indeterminate response as defined by the LYRIC criteria (1). Specifically, all patients having an indeterminate response can be continued on therapy at the discretion of the treating investigator. However, repeat imaging must be performed within 12 weeks to either confirm or refute the presence of true disease progression.

Clinical stability may be defined as:

1) Absence of symptoms and signs indicating clinically significant progression of disease (including worsening of laboratory values)

2) No decline in ECOG performance status

3) Absence of rapid progression of disease or progressive tumor at critical anatomatical sites (e.g. cord compression) requiring urgent medical intervention

If progression is confirmed on repeat imaging without an intervening response, then the subject will be discontinued from trial treatment, and the initial indeterminate response will be recategorized as disease progression as outlined in the LYRIC criteria (1). If progression is not confirmed, then the subject should continue trial treatment until disease progression is documented following the pre-determined response assessment dates outlined in the Trial Flow Chart (see Section 6.0). Where appropriate, subjects should not be discontinued from study treatment with pembrolizumab until progression is confirmed. However, the decision to continue or discontinue study treatment in the case of an intermediate response is that of the treating physician.

7.1.2.6.5 Tumor Tissue Collection and Correlative Studies Sampling

All subjects enrolled into this study must be able to provide an archived FFPE biopsy sample or preferrably a newly-obtained core needle or excisional biopsy (FNA is not adequate) to be submitted for characterization through the research collaborations organized by the principal investigator.

Serial blood and baseline stool specimens will be collected as documented in the Trial Flow Chart (Section 6.0) for additional exploratory analyses. The specific protocols for collecting serial blood and baseline stool samples is outlined in greater detail in the accompanying lab manual. Briefly however, blood will be compartmentalized into plasma, serum, and peripheral blood mononuclear cells on-site within 2 hours of sample collection and will be shipped to The University of Chicago Human Tissue Resource Center for long-term storage. Germline DNA will also be extracted from peripheral blood to provide a paired normal reference for tumor whole exome sequencing. Correlative blood samples should be obtained at the time of routine blood specimens drawn for the main trial whenever possible. Baseline stool sampling will be obtained using a home stool collection kit. Once stool has been collected at home, the kit can either be returned by the patient at their next clinic appointment or shipped directly to The University of Chicago Microbiome Core Facility using the attached return address information.

7.1.3 Laboratory Procedures/Assessments

Details regarding specific laboratory procedures/assessments to be performed in this trial are provided below.

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

Laboratory tests for hematology, chemistry, urinalysis, and others are specified in Table 5.

Table 5. Laboratory Tests

Hematology	**Chemistry**	**Urinalysis**	**Other**
Hematocrit	Albumin	Blood	Serum β-human chorionic gonadotropin†
Hemoglobin	Alkaline phosphatase	Glucose	(β-hCG)†
Platelet count	Alanine aminotransferase (ALT)	Protein	Thyroid stimulating hormone (TSH)
WBC (total and differential)	Aspartate aminotransferase (AST)	Specific gravity	Blood for correlative studies
Red Blood Cell Count	Lactate dehydrogenase (LDH)	Microscopic exam *(If abnormal)*	
Absolute Neutrophil Count	Carbon Dioxide ‡	Urine pregnancy test †	
Absolute Lymphocyte Count	*(CO_2 or biocarbonate)*		
	Uric Acid		
	Calcium		
	Chloride		
	Glucose		
	Potassium		
	Sodium		
	Total Bilirubin		
	Direct Bilirubin *(If total bilirubin is elevated above the upper limit of normal)*		
	Total protein		
	Blood Urea Nitrogen		

† Perform on women of childbearing potential only. If urine pregnancy results cannot be confirmed as negative, a serum pregnancy test will be required.

‡ If considered standard of care in your region.

Laboratory tests for the initial screening phase should be performed within 10 days prior to the first dose of treatment. After cycle 1, pre-dose laboratory procedures can be conducted up to 72 hours prior to dosing. Results must be reviewed by the investigator or qualified designee and found to be acceptable prior to each dose of trial treatment.

7.1.3.2 Correlative and Future Biomedical Research

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

- Blood and plasma for genomic and transcriptomic analyses
- Archived and leftover FFPE lymph node biopsy specimens
- Stool for microbiome analyses

7.1.4 Other Procedures

7.1.4.1 Withdrawal/Discontinuation

When a participant discontinues/withdraws prior to trial completion, all applicable activities scheduled for the final trial visit should be performed at the time of discontinuation. Any adverse events which are present at the time of discontinuation/withdrawal should be followed in accordance with the safety requirements outlined in Section 7.2 - Assessing and Recording Adverse Events. Participants who a) attain a CR or b) complete 24 months of treatment with pembrolizumab may discontinue treatment with the option of restarting treatment if they meet the criteria specified in Section 5.2.3. After discontinuing treatment following assessment of CR, these participants should return to the site for a Safety Follow-up Visit (described in Section 7.1.5.3.1) and then proceed to the Follow-Up Period of the study (described in Section 7.1.5.3.2).

7.1.4.1.1 Withdrawal From Correlative Biomedical Research

Subjects may withdraw their consent for Correlative Biomedical Research and have their specimens and all derivatives destroyed. Subjects may withdraw consent at any time by writing the principal investigator for the main trial. Subsequently, the subject's specimens will be removed from the biorepository and will be destroyed. Any analyses in progress at the time of request for destruction or already perofmed prior to the request being received by the sponsor will continue to be used as part of the overall research trial data and results. No new analyses would be generated after the request is received.

In the event that the specimens have been completely anonymized, there will no longer be a link between the subject's personal information and their specimens. In this situation, the request for specimen destruction cannot be processed.

7.1.4.2 Blinding/Unblinding

This is an open label trial and therefore there will be no patient blinding.

7.1.5 Visit Requirements

Visit requirements are outlined in Section 6.0 - Trial Flow Chart. Specific procedure-related details are provided above in Section 7.1 - Trial Procedures.

7.1.5.1 Pre-screening and Screening Phases

Approximately 28 days prior to enrollment, potential subjects interested in participating in the study will sign a pre-screening informed consent during a clinic visit. Pre-screening will then consist of a brief review of medical history to determine potential eligibility, and an evaluation for the presence of a *PD-L1* gene alteration using FISH on archived FFPE tissue (ideally obtained at the time of most recent relapse). All FISH procedures will be performed at The University of Chicago or at City of Hope using a previously validated technique (Appendix 1).

Patients fulfilling pre-screening criteria will then provide screening informed consent in order to proceed to the screening phase to determine full eligibility as set forth in Section 5.1. This will consist of a physical examination, assessment of performance status, evaluation of hematology and chemistry parameters, and a baseline evaluation of disease status using results from positron emission tomography (PET) and diagnostic computerized tomography (CT) scans (a bone marrow exam will also be performed for patients with a history of prior bone marrow involvement).

Written consent must be obtained prior to both the pre-screening and screening phases in order for a protocol specific procedure to be performed. Results of a test conducted prior to the subject signing consent as part of routine clinical management are acceptable in lieu of a screening test if performed within the specified time frame. Screening procedures are to be completed within 14 days prior to the first dose of trial treatment except for the following:

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

- Tumor imaging performed as part of routine clinical management is acceptable for use as baseline scans if they are of diagnostic quality and performed within 28 days of treatment allocation.

Subjects may be re-screened after initially failing to meet the inclusion/exclusion criteria. Results from assessments performed during the initial screening period are acceptable in lieu of a repeat screening test if performed within the specified time frame and the incusion/exclusion criteria is met. When re-screening is performed, the initially assigned screening number will be utilized.

7.1.5.2 Treatment Period

Visit requirements are outlined in Section 6.0 – Trial Flow Chart.

7.1.5.3 Post-Treatment Visits

7.1.5.3.1 Safety Follow-Up Visit

The mandatory Safety Follow-Up Visit should be conducted approximately 30 days after the last dose of study 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. Participants 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-cancer therapy, whichever occurs first. SAEs that occur within 90 days of the end of treatment or before initiation of a new anti-cancer treatment should also be followed and recorded. Participants who are eligible for retreatment/crossover with pembrolizumab (as described in Section 5.2.3) may have up to two safety follow-up visits, one after the Initial Treatment Period and one after the Second Course Treatment.

7.1.5.4 Follow-up Visits

Participants who discontinue study treatment for a reason other than disease progression will move into the Follow-Up Phase and should be assessed every 12 weeks (84 ± 7 days) by radiologic imaging to monitor disease status for up to 2 years. Every effort should be made to collect information regarding disease status until the start of new anti-cancer therapy, disease progression, death, end of the study or if the participant begins retreatment with pembrolizumab as detailed in Section 5.2.3. Information regarding post-study anti-cancer treatment will be collected if new treatment is initiated.

Participants who are eligible to receive retreatment with pembrolizumab according to the criteria in Section 5.2.3 will move from the follow-up phase to the Second Course Phase when they experience disease progression.

7.1.5.4.1 Survival Follow-up

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

7.2 Assessing and Recording Adverse Events

An adverse event is defined as any untoward medical occurrence in a patient or clinical investigation participant administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product or protocol-specified procedure, whether or not considered related to the medicinal product or protocol-specified procedure. Any worsening (i.e., any clinically significant adverse change in frequency and/or intensity) of a pre-existing condition that is temporally associated with the use of the Merck’s product, is also an adverse event.

Changes resulting from normal growth and development that do not vary significantly in frequency or severity from expected levels are not to be considered adverse events. Examples of this may include, but are not limited to, teething, typical crying in infants and children and onset of menses or menopause occurring at a physiologically appropriate time.

Merck product includes any pharmaceutical product, biological product, device, diagnostic agent or protocol-specified procedure, whether investigational (including placebo or active comparator medication) or marketed, manufactured by, licensed by, provided by or distributed by Merck for human use.

Adverse events may occur during the course of the use of Merck product in clinical trials, or as prescribed in clinical practice, from overdose (whether accidental or intentional), from abuse and from withdrawal.

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

● All AEs from the time of treatment allocation through 30 days following cessation of study treatment must be reported by the investigator.

● All AEs meeting serious criteria, from the time of treatment allocation through 90 days following cessation of study treatment, or 30 days following cessation of study treatment if the participant initiates new anti-cancer therapy, whichever is earlier must be reported by the investigator.

● All pregnancies and exposure during breastfeeding, from the time of treatment allocation/randomization through 120 days following cessation of study treatment, or 30 days following cessation of study treatment if the participant initiates new anti-cancer therapy must be reported by the investigator.

● Additionally, any SAE brought to the attention of an investigator at any time outside of the time period specified above must be reported immediately by the investigator if the event is considered to be drug-related.

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

7.2.1 Definition of an Overdose for This Protocol and Reporting of Overdose to the Sponsor and to Merck

For purposes of this study, an overdose of pembrolizumab will be defined as any dose of 1,000 mg or greater (≥5 times the indicated dose). No specific information is available on the

treatment of overdose of pembrolizumab. In the event of overdose, the participant should be observed closely for signs of toxicity. Appropriate supportive treatment should be provided if clinically indicated.

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."

All reports of overdose with and without an adverse event must be reported within 24 hours to the Sponsor and within 2 working days hours to Merck Global Safety. (Attn: Worldwide Product Safety; FAX 215-661-6229)

7.2.2 Reporting of Pregnancy and Lactation to the Sponsor and to Merck

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

Pregnancies and infant exposures during breastfeeding that occur after the consent form is signed but before treatment allocation/randomization must be reported by the investigator if they cause the participant 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, placebo treatment or a procedure.

Pregnancies and infant exposures during breastfeeding that occur from the time of treatment allocation/randomization through 120 days following cessation of Sponsor's product, or 30 days following cessation of treatment if the participant 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 24 hours to the Sponsor and within 2 working days to Merck Global Safety. (Attn: Worldwide Product Safety; FAX 215-661-6229)

7.2.3 Immediate Reporting of Adverse Events to the Sponsor and to Merck

7.2.3.1 Serious Adverse Events

A serious adverse event is any adverse event occurring at any dose or during any use of Merck's product that:

- Results in death

- Is life threatening
- Results in persistent or significant disability/incapacity
- Results in or prolongs an existing inpatient hospitalization
- Is a congenital anomaly/birth defect
- Is an other important medical event
- **Note:** In addition to the above criteria, adverse events meeting either of the below criteria, although not serious per ICH definition, are reportable to the Merck in the same timeframe as SAEs to meet certain local requirements. Therefore, these events are considered serious by Merck for collection purposes.
- Is a new cancer (that is not a condition of the study)
- Is associated with an overdose.

Refer to Table 6 for additional details regarding each of the above criteria.

For the time period beginning when the consent form is signed until treatment allocation/randomization, any serious adverse event, or follow up to a serious adverse event, including death due to any cause that occurs to any participant must be reported within 24 hours to the Sponsor and within 2 working days to Merck Global Safety if it causes the participant to be excluded from the trial, or is the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure.

For the time period beginning at treatment allocation/randomization through 90 days following cessation of treatment, or 30 days following cessation of treatment if the participant 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 whether or not related to the Merck product, must be reported within 24 hours to the Sponsor and 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.

All participants 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: +1-215-661-6229

A copy of all 15 Day Reports and Annual Progress Reports is submitted as required by FDA, European Union (EU), Pharmaceutical and Medical Devices agency (PMDA) or other local

regulators. Investigators will cross reference this submission according to local regulations to the Merck Investigational Compound Number (IND, CSA, etc.) at the time of submission. Additionally investigators will submit a copy of these reports to Merck & Co., Inc. (Attn: Worldwide Product Safety; FAX 215-661-6229) at the time of submission to FDA.

7.2.3.2 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 215-661-6229).

For the time period beginning when the consent form is signed until treatment allocation/randomization, any ECI, or follow up to an ECI, that occurs to any participant must be reported within 2 working days to Merck Global Safety if it causes the participant to be excluded from the trial, or is the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure.

For the time period beginning at treatment allocation/randomization through 90 days following cessation of treatment, or 30 days following cessation of treatment if the participant initiates new anticancer therapy, whichever is earlier, any ECI, or follow up to an ECI, whether or not related to Merck product, must be reported within 2 working days to Merck Global Safety.

Events of clinical interest for this trial include:

1. an overdose of Merck product, as defined in Section 7.2.1 - Definition of an Overdose for This Protocol and Reporting of Overdose to the Sponsor, that is not associated with clinical symptoms or abnormal laboratory results.

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

> *Note: These criteria are based upon available regulatory guidance documents. The purpose of the criteria is to specify a threshold of abnormal hepatic tests that may require an additional evaluation for an underlying etiology.

7.2.4 Evaluating Adverse Events

An investigator who is a qualified physician will evaluate all adverse events according to the NCI Common Terminology for Adverse Events (CTCAE), version 4.0. Any adverse event which changes CTCAE grade over the course of a given episode will have each change of grade recorded on the adverse event case report forms/worksheets.

All adverse events regardless of CTCAE grade must also be evaluated for seriousness.

Table 6 Evaluating Adverse Events

An investigator who is a qualified physician, will evaluate all adverse events as to:

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 participant, 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 participant 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 the Sponsor within 24 hours and 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 within 24 hours to the Sponsor and 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 participant 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?	
Relationship to Merck Product	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):	
	Exposure	Is there evidence that the participant 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?
	Time Course	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)?
	Likely Cause	Is the AE not reasonably explained by another etiology such as underlying disease, other drug(s)/vaccine(s), or other host or environmental factors

Relationship to Merck Product (continued)	**The following components are to be used to assess the relationship between the test drug and the AE: (continued)**	
	Dechallenge	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 Sponsor's product; or (3) the trial is a single-dose drug trial); or (4) Sponsor's product(s) is/are only used one time.)
	Rechallenge	Was the participant re-exposed to 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) Sponsor's product(s) is/are used only one time). NOTE: IF A RECHALLENGE IS PLANNED FOR AN ADVERSE EVENT WHICH WAS SERIOUS AND WHICH MAY HAVE BEEN CAUSED BY MERCK PRODUCT, OR IF REEXPOSURE TO MERCK PRODUCT POSES ADDITIONAL POTENTIAL SIGNIFICANT RISK TO THE PARTICIPANT, THEN THE RECHALLENGE MUST BE APPROVED IN ADVANCE BY THE SPONSOR AS PER DOSE MODIFICATION GUIDELINES IN THE PROTOCOL.
	Consistency with Trial Treatment Profile	Is the clinical/pathological presentation of the AE consistent with previous knowledge regarding Merck product or drug class pharmacology or toxicology?
The assessment of relationship will be reported on the case report forms /worksheets by an investigator who is a qualified physician according to his/her best clinical judgment, including consideration of the above elements.		
Record one of the following		**Use the following scale of criteria as guidance (not all criteria must be present to be indicative of Merck product relationship).**
Yes, there is a reasonable possibility of Merck product relationship.		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.
No, there is not a reasonable possibility of Merck product relationship		Participant 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 participant with overdose without an associated AE.)

7.2.5 Sponsor Responsibility for Reporting Adverse Events

All Adverse Events will be reported to regulatory authorities, IRB/IECs and investigators in accordance with all applicable global laws and regulations.

8.0 STATISTICAL ANALYSIS PLAN

8.1 Statistical Analysis Plan Summary

This section contains a brief summary of the statistical analysis plan for this trial. Full details are provided in the Statistical Analysis Plan (SAP) (Section 8.2).

The primary objective of this study is to identify the ORR of *PD-L1* gene-altered relapsed/refractory DLBCL patients to pembrolizumab, and to determine whether this is significantly higher than a historical control of unselected relapsed/refractory DLBCL patients treated with pembrolizumab on the KEYNOTE-013 study.

For the purposes of this clinical trial, the definition of relapsed/refractory disease includes patients who have experienced disease progression after receiving ≥ 2 lines of prior systemic therapy, ≥1 line of prior systemic therapy in those ineligible for or who have refused autologous stem cell transplantation, or patients who have received 1 line of prior therapy and have had primary refractory disease, or experienced a relapse within 12 months from initial diagnosis. The response assessment of patients enrolled on study will be determined using the LYRIC response criteria (1).

8.1.1 Efficacy Analyses

The full analysis set (FAS) population (defined as all subjects with a baseline disease burden assessment who receive at least one dose of study treatment will serve as the primary population for the analyses of efficacy data in this trial. Subjects who withdraw prior to receiving any study drug will be considered non-evaluable. Subjects in the FAS population with missing outcomes data will be considered as non-responders. An exact 95% confidence interval (two-sided) for the response rate will be estimated based on the binomial distribution, along with a one-sided test of the null hypothesis (see 8.1.3). Secondary time-to-event efficacy endpoints including PFS, OS, and DOR will be assessed by Kaplan-Meier survival analyses, and 95% confidence intervals will be calculated using Greenwood's formula.

8.1.2 Safety Analyses

The FAS population will be employed for safety analyses which will be descriptive in nature.

8.1.3 Power and Sample Size

The sample size for this study was determined using a Simon two-stage design. We project an ORR of 15%, below which the response will be unacceptable to continue the development of *PD-L1* gene alterations as a biomarker of responsiveness to pembrolizumab based upon results

from unselected DLBCL patients enrolled on the KEYNOTE-013 study; an ORR of ≥40% will be considered worthy of further exploration of this biomarker. The null hypothesis that the ORR is <15% will be tested against the alternative hypothesis that the ORR is ≥40%. The sample size computations were performed assuming a 5% level of significance, 90% power, and an optimal two-stage design.

Using these criteria, a maximum of 29 FAS patients will be enrolled (more than 29 patients may need to be enrolled to obtain the full analysis set population if there are enrolled patients that fail to receive a dose of study medication). In the first stage, 13 patients will enter the study. If 2 or fewer respond, the study will be terminated early and declared to have a negative result. If 3 or more patients respond, enrollment will be extended to a total of 29 FAS patients. At Stage 2, the biomarker strategy will be declared effective and worthy of further testing if 8 or more patients respond.

8.2 Statistical Analysis Plan

8.2.1 Responsibility of Analyses

The statistical analysis of the data obtained from this study will be the responsibility of the Biostatistics Laboratory of the University of Chicago.

This trial is being conducted as an open-label study, i.e., subjects, investigators, and personell will be aware of subject treatment assignments after each subject is enrolled and treatment is allocated.

8.2.2 Hypotheses/Estimation

Objectives and hypotheses of the study are stated in Section 3.0.

8.2.3 Analysis Endpoints

8.2.3.1 Efficacy Endpoints

Efficacy endpoints that will be evaluated are listed below followed by the desripitions of the derivations of selected endpoints.

The primary efficacy endpoint is objective overall response rate (ORR), defined as the proportion of subjects meeting the LYRIC criteria for an objective response at any time during the study. Response for the primary analysis will be assessed by the investigator.

Key secondary endpoints include:

- Progression-free survival (PFS) – defined as the time from treatment administration to documented disease progression according to LYRIC criteria or death from any cause. Patients in response who elect to proceed to stem cell transplantation will be censored on the date of stem cell infusion.

- Overall survival (OS) – defined as the time from treatment administration to death from any cause.

- Duration of response (DOR) – defined as the time from the first documented complete or partial response to disease progression or death.

8.2.4 Analysis Populations

8.2.4.1 Efficacy Analysis Populations

The Full Analysis Set (FAS) population will serve as the primary population for the analysis of efficacy data in this study. The FAS population consists of all allocated subjects who:

- Receive at least one dose of study treatment, and

- Have a baseline disease assessment

8.2.5 Statistical Methods

8.2.5.1 Statistical Methods for Efficacy Analyses

Efficacy results will be considered to be statistically significant if Type I error rates are less than 5% per the two-stage design criteria stated above. For the primary efficacy endpoint, the point estimate and 95% confidence interval will be provided using exact binomial distribution. Subjects in the primary analysis population (FAS) without response data will be counted as non-responders.

Exploratory objectives will be evaluated using a combination of comparative and descriptive statistics. For example, response rates between patients with and without *PD-L1* gene alterations will be compared using Fisher's exact test and nonparametric, Wilcoxon rank-sum tests will be performed to compare PD-L1 protein expression as assessed by immunohistochemistry (IHC) between responders and non-responders. Cox (50) regression models will be fit to determine whether other exploratory biomarkers are associated with PFS and OS, depending on the number of events observed.

8.2.5.2 Statistical Methods for Safety Analyses

Safety and tolerability will be assessed by clinical review of all relevant parameters including adverse events (AEs), laboratory tests, and vital signs.

Summary statistics (counts, percentage, mean, standard deviation, etc.) will be provided for the safety endpoints as appropriate. The 95% confidence interval for the incidence rate of grade 2 or higher adverse events with an immune etiology and incidence rate of Grade 4/5 AEs will be provided as appropriate.

8.2.5.3 Summaries of Baseline Characteristics, Demographics, and Other Analyses

8.2.5.3.1 Demographic and Baseline Characteristics

Baseline characteristics will be assessed by the use of tables and/or graphs. No statistical hypothesis tests will be performed on these characteristics. The number and percentage of subjects screened, allocated, the primary reasons for screening failure, and the primary reason for discontinuation will be displayed. Demographic variables (e.g., age, gender), baseline characeristics, primary and secondary diagnoses, and prior and concomitant therapies will be summarized by descriptive statistics or categorical tables.

8.2.6 Compliance (Medication Adherence)

A day within the study will be considered an On-Therapy day if the subject receives any dose of study medication. The number of Days Should be on Therapy is the total number of days from the first day of study medication to the date of the last dose of study medication. For each subject, percent compliance will then be calculated using the following formula:

$$\text{Percent Compliance} = \frac{\text{Number of Days on Therapy}}{\text{Number of Days Should be on Therapy}} \times 100$$

Summary statistics will be provided on percent complicance for the FAS population.

8.2.7 Extent of Exposure

Extent of Exposure for a subject is defined as number of cycles in which the subject receives a dose of study medication. Summary statistics will be provided on Extent of Exposure for the all subjects as treated population.

9.0 LABELING, PACKAGING, STORAGE AND RETURN OF CLINICAL SUPPLIES

9.1 Investigational Product

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 protocol and any applicable laws and regulations.

Pembrolizumab will be provided by Merck as summarized in Table 7.

Table 7 Product Descriptions

Product Name & Potency	Dosage Form
Pembrolizumab 100 mg/ 4mL	Solution for Injection

9.2 Packaging and Labeling Information

Supplies will be labeled in accordance with regulatory requirements.

9.3 Clinical Supplies Disclosure

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

9.4 Storage and Handling Requirements

Clinical supplies must be stored in a secure, limited-access location under the storage conditions specified on the label.

Receipt and dispensing of trial medication 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.

9.5 Returns and Reconciliation

The investigator is responsible for keeping accurate records of the clinical supplies received from Merck or designee, the amount dispensed to and returned by the participants 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.

10.0 ADMINISTRATIVE AND REGULATORY DETAILS

10.1 Confidentiality

10.1.1 Confidentiality of Data

By signing this protocol, the investigator affirms to the Sponsor that information furnished to the investigator by the Sponsor will be maintained in confidence, and such information will be divulged to the institutional review board, ethics review committee (IRB/ERC) or similar or expert committee; affiliated institution and employees, only under an appropriate

understanding of confidentiality with such board or committee, affiliated institution and employees. Data generated by this trial will be considered confidential by the investigator, except to the extent that it is included in a publication as provided in the Publications section of this protocol.

10.1.2 Confidentiality of Subject Records

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

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

10.1.3 Confidentiality of Investigator Information

By signing this protocol, the investigator recognizes that certain personal identifying information with respect to the investigator, and all subinvestigators and trial site personnel, may be used and disclosed for trial management purposes, as part of a regulatory submissions, and as required by law. This information may include:

- Name, address, telephone number, and email address
- Hospital or clinic address and telephone number
- Curriculum vitae or other summary of qualification and credentials
- Other professional documentation

Consistent with the purposes described above, this information may be transmitted to the Sponsor, and subsidiaries, affiliates and agents of the Sponsor, in your country and other countries, including countries that do not have laws protecting such information. Additionally, the investigator's name and business contact information may be included when reporting certain serious adverse events to regulatory authorities or to other investigators. By signing this protocol, the investigator expressly consents to these uses and disclosures.

If this is a multicenter trial, in order to facilitate contact between investigators, the Sponsor may share an investigator's name and contact information with other participating investigators upon request.

10.1.4 Confidentiality of IRB/IEC Information

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

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

10.2 Compliance with Financial Disclosure Requirements

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

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

10.3 Compliance with Law, Audit, and Debarment

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

The investigator also agrees to allow monitoring, audits, IRB/ERC review and regulatory authority inspection of trial-related documents and procedures and provide for direct access to all trial-related source data and documents.

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

The investigator shall prepare and maintain complete and accurate trial documentation in compliance with Good Clinical Practice standards and applicable federal, state and local laws, rules and regulations; and, for each subject participating in the trial, provide all data, and, upon completion or termination of the clinical trial, submit any other reports to the Sponsor as required by this protocol or as otherwise required pursuant to any agreement with the Sponsor.

Trial documentation will be promptly and fully disclosed to the Sponsor by the investigator upon request and also shall be made available at the trial site upon request for inspection, copying, review and audit at reasonable times by representative of the Sponsor or any

regulatory authorities. The investigator agrees to promptly take any reasonable steps that are requested by the Sponsor as a result of an audit to cure deficiencies in the trial documentation and worksheet/case report forms.

The investigator must maintain copies of all documentation and records relating to the conduct of the trial in compliance with all applicable legal and regulatory requirements. This documentation includes, but is not limited to, the protocol, worksheets/case report forms, advertising for subject participation, adverse event reports, subject source data correspondence with regulatory authorities and IRBs/ERCs, consent forms, investigator's curricula vitae, monitor visit logs, laboratory reference ranges, laboratory certification or quality control procedures and laboratory director curriculum vitae. By signing this protocol, the investigator agrees that documentation shall be retained until at least 2 years after the last approval of a maketing application in an ICH region or until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. Because the clinical development and marketing application process is variable, it is anticipated that the retention period can be up to 15 years or longer after protocol database lock. The Sponsor will determine the minimum retention period and notify the investigator when documents may be destroyed. The Sponsor also recognizes that documents may need to be retained for a longer period if required by local regulatory requirements. All trial documents shall be made available if required by relevant regulatory authorities. The investigator must consult with and obtain written approval by the Sponsor prior to discarding trial and/or subject files.

ICH Good Clinical Practice guidelines recommend that the investigator inform the subject's primary physician about the subject's participation in the trial if the subject has a primary physician and if the subject agrees to the primary physician being informed.

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

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

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

According to European legislation, a Sponsor must designate an overall coordinating investigator for a multi-center trial (including multinational). When more than one trial site is open in an EU country Merck, as the Sponsor, will designate, per country, a national prinicipal coordinator (Protocol CI), responsible for coordinating the work of the principal investigators at the different trial sites in that Member State, according to national regulations. For a single-center trial, the Protocol CI is the prinicapl investigator. In addition, the Sponsor must designate a principal or coordinating investigator to review the trial report that summarizes the trial results and confirm that, to the best of his/her knowledge, the report accurately describes

the conduct and results of the trial [Clinical Study Report (CSR) CI]. The Sponsor may consider one or more factors in the selection of the individual to serve as the Protocol CI and/or CSR CI (e.g., availability of the CI during the anticipated review process, thorough understanding of clinical trial methods, appropriate enrollment of subject cohort, timely achievement of trial milestones). The Protocol CI must be a participating trial investigator.

10.4 Compliance with Trial Registration and Results Posting Requirements

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

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

10.5 Quality Management System

By signing this protocol, the Sponsor agrees to be responsible for implementing and maintaining a quality management system with written development procedures and functional area standard operating procedures (SOPs) to ensure that trials are conducted and data are generated, documented, and reported in compliance with the protocol, accepted standards of Good Clinical Practice, and all applicable federal, state, and local laws, rules and regulations relating to the conduct of the clinical trial.

10.6 Data Management

The investigator or qualified designee is responsible for recording and verifying the accuracy of subject data. By signing this protocol, the investigator acknowledges that his/her electronic signature is the legally binding equivalent of a written signature. By entering his/her electronic signature, the investigator confirms that all recorded data have been verified as accurate.

Detailed information regarding Data Management procedures for this protocol will be provided by the Sponsor.

10.7 Publications

This trial is intended for publication, even if terminated prematurely. Publication may include any or all of the following: posting of a synopsis online, abstract and/or presentation at a scientific conference, or publication of a full manuscript. The Sponsor will work with the

authors to submit a manuscript describing trial results within 12 months after the last data become available, which may take up to several months after the last subject visit in some cases such as vaccine trials. However, manuscript submission timelines may be extended on OTC trials. For trials intended for pediatric-related regulatory filings, the investigator agrees to delay publication of the trial results until the Sponsor notifies the investigator that all relevant regulatory authority decisions on the trial drug have been made with regard to pediatric-related regulatory filings. Sponsor will post a synopsis of trial results for approved products on www.clinicaltrials.gov by 12 months after the last subjet's last visit for the primary outcome, 12 months after the decision to discontinue development, or product marketing (dispensed, administered, delivered or promoted), whichever is later.

These timelines may be extended for products that are not yet marketed, if additional time is needed for anlaysis, to protect intellectual property, or to comply with confidentiality agreements with other parties. Authors of the primary results manuscript will be provided the complete results from the Clinical Study Report, subject to the confidentiality agreement. When a manuscript is submitted to a biomedical journal, the Sponsor's policy is to also include the protocol and statistical analysis plan to facilitate the peer and editorial review of the manuscript. If the manuscript is subsequently accepted for publication, the Sponsor will allow the journal, if it so desires, to post on its website the key sections of the protocol that are relevant to evaluating the trial, specifically those sections describing the trial objectives and hypotheses, the subject inclusion and exclusion criteria, the trial design and procedures, the efficacy and safety measures, the statistical analysis plan, and any amendments relating to those sections. The Sponsor reserves the right to redact proprietary information.

For multicenter trials, subsequent to the multicenter publication (or after public disclosure of the results online at www.clinicaltrials.gov if a multicenter manuscript is not planned), an investigator and his/her colleagues may publish their data independently. In most cases, publication of individual trial site data does not add value to complete multicenter results, due to statistical concerns. In rare cases, publication of single trial site data prior to the main paper may be of value. Limitations of single trial site observations in a multicenter trial should always be described in such a manuscript.

Authorship credit should be based on 1) substantial contributions to conception and design, or acquisition of data, or analysis and interpretation of data; 2) drafting the article or revising it critically for important intellectual content; and 3) final approval of the version to be published. Authors must meet conditions 1, 2, and 3. Significant contributions to trial execution may also be taken into account to determine authorship, provided that contributions have also been made to all three of the preceding authorship criteria. Although publication planning may begin before conducting the trial, final decisions on authorship and the order of authors' names will be made based on participation and actual contributions to the trial and writing, as discussed above. The first author is responsible for defending the integrity of the data, method(s) of data analysis and the scientific content of the manuscript.

The Sponsor must have the opportunity to review all proposed abstracts, manuscripts or presentations regarding this trial 45 days prior to submission for publication/presentation. Any information identified by the Sponsor as confidential must be deleted prior to submission; this

confidentiality does not include efficacy and safety results. Sponsor review can be expedited to meet publication timelines.

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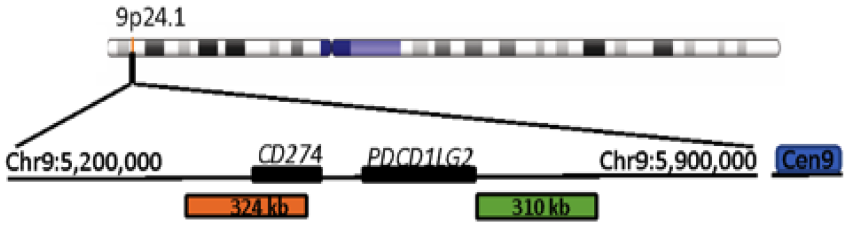
APPENDICES

Appendix 1: Detection of *PD-L1* alerations by Flourescent in-situ Hybridization (FISH)

FISH will performed utilizing a previously validated technique in a CLIA-certified cytogeneitcs laboratory at The University of Chicago or at City of Hope. Briefly, de-paraffinized FFPE slides will be incubated with FISH probes targeting *PD-L1* (*CD274*, Orange, Empire Genomics) and centromere 9 (CEP9, Aqua, Abbott Molecular). An additional probe targeting a region centromeric to *PD-L2* (RP11-610G2, Green, Empire Genomics) will also be included to assess for chromosomal translocation involving *PD-L1*. After overnight hybridization at 37 °C in a humidifier chamber, slides will be washed and counterstained with 2.5 mg/mL DAPI. Fluorescent microscopy will then be performed to identify the presence or absence of *PD-L1* gene alterations, and when present, to characterize the underlying mechanism (polysomy, relative copy gain, amplification, translocation). 30 lymphoma cells per sample will be analyzed.

Nuclei will be defined as *PD-L1* amplified if the *PD-L1*/CEP9 ratio is ≥ 3:1 or there are ≥ 6 *PD-L1* signals. Nuclei with ≥3 *PD-L1* signals and a *PD-L1*/CEP9 ratio of > 1:1 but < 3:1 will be defined as harboring *PD-L1* copy gains, and those with a probe ratio of 1:1 but with more than 2 copies of each probe will be characterized as polysomic for chromosome 9. *PD-L1* translocations will be called if there is evidence of a split signal between the *PD-L1* and translocation probe centromeric to *PD-L2.* The frequency of lymphoma cells harboring each form of *PD-L1* alteration will be assessed for each sample, and samples will be considered *PD-L1* gene-altered if ≥20% of lymphoma cell nuclei exhibit any of the above-mentioned alterations. For the purposes of the study, only patients with DLBCLs exhibiting *PD-L1* amplifications, translocations, or relative copy gains will be enrolled. DLBCLs exhibiting chromosome 9 polysomy alone without evidence of *PD-L1* copy gain, amplification, and/or translocation are not considered PD-L1 gene-altered for the purposes of this clinical trial.

A.



B.

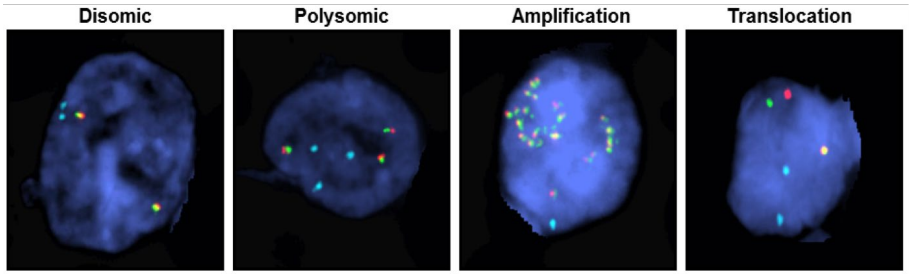


Figure 2. **A**. schematic represenation of FISH probe locations on chromosome 9, and **B**. examples of *PD-L1* gene alterations as determined by FISH.

Appendix 2: ECOG Performance Status

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

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

Appendix 3: Common Terminology Criteria for Adverse Events V4.0 (CTCAE)

The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for adverse event reporting. (http://ctep.cancer.gov/reporting/ctc.html)

Appendix 4: Contraceptive Guidance and Pregnancy Testing

Woman of Childbearing Potential (WOCBP)

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

Women in the following categories are not considered WOCBP:

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

  Note: Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.

- Postmenopausal female
  - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
    - A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, confirmation with two FSH measurements in the postmenopausal range is required.
  - Females on HRT and whose menopausal status is in doubt will be required to use one of the non-hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

Contraception Requirements

Male Participants:

Male participants with female partners of childbearing potential are eligible to participate if they agree to one of the following during the protocol defined time frame in section 6.0:

- Be abstinent from penile-vaginal intercourse as their usual and preferred lifestyle (abstinent on a long term and persistent basis) and agree to remain abstinent
- Use a male condom plus partner use of a contraceptive method with a failure rate of <1% per year as described in Table 8 when having penile-vaginal intercourse with a woman of childbearing potential who is not currently pregnant.
  - Note: Men with a pregnant or breastfeeding partner must agree to remain abstinent from penile-vaginal intercourse or use a male condom during each episode of penile penetration.

Female Participants:

Female participants of childbearing potential are eligible to participate if they agree to use a highly effective method of contraception consistently and correctly as described in Table 8 during the protocol-defined time frame in Section 6.0.

Table 8 Highly Effective Contraception Methods

Highly Effective Contraceptive Methods That Are User Dependent [a] *Failure rate of <1% per year when used consistently and correctly.*
● Combined (estrogen- and progestogen- containing) hormonal contraception [b] ○ Oral ○ Intravaginal ○ Transdermal ○ Injectable
● Progestogen-only hormonal contraception [b] ○ Oral ○ Injectable
Highly Effective Methods That Have Low User Dependency *Failure rate of <1% per year when used consistently and correctly.*
● Progestogen- only contraceptive implant [b] ● Intrauterine hormone-releasing system (IUS) ● Intrauterine device (IUD) ● Bilateral tubal occlusion
● **Vasectomized partner** A vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.
● **Sexual abstinence** Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatment. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.)
Notes: Use should be consistent with local regulations regarding the use of contraceptive methods for participants of clinical studies. a) Typical use failure rates are lower than perfect-use failure rates (i.e. when used consistently and correctly). b) If locally required, in accordance with Clinical Trial Facilitation Group (CTFG) guidelines, acceptable hormonal contraceptives are limited to those which inhibit ovulation.

Pregnancy Testing

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

Following initiation of treatment, pregnancy testing will be performed whenever an expected menstrual cycle is missed or when pregnancy is otherwise suspected; at the time points specified in the Schedule of Activities, and as required locally.

Appendix 5: LYRIC Response Criteria

Table 2. Comparison of RECIST, irRC, and Lugano Classification criteria

Criteria	CR	PR	PD
RECIST 1.1	Disappearance of all target lesions. Any pathological lymph nodes (whether target or nontarget) must have reduction in short axis to <10 mm	At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters	At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm Note: the appearance of one or more new lesions is also considered progression.
irRC	Disappearance of all lesions in two consecutive observations not less than 4 weeks apart	≥50% decrease in tumor burden compared with baseline in 2 observations at least 4 weeks apart (as measured bidimensionally)	≥25% increase in tumor burden compared with nadir (at any single time point) in 2 consecutive observations at least 4 weeks apart, where Tumor Burden = SPD index lesions + SPD new, measurable lesions
Lugano	PET-CT, score 1, 2, or 3* with or without a residual mass on 5PS† OR on CT, target nodes/nodal masses must regress to ≤1.5 cm in LDi	PET-CT score 4 or 5 with reduced uptake compared with baseline and residual mass(es) of any size. OR On CT ≥50% decrease in SPD of up to 6 target measurable nodes and extranodal sites	PET-CT score 4 or 5 with an increase in intensity of uptake from baseline and/or new FDG-avid foci consistent with lymphoma at interim or end-of-treatment assessment. OR On CT, an individual node/lesion must be abnormal with: LDi >1.5 cm and increase by ≥50% from PPD nadir and an increase in LDi or SDi from nadir 0.5 cm for lesions ≤2 cm 1.0 cm for lesions >2 cm In the setting of splenomegaly, the splenic length must increase by >50% of the extent of its prior increase beyond baseline (eg, a 15-cm spleen must increase to >16 cm). If no prior splenomegaly, must increase by ≥2 cm from baseline. New or recurrent splenomegaly New or clear progression of preexisiting nonmeasured lesions Regrowth of previously resolved lesions A new node >1.5 cm in any axis or 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 AND/OR new or recurrent involvement of the bone marrow
LYRIC	Same as Lugano	Same as Lugano	As with Lugano with the following exceptions: IR IR(1): ≥50% increase in SPD in first 12 weeks IR(2): <50% increase in SPD with a. New lesion(s), or b. ≥50% increase in PPD of a lesion or set of lesions at any time during treatment IR(3): Increase in FDG uptake without a concomitant increase in lesion size meeting criteria for PD

IR, immune response; LDi, longest diameter; PPD, product of the perpendicular diameters; SDi, short diameter; 5PS, 5-point scale.

*A score of 3 in many patients indicates a good prognosis with standard treatment, especially if at the time of an interim scan. However, in trials involving PET where de-escalation is investigated, it may be preferable to consider a score of 3 as inadequate response (to avoid undertreatment).

†PET 5PS: 1, no uptake above background; 2, uptake ≤ mediastinum; 3, uptake > mediastinum but ≤ liver; 4, uptake greater than liver; 5, uptake markedly higher than liver (2-3 times SUVmax in normal liver) and/or new lesions; X, new areas of uptake unlikely to be related to lymphoma.

Appendix 6: Collection and Management of Specimens for Biomedical Research

1. Scope of Biomedical Research

The blood, stool, DNA, and archival biopsy specimens collected in the current trial will be used to perform the exploratory research objectives listed in Section 3.3. The collected biospecimens may also be used for future biomedical research focused on the identification of potential biomarkers of response, as well as mechanisms of acquired resistance to pembrolizumab therapy.

2. Summary of Procedures for Biomedical Research

a. Subjects for Enrollment

All subjects enrolled in the clinical trial will be requested to provide archival biopsies, as well as blood and stool specimens at the timepoints outlined in the Trial Flowchart in Section 6.0.

b. Informed Consent

Informed consent to obtain archival biopsy specimens (10-20 unstained slides or a tissue block if available) for *PD-L1* FISH experiments will be requested during a pre-screening trial visit by the investigator or his or her designate. Patients fulfilling the pre-screening eligibility requirements will then be provided with a separate consent form to obtain other biospecimens (blood and stool) during the trial. Informed consent must be obtained prior to collection of all biomedical specimens. Consent forms signed by the subject will be kept at the clinical trial site under secure storage for regulatory reasons. Information contained on the consent form alone cannot be traced to any specimens, test results, or medical information once the specimens have been rendered de-identified. Patients unwilling to consent to providing the outlined biospecimens will not be eligibile for the study unless extenuating circumstances exist as deemed by a mutual agreement between the treating physician and the principal investigator.

c. Biomedical Research Specimen Collection

Serial blood, baseline stool, and archival biopsies will be collected as documented in the Trial Flow Chart (Section 6.0). All blood specimens will be obtained at a time when the subject is having blood drawn for other trial purposes. Baseline stool will be collected by the patient using a home stool collection kit.

The protocol for serial blood and baseline stool collection is outlined in more detail in the accompanying lab manual. Briefly, blood will be compartmentalized into plasma, serum, and peripheral blood mononuclear cells at the patient's trial site within 2 hours of sample collection and will be shipped to The University of Chicago Human Tissue Resource Center for long-term storage. Germline DNA will also be extracted from peripheral blood to provide a paired normal reference

for tumor whole exome sequencing. More detailed information regarding the specific reagents and blood processing techniques is provided in the accompanying lab manual. Subjects participating in the study will be provided a home stool collection kit for baseline stool sampling. After stool collection, the kit can either be returned by the patient at their next clinic appointment or shipped directly to The University of Chicago Microbiome Core Facility using the attached return address information.

3. Withdrawal of Consent to Biomedical Research

Subjects may withdraw their consent for biomedical research and have their specimens and all derivatives destroyed. Subjects may withdraw consent at any time by writing to the principal investigator. Subsequently, the subject's specimens will be removed from the biorepository and be destroyed. Any analyses in progress at the time of request for destruction or already performed prior to the request being received by the principal investigator will continue to be used as part of the overall research trial data and results. No new analyses will be generated after the request is received.

4. Retention of Specimens

Archival biopsies and blood specimens will be stored at The University of Chicago Human Tissue Resource Center for potential analysis for up to 20 years from acquisition. All baseline stool specimens will stored at The University of Chicago Microbiome Core Facility. Specimens from the trial site will be shipped to the appropriate storage facility. The specimens will be stored under strict supervision in a limited access facility which operates to assure the integrity of the specimens. Specimens will be destroyed according to the storage facility's policies and procedures and this destruction will be documented in the biorepository database.

5. Reporting of Biomedical Research Data to Subjects

There is no definitive requirement in either authoritative ethical guidelines or in relevant laws/regulation globally that research results have to be, in all circumstances, returned to the trial participant. Some guidelines advocate a proactive return of data in certain instances. No information obtained from exploratory laboratory studies will be reported to the subject or family, and this information will not be entered into the clinical database. Principle reasons not to inform or return results to the subject include: lack of relevance to subject health, limitations of predictive capability, concerns of misinterpretation and absence of good clinical practice standards in exploratory research typically used for diagnostic testing.

If any exploratory results are definitively associated with clinical significance after completion of the clinical trial, the investigator will publish the results without revealing specific subject information in order for physicians and patients to pursue clinical diagnostic testing if they wish to do so.

6. Risks Versus Benefits of Biomedical Research

For biomedical research, risks to the subject have been minimized. Risks include those associated with venipuncture to obtain the whole blood specimen. This specimen will be obtained at the time of routine blood specimens drawn in the main trial. Additionally, baseline stool collections will take place in the privacy of the patient's home and can be shipped to the storage facility by any patient representative.

Data privacy risks will also be largely limited to rare situations involving possible breach of confidentiality. In this highly unlikely situation there is risk that the information, like all medical information, may be misused.

It is necessary for subject-related data (i.e., ethnicity, age, toxicities, etc.) to be re-associated to double coded specimens at the time of data analysis. These subject data will be kept in a separate, secure database, and all specimens will be stripped of subject identifiers. No information concerning results obtained from future biomedical research will be entered into clinical recoreds, nor will it be released to outside persons or agencies, in any way that could be tied to an individual subject.