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Laura and Isaac Perlmutter Cancer Center at NYU Langone Health

TITLE: A Phase I/II Multi-Center Study of the Combination of Pembrolizumab and Lenalidomide, in Patients with Relapsed Non-Hodgkin and Hodgkin Lymphoma

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1.0 TRIAL SUMMARY

Abbreviated Title	Pembrolizumab and lenalidomide in Patients with Relapsed Refractory Non-Hodgkin and Hodgkin Lymphoma (HL)
Trial Phase	Phase I/II
Clinical Indication	Phase 1: Relapsed B cell HL and non-Hodgkin lymphoma (NHL); Phase 2: relapsed refractory (RR) HL
Trial Type	Therapeutic intervention
Type of control	n/a
Route of administration	Pembrolizumab IV; Lenalidomide PO
Trial Blinding	n/a
Treatment Groups	Phase 1: 9 patients expected (12 patients if unexpected toxicity) with relapsed HL and NHL Phase 2: 17 patients with RR HL
Number of trial subjects	26 (up to 29 if unexpected toxicity)
Estimated enrollment period	18-24 months
Estimated duration of trial	36-48 months
Duration of Participation	Until disease progression or toxicity up to 2 years

2.0 TRIAL DESIGN

2.1 Trial Design

This is a Phase 1/2 open label study of the combination of pembrolizumab and lenalidomide and in patients with relapsed/refractory (RR) non-Hodgkin lymphoma (NHL) and Hodgkin lymphoma (HL).

Dose escalation will follow a standard 3+3 design. Patients will be treated in cohorts of 3 patients starting with Dose Cohort A with lenalidomide 15mg PO day 1-14 and pembrolizumab 200mg IV day 1, in cycles of 21 days, until disease progression or toxicity up to 24 months. The number of patients expected to be enrolled in the dose escalation study is 9 (up to 12 patients if unexpected toxicity is observed).

If 0 out of 3 patients at a particular dose level experiences a dose limiting toxicity (DLT) within Cycle 1 of treatment, if in Dose Cohort A (lenalidomide 15mg) dose escalation will proceed to cohort B (lenalidomide 20mg), if in Dose Cohort B, 3 additional patients will be added. If a DLT occurs in 0 of 6 patients enrolled on Dose Cohort B this will be deemed the Maximum Tolerated Dose (MTD).

If a DLT occurs in only 1 out of 6 patients enrolled at a particular dose level, dose escalation will occur, however, if this occurs on Dose Cohort B (lenalidomide 20 mg) or Dose Cohort Z (lenalidomide 10 mg), this will be deemed the Maximum Tolerated Dose (MTD). MTD is defined as the highest dose level at which < 33% of 6 patients experience a DLT.

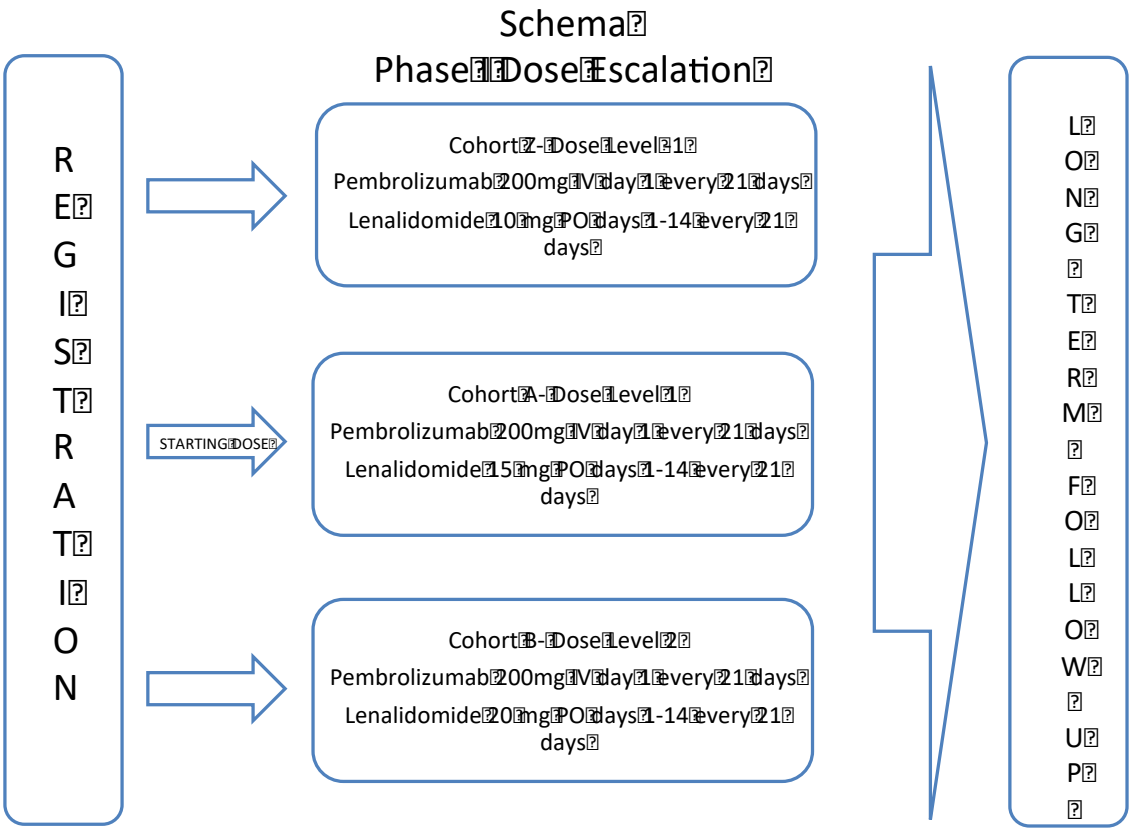
If a DLT occurs in ≥ 2 of 3 patients or ≥ 2 of 6 patients treated on Dose Cohort A (lenalidomide 15mg), there will be a dose de-escalation to Dose Cohort Z (lenalidomide 10 mg).

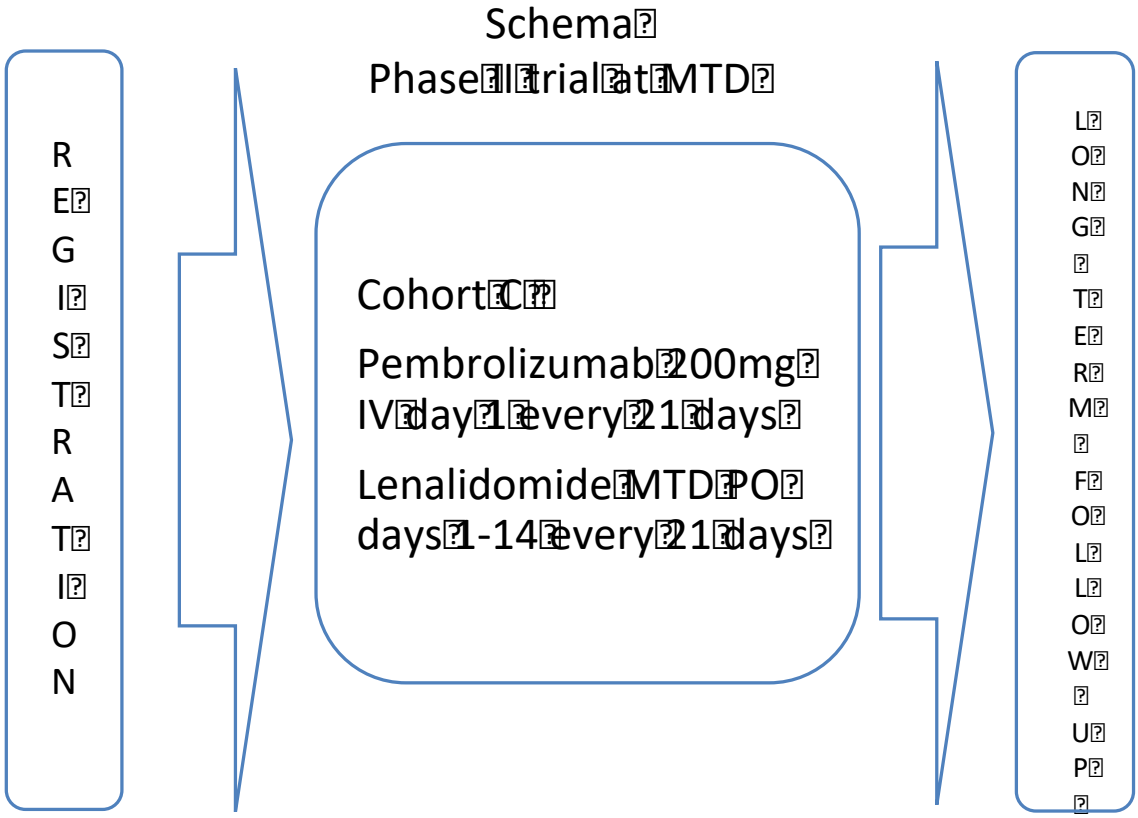
If a DLT occurs in ≥ 2 of 3 patients or ≥ 2 of 6 patients treated on Dose Cohort B (lenalidomide 20 mg) or the preceding dose level will be declared the MTD if there were no more than 1 DLT in this previous cohort.

If a DLT occurs in ≥ 2 of 3 patients or ≥ 2 of 6 patients on Dose Cohort Z (lenalidomide 10mg), the trial will be discontinued and the expanded cohort will not be implemented.

Once the MTD has been determined, 15 additional patients with relapsed refractory HL will be treated in in the Phase II portion of this trial at the MTD.

2.2 Trial Diagram




Schema
Phase I/II trial at MTD
REGISTRATION
Cohort C
Pembrolizumab 200mg IV day 1 every 21 days
Lenalidomide MTD PO days 1-14 every 21 days
LONG TERM FOLLOW UP

3.0 OBJECTIVE(S) & HYPOTHESES

3.1 Primary Objective(s) & Hypothesis

Objective:

Phase 1: To determine the maximum tolerated dose (MTD) and dose limiting toxicities (DLT) of the combination of pembrolizumab and lenalidomide, in patients with RR HL and B cell NHL.

Phase 2: To estimate the overall response rate (ORR), (complete response rate (CR) and partial response rate (PR)) in patients with RR HL

Hypothesis:

Phase 1: We hypothesize that the novel immune platform of pembrolizumab and lenalidomide, will be safe and well tolerated in patients with RR HL and NHL

Phase 2: We hypothesize that the novel immune platform of pembrolizumab and lenalidomide will result in a CR rate of 50% in patients with RR HL.

3.2 Secondary Objective(s) & Hypothesis

Objectives:

Phase 1: To estimate the ORR, (CR, PR), SD and progression free survival (PFS) for the combination within and across dose levels of lenalidomide

Phase 2: To estimate clinical benefit (including SD), the PFS and duration of response (DOR), for the combination. To confirm the safety of the combination.

Hypothesis:

Phase 1: We hypothesize that the novel immune platform of pembrolizumab and lenalidomide, will be active in RR HL and NHL patients.

3.3 Exploratory Objective

Objective:

1- To evaluate and compare changes in the circulating immune cells profile in the peripheral blood of patients treated with the combination of pembrolizumab and

lenalidomide, pre-treatment, during treatment, and at time of completion of therapy and/or progression of disease.

2- To evaluate and compare changes in the tumor microenvironment in biopsies obtained pre-treatment, during therapy and at relapse, if applicable.

3- To evaluate and compare changes in the gene expression profiling in biopsies obtained pre-treatment, during therapy and at relapse, if applicable.

Hypothesis:

1- We hypothesize that the crosstalk between HRS cells and their tumor microenvironment induces systemic effects on circulating immune cells, such as evidence of chronic activation and cell exhaustion that is reversed with treatment in responding patients.

2- We hypothesize that treatment affects the composition and abundance of the microenviroment as a function of the immune directed therapy

3- We hypothesize that gene expression profiling changes as a function of the immune directed therapy and there might be a signature predictive of response to immunotherapy in HL patients

4.0 BACKGROUND & RATIONALE

4.1 Background

4.1.1 Background DLBCL and HL

Despite recent therapeutic advances for non-Hodgkin lymphoma (NHL) and Hodgkin lymphoma (HL), approximately 40% of patients with diffuse large B cell lymphoma (DLBCL), and 25% of patients with HL will relapse following initial therapy. Although some of these patients may be salvaged with high intensity autologous stem cell transplant (ASCT) the majority, especially those who do not obtain substantial disease reduction with second line therapies, have few therapeutic options for long term disease control, and succumb to their lymphoma. Effective and innovative treatment platforms which derive from an understanding of lymphoma biology are an unmet need, and are essential to improving long-term outcomes for patients with relapsed DLBCL.

Programmed death-1 (PD-1), a member of the B7 receptor family, functions as an important checkpoint in the regulation of immune responses. The ligands for PD-1, PD-L1 and PD-L2, are up-regulated in inflammatory conditions such as the tumor microenvironment of both

solid tumors and lymphomas. In HL PDL-1 is expressed on the HL tumor cells (HRS cells) and PD-1 on the immune cells of the tumor microenvironment. PD-L1 is also expressed on a subset of DLBCL and follicular lymphoma (FL) tumors. The expression of PD-1 on peritumoral lymphocytes creates a tumor tolerant and tumor protective microenvironment. Thus activating anti-tumor immunity by blocking PD-1 signaling has a strong scientific rationale in lymphoma.

Clinically there is emerging clinical data to confirm that PD-1 blockade is safe and viable in lymphoma. In a phase 1 study of patients with relapsed follicular lymphoma (FL) treated with the combination of pidilizumab and rituximab, of 29 evaluable patients, 19 achieved ORs, 15 (52%) had CRs, and 4 (14%) had PRs; and the median PFS was 21.1 months (Westin J, ASH 2012). A recent study suggests that PD-1 blockade in high risk DLBCL patients after ASCT resulted in a longer than expected progression free survival as well as increases in circulating activated lymphocytes, suggesting an on-target effect (Armand P, JCO. 2013; 31(33)).

To develop a novel immune mediated therapeutic platform with high activity across many lymphoma subtypes, PD-1 blockade should be enhanced by rational combination with agents with complimentary immune stimulatory activity, and non-overlapping spectrums of toxicity. Lenalidomide is an immunomodulatory agent with a mechanism that involves immune modulation, antiangiogenesis, and effects on both the microenvironment and the tumor itself. Strikingly lenalidomide both enhances antibody dependent cellular toxicity (ADCC), and mononuclear cell activity leading to tumor cell apoptosis. Lenalidomide has single agent activity in relapsed NHL with a manageable safety profile. Preclinical data has shown synergy between lenalidomide and immune based therapy such as the monoclonal antibody rituximab both in vitro and in murine models. The combination of rituximab and lenalidomide has striking clinical activity in relapsed lymphoma across multiple lymphoma subtypes. In a CALGB Phase II study of relapsed FL treated with rituximab and lenalidomide the ORR was 75% and the event free survival was two years. There was no significant increase in toxicity for the combination (Leonard, ASCO 2012). In relapsed DLBCL two recent studies have demonstrated a CR rate ranging from 28-35% for the combination (Wang M, Leukemia. 2013; Zinzani P, Clin Lymph Myeloma Leuk. 2011). Strikingly the combination has shown activity in a small number of patients with transformed lymphoma, which is generally chemotherapy resistant and has a dismal prognosis. In HL both single agent rituximab and lenalidomide have single agent activity in heavily pre-treated patients. The combination of pembrolizumab and lenalidomide have recently been reported to have activity in multiply relapsed multiple myeloma (MM) (ASH Annual Meeting Abstracts, 2015).

4.1.2 This is a unique opportunity to develop a paradigm changing immune platform for relapsed lymphoma that does not rely on conventional chemotherapy. We hypothesize that the combination of pembrolizumab and lenalidomide, will have complimentary immune activating effects, with non-overlapping toxicity, and

strong therapeutic efficacy for patients with relapsed DLBCL. This platform may have relevance not only for remission induction, but as a maintenance strategy in patient with high risk remission. If this treatment strategy is safe and effective, this will provide the justification to bring this strategy in larger scale randomized trials, which may ultimately demonstrate the significance of this platform in the management of multiple B cell lymphoma subtypes.

Intact immune surveillance controls outgrowth of neoplastic transformation. Accumulating evidence shows a correlation between tumor-infiltrating lymphocytes (TILs) in cancer tissue and favorable prognosis in various malignancies. In particular, the presence of CD8+ T-cells and the ratio of CD8+ effector T-cells / FoxP3+ regulatory T-cells seems to correlate with improved prognosis and long-term survival in many solid tumors.

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). 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. 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. PD-1 was shown to be expressed on activated lymphocytes including peripheral CD4+ and CD8+ T-cells, B-cells, T regs and Natural Killer cells. Expression has also been shown during thymic development on CD4-CD8- (double negative) T-cells as well as subsets of macrophages and dendritic cells. 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. 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. 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 has been suggested to regulate tumor-specific T-cell expansion in subjects with melanoma (MEL). This suggests that the PD-1/PD-L1 pathway plays a critical role in tumor immune evasion and should be considered as an attractive target for therapeutic intervention.

Pembrolizumab is a potent and highly selective humanized monoclonal antibody (mAb) of the IgG4/kappa isotype designed to directly block the interaction between PD-1 and its ligands, PD-L1 and PD-L2. Keytruda™ (pembrolizumab) has recently been approved in the United Stated for the treatment of patients with unresectable or metastatic melanoma and disease progression following ipilumumab and, if BRAF V600 mutation positive, a BRAF inhibitor.

4.1.3 Preclinical and Clinical Trial Data

Preclinical data showed that pembrolizumab (MK-3475) potently blocks PD-1 binding to both ligands, i.e PD-L1 and PD-L2, with half maximal inhibitory concentration (IC50) values below 1 nM. MK-3475 enhances T cell responses in human donor blood cell cultures with an EC50 of ~0.1 to 0.3 nM. MK-3475 binds to cynomolgus PD-1 with similar affinity, blocking activity, and demonstrates equivalent enhancement of cynomolgus T cell responses.

MK-3475 strongly enhances T lymphocyte immune responses in cultured blood cells from healthy human donors, cancer patients, and primates. The antibody potentiates existing immune responses only in the presence of antigen-receptor stimulation and does not nonspecifically activate all T cells.

Due to the lack of cross-reactivity of MK-3475 with PD-1 from rodents, a commercially available hamster anti-mouse PD-1 analog antibody was used for in vivo efficacy studies in mice. PD-1 blockade demonstrated to significantly inhibit tumor growth in a variety of syngeneic murine tumor models. In experiments in mice, anti-PD-1 therapy is synergistic with chemotherapeutic agents such as gemcitabine and 5-FU and combination therapy results in increased efficacy and increased complete regression rates in vivo.

As of October 18th, 2013, 1,000 patients have been treated with MK-3475 at several dose schedules, in six ongoing MK-3475 clinical trials, PN001, PN002, PN006, PN010, PN011 and PN012, including 10 mg/kg every 2 weeks. MK-3475 has been generally well tolerated, as expected based on preclinical findings and other anti-PD-1 monoclonal antibodies. No serious infusions reactions have been reported in PN001 (Phase I Study of Single Agent MK-3475 in Patients with Progressive Locally Advanced or Metastatic Carcinoma, Melanoma, and Non-Small Cell Lung Carcinoma).

The preliminary data suggest that a dose of MK-3475 at 2 mg/kg Q3W is appropriate for patients with melanoma. MK-3475 monotherapy induces an ORR of 25%/27% in patients with ipilimumab exposed melanoma by central independent RECIST and oncology

review/investigator assessed immune-related response criteria (irRC), respectively. MK-3475 monotherapy induces an ORR of 39% to 43% in patients with ipilimumab-naive melanoma by central independent RECIST and oncology review/investigator assessed irRC, respectively. These responses are remarkably durable. The preliminary 1-year survival rate for patients, many of whom have had multiple therapies, including ipilimumab, who receive MK-3475 is 81%. MK-3475 monotherapy induces an ORR of 21% to 24% in patients with previously-treated NSCLC by central independent RECIST/investigator assessed irRC, respectively, with these responses also remarkably durable. Preliminary data suggest higher levels of PD-L1 expression in tumors of NSCLC are associated with increased activity (ORR 67% by investigator assessed irRC/57% by central independent RECIST); additional data are required to define the optimal PD-L1 cut point.

The most commonly reported treatment emergent AEs experienced are fatigue (43.8%), nausea (26.7%), cough (25.3%), pruritus (24.6%), diarrhea (22.3%) and rash (21.5%). Immune-related adverse events were reported in 21.4% of melanoma patients; most of these events (15.8%) were considered drug-related by the investigator. The most commonly reported, immune-related adverse events across the dose-schedules are rash (3.2%), pruritus (2.9%), vitiligo (2.9%), hypothyroidism (2.7%), arthralgia (2.2%), diarrhea (2.2%), and pneumonitis (1.9%).

In HL and NHL, preclinical data using immunohistochemical assays showed frequent expression of PD-L1 in nodular sclerosis and mixed cellularity HL, and in a variety of NHL such as subsets of follicular lymphoma (FL) and diffuse large B-cell lymphoma (DLBCL), primary mediastinal large B-cell lymphoma, T-cell/histiocyte-rich B-cell lymphoma, plasmablastic lymphoma, extranodal NK/T-cell lymphoma, and HHV8-associated primary effusion lymphoma[1]. In HL, PD-L1 is expressed by the Hodgkin Reed Stemberg (HRS) cell and it is genetically determined, as the genes encoding PD-L1/PD-L2 are located on chromosome 9p24.1, which are commonly amplified in nodular sclerosing HL[2]. Epstein barr virus (EBV) infection, which is found in nearly half of HL patients and in EBV-related lymphomas, contributes to increased expression of PD-L1 by HRS[3]. In addition, PD-1 is highly expressed on the lymphocytes surrounding the HRS cells. These data suggest that the interaction PD-1/PD-L1 plays an important role, genetically determined, in HL immune escape, and constitutes an important target for therapy.

Clinical data have supported this hypothesis. An interim subgroup analysis of data from an ongoing multicenter open label, phase 1b clinical trial (KEYNOTE-013 trial - A Trial of Pembrolizumab in Participants with Blood Cancers - NCT 01953692), pembrolizumab, as single agent, showed activity in heavily pretreated, relapsed refractory HL patients. Results of 29 out of 31 patients with relapsed HL enrolled in the trials were available at the time of data presentation. Patients had a median age of 32 years (range 20-67 years), 52% had received 5 or more lines of therapy, 69% had a prior ASCT and 28% were ineligible for it, and were treated with pembrolizumab at a dose of 10mg/kg every 2 weeks for 24 months until disease progression or intolerable toxicity. Responses were assessed at week 12 and

every 8 weeks thereafter. The study's primary endpoint was complete remission (CR) rate, with secondary endpoints including overall response rate (ORR), progression free survival (PFS) and safety. With a median follow up of 153 days (range 1-341 days), 7 patients discontinued treatment for disease progression, 1 for toxicity and 1 for CR (n=1). The median duration of response was not reached at the time the data were presented. Most common side effects included grade 1-2 thyroid disorders and pneumonitis, each observed in 10% of the patients. There were no deaths or grade 4 adverse events. The ORR was 66%, including a CR rate of 21% and a PR rate of 45%, the stable disease (SD) rate was 21%[4].

4.1.3 Lenalidomide

Lenalidomide is an IMiDs, immunomodulatory pharmaceutical compound with pleiotropic activities, including antineoplastic, antiangiogenic and pro-erythropoietic properties[5]. It is approved for use in combination with dexamethasone for the treament of multiple myeloma (MM) patients who have received at least 1 prior therapy, for the treatment of patients with transfusion-dependent anemia due to low- or intermediate-1 (INT-1) risk myelodysplastic syndromes (MDS) associated with a deletion (del) (5q) cytogenetic abnormality with or without additional cytogenetic abnormalities and for the treatment of patients with mantle cell lymphoma (MCL) whose disease has relapsed or progressed after 2 prior therapies, one of which included bortezomib.

Lenalidomide inhibits proliferation of certain hematopoietic tumor cells (including MM, lymphoma, and those with deletions of chromosome 5) [6,7], enhances T-cell and natural killer (NK)-cell-mediated immunity, increases the number of NK T cells, inhibits angiogenesis by blocking the migration and adhesion of endothelial cells and the formation of microvessels, augments fetal hemoglobin production by CD34+ hematopoietic stem cells, and inhibits production of pro-inflammatory cytokines (eg, tumor necrosis factor-alpha [TNF-α] and interleukin [IL]-6) by monocytes[8,9].

Preclinical studies have shown that in myeloma cells, lenalidomide binding to cereblon recruits the transcription factors Ikaros (encoded by the gene IKZF1) and Aiolos (encoded by the gene IKZF3) to the E3 ligase complex and promotes their ubiquitination and subsequent degradation. Decreased expression of Aiolos results in downregulation of c-myc and interferon regulatory factor 4 (IRF4) and apoptosis in MM cells [10-12]. Cereblon expression also mediates T-cell response to lenalidomide[13]. In activated T cells in which cereblon was transiently decreased by small interfering ribonucleic acid (siRNA) knock down, IL-2 and TNF-α induction by lenalidomide was markedly reduced. Similar to the action of lenalidomide in MM cells, lenalidomide results in ubiquination of Ikaros and Aiolos in T cells, resulting in enhancement of IL-2 production[14].

Overall, an estimated 419,633 patients have been exposed to lenalidomide, collectively, with a variety of diagnosis including MM, MDS, NHL (including MCL), chronic lymphocytic

leukemia (CLL) and other B-cell lymphomas, solid tumors (prostate cancer, renal cell cancer, gliomas), malignant melanoma, complex regional pain syndrome, radiculopathy, and CHF.

The identified AEs associated with the use of lenalidomide across all studied indications are commonly related to the blood and lymphatic systems, gastrointestinal disorders, infections and infestations, skin and subcutaneous tissue disorders, and vascular disorders. In clinical trials in newly diagnosed MM subjects, an increase of invasive secondary primary malignancies (SPMs), most notably AML and MDS, has been observed predominantly in subjects receiving lenalidomide in combination with melphalan or immediately following high-dose melphalan and ASCT. In these studies, the incidence rate of hematologic malignancies was 1.57 per 100 person-years for the combined MPR arms and 0.36 per 100 person-years for the MPp+p control arm. Cases of B-cell NHL and HL were observed in clinical trials where subjects received lenalidomide in the post-ASCT setting. No increased risk of SPM was observed in ongoing clinical trials of CLL, lymphomas, or MDS using lenalidomide as a monotherapy or in combination with other treatments. There is an increased risk of VTEs (predominantly deep venous thrombosis and pulmonary embolism), in MM patients treated with lenalidomide in combination with dexamethasone or other chemotherapy. The risk of VTE is lower in MDS and MCL patients treated with lenalidomide monotherapy. Finally, lenalidomide is a chemical analog of thalidomide which is a known human teratogenic active substance that causes severe, life-threatening birth defects.

The adverse event (AE) profile of lenalidomide, particularly regarding cytopenias, is more severe and twice as frequent in subjects with del(5q) MDS, than in subjects with MM, MCL, solid tumors or gliomas. The higher frequency of cytopenias in subjects with del(5q) MDS, relative to subjects with other diseases, has been attributed to replacement of the normal bone marrow progenitor cells in these subjects by dysplastic cell clones, which are more susceptible to lenalidomide. For this reason the recommended dose for MM and MCL is 25 mg orally daily for 21 days every 28 days, while in MDS is 10mg orally daily.

In NHL, the combination of lenalidomide plus rituximab was shown to have synergistic effects in vitro and in murine models by enhancing rituximab-induced apoptosis and rituximab-dependent natural-killer-cell-mediated cytotoxicity[15,16]. Based on these data a phase 2 study to assess the activity and safety of lenalidomide plus rituximab was conducted on 110 patients, with untreated FL (50), marginal zone lymphoma (MZL) (30), and small lymphocytic leukemia (SLL) (30). Patients received 20 mg oral lenalidomide on days 1-21 of each 28-day cycle, and intravenous rituximab (375 mg/m2) on day 1 of every cycle. ORR was 90%, with 63% CR rate and 28% PR rate. Median PFS was 53.8 months and estimated 3 year survival was 96.1%. No significant increase in toxicity was noted with the combination[17]. In another phase 2 study conducted on 45 patients with relapsed refractory NHL, including 32 DLBCL, 9 transformed lymphoma and 4 with FL grade 3, lenalidomide was administered orally at 20mg on days 1-21 of each 28-day cycle with intravenous rituximab (375 mg/m2) weekly during cycle 1. ORR in this cohort was 33% with a median

duration of response (DOR) of 10.2 months. Median (PFS) and OS were 3.7 and 10.7 months, respectively. Of note of the 9 patients with transformed lymphoma, which is notoriously chemotherapy resistant and with a dismal prognosis, five (56%) had a response (three CRs and two PRs). Again no significant increase in toxicity was noted with the combination[18].

In HL, in a multicenter phase 2 study, 36 patients with heavily pretreated relapsed and refractory HL patients, (87% post ASCT and 55% with refractory disease), received lenalidomide 25mg daily as single agent on days 1-21 of a 28-day cycle until disease progression or excessive toxicity. The ORR was 19%, with 1 patient achieving CR and 6 patients achieving PR. Five patients achieved SD for more than 6 months. The treatment was well tolerated[19]. Other smaller studies confirmed similar results with lenalidomide single agent in heavily pretreated relapsed HL, with a favorable toxicity profile[20,21].

The combination of pembrolizumab and lenalidomide with low dose dexamethasone has been explored in multiple myeloma in the Keynote-023 study. In that study 33 patients who had failed ≥ 2 prior therapies were treated with the combination of pembrolizumab 200mg and lenalidomide at 10mg and 25mg. The therapy was well tolerated with no significant immune toxicity and no DLTs in 10mg lenalidomide cohort. In the 25-mg lenalidomide cohort, 3 patients (3/13) experienced a dose-limiting toxicity (DLT): neutropenia (grade 3 and grade 4), infectious pneumonia (grade 3), and tumor lysis syndrome (grade 3) with hyperuricemia (grade 4). All patients recovered from the DLTs without treatment discontinuation. Based upon these data the MTD/MAD was defined as pembrolizumab 200 mg fixed dose in combination with lenalidomide 25 mg and low-dose dexamethasone 40 mg. In this heavily pretreated patient population with a median follow-up of 287 days (48-476), 13/17 patients responded to treatment. The objective response rate (ORR) was 76%, with 4 patients achieving a very good partial response and 9 patients achieving a partial response. ORR has also been observed in patients with IMiDs-refractory and double refractory disease. (ASH abstract 505 Pembrolizumab in Combination with Lenalidomide and Low-Dose Dexamethasone for Relapsed/Refractory Multiple Myeloma (RRMM): Keynote-023).

4.2 Rationale

4.2.1 Rationale for the Trial and Selected Subject Population

Checkpoint inhibitory drugs, such as pembrolizumab, targeting the PD-1/PD- L1 signaling pathway have been shown to promote marked antitumor immunity in patients with HL and in a subset of patients with NHL. Despite its activity and the high ORR seen in heavily pretreated patients with HL, pembrolizumab as single agent has shown only a modest CR rate of 21%.

We hypothesize that the combination of pembrolizumab with lenalidomide, an agent with complimentary immune stimulatory activity, and non-overlapping toxicity, might enhance its

therapeutic efficacy in patients with relapsed refractory HL. This novel treatment platform, which is chemotherapy free, may be highly effective for long term disease control as maintenance strategy or remission induction, and may have a role in earlier line management of frail elderly patients with relapsed disease, or who are unable to tolerate standard chemotherapy.

If this treatment strategy is safe and effective, this will provide the justification to bring this strategy in larger scale randomized trials, or to consider triplet combinations with rituximab which may ultimately demonstrate the significance of this platform in the management of multiple B cell lymphoma subtypes.

4.2.2 Rationale for Dose Selection/Regimen/Modification

4.2.2.1 Pembrolizumab

An open-label Phase I trial (Protocol 001) is being conducted to evaluate the safety and clinical activity of single agent MK-3475. 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 MK-3475 showed evidence of target engagement and objective evidence of tumor size reduction at all dose levels (1 mg/kg, 3 mg/kg and 10 mg/kg Q2W). No MTD has been identified to date. 10.0 mg/kg Q2W, the highest dose tested in PN001, will be the dose and schedule utilized in Cohorts A, B, C and D of this protocol to test for initial tumor activity. Recent data from other clinical studies within the MK-3475 program has shown that a lower dose of MK-3475 and a less frequent schedule may be sufficient for target engagement and clinical activity.

PK data analysis of MK-3475 administered Q2W and Q3W showed slow systemic clearance, limited volume of distribution, and a long half-life (refer to IB). Pharmacodynamic data (IL-2 release assay) suggested that peripheral target engagement is durable (>21 days). This early PK and pharmacodynamic data provides scientific rationale for testing a Q2W and Q3W dosing schedule.

A population pharmacokinetic analysis has been performed using serum concentration time data from 476 patients. Within the resulting population PK model, clearance and volume parameters of MK-3475 were found to be dependent on body weight. The relationship between clearance and body weight, with an allometric exponent of 0.59, is within the range observed for other antibodies and would support both body weight normalized dosing or a fixed dose across all body weights. MK-3475 has been found to have a wide therapeutic range based on the melanoma indication. The differences in exposure for a 200 mg fixed dose regimen relative to a 2 mg/kg Q3W body weight based regimen are anticipated to remain well within the established exposure margins of 0.5 – 5.0 for MK-3475 in the melanoma indication. The exposure margins are based on the notion of similar efficacy and

safety in melanoma at 10 mg/kg Q3W vs. the proposed dose regimen of 2 mg/kg Q3W (i.e. 5-fold higher dose and exposure). The population PK evaluation revealed that there was no significant impact of tumor burden on exposure. In addition, exposure was similar between the NSCLC and melanoma indications. Therefore, there are no anticipated changes in exposure between different indication settings.

The rationale for further exploration of 2 mg/kg and comparable doses of pembrolizumab in solid tumors is based on: 1) similar efficacy and safety of pembrolizumab when dosed at either 2 mg/kg or 10 mg/kg Q3W in melanoma patients, 2) the flat exposure-response relationships of pembrolizumab for both efficacy and safety in the dose ranges of 2 mg/kg Q3W to 10 mg/kg Q3W, 3) the lack of effect of tumor burden or indication on distribution behavior of pembrolizumab (as assessed by the population PK model) and 4) the assumption that the dynamics of pembrolizumab target engagement will not vary meaningfully with tumor type.

The choice of the 200 mg Q3W as an appropriate dose for the switch to fixed dosing is based on simulations performed using the population PK model of pembrolizumab showing that the fixed dose of 200 mg every 3 weeks will provide exposures that 1) are optimally consistent with those obtained with the 2 mg/kg dose every 3 weeks, 2) will maintain individual patient exposures in the exposure range established in melanoma as associated with maximal efficacy response and 3) will maintain individual patients exposure in the exposure range established in melanoma that are well tolerated and safe.

A fixed dose regimen will simplify the dosing regimen to be more convenient for physicians and to reduce potential for dosing errors. A fixed dosing scheme will also reduce complexity in the logistical chain at treatment facilities and reduce wastage.

4.2.2.2 Lenalidomide

Approved doses of lenalidomide for MM and MCL are 25 mg orally daily for 21 days every 28 days and for MDS 10 mg orally daily. Studies in HL have been conducted using 25mg daily as single agent on days 1-21 of a 28-day cycle[22], while in NHL a lower dose of 20 mg daily on days 1-21 of a 28 cycle was shown to be safe and effective in combination with rituximab[18]. Variable doses from 5mg to 25 mg have been evaluated in combination with rituximab containing chemotherapy[23], with manageable toxicity profile.

In the phase 1 trial we opted to start at a lower dose of 15mg to evaluate for unexpected toxicities, particularly in this novel immunomodulatory drug-checkpoint inhibitor combination, with plan to escalate to full dose of 20mg if tolerated (as per prior phase 2 studies of combination therapy in lymphomas).

We dose Lenalidomide up to 20mg. The safety for Lenalidomide at this dose has been established in combination with Rituximab and other immune agents. Although there is now

data to support full dose Lenalidomide in combination with Pembrolizumab in multiple myeloma, given that this is a first in human study of this combination in lymphoma we do not have current plans to escalate the dose of Lenalidomide above 20mg.

4.2.3 Rationale for Endpoints

4.2.3.1 Efficacy Endpoints

In the phase 1 part of the study, the primary endpoints are safety and tolerability of the combination of pembrolizumab and lenalidomide, with determination of the MTD of lenalidomide in combination.

In the phase 2 portion of the study, the primary endpoints are overall activity assessment (CR, ORR, and PR) and of the combination of pembrolizumab with the MTD of lenalidomide in patients with RR HL.

4.2.3.2 Biomarker Research

NHL and HL are cancers in which the immune system plays a vital role in tumor tolerance and tumor growth. Evaluation of changes in circulating immune cell populations, in the tumor microenvironment abundance and composition and gene expression profiling of tumor biopsies obtained longitudinally pre, during and post therapy will provide significant and novel information regarding biological effects of this immunotherapy in NHL and HL patients, and changes in patterns based on response to or resistance to therapy.

5.0 METHODOLOGY

5.1 Entry Criteria

5.1.1 Diagnosis/Condition for Entry into the Trial

Phase 1: Pathologically confirmed relapsed or refractory B cell lymphoma. Must have relapsed after initial therapy. No restriction in number of prior lines of therapy.

Phase 2: Pathologically confirmed relapsed or refractory HL. No restriction in number of prior lines of therapy.

5.1.2 Subject Inclusion Criteria

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

1. Be willing and able to provide written informed consent for the trial.

2. Be ≥ 18 years of age on day of signing informed consent.

3. Have measurable or evaluable disease, as defined in 2007 Revised Response Criteria for Malignant Lymphoma[24]. HL patients must not be currently eligible for autologous stem cell transplant.

4. Be willing to provide either archived tumor tissue or tissue from a newly obtained core or excisional biopsy of a tumor lesion. *Newly-obtained is defined as a specimen obtained up to 6 weeks (42 days) prior to initiation of treatment on Day 1.*

5. Have a performance status of 0 to 1 on the ECOG Performance Scale.

6. Demonstrate adequate organ function as defined in Table 1, all screening labs should be performed within 14 days of treatment initiation.

Table 1 Adequate Organ Function Laboratory Values

System	Laboratory Value
Hematological	
Absolute neutrophil count (ANC)	≥1,000 /mcL if no bone marrow involvement ≥800 /mcL if documented bone marrow involvement
Platelets	≥75,000 / mcL if no bone marrow involvement ≥50,000 / mcL if documented bone marrow involvement
Hemoglobin	≥8 g/dL without transfusion or EPO dependency (within 7 days of assessment)
Renal	
Serum creatinine **OR** Measured or calculated[a] creatinine clearance (GFR can also be used in place of creatinine or CrCl)	≤1.5 X upper limit of normal (ULN) **OR** ≥60 mL/min for subject with creatinine levels > 1.5 X institutional ULN
Hepatic	
Serum total bilirubin	≤ 1.5 X ULN **OR**
	Direct bilirubin ≤ ULN for subjects with total bilirubin levels > 1.5 ULN

AST (SGOT) and ALT (SGPT)	≤ 2.5 X ULN **OR** ≤ 5 X ULN for subjects with liver metastases
Albumin	≥2.5 mg/dL
Coagulation	
International Normalized Ratio (INR) or Prothrombin Time (PT)	≤1.5 X 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 X 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 should be calculated per institutional standard.	

7. Female subject of childbearing potential should have two negative urine or serum pregnancy test, one at 10-14 days before first dose of study drug and another within 24 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.

8. 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 5.7.2). Subjects of childbearing potential are those who have not been surgically sterilized or have not been free from menses for > 1 year.

9. Male subjects should agree to use an adequate method of contraception starting with the first dose of study therapy through 120 days after the last dose of study therapy.

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 therapy or used an investigational 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 a known history of active TB (Bacillus Tuberculosis)

4. Hypersensitivity to pembrolizumab or any of its excipients.

5. Has had a prior anti-cancer monoclonal antibody (mAb) within 4 weeks prior to study Day 1 or who has not recovered (i.e., ≤ Grade 1 or at baseline) from adverse events due to agents administered more than 4 weeks earlier.

6. 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 adverse events 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.

7. Has a known additional malignancy that is progressing or requires active treatment. Exceptions include basal cell carcinoma of the skin or squamous cell carcinoma of the skin that has undergone potentially curative therapy or in situ cervical cancer.

8. Has known active central nervous system (CNS) metastases and/or carcinomatous meningitis. Subjects with previously treated brain metastases 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. This exception does not include carcinomatous meningitis which is excluded regardless of clinical stability.

9. Has active autoimmune disease that has required systemic treatment in the past 2 years (i.e. with use of disease modifying agents, corticosteroids or immunosuppressive drugs). Replacement therapy (eg., thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency, etc.) is not considered a form of systemic treatment.

10. Has known history of, or any evidence of active, non-infectious pneumonitis.

11. Has an active infection requiring systemic therapy.

12. 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.

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

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

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

16. Has a known history of Human Immunodeficiency Virus (HIV) (HIV 1/2 antibodies).

17. Has known active Hepatitis B (e.g., HBsAg reactive) or Hepatitis C (e.g., HCV RNA [qualitative] is detected), or other active viral hepatitis. Patients with treated and resolved hepatitis B or C are eligible. Patients with active liver disease, except liver abnormalities directly attributable to lymphoma are ineligible,

18. Has received a live vaccine within 30 days of planned start of study therapy.

    Note: Seasonal influenza vaccines for injection are generally inactivated flu vaccines and are allowed; however intranasal influenza vaccines (e.g., Flu-Mist®) are live attenuated vaccines, and are not allowed.

5.2 Patient Recruitment and Registration

Patients will be recruited from the Investigators' clinical practices at the Perlmutter Cancer Center (PCC) at NYU Langone Health, Winship Cancer Institute of Emory University, Massachusetts General Hospital (MGH) and Beth Israel Deaconess Medical Center of MGH in Boston, MA. Prior to study entry, a patient's eligibility must be approved in writing by the NYU Clinical Trials Office.

Target accrual for this study is 26-29 patients. Prospective subjects will receive detailed information regarding this study; its investigational nature, required study procedures, alternative treatments, risks and potential benefits of the study. All questions will be answered by the PI and/or qualified research personnel.

The Principal Investigator will:

1. Obtain signed and dated informed consent from the potential subject before any study specific procedures are performed.

2. Determine patient eligibility. (See Section 5.1.2 and 5.1.3)

3. Submit registration to NYU Langone Health Perlmutter Cancer Center Clinical Trials Office (CTO)

4. Receive registration confirmation from the designated CTO staff member at NYU Perlmutter Cancer Center CTO, including a unique study identification number assigned to the patient, which will be distributed to the study team upon registration of the patient.

Enrollment in the study requires that all inclusion and exclusion criteria have been met. Enrollment occurs upon confirmation of registration from the NYU Langone Health Perlmutter Cancer Center (PCC) Clinical Trials Office (CTO). The following materials must be submitted to the research coordinator for registration:

1. Complete signed and dated informed consent form

2. Complete signed and dated eligibility checklist

3. All supporting documentation verifying each criterion has been met

Registration will occur within 48 hours of research coordinator receipt of all of the above documents. A written confirmation of enrollment including a unique study identification number assigned by the research coordinator will be disbursed to the study team upon registration. The patient will not be identified by name. This is the point, at which, the patient is considered accrued on study.

5.2.1 Informed Consent

Investigators will stress that participation in the study is completely voluntary, he/she may withdraw from the study at any time and it will not affect the care patients receive or result in any loss of benefits to which patients are otherwise entitled.

For non-English speaking patients, institutional translation services will be utilized. All procedures for consenting non-English speaking patients will be in accordance with NYU PCC CTO guidelines and policies.

For patients who cannot read; a witness, not related to the research study will be present. The consent will be read to the patient. The patient will also be allowed to ask any questions s/he may have. The investigator will ask the patient questions to ensure s/he understands the study. If the investigator determines the subject understands the study, the patient will mark an X where his/her name would go and the witness will sign the consent form.

5.2.2 Documentation of Consent

The Primary Investigator or IRB approved sub-investigator will be responsible for documentation in the medical record that consent has been obtained from all participants. A signed copy of the consent form will be given to each participant. Original consent forms will be stored in the subject's medical chart.

5.2.3 Multi-Site Surveillance

As the lead investigator in this multi-site trial, the Overall Primary Investigator is responsible for organizing and conducting bi-weekly teleconferences with all participating sites. The PI will also be responsible for including data from all of the participating sites within the overall trial's quarterly Data and Safety Monitoring report to the DSMC to include minutes from bi-weekly PI teleconferences. Each participating site will be responsible for submitting the results and recommendations from the DSMC's quarterly reviews to their IRB of record at the time of continuing review. Additionally, the NYU Langone Health PCC Clinical Trial Office, Quality Assurance Unit will provide extensive monitoring remotely, to ensure completeness and compliance with the protocol, in addition to consistency of the data.

5.2.4 Patient Informed Consent at Additional Sites

The Principal Investigator (PI) at each participating site will identify the physician members of the study team who will be obtaining consent and signing the consent form for this clinical trial. It is NYU Langone Health's policy that Nurses and Fellows cannot obtain consent to greater than minimal risk trials, unless Fellows are listed as Co-Investigators.

The Investigator must ensure that each participant, or his/her legally acceptable representative, is fully informed about the nature and objectives of the study and possible risks associated with participation. All participants must be provided a consent form describing this study and providing sufficient information for participants to make an informed decision about their participation in this study. The formal consent of a participant, using the IRB approved consent form, must be obtained before the participant is involved in any study-related procedures. The consent form must be signed and dated by the participant or the participant's legally authorized representative (if applicable), and by the person obtaining consent. The participant must be given a copy of the signed and dated consent document. The original signed copy of the consent document must be retained in the medical record or research file.

All parties will ensure protection of participant personal data and will not include participant names on any sponsor forms, reports, publications, or in any other disclosures, except where required by laws. In case of data transfer, NYU Langone Health Perlmutter Cancer Center (PCC) will maintain high standards of confidentiality and protection of participant personal data.

The informed consent form must be in compliance with ICH/GCP, local regulatory requirements, and legal requirements. The informed consent form used in this study, and any changes made during the course of the study, must be prospectively approved by both the IRB and NYU Langone Health before use.

5.2.5 Patient Registration at Additional Sites

Enrollment at additional sites can occur once each site's IRB has approved this protocol, a copy of each site's IRB approval, Citi training certificates, Medical Licenses and signed CVs are provided to NYU Langone Health Perlmutter Cancer Center Clinical Trials Office. Once, all required documents are provided to the NYU Langone Health PCC Clinical Trials Office and activation notification will be sent to the PI and research coordinator of the participating site.

Central registration for this study will take place at NYU Langone Health PCC Quality Assurance Unit (PCC-QAU@nyumc.org).

Each patient must sign and date an informed consent form before undergoing any study specific procedures unless a procedure is being performed as part of the patient's standard of care. Once a patient has signed consent, each site must notify the NYU Langone Health PCC Quality Assurance Unit and forward a copy of the signed consent with all supporting documentation to NYU Langone Health PCC Clinical Trials Office within 24 hours.

Enrollment in the study requires that all inclusion and exclusion criteria have been met. Enrollment occurs upon confirmation of registration from the NYU Langone Health PCC Clinical Trials Office. The following materials must be submitted to the Quality Assurance Unit at NYU Langone Health via email (PCC-QAU@nyumc.org):

1. Complete signed and dated informed consent form
2. Complete signed and dated informed consent checklist
3. Complete signed and dated eligibility checklist
4. All supporting documentation verifying each criterion has been met.

Registration will occur once the Senior Research Nurse for the Quality Assurance Unit conducts a central review of the submitted materials. Once eligibility is verified, a unique subject study number will be issued within 48 hours of receiving all required registration material. This number is unique to the participant and must be written on all data and correspondence for the participant. The NYU Langone Health PCC CTO will return a signed eligibility confirmation worksheet email with the subject's unique study number.

The subject will not be identified by name. This is the point, at which, the subject is considered accrued on study. Protocol treatment should begin within designated timeframe; issues that would cause treatment delays should be discussed with the overall PI, Catherine Diefenbach, MD.

All screen failures/ineligible subjects, as well as subject's who withdraw consent prior to initiation of protocol therapy must be submitted to the CTO in a manner analogous to the procedures noted above. Applicable source documentation will be required within the corresponding submissions.

Each site is responsible for reporting all unexpected problems involving risks to participants or others to the NYU Langone Health PCC Clinical Trials Office and to their IRB as per site institutional policy.

5.3 Trial Treatments

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

Table 2 Trial Treatment

Drug	Dose/Potency	Dose Frequency	Route of Administration	Regimen/ Treatment Period	Use
Pembrolizumab	200 mg	Q3W	IV infusion	Day 1 of each 3 week cycle	Experimental
Lenalidomide	10mg-20mg	Daily for 14 days every 21 days	PO	Day 1-14 of 21	Experimental

5.3.1 Dose Selection/Modification/ Dose Limiting Toxicity

5.3.1.1 Dose Selection

The rationale for selection of doses to be used in this trial is provided in Section 4.0 – Background and Rationale.

Details on preparation and administration of pembrolizumab (MK-3475) are provided in the package insert.

5.3.1.2 Dose Modification

5.2.1.2.1 Pembrolizumab

Adverse events (both non-serious and serious) associated with pembrolizumab exposure may represent an immunologic etiology. These adverse events may occur shortly after the first dose or several months after the last dose of treatment. Pembrolizumab must be withheld for drug-related toxicities and severe or life-threatening AEs as per Table 3 below. See Section 5.6.1 and Events of Clinical Interest Guidance Document for supportive care guidelines, including use of corticosteroids.

Table 3

Dose Modification Guidelines for Drug-Related Adverse Events

Toxicity	Hold Treatment For Grade	Timing for Restarting Treatment	Discontinue Subject
Diarrhea/Colitis	2-3	Toxicity resolves to Grade 0-1.	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks.
	4	Permanently discontinue	Permanently discontinue
AST, ALT, or Increased Bilirubin	2	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose.
	3-4	Permanently discontinue (see exception below)[1]	Permanently discontinue
Type 1 diabetes mellitus (if new onset) or Hyperglycemia	T1DM or 3-4	Hold pembrolizumab for new onset Type 1 diabetes mellitus or Grade 3-4 hyperglycemia associated with evidence of beta cell failure.	Resume pembrolizumab when patients are clinically and metabolically stable.
Hypophysitis	2-3	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks.
	4	Permanently discontinue	Permanently discontinue
Hyperthyroidism	3	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks.

Toxicity	Hold Treatment For Grade	Timing for Restarting Treatment	Discontinue Subject
	4	Permanently discontinue	Permanently discontinue
Hypothyroidism	2-4	Therapy with pembrolizumab can be continued while treatment for the thyroid disorder is instituted	Therapy with pembrolizumab can be continued while treatment for the thyroid disorder is instituted.
Infusion Reaction	3-4	Permanently discontinue	Permanently discontinue
Pneumonitis	2	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks.
	3-4	Permanently discontinue	Permanently discontinue
Renal Failure or Nephritis	2	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks.
	3-4	Permanently discontinue	Permanently discontinue
All Other Drug-Related Toxicity[2]	3 or Severe	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks.
	4	Permanently discontinue	Permanently discontinue

Note: Permanently discontinue for any severe or Grade 3 drug-related AE that recurs or any life-threatening event.

[1] For patients with liver metastasis who begin treatment with Grade 2 AST or ALT, if AST or ALT increases by greater than or equal to 50% relative to baseline and lasts for at least 1 week then patients should be discontinued.

[2] Patients with intolerable or persistent Grade 2 drug-related AE may hold study medication at physician discretion. Permanently discontinue study drug for persistent Grade 2 adverse reactions for which treatment with study drug has been held, that do not recover to Grade 0-1 within 12 weeks of the last dose.

Dosing interruptions are permitted in the case of medical / surgical events or logistical reasons not related to study therapy (e.g., elective surgery, unrelated medical events, patient vacation, and/or holidays). Subjects should be placed back on study therapy within 3 weeks of the scheduled interruption, unless otherwise discussed with the Sponsor. The reason for interruption should be documented in the patient's study record.

5.2.1.2.2 Lenalidomide

Adverse events (both non-serious and serious) associated with lenalidomide exposure may represent an immunologic etiology. These adverse events may occur shortly after the first dose or several months after the last dose of treatment. Lenalidomide must be withheld for drug-related toxicities and severe or life-threatening AEs as per Table 3 below

Table 4

Dose Modification Guidelines for Drug-Related Adverse Events

Toxicity	Hold Treatment For Grade	Timing for Restarting Treatment	Discontinue Subject
Neutropenia and thrombocytopenia	4	Toxicity resolves to Grade 1-2	Toxicity does not resolve within 1 month of last dose
Venous thrombosis/ Embolism	3-4	At investigator discretion after starting anticoagulation	At investigator discretion
Skin rash	4	n/a	Permanently discontinue
	2-3	Resume when rash resolves to less or equal grad 1	Toxicity does not resolve within 1 month of last dose
Neuropathy	3	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 1 month
	4	Permanently discontinue	Permanently discontinue
Hypothyroidism	2-4	Therapy with can be continued while treatment for the thyroid disorder is instituted	Therapy with can be continued while treatment for the thyroid disorder is instituted.
Allergic reaction	3-4	Permanently discontinue	Permanently discontinue
Constipation	3-4	Toxicity resolves to Grade 1-2	Toxicity does not resolve within 1month
Cardiac arrhythmias	2	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 1 month.
	3-4	Permanently discontinue	Permanently discontinue

Toxicity	Hold Treatment For Grade	Timing for Restarting Treatment	Discontinue Subject
Other non hematological Drug-Related Toxicity	3 or Severe	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 1 month.
	4	Permanently discontinue	Permanently discontinue
Note: Permanently discontinue for any severe or Grade 3 drug-related AE that recurs or any life-threatening event.			

5.3.1.3 Definition of Dose-Limiting Toxicity

Toxicities should be attributable to the study intervention to constitute a dose limiting toxicity (DLT). Toxicity will be graded using the Common Toxicity Criteria for Adverse Events (CTCAE) version 4.0. A DLT is defined by the occurrence of any of the following toxicities (CTCAE v.4.03) for up to 21 days from initiation of the combination therapy (i.e. within the first cycle of therapy) in order to evaluate the potential toxicities of these therapies.

Non-Hematological dose-limiting toxicity

Any Grade 3 or Grade 4 non-hematological toxicity that is possibly, probably or definitely attributable to the regimen pembrolizumab-lenalidomide is considered a DLT, including the following:

- Any type of grade 3-4 hypersensitivity reaction (i.e.: allergic reaction, anaphylaxis, serum sickness, skin disorders, etc.), regardless of attribution.
- Any type of grade 3-4 immune related adverse event
- Inability to receive pembrolizumab-lenalidomide therapy within a 1 month period of scheduled treatment, due to a therapy related event.
- Grade 3 nausea/vomiting/diarrhea lasting longer than 24hours despite maximal care or Grade 4 nausea/vomiting/diarrhea

Any other non-hematologic clinical toxicity considered at least possibly related to treatment defined as any Grade 3 or greater with the specific exception of:

- Grade 3 dehydration that, in the opinion of the investigator, occurs in the setting of inadequate prophylactic measures or compliance with supportive care measures and lasts for less than 48 hours
- Grade 3 fatigue or Grade 4 fatigue that lasts for ≤ 5 days
- Grade 3 fever
- Grade 3 ALT/AST elevation for which total bilirubin remains within normal limits.

Hematologic dose-limiting toxicity

The following hematological toxicity possibly, probably or definitely attributable to the regimen of pembrolizumab and lenalidomide is considered a DLT. Growth factors are allowed per treating investigator's discretion in patients at high risk for febrile neutropenia.

- Grade 4 neutropenia associated with fever (> 38.5) of any duration
- Grade 3 neutropenia associated with fever (> 38.5) of any duration
- Grade 4 thrombocytopenia or Grade 3 thrombocytopenia with bleeding or any requirement for platelet transfusion.
- Grade 4 anemia unexplained by underlying disease
- Myelosuppression that causes a delay of > 7 days in next cycle of pembrolizumab/lenalidomide

5.3.2 Timing of Dose Administration

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

All trial treatments will be administered on an outpatient basis.

Pembrolizumab 200 mg will be administered as a 30 minute IV infusion every 3 weeks. Sites should make every effort to target infusion timing to be as close to 30 minutes as possible. However, given the variability of infusion pumps from site to site, a window of -5

minutes and +10 minutes is permitted (i.e., infusion time is 30 minutes: -5 min/+10 min). Pembrolizumab will be administered before Lenalidomide. There is no required waiting time between administration of both drugs.

The package insert contains specific instructions for the preparation of the pembrolizumab infusion fluid and administration of infusion solution.

Lenalidomide will be administered at a starting dose of 15mg PO daily, from day 1 to 14, every 21 days, following a dose escalation protocol as per trial design.

5.3.3 Trial Blinding/Masking

This is an open-label trial; therefore, the Sponsor, investigator and subject will know the treatment administered.

5.4 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 investigator should discuss any questions regarding this with the Merck Clinical team. The final decision on any supportive therapy or vaccination rests with the investigator and/or the subject's primary physician.

5.4.1 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 on the case report form (CRF) including all prescription, over-the-counter (OTC), herbal supplements, and IV medications and fluids. If changes occur during the trial period, documentation of drug dosage, frequency, route, and date may also be included on the CRF.

All concomitant medications received within 28 days before the first dose of trial treatment and 30 days after the last dose of trial treatment should be recorded. Concomitant medications administered after 30 days after the last dose of trial treatment should be recorded for SAEs and ECIs as defined in Section 7.2.

5.4.2 Prohibited Concomitant Medications

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

- Antineoplastic systemic chemotherapy or biological therapy

- Immunotherapy not specified in this protocol
- Chemotherapy not specified in this protocol
- Investigational agents other than pembrolizumab
- Radiation therapy
    - Note: Radiation therapy to a symptomatic solitary lesion or to the brain may be allowed at the investigator's discretion.
- Live vaccines within 30 days prior to the first dose of trial treatment and while participating in the trial. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, varicella/zoster, yellow fever, rabies, BCG, and typhoid vaccine.
- Systemic glucocorticoids for any purpose other than to modulate symptoms from an event of clinical interest of suspected immunologic etiology. The use of physiologic doses of corticosteroids may be approved after consultation with the Sponsor.

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.

5.5 Rescue Medications & Supportive Care

5.5.1 Supportive Care Guidelines

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

Note: if after the evaluation the event is determined not to be related, the investigator is instructed to follow the ECI reporting guidance but does not need to follow the treatment guidance (as outlined in the ECI guidance document). Refer to Section 5.2.1 for dose modification.

It may be necessary to perform conditional procedures such as bronchoscopy, endoscopy, or skin photography as part of evaluation of the event. Suggested conditional procedures, as appropriate, can be found in the ECI guidance document.

- **Pneumonitis**:

    - For **Grade 2 events**, treat with systemic corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.

    - For **Grade 3-4 events**, immediately treat with intravenous steroids. Administer additional anti-inflammatory measures, as needed.

    - Add prophylactic antibiotics for opportunistic infections in the case of prolonged steroid administration.

- **Diarrhea/Colitis**:

    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).

    - All subjects who experience 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. For Grade 2 or higher diarrhea, consider GI consultation and endoscopy to confirm or rule out colitis.

    - For **Grade 2 diarrhea/colitis** that persists greater than 3 days, administer oral corticosteroids.

    - For **Grade 3 or 4 diarrhea/colitis** that persists > 1 week, treat with intravenous steroids followed by high dose oral steroids.

- When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.

- **Type 1 diabetes mellitus (if new onset, including diabetic ketoacidosis [DKA]) or ≥ Grade 3 Hyperglycemia, if associated with ketosis (ketonuria) or metabolic acidosis (DKA)**

  - For **T1DM** or **Grade 3-4** Hyperglycemia

    - Insulin replacement therapy is recommended for Type I diabetes mellitus and for Grade 3-4 hyperglycemia associated with metabolic acidosis or ketonuria.

    - Evaluate patients with serum glucose and a metabolic panel, urine ketones, glycosylated hemoglobin, and C-peptide.

- **Hypophysitis**:

  - For **Grade 2** events, treat with corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. Replacement of appropriate hormones may be required as the steroid dose is tapered.

  - For **Grade 3-4** events, treat with an initial dose of IV corticosteroids followed by oral corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. Replacement of appropriate hormones may be required as the steroid dose is tapered.

- **Hyperthyroidism or Hypothyroidism**:

  Thyroid disorders can occur at any time during treatment. Monitor patients for changes in thyroid function (at the start of treatment, periodically during treatment,

and as indicated based on clinical evaluation) and for clinical signs and symptoms of thyroid disorders.

- **Grade 2** hyperthyroidism events (and **Grade 2-4** hypothyroidism):
  - In hyperthyroidism, non-selective beta-blockers (e.g. propranolol) are suggested as initial therapy.
  - In hypothyroidism, thyroid hormone replacement therapy, with levothyroxine or liothyroinine, is indicated per standard of care.
- **Grade 3-4** hyperthyroidism
  - Treat with an initial dose of IV corticosteroid followed by oral corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. Replacement of appropriate hormones may be required as the steroid dose is tapered.

- **Hepatic**:
  - For **Grade 2** events, monitor liver function tests more frequently until returned to baseline values (consider weekly).
    - Treat with IV or oral corticosteroids
  - For **Grade 3-4** events, treat with intravenous corticosteroids for 24 to 48 hours.
  - When symptoms improve to Grade 1 or less, a steroid taper should be started and continued over no less than 4 weeks.

- **Renal Failure or Nephritis**:
  - For **Grade 2** events, treat with corticosteroids.
  - For **Grade 3-4** events, treat with systemic corticosteroids.

- When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.

Management of Infusion Reactions: Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion.

Table 5 below shows treatment guidelines for subjects who experience an infusion reaction associated with administration of pembrolizumab (MK-3475).

Table 5 Infusion Reaction 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 infusion interruption but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDS, narcotics, IV fluids); prophylactic medications indicated for < =24 hrs	**Stop Infusion and monitor symptoms.** Additional appropriate medical therapy may include but is not limited to: IV fluids Antihistamines NSAIDS Acetaminophen Narcotics Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator. If symptoms resolve within one hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (e.g., from 100 mL/hr to 50 mL/hr). Otherwise dosing will be held until symptoms resolve and the subject should be premedicated for the next scheduled dose.	Subject may be premedicated 1.5h (± 30 minutes) prior to infusion of pembrolizumab (MK-3475) with: Diphenhydramine 50 mg po (or equivalent dose of antihistamine). Acetaminophen 500-1000 mg po (or equivalent dose of antipyretic).

NCI CTCAE Grade	Treatment	Premedication at subsequent dosing
	Subjects who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further trial treatment administration.	
~~Grades 3 or 4~~ Grade 3: Prolonged (i.e., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (e.g., renal impairment, pulmonary infiltrates) Grade 4: Life-threatening; pressor or ventilatory support indicated	**Stop Infusion.** Additional appropriate medical therapy may include but is not limited to: IV fluids Antihistamines NSAIDS Acetaminophen Narcotics Oxygen Pressors Corticosteroids Epinephrine Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator. Hospitalization may be indicated. **Subject is permanently discontinued from further trial treatment administration.**	No subsequent dosing
Appropriate resuscitation equipment should be available in the room and a physician readily available during the period of drug administration.		

5.6 Diet/Activity/Other Considerations

5.6.1 Diet

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

5.6.2 Contraception

Lenalidomide may cause severe birth defects or death of the fetus if used during pregnancy. Lenalidomide is similar to thalidomide, which causes life-threatening birth defects Pembrolizumab may have adverse effects on a fetus in utero, too. 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 the Sponsor and 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.

5.6.3 Use in Pregnancy

If a subject inadvertently becomes pregnant while on treatment with lenalidomide-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 the Sponsor and to Merck without delay and within 24 hours to the Sponsor and within 2 working days to

Merck if the outcome is a serious adverse experience (e.g., death, abortion, congenital anomaly, or other disabling or life-threatening complication to the mother or newborn).

The study investigator will make every effort to obtain permission to follow the outcome of the pregnancy and report the condition of the fetus or newborn to the Sponsor. If a male subject impregnates his female partner the study personnel at the site must be informed immediately and the pregnancy reported to the Sponsor and to Merck and followed as described above and in Section 7.2.2.

5.6.4 Use in Nursing Women

It is unknown whether pembrolizumab and lenalidomide are 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.

5.7 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 or the Sponsor 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 – Other Procedures.

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 7.1.2.7.1
- 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
- Completed 24 months of uninterrupted treatment with pembrolizumab.
- 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 adverse event monitoring (serious adverse events will be collected for 90 days after the end of treatment as described in Section 7.2.3.1). Subjects who discontinue 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. After documented disease progression each subject will be followed by telephone for overall survival until death, withdrawal of consent, or the end of the study, whichever occurs first.

5.7.1 Discontinuation of Study Therapy after CR

Discontinuation of treatment may be considered for subjects who have attained a confirmed CR or after completion of 12 months of therapy.

5.8 Subject Replacement Strategy

If a subject drops out of the study before the first evaluation for reasons different than disease progression or death related to underlying lymphoma or toxicity from the treatment, he or she might be replaced.

5.9 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 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.

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6.0 TRIAL FLOW CHART

6.1 Study Flow Chart

Trial Period:			**Treatment Cycles**[a]									**End of Treatment**	**Post-Treatment**		
								To be repeated beyond 8 cycles							
Treatment Cycle/Title:	Screening (Visit 1)	Cycle 1 day 1	Cycle 1 day 8	Cycle 1 day 15	2	3	4	5	6	7	8	Discon	Safety Follow-up	Follow Up Visits	Survival Follow-Up
Scheduling Window (Days):	-28 to -1				± 3	± 3	± 3	± 3	± 3	± 3	± 3	At time of Discon	30 days post discon	Every 12 weeks	Every 12 weeks
Informed Consent	X														
Inclusion/Exclusion Criteria	X														
Demographics and Medical History	X														
Prior and Concomitant Medication Review	X	X			X	X	X	X	X	X	X				
Trial Treatment Administration-Pembrolizumab[b]		X			X	X	X	X	X	X	X				
Trial Treatment Administration-Lenalidomide[c]		X	X		X	X	X	X	X	X	X				
Post-study anticancer therapy status												X		X	X
Survival Status												X	X	X	X
Review Adverse Events		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Full Physical Examination	X	X			X	X	X	X	X	X	X	X	X	X	X

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Trial Period:			**Treatment Cycles**[a]									**End of Treatment**	**Post-Treatment**		
								To be repeated beyond 8 cycles							
Treatment Cycle/Title:	Screening (Visit 1)	Cycle 1 day 1	Cycle 1 day 8	Cycle 1 day 15	2	3	4	5	6	7	8	Discon	Safety Follow-up	Follow Up Visits	Survival Follow-Up
Scheduling Window (Days):	-28 to -1				± 3	± 3	± 3	± 3	± 3	± 3	± 3	At time of Discon	30 days post discon	Every 12 weeks	Every 12 weeks
Directed Physical Examination															
Vital Signs and Weight	X	X	X	X	X	X	X	X	X	X	X	X		X	X
Height	X														
ECOG Performance Status	X	X	X	X	X	X	X	X	X	X	X	X			
Pregnancy Test – Urine or Serum -HCG [c]	X	X			X	X	X	X	X	X	X	X			
PT/INR and aPTT	X	X						X							
Complete Blood Count with Differential	X	X	X	X	X	X	X	X	X	X	X	X		X	
Comprehensive Serum Chemistry Panel	X	X	X	X	X	X	X	X	X	X	X	X		X	
ESR	X				X	X	X	X	X	X	X	X		X	
Urinalysis	X	X			X	X	X	X	X	X	X	X		X	
T3, FT4 and TSH	X	X			X	X	X	X	X	X	X	X		X	
Tumor Imaging	X							X[A]				X		X	

Product: Pembrolizumab and Lenalidomide
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Trial Period:			**Treatment Cycles**[a]									**End of Treatment**	**Post-Treatment**		
								To be repeated beyond 8 cycles							
Treatment Cycle/Title:	Screening (Visit 1)	Cycle 1 day 1	Cycle 1 day 8	Cycle 1 day 15	2	3	4	5	6	7	8	Discon	Safety Follow-up	Follow Up Visits	Survival Follow-Up
Scheduling Window (Days):	-28 to -1				± 3	± 3	± 3	± 3	± 3	± 3	± 3	At time of Discon	30 days post discon	Every 12 weeks	Every 12 weeks
Archival or Newly Obtained Tissue Collection	X				X[B]							X			
Correlative Studies Blood Collection	X				X			X				X			

[a]Every week +/- 3 days; except Cycle 1

[b]Day 1 of 21 day cycle

[c]Day 1-14 of 21 day cycle

[A] Every 12 weeks +/- 1 week

[B]Biopsy while on therapy is optional

[C] For women of child bearing potential: Pregnancy test is required 10-14 days prior to first dose of study drug AND a second pregnancy test is required within 24 hours before first dose of study drug

TRIAL PROCEDURES

6.2 Trial Procedures

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

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

6.2.1 Administrative Procedures

6.2.1.1 Informed Consent

The Investigator must obtain documented consent from each potential subject prior to participating in a clinical trial.

6.2.1.1.1 General Informed Consent

Consent must be documented by the subject's dated signature or by the subject's legally acceptable representative's dated signature on a consent form along with the dated signature of the person conducting the consent discussion.

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

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

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

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

6.2.1.2 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.

6.2.1.3 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.

6.2.1.4 Prior and Concomitant Medications Review

6.2.1.4.1 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.

6.2.1.4.2 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.

6.2.1.5 Disease Details and Treatments

6.2.1.5.1 Disease Details

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

6.2.1.5.2 Prior Treatment Details

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

6.2.1.5.3 Subsequent Anti-Cancer Therapy Status

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

6.2.1.6 Assignment of Screening Number

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

Pembrolizumab will be administered as an infusion. Compliance check to lenalidomide tablets will be performed by the clinic staff at each visit, subjects will be asked to bring at each follow up the bottle of medication for tablet count check.

6.2.2 Clinical Procedures/Assessments

6.2.2.1 Adverse Event (AE) Monitoring

The investigator or qualified 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 (see Section 11.2). Toxicities will be characterized in terms regarding seriousness, causality, toxicity grading, and action taken with regard to trial treatment.

For subjects receiving treatment with pembrolizumab all AEs of unknown etiology associated with pembrolizumab exposure should be evaluated to determine if it is possibly an event of clinical interest (ECI) of a potentially immunologic etiology (termed immune-related adverse events, or irAEs); see the separate ECI guidance document in Appendix 4 regarding the identification, evaluation and management of potential irAEs.

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

6.2.2.2 Full Physical Exam

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

6.2.2.3 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.

6.2.2.4 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.

6.2.2.5 Eastern Cooperative Oncology Group (ECOG) Performance Scale

The investigator or qualified designee will assess ECOG status (see Section 11.1) at screening, prior to the administration of each dose of trial treatment and discontinuation of trial treatment as specified in the Trial Flow Chart.

6.2.2.6 Tumor Imaging and Assessment of Disease

Assessment of lymphoma response (CR, PR or SD) and disease progression will be evaluated according to the Revised Response Criteria for Malignant Lymphoma[24]. A full IV contrast CT scan combined with a PET scan is preferred for baseline evaluation, interim evaluation (q 12 weeks per standard of care), and at the completion of study. Overall response will be measured for all patients who complete one cycle of treatment. Kaplan-Meir methodology will be used to estimate median PFS and OS.

6.2.2.7 Tumor Tissue Collection and Correlative Studies Blood Sampling

a) Samples of peripheral blood will be collected pretreatment, at initial staging and at the end of the study in all patients. On these samples flow cytometry, and other immune analysis will be performed to characterize the peripheral blood mononuclear cells populations and their variation as a function of the therapy, and to evaluate circulating immune subsets in patients as a function of treatment.

b) Immunohistochemistry evaluation of the tumor microenvironment will be performed on patient's initial biopsy. Optional core needle biopsy early during therapy and in relapsing patients at the time of relapse will be submitted for analysis and comparison

c) Gene expression profiling of the above samples will be concurrently analyzed in collaboration with Dr Steidl at BCC Cancer Center.

d) Evaluation of PD-1 expression in tumor tissue will be performed in collaboration with Merck.

Tissue and blood storage
All blood and tissue samples will be processed immediately and stored indefinitely for later analysis in a locked -80°C freezer in the NYU Biorepository Core for research purposes only. No germline genetic testing will be performed on any specimens collected during this trial. Subjects will not receive the results of any testing.

These specimens will not be linked to any clinical data and will be de-identified in the clinical research database. Only the PI and data manager will have the linking key. Only the investigators listed on this protocol will have access to these samples. After both blood and tissue samples are analyzed at a later date unutilized samples will be preserved indefinitely in the NYU Biorepository for potential future research. All patients enrolled will be given a unique identifier. Only the data manager will know the code linking patient and study ID number. Patients will be assigned a unique code number. All specimens collected will be deidentified and assigned the same unique study number of the corresponding patient and will also be marked with the collection time point. Clinical information regarding toxicities and response will likewise be stored in a deidentified database using only the unique identifier. For patients enrolled at a participating site, measures to assure secure and HIPAA compliant storage of quality biospecimens will be determined by participating site institutional protocols. Storage of tissue and blood for future research is optional. Patients may decide to withdraw their samples from storage or future use at any time after informed consent either verbally or in writing.

6.2.3 Laboratory Procedures/Assessments

Details regarding specific laboratory procedures/assessments to be performed in this trial are provided below Laboratory Safety Evaluations (Complete Blood Count, Comprehensive Serum Chemistry Panel and Urinalysis)

Laboratory tests for complete Blood Count, comprehensive serum chemistry Panelurinalysis, and others are specified in Table 6.

Table 6 Laboratory Tests

Hematology	Chemistry	Urinalysis	Other
Hematocrit	Albumin	Blood	Serum β-human chorionic gonadotropin†
Hemoglobin	Alkaline phosphatase	Glucose	(β-hCG)†
Platelet count	Alanine aminotransferase (ALT)	Protein	PT (INR)
WBC (total and differential)	Aspartate aminotransferase (AST)	Specific gravity	aPTT
Red Blood Cell Count	Lactate dehydrogenase (LDH)	Microscopic exam *(If abnormal)*	Total thriiodothyronine (T3)
Absolute Neutrophil Count	Carbon Dioxide ‡	results are noted	Free tyroxine (T4)
Absolute Lymphocyte Count	*(CO_2 or biocarbonate)*	Urine pregnancy test †	Thyroid stimulating hormone (TSH)
	Uric Acid		
	Calcium		
	Chloride		Blood for correlative studies
	Glucose		
	Phosphorus		
	Potassium		
	Sodium		
	Magnesium		

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Hematology	Chemistry	Urinalysis	Other
	Total Bilirubin		
	Direct Bilirubin *(If total bilirubin is elevated above the upper limit of normal)*		
	Total protein		
	Blood Urea Nitrogen		

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

‡ If considered standard of care in your region.

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

6.2.3.1 Pharmacokinetic/Pharmacodynamic Evaluations

6.2.3.1.1 Blood Collection for Serum Pembrolizumab

Sample collection, storage and shipment instructions for peripheral blood samples will be provided in the Laboratory Manual.

6.2.3.1.2 Blood Collection for Anti-Pembrolizumab Antibodies

Sample collection, storage and shipment instructions for peripheral blood samples will be provided in the Laboratory Manual.

6.2.3.2 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. Any adverse events which are present at the time of discontinuation/withdrawal should be followed in accordance with the safety requirements outlined in Section 7.2 - Assessing and Recording Adverse Events. Subjects who a) attain a CR or b) complete 24 months of treatment with pembrolizumab may discontinue treatment with the option of restarting treatment if they meet the criteria specified in Section 7.1.5.5. After discontinuing treatment following assessment of CR, these subjects should return to the site for a Safety Follow-up Visit (described in Section 7.1.5.3.1) and then proceed to the Follow-Up Period of the study (described in Section 7.1.5.4).

6.2.4 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.

6.2.4.1 Screening

6.2.4.1.1 Screening Period

The screening phase is the interval between the signing of the Informed Consent Form (IFC) and the day the subject is enrolled in the study (cycle 1 day 1). Informed consent must be obtained prior to performing any study-specific procedures. Assessments that are required to

demonstrate eligibility may be performed over 1 or more days during this phase. The maximum screening period is 30 days.

Results from the screening visit evaluations will be reviewed to confirm subject eligibility prior to enrollment/administration of study drug(s). Tests with results that fail eligibility requirements maybe repeated once during the screening phase, if the Investigator believes the results to be in error or not representative. Additionally, a subject who fails screening may repeat the screening process 1 time, if the Investigator believes there has been a change in eligibility status (e.g. following recovery from an infection).

Additionally the screening period will be utilized to determine the baseline assessments of clinical condition and disease status. Tumor assessments appropriate to the type of malignancy will be performed and recorded in CRF.

6.2.4.2 Treatment Period

One therapy cycle is 21 days, treatment will continue until disease progression or toxicity up to 12 months

6.2.4.3 Post-Treatment Visits

7.1.5.3.1 Safety Follow-Up Visit

The mandatory Safety Follow-Up Visit should be conducted approximately 30 days after the last dose of 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. Subjects with an AE of Grade > 1 will be followed until the resolution of the AE to Grade 0-1 or until the beginning of a new anti-neoplastic therapy, whichever occurs first. SAEs that occur within 90 days of the end of treatment or before initiation of a new anti-cancer treatment should also be followed and recorded. Subjects who are eligible for retreatment with pembrolizumab (as described in Section 7.1.5.5) may have up to two safety follow-up visits, one after the Treatment Period and one after the Second Course Phase.

6.2.4.4 Follow-up Visits

Subjects who discontinue trial treatment for a reason other than disease progression will move into the Follow-Up Phase and tumor imaging will occur every 12 weeks (± 7 days). Every effort should be made to collect information regarding disease status until the start of new anti-neoplastic therapy, disease progression, death, end of the study or if the subject begins retreatment with pembrolizumab as detailed in Section 7.1.5.5. Information regarding post-study anti-neoplastic treatment will be collected if new treatment is initiated.

Subjects who are eligible to receive retreatment with pembrolizumab according to the criteria in Section 7.1.5.5 will move from the follow-up phase to the Second Course Phase when they experience disease progression.

6.2.4.4.1 Survival Follow-up

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

6.2.4.5 Second Course Phase (Retreatment Period)

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

- **Either**
    - Stopped initial treatment with pembrolizumab after attaining an investigator-determined confirmed CR according to revised response criteria for lymphoid malignancies[24] and
        - Was treated for at least 24 weeks with pembrolizumab before discontinuing therapy
        - Received at least two treatments with pembrolizumab beyond the date when the initial CR was declared

OR

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

AND

- Experienced an investigator-determined confirmed radiographic disease progression after stopping their initial treatment with pembrolizumab
- Did not receive any anti-cancer treatment since the last dose of pembrolizumab

- Has a performance status of 0 or 1 on the ECOG Performance Scale
- Demonstrates adequate organ function as detailed in Section 5.1.2
- Female subject of childbearing potential should have a negative serum or urine pregnancy test within 72 hours prior to receiving retreatment with study medication.
- Female subject of childbearing potential should be willing to use 2 methods of birth control or be surgically sterile, or abstain from heterosexual activity for the course of the study through 120 days after the last dose of study medication (Reference Section 5.7.2). Subjects of child bearing potential are those who have not been surgically sterilized or have been free from menses for > 1 year.
- Male subject should agree to use an adequate method of contraception starting with the first dose of study therapy through 120 days after the last dose of study therapy.
- Does not have a history or current evidence of any condition, therapy, or laboratory abnormality that might interfere with the subject's participation for the full duration of the trial or is not in the best interest of the subject to participate, in the opinion of the treating investigator.

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

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

6.3 Assessing and Recording Adverse Events

An adverse event 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 adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product or protocol-specified procedure, whether or not considered related to the medicinal product or protocol-specified procedure. Any worsening (i.e., any clinically significant adverse change in frequency and/or intensity) of a preexisting condition that is temporally associated with the use of the Merck's product, is also an adverse event.

Changes resulting from normal growth and development that do not vary significantly in frequency or severity from expected levels are not to be considered adverse events.

Examples of this may include, but are not limited to, teething, typical crying in infants and children and onset of menses or menopause occurring at a physiologically appropriate time.

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

Adverse events may occur during the course of the use of Merck product in clinical trials or 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.

Progression of the cancer under study is not considered an adverse event unless it is considered to be drug related by the investigator.

All adverse events will be recorded from the time the consent form is signed through 30 days following cessation of treatment and at each examination on the Adverse Event case report forms/worksheets.

6.3.1 Investigator reporting: notifying the study sponsor, NYU IRB, and Perlmutter Cancer Center Clinical Trials Office

The following describes events must be reported to the study sponsor in an expedited fashion.

Initial Report: within 24 hours:

The following events must be reported to the PCC Clinical Trials Office and the study sponsor by telephone within 24 hours of awareness of the event:

- Unanticipated problems related to study participation,
- Serious adverse events, regardless of whether they are unexpected.

Additionally, an FDA Form 3500A (MEDWATCH Form) must be completed by the investigator and faxed/emailed to the study sponsor and PCC Clinical Trials Office within 24 hours. The investigator shall maintain a copy of the MEDWATCH Form on file at the study site.

NYUPCCsafetyreports@nyumc.org

AND

Catherine Diefenbach, MD
240 East 38th Street, 19th Floor
New York, NY 10016
Phone: 212-731-5670
Email: Catherine.Diefenbach@nyumc.org

Follow-up report: within 48 hours:

As a follow-up to the initial report, within the following 48 hours of awareness of the event, the investigator shall provide further information, as applicable, on the unanticipated device event or the unanticipated problem in the form of a written narrative. This should include a copy of the completed Unanticipated Problem form, and any other diagnostic information that will assist in the understanding of the event. Significant new information on ongoing unanticipated adverse device effects shall be provided promptly to the study sponsor. All report forms must be signed and dated by the Principal Investigator. If the Principal Investigator is not available at the time of the initial report, then the form can be submitted by a Sub-Investigator. This form should be reviewed by the Principal Investigator, whom sign/date initial report upon return.

Other Reportable events:

- **Deviations from the study protocol**

Deviations from the protocol must receive both Sponsor and the investigator's IRB approval before they are initiated. Any protocol deviations initiated without Sponsor and the investigator's IRB approval that may affect the scientific soundness of the study, or affect the rights, safety, or welfare of study subjects, must be reported to the Sponsor and to the investigator's IRB as soon as a possible, but ***no later than 5 working days*** of the protocol deviation.

- ***Withdrawal of IRB approval***

  An investigator shall report to the sponsor a withdrawal of approval by the investigator's reviewing IRB as soon as a possible, but ***no later than 5 working days*** of the IRB notification of withdrawal of approval.

6.3.2 Investigator reporting: notifying the IRB

Federal regulations require timely reporting by investigators to their local IRB of unanticipated problems posing risks to subjects or others. The following describes the NYULMC IRB reporting requirements, though Investigators at participating sites are responsible for meeting the specific requirements of their IRB of record. The NYU IRB address is:

NYU School of Medicine IRB
1 Park Avenue, 6th Floor
New York, NY 10016

Report promptly, but no later than 5 working days:

Researchers are required to submit reports of the following problems promptly but no later than 5 working days from the time the investigator becomes aware of the event:

- ***Unanticipated problems including adverse events*** **that are unexpected and related**
  - *Unexpected: An event is "unexpected" when its specificity and severity are not accurately reflected in the protocol-related documents, such as the IRB-approved research protocol, any applicable investigator brochure, and the current IRB-approved informed consent document and other relevant sources of information, such as product labeling and package inserts.*
  - *Related to the research procedures: An event is related to the research procedures if in the opinion of the principal investigator or sponsor, the event was more likely than not to be caused by the research procedures.*
  - *Harmful: either caused harm to subjects or others, or placed them at increased risk*

Other Reportable events:

The following events also require prompt reporting to the IRB, though ***no later than 5 working days***:

- ***Complaint of a research subject*** when the complaint indicates unexpected risks or the complaint cannot be resolved by the research team.
- ***Protocol deviations or violations*** (includes intentional and accidental/unintentional deviations from the IRB approved protocol) for any of the following situations:
  - *one or more participants were placed at increased risk of harm*

- *the event has the potential to occur again*
- *the deviation was necessary to protect a subject from immediate harm*

- ***Breach of confidentiality***
- ***Incarceration of a participant*** when the research was not previously approved under Subpart C and the investigator believes it is in the best interest of the subject to remain on the study.
- ***New Information indicating a change to the risks or potential benefits*** of the research, in terms of severity or frequency. (e.g. analysis indicates lower-than-expected response rate or a more severe or frequent side effect; Other research finds arm of study has no therapeutic value; FDA labeling change or withdrawal from market)

Reporting Process

The reportable events noted above will be reported to the IRB using the form: "Reportable Event Form" or as a written report of the event (including a description of the event with information regarding its fulfillment of the above criteria, follow-up/resolution and need for revision to consent form and/or other study documentation).

Copies of each report and documentation of IRB notification and receipt will be kept in the Clinical Investigator's study file.

At the time of each annual review any protocol deviations stated above, such as dose-reductions (even if done in accordance with protocol guidelines) must be reported to the IRB.

6.3.3 Sponsor reporting: Notifying the FDA

The study sponsor is required to report certain study events in an expedited fashion to the FDA. These written notifications of adverse events are referred to as IND safety reports. The

following describes the safety reporting requirements by timeline for reporting and associated type of event:

- ***Within 7 calendar days*** *(via telephone or facsimile report)*

  Any study event that is:
  - associated with the use of the study drug
  - unexpected,
  - fatal or life-threatening

- ***Within 15 calendar days*** *(via written report)*

  Any study event that is:
  - associated with the use of the study drug,
  - unexpected, and
  - serious, but not fatal or life-threatening

    -or-
  - a previous adverse event that was not initially deemed reportable but is later found to fit the criteria for reporting (reporting within 15 calendar days from when event was deemed reportable).

  Any finding from tests in laboratory animals that:
  - Suggest a significant risk for human subjects including reports of mutagenicity, teratogenicity, or carcinogenicity.

Additional reporting requirements

Sponsors are also required to identify in IND safety reports all previous reports concerning similar adverse events and to analyze the significance of the current event in light of the previous reports.

Reporting Process

Adverse events may be submitted on FDA Form 3500A (MEDWATCH Form), or in a narrative format. The contact information for submitting IND safety reports is noted below:

Email: NYUPCCsafetyreports@nyumc.org

Tel: 212-263-2748

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

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

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

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

All reports of overdose with and without an adverse event must be reported within 24 hours to the Sponsor and within 2 working days hours to Merck Global Safety. (Attn: Worldwide Product Safety; FAX 215 993-1220)

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

Although pregnancy and lactation are not considered adverse events, it is the responsibility of investigators or their designees to report any pregnancy or lactation in a subject (spontaneously reported to them), 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 24 hours to the Sponsor and within 2 working days to Merck Global Safety. (Attn: Worldwide Product Safety; FAX 215 993-1220)

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

6.3.1.1 Serious Adverse Events

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

- Results in death;
- Is life threatening;
- Results in persistent or significant disability/incapacity;
- Results in or prolongs an existing inpatient hospitalization;
- Is a congenital anomaly/birth defect;
- Is a new cancer (that is not a condition of the study);
- Is associated with an overdose;
- Is another important medical event

Refer to Table 7 for additional details regarding each of the above criteria.

Any serious adverse event, or follow up to a serious adverse event, including death due to any cause other than progression of the cancer under study that occurs to any subject from the time the consent is signed through 90 days following cessation of treatment, or the initiation of new anti-cancer therapy, whichever is earlier, whether or not related to Merck product, must be reported within 24 hours to the Sponsor and within 2 working days to Merck Global Safety.

Non-serious Events of Clinical Interest will be forwarded to Merck Global Safety and will be handled in the same manner as SAEs.

Additionally, any serious adverse event, considered by an investigator who is a qualified physician to be related to Merck product that is brought to the attention of the investigator at any time outside of the time period specified in the previous paragraph also must be reported immediately to the Sponsor and to Merck.

SAE reports and any other relevant safety information are to be forwarded to the Merck Global Safety facsimile number: +1-215-993-1220

A copy of all 15 Day Reports and Annual Progress Reports is submitted as required by FDA, European Union (EU), Pharmaceutical and Medical Devices agency (PMDA) or other local regulators. Investigators will cross reference this submission according to local regulations to the Merck Investigational Compound Number (IND, CSA, etc.) at the time of submission. Additionally investigators will submit a copy of these reports to Merck & Co., Inc. (Attn: Worldwide Product Safety; FAX 215 993-1220) at the time of submission to FDA.

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

6.3.1.2 Events of Clinical Interest

Selected non-serious and serious adverse events are also known as Events of Clinical Interest (ECI) and must be recorded as such on the Adverse Event case report forms/worksheets and reported within 24 hours to the Sponsor and within 2 working days to Merck Global Safety. (Attn: Worldwide Product Safety; FAX 215 993-1220)Events of clinical interest for this trial include:

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

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

   *Note: These criteria are based upon available regulatory guidance documents. The purpose of the criteria is to specify a threshold of abnormal hepatic tests that may require an additional evaluation for an underlying etiology. The trial site guidance for assessment and follow up of these criteria can be found in the Investigator Trial File Binder (or equivalent).

1. Additional adverse events:

A separate guidance document has been provided entitled "Event of Clinical Interest Guidance Document" (previously entitled, "Event of Clinical Interest and Immune-Related Adverse Event Guidance Document"). This document can be found in Appendix 4 and provides guidance regarding identification, evaluation and management of ECIs and irAEs.

ECIs (both non-serious and serious adverse events) identified in this guidance document from the date of first dose through 90 days following cessation of treatment, or 30 days after the initiation of a new anticancer therapy, whichever is earlier, need to be reported within 24 hours to the Sponsor and within 2 working days to Merck Global Safety. (Attn: Worldwide Product Safety; FAX 215 993-1220), regardless of attribution to study treatment, consistent with standard SAE reporting guidelines.

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.

6.3.2 Evaluating Adverse Events

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

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

Table 7 Evaluating Adverse Events

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

V4.0 CTCAE Grading	**Grade 1**	**Mild; asymptomatic or mid symptoms; clinical or diagnostic observations only; intervention not indicated.**
	Grade 2	**Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL.**
	Grade 3	**Severe or medically significant but not immediately life-threatening; hospitalization or prolongation or hospitalization indicated; disabling; limiting self-care ADL.**
	Grade 4	**Life threatening consequences; urgent intervention indicated.**
	Grade 5	**Death related to AE**
Seriousness	A serious adverse event is any adverse event occurring at any dose or during any use of Merck product that:	
	†**Results in death**; or	
	†**Is life threatening; or** places the subject, in the view of the investigator, at immediate risk of death from the event as it occurred (Note: This does not include an adverse event that, had it occurred in a more severe form, might have caused death.); or	
	†**Results in a persistent or significant disability/incapacity** (substantial disruption of one's ability to conduct normal life functions); or	
	†**Results in or prolongs an existing inpatient hospitalization** (hospitalization is defined as an inpatient admission, regardless of length of stay, even if the hospitalization is a precautionary measure for continued observation. (Note: Hospitalization [including hospitalization for an elective procedure] for a preexisting condition which has not worsened does not constitute a serious adverse event.); or	
	†**Is a congenital anomaly/birth defect** (in offspring of subject taking the product regardless of time to diagnosis);or	
	Is a new **cancer;** (that is not a condition of the study) **or**	
	Is an overdose (whether accidental or intentional). Any adverse event associated with an overdose is considered a serious adverse event. An overdose that is not associated with an adverse event is considered a non-serious event of clinical interest and must be reported within 24 hours.	
	Other important medical events that may not result in death, not be life threatening, or not require hospitalization may be considered a serious adverse event when, based upon appropriate medical judgment, the event may jeopardize the subject and may require medical or surgical intervention to prevent one	

	of the outcomes listed previously (designated above by a †).	
Duration	Record the start and stop dates of the adverse event. If less than 1 day, indicate the appropriate length of time and units	
Action taken	Did the adverse event cause the Merck product to be discontinued?	
Relationship to test drug	Did the Merck product cause the adverse event? The determination of the likelihood that the Merck product caused the adverse event will be provided by an investigator who is a qualified physician. The investigator's signed/dated initials on the source document or worksheet that supports the causality noted on the AE form, ensures that a medically qualified assessment of causality was done. This initialed document must be retained for the required regulatory time frame. The criteria below are intended as reference guidelines to assist the investigator in assessing the likelihood of a relationship between the test drug and the adverse event based upon the available information. **The following components are to be used to assess the relationship between the Merck product and the AE**; the greater the correlation with the components and their respective elements (in number and/or intensity), the more likely the Merck product caused the adverse event (AE):	
	Exposure	Is there evidence that the subject was actually exposed to the Merck product such as: reliable history, acceptable compliance assessment (pill count, diary, etc.), expected pharmacologic effect, or measurement of drug/metabolite in bodily specimen?
	Time Course	Did the AE follow in a reasonable temporal sequence from administration of the Merck product? Is the time of onset of the AE compatible with a drug-induced effect (applies to trials with investigational medicinal product)?
	Likely Cause	Is the AE not reasonably explained by another etiology such as underlying disease, other drug(s)/vaccine(s), or other host or environmental factors

Relationship to Merck product (continued)	**The following components are to be used to assess the relationship between the test drug and the AE: (continued)**	
	Dechallenge	Was the Merck product discontinued or dose/exposure/frequency reduced? If yes, did the AE resolve or improve? If yes, this is a positive dechallenge. If no, this is a negative dechallenge. (Note: This criterion is not applicable if: (1) the AE resulted in death or permanent disability; (2) the AE resolved/improved despite continuation of the Merck product; or (3) the trial is a single-dose drug trial); or (4) Merck product(s) is/are only used one time.)

	Rechallenge	Was the subject re-exposed to the Merck product in this study? If yes, did the AE recur or worsen? If yes, this is a positive rechallenge. If no, this is a negative rechallenge. (Note: This criterion is not applicable if: (1) the initial AE resulted in death or permanent disability, or (2) the trial is a single-dose drug trial); or (3) Merck product(s) is/are used only one time). NOTE: IF A RECHALLENGE IS PLANNED FOR AN ADVERSE EVENT WHICH WAS SERIOUS AND WHICH MAY HAVE BEEN CAUSED BY THE MERCK PRODUCT, OR IF REEXPOSURE TO THE MERCK PRODUCT POSES ADDITIONAL POTENTIAL SIGNIFICANT RISK TO THE SUBJECT, THEN THE RECHALLENGE MUST BE APPROVED IN ADVANCE BY THE U.S. CLINICAL MONITOR AS PER DOSE MODIFICATION GUIDELINES IN THE PROTOCOL.
	Consistency with Trial Treatment Profile	Is the clinical/pathological presentation of the AE consistent with previous knowledge regarding the Merck product or drug class pharmacology or toxicology?
The assessment of relationship will be reported on the case report forms /worksheets by an investigator who is a qualified physician according to his/her best clinical judgment, including consideration of the above elements.		
Record one of the following		**Use the following scale of criteria as guidance (not all criteria must be present to be indicative of a Merck product relationship).**
Yes, there is a reasonable possibility of Merck product relationship.		There is evidence of exposure to the Merck product. The temporal sequence of the AE onset relative to the administration of the Merck product is reasonable. The AE is more likely explained by the Merck product than by another cause.
No, there is not a reasonable possibility Merck product relationship		Subject did not receive the Merck product OR temporal sequence of the AE onset relative to administration of the Merck product is not reasonable OR there is another obvious cause of the AE. (Also entered for a subject with overdose without an associated AE.)

6.3.3 Sponsor Responsibility for Reporting Adverse Events

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

7.0 STATISTICAL ANALYSIS PLAN

7.1 Phase I Statistical Analysis Plan

The primary objective of the Phase I portion of this trial is to identify the MTD (Phase II dose) which is the dose at which the estimated proportion of patients with DLTs is less than 0.33. The standard 3+3 design is employed. Patients will be treated in cohorts of 3 patients starting with Dose Cohort A with lenalidomide 15mg PO day 1-14 and pembrolizumab 200mg IV day 1, in cycles of 21 days, until disease progression or toxicity up to 24 months. The number of patients expected to be enrolled in the dose escalation study is 9 (up to 12 patients if unexpected toxicity is observed).

If 0 out of 3 patients at a particular dose level experiences a dose limiting toxicity (DLT) within Cycle 1 of treatment, if in Dose Cohort A (lenalidomide 15mg) dose escalation will proceed to cohort B (lenalidomide 20mg), if in Dose Cohort B, 3 additional patients will be added. If a DLT occurs in 0 of 6 patients enrolled on Dose Cohort B this will be deemed the Maximum Tolerated Dose (MTD).

If a DLT occurs in only 1 out of 6 patients enrolled at a particular dose level, dose escalation will occur, however, if this occurs on Dose Cohort B (lenalidomide 20 mg) or Dose Cohort Z (lenalidomide 10 mg), this will be deemed the Maximum Tolerated Dose (MTD). MTD is defined as the highest dose level at which < 33% of 6 patients experience a DLT.

If a DLT occurs in ≥ 2 of 3 patients or ≥ 2 of 6 patients treated on Dose Cohort A (lenalidomide 15mg), there will be a dose de-escalation to Dose Cohort Z (lenalidomide 10 mg).

If a DLT occurs in ≥ 2 of 3 patients or ≥ 2 of 6 patients treated on Dose Cohort B (lenalidomide 20 mg) or the preceding dose level will be declared the MTD if there were no more than 1 DLT in this previous cohort.

If a DLT occurs in ≥ 2 of 3 patients or ≥ 2 of 6 patients on Dose Cohort Z (lenalidomide 10mg), the trial will be discontinued and the expanded cohort will not be implemented.

Once the MTD has been determined, 17 additional patients with relapsed refractory HL will be treated in in the Phase II portion of this trial at the MTD.

While clinical benefit rates and other outcome rates for each dose cohort will be estimated, all of the summary of patient outcomes is descriptive.

7.2 Phase II Statistical Analysis Plan

This is an open label single arm Phase II study to test the hypothesis that the CR rate is less than or equal to 20% versus the alternative hypothesis that the CR rate is greater than or equal to 50%.

Our sample size estimate is based on our primary hypothesis that evaluates CR rate in the HL cohort. One-sided binomial tests will used to assess these changes. Given a baseline CR of 21% for single agent pembrolizumab in relapsed HL, we hypothesize that combination of lenalidomide and pembrolizumab will have a CR rate of 50% or greater for the combination at a significance level of 0.05 with 80% power (PASS, 2008).

With 17 patients entered into this trial, with 83% power and alpha of 0.04, we can reject the null hypothesis if 6 or fewer responses are observed.

Patient and disease characteristics will be summarized at baseline using descriptive statistics (means, medians, quartiles, standard deviations, etc.) and graphical displays including boxplots for continuous variables and frequency distributions for qualitative variables.

The complete response rate will be estimated with exact 95% confidence intervals. Other secondary response measures will be summarized using frequency distributions. Distributions of dose and time on treatment will also be summarized. Time to failure will be estimated using Kaplan Meier methods (failures include progression or death, death). Descriptive summaries of response duration and transfusion independence duration will also be summarized using Kaplan Meier methods [25].

7.3 Correlative Studies Statistical Analysis Plan

For each of the correlative studies, summary statistics and graphical displays will be provided over time, changes from baseline will be summarized similarly over time, and baseline levels and changes from baseline will be displayed by response over time.

8.0 MEDICAL Monitoring

It is the responsibility of the Principal Investigator to oversee the safety of the study at his/her site. This safety monitoring will include careful assessment and appropriate reporting of adverse events as noted above, as well as the construction and implementation of a site data and safety-monitoring plan detailed below. Adverse events are evaluated regularly by the principal investigator in conjugation with the research team. The Data Safety and Monitoring Committee (DSMC) will review the study regularly as designated by the Data Safety and Monitoring Plan. Medical monitoring will include regular assessments of the number and type of serious adverse events as well as events of Clinical Interest.

8.1 Data Monitoring Committee

This investigator-initiated study will be monitored by the Data Safety Monitoring Committee (DSMC) of the New York University (NYU) Perlmutter Cancer Center (PCC). The DSMC

operates based on the 2014 National Cancer Institute approved Charter. It is an existing and multidisciplinary committee (consisting of clinical investigators/oncologists, biostatisticians, nurses, and research administration staff knowledgeable of research methodology and design and in proper conduct of clinical trials) that is responsible for monitoring safety, conduct and compliance in accordance with protocol data monitoring plans for clinical trials conducted in the NYU Langone Health Perlmutter Cancer Center that are not monitored by another institution or agency. The DSMC reports to the Director of the NYU Langone Health PCC.

Per the NYU PCC Institutional Data Safety and Monitoring Plan, this phase I/II trial will be monitored by the DSMC quarterly (from the date the first patient is enrolled), at times of pre-specified response assessment, and at the completion of the study, prior to study closure. This review includes accrual data, subject demographics, and adverse events. Principal Investigators are required to attend the review of their studies. Additional interim reviews can be scheduled based on SAE reports, investigator identified issues, external information, etc. The DSMC will review safety data every 3 months.

External sites will be monitored and informed of other adverse events by the medical monitor within 7 days of toxicities and within 3 business days of SAE. Additional conference calls will be scheduled as indicated based on the recommendations from the medical monitor, and the Overall PI of this study.

Data and Safety Monitoring Plan:

The principal investigator will conduct bi-weekly meetings with the research team, to monitor toxicity while there are active patients. The study will be reviewed by the NYU Perlmutter Cancer Center Data and Safety Monitoring Committee (DSMC). The DSMC reviews all data for patient safety according to the DSMC policies. This review includes an examination of patient accrual, adverse events and study results. For phase I, dose finding trials, a review of toxicity after the first defined cohort is conducted to assure no DLTs are found before proceeding to the next cohort, per the protocol definition. If additional cohorts are required to establish the recommended dose for the extended safety cohort or phase II component of a phase I/II trial, these cohorts will be evaluated in a similar manner. By definition, dose finding cohort data will have to be confirmed or extended, by the trial definition, prior to proceeding to the next treatment group. Reviews will be done within 2-3 days of the complete cohort data set being available, even if not coinciding with a scheduled monthly meeting, so as to not delay study accrual. Once the recommended dose is established, further interim reviews will be performed at accrual points established by the protocol. All studies are required to be reviewed at least annually, regardless of their accrual status. Principal Investigators are required to attend the review of their studies.

All sites will participate in a bi-weekly teleconference to discuss all toxicities for all patients enrolled up to cycle 5 of therapy.

9.0 LABELING, PACKAGING, STORAGE AND RETURN OF CLINICAL SUPPLIES

9.1 Investigational Product

The investigator shall take responsibility for and shall take all steps to maintain appropriate records and ensure appropriate supply, storage, handling, distribution and usage of investigational product in accordance with the protocol and any applicable laws and regulations.

Pembrolizumab will be provided by Merck. Lenalidomide will not be provided by this study.

Table 8: Product Descriptions

Product Name & Potency	Dosage Form
Pembrolizumab 50 mg	Lyophilized Powder for Injection
Pembrolizumab 100 mg/ 4mL	Solution for Injection
Lenalidomide, 10mg, 15mg, 20 mg	Tablets

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 must be recorded by an authorized person at the trial site.

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

9.5 Returns and Reconciliation

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

Subject names will not be supplied to the Sponsor. Only the subject number and subject initials will be recorded in the CRF, and if the subject name appears on any other document (eg, laboratory report), it must be obliterated on the copy of the document to be supplied to the Sponsor. Study findings stored on a computer will be stored in accordance with local data protection laws. The subjects will be informed that representatives of the Sponsor, IRB/IEC, or regulatory authorities may inspect their medical records to verify the information collected, and that all personal information made available for inspection will be handled in strictest confidence and in accordance with local data protection laws.

10.2 Compliance with Financial Disclosure Requirements

All clinical Investigators participating in clinical studies subject to FDA Regulation Title 21 Code of Federal Regulation (CFR) Part 54- Financial Disclosure by Clinical Investigators, are required prior to study initiation to submit a completed Clinical Investigator Financial Disclosure Request Form that sufficiently details any financial interests and arrangements that apply. For the purpose of this regulation, clinical Investigator is defined as any investigator or subinvestigators who is directly involved in the treatment or evaluation of research subjects, including spouse and each dependent child of the clinical Investigator. These requirements apply to both US and foreign clinical investigators conducting covered clinical studies.

Any new Investigators of sub-investigators added to the covered clinical study during its conduct must also submit a completed Clinical Investigator Financial Disclosure Request Form. During a covered clinical study, any changes to the financial information previously reported by a clinical Investigator must be reported to the Sponsor/designee. At the conclusion of the covered clinical study, the clinical Investigators will be reminded of their obligation to report to the Sponsor/designee any changes to the financial information previously reported. The clinical Investigators will be also reminded that they must report

any changes in their financial information for a period of 1 year after completion of the covered clinical study.

10.3 Compliance with Law, Audit and Debarment

The investigator and the Sponsor must adhere to applicable data privacy laws and regulations. The investigator and Sponsor are responsible for ensuring that sensitive information is handled in accordance to local requirements (eg HIPAA). Appropriate consent and authorizations for use and disclosure and/or transfer (if applicable) of protected information must be obtained.

The Sponsor will be allowed to conduct site visits to the Investigation facilities for the purpose of monitoring any aspect of the study. The Investigator agrees to allow the monitor to inspect the drug storage area, study drug stocks, drug accountability records, subject charts and study source documents, and other records relative to study conduct

The Investigator must ensure that all records pertaining to the conduct of the clinical study (as listed above) are adequately maintained for a period of 2 years after that last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region, or at least 2 years have elapsed since the formal termination of clinical development of the investigational product

10.4 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.

10.5 Quality Management System

At some point during the study, individuals from the Sponsor's Quality Assurance department and /or their authorized representative may visit the Investigator's site to conduct an audit of the study. The purpose of this visit will be to determine the Investigator's adherence to the protocol, applicable regulations, and the Sponsor's procedures, in addition to assessing the accuracy of the study data. Prior to initiating this audit, the Investigator will be contacted by the Sponsor to arrange a convenient time for this visit. The Investigator and staff are expected to cooperate with the auditors and allow access to all subject records supporting CRFs and other study-related documents.

10.6 Data Management and Source Documentation

The investigator will be provided with a CRF for each subject. Entries made in the CRF must be verifiable against source documents; any discrepancies should be explained and

documented. The Investigator will be responsible for reviewing all data and CRF entries and will sign and date the designated pages in each subject's CRF, verifying that the information is true and correct. The Investigator is responsible for the review and approval of all responses.

Data management will be performed from CRFs. All CRF data will be entered into a validated database. The primary data collection instrument for the study, will be Velos. All data requested in the system must be reported and all missing data must be explained. The quality assurance specialists will monitor this trial every 4-6 weeks for data entry and accuracy. The database will be authorized for lock once all defined procedures are completed.

11.0 APPENDICES

11.1 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.	

11.2 Common Terminology Criteria for Adverse Events V4.0 (CTCAE)

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

11.3 Revised response criteria for malignant lymphoma

Revised response criteria for malignant lymphoma by Cheson et al, as outlined in Table 9 will be used in this study for assessment of lymphoma response [24].

Table 9: Revised Response Criteria for Malignant Lymphoma.

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

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

11.4 SUMMARY OF CHANGES

Version 2 November 4, 2016

Section	Change
Header	Changed Version 1 May 27, 2016 to Version 2 November 4, 2016
4.2.2.2	Clarified that Lenalidomide dosage will go up to 20mg
Table 1	• Changed ANC requirement of ≥1,000 /mcL to ANC ≥1,000 /mcL if no bone marrow involvement and ≥800 /mcL if documented bone marrow involvement • Changed Platelet requirement of ≥75,000 / mcL to ≥75,000 / mcL if no bone marrow involvement and ≥50,000 / mcL if documented bone marrow involvement • Changed hemoglobin requirement from ≥ 9 g/dL to ≥ 8 g/dL
5.2.1.3	• Changed DLT period from 30 days to 21 days • Changed DLT of grade 3 fatigue lasting ≤ 5 days or Grade 4 fatigue to Grade 4 fatigue ≥ 5 days • Changed Grade 3 fatigue that lasts for ≤ 5 days to Grade 3 fatigue and Grade 4 fatigue that lasts for ≤ 5 days to the exceptions of non-hematological toxicity DLT definitions
5.2.2	• Clarified that Pembrolizumab will be administered before Lenalidomide and that there is no waiting time between administration of both drugs.
6.1	• Updated table to include cycle 1 day 8 and cycle 1 day 15 visit
Table 6	• Removed PK as a laboratory test
7.2	• Updated statistical analysis plan
8.1	• Clarified that Pembrolizumab will be provided by Merck and that Lenalidomide will not be provided by this study.

Version 3 May 25, 2017

Section	Changes
Header	Updated protocol version to protocol version 3 and date to May 25, 2017
Section 5.1.1	Modified the prior therapy inclusion criterion to include all subjects

	regardless of number of prior therapies
Section 5.1.2	Modified the prior therapy inclusion criterion to include all subjects regardless of number of prior therapies
Section 5.2.1.3	Modified the DLT criterion for grade 4 neutropenia. This was clarified to specify that Grade 4 neutropenia associated with fever (>38.5) of any duration qualifies as a DLT.
Trial Flow chart	Added ESR as a required laboratory assessment at Screening, all cycles but cycle 1, discontinuation, an follow up visits

Version 3.1 July 18, 2017

Section	**Changes**
Header	Updated protocol version to protocol v3.1 and date to July 18th, 2017 Revised study title to reflect sub-sites participation Added Principal Investigator and Biostatistician contact information
Page 2	Added participating sites contact information
Section 5.2	Added a section on Patient Recruitment and Registration processes
Section 5.2.1	Added this section on Informed Consent processes
Section 5.2.2	Added this section on Documentation of Informed Consent
Section 5.2.3	Added this section on Multi-site surveillance
Section 5.2.4	Added this section on Informed Consent process at sub-sites
Section 5.2.5	Added this section on Patient Registration at sub-sites
Section 5.3	Specified the dosage for Lenalidomide (from TBD to 10mg – 20mg)
Section 6.1	Study Flow Chart: Clarified the study drug dosing schedule for Pembrolizumab Added study drug dosing schedule for Lenalidomide Added Cycle 1 Day 1 and Cycle 1 Day 8 as additional timepoints for Adverse Events review
Section 6.3.1	Added this section on Serious Adverse Events reporting processes
Section 6.3.2	Added this section on IRB notification process once a reportable event has occurred
Section 8.0	Added this section on Medical Monitoring and Data Safety Monitoring Plan
Section 10.6	Data Management section to include information regarding data storage and monitoring frequency
Overall	Revised the section numbering throughout the protocol for consistency

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