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Phase II study of rituximab plus pembrolizumab (MK-3475) in subjects with relapsed follicular lymphoma

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Investigational Drug: Pembrolizumab

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1.0 TRIAL SUMMARY

Abbreviated Title	Rituximab plus pembrolizumab (MK-3475) in relapsed follicular lymphoma
Trial Phase	II
Clinical Indication	The treatment of subjects with relapsed/refractory follicular and diffuse large B-cell lymphoma.
Trial Type	Interventional
Type of control	Historical control
Route of administration	Intravenous and po
Trial Blinding	Unblinded, open-label
Treatment Groups	Cohort 1: Rituximab (375 mg/m^2 weekly x 4 weeks) and pembrolizumab (200 mg every 3 weeks for up to 16 infusions) in subjects with relapsed or refractory follicular lymphoma. Cohort 2: Rituximab (375 mg/m^2 weekly x 4 weeks), pembrolizumab (200 mg every 3 weeks for up to 2 years) and lenalidomide (days 1-14 of a 3 week cycle for 12 cycles in relapsed/refractory follicular lymphoma or diffuse large B-cell lymphoma patients who have failed CAR T cell therapy
Number of trial subjects	Cohort 1: 32, Cohort 2: 40
Estimated duration of trial	It is estimated that the trial will require approximately 60 months from the time the first subject signs the informed consent until the last subject's last visit.
Duration of Participation	Each subject will participate in the trial from the time the subject signs the Informed Consent Form through the final protocol-specified contact. After a screening phase of 28 days, eligible subjects in cohort 1 will receive treatment with rituximab (375 mg/m^2) on day 1, 8, 15, and 22 of cycle 1. Pembrolizumab (200 mg) will begin on Day 2 of cycle 1 and repeated every 3 weeks for up to 16 infusions. In cohort 2, subjects will receive treatment with rituximab (375 mg/m^2) on day 1, 8, and 15 of cycle 1 and Day 1 of cycle 2. Pembrolizumab (200 mg) will begin on day 1 of cycle 1 and repeated every 3 weeks for up to 2 years. Per the investigator's discretion, subjects who attain an investigator-determined confirmed complete response (CR) may consider stopping pembrolizumab treatment after receiving at least 24 weeks of pembrolizumab therapy. At least two doses must be received after CR is documented. The phase II dose of lenalidomide will be determined following a dose escalation of lenalidomide, starting at 2.5 mg on days 1-14 of each cycle for up to 12 cycles. Study treatment will continue until documented 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, administrative reasons, or the subject has completed the planned therapy. After the end of treatment, adverse events will be collected for 30 days and serious adverse events for 90 days. 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. Disease assessment will be performed every 3 months during therapy and for the first year after discontinuation of therapy, and every 6 months thereafter.

2.0 TRIAL DESIGN

2.1 Trial Design

This is a single center, nonrandomized trial of rituximab in combination with pembrolizumab in subjects with relapsed follicular lymphoma (FL). Cohort 1 will consist of 32 subjects enrolled to examine the safety and efficacy of rituximab in combination with pembrolizumab in patients with relapsed FL with rituximab-sensitive FL. Rituximab will be administered at a dose of 375 mg/m^2 weekly for 4 weeks and pembrolizumab administered at a dose of 200 mg every 3 weeks (Q3W) for a maximum of 16 infusions.

Cohort 2 has been added to examine the safety and efficacy of rituximab in combination with pembrolizumab and lenalidomide in approximately 40 subjects with relapsed/refractory FL and DLBCL patients who have progressed following chimeric antigen receptor (CAR) T cell therapy. Patients will receive rituximab at a dose of 375 mg/m^2 weekly for 4 weeks, pembrolizumab administered at a dose of 200 mg every 3 weeks for a maximum of 2 years, and lenalidomide will be dose escalated from 2.5mg to a maximum of 10mg on days 1-14 of cycles 1-12. The prolonged course of pembrolizumab in this cohort is based on observations of delayed responses with pembrolizumab in patients with lymphoma enrolled in other prospective studies observed beyond the 16 doses planned in the original cohort. The rationale for the combination is to explore the efficacy and safety of this novel immune therapy combination in patients with refractory disease with limited treatment options and very poor outcomes. The addition of lenalidomide to the combination of rituximab and pembrolizumab is anticipated to provide synergism by further activating the innate and adaptive immune response. Patients who fail to respond to CAR T cell therapy have a very poor outcome. Mechanisms of resistance are actively being explored, but PD-L1 expression has been reported as one potential mechanism and prospective studies are underway exploring the combination of anti PD-1 or PD-L1 therapies with CAR T cell therapy. We also have anecdotal experience in our department with patients achieving a response post CAR T cell failure with lenalidomide. Therefore, the combination may be an effective strategy to overcome resistance to CAR T cell therapy in high risk patients.

Adverse events (AEs) 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. Response will be determined according to the Recommendations for Initial Evaluation, Staging, and Response Assessment of Hodgkin and Non-Hodgkin Lymphoma: The Lugano Classification.[1] Study treatment will continue until documented progression of disease (PD), unacceptable AE(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, administrative reasons, or the subject has completed 16 cycles. After the end of treatment, each subject will be followed for 30 days for AE monitoring (serious adverse events (SAEs) will be collected for 90 days after the end of treatment). Subjects who discontinue treatment 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.

The primary objective of the trial is to determine the overall response rate (ORR) in subjects

with relapsed FL and DLBCL treated with rituximab, pembrolizumab ± lenalidomide. Secondary objectives include assessment of safety, complete response rate (CRR), progression-free survival (PFS), compare PFS between patients relapsing ≤ one year vs > one year after last prior therapy, and overall survival (OS). Exploratory objectives include evaluation of immunological effects of therapy and determination of the relationship of candidate efficacy/resistance biomarkers and anti-tumor activity of pembrolizumab.

This study will be conducted in conformance with Good Clinical Practices.

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.

2.2 Trial Diagram

The trial design is depicted in **Figure 1**.

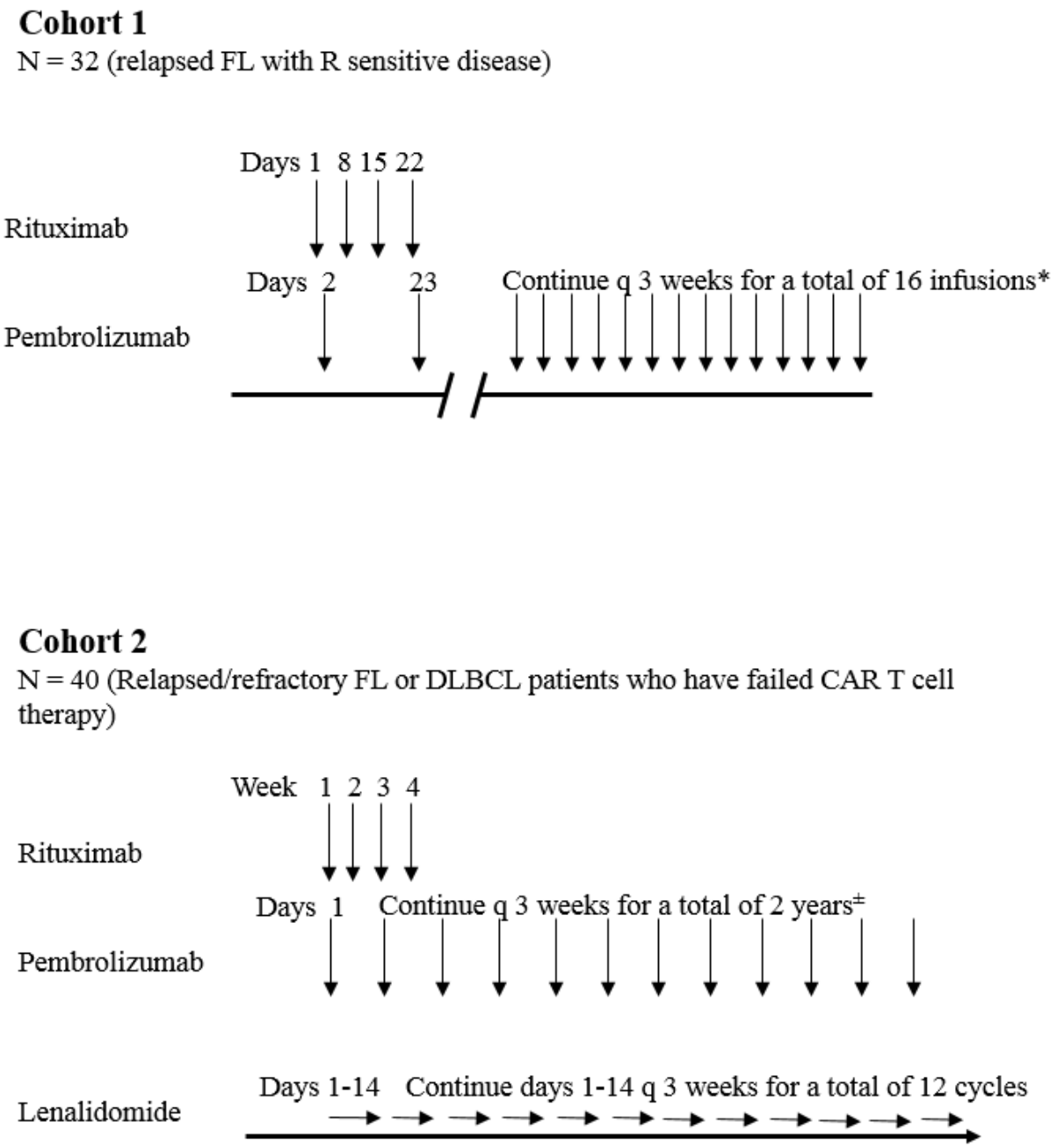

Figure 1. **Clinical trial schema**. Eligible subjects in Cohorts 1 will receive treatment with rituximab at 375 mg/m^2 on day 1, 8, 15, and 22 of cycle 1. *Subjects with also receive pembrolizumab at 200 mg infusion every 3 weeks starting on day 2 of cycle 1 for up to 16 infusions. A time window of +/- 1 day for rituximab infusions on days 8, 15, and 22, and +/- 3 days for 2nd through 16th infusion of pembrolizumab is allowed. A minimum of 18 hours interval is required between the end of rituximab infusion and beginning of pembrolizumab infusion on days 2 and 23.

Cohort 2 was added with the amendment. Subjects will receive 4 weekly doses of rituximab 375 mg/m^2 starting on day 1 of cycle 1. ±Subjects will also receive pembrolizumab 200 mg infusion starting on day 1

of cycle 1 and continued every 3 weeks starting for up to 2 years. Per the investigator's discretion, subjects who attain an investigator-determined CR may consider stopping pembrolizumab treatment after receiving at least 24 weeks of pembrolizumab therapy. At least two doses must be received after CR is documented. A time window of +/- 1 day for rituximab infusions on doses 2, 3, and 4day 1, and +/- 3 days for 2nd through the remaining infusions of pembrolizumab is allowed. Subjects will also receive lenalidomide on days 1-14 of cycles 1-12.

3.0 OBJECTIVE(S) & HYPOTHESIS(ES)

3.1 Primary Objective(s) & Hypothesis(es)

(1) **Objective:** The primary objective of the study is to determine the ORR in subjects with relapsed FL treated with rituximab plus pembrolizumab.

Hypothesis: Therapy with rituximab plus pembrolizumab in subjects with relapsed FL will result in improvement in ORR by at least 20% as compared with historical results with rituximab monotherapy.

3.2 Secondary Objective(s) & Hypothesis(es)

(1) **Objective**: To determine the safety and toxicity.

(2) **Objective**: To determine the CRR.

(3) **Objective**: To determine the overall PFS.

(4) **Objective**: To compare PFS between patients relapsing ≤ one year vs > one year after last prior therapy.

(5) **Objective**: To determine the OS.

Hypothesis: Therapy with rituximab plus pembrolizumab in subjects with relapsed FL will be safe and well tolerated and result in clinically meaningful improvement in CRR and PFS as compared with historical results with rituximab monotherapy.

3.3 Exploratory Objective

(1) **Objective:** To determine effects of rituximab plus pembrolizumab therapy on peripheral blood T cells.

(2) **Objective:** To correlate features of peripheral blood T cells with toxicities after rituximab plus pembrolizumab therapy.

(3) **Objective:** To correlate features of peripheral blood T cells with response and PFS after rituximab plus pembrolizumab therapy.

(4) **Objective:** To correlate baseline tumor characteristics with response and PFS after rituximab plus pembrolizumab therapy.

3.4 Objective(s) & Hypothesis(es) of Cohort 2

(1) **Objective:** To determine the ORR in subjects with relapsed/refractory FL and relapsed/refractory DLBCL who have failed CAR T cell therapy and are treated with rituximab in combination with pembrolizumab and lenalidomide.

(2) **Objective:** To determine the safety and toxicity.

(3) **Objective:** To determine the CRR.

(4) **Objective:** To determine the overall PFS.

(5) **Objective:** To compare PFS between patients relapsing ≤ one year vs > one year after last prior therapy.

(6) **Objective:** To determine the OS.

(7) **Objective:** To determine effects of rituximab, pembrolizumab, and lenalidomide therapy on peripheral blood T cells.

(8) **Objective:** To correlate features of peripheral blood T cells with toxicities after rituximab, pembrolizumab, and lenalidomide therapy.

(9) **Objective:** To correlate features of peripheral blood T cells with response and PFS after rituximab, pembrolizumab, and lenalidomide therapy.

(10) **Objective:** To correlate baseline tumor characteristics with response and PFS after rituximab, pembrolizumab, and lenalidomide therapy

Hypothesis: Therapy with rituximab, pembrolizumab, and lenalidomide in subjects with relapsed/refractory FL and DLBCL who have failed CAR T cell therapy (Cohort 2) will be safe and well tolerated and will result in improvement in ORR by at least 10% as compared with historical results with rituximab and lenalidomide.

4.0 BACKGROUND & RATIONALE

4.1 Background

4.1.1 *Current therapy and prognosis of FL.* In 2014, it is estimated that 70,800 patients will be diagnosed, and an estimated 18,990 will die due to non-Hodgkin's lymphoma (NHL) in the United States. Follicular lymphoma is the most common low-grade lymphoma and comprises 22% of all NHL cases worldwide.[2] Stage I or II FL is potentially curable with radiation therapy but is present in only 10-15% of patients at the time of initial diagnosis. Greater than 85% of patients with FL have advanced stage disease at the time of initial diagnosis. Although advanced stage FL has a generally indolent course and a median survival of over 12 years, it is considered incurable with the available treatment options. It is highly responsive to various therapies such as chemotherapy, radiation therapy, and/or biologic therapy, but is characterized by repeated remissions and relapses and most patients eventually die of their disease.[3] The inclusion of rituximab, in combination chemotherapy regimens has improved the response rates, PFS, and OS of patients with FL. However, even these combinations do not appear to be curative since no plateau in the survival curves has been demonstrable.[4-6] Therefore, novel treatment options are needed to improve clinical outcome in these patients.

Immunotherapy for FL. Several studies have demonstrated that immunotherapy could induce meaningful and durable clinical remissions in FL. First, treatment with custom-made anti-idiotype antibodies generated against the clonal tumor immunoglobulin expressed on the

surface of FL induced clinical responses in 66% of the patients with 13% experiencing complete remission lasting many years.[7] Second, administration of rituximab, an anti-CD20 monoclonal antibody, as a single agent induced clinical remission in a significant proportion of patients with FL.[8-11] Third, a high PFS of 83% was observed after a median follow-up of five years following non-myeloablative allogeneic stem cell transplantation suggesting that a graft versus tumor effect mediated by the immune system can lead to prolonged clinical remission in FL.[12, 13] Fourth, immunization with customized therapeutic vaccines in FL has been shown to improve disease-free survival when administered in the setting of minimal residual disease.[14] Taken together, these results suggest that immunotherapy involving the humoral and/or the cellular arms of the immune system may induce durable clinical responses in FL.

Rituximab monotherapy in FL. Rituximab, a chimeric anti-CD20 monoclonal antibody has been shown to induce a 48% response rate in relapsed indolent lymphomas in the pivotal phase II study.[10] The median time to progression was 13 months in responders and 9 months for all evaluable patients. Rituximab was also effective when used in indolent lymphoma patients who relapsed after a prior response to rituximab. Re-treatment with rituximab induced responses in 40% of patients and median time-to-progression among responders was 17.8 months.[15] Rituximab as single agent first-line therapy has been shown to induce response rates in 47% to 73% of patients in previously untreated indolent lymphomas. Median time-to-progression was 18 months to 2.2 years.[11, 16] Taken together, these results suggest that rituximab has significant clinical activity as single agent in FL patients either previously untreated or treated with rituximab.

Rituximab plus lenalidomide in FL. Lenalidomide, a thalidomide derivative, is a second generation immunomodulatory drug, proposed to have multiple mechanisms of action, including beneficial effects on both tumor and the microenvironment. Lenalidomide has been shown to induce growth arrest and apoptosis of lymphoma cell lines and enhance the NK-cell–mediated antibody-dependent cellular cytotoxicity (ADCC) of rituximab [17], suggesting lenalidomide and rituximab could be a synergistic immune therapy approach in FL. Witzig et al reported a phase II study of lenalidomide (25 mg/d for 21 of 28 days) in patients with relapsed or refractory indolent NHL.[18] Among 27 assessable patients with a median of three (range, 1-17) prior therapies, the ORR was 26% (n = 7) including 2 CRs, whereas the overall clinical benefit (stable disease or better response) was observed in 59% of the patients. Investigators within our department conducted a phase II study with lenalidomide and rituximab in relapsed/refractory DLBCL and FL including patients with transformed lymphoma. Patients received lenalidomide 20 mg/day on days 1-21 of each 28 day cycle. Rituximab was given weekly during cycle 1 at 375 mg/m^2. ORR in this study was 33%, with a median duration of response of 10.2 months.[19] We also conducted a phase II study of the combination of lenalidomide and rituximab in patients with untreated indolent NHL.[20] We reported high overall response rates in this untreated population, with a complete response rate of 87% in patients with follicular lymphoma. Toxicity was mild to moderate, with the most common non-hematologic adverse event reported as grade 1-2 fatigue and rash. Hematologic toxicity included 35% ≥ grade 3 neutropenia and 4% with ≥ grade 3 thrombocytopenia. These results suggest that enhancing the innate immune system as a therapeutic target can be effective in FL.

Effects of immune system on cancer. A series of elegant studies in mouse cancer models conducted over the past decade has provided strong and convincing data that the innate and adaptive immune systems can not only prevent development of tumors (cancer immunosurveillance or cancer elimination), but can also participate in the generation of a sculpted tumor cell repertoire that displays either reduced immunogenicity or an increased capacity to inhibit protective antitumor immune responses (cancer immunoediting).[21, 22] The recognition of the dual effects of the immune system on developing tumors has evolved into the "cancer immunoediting hypothesis" that suggests three phases in the tumor development process termed the "three Es of cancer immunoediting": elimination, equilibrium, and escape.[21, 22]

Endogenous anti-tumor immunity in FL. The natural history of FL characterized by stable disease or spontaneous remissions[23] lasting months to years while on observation in a significant proportion of patients, suggests that it may go through a phase of equilibrium where the tumor is probably kept in check by the immune system before escape mechanisms develop resulting in progression of the tumor. Recent studies support the notion that the immune system may play a significant role in the control of this tumor. First, the survival of patients with FL appeared to correlate with the gene expression signatures of infiltrating nonmalignant immune cells in the tumor.[24] Second, high levels of $CD8^+$ T-cell content in diagnostic lymph nodes correlated with better prognosis.[25] Third, the presence of an immunosurveillance pattern ($CD8^+$ T cells) or an immune-escape pattern ($CD57^+$ T cells), correlated with good or poor prognosis, respectively.[26] Finally, tumor-specific T cells could be easily isolated from the peripheral blood and tumor microenvironment in FL.[27, 28] Together, these results suggest that endogenous antitumor immune responses are naturally induced in patients with FL but these immune responses eventually become ineffective to control the tumor presumably due to development of various immunosuppressive mechanisms in the tumor microenvironment.

Immunosuppressive mechanisms. Recently, several immunosuppressive mechanisms were shown to impair the function of tumor-specific effector T cells in the tumor microenvironment in various animal models and in some human cancers.[29] Development of such immunosuppressive mechanisms could result in the progression of FL and other cancers from an "equilibrium" phase to the "escape" phase. Important negative regulatory pathways that inhibit T-cell function include extrinsic suppression by regulatory T cells (Tregs); direct inhibition through inhibitory ligands such as programmed death-ligand 1 (PD-L1), PD-L2, and B7-H4; soluble factors such as transforming growth factor β and interleukin (IL)-10; and metabolic dysregulation of essential amino acids such as tryptophan.[29] In the current trial, we intend to reverse the inhibitory effects of one of these mechanisms, the PD-1/PD-ligand pathway, on tumor-specific effector T cells in FL.

Immunotherapy for DLBCL. There is more evidence for targeting the immune microenvironment via the PD-1/PD-ligand pathway in Hodgkin and FL, but may be less well understood in other lymphoma subtypes.[30] T cell exhaustion via the PD-1 pathway is often exploited by tumors to evade immune surveillance. Immune blockade of PD-1/PD-L1 by monoclonal antibodies can restore the antitumor activity of cytotoxic T-cells and attenuate T-cell mediated immune responses across malignancies.[31] A phase I, open-label, dose-escalation study of nivolumab (anit-PD-1 monoclonal antibody) reported an objective

response of 36% in 11 subjects with relapsed/refractory DLBCL. [32] Though small number of subjects, the results are encouraging particularly if the responses are durable. In an international phase II trial of single agent lenalidomide, patients with relapsed or refractory DLBCL (n=108) had an ORR of 28%.[33] In our own single-center phase II study, with the rationale to increase antibody-dependent cell-mediated cytotoxicity, lenalidomide in combination with rituximab in relapsed or refractory DLBCL (n=32) or transformed lymphoma (n=9), we observed an ORR of 28% and 56%.[19] An analysis of the international CORAL Study which reported on the outcomes for patients (n=203) who were ineligible for autologous stem cell transplant, ORR with third-line chemotherapy was 39%, with a median overall survival of 4.4 months.[34] There is an unmet need for patients with relapsed/refractory DLBCL who fail to respond to standard chemotherapy based approaches. Rationale immune therapy combinations appear promising, hence the rationale for rituximab, pembrolizumab and lenalidomide in relapsed/refractory DLBCL.

4.1.2 Pharmaceutical and Therapeutic Background

PD-1/PD-ligand pathway. The PD-1 receptor-ligand interaction is a major pathway hijacked by tumors to suppress immune control. The normal function of PD-1, expressed on the cell surface of activated T-cells under healthy conditions, is to down-modulate unwanted or excessive immune responses, including autoimmune reactions. PD-1 (encoded by the gene Pdcd1) is an Ig superfamily member related to CD28 and CTLA-4, which has been shown to negatively regulate antigen receptor signaling upon engagement of its ligands (PD-L1 and/or PD-L2).[35] The structure of murine PD-1 has been resolved. PD-1 and family members are type I transmembrane glycoproteins containing an Ig Variable-type (V-type) domain responsible for ligand binding and a cytoplasmic tail which is responsible for the binding of signaling molecules. The cytoplasmic tail of PD-1 contains 2 tyrosine-based signaling motifs, an immunoreceptor tyrosine-based inhibition motif (ITIM) and an immunoreceptor tyrosine-based switch motif (ITSM). Following T-cell stimulation, PD-1 recruits the tyrosine phosphatases SHP-1 and SHP-2 to the ITSM motif within its cytoplasmic tail, leading to the dephosphorylation of effector molecules such as CD3ζ, PKCθ and ZAP70 which are involved in the CD3 T-cell signaling cascade.[35] The mechanism by which PD-1 down modulates T-cell responses is similar to, but distinct from that of CTLA-4 as both molecules regulate an overlapping set of signaling proteins.[36] PD-1 was shown to be expressed on activated lymphocytes including peripheral CD4+ and CD8+ T-cells, B-cells, Tregs and Natural Killer cells.[35] Expression has also been shown during thymic development on CD4-CD8- (double negative) T-cells as well as subsets of macrophages and dendritic cells.[35] The ligands for PD-1 (PD-L1 and PD-L2) are constitutively expressed or can be induced in a variety of cell types, including non-hematopoietic tissues as well as in various tumors.[35, 37] Both ligands are type I transmembrane receptors containing both IgV- and IgC-like domains in the extracellular region and contain short cytoplasmic regions with no known signaling motifs. Binding of either PD-1 ligand to PD-1 inhibits T-cell activation triggered through the T-cell receptor. PD-L1 is expressed at low levels on various non-hematopoietic tissues, most notably on vascular endothelium, whereas PD-L2 protein is only detectably expressed on antigen-presenting cells found in lymphoid tissue or chronic inflammatory environments. PD-L2 is thought to control immune T-cell activation in lymphoid organs, whereas PD-L1 serves to dampen unwarranted T-cell function in

peripheral tissues.[35-37] Although healthy organs express little (if any) PD-L1, a variety of cancers were demonstrated to express abundant levels of this T-cell inhibitor.

PD-1 is markedly upregulated on intratumoral and peripheral blood $CD4^+$ and $CD8^+$ T cells of patients with FL. More importantly, PD-1 expression is associated with impaired T-cell function, and blocking PD-1 restores the function of these T cells against autologous tumor cells.[38, 39] Although FL tumor cells do not express PD-L1, its expression was observed on T cells and other stromal cells in the tumor microenvironment.[40] These data suggest that the PD-1/PD-ligand pathway plays a critical role in tumor immune evasion and should be considered as an attractive target for therapeutic intervention in FL.

Pembrolizumab. Pembrolizumab (previously known as MK-3475 and SCH 900475) is a potent and highly selective humanized monoclonal antibody (mAb) of the IgG4/kappa isotype designed to directly block the interaction between PD-1 and its ligands, PD-L1 and PD-L2 without ADCC or CDC activity.

Rituximab. Rituximab is an FDA approved drug for the treatment of relapsed FL and will be obtained through standard commercial sources. Rituximab (Rituxan®) is a chimeric monoclonal antibody against CD20 a receptor on the surface of malignant B-cell lymphocytes. The drug has activity against aggressive and indolent NHL of B-cell origin, and has been used in combination with chemotherapy. The drug is administered intravenously at doses of 375 mg mg/m². Side effects are as follows:

In clinical trials, Grade 3 and 4 cytopenias were reported in 48% of patients treated with Rituximab; these include: lymphopenia (40%), neutropenia (6%), leukopenia (4%), anemia (3%), and thrombocytopenia (2%). The median duration of lymphopenia was 14 days (range, 1 to 588 days) and of neutropenia was 13 days (range, 2 to 116 days). A single occurrence of transient aplastic anemia (pure red cell aplasia) and two occurrences of hemolytic anemia following Rituximab therapy were reported.

In addition, there have been a limited number of post-marketing reports of prolonged pancytopenia, marrow hypoplasia, progressive multifocal leucoencephalopathy, and late onset neutropenia (defined as occurring 40 days after the last dose of Rituximab) in patients with hematologic malignancies. In reported cases of late onset neutropenia (Grade 3 and 4), the median duration of neutropenia was 10 days (range 3 to 148 days). Documented resolution of the neutropenia was described in approximately one-half of the reported cases; of those with documented recovery, approximately half received growth factor support. In the remaining cases, information on resolution was not provided. More than half of the reported cases of delayed onset neutropenia occurred in patients who had undergone prior autologous stem cell transplantation.

Lenalidomide. Lenalidomide, an oral agent, is a thalidomide derivative that belongs to a class of agents known as immunomodulatory drugs (IMiDs). Lenalidomide has clinical activity in NHL and has been shown to possess several immunomodulatory properties. It enhances the proliferative and functional capacity of T cells, repairs effector T-cell synapses, increases NK cell mediated ADCC, upregulates costimulatory molecules on the tumor cell surface, and has non-immunomodulatory actions that include inhibition of angiogenesis.[17, 41-44] The molecular action of lenalidomide, and the related development of resistance, involve its

binding to protein targets cereblon, Ikaros, and Aiolos, and subsequent effects on protein ubiquitination and degradation.[45, 46]

Lenalidomide is available in 2.5mg, 5 mg, 10 mg, 15mg, 20mg, and 25mg capsules for oral administration. Each capsule contains lenalidomide as the active ingredient and the following inactive ingredients: lactose anhydrous, microcrystalline cellulose, croscarmellose sodium, and magnesium stearate.

4.1.3 Preclinical and Clinical Trial Data with Pembrolizumab

Therapeutic studies in mouse models have shown that administration of antibodies blocking PD-1/PD-L1 interaction enhances infiltration of tumor-specific CD8+ T-cells and leads ultimately to tumor rejection, either as a monotherapy or in combination with other treatment modalities. Anti-mouse PD-1 or anti-mouse PD-L1 antibodies have demonstrated anti-tumor responses as a monotherapy in models of squamous cell carcinoma, pancreatic carcinoma, melanoma, and colorectal carcinoma. Blockade of the PD-1 pathway effectively promoted CD8+ T-cell infiltration into the tumor and the presence of IFN-γ, granzyme B, and perforin, indicating that the mechanism of action involved local infiltration and activation of effector T-cell function in vivo.[35-37] Experiments have confirmed the in vivo efficacy of PD-1 blockade as a monotherapy as well as in combination with chemotherapy in syngeneic mouse tumor models (see the Investigator's Brochure).

Recent clinical data of nivolumab (MDX-1106, BMS-936558), an IgG4 monoclonal antibody against PD-1, have validated PD-1 as an attractive target for clinical therapeutic intervention. Nivolumab was tested in multiple solid tumors and promising clinical activity was noted in melanoma, renal cell carcinoma (RCC), and non-small cell lung cancer (NSCLC) at multiple doses.[47] Similarly, treatment with pembrolizumab resulted in high rate of sustained tumor regression in patients with advanced melanoma and NSCLC.[48, 49] The most common adverse events (AEs) with pembroliuzmab included fatigue, fever, chills, myalgias, and headaches. Observed immune-related AEs (irAEs) included pruritus, skin rash, pneumonitis, transaminitis, hypothyroidism, vitiligo, and diarrhea. Please refer to the Investigator's Brochure for complete details on Clinical data.

4.1.4 Ongoing Pembrolizumab Clinical Trials

Ongoing clinical trials are being conducted in advanced melanoma, non-small cell lung cancer, head and neck cancer, urothelial tract cancer, triple negative breast cancer, gastric cancer, and hematological malignancies. For study details please refer to the Investigator's Brochure.

4.2 Rationale

4.2.1 Rationale for the Trial and Selected Subject Population

As described above, we and others have observed that PD-1 is markedly overexpressed on intratumoral $CD4^+$ and $CD8^+$ T cells in FL. Its expression is associated with impaired T-cell function and blocking PD-1 enhanced the function of intratumoral $CD4^+$ and $CD8^+$ T-cells in FL. Therefore, administration of pembrolizumab may augment the naturally induced endogenous antitumor immunity in patients with FL. Rituximab targets CD20 on the tumor cells and induces apoptosis via antibody-dependent cellular cytotoxicity (ADCC) mediated

by NK cells and/or macrophages. By blocking PD-1, pembrolizumab activates antitumor T cells and therefore would induce complementary effects to rituximab. Furthermore, the apoptosis of tumor cells induced by rituximab might result in release of tumor antigens and lead to activation of additional T cells, the function of which might be enhanced by pembrolizumab. Therefore, the combination of rituximab and pembrolizumab might even have synergistic effects. Furthermore, activating multiple arms of the immune system is likely to minimize the emergence of immune escape variants and recurrence of lymphoma in these patients. Based on the known mechanisms of action of rituximab and pembrolizumab and the established safety profile of the two agents, the combination is not expected to increase the toxicity of either agent.

Indeed, in a recent single arm phase II trial, we showed that the use of rituximab in combination with another immune checkpoint inhibitor, pidilizumab was safe and induced an ORR of 66%, CRR of 52%), and improved PFS in patients with relapsed FL compared to historical controls of rituximab monotherapy (ORR of 40% and CRR of 11%).[50] The reported affinity of pembrolizumab to PD-1 is almost 3 logs higher compared to pidilizumab and the reported efficacy of pembrolizumab is much higher than pidilizumab in melanoma patients.[48, 51] Therefore, the combination of rituximab and pembrolizumab is likely to be highly effective and possibly superior to what was observed with rituximab plus pidilizumab. Furthermore, based on the known mechanisms of actions of the two agents and based on the observation that the combination of rituximab plus pidilizumab was well tolerated, we do not expect to see any increased toxicity with the combination of rituximab plus pembrolizumab. Given that the median age at diagnosis for FL is 60 years, development of such therapeutic strategies that increase efficacy without increasing toxicity is highly desirable.

A recent analysis of the National LymphoCare study revealed a high risk group of patients with FL in need of novel therapies as their median survival was approximately five years.[52] These high risk patients were characterized as having an early progression event within two years of diagnosis. The eligibility criteria in the initial design of this study restricted inclusion to patients that were sensitive to rituximab similar to our previous phase II study investigating rituximab in combination with pidilizumab. This restricted eligibility to patients with longer remission durations following therapy and inadvertently, excluded many of these high risk patients in which a non-chemotherapy approach may be appealing. Therefore, we are proposing to explore this novel immune therapy combination in patients with both rituximab sensitive and refractory disease and we aim to explore whether the addition of an additional immune therapy agent, lenalidomide will result in added efficacy without additional toxicity in comparison to historical controls.

We have extensive experience with lenalidomide and rituximab in lymphoma, having completed phase I/II investigator initiated studies [19, 20, 53] and several ongoing trials with this combination. Pembrolizumab has been combined with lenalidomide and dexamethasone in relapsed/refractory multiple myeloma (KEYNOTE-023, NCT02036502) with preliminary findings suggesting the combination was tolerable and efficacy was promising with the recommended phase II dose of 200mg of pembrolizumab and lenalidomide dose as high as 25mg.[54] It is important to note, KEYNOTE-185 (NCT02579863) is a randomized study examining pembrolizumab (200mg), plus lenalidomide (25mg) and dexamethasone (40mg)

versus lenalidomide and dexamethasone in untreated multiple myeloma. The preliminary safety data reported at ASCO 2018 was concerning for a death rate of 13% in the pembrolizumab containing arm (13 deaths due to AEs) and 6% in the control arm (8 deaths due to AEs) suggesting the efficacy-safety profile was unfavorable for pembrolizumab in combination with lenalidomide and dexamethasone in untreated multiple myeloma. This safety concern was not observed in the relapsed/refractory setting suggesting that treatment status may be associated with toxicity with the combination.

We have experience with lenalidomide and rituximab in a similar patient population (relapsed/refractory FL and DLBCL), and understand the safety profile of lenalidomide and rituximab. We will perform a dose escalation in cohort 2 to ensure adequate safety of the triplet combination starting with lenalidomide at 2.5 mg on days 1-14 of cycles 1-12 and escalating to a maximum of 10mg if the maximum tolerated dose (MTD) is not reached. Once the recommended phase II dose (R2PD) has been established, we will complete the dose expansion at the RP2D of lenalidomide.

Rationale for Dose Selection/Regimen/Modification

The dose regimen of 200 mg Q3W of pembrolizumab is planned for this study. Available PK results in subjects with melanoma, NSCLC, and other solid tumor types support a lack of meaningful difference in PK exposures obtained at a given dose among tumor types. An open-label Phase 1 trial (PN001) in melanoma subjects is being conducted to evaluate the safety and clinical activity of single agent pembrolizumab. The dose escalation portion of this trial evaluated three dose levels, 1 mg/kg, 3 mg/kg, and 10 mg/kg, administered every 2 weeks (Q2W) in subjects with advanced solid tumors. All three dose levels were well tolerated and no dose-limiting toxicities were observed. This first in human study of pembrolizumab showed evidence of target engagement and objective evidence of tumor size reduction at all dose levels (1 mg/kg, 3 mg/kg and 10 mg/kg Q2W). No maximum tolerated dose (MTD) has been identified.

In KEYNOTE-001, two randomized cohort evaluations of melanoma subjects receiving pembrolizumab at a dose of 2 mg/kg versus 10 mg/kg Q3W have been completed. The clinical efficacy and safety data demonstrate a lack of clinically important differences in efficacy response or safety profile at these doses. For example, in Cohort B2, advanced melanoma subjects who had received prior ipilimumab therapy were randomized to receive pembrolizumab at 2 mg/kg versus 10 mg/kg Q3W. The ORR was 26% (21/81) in the 2mg/kg group and 26% (25/79) in the 10 mg/kg group (full analysis set (FAS)). The proportion of subjects with drug-related adverse events (AEs), grade 3-5 drug-related AEs, serious drug-related AEs, death or discontinuation due to an AE was comparable between groups or lower in the 10 mg/kg group.

Available pharmacokinetic results in subjects with melanoma, NSCLC, and other solid tumor types support a lack of meaningful difference in pharmacokinetic exposures obtained at a given dose among tumor types. Population PK analysis has been performed and has confirmed the expectation that intrinsic factors do not affect exposure to pembrolizumab to a clinically meaningful extent. Taken together, these data support the use of lower doses

(with similar exposure to 2 mg/kg Q3W) in all solid tumor indications. 2 mg/kg Q3W is being evaluated in NSCLC in PN001, Cohort F30 and PN010, and 200 mg Q3W is being evaluated in head and neck cancer in PN012, which are expected to provide additional data supporting the dose selection.

Selection of 200 mg as the appropriate dose for a switch to fixed dosing is based on simulation results indicating that 200 mg will provide exposures that are reasonably consistent with those obtained with 2 mg/kg dose and importantly will maintain individual patient exposures within the exposure range established in melanoma as associated with maximal clinical response. A population PK model, which characterized the influence of body weight and other patient covariates on exposure, has been developed using available data from 476 subjects from PN001. The distribution of exposures from the 200 mg fixed dose are predicted to considerably overlap those obtained with the 2 mg/kg dose, with some tendency for individual values to range slightly higher with the 200 mg fixed dose. The slight increase in PK variability predicted for the fixed dose relative to weight-based dosing is not expected to be clinically important given that the range of individual exposures is well contained within the range of exposures shown in the melanoma studies of 2 and 10 mg/kg to provide similar efficacy and safety. The population PK evaluation revealed that there was no significant impact of tumor burden on exposure. In addition, exposure was similar between the NSCLC and melanoma indications. Therefore, there are no anticipated changes in exposure between different tumor types and indication settings.

4.2.2 Rationale for Endpoints

4.2.2.1 Efficacy Endpoints

The primary efficacy endpoint is to determine the ORR in subjects with relapsed/refractory FL or DLBCL. Secondary efficacy endpoints include assessment of safety and toxicity, CRR, PFS, compare PFS between patients relapsing ≤ one year vs > one year after last prior therapy, and OS. Cheson 2014 Lugano Classification response criteria for malignant lymphoma will be used to assess clinical responses.[1] Subjects enrolled on this study are expected to have relapsed after responding to prior rituximab-based therapies. Retreatment with rituximab in such patients induces an ORR of 40% and CRR of 11%.[15] Since the combination of rituximab plus pembrolizumab is likely to be complementary and possibly synergistic, we expect to observe an improvement in ORR by at least 20% in cohort 1 of this trial. We may also observe an improvement in CRR and PFS as compared with rituximab monotherapy.

Among patients in cohort 2 with relapsed/refractory FL or DLBCL, ORR of approximately 30% have been observed with lenalidomide and rituximab [19] and PD-1 antibodies [32]. Standard of care third-line chemotherapy has been associated with an ORR of 39%, with a median duration of response of less than 5 months and an unfavorable toxicity profile.[34] With the combination of rituximab, pembrolizumab, and lenalidomide we expect to observe an improvement in ORR by at least 10% in cohort 2 which is a higher risk population than cohort 1.

4.2.2.2 Biomarker Research

Blood samples and tumor biopsies will be obtained from consenting patients at baseline and/or on treatment from subjects enrolled on the study at the indicated time points shown in the Trial Flow Chart under Section 6.0. The overall goal of the biomarker studies is to identify predictive, surrogate, mechanistic, and pharmacodynamic biomarkers of rituximab plus pembrolizumab therapy. Peripheral blood mononuclear cells (PBMC) and serum will be isolated from blood samples and cryopreserved for batched analysis.

PBMC samples will be analyzed by up to 10-color multiparametric flow cytometry to determine alteration in effector and regulatory T cell subsets and to determine expression of various co-stimulatory and co-inhibitory receptors on T cells. Serum samples will be analyzed for alteration in various cytokines and chemokines. Tumor biopsies will be analyzed by whole genome gene expression profiling (GEP), immunohistochemistry (IHC), and/or flow cytometry. IHC/flow cytometry assessment will include PD-1, PD-L1, and PD-L2 expression besides evaluation of effector and regulatory T cell subsets. We will also assess the predictive significance of the intratumoral effector T cell gene signature that was associated with clinical outcome in FL patients treated with rituximab plus pidilizumab therapy that was recently described by us.[50]

5.0 METHODOLOGY

5.1 Entry Criteria

5.1.1 Diagnosis/Condition for Entry into the Trial

5.1.2 In order to be eligible for participation in this trial, the subject must:

1. **For cohort 1**: Male or female subjects with histologic proof of follicular lymphoma grade 1, 2, or 3a relapsing after at least one prior systemic therapy that included rituximab (or other monoclonal CD20 antibody). Patients should have documented rituximab-sensitive disease defined as a documented complete or partial response lasting at least 6 months after the last rituximab-containing therapy.
2. **For cohort 2**: Male or female subjects with histologic proof of follicular lymphoma grade 1, 2, or 3a relapsing after at least two prior systemic therapies, which must include CAR T cell therapy or histologic proof of DLBCL relapsing after at least two prior systemic therapies, which must include CAR T cell therapy.
3. Either the subject or his/her legally authorized representative be willing and able to provide written informed consent for the trial.
4. Be ≥ 18 years of age on day of signing informed consent.
5. Have measurable disease (≥ 1.5 cm in the longest diameter for nodal or extranodal disease).
6. Have a performance status of 0 or 1 on the ECOG Performance Scale.
7. Demonstrate adequate organ function as defined in Table 1, all screening labs should be performed within 28 days of treatment initiation.

8. Female subject of childbearing potential should have a negative urine or serum pregnancy test within 72 hours prior to receiving the first dose of study medication. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required.
9. Female subjects of childbearing potential should be willing to use 2 methods of birth control or be surgically sterile, or abstain from heterosexual activity for the course of the study through 120 days after the last dose of study medication (Reference Section 5.5.1). Female subjects of childbearing potential are those who have not been surgically sterilized or have not been free from menses for > 1 year.
    a. Females of reproductive potential enrolled in the lenalidomide cohort must adhere to the scheduled pregnancy testing as required in the Revlimid REMS® program.
10. Male subjects should agree to use two methods of contraception starting with the first dose of study therapy through 120 days after the last dose of study therapy.
11. All study participants enrolled in the lenalidomide containing cohort (cohort 2) must be registered into the mandatory Revlimid REMS® program, and be willing and able to comply with the requirements of the REMS® program.

Table 1. Adequate Organ Function Laboratory Values.

System	Laboratory Value
Hematological	
Absolute neutrophil count (ANC)	≥1.0 × 10^9/L
Platelets	≥50 × 10^9/L
Hemoglobin	≥8.0 g/dL
Renal	
Serum creatinine **OR** Measured or calculated[a] creatinine clearance (GFR can also be used in place of creatinine or CrCl)	≤1.5 × upper limit of normal (ULN) **OR** ≥60 mL/min GFR or CrCl for subjects with creatinine levels > 1.5 × institutional ULN
Hepatic	
Serum total bilirubin	≤ 1.5 × ULN **OR**
	Direct bilirubin ≤ ULN for subjects with total bilirubin levels > 1.5 ULN
AST (SGOT) and ALT (SGPT)	≤ 2.5 × ULN **OR** ≤ 5 × ULN for subjects with lymphoma in the liver
Coagulation	
International Normalized Ratio (INR) or Prothrombin Time (PT)	≤1.5 × ULN unless subject is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants
Activated Partial Thromboplastin Time (aPTT)	≤1.5 × ULN unless subject is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants
[a]Creatinine clearance will be calculated per institutional standard.	

5.1.3 Subject Exclusion Criteria

The subject must be excluded from participating in the trial if the subject:

1. Is currently participating and receiving study therapy or has participated in a study of an investigational agent and received study drug or using an investigation device within 4 weeks of the first dose of treatment.
2. Has a diagnosis of immunodeficiency or is receiving systemic steroid therapy or any other form of immunosuppressive therapy within 7 days prior to the first dose of trial treatment.
3. Has had a prior monoclonal antibody within 4 weeks prior to study Day 1 or who has not recovered (i.e., ≤ Grade 1 or at baseline) from AEs due to agents administered more than 4 weeks earlier.
4. Has had prior chemotherapy, targeted small molecule therapy, or radiation therapy within 2 weeks prior to study Day 1 or who has not recovered (i.e., ≤ Grade 1 or at baseline) from AEs due to a previously administered agent.
    - Note: Subjects with ≤ Grade 2 neuropathy are an exception to this criterion and may qualify for the study.
    - Note: If subject received major surgery, they must have recovered adequately from the toxicity and/or complications from the intervention prior to starting therapy.
5. Has a known additional malignancy that is progressing and requires active treatment. Exceptions include basal cell carcinoma of the skin, squamous cell carcinoma of the skin, or in situ cervical cancer that has undergone potentially curative therapy.
6. Has known active central nervous system (CNS) lymphoma and/or lymphomatous meningitis. Subjects with previously treated CNS lymphoma and/or lymphomatous meningitis may participate provided they are stable (without evidence of progression by imaging for at least four weeks prior to the first dose of trial treatment and any neurologic symptoms have returned to baseline), have no evidence of new or enlarging brain metastases, and are not using steroids for at least 7 days prior to trial treatment.
7. No active autoimmune disease that has required systemic treatment in 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. Subjects with vitiligo or resolved childhood asthma/atopy would be an exception to this rule. Subjects that require intermittent use of bronchodilators, local steroid injections or inhaled or topical steroids would not be excluded from the study. Subjects with hypothyroidism stable on hormone replacement or Sjorgen's syndrome will not be excluded from the study.
8. Has evidence of interstitial lung disease or active, non-infectious pneumonitis that required steroids or current pneumonitis.
9. Has an active infection requiring systemic therapy.

10. Has a history or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the trial, interfere with the subject's participation for the full duration of the trial, or is not in the best interest of the subject to participate, in the opinion of the treating investigator.
11. Has known psychiatric or substance abuse disorders that would interfere with cooperation with the requirements of the trial.
12. Is pregnant or breastfeeding, or expecting to conceive or father children within the projected duration of the trial, starting with the pre-screening or screening visit through 120 days after the last dose of trial treatment.
13. Has received prior therapy with an anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, or anti-Cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4) antibody (including ipilimumab or any other antibody or drug specifically targeting T-cell co-stimulation or checkpoint pathways).
    - Note: Subjects that received prior therapy with pidilizumab are an exception to this criterion and may qualify for the study.
14. Has a known history of Human Immunodeficiency Virus (HIV) (HIV 1/2 antibodies).
15. Has known active Hepatitis B (e.g., HBsAg reactive) or Hepatitis C (e.g., HCV RNA [qualitative] is detected).
16. Has received a live vaccine within 30 days prior to the first dose of trial treatment.

5.2 Trial Treatments

The treatment to be used in this trial is outlined below in **Table 2**. There will be 2 cohorts. Cohort 1 will include patients with relapsed FL with rituximab-sensitive and rituximab-refractory disease. Treatment will consist of rituximab + pembrolizumab. Cohort 2 will include patients with relapsed/refractory FL or DLBCL and will consist of rituximab + pembrolizumab + lenalidomide.

Table 2. Trial Treatment

Drug	Dose/Potency	Dose Frequency	Route of Administration	Regimen/ Treatment Period	Use
Cohort 1: Relapsed FL					
Rituximab	375 mg/m^2	weekly	IV infusion	4 infusions over 4 weeks	Standard
Pembrolizumab	200 mg	Q 3 weeks	IV infusion	16 infusions over 1 year	Experimental
Cohort 2: Relapsed/refractory FL or DLBCL					
Rituximab	375 mg/m^2	weekly	IV infusion	4 infusions over 4 weeks	Standard
Pembrolizumab	200 mg	Q 3 weeks	IV infusion	up to 2 years*	Experimental

Drug	Dose/Potency	Dose Frequency	Route of Administration	Regimen/ Treatment Period	Use
Lenalidomide	2.5mg±	Days 1-14 of cycles 1-12	PO	Days 1-14 of cycles 1-12	Experimental
*Pembrolizumab will be administered every 3 weeks starting on day 1 up to 2 years of therapy. Per the investigator's discretion, subjects who attain an investigator-determined CR may consider stopping pembrolizumab treatment after receiving at least 24 weeks of pembrolizumab therapy. At least two doses must be received after CR is documented. ± There will be a dose escalation phase of lenalidomide in cohort 2 as outlined in Section 5.2.1.2.2.1. Dose level 1 will include lenalidomide 2.5mg on days 1-14 of cycles 1-12. Dose level 2 will include lenalidomide 5mg on days 1-14 of cycles 1-12. Dose level 3 will include lenalidomide 10mg on days 1-14 of cycles 1-12. The dosing of pembrolizumab and/or lenalidomide may be altered due to toxicity as described in Section 5.2.1.2.					

5.2.1 Dose Selection/Modification

5.2.1.1 Dose Selection

The rationale for selection of doses to be used in this trial is provided in Section 4.0 – Background and Rationale. There is no dose modification for rituximab.

5.2.1.2 Guidelines for Dose Modification

5.2.1.2.1 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. Subjects should be placed back on study therapy within 3 weeks of the scheduled interruption, unless otherwise discussed with the PI. The reason for interruption should be documented in the patient's study record. Pembrolizumab may be restarted when clinically indicated according to any applicable dose modification guidelines and the dosing schedule conforms to the schedule of the normal dosing Cycle. Pembrolizumab will be withheld for drug-related Grade 4 hematologic toxicities, non-hematological toxicity ≥ Grade 3 including laboratory abnormalities, and severe or life-threatening AEs as per **Table 3** and **Table 4** below.

Table 3: Dose modification guidelines for Hematological drug-related AEs.

Toxicity	**Grade**	**Hold Treatment (Y/N)**	**Timing for restarting treatment**	**Dose/Schedule for restarting treatment**	**Discontinue Subject**
Hematological Toxicity	1, 2, 3	No	N/A	N/A	N/A
	4	Yes	Toxicity resolves to	May restart pembrolizumab	Toxicity does not resolve

			Grade 0-1 or baseline	at 200 mg Q 3 weeks	within 4 weeks of last infusion Permanent discontinuation should be considered for any severe or life-threatening event

Table 4: Dose modification guidelines for Non-Hematological drug-related AEs.

Toxicity	Grade	Hold Treatment (Y/N)	Timing for restarting treatment	Dose/Schedule for restarting treatment	Discontinue Subject
Non-hematological toxicity Note: Exception to be treated similar to Grade 1 toxicity • Grade 2 alopecia • Grade 2 fatigue For additional information regarding Adverse Events with a potential Immune-Etiology reference Section 5.4.1.1 and 5.4.1.2.	1	No	N/A	N/A	N/A
	2	Consider withholding for persistent symptoms [1,2]	Toxicity resolves to Grade 0-1 or baseline	*Clinical AE resolves within 4 weeks*: Same dose and schedule (reference Section 5.4.1.2 for recommendations regarding pneumonitis)	Toxicity does not resolve within 4 weeks of last infusion
	3	Yes [3]	Toxicity resolves to Grade 0-1 or baseline	May restart pembrolizumab at 200 mg Q 3 weeks	Toxicity does not resolve within 4 weeks of last infusion
	4	NA	NA	NA	Pembrolizumab will be permanently discontinued

[1] During DLT evaluation period, depending on the nature of AE, for subjects who develop **Grade 2** non-heme drug-related AE, MK-3475 will not be held, if symptoms improve with appropriate supportive care and symptomatic treatment within 3 days.

[2] During DLT evaluation period, depending on the nature of AE, for subjects who develop **Grade 2** non-heme drug-related AE, MK-3475 will be held, if symptoms do not improve with appropriate supportive care and symptomatic treatment within 3 days and it will be considered DLT.

[3] During DLT evaluation period, for subjects who develop **Grade 3** non-heme drug-related AE, MK-3475 will be held (except for inadequately treated nausea, hypersensitivity reactions, or fatigue lasting less than 3 days) and it will be considered DLT.

For toxicity related to pembrolizumab that does not resolve to Grade 0-1 within 4 weeks after last infusion, trial treatment should be discontinued. For information on the management of AEs, see Section 5.4.

For subjects who experience a recurrence of the same AE(s) at the same grade or greater with rechallenge of pembrolizumab, the subject must discontinue trial treatment

Subjects who experience a recurrence of the same severe or life-threatening event at the same grade or greater with re-challenge of pembrolizumab should be discontinued from trial treatment.

5.2.1.2.2 Lenalidomide

Patients in cohort 2 with creatinine clearance (CrCl) >60 mL/min as determined by modified Crockcroft-Gault (see Appendix) will receive a total of 12 cycles of lenalidomide as outlined in Section 5.2, **Table 2**. Subjects with renal impairment (CrCl ≤ 60 ml/min) will be dosed based on **Table 5**. CrCL assessment will occur on: Day 1 of each cycle. However, if a subject has a creatinine obtained at any time during the administration of lenalidomide on study because it was clinically indicated, a dose reduction based on CrCL and **Table 5** should be performed.

For subjects with renal impairment (CrCl ≤ 60 ml/min) necessitating dose adjustment on Day 1 of a cycle according to **Table 5**, but then stably improves, a dose increase based on CrCL will not occur until day 1 of the next cycle. At any point, should a patient require dose reduction due to reduced CrCl, and the CrCl then stably improves, dose escalation will not occur until day 1 of the next cycle.

Table 5: Lenalidomide Dose Adjustment in Cohort 2.

Category	**Renal Function (modified Cockcroft-Gault)**	**Dose level 1***	**Dose level 2**	**Dose level 3**
Mild or no renal impairment	CrCl > 60 mL/min	2.5 mg once daily	5mg once daily	10 mg once daily
Moderate renal impairment	CrCl 30-60 mL/min	2.5 mg every 48 hours	2.5 mg once daily	5 mg every 24 hours
Severe renal impairment	CrCl <30mL/min (not requiring dialysis)	2.5 mg every 72 hours	2.5 mg every 48 hours	5 mg every 48 hours

5.2.1.2.2.1 Dose Escalation Phase: Cohort 2

The dose escalation phase of cohort 2 will assess the safety/tolerability of escalating doses of lenalidomide combined with rituximab and pembrolizumab as outlined in Table 2.

All adverse events including dose limiting toxicity (DLT) will be reported according to the instructions in Section 7.2 and graded according to NCI CTCAE v. 4.

During the dose escalation phase, a DLT will be defined as any of the following adverse events which occur from Cycle 1 Day 1 through Cycle 1 Day 28.

- Grade 4 neutropenia lasting > 7 days
- Grade 3 neutropenia associated with fever (single temperature of > 38.3 ºC, or with a sustained temperature of ≥ 38 º C lasting > 1 hour)
- Grade 4 thrombocytopenia
- Grade 3 or 4 non-hematologic adverse event not considered by the investigator to be attributable to another clearly identifiable cause

Patients who discontinue from the study prior to completing the DLT assessment window for reasons other than a DLT will be considered non-evaluable for dose-escalation decisions and will be replaced by an additional patient at that same dose level. Subjects must be monitored for the entirety of the DLT window (28 days) before the next dose level cohort can begin.

Initial dose escalation will utilize single patient cohorts and the dose levels outlined in Table 5 until one of the following occurs:

1. A DLT occurs
2. Escalation reaches a dose of 10mg of lenalidomide (level 3)

If any one of the above conditions is met, whichever occurs first, the dose escalation will be modified to a standard 3+ 3 design (at the same dose level) and conducted in accordance with the following rules:

1. A minimum of 3 patients will initially be enrolled in each cohort unless the first 2 enrolled patients experience a protocol-defined DLT (see above) in which case enrollment into the cohort will be terminated.
2. If none of the first 3 DLT-evaluable patients experiences a DLT, enrollment of the next cohort at the next highest dose level may proceed.
3. If 1 of the first 3 DLT-evaluable patients experiences a DLT, the cohort will be expanded to at least 6 patients. All patients will be evaluated for DLTs before any dose-escalation decision.
    a. If DLTs are observed in 1 of 6 DLT-evaluable pateitns, enrollment of the next dose-escalation cohort may proceed.
    b. If DLTs are observed in ≥ 2 of 6 subjects, the dose-escalation will be halted and that dose declared as exceeding the maximum tolerated dose (MTD).
4. The MTD will be defined as the highest dose level resulting in DLTs in ≤ 1 of 6 patients.
5. If the MTD is not exceeded, the highest dose administered in this study will be declared dose level 3.

Once the MTD has been defined, dose-escalation will stop and enrollment at MTD or recommended phase 2 dose (R2PD) will commence for the dose expansion phase.

5.2.1.2.2.2 Dose Expansion Phase: Cohort 2

Toxicities necessitating dose modification of lenalidomide or delay during the dose expansion phase will be defined as any non-hematologic or hematologic toxicity listed below. Treatment with rituximab, pembrolizumab, and/or lenalidomide should be discontinued in the event of a toxicity lasting more than 4 weeks despite appropriate medical management, unless reviewed and approved by the Principal Investigator. The action in **Table 6** should be taken for the following lenalidomide toxicities:

Non-hematologic toxicity will be defined as any of the following:

- Any unmanageable Grade 3 or 4 non-hematologic toxicity with failure to improve (< Grade 2) or recover to baseline within 14 days of withholding drug
- Grade 3 non-blistering rash that does not resolve to < Grade 2 within 14 days
- Any desquamating (blistering) or grade 4 rash
- Any grade Stevens-Johnson syndrome or toxic epidermal necrolysis
- Grade 3 or 4 thrombosis/embolism
- Grade 3 or 4 peripheral neuropathy which began or worsened while on study

Hematologic toxicity will be defined as any of the following:

- Grade 3 neutropenia with infection or fever (single temperature of > 38.3 ºC, or with a sustained temperature of ≥ 38 º C lasting > 1 hour).
- Grade 4 neutropenia (ANC<500/µL) lasting > 7 days.
- Grade 4 thrombocytopenia (<25,000/µL)

The following action in **Table 6** should be taken for any unmanageable toxicity that is consistent with the rules outlined above:

Table 6. Dose Modification for Lenalidomide Toxicity.

Toxicity Grade	Action to be Taken

Grade 3 neutropenia associated with fever (single temperature of > 38.3 ºC, or with a sustained temperature of ≥ 38 º C lasting > 1 hour) OR Grade 4 neutropenia lasting > 7 days.	•Hold lenalidomide. •Follow CBC weekly. •If neutropenia has resolved to < Grade 2 prior to Day 21 of the current cycle, restart lenalidomide at next lower dose level, (see Table 5) and continue through the scheduled Day 21 of the current cycle. Otherwise, omit for remainder of cycle and reduce the dose of lenalidomide by 1 dose level at the start of the next cycle. •Omitted doses are not made up. •G-CSF may be used. •Hold pembrolizumab and rituximab for grade 4 neutropenia until resolved to ≤ Grade 1.
Grade 3 thrombocytopenia	• Follow CBC weekly. • Hold prophylactic anti-coagulation including aspirin, if applicable. • Restart prophylactic anti-coagulation and/or aspirin when platelet count is ≥ 50,000/mm³.
≥ Grade 4 thrombocytopenia	• Hold lenalidomide. • Follow CBC weekly. • If thrombocytopenia resolves to < Grade 2 prior to Day 21 of the current cycle, restart lenalidomide at next lower dose level and continue through the scheduled Day 21 of the current cycle. Otherwise, omit for remainder of cycle and reduce the dose of lenalidomide by 1 dose level at the start of the next cycle. • Omitted doses are not made up. • Hold prophylactic anti-coagulation including aspirin, if applicable. • Restart prophylactic anti-coagulation and/or aspirin when platelet count is ≥ 50,000/mm³. • Hold pembrolizumab and rituximab until resolved to ≤ Grade 1.
Non-blistering rash ≥ Grade 3	• If Grade 3, hold lenalidomide. • Follow weekly. • If the toxicity resolves to < Grade 2 prior to Day 21 of the current cycle, restart lenalidomide at original dose level (for first occurrence) and continue through the scheduled Day 21 of the current cycle. Otherwise, omit for remainder of cycle. • Omitted doses are not made up.

	• For the second occurrence of Grade 3, hold lenalidomide, and follow weekly. If the toxicity resolves to ≤ Grade 2 prior to Day 21 of the current cycle, restart lenalidomide at next lower dose level and continue through the scheduled Day 21 of the current cycle. Otherwise, omit for remainder of cycle and reduce the dose of lenalidomide by 1 dose level at the start of the next cycle. Omitted doses are not made up. • Treatment with 10mg of prednisone or equivalent for 10 days (with or without taper) and/or antihistamines PO daily is recommended. •If Grade 3 rash has not improved to at least Grade 2 within 14 days of drug being withheld and administration of 10mg of steroids and/or antihistamines daily, the subject will discontinue study treatment. •Hold pembrolizumab for grade 3 rash until resolved to ≤ Grade 1. •Permanently discontinue pembrolizumab for grade 4 rash.
Desquamating (blistering) rash Any grade	• Discontinue rituximab, pembrolizumab and lenalidomide. Remove patient from study. • Start supportive care: daily antihistamine, 10mg or higher of prednisone or corticosteroid equivalent as clinically indicated
≥ Grade 3 thrombosis/embolism	•Hold lenalidomide and start therapeutic anticoagulation. •Restart lenalidomide at investigator's discretion (maintain dose level) after anticoagulation is initiated.
Peripheral neuropathy Grade 3 Grade 4	•If Grade 3, hold lenalidomide dose. Follow at least weekly. •If the toxicity resolves to ≤ grade 1 prior to Day 21 of the current cycle, restart lenalidomide at next lower dose level and continue through the scheduled Day 21 of the current cycle. Otherwise, omit for remainder of cycle and reduce the dose of lenalidomide by 1 dose level at the start of the next cycle. Omitted doses are not made up. •If Grade 4, discontinue lenalidomide. Remove patient from study.
Other non-hematologic toxicity ≥ Grade 3	• Hold lenalidomide. Follow at least weekly. • If the toxicity resolves to < Grade 2 prior to Day 21 of the current cycle, restart lenalidomide and continue through the scheduled Day 21 of the current cycle. Otherwise, omit for remainder of cycle. Omitted doses are not made up. For toxicity attributed to lenalidomide, reduce the lenalidomide dose by 1 dose level when restarting lenalidomide.

	• Hold pembrolizumab Grade 3 non-hematologic toxicity until resolved to ≤ Grade 1. • Permanently discontinue pembrolizumab for Grade 4 toxicity.

The dose of lenalidomide may be reduced successively by one level from starting dose, **Table 5**. Once a patient's dose has been reduced, no dose re-escalation is permitted. Patients who cannot tolerate the lowest applicable dose level are to be discontinued from study. Dose modification should also meet the specifications outlined for those subjects with renal insufficiency as outlined in **Table 5**.

5.2.2 Timing of Dose Administration

Trial treatment should be administered after all procedures/assessments have been completed as detailed on the Trial Flow Chart (Section 6.0). A time window of +/- 1 day for rituximab infusions on days 8, 15, and 22, +/- 3 days for 2nd through final infusion of pembrolizumab and +/- 3 days for initiation of lenalidomide for cycles 1-12 is allowed.

All trial treatments will be administered on an outpatient basis.

Rituximab will be administered as per standard protocol.

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

The Procedures Manual contains specific instructions for pembrolizumab dose calculation, reconstitution, preparation of the infusion fluid, and administration.

Lenalidomide (Revlimid®) will be provided in accordance with the Celgene Corporation's Revlimid REMS® program. Per standard Revlimid REMS® program requirements, all physicians who prescribe lenalidomide for research subjects enrolled into this trial, and all research subjects enrolled into this trial, must be registered in, and must comply with, all requirements of the Revlimid REMS® program.

Further information about the Revlimid REMS® program is available at www.celgeneriskmanagement.com.

Drug will be shipped on a per patient basis by the contract pharmacy to the clinic site for IND studies. Only enough lenalidomide for one cycle of therapy will be supplied to the patient each cycle.

Lenalidomide should be taken orally at about the same time each day, either with or without food. Lenalidomide capsules should be swallowed whole with water, and should not be opened, broken, or chewed. If a dose is missed, it can be taken as soon as possible on the same day with a return to the normal schedule the following day. No extra capsules to make up the missed dose should be taken. Females of childbearing potential should not handle or administer lenalidomide unless they are wearing gloves.

Additional prescribing information can be found at www.revlimid.com/wp-content/uploads/2013/11/PI.pdf

A subject with *unconfirmed* PD may continue trial treatment until PD is confirmed at the next scheduled assessment (refer to Section 7.1.2.6.3 for details). Subjects may only receive study treatment while waiting for confirmation of PD if the following criteria are met:

- Absence of signs and symptoms (including worsening of laboratory values) indicating disease progression
- No decline in ECOG performance status
- Absence of rapid PD
- Absence of progressive tumor at critical anatomical sites (e.g. cord compression) requiring urgent alternative medical intervention

If a subject is noted to have *confirmed* PD by the respective response criteria, the subject should not receive further treatment with study medication except if PD was at week 12 assessment (see Section 7.1.2.6.4 for details).

5.3 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 subject's primary physician. However, the decision to continue the subject on trial therapy or vaccination schedule requires the mutual agreement of the Investigator and the subject.

5.3.1 Acceptable Concomitant Medications

All treatments that the investigator considers necessary for a subject's welfare may be administered at the discretion of the investigator in keeping with the community standards of medical care. All concomitant medication will be recorded in the medical record 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. Subjects may remain on anti-coagulation therapy as long as the PT or PTT is within therapeutic range of the intended use of anticoagulants.

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 events of clinical interests (ECIs) as defined in Section 7.2.

5.3.2 Prohibited Concomitant Medications

Subjects are prohibited from receiving the following therapies during the Treatment Phase of this trial:

- Antineoplastic systemic chemotherapy or biological therapy
- Immunotherapy not specified in this protocol
- Chemotherapy not specified in this protocol
- Investigational agents other than pembrolizumab
- Radiation therapy
- Live vaccines within 30 days prior to the first dose of trial treatment and while participating in the trial. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, chicken pox, yellow fever, rabies, BCG, and typhoid (oral) vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed; however intranasal influenza vaccines (e.g. Flu-Mist®) are live attenuated vaccines, and are not allowed.
- Systemic use of glucocorticoids for any purpose other than to modulate symptoms from an ECI of suspected immunologic etiology or for patients undergoing CT scan with a contrast allergy. The use of physiologic doses of corticosteroids may be allowed.

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

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

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

5.4 Rescue Medications & Supportive Care

5.4.1 Supportive Care Guidelines

Subjects should receive appropriate supportive care measures as deemed necessary by the treating investigator including but not limited to the items outlined below:

- Diarrhea: Subjects should be carefully monitored for signs and symptoms of enterocolitis (such as diarrhea, abdominal pain, blood or mucus in stool, with or without fever) and of bowel perforation (such as peritoneal signs and ileus). In symptomatic subjects, infectious etiologies should be ruled out, and if symptoms are persistent and/or severe, endoscopic evaluation should be considered. Please refer to **Table 8** for toxicity management guidelines for immune-related AEs.
    - In subjects with severe enterocolitis (Grade 4), pembrolizumab will be permanently discontinued and treatment with systemic corticosteroids should be initiated at a dose of 1 to 2 mg/kg/day of prednisone or equivalent. When symptoms improve to Grade 1 or less, corticosteroid taper should be started and continued over at least 1 month.
    - In subjects with moderate enterocolitis (Grade 2 or 3), pembrolizumab should be withheld and anti-diarrheal treatment should be started. Systemic corticosteroids

should be initiated (e.g., 1-2 mg/kg/day of prednisone or equivalent). Consider GI consultation for endoscopy to rule out colitis. When symptoms improve to Grade 1 or less, corticosteroid taper should be started and continued over at least 1 month. Regarding guidelines for continuing treatment with pembrolizumab, see Section 5.2.

- All subjects who experience diarrhea 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.

- Nausea/vomiting: Nausea and vomiting should be treated aggressively, and consideration should be given in subsequent cycles to the administration of prophylactic antiemetic therapy according to standard institutional practice. Subjects should be strongly encouraged to maintain liberal oral fluid intake.
- Anti-infectives: Subjects with a documented infectious complication should receive oral or IV antibiotics or other anti-infective agents as considered appropriate by the treating investigator for a given infectious condition, according to standard institutional practice.
- Thrombosis Prophylaxis: It is recommended that patients in cohort 2 assigned to the lenalidomide cohort receive prophylactic aspirin (81mg) daily unless contraindicated. If aspirin is contraindicated, use of low molecular weight heparin or warfarin (or equivalent Vitamin K antagonist) to keep the international normalized ratio (INR) in the range of 2-3, or use of other anti-thrombotic therapy according to hospital guidelines, or physician preference, is acceptable. However, the choice of anticoagulant for prophylaxis for VTE relies upon the investigator's discretion and should be tailored to the patient's individual risk/benefit profile by taking into account the individual thrombotic risk (e.g., history of venous thrombosis), bleeding risk, and the quality of compliance with antithrombotic treatment. In the setting of thrombocytopenia, thromboembolism prophylaxis should be held in accordance with the guidelines established in **Table 6**. All patients who develop a deep venous thromboembolism in any location must be treated appropriately with low molecular weight heparin. Heparin should continue for at least 3 months, however treating physician discretion is allowed. Study treatment is to continue during heparin use. For subjects in whom low molecular weight heparin is contraindicated (i.e., renal impairment), a vitamin K antagonist anti-coagulant can be used instead where medically appropriate.
- Immune-related AEs: Please see Section 5.4.1.1 below and the separate guidance document regarding diagnosis and management of adverse experiences of a potential immunologic etiology.

- Management of Infusion Reactions: 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 below in in **Table 7.**

Table 7. 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 subject 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 subject 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 subject should be premedicated for the next scheduled dose. **Subjects who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further study drug treatment**	Subject may be premedicated 1.5h (± 30 minutes) prior to infusion of pembrolizumab 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 subject is deemed medically stable in the opinion of the investigator. Hospitalization may be indicated. **In cases of anaphylaxis, epinephrine should be used immediately. **Subject 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		

5.4.1.1 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 trial data, most irAEs were reversible and could be managed with interruptions of pembrolizumab, administration of corticosteroids and/or other supportive care. For suspected irAEs, ensure adequate evaluation to confirm etiology or exclude other causes. Additional procedures or tests such as bronchoscopy, endoscopy, skin biopsy may be included as part of the evaluation. Based on the severity of irAEs, withhold or permanently discontinue pembrolizumab and administer corticosteroids. Dose modification and toxicity management guidelines for irAEs associated with pembrolizumab are provided in **Table 8**.

In addition, a Guidance Document for management of Events of Clinical Interest and irAEs is attached as an Appendix.

Table 8. Dose modification and toxicity management guidelines for immune-related AEs associated with pembrolizumab

General instructions:

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

Immune-related AEs	Toxicity grade or conditions (CTCAEv4.0)	Action taken to pembrolizumab	irAE management with corticosteroid and/or other therapies	Monitor and follow-up
Pneumonitis	Grade 2	Withhold	• Administer corticosteroids (initial dose of 1-2mg/kg prednisone or equivalent) followed by taper	• Monitor subjects for signs and symptoms of pneumonitis • Evaluate subjects with suspected pneumonitis with radiographic imaging and initiate corticosteroid treatment • Add prophylactic antibiotics for opportunistic infections
	Grade 3 or 4, or recurrent grade 2	Permanently discontinue		

Diarrhea / colitis	Grade 2 or 3	Withhold	• Administer corticosteroids (initial dose of 1-2mg/kg prednisone or equivalent) followed by taper	• Monitor subjects for signs and symptoms of enterocolitis (i.e. diarrhea, abdominal pain, blood or mucus in stool with or without fever) and of bowel perforation (i.e. peritoneal signs and ileus). • Subjects with ≥ Grade 2 diarrhea suspecting colitis should consider GI consultation and performing endoscopy to rule out colitis. • Subjects with diarrhea/colitis should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion.
	Grade 4	Permanently discontinue		
AST / ALT elevation or Increased Bilirubin	Grade 2	Withhold	• Administer corticosteroids (initial dose of 0.5- 1mg/kg prednisone or equivalent) followed by taper	• Monitor with liver function tests (consider weekly or more frequently until liver enzyme value returned to baseline or is stable
	Grade 3 or 4	Permanently discontinue	• Administer corticosteroids (initial dose of 1-2mg/kg prednisone or equivalent) followed by taper	
Type 1 diabetes mellitus (T1DM) or Hyperglycemia	Newly onset T1DM or Grade 3 or 4 hyperglycemia associated with evidence of β-cell failure	Withhold	• Initiate insulin replacement therapy for subjects with T1DM • Administer anti-hyperglycemic in subjects with hyperglycemia	• Monitor subjects for hyperglycemia or other signs and symptoms of diabetes.
Hypophysitis	Grade 2	Withhold	• Administer corticosteroids	• Monitor for signs and symptoms of

	Grade 3 or 4	Withhold or permanently discontinue[1]	and initiate hormonal replacements as clinically indicated.	hypophysitis (including hypopituitarism and adrenal insufficiency)
Hyperthyroidism	Grade 2	Continue	• Treat with non-selective beta-blockers (e.g. propranolol) or thionamides as appropriate	• Monitor for signs and symptoms of thyroid disorders.
	Grade 3 or 4	Withhold or Permanently discontinue[1]		
Hypothyroidism	Grade 2-4	Continue	• Initiate thyroid replacement hormones (e.g. levothyroxine or liothyroinine) per standard of care	• Monitor for signs and symptoms of thyroid disorders.
Nephritis and renal dysfunction	Grade 2	Withhold	• Administer corticosteroids (prednisone 1-2mg/kg or equivalent) followed by taper.	• Monitor changes of renal function
	Grade 3 or 4	Permanently discontinue		
All Other immune-related AEs	Grade 3, or intolerable/ persistent Grade 2	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology or exclude other causes
	Grade 4 or recurrent Grade 3	Permanently discontinue		

NOTES:
1. Withhold or permanently discontinue pembrolizumab is at the discretion of the investigator or treating physician.
2. For subjects with Grade 3 or 4 immune-related endocrinopathy where withhold of pembrolizumab is required, pembrolizumab may be resumed when AE resolves to ≤ Grade 2 and is controlled with hormonal replacement therapy or achieved metabolic control (in case of T1DM)

5.5 Other Considerations

5.5.1 Contraception

Pembrolizumab may have adverse effects on a fetus in utero. Furthermore, it is not known if pembrolizumab has transient adverse effects on the composition of sperm. Non-pregnant, non-breast-feeding women may be enrolled if they are willing to use 2 methods of birth control or are considered highly unlikely to conceive. Highly unlikely to conceive is defined as 1) surgically sterilized, or 2) postmenopausal (a woman who is ≥45 years of age and has not had menses for greater than 1 year will be considered postmenopausal), or 3) not heterosexually active for the duration of the study. The two birth control methods can be either two barrier methods or a barrier method plus a hormonal method to prevent pregnancy. Subjects should start using birth control from study Visit 1 throughout the study period up to 120 days after the last dose of study therapy.

The following are considered adequate barrier methods of contraception: diaphragm, condom (by the partner), copper intrauterine device, sponge, or spermicide. Appropriate hormonal contraceptives will include any registered and marketed contraceptive agent that contains an estrogen and/or a progestational agent (including oral, subcutaneous, intrauterine, or intramuscular agents).

Subjects should be informed that taking the study medication may involve unknown risks to the fetus (unborn baby) if pregnancy were to occur during the study. In order to participate in the study they must adhere to the contraception requirement (described above) for the duration of the study and during the follow-up period defined in section 7.2.2-Reporting of Pregnancy and Lactation to Merck. If there is any question that a subject will not reliably comply with the requirements for contraception, that subject should not be entered into the study.

5.5.2 Use in Pregnancy

If a subject inadvertently becomes pregnant while on treatment with pembrolizumab, the subject will immediately be removed from the study. The site will contact the subject at least monthly and document the subject's status until the pregnancy has been completed or terminated. The outcome of the pregnancy will be reported to Merck without delay and within 24 hours if the outcome is a serious adverse experience (e.g., death, abortion, congenital anomaly, or other disabling or life-threatening complication to the mother or newborn). The study investigator will make every effort to obtain permission to follow the outcome of the pregnancy and report the condition of the fetus or newborn to Merck. If a male subject impregnates his female partner the study personnel at the site must be informed immediately and the pregnancy reported to Merck and followed as described above and in Section 7.2.2.

The pregnancy, suspected pregnancy, or positive pregnancy test must also be reported to Celgene Drug Safety immediately by facsimile, or other appropriate method, using the Pregnancy Initial Report Form, or approved equivalent form. The female subject may be referred to an obstetrician-gynecologist (not necessarily one with reproductive toxicity experience) or another appropriate healthcare professional for further evaluation.

The Investigator will follow the female subject until completion of the pregnancy, and must notify Celgene Drug Safety immediately about the outcome of the pregnancy (either normal or abnormal outcome) using the Pregnancy Follow-up Report Form, or approved equivalent form.

IF THE OUTCOME OF THE PREGNANCY WAS ABNORMAL (E.G., SPONTANEOUS OR THERAPEUTIC ABORTION), THE INVESTIGATOR SHOULD REPORT THE ABNORMAL OUTCOME AS AN AE. IF THE ABNORMAL OUTCOME MEETS ANY OF THE SERIOUS CRITERIA, IT MUST BE REPORTED AS AN SAE TO CELGENE DRUG SAFETY IMMEDIATELY BY FACSIMILE, OR OTHERAPPROPRIATE METHOD, WITHIN 24 HOURS OF THE INVESTIGATOR'S KNOWLEDGE OF THE EVENT USING THE SAE REPORT FORM, OR APPROVED EQUIVALENT FORM.

All neonatal deaths that occur within 28 days of birth should be reported, without regard to causality, as SAEs. In addition, any infant death after 28 days that the Investigator suspects is related to the in utero exposure to the IP should also be reported to Celgene Drug Safety immediately by facsimile, or other appropriate method, within 24 hours of the Investigator's knowledge of the event using the SAE Report Form, or approved equivalent form.

Male Subjects

If a female partner of a male subject taking investigational product becomes pregnant, the male subject taking lenalidomide should notify the Investigator, and the pregnant female partner should be advised to call their healthcare provider immediately.

5.5.3 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, subjects who are breast-feeding are not eligible for enrollment.

5.6 Subject Withdrawal/Discontinuation Criteria

Subjects may withdraw consent at any time for any reason or be dropped from the trial at the discretion of the investigator should any untoward effect occur. In addition, a subject may be withdrawn by the investigator if enrollment into the trial is inappropriate, the trial plan is violated, or for administrative and/or other safety reasons. Specific details regarding discontinuation or withdrawal are provided in Section 7.1.4.

A subject must be discontinued from the trial for any of the following reasons:

- The subject or legal representative (such as a parent or legal guardian) withdraws consent.
- Confirmed radiographic disease progression

  Note: For unconfirmed radiographic disease progression, please see Section 5.2.2

  Note: A subject may be granted an exception to continue on treatment with confirmed radiographic progression if clinically stable or clinically improved, please see Section 7.1.2.6.4
- Unacceptable adverse experiences as described in Section 5.2.1.2
- Intercurrent illness that prevents further administration of treatment
- Investigator's decision to withdraw the subject
- The subject has a confirmed positive serum pregnancy test

- Noncompliance with trial treatment or procedure requirements
- The subject is lost to follow-up
- Administrative reasons

The End of Treatment and Follow-up visit procedures are listed in Section 6 (Protocol Flow Chart) and Section 7.1.5 (Visit Requirements). After the end of treatment, each subject will be followed for 30 days for AE monitoring (serious AEs will be collected for 90 days after the end of treatment as described in Section 7.2.3.1). Subjects who discontinue treatment for reasons other than progressive disease 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.

5.7 Subject Replacement Strategy

Additional subjects may be enrolled to ensure that the required number of evaluable subjects is achieved in the applicable analysis population.

5.8 Clinical 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 with pembrolizumab indicates a potential health hazard to subjects
4. Plans to modify or discontinue the development of the study drug

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

6.0 TRIAL FLOW CHART

6.1 Study Flow Chart – Table 9.

Trial Period:	**Screening Phase**	**Treatment Cycles**[a]								**End of Treatment**	**Post-Treatment**	
Treatment Cycle/Title:	Screening (Visit 1)	1	2	3	4	To be repeated up to 2 years 5	6	7	8	Discontinuation	Safety Follow-up	Follow-up Visits[b]
Scheduling Window (Days)[c]:	-28 to -1			± 3	± 3	± 3	± 3	± 3	± 3	At time of Discontinuation	30 days +/- 7 days	Q 3 mo x 1 yr and then Q 6 mo (+/- 14 days)
Administrative Procedures												
Informed Consent[d]	X											
Inclusion/Exclusion Criteria	X											
Demographics and Medical History	X											
Prior and Concomitant Medication Review[e]	X	Day 1	X	X	X	X	X	X	X	X	X	
Rituximab Administration[s]		Days 1, 8, 15	X									
Pembrolizumab Administration[t]		Day 1	X	X	X	X	X	X	X			
Lenalidomide Administration[w]		Days 1-14	Days1-14	Days 1-14	Days 1-14	Days 1-14	Days 1-14	Days 1-14	Days 1-14			
Clinical Assessments												
Review Adverse Events[f]	X	Day 1	X	X	X	X	X	X	X	X	X[g]	X
Full Physical Examination	X											
Directed Physical Examination			X	X	X	X	X	X	X	X	X	X
Vital Signs and Weight[h]	X	Day 1	X	X	X	X	X	X	X			
ECOG Performance Status	X	Day 1	X	X	X	X	X	X	X			
Laboratory Assessments												
Pregnancy Test – Urine or Serum β-HCG[l]	X											
PT/INR and aPTT[m]	X											
HIV 1 and 2 antibody	X											
HBsAg, Hep C Ab[u]	X											
CBC with Differential[o]	X[n]		X	X	X	X	X	X	X	X	X[p]	X
Comprehensive Serum Chemistry Panel[o]	X[n]		X	X	X	X	X	X	X	X	X[p]	X

Trial Period:	**Screening Phase**	**Treatment Cycles**[a]								**End of Treatment**	**Post-Treatment**	
						To be repeated up to 2 years						
Treatment Cycle/Title:	Screening (Visit 1)	1	2	3	4	5	6	7	8	Discontinuation	Safety Follow-up	Follow-up Visits[b]
Scheduling Window (Days)[c]:	-28 to -1			± 3	± 3	± 3	± 3	± 3	± 3	At time of Discontinuation	30 days +/- 7 days	Q 3 mo x 1 yr and then Q 6 mo (+/- 14 days)
Urinalysis	X					X[q]					X[p]	
Free T4 and TSH	X			X		X		X[v]			X[p]	X
β2 microglobulin	X											
Quantitative immunoglobulins – IgG, IgA, and IgM	X					X[q]					X	X
Bone marrow biopsy and aspirate[r]						X[r]						
Imaging Studies												
CT Neck, Chest, Abdomen, and Pelvis[i]						X[j]						X
PET-CT[i]	X								X	X[k]		
Biomarker Studies												
Archival or Newly Obtained Tissue Collection (Optional)	X											
Biomarkers Blood Collection (Optional)	X	Day 8	Day 22			X				X		

a. In general, assessments/procedures are to be performed on Day 1 and prior to the first dose of treatment for each cycle unless otherwise specified. Treatment cycles are 3 weeks; however the treatment cycle interval may be increased due to toxicity according to the dose modification guidelines provided in Section 5.2.1.2. If the interval is increased, all procedures except for response assessment should be performed based on the new dosing schedule.

b. In subjects who discontinue study therapy without documented disease progression, every effort should be made to continue monitoring their disease status as per the follow-up schedule until (1) the start of new anti-cancer treatment, (2) documented disease progression, (3) death, or (4) the end of the study, whichever occurs first.

c. In general, the window for each visit is ± 3 days unless otherwise noted.

d. Written consent must be obtained prior to performing any protocol specific procedure. Results of a test performed 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 (e.g., within 28 days prior to the first dose of trial treatment). Screening number will be assigned when the study informed consent is signed.

e. Prior medications – Record all medications taken within 28 days of screening visit. Concomitant medications – Enter new medications started during the

trial through the Safety Follow-up visit. Record all medications taken for SAEs as defined in Section 7.2.

f. AEs and laboratory safety measurements will be graded per NCI CTCAE version 4.0. All AEs, will also be evaluated for seriousness.

g. Record all AEs occurring within 30 days after the last dose of trial treatment. Report all SAEs (related and unrelated to trial treatment) and ECIs occurring up until 90 days after the last dose of trial treatment or the start of new anti-cancer treatment, whichever comes first. Afterwards, report only SAEs and ECIs that are related to trial treatment.

h. Vital signs to include temperature, pulse, respiratory rate, weight and blood pressure. Height will be measured at visit 1 only.

i. Disease response assessment is based upon Cheson 2014 lymphoma response criteria. "Diagnostic quality" PET-CT with oral contrast/water and IV contrast should be performed at Screening unless there is a contraindication. In general, follow-up assessments during therapy will be done by CT scans. PET-CT scan will be repeated to confirm complete remission and/or at treatment discontinuation. For lymphomas that are not FDG-avid at screening, PET does not need to be repeated in subsequent assessments. Response assessments should occur at Screening (within 42 days prior to first dose of trial treatment), after Wk 12, and every 3 months (+/- 14 days) during therapy and for one year after treatment discontinuation and then every 6 months (+/- 14 days) until (1) the start of new anti-cancer treatment, (2) documented disease progression, (3) death, or (4) the end of the study, whichever occurs first. Imaging timing should follow calendar days and should not be adjusted for delays in cycle starts or extension of pembrolizumab cycle frequencies. For subjects who discontinue for reasons other than PD, assessments should continue until the subject has documented PD. The first assessment may be performed earlier than 12 weeks if in the opinion of the investigator the patient is clinically progressing.

j. Subjects who have progressive disease at the Wk 12 assessment should have a confirmation assessment performed at least 28 days later (after Wk 16) (+7 days). If subjects have stable disease, partial response, or complete response a confirmation assessment is not required, they should continue on the assessment schedule.

k. In subjects who discontinue study therapy without confirmed disease progression, a radiological assessment should be performed at the time of treatment discontinuation (i.e. date of discontinuation ± 4 week window). If previous scan was obtained within 4 weeks prior to the date of discontinuation, then a repeat scan at treatment discontinuation isn't mandatory.

l. For women of reproductive potential in cohort 1, a urine pregnancy test should be performed within 72 hours prior to first dose of trial treatment. If urine pregnancy results cannot be confirmed as negative, a serum pregnancy test will be required. For cohort 2, for females of child bearing potential, pregnancy tests must be done in accordance with REMS.

m. Coagulation factors (PT/INR and aPTT) should be tested as part of the screening procedures for all subjects. Any subject receiving anticoagulant therapy should have coagulation factors monitored closely throughout the trial.

n. These screening tests need to be repeated if performed more than 7 days prior to the first dose of rituximab. See Section 7.1.3 for details regarding laboratory tests.

o. After Cycle 1, lab samples can be collected up to 72 hours prior to the scheduled time point. See Section 7.1.3 for details regarding laboratory tests.

p. Unresolved abnormal labs that are drug related AEs should be followed until resolution. Labs do not need to be repeated after the end of treatment if labs are within normal range.

q. To be repeated every 4 cycles after Cycle 5.

r. Bone marrow assessments will only be performed in subjects who achieved a CR by imaging criteria and had known bone marrow involvement at baseline. Repeat marrow assessment is not required in subjects who do not achieve a CR by imaging criteria.

s. Rituximab 375 mg/m^2 on day 1 and +/- 1 day on days 8, 15, and 22 (for cohort 2, day 22 will be considered cycle 2, day 1).

t. Pembrolizumab will be administered on day 2, day 23 and day 1 +/- 3 days for cycle 2 through16 in cohort 1. For cohort 2, pembrolizumab will be administered every 3 weeks starting on day 1 of cycle 1 for up to 2 years. Per the investigator's discretion, subjects who attain an investigator-determined CR may consider stopping pembrolizumab treatment after receiving at least 24 weeks of pembrolizumab therapy. At least two doses must be received after CR is documented. A minimum of 18 hours interval is required between the end of rituximab infusion and beginning of pembrolizumab infusion on days 2 and 23.

u. HCV RNA will be performed if Hep C Ab is positive.
v. To be repeated every 2 cycles after cycle 7.
w. Lenalidomide will be administered in cohort 2 only in combination with rituximab and pembrolizumab on days 1-14 (± 3 days) of cycles 1-12.

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.

7.1.1 Administrative Procedures

7.1.1.1 Informed Consent

The informed consent will adhere to IRB 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 subject 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 subject 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 subject within 28 days before starting the trial. Treatment for the disease for which the subject 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 subject 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 possible, the 30 day Safety Follow-up visit must occur before the first dose of the new therapy. Once new anti-cancer therapy has been initiated the subject will move into survival follow-up.

7.1.2 Clinical Procedures/Assessments

7.1.2.1 Adverse Event Monitoring

The investigator or a physician designee will assess each subject 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. Toxicities will be characterized in terms regarding seriousness, causality, toxicity grading, and action taken with regard to trial treatment.

All AEs of unknown etiology associated with pembrolizumab exposure should be evaluated to determine if it is possibly an ECI of a potentially immunologic etiology (irAE). See Section 5.4.1.1 and the separate guidance document regarding the identification, evaluation and management of AEs of a potential immunological etiology.

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 full physical exam during the screening period. After the first dose of trial treatment new clinically significant abnormal findings should be recorded as AEs.

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 (see Section 12.1) at screening, prior to the administration of each dose of trial treatment and discontinuation of trial treatment as specified in the Trial Flow Chart.

7.1.2.6 Tumor Imaging and Assessment of Disease

7.1.2.6.1 Criteria for Assessment of Disease

The Recommendations for Initial Evaluation, Staging, and Response Assessment of Hodgkin and Non-Hodgkin Lymphoma: The Lugano Classification [1] criteria will be applied as the primary measure for assessment of disease response and as a basis for all protocol guidelines related to disease status (e.g. discontinuation of study therapy).

7.1.2.6.2 Initial Disease Assessment

Initial disease assessment or tumor imaging must be performed within 42 days prior to the first dose of trial treatment. PET-CT fusion imaging scans with oral contrast/water and IV contrast will be used for initial disease assessment unless there is a contraindication. Disease assessments or scans performed as part of routine clinical management are acceptable for use as the screening scan if they are of diagnostic quality and performed within 42 days prior to the first dose of trial treatment.

7.1.2.6.3 Disease Assessment During Trial

Disease response assessments will occur every 12 weeks during therapy and for the first year after discontinuation of therapy, and then every 6 months thereafter. There is a ±14-day window for all imaging assessments. Disease response assessments will be performed by CT scans or PET-CT scan at the indicated time points (see Trial Flow Chart - Section 6.0).

In subjects achieving a complete remission by CT scan criteria, PET-CT scan will be repeated once to confirm response. In addition, unilateral bone marrow aspiration and biopsy will be repeated once in such patients if the bone marrow was involved with lymphoma at baseline.

Disease assessments or scans should not be delayed for delays in cycle starts or extension of pembrolizumab cycle intervals. Disease assessments and 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 the study, whichever occurs first. Subjects who have unconfirmed disease progression may continue on treatment until progression is confirmed by imaging provided they have met the conditions detailed in Section 7.1.2.6.4. For lymphomas that are not FDG-avid at screening, PET does not need to be repeated in follow-up assessments

Immunotherapeutic agents such as pembrolizumab may produce antitumor effects by potentiating endogenous cancer-specific immune responses, which may be functionally anergic. The response patterns seen with such an approach may extend beyond the typical time course of responses seen with cytotoxic agents, and can manifest a clinical response after an initial increase in tumor burden or even the appearance of new lesions. Standard response assessment criteria may not provide a complete response assessment of immunotherapeutic agents such as pembrolizumab. Therefore, in the setting where a subject's assessment shows PD at the first disease response assessment at Week 12, a subject may be granted an exception to continue on treatment until progression is confirmed at least 4 weeks later, provided that the subject's clinical condition is stable as detailed in Section 7.1.2.6.4.

7.1.2.6.4 Confirmation Assessments

A subject with progression of disease documented at the Wk 12 assessment may continue trial treatment at the discretion of the investigator until confirmation of progression of disease is documented per the response evaluation criteria at least 28 days later (after Wk 16) (+ 7 day window). When feasible, subjects should not be discontinued until repeat disease response assessment is performed at least 28 days later. Subjects may only receive treatment while waiting for confirmation of PD if the following criteria are met:

- Absence of signs and symptoms (including worsening of laboratory values) indicating disease progression
- No decline in ECOG performance status
- Absence of rapid progression of disease (defined as: rapidly growing mass that is greater than 5 cm in the long axis, weight loss, drenching night sweats, marked fatigue, or fever in the absence of an infection) based on the clinical judgment of the investigator.
- Absence of progressive tumor at critical anatomical sites (e.g. cord compression) requiring urgent alternative medical intervention

Subjects that are deemed clinically unstable after first disease response assessment (Week 12) are not required to have a repeat assessment 28 days later (after Week 16).

7.1.2.7 Blood Sampling and Tumor Tissue Collection for Correlative Studies

Blood and tumor sample collection for biomarker studies is optional. In consenting subjects, 5 ml of blood sample [one purple top (5ml, EDTA) one red top tube (10 ml) and 3 heparin containing green top tubes (30 ml)] will be collected within 28 days prior to the first infusion of rituximab, prior to second and fourth infusions of rituximab (days 8 and 22), and at the time of response assessment, week 12, and at the time of disease progression. After collection of blood sample prior to the first infusion of rituximab, pre-dose blood samples can be collected up to 72 hours prior to dosing. These samples will be transported within 6 hours of collection to Dr. Neelapu's laboratory for processing at the South Campus Research Building I, Room 4.3206, at M. D. Anderson Cancer Center (MDACC). Blood from red top and green top tubes will be processed for isolation of serum and PBMC, respectively using standard laboratory protocols. The isolation of serum and PBMC may also be performed at the Clinical and Translational Research Center (CTRC) Laboratory at MDACC using standard laboratory protocols.

In consenting patients, core needle biopsies and fine needle aspirates (FNA) will be obtained by Interventional Radiology from accessible lymph node under ultrasound or CT-scan guidance within 28 days prior to the first infusion of rituximab. Whenever feasible, up to 3 cores will be obtained using 18 or 20 gauge needles as deemed appropriate by an Interventional Radiologist. The three cores will be processed as follows: i) the first core biopsy specimen will be preserved in RNAlater for microarray studies; ii) second core will be formalin-fixed and paraffin-embedded for IHC; and iii) third core will be snap frozen for DNA, RNA, or protein isolation. FNA sample will be analyzed by flow cytometry. These samples will be transported in RNAlater (core # i)/formalin (core # ii)/normal saline (cores # iii and FNA) within 6 hours of collection on ice to Dr. Neelapu's laboratory for

processing at the South Campus Research Building I, Room 4.3206, at MDACC. If fresh biopsies are not feasible, archival tissue from prior tumor biopsy may be used for biomarker studies.

Samples will be maintained until the study has been terminated.

7.1.3 Laboratory Procedures/Assessments

Details regarding specific laboratory procedures/assessments to be performed in this trial are provided below. The schedule for laboratory assessments is provided under the Trial Flow Chart.

Laboratory tests for screening or entry into the trial should be performed within 28 days prior to the first dose of treatment. CBC with differential and serum chemistry panel will need to be repeated if screening tests were performed more than 7 days prior to the first dose of rituximab as detailed under Trial Flow Chart. After Cycle 1 of pembrolizumab, 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.

The schedule for laboratory assessments is provided under the Trial Flow Chart. CBC with differential should include total white count, absolute neutrophil count, absolute lymphocyte count, hemoglobin, and platelet count. Comprehensive serum chemistry panel should include sodium (Na), potassium (K), chloride (Cl), glucose, bicarbonate (CO_2), blood urea nitrogen (BUN), creatinine (Cr), calcium (Ca), magnesium (Mg), phosphorus, total protein, albumin, alkaline phosphatase, aspartate transaminase (AST), alanine transaminase (ALT), total bilirubin, uric acid, and lactate dehydrogenase (LDH). Direct bilirubin should be obtained if total bilirubin is above the upper limit of normal. Urinalysis should include blood, glucose, protein, and specific gravity. If blood, glucose, and protein are abnormal on urinalysis, a urine microscopic exam should be performed. Total triiodothyronine (T3) will be performed if TSH is abnormal.

7.1.4 Withdrawal/Discontinuation

When a subject discontinues/withdraws prior to trial completion, all applicable activities scheduled for the final trial visit should be performed at the time of discontinuation, if the patient consents. Any AEs 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 AEs, if the patient consents. After discontinuing treatment following assessment of CR, these subjects should return to the site for a Safety Follow-up Visit (described in Section 7.1.5.2) and then proceed to the Follow-Up Period of the study (described in Section 7.1.5.3). However, the follow-ups do not apply when consent and/ or authorization are withdrawn by the subject.

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 Screening Period

Approximately 28 days prior to enrollment, potential subjects will be evaluated to determine that they fulfill the entry requirements as set forth in Section 5.1. Visit requirements are outlined in Section 6.0 – Trial Flow Chart.

Written consent for the main study must be obtained prior to performing any protocol specific procedure. Results of a test performed 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 28 days prior to the first dose of trial treatment except for the following:

- Laboratory tests are to be performed within 7 days prior to the first dose of trial treatment.
- For women of reproductive potential in cohort 1, 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). For women of reproductive potential in cohort 2, pregnancy tests will be performed in accordance with REMS.

Subjects may be rescreened 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 inclusion/exclusion criteria is met.

7.1.5.2 Post-Treatment Safety Follow-Up Visit

If possible, the Safety Follow-Up Visit should be conducted approximately 30 days after the last dose of trial treatment or before the initiation of a new anti-cancer treatment, whichever comes first. All AEs that occur prior to the Safety Follow-Up Visit should be recorded. SAEs that occur within 90 days of the end of treatment or before initiation of a new anti-cancer treatment should be followed and recorded.

7.1.5.3 Follow-up Visits

Subjects who discontinue trial treatment for a reason other than disease progression will move into the Follow-Up Phase and should be assessed by radiologic imaging to monitor disease status. Imaging assessments will be performed every 3 months during therapy and for the first year after discontinuation of therapy, and every 6 months thereafter. Every effort should be made to collect information regarding disease status until the start of new anti-neoplastic therapy, disease progression, death, or end of the study.

7.2 Assessing and Recording AEs

Data will be recorded in PDMS/Core or RedCap.

An AE is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. An AE 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 preexisting condition that is temporally associated with the use of the Merck's product, is also an AE.

Changes resulting from normal growth and development that do not vary significantly in frequency or severity from expected levels are not to be considered AEs. 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 within the follow-up period specified by the protocol, or prescribed in clinical practice, from overdose (whether accidental or intentional), from abuse and from withdrawal.

Adverse events may also occur in screened subjects during any pre-allocation baseline period as a result of a protocol-specified intervention, including washout or discontinuation of usual therapy, diet, placebo treatment or a procedure.

All AEs will be recorded from the time the consent form is signed through 30 days following cessation of treatment and at each examination on the AE CRFs/worksheets. The reporting timeframe for AEs meeting any serious criteria is described in Section 7.2.3.1.

Adverse events will not be collected for subjects during the pre-screening period (for determination of archival tissue status) as long as that subject has not undergone any protocol-specified procedure or intervention. If the subject requires a blood draw, fresh tumor biopsy etc., the subject is first required to provide consent to the main study and AEs will be captured according to guidelines for standard AE reporting. The AE reporting guidelines are detailed in the **Table 10** below:

Recommended Adverse Event Recording Guidelines					
Attribution	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Unrelated	Phase I	Phase I	Phase I Phase II	Phase I Phase II Phase III	Phase I Phase II Phase III
Unlikely	Phase I	Phase I	Phase I Phase II	Phase I Phase II Phase III	Phase I Phase II Phase III
Possible	Phase I Phase II	Phase I Phase II Phase III	Phase I Phase II Phase III	Phase I Phase II Phase III	Phase I Phase II Phase III
Probable	Phase I Phase II	Phase I Phase II Phase III	Phase I Phase II Phase III	Phase I Phase II Phase III	Phase I Phase II Phase III
Definitive	Phase I Phase II	Phase I Phase II Phase III	Phase I Phase II Phase III	Phase I Phase II Phase III	Phase I Phase II Phase III

7.2.1 Definition of an Overdose for This Protocol and Reporting of Overdose

For purposes of this trial, an overdose will be defined as any dose exceeding the prescribed dose for pembrolizumab by 20% over the prescribed dose. No specific information is available on the treatment of overdose of pembrolizumab. In the event of overdose, pembrolizumab should be discontinued and the subject should be observed closely for signs of toxicity. Appropriate supportive treatment should be provided if clinically indicated.

If an AE(s) is associated with ("results from") the overdose of a Merck product, the AE(s) is reported as a serious AE, 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 ECI, using the terminology "accidental or intentional overdose without adverse effect."

On a per dose basis, an overdose of lenalidomide is defined as any amount over the protocol-specified dose.

Overdoses must be reported within 2 working days to MD Anderson Cancer Center IND Office (IND Sponsor) and Merck Global Safety (Attn: Worldwide Product Safety; FAX 215 993-1220), unless they are life threatening or result in an SAE in which case they will be reported within 24 hours to MD Anderson Cancer Center IND Office (IND Sponsor).

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

Although pregnancy and lactation are not considered AEs, it is the responsibility of investigators or their designees to report any pregnancy or lactation in a subject (spontaneously reported to them), including the pregnancy of a male subject's female partner that occurs during the trial or within 120 days of completing the trial completing the trial, or 30 days following cessation of treatment if the subject initiates new anticancer

therapy, whichever is earlier. All subjects and female partners of male subjects who become pregnant must be followed to the completion/termination of the pregnancy. Pregnancy outcomes of spontaneous abortion, missed abortion, benign hydatidiform mole, blighted ovum, fetal death, intrauterine death, miscarriage and stillbirth must be reported as serious events (Important Medical Events). If the pregnancy continues to term, the outcome (health of infant) must also be reported.

Such events must be reported within 2 working days to MD Anderson Cancer Center IND Office (IND Sponsor) and Merck Global Safety (Attn: Worldwide Product Safety; FAX 215 993-1220), unless they are life threatening or result in an SAE in which case they will be reported within 24 hours to MD Anderson Cancer Center IND Office (IND Sponsor).

7.2.3 Immediate Reporting of AEs to the Sponsor and to Merck

7.2.3.1 Serious Adverse Events (SAEs)

An adverse event or suspected adverse reaction is considered "serious" if, in the view of either the investigator or the sponsor, it results in any of the following outcomes:

- Death
- A life-threatening adverse drug experience – any adverse experience that places the patient, in the view of the initial reporter, at immediate risk of death from the adverse experience as it occurred. It does not include an adverse experience that had it occurred in a more severe form, might have caused death.
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
- A congenital anomaly/birth defect.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse (21 CFR 312.32).

- **Important medical events as defined above, may also be considered serious adverse events. Any important medical event can and should be reported as an SAE if deemed appropriate by the Principal Investigator or the IND Sponsor, IND Office.**

- All events occurring during the conduct of a protocol and meeting the definition of a SAE must be reported to the IRB in accordance with the timeframes and procedures outlined in "The University of Texas M. D. Anderson Cancer Center

Institutional Review Board Policy for Investigators on Reporting Unanticipated Adverse Events for Drugs and Devices". Unless stated otherwise in the protocol, all SAEs, expected or unexpected, must be reported to the IND Office, regardless of attribution (within 5 working days of knowledge of the event).

- **All life-threatening or fatal events,** that are unexpected, and related to the study drug, must have a written report submitted within **24 hours** (next working day) of knowledge of the event to the Safety Project Manager in the IND Office and within 2 working days to Merck Global Safety.

- **Unless otherwise noted, the electronic SAE application (eSAE) will be utilized for safety reporting to the IND Office and MDACC IRB.**

- **Serious adverse events will be captured from the time of the first protocol-specific intervention, until 90 days after the last dose of drug, or the initiation of new anti-cancer therapy, whichever is earlier, whether or not related to Merck product, unless the participant withdraws consent. Serious adverse events must be followed until clinical recovery is complete and laboratory tests have returned to baseline, progression of the event has stabilized, or there has been acceptable resolution of the event.**

- **Additionally, any serious adverse events that occur after the 30 day time period that are related to the study treatment must be reported to the IND Office. This may include the development of a secondary malignancy.**

Reporting to FDA:

- Serious adverse events will be forwarded to FDA by the IND Sponsor (Safety Project Manager IND Office) according to 21 CFR 312.32.

It is the responsibility of the PI and the research team to ensure serious adverse events are reported according to the Code of Federal Regulations, Good Clinical Practices, the protocol guidelines, the sponsor's guidelines, and Institutional Review Board policy.

Investigator Communication with Supporting Companies:

All SAEs will be reported within 2 working days to Merck Global Safety (Attn: Worldwide Product Safety; FAX 215 993-1220). Non-serious Events of Clinical Interest (see section 7.2.3.2) will be forwarded to Merck Global Safety and will be handled in the same manner as SAEs.

A copy of all 15-Day Reports and Annual Progress Reports is submitted as required by FDA. 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 215 993-1220) at the time of submission to FDA.

7.2.3.2 Events of Clinical Interest

Selected non-serious Events of Clinical Interest (ECI) must be recorded as such on the AE CRFs/worksheets and reported within 2 working days to MD Anderson Cancer Center IND Office (IND Sponsor) and Merck Global Safety. (Attn: Worldwide Product Safety; FAX 215 993-1220), unless they are life threatening or result in an SAE in which case they will be reported within 24 hours to MD Anderson Cancer Center IND Office (IND Sponsor).

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 IND 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.

A separate guidance document has been provided entitled “Event of Clinical Interest and Immune-Related Adverse Event Guidance Document.” This document provides guidance regarding identification, evaluation and management of ECIs and irAEs. Additional ECIs are identified in this guidance document and also need to be reported to MD Anderson Cancer Center IND Office (IND Sponsor) and to Merck Global Safety within 2 working days of the event.

Subjects should be assessed for possible ECIs prior to each dose. Lab results should be evaluated and subjects should be asked for signs and symptoms suggestive of an immune-related event. Subjects who develop an ECI thought to be immune-related should have additional testing to rule out other etiologic causes. If lab results or symptoms indicate a possible immune-related ECI, then additional testing should be performed to rule out other etiologic causes. If no other cause is found, then it is assumed to be immune-related.

ECIs that occur in any subject from the date of first dose through 90 days following cessation of treatment, or the initiation of a new anticancer therapy, whichever is earlier, whether or not related to the Merck’s product, must be reported to MD Anderson Cancer Center IND Office (IND Sponsor) and to Merck Global Safety within 2 working days.

7.2.4 Evaluating AEs

AEs will be evaluated according to the NCI Common Terminology for Adverse Events (CTCAE), version 4.0. Any AE which changes CTCAE grade over the course of a given episode will have each change of grade recorded on the AE CRFs/worksheets. All AEs regardless of CTCAE grade must also be evaluated for seriousness.

8.0 STATISTICAL ANALYSIS PLAN

This is an investigator-initiated, open label, Phase II clinical trial to evaluate the efficacy and safety of pembrolizumab given in combination with rituximab in patients with relapsed/refractory FL (cohort 1, maximum of 32 subjects) and in combination with lenalidomide in relapsed/refractory FL and DLBCL who have failed CAR T cell therapy (cohort 2, maximum of 40). The maximum number of patients to be recruited for the study is 72.

8.1 Power and Sample Size

Cohort 1: Rituximab plus pembrolizumab in rituximab-sensitive and rituximab-refractory FL

*The **primary objective** of Cohort 1 is to determine the overall response (OR) rate (complete + partial responses) in patients with relapsed FL with rituximab-sensitive disease who receive pembrolizumab in combination with rituximab. The **secondary objectives** are to determine the safety and toxicity, CRR, PFS, compare PFS between patients relapsing ≤ one year vs > one year after last prior therapy, and OS.*

Cohort 1

It is expected for the cohort 1 that the two-drug combination will achieve an OR rate of 50% while the toxicity rate is under 30%. A sample size of 32 ensures that, if the trial is not terminated early, a posterior 90% credibility interval for response rate will have width of 0.254 at most, under the assumption of a 50% OR. The prior probabilities of OR and toxicity for the regimen are modeled by beta distributions (*Beta*(.5, .5) and *Beta*(.3, .7), respectively). Denoting the probabilities of OR rate and toxicity rate by {p(OR) , p(TOX)}, the following decision criteria will be applied:

1) Stop if Prob{p(OR) < 50% | data} > 0.985, and
2) Stop if Prob{p(TOX) > 30% | data} > 0.975

Patients will be monitored according to the following stopping boundaries for OR. If the number of responses required for moving the trial to next stage has not been achieved, the patient enrollment will be halted until enough responses observed.

Number of patients	Stop if ≤ OR	Stop if ≥ study drug-

evaluated	observed	related toxicity observed
5	0	5
10	0-1	7-10
15	0-3	9-15
20	0-5	11-20
25	0-7	13-25
30	0-9	15-30
35	0-11	17-35
40	Always stop with this many patients	

The operating characteristics are summarized in the following table (based on simulations from 10,000 trials).

True Toxicity Rate	True OR Rate	Prob(stop the trial early)	Average number of patients treated
0.10	0.30	0.7350	23.74
	0.40	0.3079	33.34
	0.50	0.0726	38.15
	0.60	0.0138	39.56
	0.70	0.0026	39.91
0.20	0.30	0.7355	23.72
	0.40	0.3094	33.30
	0.50	0.0746	38.09
	0.60	0.0159	39.51
	0.70	0.0047	39.85
0.30	0.30	0.7466	23.35
	0.40	0.3383	32.64
	0.50	0.1135	37.28
	0.60	0.0572	38.65
	0.70	0.0465	38.99
0.40	0.30	0.8096	21.50
	0.40	0.5026	29.23
	0.50	0.3336	33.08
	0.60	0.2913	34.23
	0.70	0.2833	34.52
0.50	0.30	0.9222	17.58
	0.40	0.7969	22.22
	0.50	0.7279	24.50
	0.60	0.7106	25.22
	0.70	0.7073	25.41

Cohort 2

Promising results have been observed with rituximab plus pembrolizumab for the patients with

rituximab-sensitive disease in the existing study. We would like to explore the efficacy with the addition of lenalidomide (a triplet combination). We will add the following cohort to the existing study: Pembrolizumab + rituximab + lenalidomide in refractory DLBCL and FL to CAR T cell therapy.

The added cohort consists of two parts: Part 1 – dose escalation to determine the MTD of lenalidomide when given in combination with pembrolizumab and rituximab, and Part 2 – dose expansion to determine the efficacy and safety of the triplet combination.

A maximum of 40 patients that will be recruited for the additional cohort.

Part 1: Dose escalation

The modified "3+3" design is applied with 3 pre-defined dose levels for lenalidomide while the standard dosing for the other two drugs remains.

Dose level	Lenalidomide (mg)
1	2.5
2	5
3	10

Dose limiting toxicity (DLT) is defined as the following toxicities observed during cycle 1 of the treatment:

- Grade 4 neutropenia lasting > 7 days
- Grade 3 neutropenia associated with fever (single temperature of > 38.3 ºC, or with a sustained temperature of ≥ 38 º C lasting > 1 hour)
- Grade 4 thrombocytopenia
- Grade 3 or 4 non-hematologic adverse event not considered by the investigator to be attributable to another clearly identifiable cause

Applying the 3+3 design, the first cohort of 3 patients will be treated at dose level 1 and evaluated for DLT at the end of first cycle (28 days). The algorithm is as follows: (1) If 0 out of 3 patients experiences dose-limiting toxicity (DLT), the next cohort of 3 patients will be treated at the next higher dose level. (2) If 1 out of 3 patients develop a DLT, an additional 3 patients will be treated at the same dose level. If no more DLTs develop at this dose, i.e. 1 out of a total of 6 patients develops a DLT, the dose escalation continues for the next cohort of 3 patients. (3) At any given dose, if greater than 1 out 3 patients or 1 out of 6 patients experience DLT, the dose level exceeds the MTD and 3 more patients will be treated at the next lower dose if there are less than 6 patients already treated at that dose. Following the above scheme, MTD is defined as the highest dose level in which 6 patients have been treated with less than 2 instances of DLT. It is anticipated that up to 12 eligible patients are required for Part 1.

Part 2: Dose expansion

The primary objective for Part 2 is to further evaluate the safety and efficacy of the three–drug combination at the MTD determined in Part 1. The 6 patients treated at the MTD in Part 1 will be counted as the first group of patients in Part 2. Additional 24 patients will be enrolled if the trial is not terminated early due to futility or excessive toxicity.

The overall response (OR) and toxicity assessed after completion of 8 treatments with pembrolizumab and 4 doses of rituximab will be monitored simultaneously using the Bayesian stopping boundaries calculated based on beta-binomial distributions. Toxicity is defined as any grade 3 or 4 non-hematologic toxicity that in the opinion of the PI is at least possibly related to study treatment. Independence was assumed between OR and toxicity.

It is expected that the three-drug combination will achieve an OR rate of 40% while the toxicity rate is under 30% for the patients. A sample size of 40 ensures that, if the trial is not terminated early, a posterior 90% credibility interval for response rate will have width of 0.285 at most, under the assumption of a 40% OR. The prior probabilities of OR and toxicity for the regimen are modeled by beta distributions (*Beta*(.4, .6) and *Beta*(.3, .7), respectively). Denoting the probabilities of OR rate and toxicity rate by {p(OR) , p(TOX)}, the following decision criteria will be applied:

1) Stop if Prob{p(OR) < 40% | data} > 0.975, and
2) Stop if Prob{p(TOX) > 30% | data} > 0.975

After the first 10 patients are treated in Part 2 (including the 6 patients treated at the MTD in Part 1), patients will be monitored in a cohort size of 5 according to the following stopping boundaries for OR and toxicity. If the number of responses required for moving the trial to next

stage has not been achieved, the patient enrollment will be halted until enough responses observed.

Number of patients evaluated	Stop if ≤ OR observed	Stop if ≥ study drug-related toxicity observed
10	0-1	7-10
15	0-2	9-15
20	0-3	11-20
25	0-5	13-25
40	Always stop with this many patients	

The operating characteristics are summarized in the following table (based on simulations from 10,000 trials).

True Toxicity Rate	True OR Rate	Prob(stop the trial early)	Average number of patients treated
0.10	0.20	0.6829	19.65
	0.30	0.2773	25.87
	0.40	0.0715	28.83
	0.50	0.0134	29.76
	0.60	0.0018	29.96
0.20	0.20	0.6835	19.64
	0.30	0.2786	25.85
	0.40	0.0732	28.81
	0.50	0.0152	29.73
	0.60	0.0036	29.94
0.30	0.20	0.6938	19.44
	0.30	0.3021	25.51
	0.40	0.1034	28.40
	0.50	0.0473	29.30
	0.60	0.0361	29.50

0.40	0.20	0.7482	18.49
	0.30	0.4262	23.81
	0.40	0.2629	26.34
	0.50	0.2167	27.13
	0.60	0.2075	27.31
0.50	0.20	0.8603	16.31
	0.30	0.6816	19.99
	0.40	0.5909	21.73
	0.50	0.5653	22.28
	0.60	0.5602	22.41

The above stopping boundaries and operating characteristics are calculated using MultcLean (v.2.0.0) design software downloaded from http://biostatistics.mdanderson.org/SoftwareDownload.

Cohort 2:

- Escalation Phase:

A toxicity summary will be submitted after the first evaluable subject completes cycle one of study treatment, and every evaluable subject thereafter. IND Office approval must be obtained prior to advancing/changing dose levels. If a DLT occurs during the single subject escalation portion, or if the dose escalation reaches a dose of 10mg of lenalidomide (level 3), the statistical design will switch to a standard 3+3 design and the summaries for the escalation phase will be submitted every three evaluable subjects when the third subject completes cycle one, with IND Office approval prior to advancing or changing dose levels.

- Expansion Phase:

After the first five evaluable subjects complete 24 weeks of study treatment, and every five evaluable subjects thereafter.

A copy of the cohort summary should be placed in the Investigator's Regulatory Binder under "sponsor correspondence".

8.2 Analysis Plans

The analysis on each patient cohort will be performed separately. Summary statistics including mean, standard deviation, median, and range for continuous variables, and frequency count and percentage for categorical variables will be provided. Response rate and its 95% confidence

interval will be reported. Logistic regression will be utilized to assess the effect of patient prognostic factors on the response rate and the toxicity rate. The distribution of time-to-event endpoints including overall survival and progression free survival will be estimated using the method of Kaplan and Meier. Comparison of time-to-event endpoints by important subgroups will be made using the log-rank test.

Toxicity data will be summarized by frequency tables for all patients. For the efficacy endpoints, intend-to-treat analysis will be applied to the eligible patients. For the toxicity endpoint, per-treated analysis will be performed to include any patient who received the treatment regardless of the eligibility nor the duration or dose of the treatment received.

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.

Clinical Supplies of pembrolizumab will be provided by Merck as summarized in **Table 17**. Rituximab will be obtained through standard commercial sources.

Table 17. Investigational Product Descriptions

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

9.2 Packaging and Labeling Information

Clinical supplies will be affixed with a clinical label in accordance with regulatory requirements.

9.3 Clinical Supplies Disclosure

This trial is open-label; therefore, the subject, 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 will 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 subjects 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 IND Annual Reports

If the FDA has granted an IND number, it is a requirement of 21 CFR 312.33, that an annual report is provided to the FDA within 60-days of the IND anniversary date. 21 CRF 312.33 provides the data elements that are to be submitted in the report. The Annual Report should be filed with MD Anderson Cancer Center IND Office (IND Sponsor), who will then forward to FDA. An additional copy should be placed in the study's Regulatory Binder and a copy must be sent to Merck as a supporter of this study.

10.2 IND Safety Reports

Merck shall notify the Investigator via an IND Safety Report of the following information:

- Any AE associated with the use of study drug in this study or in other studies that is both serious and unexpected.
- Any finding from tests in laboratory animals that suggests a significant risk for human subjects including reports of mutagenicity, teratogenicity, or carcinogenicity.

The Investigator shall notify his IRB promptly of these new serious and unexpected AE(s) or significant risks to subjects.

The Investigator must keep copies of all AE information, including correspondence with Merck and the IRB on file.

10.3 Compliance with Trial Registration and Results Posting Requirements

Under the terms of the Food and Drug Administration Modernization Act (FDAMA) and the Food and Drug Administration Amendments Act (FDAAA), the Sponsor of the trial is solely responsible for determining whether the trial and its results are subject to the requirements for submission to the Clinical Trials Data Bank, http://www.clinicaltrials.gov. 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.

10.4 Data Confidentiality Plan

All information, including but not limited to patient data/information, biomarker research data, and information related to the conduct of the study will be kept confidential. Blood and tissue samples will be identified by coded numbers. Data will be stored in password-protected databases, protected by an institutional firewall. All data collected for this project, including all clinical information, will be kept confidential by limiting access only to the investigators involved in the study. In order to maintain confidentiality, the investigator will maintain a personal patient identification list (coded numbers for blood and tissue samples corresponding with patient identifiers) to enable records to be identified and verified as authentic. This list will be maintained at the study site with other study records under adequate security and restricted access.

11.0 REFERENCES

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12.0 APPENDICES

12.1 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.

12.2 Response Evaluation Criteria

Response will be determined by the Principal Investigator according to the Recommendations for Initial Evaluation, Staging, and Response Assessment of Hodgkin and Non-Hodgkin Lymphoma: The Lugano Classification[1] and documented in the CRFs. The response criteria are summarized below:

Response and Site	PET-CT–Based Response	CT-Based Response
Complete	Complete metabolic response	Complete radiologic response (all of the following)
Lymph nodes and extralymphatic sites	Score 1, 2, or 3* with or without a residual mass on 5PS†	Target nodes/nodal masses must regress to ≤ 1.5 cm in LDi
	It is recognized that in Waldeyer's ring or extranodal sites with high physiologic uptake or with activation within spleen or marrow (eg, with chemotherapy or myeloid colony-stimulating factors), uptake may be greater than normal mediastinum and/or liver. In this circumstance, complete metabolic response may be inferred if uptake at sites of initial involvement is no greater than surrounding normal tissue even if the tissue has high physiologic uptake	No extralymphatic sites of disease
Nonmeasured lesion	Not applicable	Absent
Organ enlargement	Not applicable	Regress to normal
New lesions	None	None
Bone marrow	No evidence of FDG-avid disease in marrow	Normal by morphology; if indeterminate, IHC negative
Partial	Partial metabolic response	Partial remission (all of the following)
Lymph nodes and extralymphatic sites	Score 4 or 5† with reduced uptake compared with baseline and residual mass(es) of any size	≥ 50% decrease in SPD of up to 6 target measurable nodes and extranodal sites
	At interim, these findings suggest responding disease	When a lesion is too small to measure on CT, assign 5 mm × 5 mm as the default value
	At end of treatment, these findings indicate residual disease	When no longer visible, 0 × 0 mm
		For a node > 5 mm × 5 mm, but smaller than normal, use actual measurement for calculation
Nonmeasured lesions	Not applicable	Absent/normal, regressed, but no increase
Organ enlargement	Not applicable	Spleen must have regressed by > 50% in length beyond normal
New lesions	None	None
Bone marrow	Residual uptake higher than uptake in normal marrow but reduced compared with baseline (diffuse uptake compatible with reactive changes from chemotherapy allowed). If there are persistent focal changes in the marrow in the context of a nodal response, consideration should be given to further evaluation with MRI or biopsy or an interval scan	Not applicable
No response or stable disease	No metabolic response	Stable disease
Target nodes/nodal masses, extranodal lesions	Score 4 or 5 with no significant change in FDG uptake from baseline at interim or end of treatment	< 50% decrease from baseline in SPD of up to 6 dominant, measurable nodes and extranodal sites; no criteria for progressive disease are met
Nonmeasured lesions	Not applicable	No increase consistent with progression
Organ enlargement	Not applicable	No increase consistent with progression
New lesions	None	None
Bone marrow	No change from baseline	Not applicable
Progressive disease	Progressive metabolic disease	Progressive disease requires at least 1 of the following
Individual target nodes/nodal masses	Score 4 or 5 with an increase in intensity of uptake from baseline and/or	PPD progression:
Extranodal lesions	New FDG-avid foci consistent with lymphoma at interim or end-of-treatment assessment	An individual node/lesion must be abnormal with: LDi > 1.5 cm and Increase by ≥ 50% from PPD nadir and An increase in LDi or SDi from nadir 0.5 cm for lesions ≤ 2 cm 1.0 cm for lesions > 2 cm In the setting of splenomegaly, the splenic length must increase by > 50% of the extent of its prior increase beyond baseline (eg, a 15-cm spleen must increase to > 16 cm). If no prior splenomegaly, must increase by at least 2 cm from baseline New or recurrent splenomegaly
Nonmeasured lesions	None	New or clear progression of preexisting nonmeasured lesions

New lesions	New FDG-avid foci consistent with lymphoma rather than another etiology (eg, infection, inflammation). If uncertain regarding etiology of new lesions, biopsy or interval scan may be considered	Regrowth of previously resolved lesions A new node > 1.5 cm in any axis A new extranodal site > 1.0 cm in any axis; if < 1.0 cm in any axis, its presence must be unequivocal and must be attributable to lymphoma Assessable disease of any size unequivocally attributable to lymphoma
Bone marrow	New or recurrent FDG-avid foci	New or recurrent involvement

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

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

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

12.3 Calculation of Creatinine Clearance Using the Cockcroft-Gault Formula

$$\text{Creatinine Clearance (men)} = \frac{(140\text{-Age}) \times \text{Lean Body Weight [kilograms]}}{\text{Serum Creatinine (mg/dL)} \times 72}$$

$$\text{Creatinine Clearance (women)} = \frac{0.85 \times (140\text{-Age}) \times \text{Lean Body Weight [kilograms]}}{\text{Serum Creatinine (mg/dL)} \times 72}$$

Reference:

Gault MH, Longerich LL, Harnett JD, et al. Predicting glomerular function from adjusted serum creatinine (editorial). Nephron 1992;62:249.