NU Study Number: NU 16H08
Merck Study Number: 53957

Phase II study of PET-directed frontline therapy with pembrolizumab and AVD for patients with classical Hodgkin lymphoma

Principal Investigator: Jane N. Winter, M.D.
Northwestern University, Feinberg School of Medicine and the Robert H. Lurie Comprehensive Cancer Center, Division of Hematology/Oncology
676 North St. Clair, Suite 850 Chicago, IL 60611
Phone: (312) 695-4538
Pager: (312) 695-9911
Fax: (312) 695-6189
Email: j-winter@northwestern.edu

Sub-Investigator(s): Local Sub-investigators:
Leo Gordon, M.D.
Barbara Pro, M.D.
Shuo Ma, M.D., Ph.D
Reem Karmali, M.D.

Andrew Evens, D.O., MSc
Rutgers Cancer Institute of New Jersey
195 Little Albany Street
New Brunswick, NJ 08901
Phone: (732) 235-5459
Fax: (732) 448-7894
Email: andew.evens@rutgers.edu

Ranjana Advani, M.D.
Stanford Cancer Institute
875 Blake Wilbur Drive
Stanford, CA 94305
Phone: (650) 725-6456
Email: radvani@stanford.edu

Pamela Allen, M.D.
Emory University School of Medicine
1365 Clifton Road NE
Atlanta, GA 30322
Phone: (404) 718-1900
pamela.b.allen@emory.edu

Collaborator(s): Kristy Wolniak, M.D.,Northwestern University, Department of Pathology
Hatice Savas, M.D. Northwestern University, Department of Radiology

Biostatistician: Denise Scholtens, Ph.D. Northwestern University, Biostatistics

Study Intervention(s): **Pembrolizumab, Keytruda**

IND Number: *132372*

IND Holder: Jane Winter, MD

Funding Source: Merck Pharmaceuticals

Version Date: **March 29, 2019 (Amendment 6)**

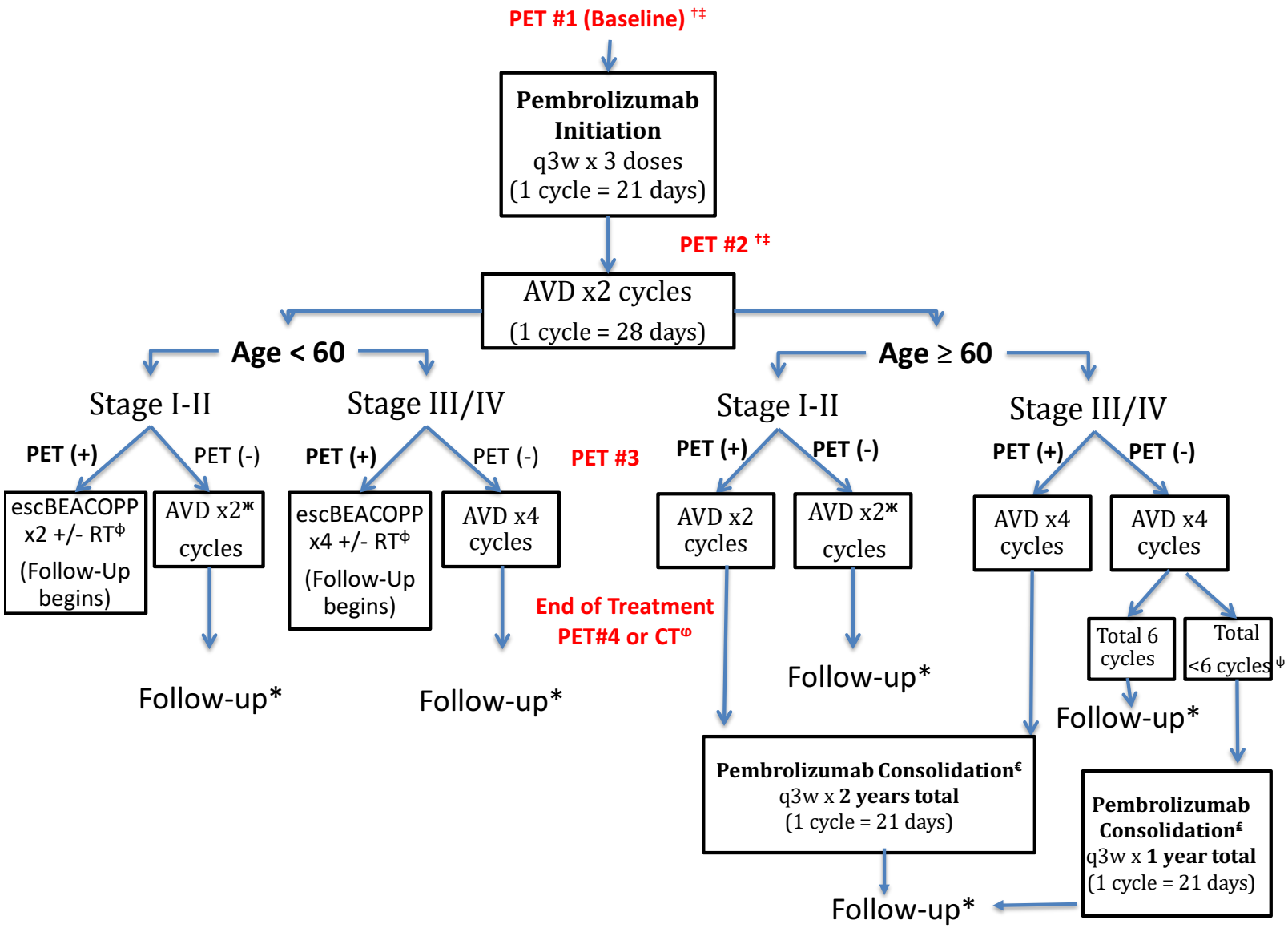
Coordinating Center: **Clinical Trials Office**
Robert H. Lurie Comprehensive Cancer Center
Northwestern University
676 N. St. Clair, Suite 1200
Chicago, IL 60611
Phone: (312) 695-0990
www.cancer.northwestern.edu/research/clinical-trials-office/index.html

LIST OF ABBREVIATIONS

AdEERS	Adverse Event Expedited Reporting System
AE	Adverse Event
ALT	Alanine Aminotransferase
ALC	Absolute Lymphocyte Count
ASCO	American Society of Clinical Oncology
AST	Aspartate Aminotransferase
A(B)VD	Adriamycin, (Bleomycin), Vincristine, Dacarbazine
BUN	Blood Urea Nitrogen
CBC	Complete Blood Count
cHL	Classical Hodgkin Lymphoma
CMP	Comprehensive Metabolic Panel
CNS	Central Nervous System
CR	Complete Response
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Events
DLT	Dose Limiting Toxicity
DSMB	Data and Safety Monitoring Board
DSMC	Data and Safety Monitoring Committee
DV	Deauville
EBV	Epstein Barr Virus
ECI	Events of Clinical Interest
ECOG	Eastern Cooperative Oncology Group
EFS	Event-Free Survival
EORTC	European Organization for Research and Treatment of Cancer
ESR	Erythrocyte Sedimentation Rate
escBEACOPP	Escalated Bleomycin, Etoposide, Adriamycin, Cyclophosphamide, Oncovin ®, Procarbazine, Prednisone
FDG	Fluorodeoxyglucose
G-CSF	Granulocyte Colony-Stimulating Factor
GHSG	German Hodgkin Study Group
HbsAg	Hepatitis B Surface Antigen
HCV	Hepatitis C Virus
HL	Hodgkin Lymphoma
H&PE	History & Physical Exam
IND	Investigational New Drug
INRT	Involved-node Radiotherapy
IPS	International Prognostic Score
irAE	Immune-Related Adverse Event
IV (or iv)	Intravenously
MTD	Maximum Tolerated Dose
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute

NLPHL	Nodular Lymphocyte Predominant Hodgkin Lymphoma
NSCLC	Non-Small Cell Lung Cancer
ORR	Overall Response Rate or Objective Response Rate
OS	Overall Survival
PBMCs	Peripheral Blood Mononuclear Cells
PD	Progressive Disease
PD-1 / PD-L1	Programmed Death-Ligand 1
PET-CT	Positron Emission Tomography and Computed Tomography
PFS	Progression Free Survival
PO (or p.o.)	Per os/by mouth/orally
PR	Partial Response
RFS	Relapse-free Survival
RT	Radiotherapy
SAE	Serious Adverse Event
SD	Stable Disease
SGOT	Serum Glutamic Oxaloacetic Transaminase
SJS	Stevens-Johnson Syndrome
SPGT	Serum Glutamic Pyruvic Transaminase
TARC	Thymus and Activation Related Chemokine
TB	Tuberculosis
TEN	Toxic Epidermal Necrosis
TIL's	Tumor Infiltrating Lymphocytes
UPIRSO	Unanticipated Problems Involving Risks to Subject or Others
WBC	White Blood Cells
WHO	World Health Organization

STUDY SCHEMA



† Biopsy in consenting patients and correlative studies to include: chromosome 9p24.1 alterations and PD-1 and PD-L1 expression

‡ Correlative studies: Including flow cytometry, serum cytokines, and TARC

*See Study Procedures for follow up. Patients with progressive disease will come off study.

ϕ escalated BEACOPP recommended but not required per protocol

ψ Patients ≥ age 60 unable to complete a total of 6 cycles of AVD chemotherapy due to poor tolerance

€ Total pembrolizumab treatment: 3 cycles of induction + 32 cycles of consolidation

£ Total pembrolizumab treatment: 3 cycles of induction + 14 cycles of consolidation

ω All patients will have imaging 2-6 weeks after completing chemotherapy and prior to pembrolizumab consolidation (where applicable). Imaging will consist of a PET-CT (PET#4) for all patients except those with Stage I/II disease and a negative PET#3, who may have a diagnostic CT scan.

ж Patients with bulky disease (a mass >10 cm) at baseline and a negative PET #3 may receive 4-6 cycles of AVD per investigator discretion

STUDY SUMMARY

Title	**Phase II study of PET-directed frontline therapy with pembrolizumab and AVD for patients with classical Hodgkin lymphoma**
Version	March 29th, 2019 (Amendment 6)
Study Design	This Phase II clinical trial will evaluate the use of pembrolizumab as frontline treatment of newly diagnosed Hodgkin lymphoma Stages I-IV followed by AVD. Patients will be treated with pembrolizumab at a flat dose of 200 mg every 3 weeks for 3 cycles followed by PET-CT to assess treatment response to pembrolizumab alone. Patients will then be treated with AVD chemotherapy for 4-6 cycles. Additional consolidation pembrolizumab will be given in elderly patients (≥ 60 years old) after chemotherapy who either: 1. Have a Deauville score of 4 or 5 following interim PET-CT (PET #3; 32 additional doses), OR 2. Have a Deauville score of 1-3 following interim PET-CT (PET#3) and receive less than the intended 6 cycles of AVD chemotherapy for stage III/IV disease because of poor tolerance (14 additional doses).
Study Center(s)	Robert H. Lurie Comprehensive Cancer Center Rutgers Cancer Institute of New Jersey Stanford University Medical Center Emory University
Objectives	Primary Objective: To assess the rate of complete response (CR) to single-agent pembrolizumab induction among patients with cHL Secondary Objectives: 1. To evaluate the safety and tolerability of pembrolizumab with AVD in the frontline treatment of patients with cHL. 2. Determine the PFS and OS of the group as a whole. 3. Determine the predictive value of FDG uptake, using a semi-quantitative approach (eg, Deauville score), after pembrolizumab induction, and after subsequent chemotherapy. Exploratory Objectives: Assess value of tissue biomarkers and T-cell subsets as predictors of response to pembrolizumab.
Sample Size	Up to 30 patients; (for 26 evaluable) enrolling concurrently

Diagnosis & Key Eligibility Criteria	Inclusion Criteria • Histologically confirmed, classical Hodgkin lymphoma (cHL) • Patients with Stage III and IV disease may have any International Prognostic Score (IPS) • Patients with Stage I and II disease must have at least one NCCN unfavorable risk factor (see Appendix D) • Age ≥18 • Previously untreated disease (except for one week or less of corticosteroids). • ECOG performance status 0, 1. • Adequate organ and marrow function Exclusion Criteria • Prior chemotherapy for cHL • Concurrent active malignancy that is life-limiting • Interstitial lung disease or idiopathic pulmonary fibrosis • Uncontrolled intercurrent illness • Active infection or autoimmune disease
Treatment Plan	For all patients, PET-CT will be performed prior to treatment (PET#1). Treatment will commence with pembrolizumab at 200 mg, flat dosing, intravenously, every three weeks for three total doses, followed by re-staging of disease with PET-CT (PET#2). All patients will then be treated with 2 cycles of AVD followed by PET#3. Subsequent therapy will then be based on age, stage, and results of this PET-CT (PET#3). **<u>Younger patients (<60 years old):</u>** • Stage I/II: Those with negative PET#3 (DV Score 1-3) proceed to 2 additional cycles of AVD (4 cycles permissable for bulky masses per investigator discretion) For those with a Deauville Score (DV) of 4-5, it is recommended that they receive 2 cycles of escBEACOPP +/- RT at investigator discretion. • Stage III/IV: Patients with negative PET#3 (DV Score of 1-3) will receive 4 cycles of AVD as tolerated to complete a total of 6 cycles of AVD. It is recommended that those with a Deauville Score (DV) of 4-5 receive 4 cycles of escBEACOPP +/- RT at investigator discretion. **<u>Elderly patients (≥60 years old):</u>** • Stage I/II: Following PET#3, all patients will receive 2 additional cycles of AVD (4 total cycles) regardless of Deauville score with the option for 4 additional cycles or six total for those with bulky disease, per investigator discretion. Those with Deauville 1, 2, or 3 (PET#3) will then continue to followup. Those with Deauville 4 or 5, should receive consolidation treatment with pembrolizumab for 2 years total (3 doses in induction + 32 doses in consolidation). • Stage III/IV: Following PET#3, all patients will receive 4 additional cycles of AVD (6 total cycles) regardless of Deauville score. Those with Deauville 4 or 5 (PET#3) should receive consolidation treatment with pembrolizumab for 2 years total (3 doses in induction + 32 doses in consolidation). Those with

	Deauville 1, 2, 3 (PET#3) will continue to follow-up if they receive all 6 AVD doses successfully. If they were unable to receive the full intended 6 cycles of chemotherapy for stage III/IV disease because of poor tolerance, they should receive consolidation with pembrolizumab for up to 1 year (3 doses in initiation + 14 doses in consolidation). Total Study Duration: 9 weeks of initiation therapy with pembrolizumab + 16-24 weeks of chemotherapy + consolidation for up to 96 weeks (select elderly patients) + 2 years of follow-up
Statistical Methodology	The treatment paradigm of this trial will be considered worthy of further evaluation if at least 40% of patients achieve CR at PET#2 (defined as Deauville 1-3). In order to have 84% power to detect an increase from the historical control of 20% rates of CR for patients with rel/ref cHL treated with pembrolizumab, at a one-tailed alpha of 10%, approximately 26 evaluable patients will be required total. The accrual goal is 30 patients to account for possible unevaluable patients.

1.0 INTRODUCTION – BACKGROUND & RATIONALE

1.1 Disease Background

Classical Hodgkin Lymphoma (cHL) has an excellent prognosis with 5-year progression free survival exceeding 75-80%[1,2]. In spite of many advances in the field, elderly patients continue to have inferior outcomes compared to their younger counterparts, with 5-year relapse-free-survival (RFS) estimates ranging from 30-50%[3-5]. Reasons for the disproportionately inferior outcomes have been postulated. Elderly patients tend to have higher risk baseline features[6], treatment related toxicity, and subsequently significantly fewer elderly patients receive the intended full doses of chemotherapy[6,7]. Young patients, though often cured from their disease, may also suffer late effects from therapy reducing their length and quality of life. As such, multiple efforts have focused on identifying more tolerable treatment combinations or de-escalation of therapy, particularly those with favorable disease characteristics. Some approaches to limiting toxicity include the elimination of bleomycin from upfront treatment[8], treatment with an abbreviated course of chemotherapy[9], as well as combining novel drugs with more tolerable side effects. One such class of drugs that has demonstrated promise and tolerability in cHL includes checkpoint inhibitors. The advent of immunotherapy has transformed the therapeutic landscape, changing the standard of care across the field and raising questions of how best to utilize and assess response to this novel class of drugs. Checkpoint inhibitors, such as pembrolizumab, have shown efficacy and tolerability in relapsed Hodgkin lymphoma, however their efficacy in the frontline setting combined with chemotherapy has not been studied.

1.1.1 Treatment of Early Stage HL's

60% of patients with newly diagnosed HL have early stage disease (stage I/II), and the majority are classified as non-bulky disease[10]. Patients may be further classified as "favorable" or "unfavorable" based on additional factors including bulky disease, B symptoms, erythrocyte sedimentation rate (ESR), and number of lymph node regions involved. There are 4 major prognostic systems, with the German Hodgkin Study Group (GHSG) providing the most stringent criteria. Standard treatment for patients with early stage favorable disease consists of ABVD (Adriamycin, bleomycin, vinblastine, dacarbazine) with or without involved field radiotherapy[11,12]. Patients with favorable disease by the stringent GHSG criteria represent a particularly good prognostic group that may be treated with only two cycles of ABVD followed by 20 GY of involved field radiotherapy (IFRT). Additional studies have supported the use of radiation free approaches[13]. In particular, the HD.6 study demonstrated that patients with a complete response (CR) by CT scan after 2 cycles of chemotherapy had exceptional outcomes with 4 cycles of ABVD alone. Further analysis of individual patient data from HD.6, HD10, and HD11 using comparison in the ABVD alone arms further supported a chemotherapy alone approach in patients achieving a CR by CT after 2 cycles of therapy. Thus the standard of care for non-bulky, early favorable HL responding after 2 cycles of therapy is ABVD for 4 cycles without radiation therapy. Further radiation-free approaches were assessed in patients with early-stage Hodgkin lymphoma, included the RAPID-UK[14], and CALGB 50203[15] studies. These trials also looked at the utility of PET in predicting response to therapy, and PET-adapted approaches, further improving the predictive value of interim scans using the more sensitive FDG-PET. The need to reduce radiation exposure in those with favorable disease was further highlighted by a recent publication in the *New England Journal of Medicine*[16] which showed that risks of radiation persisted even 30 years after treatment. Of further concern, despite changes in radiation techniques long-term radiation toxicity did not decrease in the more contemporary cohort.

1.1.2 Treatment of elderly HL:

There are no standard treatment recommendations for elderly HL patients (defined as age ≥ 60), and prospective studies assessing novel treatment options in this population are limited. Two prospective trials for older HL were recently reported. The first

compared VEPEMB (vinblastine, cyclophosphamide, procarbazine, etoposide, mitoxantrone and bleomycin) to ABVD[17], while the second compared COPP-ABVD and $BEACOPP_{baseline}$[18]. Unfortunately, neither trial improved upon ABVD as the standard of care, and the results with VEPEMB were overall disappointing. While ABVD remains an option, bleomycin lung toxicity is a particular concern in elderly patients[3,19,20]. Evens and colleagues reported the incidence of bleomycin lung toxicity (BLT) in the elderly was 32%, with an associated mortality rate of 25%. Similarly, The Mayo Clinic reported an incidence of BLT of 33% for patients > age 40 years compared with 11% for younger patients[21]. Efforts aimed at eliminating bleomycin in early-favorable HL[22], showed decreased local control when bleomycin was omitted, however long term survival was not compromised and rates exceeded 98%.

1.1.3 Role of FDG-PET

3-Fluorodeoxyglucose-positron emission tomography (PET) has become a standard imaging modality complementing CT scans in the management of HL[23-26]. PET has been studied in both early and advanced stage disease, as a prognostic tool, as well as a means to direct therapy. CALGB 50203[15] enrolled 104 HL patients with stage I/II, non-bulky disease. PET-CT was performed after 2 cycles of ABVD. Positivity was defined as Deauville score of 4-5. Eighty-one percent of patients were PET negative after 2 cycles of chemotherapy, and 2-year PFS for PET-2 negative and positive patients was 88 and 54%, respectively. Although PFS was lower than other early stage HL trials, this was partially explained by the presence of older and higher risk patients; 72.1% of patients were unfavorable by the EORTC criteria. The prognostic implications of early negative PET were also confirmed in advanced-stage HL[27]. Moreover, PET-2 superseded IPS in prognostic importance. Building on this prognostic data, recent studies have incorporated PET-directed therapy to identify patients who may be treated with a limited number of cycles of chemotherapy. The RAPID-UK study included a total of 602 patients with non-bulky early stage HL. The primary endpoint of the study was to assess the non-inferiority of no further treatment, given a negative PET-CT after three cycles of ABVD. PET positivity was defined as a Deauville score of 1-2. Patients with a positive PET were treated with an additional cycle of chemotherapy and 30 Gy of IFRT, while those with a negative PET were randomized to no further treatment or 30 Gy of IFRT. Results demonstrated that 75% of patients had negative PET (Deauville 1-2). The 3-year overall survival rate was exceeded 97% in both groups, with a non-significant rate ratio of 0.51 in favor of no further therapy ($p = 0.27$). Although the study did not meet its primary endpoint of non-inferiority, it demonstrated that patients with favorable disease and a negative PET after three cycles have excellent short-term outcomes with 3 cycles of ABVD alone. However, long-term data is lacking, and the majority of patients (65-75%) were favorable by the most stringent GHSG criteria, including 75% of the group with a negative PET. This is a population that otherwise would be eligible for treatment with 2 cycles of ABVD and 20Gy of IFRT according to HD10[11].

The H10 Trial (EORTC/LYSA/FIL)[28] assessed PET-intensification in early stage disease. Although the initial study was terminated early due to a pre-specified early stopping rule, updated results presented at the Lugano meeting[29] demonstrated that patients with a positive PET2 had improved outcomes (PFS) from intensification to escalated BEACOPP chemotherapy followed by involved-node radiotherapy (INRT) compared to standard ABVD and INRT, with a 13% overall improvement in 5 year PFS. Preliminary reports from studies assessing a PET – adapted approach in advanced stage disease are encouraging as well [Johnson et al. RATHL Study CRUK/07/033 Lugano 2015][30]. Several key issues regarding PET response-adapted therapy need to be considered including consistent definitions of PET-negativity versus positivity. Studies assessing PET-adapted treatment intensification are encouraging, but more data is needed to assess the efficacy of this approach. Furthermore, the implications of

a negative PET following novel therapies and in particular immunotherapy are not clear.

Refer to the Investigator's Brochure (IB)/approved labeling for detailed background information on MK-3475.

1.2 Intervention Background & Overview

The importance of intact immune surveillance in controlling outgrowth of neoplastic transformation has been known for decades. 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.

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

1.2.1 Preclinical and Clinical Trial Data

Please refer to the Investigator's Brochure for more detailed information regarding Preclinical and Clinical data.

PD-1 antibodies have demonstrated clinical activity in HL in the relapsed and refractory setting. Dr. Ansell and colleagues demonstrated the single agent activity of nivolumab in a group of patients with heavily pre-treated relapsed/refractory HL[31]. They conducted a phase 1 study of hematologic malignancies including 23 patients with cHL treated continuously with nivolumab for 2 years or until disease progression. Results demonstrated a high rate of response; 87% objective response, 17% complete response, and 86% PFS at 24 weeks. Drug related adverse events were reported in 18 patients (78%) including: rash (in 22%) and a decreased platelet count (in 17%). Drug-related grade 3 adverse events, which were reported in 5 patients (22%), included the myelodysplastic syndrome, pancreatitis, pneumonitis, stomatitis, colitis, gastrointestinal inflammation, thrombocytopenia, an increased lipase level, a decreased lymphocyte level, and leukopenia. There were no drug-related grade 4 or 5 adverse events.

Pembrolizumab demonstrated equally impressive response rates in the preliminary results from the phase 1b study, KEYNOTE-013[32], which assessed the single agent activity of Pembrolizumab in patients with classical Hodgkin lymphoma after brentuximab vedotin failure. Treatment consisted of pembrolizumab 10mg/kg administered intravenously every 2 weeks until confirmed tumor progression, excessive toxicity, or completion of 2 years of therapy. The results of 15 patients were reported who were evaluable at the 12-week time point. Patients were heavily pre-treated and 67% had also failed a prior autologous stem cell transplant. There were no serious adverse events, and only one patient experienced a grade 3-5 events. 3 patients (20%) had a CR at 12 weeks, 5 additional patients had a partial remission (33%), for an overall response rate of 53%. 4 patients had progressive disease (27%), however all of these actually experienced a decrease in their overall tumor burden. The authors concluded that pembrolizumab showed safety and efficacy in a heavily pretreated population including patients who progressed after transplantation who generally have limited additional treatment options.

1.3 Rationale for the Current Study

cHL is unique among lymphoid malignancies in that the malignant RS-cell are relatively rare, whereas the bulk of the tumor is composed of an extensive but ineffective inflammatory infiltrate[33]. The low ratio of tumor to immune and inflammatory cells suggests an underlying mechanism inducing anti-immunity, and furthermore, that activation of the senescent t-cells could represent an effective means of controlling the disease.

The PD-1 PD-L1 ligand system impairs immune response to tumors. PD-1 is up regulated in HL, specifically in the malignant RS-cell, and PD-1 is markedly elevated in tumor-infiltrating T cells of HL[34]. Chemitz et al demonstrated that PD-1 signaling has an inhibitory effect on T-cell response in HL[35]. Epstein Barr Virus (EBV), commonly associated with HL, increases PDL-1 expression on tumor cells, and increases binding of PD-L-1 to PD-1 on T-cells leading to t-cell exhaustion[36] . Blockade of the PD-1/PD- ligand pathway restores the cytotoxic function of tumor infiltrating T-cells, as assessed by increased IFN-gamma production[34]. In addition to EBV induced amplification of the PDL-1 pathway, Green et al. demonstrated a genetic origin for this increased expression in HL. Amplification of 9p24.1 was demonstrated in RS-cell of nodular-sclerosing HL[33]. Increased gene expression led to increased expression of PD-1, PDL-1, PD-L2, and JAK2. Increased activation of the JAK-STAT pathway through JAK2 signaling induced further increases in PDL-1 transcription.

The genetic overexpression of markers in the PD pathway suggest tumor dependence on this pathway to escape immune surveillance, and that mechanisms aimed at blocking this pathway could allow immune activation and control of disease.

1.3.1 Rationale for the Trial and Selected Subject Population

Based on this accumulated data, we propose a Phase II trial to evaluate the safety and efficacy of pembrolizumab followed by PET-directed combination chemotherapy, for patients with previously-untreated cHL. We propose evaluation of patients with stage I-IV disease including elderly patients.

Elderly patients have poor tolerance and outcomes with standard chemotherapy. By specifically assessing the elderly cohort, we hope to improve the efficacy and tolerability of frontline therapy in a group that otherwise employs a disparate prognosis. In this group bleomycin will be omitted, and pembrolizumab will be given both prior to AVD, as well as following AVD as consolidation. In the young cohort, we predict that the increased efficacy of pembrolizumab added to AVD will improve rates of CR as assessed on interim FDG-PET, and thus reduce the total number of patients requiring radiation therapy. By avoiding radiation in this cohort we hope to reduce the rates of late effects of therapy and second malignancies. Our strategy of administering anti-PD-1 therapy upfront prior to chemotherapy will allow us to assess the rates of CR on PET-CT scan which will further increase our understanding of the prognostic significance of PET-CT scans with this novel class of agents in HL.

1.3.2 Rationale for Dose Selection/Regimen/Modification

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. 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.

1.3.3 Rationale for Endpoints

Efficacy Endpoints

Our primary endpoint is to assess rate of complete response following pembrolizumab alone. Among those patients whose disease has failed frontline treatment, as well as treatment with brentuximab vedotin (BV), pembrolizumab has shown dramatic activity, with a 53% overall response rate (ORR), 20% rate of CR, and disease regression in 14 of 15 patients[37]. We predict an improvement in CR rate of 50% to pembrolizumab alone as assessed by PET-CT prior to initiation of chemotherapy among patients treated in the frontline setting.

Exploratory Studies

The mechanism of suppression of the anti-tumor response is well understood for the PD-1 pathway[36,38]. Utilization of PD-1 blockade in solid malignancies has revealed changes in the T-cell lymphocytic subset consistent with on-target effects of anti-PD-1 agents[39]. Prior clinical trials for the PD-1 inhibitor, nivolumab, included correlates investigating biomarkers of response. Correlative studies in participating patients demonstrated copy-number gains in PDL1 and PDL2 and increased expression of these ligands. Reed-Sternberg cells showed nuclear positivity of phosphorylated STAT3, indicative of active JAK-STAT signaling. Interestingly, tumor infiltrating T- cells expressed low levels of PD-1 on immunohistochemical analysis. Overall, levels of PD-1 expression were not significantly predictive of response, in contrast to studies in solid tumors, where this seems to be more predictive of response. The author's postulated PD-1 blockade may selectively enhance the function of CD8+ T cells with low levels of PD-1 expression.

In addition to PD-1 and PD-L1 expression, multiple lines of evidence support the evaluation of different biomarkers for patients with cHL treated with PD-1 blockade. Serum receptors/cytokines CD30, CCL17, and CCL22, may have prognostic value with respect to PFS and OS among patients with cHL[40]. Moreover, CD8+ T-cell density, along with PD-1+ and PD-L1+ tumor/T-cell expression/density, may predict for activity of pembrolizumab[41,42]. And clinical data have shown that PD-1 inhibition yield significant increases in number of host PD-L1-bearing activated T-cells[43]. These data suggest that baseline tumor features, as well as dynamic host features, may be important predictors of response to pembrolizumab. Furthermore, a recent abstract by

Moscowitz et al[44] demonstrated cysteine-cysteine thymus and activation related chemokine (TARC) as a biomarker for response and PET normalization in HL after treatment with BV. This biomarker warrants additional investigation.

2.0 OBJECTIVES & ENDPOINTS

2.1 Primary Objective

Objective: Assess the percent of patients who achieve a complete response (CR) to single-agent pembrolizumab induction, among patients with cHL using Lugano 2014 criteria, as measured at PET#2.

Hypothesis: We hypothesize that frontline pembrolizumab, followed by FDG-PET-directed combination chemotherapy, will produce excellent efficacy. We predict a CR rate of 50% to pembrolizumab alone as assessed by PET-CT prior to initiation of chemotherapy. Furthermore, the addition of standard chemotherapy utilizing an age and stage-adjusted approach will result in an increased number of patients with PET-negativity at interim PET, and the ability to limit the number of cycles of chemotherapy, and further reduce the need for radiation therapy, thereby minimizing acute and chronic toxicity.

2.2 Secondary Objectives

Objective: Assess the safety and tolerability of pembrolizumab in combination with chemotherapy in the frontline setting.

Hypothesis: The combination of pembrolizumab with AVD as frontline treatment will be well tolerated. Furthermore, the addition of standard chemotherapy utilizing an age and stage-adjusted approach will result in an increased number of patients with PET-negativity at interim PET, and the ability to limit the number of cycles of chemotherapy, and further reduce the need for radiation therapy, thereby minimizing acute and chronic toxicity

Objective: Determine the extent of FDG uptake, using a semi-quantitative approach (eg, Deauville score), after pembrolizumab induction, and after subsequent chemotherapy.

Hypothesis: The percentage of patients with a Deauville score of 1-2 after pembrolizumab alone will be 50%. The percentage of patients with a Deauville score of 1-2 following two cycles of chemotherapy will exceed 75%.

2.3 Exploratory Objectives

Exploratory objectives will assess the value of tissue biomarkers as predictors of response to pembrolizumab, including the following:

- To characterize PD-1 pathway specific expression and correlate with response
- To characterize serum biomarkers of immune, inflammatory response and other biomarkers during treatment
- To characterize levels of soluble PD-L1 related to treatment with pembrolizumab
- To characterize T-lymphocyte subset changes to treatment with pembrolizumab
- To investigate the prevalence and clinical correlation of chromosome 9p24.1 alterations for this population
- Assess cysteine-cysteine thymus and activation related chemokine (TARC) as a biomarker for response and PET normalization

Each enrolled patient will provide a fresh tissue biopsy sample if available from the biopsy performed for diagnosis, or an archived sample as agreed upon by the PI for additional marker expression analysis. Peripheral blood will be obtained at specified time points for serum marker analysis.

PD-1 Pathway Marker Expression
Tissue sample slides from the baseline biopsy will be evaluated by immunohistochemistry for expression of PD-1 and PD-L1 on either malignant cells or within the tumor microenvironment. Samples will be deemed either positive or negative for marker expression. Presence/absence (binary) of PD-1 and PD-L1 will be correlated with response to pembrolizumab and clinical outcomes.

Immune and Inflammatory Markers
Peripheral blood will be tested for serum levels of TNF-α, IFN-γ, IL-2, galectin-1, TGF-β, IL-10, IL-13, and indoleamine 2 3-dioxygenase (IDO). Testing will be performed using commercially available kits. Levels will be compared from specified time points through treatment.

Soluble PD-L1
Peripheral blood obtained at day 1 of cycle #1 then at the off-treatment visit will be analyzed by a commercially available ELISA assay (USCN Life Sciences – product number SEA788Hu). Levels will be compared to evaluate for a change (increase/decrease) following treatment with pembrolizumab.

Lymphocyte Subset Changes
The endpoint is whether or not a patient is a lymphocyte subset responder. Responders are defined as either a) a 50% increase or b) a half standard deviation increase in lymphocyte subsets. Lymphocyte subsets will be evaluated by flow cytometry on peripheral blood obtained at specified time points through the treatment period41-43. Flow cytometry analysis will include the following surface markers: CCR7, CD3, CD4, CD8, CD14, CD16, CD20, CD25, CD45RO, CD56, CD57, CD62L, CD107a, CD127, FoxP3, B7-H1 (PD-L1), B7-DC (PD-L2), HLADR, and PD-1. The following intracellular markers will be evaluated: TIA1, granzyme, perforin. We will complete an 8-10 color flow cytometry analysis to properly group biomarkers for determination of specific lymphocyte populations. Two specific lymphocyte populations will be evaluated: CD4+CD25+PD-L1+ T lymphocytes and CD4+CD62L+CD127+ T lymphocytes. Lymphocyte subsets are continuous measurements in cells/μL.

Chromosome 9p24.1 Alterations
Tissue sample slides from the baseline biopsy will be evaluated by FISH break-apart probes for mutations at chromosome 9p24.1. Presence of amplifications. Frequency and magnitude of 9p24.1 alterations-polysomy, copy gain, and amplification will be determined. We will also assess the association of 9p24.1 alterations with clinical parameters, including stage (early stage I/II favorable risk, early stage unfavorable risk, advanced stage (AS, III/IV) and progression-free survival (PFS), as well as age.

TARC Thymus and Activation-Regulated Chemokine/CCL17 (TARC)
Patients will have TARC assessed prior to therapy utilizing patient's serum. TARC will be measured using a commercially available double antibody sandwich ELISA. Elevation of TARC has been associated with decreased response to chemotherapy and an increased inflammatory environment. We will correlate pre-treatment TARC levels with PET responses and assess for changes in TARC levels after treatment with immunotherapy.

3.0 PATIENT ELIGIBILITY

The target population for this study is patients with Hodgkin lymphoma. This will be a multicenter trial conducted at the Robert H. Lurie Comprehensive Cancer Center of Northwestern University. Northwestern University will serve as the lead site and coordinating center for this study. Participating sites will include Rutgers Cancer Institute, Memorial Sloan Kettering Comprehensive Cancer Center, and Emory University.

A total of 26 evaluable subjects will be needed for this trial (therefore up to 30 may be enrolled in order to achieve this goal). Potential patients may be referred to the Principal Investigator (PI) at Northwestern University, Dr. Jane Winter at (312) 695-4538, or to the local PI at each participating site.

Eligibility will be evaluated by the study team according to the following criteria. Eligibility waivers are not permitted. Subjects must meet all of the inclusion and none of the exclusion criteria to be registered to the study. Study treatment may not begin until a subject is registered. Please refer to Section 11.3 for complete instructions regarding registration procedures.

3.1 Inclusion Criteria

3.1.1 Patients must have a histologically confirmed diagnosis of classical Hodgkin lymphoma including nodular sclerosis, mixed cellularity, lymphocytic-rich, and lymphocyte depleted subtypes by the 4th edition of the WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues published in 2008 (NLPHL excluded).[45]

3.1.2 Patients must have measurable disease by the Lugano Criteria (Appendix C).

3.1.3 Patients must have previously untreated disease (except for one week or less of corticosteroids).

3.1.4 Patients must be age ≥ 18 years.

3.1.5 Patients must exhibit a/an ECOG performance status of 0-1.

3.1.6 Stage III and IV patients may any International Prognostic Score (IPS).

3.1.7 Stage I and II patients must have at least one NCCN unfavorable risk factor (see Appendix D).

3.1.8 Patients must have adequate organ and bone marrow function within 14 days prior to registration, as defined below:

- leukocytes ≥ 3,000/mcL
- absolute neutrophil count ≥ 1,500/mcL
- platelets ≥ 100,000/mcl
- total bilirubin within normal institutional limits
- AST(SGOT)/ALT(SPGT) ≤ 2.5 X institutional upper limit of normal (ULN)
- creatinine within normal institutional limits

Platelet transfusions are acceptable prior to treatment to achieve the above numbers, however growth factors are not allowed within 14 days of registration.

3.1.9 Females of child-bearing potential (FOCBP) and males must agree to avoid becoming pregnant, or impregnating a partner, respectively, by complying with any of the approved contraception techniques (see section 4.5.2) prior to registration, for the duration of study participation, and for 120 days following completion of therapy. Abstinence is acceptable if this is the usual lifestyle and preferred contraception for the subject. Should a female patient become pregnant or suspect she is pregnant while participating in this study, she should inform her treating physician immediately.

NOTE: Male patients will be considered of non-reproductive potential if they have azoospermia. Female patients will be considered of non-reproductive potential if they are either:

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

3.1.10 FOCBP must have a negative pregnancy test within 7 days prior to registration on study. NOTE: a negative pregnancy test is also required within 3 days prior to first dose of pembrolizumab and therefore may need to be repeated if screening test is more than 3 days prior to first dose.

3.1.11 Patients must have the ability to understand and the willingness to sign a written informed consent prior to registration on study.

3.2 Exclusion Criteria

3.2.1 Patients are not eligible who have had prior chemotherapy, targeted small molecule therapy, or radiation therapy prior to registration.
NOTE: If subject received major surgery, they must have recovered adequately from the toxicity and/or complications from the intervention prior to starting therapy.

3.2.2 Patients who have a diagnosis of immunodeficiency or are receiving systemic steroid therapy or any other form of immunosuppressive therapy within 7 days prior to registration are not eligible.

3.2.3 Patients who have a known history of active TB (Bacillus Tuberculosis) are not eligible.

3.2.4 Patients must not have a history of allergic reactions attributed to compounds of similar chemical or biologic composition to pembrolizumab.

3.2.5 Patients who have an uncontrolled intercurrent illness including, but not limited to any of the following, are not eligible:

- Symptomatic congestive heart failure (ejection fraction lower than institutional lower limit of normal [LLN]
- Unstable angina pectoris
- Cardiac arrhythmia

3.2.6 Patients who have a known additional malignancy that is progressing or requires active treatment are not eligible. *NOTE: 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.*

3.2.7 Patients who have known active central nervous system (CNS) metastases and/or carcinomatous meningitis are not eligible.

NOTE: 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 registration. This exception does not include carcinomatous meningitis which is excluded regardless of clinical stability.

3.2.8 Patients who have active autoimmune disease that has required systemic treatment in the past 2 years are not eligible (i.e. with use of disease modifying agents, corticosteroids or immunosuppressive drugs).
NOTE: Replacement therapy (e.g. Thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency, etc.) is not considered a form of systemic treatment.

3.2.9 Patients who have a history of (non-infectious) pneumonitis that required steroids or current pneumonitis are not eligible.

3.2.10 Patients who have an active infection requiring systemic therapy are not eligible, except for uncomplicated urinary tract infections.

3.2.11 Patients are not eligible who have 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.

3.2.12 Patients who have known psychiatric or substance abuse disorders that would interfere with cooperation with the requirements of the trial are not eligible.

3.2.13 Patients may not be pregnant or breastfeeding, or expecting to conceive or father children within the projected duration of the trial, from registration through 120 days after the last dose of trial treatment.

3.2.14 Patients who have received prior therapy with an anti-PD-1, anti-PD-L1, or anti-PD-L2 agent are not eligible.

3.2.15 Patients who have a known history of Human Immunodeficiency Virus (HIV) (HIV 1/2 antibodies) are not eligible.

3.2.16 Patients who have active Hepatitis B (e.g., HbsAg reactive) or Hepatitis C (e.g., HCV RNA [qualitative] is detected) are not eligible.

3.2.17 Patients who received a live vaccine within 30 days of planned start of study therapy are not eligible. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, varicella/zoster, yellow fever, rabies, BCG, and typhoid vaccine.
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.

4.0 TREATMENT PLAN

4.1 Overview

Patients with *de novo* classical Hodgkin lymphoma with any stage disease will be eligible for participation. All patients must have a baseline PET-CT prior to treatment (PET#1). Treatment will be divided into three phases:

- **Pembrolizumab "lead in"** for 3 cycles (21-days each) followed by PET-CT (PET#2)
- **Standard chemotherapy:**
  AVD for 2 cycles (28 days each) followed by interim PET-CT (PET#3) followed by AVD for an additional 2-4 cycles (depending on age, stage, and PET-CT results: 2 cycles** for Stage I/II and 4 cycles for Stage III/IV). Patients <60 years old with positive PET-CT (PET #3, Deauville 4, 5) will NOT receive additional AVD, and may receive escBEACOPP at investigator's discretion (x2 cycles for Stage I/II and x4 cycles for Stage III/IV) with an option for consolidative radiotherapy.
  **Patients with bulky disease (>10 cm) at baseline and a negative PET #3 may receive a total of 4-6 cycles of AVD per investigator discretion
- **Pembrolizumab consolidation** for up to 2 years total treatment (3 doses in induction + 32 or 14 doses in consolidation) in select patients ≥60 years old who have either positive PET#3 or advanced stage disease and receive less than the intended 6 cycles of AVD because of poor tolerance.

PET/CT completed at the timepoints outlined above will be reviewed centrally. See Section 6.3.1 for central review requirements.

4.2 Treatment Administration

4.2.1 Pembrolizumab Induction

All patients will receive 3 cycles of pembrolizumab starting cycle 1 day 1. Pembrolizumab should be administered on Day 1 of each 21-day cycle after all procedures/assessments have been completed as detailed on the Study Procedures Table (Section 5.0). Pembrolizumab 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. This treatment will be followed by an investigational PET/CT (PET#2), 3 weeks after completion of cycle 3 (+/- 3 days).

Pembrolizumab 200 mg will be administered as an approximately 30 minute IV infusion on day 1 of each 21-day cycle. Sites should make every effort to target infusion timing to be as close to 30 minutes as possible. However, given the variability of infusion pumps from site to site, a window of -5 minutes and +10 minutes is permitted (i.e., infusion time is 30 minutes: -5 min/+10 min). The Pharmacy Manual contains specific instructions for the preparation of the pembrolizumab infusion fluid and administration of infusion solution.

Patients will receive pre-treatment acetaminophen 650 mg po and diphenhydramine 50 mg po given 30 minutes prior to the pembrolizumab infusion. Pembrolizumab 200 mg IV in 50 mL of 0.9% NaCl will be infused over 30 minutes on day 1 of each 21 day cycle.

4.2.2 Standard Chemotherapy

4.2.2.1 <u>Cycle 1 & 2</u>: AVD chemotherapy post pembrolizumab "lead in"

Treatment should be administered on day 1 of each 28 day cycle after all procedures/assessments have been completed as detailed

on the Study Procedures Table (Section 5.0). Trial treatment may be administered up to 3 days before or after the scheduled Day 1 of each cycle due to administrative reasons.

Doxorubicin (Adriamycin) 25 mg/m^2, vinblastine 6 mg/ $m^{2,}$ and dacarbazine 375mg/ m^2 will be on day 1 and 15 of a four week cycle.

- All patients will receive treatment with 2 cycles of AVD.
- Treatment will commence 21 days after final dose of induction pembrolizumab, but not prior to PET #2 (+/- 3 days). Treatments will be on days 1 and 15 of a 28-day cycle.
- PET-CT (PET#3) should occur on day 117-120, or day 26-29 of AVD cycle 2 as listed in section 5.0.

AVD supportive care measures
Pre-medications:
We recommend patients receive pre-treatment with acetaminophen 650 mg po and diphenhydramine 50 mg po given 30 minutes prior to AVD as per institutional protocol.

Prophylactic antibiotics:
Prophylactic antibiotic use (e.g., Levaquin, nystatin) is at the discretion of the treating physician.

Growth factor protocol:
In elderly patients granulocyte colony stimulating factor (e.g., G-CSF) is recommended and in accordance with ASCO guidelines. Please record all granulocyte (or erythrocyte) colony stimulating factors on the treatment forms.

4.2.2.2 Cycle 3-6: AVD (or escBEACOPP)

4.2.2.2.1 For those with a negative PET #3

For all patients with a negative PET #3, additional AVD should commence 4 weeks after day 1 cycle 2 of AVD (after PET#3). Patients will receive a total of 4-6 cycles depending on stage and tolerability.

a. Patients with stage I/II disease should receive two additional cycles of AVD for a total of 4 cycles of AVD. Patients with bulky disease (>10 cm mass) at baseline and a negative PET #3 may receive 4-6 cycles of AVD per investigator discretion.
b. Patients with stage III/IV disease should receive four additional cycles of AVD for a total of 6 cycles of AVD

4.2.2.2.2 For those with a positive PET #3 (Deauville 4,5)

PET- Adapted Treatment for patients <60 with positive PET#3:
Patients age <60 with Deauville score of 4-5 on PET#3 may transition to escBEACOPP (escalated bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine) +/- radiation therapy (RT) at the investigators' discretion

a. Patients with stage I/II disease may transition to 2 cycles of escBEACOPP +/- RT
b. Patients with stage III/IV disease may transition to 4 cycles of escBEACOPP +/- RT

c. Patients with progressive/relapsed disease as defined in section 6.1.2.1 will be taken off study.

Patients 60 or older with a Deauville score of 4, 5 positive PET #3 will continue on AVD for a total of four- six cycles of AVD, depending on stage and tolerability.

4.2.2.2.3 Repeat Imaging (PET#4 or CT Scan)
All patients will have repeat imaging 2-6 weeks after completing chemotherapy and prior to pembrolizumab consolidation (where applicable). Imaging will consist of a PET-CT (PET#4) for all patients except those with Stage I/II disease and a negative PET#3, who may have a diagnostic CT scan.

4.2.3 Pembrolizumab Consolidation

Patients who are ≥60 may receive pembrolizumab consolidation (either 14 or 32 additional doses) if they fall into the categories below:

- Elderly patients with any stage disease with a positive PET #3 (Deauville 4, 5) will proceed to pembrolizumab consolidation at a dose of 200mg IV flat dose every 21 days for 2 years total treatment (3 induction doses + 32 consolidation doses).
- Patients with stage III/IV disease with a negative PET #3 who receive < the planned 6 cycles of AVD therapy will proceed to pembrolizumab consolidation at a dose of 200mg IV flat dose every 21 days for up to 1 year total treatment (3 induction doses + 14 consolidation doses).
- In patients receiving consolidation therapy, pembrolizumab should commence 4 weeks after day 1 of the final cycle of AVD. For patients in remission having received fewer than six full cycles of AVD, patients may be followed with CT scans every three months during consolidation. For other patients receiving consolidation, PET/CT is recommended every 3 months during consolidation therapy until negative. Once PET-CT is negative, CT's should be obtained every three months during consolidation.

4.3 Toxicity Management & Dose Delays/Modifications

Any patient who receives at least one dose of study therapy will be evaluable for toxicity endpoints. Each patient will be assessed for the development of toxicity according to the timeframe referenced in the Schedule of Events table. Toxicity will be assessed according to the CTCAE (version 4.03)

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 PI and approved by DSMC. The reason for interruption should be documented in the appropriate eCRF. Once subjects resume treatment, they will continue with the full number of planned cycles of therapy (i.e. treatments will be delayed not skipped).

4.3.1 Pembrolizumab Dose Modifications

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 4.1 below. See Section 4.5.3 for supportive care guidelines, including use of corticosteroids.

Table 4.1: Dose Modification Guidelines for Pembrolizumab-Related Adverse Events

General instructions:

1. Corticosteroid taper should be initiated upon AE improving to Grade 1 or less and continue to taper over at least 4 weeks.
2. For situations where pembrolizumab has been withheld, pembrolizumab can be resumed after AE has been reduced to Grade 1 or 0 and corticosteroid has been tapered. Pembrolizumab should be permanently discontinued if AE does not resolve within 12 weeks of last dose or corticosteroids cannot be reduced to ≤10 mg prednisone or equivalent per day within 12 weeks.
3. For severe and life-threatening irAEs, IV corticosteroid should be initiated first followed by oral steroid. Other immunosuppressive treatment should be initiated if irAEs cannot be controlled by corticosteroids.
4. For signs or symptoms of Stevens-Johnson Syndrome (SJS) or Toxic Epidermal Necrolysis (TEN), withhold pembrolizumab and refer the patient for specialized care for assessment and treatment.

Immune-related AEs	**Toxicity grade or conditions (CTCAEv4.03)**	**Action taken to pembro**	**irAE management with corticosteroid and/or other therapies**	**Monitor and follow-up**
Pneumonitis	Grade 2	Withhold	• Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper	• Monitor participants for signs and symptoms of pneumonitis • Evaluate participants with suspected pneumonitis with radiographic imaging and initiate corticosteroid treatment • Add prophylactic antibiotics for opportunistic infections
	Grade 3 or 4, or recurrent Grade 2	Permanently discontinue		
Diarrhea / Colitis	Grade 2 or 3	Withhold	• Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper	• Monitor participants for signs and symptoms of enterocolitis (ie, diarrhea, abdominal pain, blood or mucus in stool with or without fever) and of bowel perforation (ie, peritoneal signs and ileus). • Participants with ≥ Grade 2 diarrhea suspecting colitis should consider GI consultation and performing endoscopy to rule out colitis. • Participants with diarrhea/colitis should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion.
	Grade 4	Permanently discontinue		
AST / ALT elevation or Increased bilirubin	Grade 2	Withhold	• Administer corticosteroids (initial dose of 0.5- 1 mg/kg prednisone or equivalent) followed by taper	• Monitor with liver function tests (consider weekly or more frequently until liver enzyme value returned to baseline or is stable
	Grade 3 or 4	Permanently discontinue	• Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper	

Type 1 diabetes mellitus (T1DM) or Hyperglycemia	Newly onset T1DM or Grade 3 or 4 hyperglycemia associated with evidence of β-cell failure	Withhold	• Initiate insulin replacement therapy for participants with T1DM • Administer anti-hyperglycemic in participants with hyperglycemia	• Monitor participants for hyperglycemia or other signs and symptoms of diabetes.
Hypophysitis	Grade 2	Withhold	• Administer corticosteroids and initiate hormonal replacements as clinically indicated.	• Monitor for signs and symptoms of hypophysitis (including hypopituitarism and adrenal insufficiency)
	Grade 3 or 4	Withhold or permanently discontinue[1]		
Hyperthyroidism	Grade 2	Continue	• Treat with non-selective beta-blockers (eg, propranolol) or thionamides as appropriate	• Monitor for signs and symptoms of thyroid disorders.
	Grade 3 or 4	Withhold or permanently discontinue[1]		
Hypothyroidism	Grade 2-4	Continue	• Initiate thyroid replacement hormones (eg, levothyroxine or liothyroinine) per standard of care	• Monitor for signs and symptoms of thyroid disorders.
Nephritis and Renal dysfunction	Grade 2	Withhold	• Administer corticosteroids (prednisone 1-2 mg/kg or equivalent) followed by taper.	• Monitor changes of renal function
	Grade 3 or 4	Permanently discontinue		
Myocarditis	Grade 1 or 2	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 3 or 4	Permanently discontinue		
All other immune-related AEs	Intolerable/ persistent Grade 2	Withhold	• Based on type and severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 3	Withhold or discontinue based on the type of event. Events that require discontinuation include and not limited to: Gullain-Barre Syndrome, encephalitis		
	Grade 4 or recurrent Grade 3	Permanently discontinue		

1. Withhold or permanently discontinue pembrolizumab is at the discretion of the investigator or treating physician.

NOTE:
For participants with Grade 3 or 4 immune-related endocrinopathy where withhold of pembrolizumab is required, pembrolizumab may be resumed when AE resolves to ≤ Grade 2 and is controlled with hormonal replacement therapy or achieved metabolic control (in case of T1DM).

4.3.2 AVD Dose Modifications

Dose delays and reductions of AVD chemotherapy only are to be done at the discretion of the treating physician and must be clearly documented on the Treatment eCRF in NOTIS along with the CTCAE (version 4.03) grade. Delays of greater than 5 weeks from the last dose due to AVD toxicity must be approved by the PI, and the QAM must be included on this correspondence. The following are only recommendations (are not mandatory) for modifications for AVD; pembrolizumab modifications are mandatory and are described above in Table 4.2.

Table 4.2: AVD Dose Modification Guidelines for Drug-Related Adverse Events

Toxicity	Grade/Description	Doxorubicin	Vinblastine	Dacarbazine
Hematologic Toxicities				
Thrombocytopenia	Grade 1 or 2	Maintain dose level.	Maintain dose level	Maintain dose level.
	Grade 3 or 4	Transfuse to maintain platelets >20	Transfuse to maintain platelets >20	Transfuse to maintain platelets >20
Neutropenia*	Grade 1-3 (without fever)	Maintain dose level.	Maintain dose level	Maintain dose level.
	Grade 3 (ANC 500-1000) w/ fever or Grade 4 (ANC <500)	Patients with severe persistent neutropenia, especially despite use of granulocyte growth factor, could have a reduction of doxorubicin and vinblastine by 25%.	Patients with severe persistent neutropenia, especially despite use of granulocyte growth factor, could have a reduction of doxorubicin and vinblastine by 25%.	Maintain dose level
Non-hematologic Toxicities				
Allergic reaction or hypersensitivity	≤ Grade 3	Hold dose until resolved to ≤ Grade 1 & then resume at same dose level.	Hold dose until resolved to ≤ Grade 1 & then resume at same dose level.	Hold dose until resolved to ≤ Grade 1 & then resume at same dose level.
	Grade 4	Permanently discontinue	Permanently discontinue	Permanently discontinue
Gastrointestinal	Grade 3-4 oral ulceration or diarrhea	Hold chemotherapy until symptoms clear, then may reinstate at 75% full dose. Doses may be re-escalated as tolerated.	Hold chemotherapy until symptoms clear, then may reinstate at 75% full dose. Doses may be re-escalated as tolerated.	Hold chemotherapy until symptoms clear, then may reinstate at 75% full dose. Doses may be re-escalated as tolerated.
	Grade 4 constipation	N/a	Decrease dose by 50%, then re-escalate on a vigorous bowel regimen[ϕ]	N/a
Hepatotoxicity[+]	Bilirubin > 1.5 <3.0	50% dose reduction	50% dose reduction	Maintain dose level
	Bilirubin ≥ 3.0<5.0	75% dose reduction	75% dose reduction	
	Bilirubin > 5	Omit doxorubicin, may consider substituting cyclophosphamide	Hold therapy and investigate cause	Hold therapy and investigate cause

	Transaminases 2-3x ULN	25% dose reduction	Maintain dose level	No dose adjustment specified, follow institutional guidelines
	Transaminases > 2-3x ULN	50% dose reduction	Maintain dose level	Hold and investigate the cause
Infection	≥ Grade 3	Hold dose until systemic treatment for infection is complete. If no neutropenia, resume at same dose level. If neutropenic, follow instructions above (hematologic section).		
Hepatitis B** reactivation	Any grade	If the hepatitis B virus DNA level rises during this monitoring, management should be reviewed with an appropriate specialist with experience managing hepatitis and consideration given to halting chemotherapy.		
Neuropathy	Grade 2 w/ pain or Grade 3	Maintain dose level	Consideration for 50% dose reduction	Maintain dose level
	Grade 4 (severe motor neuropathy)	N/a	Permanently discontinue vinblastine	n/a
Renal dysfunction	**$CrCl_{cr}$ 46-60 mL/minute**	Maintain dose level	Maintain dose level	Administer 80% of dose
	$CrCL_{cr}$ 31-45 mL/minute	Maintain dose level	Maintain dose level	Administer 75% of dose
	$CrCl_{cr}$ <30 mL/minute	No dose adjustment per protocol, consult with a pharmacist	No dose adjustment per protocol, consult with a pharmacist	Administer 70% of dose
Cardiac toxicity¥	If LVEF below the institutional lower limit of normal and at least a 5% absolute decrease from the baseline LVEF value OR Any absolute decrease of ≥15% from the patient's baseline value	Hold drug: If LVEF improves back to baseline prior to the next doxorubicin and/or if an arrhythmia has been controlled, doxorubicin may be administered if it is felt by the managing physician to be in the best interest of the patient.	n/a	n/a
Pulmonary	Any Grade	n/a	n/a	n/a

* Routine use of growth factors is not recommended in patients receiving bleomycin. Leukopenia is not a factor for delay of treatment or reduction of dose intensity in patients receiving bleomycin. Also, if drug dose is reduced due to hematologic toxicity, full dose should be resumed when blood counts return to normal.

** All lymphoma patients should be tested for both HbsAg and HbcoreAb. If either test is positive, such patients should be treated with lamiVUDine during chemotherapy and for six months afterwards. Such patients should also be monitored with frequent liver function tests and hepatitis B virus DNA at least every two months.

+ May give full dose with recovery of bilirubin < 1.5, Gilberts disease is not included.

Φ Vinblastine may cause severe hypomotility with constipation or ileus. Inform patients prior to administration and advise the patient to maintain regular bowel function.

¥ Doxorubicin may result in congestive heart failure. MUGA scans (or echocardiogram) should be repeated routinely s/p cycle 4 of AVD as described in the Schedule of Activities, or earlier and more frequently, if clinically indicated.

Hematologic Toxicity

For absolute neutrophil count of <500 on the day of treatment, addition of G-CSF (filgrastin) therapy should be considered. This is strongly preferred due to the long half-life of pegfilgrastim.

Growth factors may be used prophylactically. Additionally, patients with severe persistent neutropenia, especially despite use of granulocyte growth factor, could have a reduction of doxorubicin and vinblastine by 25%.

Other Considerations:
There may be other toxicities whereby the treating physician believes it would be 'best medical practice' to dose reduce a particular chemotherapy agent. This should be discussed with the study PI on a case-by-case basis and the QAM should be included on all such correspondence.

Chemotherapy intolerance
If any of the above grade 3 or 4 non-hematologic toxicities or grade 4 hematologic toxicities last > 2 weeks or if the severe toxicity is 'recurrent', the patient may be deemed "chemotherapy intolerable" and stop further chemotherapy. This designation should be discussed with the study PI. In addition, this designation may be applicable for any other grade 3 or 4 non-hematologic toxicities not listed above and it is deemed by the treating physician that the patient should not continue further chemotherapy. Chemotherapy intolerable patients may still proceed with consolidation pembrolizumab therapy if they have achieved either a PR or CR at time of chemotherapy intolerable designation. These patients should have repeat staging CT scans performed prior to initiation of pembrolizumab consolidation therapy.

4.4 Concomitant Medications/Treatments

Medications or vaccinations specifically prohibited in the exclusion criteria are not allowed during the ongoing trial and are listed in section 4.5.2. If there is a clinical indication for one of these or other medications or vaccinations specifically prohibited during the trial, discontinuation from trial therapy or vaccination may be required. The final decision on any supportive therapy or vaccination rests with the investigator and/or the subject's primary physician.

4.4.1 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 appropriate eCRF 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 eCRF.

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 for the purpose of toxicity management beyond 30 days after the last dose of trial treatment should be recorded for SAEs and ECIs as defined in Section 7.

4.4.2 Prohibited Concomitant Medications

Subjects are prohibited from receiving the following therapies during the trial:

- Antineoplastic systemic chemotherapy or biological therapy
- Immunotherapy not specified in this protocol
- Chemotherapy not specified in this protocol

- Investigational agents other than pembrolizumab
- Patients requiring radiation therapy (except as specified in the protocol for those age < 60 with a Deauville score of 4-5 on interim PET/CT (PET#3)) will be taken off study.
- 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 during and within 1 week of treatment for any purpose other than to modulate symptoms from an event of clinical interest of suspected immunologic etiology.
  NOTE: The use of physiologic doses of corticosteroids may be approved after consultation with the PI.
  NOTE: Dexamethasone is permitted as a pre-medication only during AVD chemotherapy.

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.

4.5 Rescue/Supportive Care Medications & Lifestyle 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. Where appropriate, these guidelines include the use of oral or intravenous treatment with corticosteroids as well as additional anti-inflammatory agents if symptoms do not improve with administration of corticosteroids. Note that several courses of steroid tapering may be necessary as symptoms may worsen when the steroid dose is decreased. For each disorder, attempts should be made to rule out other causes such as metastatic disease or bacterial or viral infection, which might require additional supportive care. The treatment guidelines are intended to be applied when the investigator determines the events to be related to pembrolizumab. Note: if after the evaluation the event is determined not to be related, the investigator does not need to follow the treatment guidance (as outlined below). Refer to Section 4.4 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.

<u>Pneumonitis:</u>

- 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.

<u>Diarrhea/Colitis:</u>

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,** administer oral corticosteroids.
- For **Grade 3 or 4 diarrhea/colitis,** 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.

4.5.1 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 4 below shows treatment guidelines for subjects who experience an infusion reaction associated with administration of pembrolizumab (MK-3475).

Table 4.3 Pembrolizumab 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. **Subjects who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further trial treatment administration.**	Subject may be premedicated 1.5h (± 30 minutes) prior to infusion of pembrolizumab (MK-3475) with: Diphenhydramine 50 mg po (or equivalent dose of antihistamine). Acetaminophen 500-1000 mg po (or equivalent dose of antipyretic).
Grades 3 or 4 Grade 3: Prolonged (i.e., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (e.g., renal impairment, pulmonary infiltrates) Grade 4: Life-threatening; pressor or 33rticarial 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.		

4.5.2 Management of Cardiac Toxicities

During treatment with pembrolizumab, patients will be closely monitored for cardiac toxicities. For patients with evidence of congestive heart failure, myocardial infarction, cardiomyopathy, or myositis, cardiac evaluation should take place including lab tests and cardiology consultations as clinically indicated including ECG, CPK, troponin, and ECHO.

Pembrolizumab dosing should be modified according to Table 4.5.

Table 4.4 – Management of Cardiac Toxicities

Cardiac *	Management/Next Dose for Pembrolizumab Cardiac Toxicities
≤ Grade 1	Hold dose pending evaluation and observation.** Evaluate for signs and symptoms of CHF, ischemia, arrhythmia or myositis. Obtain history EKG, CK (for concomitant myositis), CK-MB. Repeat troponin, CK and EKG 2-3 days. If troponin and labs normalize may resume therapy. If labs worsen or symptoms develop then treat as below. Hold pending evaluation
Grade >2 with suspected myocarditis	Hold dose.** Admit to hospital. Cardiology consult. Rule out MI and other causes of cardiac disease. Cardiac Monitoring. Cardiac Echo. Consider cardiac MRI and cardiac biopsy. Initiate high dose methylprednisolone. If no improvement within 24 hours, add either infliximab, ATG or tacrolimus. Consult algorithm for more details. Resume therapy if there is a return to baseline and myocarditis is excluded or considered unlikely.
Grade >2 with confirmed myocarditis	Off protocol therapy. Admit to CCU (consider transfer to nearest Cardiac Transplant Unit). Treat as above. Consider high dose methylprednisolone Add ATG or tacrolimus if no improvement. Off treatment.
**Including CHF, LV systolic dysfunction, Myocarditis, CPK, and troponin* ***Patients with evidence of myositis without myocarditis may be treated according as "other event"* Note: The optimal treatment regimen for immune mediated myocarditis has not been established. Since this toxicity has caused patient deaths, an aggressive approach is recommended.	

4.5.3 Diet/Activity/Contraception/Other Considerations

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

Pembrolizumab may have adverse effects on a fetus in utero. Furthermore, it is not known if pembrolizumab has transient adverse effects on the composition of sperm. For this trial, male subjects will be considered to be of non-reproductive potential if they have azoospermia (whether due to having had a vasectomy or due to an underlying medical condition).
Female subjects will be considered of non-reproductive potential if they are either:

(1) post-menopausal (defined as at least 12 months with no menses without

an alternative medical cause; in women < 45 years of age a high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a post-menopausal state in women not using hormonal contraception or hormonal replacement therapy. In the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.);
OR

(2) have had a hysterectomy and/or bilateral oophorectomy, bilateral salpingectomy or bilateral tubal ligation/occlusion, at least 6 weeks prior to screening;
OR

(3) has a congenital or acquired condition that prevents childbearing.

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

(1) practice abstinence† from heterosexual activity;
OR

(2) use (or have their partner use) acceptable contraception during heterosexual activity.

Acceptable methods of contraception are‡:

- Single method (one of the following is acceptable):
  - intrauterine device (IUD)
  - vasectomy of a female subject's male partner
  - contraceptive rod implanted into the skin

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

†Abstinence (relative to heterosexual activity) can be used as the sole method of contraception if it is consistently employed as the subject's preferred and usual lifestyle and if considered acceptable by local regulatory agencies and ERCs/IRBs. Periodic abstinence (e.g., calendar, ovulation, 35rticar-thermal, post-ovulation methods, etc.) and withdrawal are not acceptable methods of contraception.

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

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 subjects of childbearing potential must adhere to the contraception requirement (described above)

from the day of study medication initiation (or 14 days prior to the initiation of study medication for oral contraception) throughout the study period up to 120 days after the last dose of trial therapy. If there is any question that a subject of childbearing potential will not reliably comply with the requirements for contraception, that subject should not be entered into the study.

4.5.4 Use in Pregnancy

If a subject inadvertently becomes pregnant while on treatment with pembrolizumab, the subject will immediately be removed from the study. The site will contact the subject at least monthly and document the subject's status until the pregnancy has been completed or terminated. The outcome of the pregnancy will be reported to the PI and to Merck without delay, and within 24 hours to the PI 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 treating 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 PI. If a male subject impregnates his female partner the study personnel at the site must be informed immediately and the pregnancy reported to the PI and to Merck and followed as described above and in Section 7.3.5.2

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

4.6 Duration of Trial

4.6.1 Duration of Therapy

Patients will be treated with 3 cycles of pembrolizumab (9 weeks) followed by AVD for 4-6 cycles (4-6 months) followed by pembrolizumab consolidation (selected patients) for up to 2 total years of pembrolizumab.

4.6.2 Duration of Follow Up

Once patients are off treatment for any reason, they will have a final off-treatment visit approximately 30 days post-last dose of study therapy. Thereafter, they will be followed with at least one clinic visit every 3 months for up to 2 years from end of treatment. Patients removed from treatment for unacceptable adverse events will be followed until resolution or stabilization of the adverse event.

For patients who undergo allogeneic stem cell transplant (SCT) within 2 years of study treatment, transplant parameters and adverse events will be recorded as detailed in section 4.6.3.

4.6.3 Subject Withdrawal/Discontinuation Criteria from Treatment and/or Overall Study

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 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 Table 4.1.

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

- Patient voluntarily withdraws from treatment (follow-up permitted)
- The subject or legal representative (such as a parent or legal guardian) withdraws consent (no follow-up permitted).
- Confirmed radiographic disease progression
- *Note*: For unconfirmed radiographic disease progression, please see Section 5.1.6
- Unacceptable toxicity/adverse experiences as described in Section 4.4
- Intercurrent illness that prevents further administration of treatment
- Investigator's decision to withdraw the subject (i.e. continuation not in the patient's best interest)
- The subject has a confirmed positive serum pregnancy test
- Patient develops a second malignancy that requires treatment which would interfere with this study
- Noncompliance or inability to comply with trial treatment or procedure requirements
- The subject is lost to follow-up
- Administrative reasons

The End of Treatment and Follow-up visit procedures are listed in Section 5 (Protocol Flow Chart). 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. 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.

Patients who undergo allogeneic transplant will be monitored for adverse events. For subjects who have an allogeneic SCT within 24 months of last study treatment, transplant parameters will be collected and specific events will be collected for 18 months from the date of the allogeneic transplant to include graft-versus-host-disease (acute and/or chronic), veno-occlusive disease, febrile syndrome (a steroid-requiring febrile illness without an infectious cause), and encephalitis, for all grades, and regardless of relationship to study drug. Additional medically important adverse events post-allogeneic SCT may be submitted at the Investigator's discretion. If available and relevant to an event post-allogeneic SCT, concomitant medications and/or laboratory results may also be reported.

4.6.4 Patient Replacement

Any patient who is registered to the study and then withdrawn without receiving any study treatment may be replaced. Any patient who completes fewer than 2 total cycles of therapy and is withdrawn for any reason except PD or toxicity will still be considered evaluable for toxicity endpoints; however, for the purpose of efficacy endpoints, another patient may be added; if the maximum accrual of 30 is reached without achieving the 26 evaluable necessary for evaluation of efficacy, an increase to the accrual goal may be requested with the approval of the Data and Safety Monitoring Committee (DSMC) at Northwestern University. No follow-up is required for patients that withdrew and did not receive any study treatment.

5.0 STUDY PROCEDURES

Trial Period:	**Screening Phase**	**Treatment Cycles[1]**									**Off Rx**	**Surveillance**
Treatment Cycle/Title:	Main Study Screening	Pembrolizumab 1	Pembrolizumab 2	Pembrolizumab 3	PET #2	AVD[2,3] 1-2	PET #3	AVD[3,4] 3-6[6]	Post-Chemo Assessment	Pembrolizumab[5] 4-35	Discont	Survival Follow-Up
Scheduling Window (Days):	Within 28 days of registration	1 ± 3	22 ± 3	43 ± 3		64 ± 3		120 ± 3		2-4 weeks after last dose of chemotherapy ± 3	30 days after last dose (pembro or AVD, ±5 days)	Every 12 weeks
Administrative Procedures												
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	
Trial Treatment Administration		x	x	x		x		x		x		
Post-study anticancer therapy status											x	x
Survival Status[7]												x
Clinical Procedures/Assessments												
Review Adverse Events		x	x	x		x		x		x	X[20]	X[20]
Physical Examination	x	x	x	x		x		x		x	x	
Vital Signs[8] Weight and Height[24]	x	x	x	x		x		x		x	x	
ECOG Status[9]	x	x	x	x		x		x		x	x	
Echocardiogram/MUGA	x							X[21]				
Unfavorable risk factors/IPS[10]	x											
Laboratory Procedures/Assessments: analysis performed by LOCAL laboratory												
Pregnancy Test – Urine or Serum β-HCG	x[22]	x[22]										
PT/INR and aPTT	x											

Trial Period:	**Screening Phase**	**Treatment Cycles[1]**									**Off Rx**	**Surveillance**
		Pembrolizumab			PET #2	AVD[2,3]	PET #3	AVD[3,4]	Post-Chemo Assessment	Pembrolizumab[5]	Discont	Survival Follow-Up
Treatment Cycle/Title:	Main Study Screening	1	2	3		1-2		3-6[6]		4-35		
Scheduling Window (Days):	Within 28 days of registration	1 ± 3	22 ± 3	43 ± 3		64 ± 3		120 ± 3		2-4 weeks after last dose of chemotherapy ± 3	30 days after last dose (pembro or AVD, ±5 days)	Every 12 weeks
CBC with ANC[11]	x[11]	x	x	x		x[3]		x[3]		x	x	
Comprehensive Serum Chemistry Panel[11]	x[11]	x	x	x		x[3]		x[3]		x	x	
Urinalysis	x											
T3, FT4 and TSH[12]	x			x						x		
ESR	x											
HIV, Hepatitis B, Hepatitis C[13]	x											
Quantiferon-gold TB blood test[25]	x[25]											
Efficacy Measurements												
PET-CT[14]	x[14]				x[14]		x[14]		X[15]	x[16]	x[15]	
CT scan[17]	x									x[23]	x	
Tumor Biopsies/Archival Tissue Collection/Correlative Studies Blood performed by CENTRAL laboratory												
Archival or Newly Obtained Tissue Collection[18]	x	x[18]										
Correlative Studies Blood Collection[19]		x				x					x	

[1] Treatment cycle of pembrolizumab defined as 21 days, Treatment cycle of AVD defined as 28 days with treatment on days 1 and 15

[2] Interim assessment by FDG-PET #2 for primary endpoint assessment on day 64 +/- 3 days

[3]Labs including CBC w/ANC and comprehensive chemistry panel, physician visit with physical examination and vital signs to be performed on day 1 of each cycle of AVD.

[4] Interim assessment by FDG-PET #3 for PET-directed therapy on day 117-120 prior to AVD cycle 3

[5] Elderly patients may receive consolidation for a total of up to 1 or 2 years pembrolizumab treatment. Elderly patients who do not achieve CR after additional AVD will have pembrolizumab consolidation for up to 32 additional doses. Elderly patients with Stage III/IV disease who achieve CR after <6 cycles AVD will receive pembrolizumab consolidation for up to 14 additional doses. See section 4.2.3 for details.

[6] See study schema in 1.2

[7] Patients will be followed (either by routine clinic visit or by phone call) for survival every 12 weeks (±7 days) for 2 years from the last dose of study drug. Patients should also be monitored for occurrence of an allogeneic stem cell transplant within 24 months from the last study treatment. If patient undergoes an allo-SCT in this timeframe, transplant parameters and adverse events must be reported as specified in section 4.6.3 (up to 18 months from the time of SCT).

[8] Vital Signs include: Blood pressure, pulse, respiratory rate, and oxygen saturation

[9] See Appendix A

[10] See Appendix D

[11] Comprehensive chemistry panel and CBC with differential are required within 14 days of study registration. Chemistry panel will include glucose, calcium, albumin, ALT, AST, sodium, potassium, total bilirubin, alk phose, and creatinine. CBC with differential must include Absolute Neutrophil Count.

[12] At baseline and every 6 weeks while on therapy with pembrolizumab.

[13]Patients must have HIV Ab screen; and Hepatitis B Sag, Sab, and core; and Hepatitis C Ab testing within 6 weeks of registration.

[14] PET/CT is required for eligibility within 6 weeks prior to registration (standard of care) and at specified time points for tumor assessment for the primary endpoint analysis. PET#2 should take place prior to starting AVD (research procedure). PET#3 should take place at the end of AVD Cycle 2 (standard of care) . Copies of PET/CT scans should be de-identified and CD disks with DICOM files shipped within 30 days for central review as outlined in section 6.3.1.

[15] All patients will have a PET/CT 2-6 weeks after the completion of chemotherapy (or diagnostic CT's for patients with Stage I/II disease and a negative PET#3) (standard of care). This will be prior to starting consolidation treatment (when applicable) or as part of the procedures for study discontinuation. Patients receiving consolidation will also have a final PET/CT as part of study discontinuation.

[16] For patients who receive pembrolizumab consolidation, imaging is recommended every 3 months. Once a PET-CT is negative, patients may undergo CT's every three months during consolidation.

[17] Diagnostic quality CT scan of the chest/abdomen/pelvis is required within 6 weeks prior to registration. If there is involvement of the neck then a diagnostic quality CT Neck is required.

[18] Correlative studies on tissue specimens are recommended if there is adequate tissue on the baseline sample acquired for diagnosis. Patients who agree to undergo a repeat biopsy (optional: done as a research procedure) for the interim assessment will provide tissue 2-4 weeks after the first dose of pembrolizumab as specified in the lab manual, however repeat biopsy is not required.

[19] See separate lab manual for details of correlative studies (research procedures). Study labs include:

(1) sodium heparin tube for FlowCore,

(2) SST tube for Inflammatory and Immune Markers,

(3) SST tube for Soluble PD-L1

(4) SST for CCL17

Trial Period:	**Screening Phase**	**Treatment Cycles[1]**									**Off Rx**	**Surveillance**
		Pembrolizumab			PET #2	AVD[2,3]	PET #3	AVD[3,4]	Post-Chemo Assessment	Pembrolizumab[5]	Discont	Survival Follow-Up
Treatment Cycle/Title:	Main Study Screening	1	2	3		1-2		3-6[6]		4-35		
Scheduling Window (Days):	Within 28 days of registration	1 ± 3	22 ± 3	43 ± 3		64 ± 3		120 ± 3		2-4 weeks after last dose of chemotherapy ± 3	30 days after last dose (pembro or AVD, ±5 days)	Every 12 weeks

[20] Adverse events will be followed for the first 30 days after treatment discontinuation. SAE's will be recorded for 90 days after treatment discontinuation. For patients who undergo allogeneic stem cell transplant (SCT) within 24 months of last study treatment, transplant parameters and adverse events will be recorded according to section 4.6.3 (up to 18 months from the time of SCT).

[21] Echo or MUGA to be repeated after 4 cycles of doxorubicin

[22] Pregnancy test (serum or urine) is required within 7 days of registration. Pregnancy test should also be repeated C1D1 if not done within 72 hours of study treatment.

[23] CT scans to be performed at baseline and every three months during pembrolizumab consolidation after PET-CT is negative (see footnote 14)

[24] Height required at baseline but not at subsequent visits

[25] Within 6 weeks prior to registration.

6.0 RESPONSE ASSESSMENT

6.1 Measurability of lesions

6.1.1 Measurable disease

Lesions that may be accurately measured in two dimensions by CT, MRI, plain x-ray, or other conventional technique and have a greatest transverse diameter of 1 cm or greater; or palpable lesions with both diameters 2 cm or greater. Splenomegaly alone is not sufficient to qualify as measurable disease. NOTE: PET scans are insufficient for evaluation of measurable disease.

6.1.2 Non-measurable disease

All other lesions including unidimensional lesions, lesions too small to be considered measurable, pleural or pericardial effusion, ascites, bone disease, leptomeningeal disease, lymphangitis, pulmonitis, abdominal masses not confirmed or followed by CT or disease documented only by PET imaging or indirect evidence (e.g., lab values).

6.2 Lymphoma Response Criteria

NOTE: These criteria are based upon the criteria for the LUGANO 2014 Response Criteria (Appendix C). Patients who receive consolidation with pembrolizumab will also have disease assessed by the Immune Response Criteria (Appendix F) as an exploratory assessment.

The criteria use the following categories of response: Complete Response (CR), Partial Response (PR), Stable Disease (SD), Relapse and Progression (PD). In the case of stable disease, follow-up assessments must have met the SD criteria at least once after study entry at a minimum interval of six weeks.

6.3 FDG-PET/CT Guidelines

All patients should have a pre-treatment FDG-PET/CT scan as a baseline to compare with subsequent scans to assess response. This should be performed no more than 35 days (5 weeks) before registration, as is consistent with standard of care.

Investigational FDG-PET/CT (PET #2) will be performed to assess the response to the first three (3) cycles of pembrolizumab lead-in, our primary endpoint,

Subsequent FDG-PET/CT (PET #3) will be completed after the 2nd cycle of AVD.

A fourth FDG-PET/CT (PET#4) will be performed after completion of chemotherapy, prior to starting pembrolizumab consolidation (if applicable), unless patient is Stage I/II and has a negative PET#3; these patients can have a diagnostic CT scan.

Subsequent FDG-PET/CT scans are recommended every 3 months during consolidation until a patient achieves PET-negativity, then only CTs will be obtained. See Section 5-Schedule of Activities for other times of response assessments.

Only full-ring integrated FDG-PET/CT scanners are acceptable (coincidence cameras are not acceptable). The CT of the FDG- PET/CT is used for attenuation correction of PET data and anatomic localization. CT settings and patient preparation should follow institutional guidelines.

6.3.1 Central Review of PET/CT

All patients will have a retrospective central review PET/CT (PET#1, PET#2, PET#3, and PET#4) for research purposes. As scans are performed in real time, a de-identified image of the PET should be sent for reviewed at the Northwestern University by Dr. Savas

Results of central reads will not be reported in real time and will therefore not be the determinant for patient care. Findings will be communicated to participating sites retrospectively, including any discrepancies between the central research read and local radiology read.

PET/CT scans should be de-identified and put on CD disks as DICOM files to be shipped to Northwestern QAM (See address below). Disks should be shipped with a completed Imaging Shipping Form (See NOTIS for Imaging Shipping Form). At the time of shipping, QAM should be notified (croqualityassurance@northwestern.edu), and can provide any specific shipping instructions. Scans will be stored electronically at Northwestern.

Shipping address:

Clinical Trials Office – Quality Assurance
Robert H. Lurie Comprehensive Cancer Center
Northwestern University
676 N. St. Clair, Suite 1200
Chicago, IL 60611

6.1.1.1 Analysis Using Total Metabolic Volume

We will measure the total metabolic tumor volume, TMTV, to estimate the total tumor burden and correlate with outcome. We will utilize methodology recommended by the European Association of Nuclear Medicine for solid tumors and widely used for Hodgkin lymphoma. [41]

6.4 Endpoint assessment

6.4.1 Primary Endpoint

Our primary endpoint is to assess rate of complete response following pembrolizumab alone on FDG-PET (PET#2). This will be performed following three cycles of pembrolizumab on week 10. The scheduling window is day 64 +/- 3 days. Negative PET is defined as Deauville score of 1-3 as assessed by central review. Patients will be considered evaluable for this endpoint if they have received at least one dose of pembrolizumab.

6.4.2 Secondary Endpoints

Toxicity Endpoints

The frequency and severity of adverse events by type, severity (grade), timing, and attribution to pembrolizumab will be assessed once per cycle according the NCI-CTCAE version 4.03. All patients who receive at least one dose of pembrolizumab will be evaluable for toxicity endpoints.

Efficacy Endpoints

Response and progression will be evaluated using the LUGANO 2014 Response Criteria[46].

Patients treated with pembrolizumab consolidation will also have disease assessed by the updated immune response criteria[47] in addition to LUGANO response criteria as an exploratory assessment.

6.4.3 Relapsed Disease (RD)

RD includes the following:

- Lymph nodes should be considered abnormal if the long axis is more than 1.5 cm regardless of the short axis. If a lymph node has a long axis of 1.1 to 1.5 cm, it should only be considered abnormal if its short axis is

more than 1.0. Lymph nodes ≤ 1.0 x ≤ 1.0 cm will not be considered as abnormal for relapse or progressive disease;

- Appearance of any new lesion more than 1.5 cm in any axis during or at the end of therapy, even if other lesions are decreasing in size. Increased FDG uptake in a previously unaffected site should only be considered relapsed or progressive disease after confirmation with other modalities. In patients with no prior history of pulmonary lymphoma, new lung nodules identified by CT are mostly benign. Thus, a therapeutic decision should not be made solely on the basis of the PET without histologic confirmation;
- At least a 50% increase from nadir in the sum of the product of the diameter (SPD) of any previously involved nodes, or in a single involved node, or the size of other lesions (eg, splenic or hepatic nodules). To be considered progressive disease, a lymph node with a diameter of the short axis of less than 1.0 cm must increase by ≥ 50% and to a size of 1.5 x 1.5 cm or more than 1.5 cm in the long axis;
- At least a 50% increase in the longest diameter of any single previously identified node more than 1 cm in its short axis;
- Lymphoma confirmed by repeat biopsy.

6.4.4 Progression Free Survival (PFS)

PFS will be defined as the length of time from treatment on protocol until the first occurrence of disease relapse, progression, re-initiation of cytotoxic chemotherapy, or death due to disease, or until last contact if the patient did not experience any of these from the end of treatment through two years of follow up.

6.4.5 Overall Survival (OS)

OS will be defined as time from study enrollment until death, or until last contact if the patient did not die from the end of treatment through two years of follow up.

7.0 ADVERSE EVENTS

This study will be conducted in compliance with the Data Safety Monitoring Plan (DSMP) of the Robert H. Lurie Comprehensive Cancer Center of Northwestern University (please refer to Appendices for additional information). The level of risk attributed to this study requires a high level of monitoring, as outlined in the DSMP. In addition, the study will abide by all safety reporting regulations, as set forth in the Code of Federal Regulations and as required by the NCI AdEERS Reporting Guidelines.

7.1 Adverse Event Monitoring

Adverse event data collection and reporting, which are required as part of every clinical trial, are done to ensure the safety of subjects enrolled in the studies as well as those who will enroll in future studies using similar agents. Adverse events are reported in a routine manner at scheduled times during a trial (see Section 5 for timepoints). In addition, certain adverse events must be reported in an expedited manner to allow for optimal monitoring and patient safety and care.

All patients experiencing an adverse event, regardless of its relationship to study drug, will be followed until:

- the adverse event resolves or the symptoms or signs that constitute the adverse event return to baseline;
- any abnormal laboratory values have returned to baseline;
- there is a satisfactory explanation other than the study drug for the changes observed; or
- death.

7.2 Definitions & Descriptions

7.2.1 Adverse Event

An adverse event (AE) is any untoward medical occurrence in a patient receiving study treatment and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an experimental intervention, whether or not related to the intervention.

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 as prescribed in clinical practice, from overdose (whether accidental or intentional), from abuse and from withdrawal.

Progression of the cancer under study is not considered an adverse event.

All adverse events that occur after the consent form is signed but before treatment allocation/randomization must be reported by the investigator if they cause the subject to be excluded from the trial, or are the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure.

From the time of treatment allocation/randomization through 30 days following cessation of treatment, all adverse events must be reported by the investigator. Such events will be recorded at each examination on the Adverse Event eCRFs. The reporting timeframe for adverse events meeting any serious criteria is described in section 7.3. The investigator will make every attempt to follow all subjects with non-serious adverse events for outcome.

Recording of AEs should be done in a concise manner using standard, acceptable medical terms. In general, AEs are not procedures or measurements, but should reflect the reason for the procedure or the diagnosis based on the abnormal measurement. Preexisting conditions that worsen in severity or frequency during the study should also be recorded (a preexisting condition that does not worsen is not an AE). Further, a procedure or surgery is not an AE; rather, the event leading to the procedure or surgery is considered an AE.

If a specific medical diagnosis has been made, that diagnosis or syndrome should be recorded as the AE whenever possible. However, a complete description of the signs, symptoms and investigations which led to the diagnosis should be provided. For example, if clinically significant elevations of liver function tests are known to be secondary to hepatitis, "hepatitis" and not "elevated liver function tests" should be recorded. If the cause is not known, the abnormal test or finding should be recorded as an AE, using appropriate medical terminology (e/g/ thrombocytopenia, peripheral edema, QT prolongation).

7.2.2 Severity of AE's

All non-hematologic adverse events will be graded according to the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.03. The CTCAE v4.03 is available at http://ctep.cancer.gov/reporting/ctc.html

If no CTCAE grading is available, the severity of an AE is graded as follows:

- Mild (grade 1): the event causes discomfort without disruption of normal daily activities.
- Moderate (grade 2): the event causes discomfort that affects normal daily activities.
- Severe (grade 3): the event makes the patient unable to perform normal daily activities or significantly affects his/her clinical status.
- Life-threatening (grade 4): the patient was at risk of death at the time of the event.
- Fatal (grade 5): the event caused death.

7.2.3 Serious Adverse Events (SAEs)

All SAEs, regardless of attribution, occurring from time of signed informed consent, through 90 days after the last administration of study drug, must be reported upon discovery or occurrence.

An SAE is defined in regulatory terminology as any untoward medical occurrence that:

- Results in *death*.
  If death results from (progression of) the disease, the disease should be reported as event (SAE) itself.
- Is life-threatening.
  The patient was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe.
- Requires in-patient hospitalization or prolongation of existing hospitalization for ≥ 24 hours.
- Results in persistent or significant disability or incapacity.
- Is a congenital anomaly/birth defect.
- Is an important medical event.
  Any event that does not meet the above criteria, but that in the judgment of the investigator jeopardizes the patient, may be considered for reporting as a serious adverse event. The event may require medical or surgical intervention to prevent one of the outcomes listed in the definition of "Serious Adverse Event".
  For example: allergic bronchospasm requiring intensive treatment in an emergency room or at home; convulsions that may not result in hospitalization; development of drug abuse or drug dependency.

- **Note:** In addition to the above criteria, adverse events meeting either of the below criteria, although not serious per ICH definition, are reportable to the Merck in the same timeframe as SAEs to meet certain local requirements. Therefore, these events are considered serious by Merck for collection purposes.
  - Is a new cancer (that is not a condition of the study);
  - Is associated with an overdose.

7.2.4 Unanticipated Problems Involving Risks to Subject or Others

A UPIRSO is a type of SAE that includes events that meet ALL of the following criteria:

- Is *unanticipated* in terms of nature, severity, or frequency
- Places the research subject or others at a different or *greater risk of harm*
- Is deemed to be *at least possibly related* to participation in the study.

7.3 Adverse Event Reporting

7.3.1 Routine Reporting

All routine adverse events, such as those that are expected, or are unlikely or definitely not related to study participation, are to be reported on the appropriate eCRF according to the time intervals noted in the appendices. Routine Aes will be reviewed by the Data and Safety Monitoring Committee (DSMC) according to the study's phase and risk level, as outlined in the DSMP.

7.3.2 Determining if Expedited Reporting is Required

This includes all events that occur within 90 days of the last dose of protocol treatment. Any event that occurs more than 30 days after the last dose of treatment and is attributed (possibly, probably, or definitely) to the agent(s) must also be reported accordingly.

1) Identify the type of adverse event using the NCI CTCAE v 4.03.
2) Grade the adverse event using the NCI CTCAE v 4.03.
3) Determine whether the adverse event is related to the protocol therapy. Attribution categories are as follows:
   - Definite: AE is clearly related to the study treatment.
   - Probable: AE is likely related to the study treatment.
   - Possible: AE may be related to the study treatment.
   - Unlikely: AE not likely to be related to the study treatment.
   - Unrelated: AE is clearly NOT related to the study treatment.
4) Determine the prior experience of the adverse event.
   Expected events are those that have been previously identified as resulting from administration of the agent. An adverse event is considered unexpected, for expedited reporting purposes only, when either the type of event or the severity of the event is not listed in:
   - the current protocol
   - the drug package insert
   - the current Investigator's Brochure

7.3.3 Expedited Reporting to the Northwestern University QAM/DSMC

All SAEs must be reported to the assigned QAM within 24 hours of becoming aware of the event. Completion of the NU CTO SAE Form is required.

The completed form should assess whether or not the event qualifies as a UPIRSO. The report should also include:

- Protocol description and number(s)
- The patient's identification number
- A description of the event, severity, treatment, and outcome (if known)
- Supportive laboratory results and diagnostics
- The hospital discharge summary (if available/applicable)

All SAEs will be reported to, and reviewed by, the DSMC at their next meeting.

7.3.4 Expedited Reporting to the Northwestern University IRB

The following information pertains to the responsibilities of the lead site (Northwestern University). Additional participating sites should follow their local IRB guidelines for reporting to their local IRBs.

- Any death of an NU subject that is unanticipated in nature and at least possibly related to study participation will be promptly reported to the NU IRB within 24 hours of notification.
- Any death of a non-NU subject that is unanticipated and at least possibly related and any other UPIRSOs will be reported to the NU IRB within 5 working days of notification.
- All other deaths of NU subjects not previously reported, other non-NU subject deaths that were unanticipated and unrelated, and any other SAEs that were not previously reported as UPIRSOs will be reported to the NU IRB at the time of annual continuing review.

7.3.5 Reporting to the FDA

The FDA will be notified within 7 calendar days of any SAE that is associated with study treatment, is unexpected, and is fatal or life-threatening.

The FDA will be notified within 15 calendar days of any SAE that is associated with the study treatment, unexpected, and serious but *not fatal or life-threatening*. This includes any previous SAEs that were not initially deemed reportable, but are later determined to meet the criteria for reporting (i.e. by the DSMC).

All other SAEs will be reported on an annual basis as part of the annual FDA report.

7.3.6 Expedited Reporting to Merck

For the time period beginning when the consent form is signed until treatment allocation/randomization, any serious adverse event, or follow up to a serious adverse event, including death due to any cause other than progression of the cancer under study (reference Section 7.2.3.5 for additional details) that occurs to any subject must be reported within 24 hours to the NU QA and/or IRB (see section 7.3.3.1 and 7.3.3..2) and within 2 working days to Merck Global Safety if it causes the subject to be excluded from the trial, or is the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure. The NU CTO SAE form will be used.

For the time period beginning at treatment allocation/randomization through 90 days following cessation of treatment, or 30 days following cessation of treatment if the subject initiates new anticancer therapy, whichever is earlier, any serious adverse event, or follow up to a serious adverse event, including death due to any cause other than progression of the cancer under study (reference Section 7.2.3.5 for additional details whether or not related to the Merck product, must be reported within 24 hours to the S and within 2 working days to Merck Global Safety. The NU CTO SAE form will be used.

Additionally, any serious adverse event, considered by an investigator who is a qualified physician to be related to Merck product that is brought to the attention of the investigator at any time following consent through the end of the specified safety follow-up period specified in the paragraph above, or at any time outside of the time period specified in the previous paragraph also must be reported immediately to the Sponsor and to Merck Global Safety.

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

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

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.

7.4 Other Events Requiring Expedited Reporting

7.4.1 Overdose

For purposes of reporting to Merck, an overdose of pembrolizumab will be defined as any dose of 1,000 mg or greater (≥5 times the indicated dose). NOTE: the Northwestern University IRB requires reporting of any overdose according to their Reportable New Information criteria. 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 using the NU CTO SAE form within 24 hours to the PI and within 2 working days hours to Merck Global Safety. (Attn: Worldwide Product Safety; FAX 215 993-1220)

7.4.2 Reporting of Pregnancy and Lactation

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

Pregnancies and lactations that occur after the consent form is signed but before treatment allocation/randomization must be reported by the investigator if they cause the subject to be excluded from the trial, or are the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure.

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

Events). If the pregnancy continues to term, the outcome (health of infant) must also be reported.

Such events must be reported using the NU CTO SAE form within 24 hours to the Sponsor and within 2 working days to Merck Global Safety. (Attn: Worldwide Product Safety; FAX 215 993-1220)

7.4.3 Events of Clinical Interest

Selected non-serious and serious adverse events are also known as Events of Clinical Interest (ECI) and must be reported within 24 hours to the Sponsor and within 2 working days to Merck Global Safety. (Attn: Worldwide Product Safety; FAX 215 993-1220).

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

For the time period beginning at treatment allocation/randomization through 90 days following cessation of treatment, or 30 days following cessation of treatment if the subject initiates new anticancer therapy, whichever is earlier, any ECI, or follow up to an ECI, whether or not related to Merck product, must be reported within 24 hours to the Sponsor and within 24 hours to Merck Global Safety.

Events of clinical interest for this trial include:
1. an overdose of Merck product, as defined in Section 7.4.1 that is not associated with clinical symptoms or abnormal laboratory results.
2. an elevated AST or ALT lab value that is greater than or equal to 3X the upper limit of normal and an elevated total bilirubin lab value that is greater than or equal to 2X the upper limit of normal and, at the same time, an alkaline phosphatase lab value that is less than 2X the upper limit of normal, as determined by way of protocol-specified laboratory testing or unscheduled laboratory testing.*

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

7.4.4 Protocol-Specific Exceptions to Serious Adverse Event Reporting

Efficacy endpoints as outlined in this section will not be reported to Merck unless there is evidence suggesting a causal relationship between the drug and the event. Any such event will be submitted to the PI within 24 hours and to Merck Global Safety within 2 working days either by electronic or paper media.

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

The Northwestern University DSMC will monitor 50rticaria aggregated efficacy endpoint events and safety data to ensure the safety of the subjects in the trial. Any suspected endpoint which upon review is not progression of the cancer under study will be forwarded to Merck Global Safety as a SAE within 2 working days of determination that the event is not progression of the cancer under study

Hospitalization related to convenience (e.g.transportation issues etc.) will not be considered a SAE.

8.0 DRUG INFORMATION

8.1 Pembrolizumab

8.1.1 Other names:

MK-3475; Keytruda®

8.1.2 Classification – type of agent

Immunotherapy (Antineoplastic Agent, Anti-PD-1 Monoclonal Antibody)

8.1.3 Mode of action

Binding of the PD-1 ligands, PD-L1 and PD-L2, to the PD-1 receptor found on T cells, inhibits T cell proliferation and cytokine production. Upregulation of PD-1 ligands occurs in some tumors and signaling through this pathway can contribute to inhibition of active T-cell immune surveillance of tumors. Pembrolizumab is a monoclonal antibody that binds to the PD-1 receptor and blocks its interaction with PD-L1 and PD-L2, releasing PD-1 pathway-mediated inhibition of the immune response, including the anti-tumor immune response. In syngeneic mouse tumor models, blocking PD-1 activity resulted in decreased tumor growth.

8.1.4 Storage and stability

Clinical supplies must be stored in a secure, limited-access location. Store pembrolizumab vials under refrigeration at 2 to 8 degrees Celsius I or 36 to 46 degrees Fahrenheit (F). Do not freeze; do not shake. Storage following dilution: Store at room temperature for up to 4 hours (the 4 hour countdown begins when the vial is pierced, and includes room temperature storage of admixture solutions in the IV bags and the duration of infusion) or refrigerated at 2—8 degrees C (36—46 degrees F) for up to 20 hours. If refrigerated, allow the IV bags to come to room temperature prior to use. Do not freeze. 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.

8.1.5 Protocol dose specifics

Pembrolizumab 200 mg will be administered as a set dose of 200 mg IV for all cycles regardless of weight. There are no dose modifications for toxicity.

8.1.6 Preparation

Preparation for Intravenous Infusion

- Visually inspect the solution for particulate matter and discoloration prior to administration. The solution is clear to slightly opalescent, colorless to slightly yellow. Discard the vial if visible particles are observed.
- Dilute pembrolizumab injection (solution) to intravenous administration.
- Withdraw the required volume from the vial(s) of pembrolizumab and transfer into an intravenous (IV) bag containing 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP. Mix diluted solution by gentle inversion. The final concentration of the diluted solution should be between 1 mg/mL to 10 mg/mL.
- Discard any unused portion left in the vial.

8.1.7 Route of administration for this study

Administer infusion solution intravenously over 30 minutes through an intravenous line containing a sterile, non-pyrogenic, low-protein binding 0.2 micron to 5 micron in-line or add-on filter.

8.1.8 Incompatibilities

No specific incompatibilities are listed. Do not co-administer other drugs through the same infusion line.

8.1.9 Availability & Supply

Merck will supply pembrolizumab (investigational / clinical supply) directly to the NU Investigational Pharmacy at no charge to subjects participating in this clinical trial. The Merck Drug Request Form, provided by Merck and available in NOTIS, should be completed and emailed to the contacts listed on the form.

The treating 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.

8.1.10 Side effects

The following are some of the adverse events that have occurred in prior clinical trials. Please refer to the current investigator's brochure for a complete listing of all adverse events.

Most common (seen in >10% of patients):

- Fatigue
- Headache
- Chills
- Difficulty sleeping
- Dizziness
- Leg swelling
- Itching and/or rash
- Elevated blood sugar level
- High triglycerides (type of cholesterol)
- Lower levels of calcium or sodium in the blood
- Nausea and/or vomiting
- Decreased appetite
- Diarrhea or constipation
- Pain in the abdomen
- Cough
- Shortness of breath
- Fever

Less common (seen in 1 to 10% of patients):

- Skin infection
- Abnormal thyroid function (decreased or increased)
- Colitis (inflammation or infection of the colon [large intestine]
- Sepsis (infection in the bloodstream)
- Kidney failure
- Pneumonitis (inflammation of the lung) or pneumonia (infection in the lung)

Rare but serious or life-threatening (seen in <1% of patients)
Immune system attacking adrenal gland (adrenocortical insufficiency), joints (arthritis), liver (hepatitis), kidneys (nephritis), skin (dermatitis) muscles (myositis), eyes (optic neuritis or uveitis), pancreas (pancreatitis), brain (partial epilepsy), or other organs causing possibly irreversible damage to these organs

8.1.11 Nursing implications

Administer pre-treatment medications per protocol. Advise patients on the possible side effect profile. Follow infusion rate protocol with vigilant monitoring for possible infusion-related effects.

Pembrolizumab will be administered as an IV infusion ((dilution as stated above) over approximately 30 minutes Every effort should be made to target infusion timing to be as close to 30 minutes as possible. However, a window of -5 minutes and +10 minutes is permitted (i.e., infusion time is 30 minutes: -5 min/+10 min).

When an IV bag is used for the infusion, the IV line will be flushed with a volume of normal saline equal to the priming volume of the infusion set used after the contents of the IV bag are fully administered

Since the compatibility of with other IV medications and solutions, other than normal saline (0.9% [w/v] sodium chloride for injection) and D_5W , is not known, the Pembrolizumab solution should not be infused through an IV line in which other solutions or medications are being administered. The date, start time, interruption, and completion time of Pembrolizumab administration must be recorded in the source documents.

8.1.12 Return and Retention of Study Drug

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.

8.2 Doxorubicin

8.2.1 Other names.

Adriamycin, Rubex, Adriamycin RDF, Adriamycin PFS, hydroxydaunorubicin, hydroxydaunomycin, ADR.

8.2.2 Classification

Anthracycline antibiotic.

8.2.3 Mode of Action.

Intercalation between adjoining nucleotide pairs in the DNA helix causes inhibition of DNA and DNA-dependent RNA synthesis. Free radical generation is responsible for cardiac toxicity. Doxorubicin also inhibits topoisomerase II.

8.2.4 Storage and stability.

Rubex or Adriamycin RDF intact vials are stable protected from light at room temperature. Adriamycin PFS vials must be refrigerated. Reconstituted solutions are stable for 24 hours at room temperature and 48 hours under refrigeration. The Adriamycin RDF 150 mg multidose vial is stable after reconstitution for 7 days at room temperature or 15 days if refrigerated and protected from sunlight.

8.2.5 Dose specifics.

Doxorubicin will be given intravenously at a dose of 25 mg/m2 on days 1 and 15 of each AVD chemotherapy cycle. A cycle will be repeated every 28 days. Use actual weight to calculate body surface area and doses. See section 4.4 regarding dose modifications (toxicity-related).

8.2.6 Preparation.
Add 5, 10, 25, 50, or 75 ml of preservative-free normal saline to the 10, 20, 50, 100, or 150 mg vial to produce a solution containing 2 mg/ml.

8.2.7 Administration.
Intravenously as a bolus injection. Peripheral vein administration is allowed.

8.2.8 Incompatibilities.
Physically incompatible with heparin, fluorouracil, aminophylline, cephalothin, dexamethasone, diazepam, hydrocortisone, and furosemide.

Stable with vincristine in normal saline for 5 days at room temperature protected from light. Also compatible in solution with cyclophosphamide.

8.2.9 Availability.
Commercially available as powder for injection in 10, 20, 50, 100, 150 mg vials, and as 2 mg/ml solution for injection in 10, 20, 50, and 200 mg vials.

8.2.10 Side effects.
Hematologic: Leukopenia (dose-limiting), also thrombocytopenia and anemia. Nadir 10-14 days, recovery in 21 days. Dermatologic: Alopecia, usually complete; hyperpigmentation of nail beds and dermal creases; radiation recall. Gastrointestinal: Nausea and vomiting, sometimes severe; anorexia, diarrhea; mucositis, especially with daily x 3 schedule. Cardiovascular: Arrhythmias, ECG changes; rarely sudden death. Congestive heart failure due to cardiomyopathy related to total cumulative dose; risk is greater with total doses > 550 mg/m2, mediastinal irradiation pre-existing cardiac disease, advanced age; risk is reduced with weekly or continuous infusion regimens. Other: Red discoloration of urine; fever; anaphylactoid reaction; may enhance cyclophosphamide cystitis or mercaptopurine hepatotoxicity. Local effects: Vesicant if extravasated; flush along vein, facial flush.

8.2.11 Nursing/patient implications.
Monitor CBC, platelet counts. Vesica–t - do not extravasate. Refer to extravasation protocol if inadvertent infiltration occurs. Advise patient of alopecia. Instruct on how to obtain wig, hairpiece, etc. Hair loss generally occurs 2-4 weeks after injection and is usually complete. Advise patient of red discoloration of urine for 24 hours after administration of the drug. Administer antiemetics as indicated. Assess for stomatitis and treat symptomatically. Generally occurs 7-10 days after injection. Be aware “f "Ad”ia" fla–e - most common reaction consists of an erythematous streak up the vein. It is associated wi54rticarialria and pruritus. Occasionally the use of corticosteroids and/or antihistamines has been useful. Monitor for signs and symptoms of cardiomyopathy. Calculate total cumulative dose with each administration.

8.3 Vinblastine

8.3.1 Other names.
Velban, vinblastine sulfate, vincaleukoblastine, VLB, Velsar, Alkaban AQ.

8.3.2 Classification
Vinca alkaloid (tubulin inhibitor).

8.3.3 Mode of Action.
Vinblastine binds to tubulin, a protein that forms microtubules, thus interfering with spindle formation during metaphase and causing cessation of cellular mitosis.

8.3.4 Storage and stability.
Drug vials are stored in the refrigerator. Reconstituted vinblastine, 1 mg/ml, is stable for 30 days in the refrigerator. Further diluted to a concentration of 0.01 mg/ml in normal saline or 5% dextrose, vinblastine is stable for 24 and 72 hours, respectively, at room temperature.

8.3.5 Dose specifics
Patients will receive Velban intravenously at a dose of 6 mg/m$_2$ on days 1 and 15 of each AVD chemotherapy cycle. A cycle will be repeated every 28 days. Use actual weight to calculate body surface area and doses. See section 5.3.3 regarding dose modifications (toxicity-related).

8.3.6 Preparation.
The 10 mg vial is reconstituted with 10 ml of bacteriostatic normal saline, yielding a concentration of 1 mg/ml. Doses for continuous infusion may be further diluted with 50 ml or more of normal saline or 5% dextrose in water.

8.3.7 Administration.
Intravenously as a bolus injection.

8.3.8 Incompatibilities.
Furosemide, heparin; Infusaid pumps.

Compatibilities. Vinblastine is physically stable in normal saline solutions for at least 5 days, alone or mixed with doxorubicin, at 8, 25, and 32°C. Vinblastine is also compatible in solution with metoclopramide and bleomycin.

8.3.9 Availability.
Vinblastine is commercially available in 10 mg vials, as a lyophilized powder and as a 1 mg/ml solution.

8.3.10 Side effects.
Hematologic: Leukopenia, thrombocytopenia, anemia. Dermatologic: Alopecia, epilation; skin and soft tissue damage if extravasated (the manufacturer recommends subcutaneous injection of hyaluronidase and application of heat to help disperse the drug); rash, photosensitivity. Gastrointestinal: Nausea, vomiting (preventable); constipation (see neurological side effects); abdominal pain (cramps), anorexia, diarrhea, mucositis, gastrointestinal hemorrhage. Neurologic: Peripheral neuropathy (loss of deep tendon reflexes, paresthesias, paralysis); autonomic neuropathy (constipation, paralytic ileus, urinary retention, orthostasis); vocal cord paralysis; myalgias; Raynaud's phenomenon; headache, seizures, depression, dizziness, malaise; may be enhanced by concomitant use of interferon. Pulmonary; Bronchospasm (acute shortness of breath), more common when administered with mitomycin; pulmonary edema. Other: Severe pain in the jaw, pharynx, bones, back or limbs following injection; syndrome of inappropriate antidiuretic hormone (SIADH); fever; ischemic cardiotoxicity; enhanced interferon toxicity.

8.3.11 Nursing/patient implications.
Premedicate with antiemetics as needed. Administer by slow IV push. Vesica–t - do not extravasate. Refer to extravasation protocol if inadvertent infiltration occurs. Assess for neurotoxicity. Assess for constipation. Monitor CBC and platelet count.

8.4 Dacarbazine

8.4.1 Other names

DTIC, DTIC-D'me,, DIC, imidazole carboxamide, dimethyl triazeno imidazole carboxamide.

8.4.2 Classification.

Alkylating agent.

8.4.3 Mode of Action.

Activity may be the result of at least 3 mechanisms: 1) alkylation; 2) antimetabolite activity as a purine precursor; and 3) interaction with sulfhydryl (SH) groups in proteins. Dacarbazine appears to be more active in G2 phase but is not particularly cell cycle phase specific.

8.4.4 Storage and stability.

Store vials under refrigeration and protected from light. In solution, dacarbazine is stable for 96 hours if refrigerated and protected from light, 24 hours if not refrigerated but protected from light. When further diluted in 500 ml D5W or NS, it is stable for 24 hours if refrigerated, and 8 hours at room temperature and protected from light. Photodegradation: The manufacturer of dacarbazine states that the drug does not decompose when left at room temperature under normal lighting conditions for eight hours.

NOTE: A change in color of solution from pale yellow to pink is indicative of decomposition of the drug.

8.4.5 Dose specifics.

Patients will receive Dacarbazine intravenously at a dose of 375 mg/m2 on days 1 and 15 of each cycle of AVD chemotherapy. Cycles will be repeated every 28 days. Use actual weight to calculate body surface area and doses. See section 5.3.3 regarding dose modifications (toxicity- related).

8.4.6 Preparation.

Dilute the 100, 200, and 500 mg vials with 9.9, 19.7, and 49.5 ml of sterile water, respectively, resulting in a concentration of 10 mg/ml. Protect the drug from direct light. Do not freeze. Discard if solution turns pink/red. The drug can be further diluted in 50-500 ml of 5% dextrose or normal saline.

8.4.7 Administration.

Usually administered by intravenous infusion over 30 minutes or longer; has also been given IV push.

8.4.8 Incompatibilities.

Metabolism of dacarbazine may be induced by phenytoin or phenobarbital. Toxicity may be enhanced if given concomitantly with allopurinol, azathioprine, or mercaptopurine. Dacarbazine is physically incompatible with hydrocortisone sodium succinate and heparin.

8.4.9 Side effects.

Central nervous system: Infusion-site pain; Dermatologic: Alopecia Gastrointestinal: Nausea and vomiting (>90%), anorexia; Hematologic & oncologic: Bone marrow depression (onset: 5 to 7 days; nadir: 7 to 10 days; recovery: 21 to 28 days), leukopenia, thrombocytopenia <1% (Limited to important or life-threatening): Anaphylaxis, anemia, diarrhea, dysgeusia, eosinophilia, erythema, facial flushing, facial paresthesia, flu-like symptoms

(fever, myalgia, malaise), hepatic necrosis, increased liver enzymes (transient), paresthesia, renal function test abnormality, skin photosensitivity, skin rash, urticaria, venous obstruction (hepatic vein)

8.4.10 Nursing implications

Premedicate with antiemetics as agent is highly emetogenic. Infuse over 15-60 minutes. Irritant- rapid infusion may cause severe venous irritation. Assess for allergic reactions. Monitor CBC and platelet count.

8.4.11 Availability.

Commercially available in vials containing 100 mg, 200 mg, or 500 mg of lyophilized drug.

9.0 CORRELATIVES/SPECIAL STUDIES

Several correlative studies are included in the clinical trial protocol. Expression of PD-1 and PD-L1 has been identified on malignant cells and cells of the tumor microenvironment in hematologic malignancies including Hodgkin's lymphoma[48]. We will analyze the previously obtained biopsy specimens from patients' diagnostic samples (if available) to determine PD-1 and PD-L1 expression. An optional biopsy specimen will also be collected 2-4 weeks after the first dose of pembrolizumab for patients who provide consent. Expression of both PD-1 and PD-L1 has been correlated with responses following anti-PD-1 therapy. For HL, mutations at chromosome 9p24.1 led to amplification of gene expression of PD-L1 and PD-L2[31]. We will perform FISH testing to identify mutations in chromosome 9p24.1 and attempt to correlate with both PD-L1 expression as well as clinical outcomes. Prior studies using anti-PD-1 blockade have shown alterations in the T-lymphocytes subsets following therapy[43]. The correlative investigations will determine lymphocyte subset changes during treatment with pembrolizumab. Levels of serum markers associated with inflammatory and immune response will include TNF-α, IFN-γ, IL-2, IL-6, IL-7, and galectin-1. Correlation of these biomarkers will be investigated as potential measures to determine response to therapy. More recently the use of an ELISA assay for soluble PD-L1 (sPD-L1) has emerged as a potential biomarker for response to PD-1 blockade in DLBCL[49]. The role of sPD-L1 in HL is unclear and this will be part of our correlative investigations.

9.1 Diagnostic Biopsy – Specimen Procurement & Shipping

Tissue will be obtained for correlative studies from the diagnostic biopsy performed at baseline, if available. Archival tissue will be approved if appropriately preserved in paraffin embedded block, and if the specimen is deemed adequate for correlative studies by the onsite pathologist. An optional biopsy specimen will also be collected 2-4 weeks after the first dose of pembrolizumab for patients who provide consent. The biopsy samples for each patient will be obtained for PD-1 pathway marker analysis and chromosome 9p24.1 alterations. For each biopsy specimen, either 10 unstained slides (5 microns) or a paraffin-embedded block will be submitted for :

- Immunohistochemical (IHC) analysis of PD-1 and PD-L1 expression.
- A block section is also required to complete FISH analysis for alterations at chromosome 9p24.1.

See separate lab manual for details on processing and shipping.

9.2 Biopsy Specimen Analysis

Immunohistochemical stains for PD-1 and PD-L1 will be performed by the Northwestern PathCore facility with proper controls. We will also perform IHC for CD3 and CD20 for identification of tumor cells and the tumor microenvironment. Samples will be reported as "present" or "absence" of marker expression. Expression will be quantified by percentage of cells with differentiation between malignant cell expression and/or tumor microenvironment expression. We will consider >20% as "positive" for PD-1 or PD-L1 expression.

<u>FISH</u>

Fluorescence in situ hybridization (FISH) will be performed by the Northwestern pathology department on tissue sections to assess alterations of chromosome 9p24.1. Chromosomal alterations will be characterized as amplification, copy gain, polysomy, or normal copy number (disomy). The bacterial artificial chromosome probes (CHORI; www.chori.org) RP11-599H2O, which maps to 9p24.1 and includes CD274 (encoding PD-L1, labeled with Spectrum Orange), and RP11-635N21, which also maps to 9p24.1 and includes PDCD1LG2 (encoding PD-L2, labeled with Spectrum Green), will be co-hybridized. A control centromeric probe, Spectrum Aqua–labeled CEP9 (Abbott Molecular) that maps to 9p11-q11, will be used. An additional probe, Spectrum-Green-labeled RP11-6010G2, which maps upstreatm of PDCD1LG2, will be used to confirm a possible chromosomal translocation.

Double Immunohistochemistry Staining

Slides will be double stained for the presence of PD-L1 and PAX5 (24/Pax-5;BD Biosciences, San Jose, CA) as well as PD-L2 clone and pSTAT3 (D3A7; Cell Signaling, Danvers, MA). These stains will be performed with an automated staining system (Bond III; Leica Biosystems, Buffalo Grove, IL). Stained slides will be scored by an expert hematopathologist for average percentage of positive cells and intensity of staining on a scale (1-3+).

9.3 Peripheral Blood Correlatives

9.3.1 Flow Cytometry – Sample Procurement

Lymphocyte subsets will be evaluated by flow cytometry on peripheral blood obtained at specified time points through the treatment period. See separate lab manual for collection and processing details.

9.3.3 Flow Cytometry Analysis

Flow cytometry analysis will include the following surface markers: CCR7, CD3, CD4, CD8, CD14, CD16, CD20, CD25, CD45RO, CD56, CD57, CD62L, CD107a, CD127, FoxP3, B7-H1 (PD-L1), B7-DC (PD-L2), HLADR, and PD-1. The following intracellular markers will be evaluated: TIA1, granzyme, perforin. We will complete an 8-10 color flow cytometry analysis to properly group biomarkers for determination of specific lymphocyte populations. Two specific lymphocyte populations will be evaluated as the primary endpoint and include CD4+CD25+PD-L1+ T lymphocytes and CD4+CD62L+CD127+ T lymphocytes. Further groupings of marker expression will be performed to best identify activated T-cell and NK-cell populations, cytotoxic T-cells, monocyte populations, and lymphocyte populations with PD-1 or PD-L1 expression

9.3.4 Correlative Inflammatory and Immune Markers

Peripheral blood samples will be obtained at specified time points per the treatment protocol. Serum marker evaluations will include TNF-α, IFN-γ, IL-2, IL-6, IL-7, and galectin-1. See separate lab manual for collection and processing details. For each specified time point, peripheral blood sampling will require an 8.5mL SST tube. Samples will be spun, frozen and stored appropriately until testing is performed. Values will be reported with units and reference ranges based on the respective commercially available tests. All patient samples will be stored until final tissue acquisition, following by batch analysis.
Blood fractions, including serum and PBMCs will be stored for analysis
Samples will be stored until study completion

9.3.4 Thymus and Activation-Regulated Chemokine/CCL17 (TARC)

For the CCL17 ELISA (https://www.rndsystems.com/products/human-ccl17-tarc-quantikine-elisa-kit_ddn00.), peripheral blood samples will be obtained at specified time points per the treatment protocol along with the inflammatory

markers. See separate lab manual for collection and processing details.

9.3.5 Soluble PDL-1

Peripheral blood samples will be obtained at specified time points per the treatment protocol. See separate lab manual for collection and processing details.

9.4 Specimen Banking

Patient samples collected for this study will be retained at Robert H Lurie Cancer Center of Northwestern University Pathology Core Facility. Specimens will be stored indefinitely or until they are used up. If future use is denied or withdrawn by the patient, best efforts will be made to stop any additional studies and to destroy the specimens.

Dr. Jane Winter will be responsible for reviewing and approving requests for clinical specimen from potential research collaborators outside of Northwestern University. Collaborators will be required to complete an agreement (a Material Transfer Agreement or recharge agreement) that states specimens will only be released for use in disclosed research. Any data obtained from the use of clinical specimen will be the property of Northwestern University for publication and any licensing agreement will be strictly adhered to.
The following information obtained from the subject's medical record may be provided to research collaborators when specimens are made available:

- Diagnosis
- Collection time in relation to study treatment
- Clinical outcome – if available
- Demographic data

10.0 STATISTICAL CONSIDERATIONS

This is a Phase II trial to estimate the clinical response (complete response rate) following administration of pembrolizumab with AVD chemotherapy for patients with de novo Hodgkin's lymphoma. We will also describe toxicity and gather preliminary data about efficacy (EFS and OS). Biologic correlates will be studied in an exploratory fashion.

10.1 Evaluability

To be evaluable for inclusion in the analysis to address the primary objective, patients must:

- have received at least one dose of pembrolizumab
  AND
- have a FDG-PET/CT scan following cycle #3 of pembrolizumab (PET#2)

10.2 Sample Size and Accrual

This is a Phase II study in which the primary aim will be to determine the complete response rate to up front pembrolizumab. The treatment paradigm of this trial will be considered worthy of further evaluation if at least 40% of patients achieve CR at PET#2 (defined as Deauville 1-3).

The target sample size for the primary response analysis is 26 patients, with 4 additional patients to be accrued to account for dropout, so that the total target sample size is 30 patients in order to increase the CR rate to single agent pembrolizumab from the baseline level of 20% in relapsed/refractory patients, to 40% with a power of 84% at an alpha level of 10%. For the analysis of complete response by PET, a single arm single stage Bayesian design with 26 patients may also be used. Response is defined as a Deauville score of 1-3 after the initial treatment with pembrolizumab alone. The posterior probability of a response rate being greater than 50% will be calculated using a non-informative prior

distribution. With 26 patients, the following table gives this posterior probability for an observed number of responses.

Observed number of responses/26:	11	12	13	14	15
Probability that response rate > 40%:	0.61	0.75	0.86	0.92	0.96

Therefore, to be more than 80% sure that the response rate exceeds 40%, at least 13 of 26 responses would need to be observed in the total population. After PET#3, patients will be analyzed as a total population as well as by age cohort for response rate, PFS, and OS.

10.3 Data Analyses Plans

10.3.1 Analytic Plan for Primary Objective

To assess the primary objective of response rate following PET (2) performed after 3 doses of pembrolizumab, we will assess PET response using the 5 point Deauville criteria. Patients with a Deauville score of 1-3 will be considered a complete response. Patients will be evaluable for response assessment if they have received at least one dose of pembrolizumab. Response will be determined in all patients after induction (PET # 2) and after chemotherapy (PET # 3) using a proportion and an exact binomial 95% confidence interval. It will be observed whether 50% is in the confidence interval. Continuous futility monitoring will occur using the method of Lee & Liu.[50] While this method may be used to identify a futile level of response after each patient, it will begin monitoring after 10 patients. Futility will be indicated if at most 1/10, 3/15 or 5/20 evaluable patients have a response, assuming 26 total evaluable patients will be observed. For these calculations, futility means that the posterior probability that the response rate exceeds 50% is less than 10%.

10.3.2 Analytic Plan for Secondary Objectives

To assess safety and tolerability, all adverse events will be summarized in terms of type, grade, timing and attribution to treatment. All enrolled patients who receive at least one injection of study drug or undergo a study-related procedure will be included in the safety analysis. The highest toxicity grades per patient will be tabulated for AEs and laboratory measurements, and the number and percent of patients reporting AEs will be quantified. Listings will be required for all on-study deaths, SAEs and AEs that lead to withdrawal from study. Narratives for all SAEs and deaths on-study will be required. These summaries will be done by age cohort.

Continuous toxicity monitoring will occur using the method of Ivanova et al.[51] While this method may be used to identify an unacceptable level of toxicity after each patient, only values for every 5 patients will be given here. The following table gives the number of unacceptable toxicities that need to be observed after 5, 10, 15, 20, 25, 30 patients to identify an adverse toxicity rate exceeding 20% with a false positive rate (after each patient) of 2% and a desired probability of early stopping of 5%. Unacceptable toxicity is defined as any toxicity requiring discontinuation of pembrolizumab, as defined in Table 4.1.

Number of patients observed:	5	10	15	20	25	30
Number of observed toxicities:	4	6	8	9	11	12

Response assessment: Anti-tumor activity will be assessed using the LUGANO 2014 Response Criteria (Appendix C). Patients who receive consolidation with pembrolizumab will also have disease assessed by the Immune Response Criteria (Appendix F) as an exploratory assessment. To assess progression free survival

(PFS) and overall survival (OS), Kaplan Meier curves for progression and survival will be calculated for each cohort. The 3-year PFS will be determined from this curve for all patients

10.3.3 Analytic Plan for Exploratory Objectives

All enrolled patients who receive at least one injection of study drug and have a correlative sample will be included in the exploratory immune biomarker analysis. Tabulation, summarization and descriptive statistics will be performed describing the baseline and post pembrolizumab biomarkers. To assess whether PD-1 and PD-L1 and related pathway expression on paired biopsy samples prior to and following single agent pembrolizumab is related to response, the difference in biomarker expression will be calculated. A signed rank test will determine whether this change is significant and a rank sum test will determine whether the level of biomarker change before and after pembrolizumab is related to response as measured by PET#2. A similar analysis will be done for changes in serum cytokines, markers of immune/inflammatory response changes in lymphocyte subsets by flow cytometry and cysteine-cysteine thymus and activation related chemokine (TARC).

Genetic alterations in chromosome 9p24.1 (amplification, increased copy number, polysomy, and disomy) measured at baseline will be related to response using logistic regression.

11.0 STUDY MANAGEMENT

11.1 Institutional Review Board (IRB) Approval and Consent

It is expected that the IRB will have the proper representation and function in accordance with federally mandated regulations. The IRB should approve the consent form and protocol.

In obtaining and documenting informed consent, the investigator should comply with the applicable regulatory requirement(s), and should adhere to Good Clinical Practice (GCP) and to ethical principles that have their origin in the Declaration of Helsinki.

Before recruitment and enrollment onto this study, the patient will be given a full explanation of the study and will be given the opportunity to review the consent form. Each consent form must include all the relevant elements currently required by the FDA Regulations and local or state regulations. Once this essential information has been provided to the patient and the investigator is assured that the patient understands the implications of participating in the study, the patient will be asked to give consent to participate in the study by signing an IRB approved consent form.

Prior to a patient's participation in the trial, the written informed consent form should be signed and personally dated by the patient and by the person who conducted the informed consent discussion.

11.2 Amendments

The Principal Investigator will formally initiate all amendments to the protocol and/or informed consent. All amendments will be subject to the review and approval of the appropriate local, institutional, and governmental regulatory bodies, as well as by Janssen Scientific Affairs. Amendments will be distributed by the lead institution (Northwestern) to all affiliate sites upon approval by the Northwestern University IRB.

11.3 Registration Procedures

Patients may not begin protocol treatment prior to registration. All patient registrations will be registered centrally through the Clinical Trials Office at Northwestern University before enrollment to study. Please contact the assigned Quality Assurance Monitor (QAM) or email the QA Department (croqualityassurance@northwestern.edu) for questions regarding patient registration.

Prior to registration, eligibility criteria must be confirmed by the assigned QAM. The study coordinator will screen all subjects for potential registration via the web-based application NOTIS (Northwestern Oncology Trial Information System), which is available at: https://notis.nubic.northwestern.edu. Please note that a username and password is required to use this program, and will be provided during site activation prior to training on the NOTIS system.

BEFORE a patient can be treated on study, please complete and submit the following items to confirm eligibility and receive an identification number:

- Patient's signed and dated informed consent form (upload to NOTIS and keep original hard copy in a secure location/study chart)
- Eligibility checklist (signed and dated by the treating physician – upload to NOTIS)
- Eligibility eCRF (complete in NOTIS)
- Copy of the pathology report (upload to NOTIS)

Training on eCRF completion will be provided at the time of site activation. Please refer to the eCRF demonstration videos on the CTO website for additional instructions on registering a patient.

The QAM will review the registration, register the patient, assign a subject identification number, and send a confirmation of registration to study personnel. Registration will then be complete and the patient may begin study treatment.

11.4 Instructions for Participating Sites

Before the study can be initiated at any site, the following documentation must be provided to the Clinical Trials Office at Northwestern University:

- Signed and completed Letter of Invitation to participate in the study.
- Signed copy of Northwestern University's Data and Safety Monitoring Committee policy pertaining to data submission.
- Draft informed consent form should for review/approval prior to submission to the local IRB
- A copy of the official IRB approval letter for the protocol and informed consent.
- CVs and medical licensure for the local PI and any sub-investigators who will be involved in the study at the site.
- Form FDA 1572 appropriately filled out and signed with appropriate documentation.

Additional activities may be required prior to site activation (i.e. contract execution, study-specific training). Full requirements will be outlined in a memo upon receipt of the signed Letter of Invitation.

11.5 Data Management and Monitoring/Auditing

This study will be conducted in compliance with the Data Safety Monitoring Plan (DSMP) of the Robert H. Lurie Comprehensive Cancer Center of Northwestern University. The level of risk attributed to this study requires high risk monitoring as outlined in the DSMP. The assigned QAM, with oversight from the Data and Safety Monitoring Committee, will monitor this study in accordance with the study phase and risk level. Generally, for all phase II patients, data are due within 10 days of completion of every cycle.

11.6 Adherence to the Protocol

Except for an emergency situation in which proper care for the protection, safety, and well-being of the study patient requires alternative treatment, the study shall be conducted exactly as described in the approved protocol.

11.6.1 Emergency Modifications

Investigators may implement a deviation from, or a change of, the protocol to eliminate an immediate hazard(s) to trial subjects without prior IRB approval.

For any such emergency modification implemented, an IRB modification form must be completed within 5 business days of making the change, and the QAM must be notified within 24 hours of such change.

11.6.2 Other Protocol Deviations

All other deviations from the protocol must be reported to the assigned QAM using the appropriate form.

A protocol deviation is any unplanned variance from an IRB approved protocol that:

- Is generally noted or recognized after it occurs.
- Has no substantive effect on the risks to research participants.
- Has no substantive effect on the scientific integrity of the research plan or the value of the data collected.
- Did not result from willful or knowing misconduct on the part of the investigator(s).

A protocol deviation may be considered an instance of Reportable New Information (RNI) if it:

- Has harmed or increased the risk of harm to one or more research participants.
- Has damaged the scientific integrity of the data collected for the study.
- Results from willful or knowing misconduct on the part of the investigator(s).
- Demonstrates serious or continuing noncompliance with federal regulations, State laws, or University policies.

11.7 Investigator Obligations

The Principal Investigator is responsible for the conduct of the clinical trial at the site in accordance with Title 21 of the Code of Federal Regulations and/or the Declaration of Helsinki. The PI is responsible for personally overseeing the treatment of all study patients. The PI must assure that all study site personnel, including sub-investigators and other study staff members, adhere to the study protocol and all FDA/GCP/NCI regulations and guidelines regarding clinical trials both during and after study completion.

The Principal Investigator at each institution or site will be responsible for assuring that all the required data will be collected, entered onto the appropriate eCRFs, and submitted within the study-specific timeframes. Periodically, monitoring visits may be conducted and the Principal Investigator will provide access to his/her original records to permit verification of proper entry of data. The study may also be subject to routine audits by the Audit Committee, as outlined in the DSMP.

11.8 Publication Policy

All potential publications and/or data for potential publications (e.g. manuscripts, abstracts, posters, clinicaltrials.gov releases) must be approved in accordance with the policies and processes set forth in the Lurie Cancer Center DSMP. The assigned QAM will prepare a preliminary data summary (to be approved by the DSMC) no later than 3

months after the study reaches its primary completion date (the date that the final subject is examined or receives an intervention for the purposes of final data collection for the primary endpoint). If the investigator's wish to obtain DSMC-approved data prior to this point (or prior to the point dictated by study design), the PI must send a written request for data to the QAM which includes justification. If the request is approved, data will be provided no later than 4 weeks after this request approval. The data will be presented to the DSMC at their next available meeting, and a final, DSMC-approved dataset will be released along with any DSMC decisions regarding publication. The investigators are expected to use only DSMC-approved data in future publications. The investigators should submit a copy of the manuscript to the biostatistician to confirm that the DSMC-approved data are used appropriately. Once the biostatistician gives final approval, the manuscript may be submitted to external publishers.

REFERENCES

1. Roy P, Vaughan Hudson G, Vaughan Hudson B, Esteve J, Swerdlow AJ. Long-term survival in Hodgkin's disease patients. A comparison of relative survival in patients in trials and those recorded in population-based cancer registries. *Eur J Cancer.* 2000;36(3):384-389.
2. Brenner H, Gondos A, Pulte D. Ongoing improvement in long-term survival of patients with Hodgkin disease at all ages and recent catch-up of older patients. *Blood.* 2008;111(6):2977-2983.
3. Evens AM, Hong F, Gordon LI, et al. The efficacy and tolerability of adriamycin, bleomycin, vinblastine, dacarbazine and Stanford V in older Hodgkin lymphoma patients: a comprehensive analysis from the North American intergroup trial E2496. *British journal of haematology.* 2013;161(1):76-86.
4. Evens AM, Sweetenham JW, Horning SJ. Hodgkin lymphoma in older patients: an uncommon disease in need of study. *Oncology (Williston Park).* 2008;22(12):1369-1379.
5. Stark GL, Wood KM, Jack F, et al. Hodgkin's disease in the elderly: a population-based study. *British journal of haematology.* 2002;119(2):432-440.
6. Engert A, Ballova V, Haverkamp H, et al. Hodgkin's lymphoma in elderly patients: a comprehensive retrospective analysis from the German Hodgkin's Study Group. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology.* 2005;23(22):5052-5060.
7. Janssen-Heijnen ML, van Spronsen DJ, Lemmens VE, Houterman S, Verheij KD, Coebergh JW. A population-based study of severity of comorbidity among patients with non-Hodgkin's lymphoma: prognostic impact independent of International Prognostic Index. *British journal of haematology.* 2005;129(5):597-606.
8. Borchmann P, Diehl, V. & Görgen, H. Dacarbazine is an essential component of ABVD in the treatment of early favourable Hodgkin lymphoma: results of the second interim analysis of the GHSG HD13 trial [abstract]. *Haematologica 95 (Suppl 2), a1146.* 2010.
9. Radford J, Illidge T, Counsell N, et al. Results of a trial of PET-directed therapy for early-stage Hodgkin's lymphoma. *N Engl J Med.*372(17):1598-1607.
10. Campo E, Swerdlow SH, Harris NL, Pileri S, Stein H, Jaffe ES. The 2008 WHO classification of lymphoid neoplasms and beyond: evolving concepts and practical applications. *Blood.* 2011;117(19):5019-5032.
11. Engert A, Plutschow A, Eich HT, et al. Reduced treatment intensity in patients with early-stage Hodgkin's lymphoma. *The New England journal of medicine.* 2010;363(7):640-652.
12. Eich HT, Diehl V, Gorgen H, et al. Intensified chemotherapy and dose-reduced involved-field radiotherapy in patients with early unfavorable Hodgkin's lymphoma: final analysis of the German Hodgkin Study Group HD11 trial. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology.* 2010;28(27):4199-4206.
13. Meyer RM, Gospodarowicz MK, Connors JM, et al. ABVD alone versus radiation-based therapy in limited-stage Hodgkin's lymphoma. *The New England journal of medicine.* 2012;366(5):399-408.

14. Radford J, Illidge T, Counsell N, et al. Results of a trial of PET-directed therapy for early-stage Hodgkin's lymphoma. *The New England journal of medicine.* 2015;372(17):1598-1607.
15. Straus DJ, Johnson JL, LaCasce AS, et al. Doxorubicin, vinblastine, and gemcitabine (CALGB 50203) for stage I/II nonbulky Hodgkin lymphoma: pretreatment prognostic factors and interim PET. *Blood.* 2011;117(20):5314-5320.
16. Schaapveld M, Aleman BM, van Eggermond AM, et al. Second Cancer Risk Up to 40 Years after Treatment for Hodgkin's Lymphoma. *The New England journal of medicine.* 2015;373(26):2499-2511.
17. Zallio F, Tamiazzo S, Monagheddu C, et al. Reduced intensity VEPEMB regimen compared with standard ABVD in elderly Hodgkin lymphoma patients: results from a randomized trial on behalf of the Fondazione Italiana Linfomi (FIL). *British journal of haematology.* 2016.
18. Ballova V, Ruffer JU, Haverkamp H, et al. A prospectively randomized trial carried out by the German Hodgkin Study Group (GHSG) for elderly patients with advanced Hodgkin's disease comparing BEACOPP baseline and COPP-ABVD (study HD9elderly). *Annals of oncology : official journal of the European Society for Medical Oncology / ESMO.* 2005;16(1):124-131.
19. Boll B, Goergen H, Behringer K, et al. Bleomycin in older early-stage favorable Hodgkin lymphoma patients: analysis of the German Hodgkin Study Group (GHSG) HD10 and HD13 trials. *Blood.* 2016.
20. Evens AM, Helenowski I, Ramsdale E, et al. A retrospective multicenter analysis of elderly Hodgkin lymphoma: outcomes and prognostic factors in the modern era. *Blood.* 2012;119(3):692-695.
21. Mir R, Anderson J, Strauchen J, et al. Hodgkin disease in patients 60 years of age or older. Histologic and clinical features of advanced-stage disease. The Cancer and Leukemia Group B. *Cancer.* 1993;71(5):1857-1866.
22. Behringer K, Goergen H, Hitz F, et al. Omission of dacarbazine or bleomycin, or both, from the ABVD regimen in treatment of early-stage favourable Hodgkin's lymphoma (GHSG HD13): an open-label, randomised, non-inferiority trial. *Lancet.* 2015;385(9976):1418-1427.
23. Friedberg JW, Fischman A, Neuberg D, et al. FDG-PET is superior to gallium scintigraphy in staging and more sensitive in the follow-up of patients with de novo Hodgkin lymphoma: a blinded comparison. *Leukemia & lymphoma.* 2004;45(1):85-92.
24. Jerusalem G, Beguin Y, Fassotte MF, et al. Early detection of relapse by whole-body positron emission tomography in the follow-up of patients with Hodgkin's disease. *Annals of oncology : official journal of the European Society for Medical Oncology / ESMO.* 2003;14(1):123-130.
25. Jerusalem G, Beguin Y, Fassotte MF, et al. Whole-body positron emission tomography using 18F-fluorodeoxyglucose compared to standard procedures for staging patients with Hodgkin's disease. *Haematologica.* 2001;86(3):266-273.
26. Stumpe KD, Urbinelli M, Steinert HC, Glanzmann C, Buck A, von Schulthess GK. Whole-body positron emission tomography using fluorodeoxyglucose for staging of lymphoma: effectiveness and comparison with computed tomography. *Eur J Nucl Med.* 1998;25(7):721-728.

27. Gallamini A, Hutchings M, Rigacci L, et al. Early interim 2-[18F]fluoro-2-deoxy-D-glucose positron emission tomography is prognostically superior to international prognostic score in advanced-stage Hodgkin's lymphoma: a report from a joint Italian-Danish study. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology.* 2007;25(24):3746-3752.
28. Raemaekers JM, Andre MP, Federico M, et al. Omitting radiotherapy in early positron emission tomography-negative stage I/II Hodgkin lymphoma is associated with an increased risk of early relapse: Clinical results of the preplanned interim analysis of the randomized EORTC/LYSA/FIL H10 trial. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology.* 2014;32(12):1188-1194.
29. Early FDG-PET Adapted Treatment Improves the Outcome of Early FDG-PET-Positive Patients With Stages I/II Hodgkin Lymphoma (HL): Final Results of the Randomized Intergroup EORTC/LYSA/FIL H10 Trial. *Clin Adv Hematol Oncol.* 2015;13(8 Suppl 9):16-17.
30. Zinzani PL, Broccoli A, Gioia DM, et al. Interim Positron Emission Tomography Response–Adapted Therapy in Advanced-Stage Hodgkin Lymphoma: Final Results of the Phase II Part of the HD0801 Study. *Journal of Clinical Oncology.* 2016.
31. Ansell SM, Lesokhin AM, Borrello I, et al. PD-1 blockade with nivolumab in relapsed or refractory Hodgkin's lymphoma. *The New England journal of medicine.* 2015;372(4):311-319.
32. Moskowitz CH, Ribrag V, Michot J-M, et al. PD-1 Blockade with the Monoclonal Antibody Pembrolizumab (MK-3475) in Patients with Classical Hodgkin Lymphoma after Brentuximab Vedotin Failure: Preliminary Results from a Phase 1b Study (KEYNOTE-013). *Blood.* 2014;124(21):290-290.
33. Green MR, Monti S, Rodig SJ, et al. Integrative analysis reveals selective 9p24.1 amplification, increased PD-1 ligand expression, and further induction via JAK2 in nodular sclerosing Hodgkin lymphoma and primary mediastinal large B-cell lymphoma. *Blood.* 2010;116(17):3268-3277.
34. Yamamoto R, Nishikori M, Kitawaki T, et al. PD-1-PD-1 ligand interaction contributes to immunosuppressive microenvironment of Hodgkin lymphoma. *Blood.* 2008;111(6):3220-3224.
35. Chemnitz JM, Eggle D, Driesen J, et al. RNA fingerprints provide direct evidence for the inhibitory role of TGFbeta and PD-1 on CD4+ T cells in Hodgkin lymphoma. *Blood.* 2007;110(9):3226-3233.
36. Green MR, Rodig S, Juszczynski P, et al. Constitutive AP-1 activity and EBV infection induce PD-L1 in Hodgkin lymphomas and posttransplant lymphoproliferative disorders: implications for targeted therapy. *Clinical cancer research : an official journal of the American Association for Cancer Research.* 2012;18(6):1611-1618.
37. CH M. PD-1 Blockade with the Monoclonal Antibody Pembrolizumab (MK-3475) in Patients with Classical Hodgkin Lymphoma after Brentuximab Vedotin Failure: Preliminary Results from a Phase 1b Study (KEYNOTE-013). *ASH Annual Meeting Abstract 290.* 2014.
38. Keir ME, Butte MJ, Freeman GJ, Sharpe AH. PD-1 and its ligands in tolerance and immunity. *Annual review of immunology.* 2008;26:677-704.
39. Brahmer JR, Drake CG, Wollner I, et al. Phase I study of single-agent anti-programmed death-1 (MDX-1106) in refractory solid tumors: safety, clinical

activity, pharmacodynamics, and immunologic correlates. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology.* 2010;28(19):3167-3175.

40. Hsi ED. Biologic features of Hodgkin lymphoma and the development of biologic prognostic factors in Hodgkin lymphoma: tumor and microenvironment. *Leuk Lymphoma.* 2008;49(9):1668-1680.
41. Tumeh PC, Harview CL, Yearley JH, et al. PD-1 blockade induces responses by inhibiting adaptive immune resistance. *Nature.* 2014;515(7528):568-571.
42. Topalian SL, Hodi FS, Brahmer JR, et al. Safety, activity, and immune correlates of anti-PD-1 antibody in cancer. *N Engl J Med.* 2012;366(26):2443-2454.
43. Armand P, Nagler A, Weller EA, et al. Disabling immune tolerance by programmed death-1 blockade with pidilizumab after autologous hematopoietic stem-cell transplantation for diffuse large B-cell lymphoma: results of an international phase II trial. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology.* 2013;31(33):4199-4206.
44. Moskowitz AJ, Cho S, Fleisher M, et al. TARC Predicts PET-Normalization and Event Free Surival in Relapsed/Refractory Hodgkin Lymphoma Patients Treated with Brentuximab Vedotin. *Blood.* 2015;126(23):180-180.
45. Swerdlow SH, International Agency for Research on Cancer., World Health Organization. *WHO classification of tumours of haematopoietic and lymphoid tissues.* 4th ed. Lyon, France: International Agency for Research on Cancer; 2008.
46. Cheson BD, Fisher RI, Barrington SF, et al. Recommendations for Initial Evaluation, Staging, and Response Assessment of Hodgkin and Non-Hodgkin Lymphoma: The Lugano Classification. *J Clin Oncol.* 2014.
47. Cheson BD, Ansell S, Schwartz L, et al. Refinement of the Lugano Classification lymphoma response criteria in the era of immunomodulatory therapy. *Blood.* 2016;128(21):2489-2496.
48. Muenst S, Hoeller S, Dirnhofer S, Tzankov A. Increased programmed death-1+ tumor-infiltrating lymphocytes in classical Hodgkin lymphoma substantiate reduced overall survival. *Human pathology.* 2009;40(12):1715-1722.
49. Rossille D, Gressier M, Damotte D, et al. High level of soluble programmed cell death ligand 1 in blood impacts overall survival in aggressive diffuse large B-Cell lymphoma: results from a French multicenter clinical trial. *Leukemia.* 2014;28(12):2367-2375.
50. Lee JJ, Liu DD. A predictive probability design for phase II cancer clinical trials. *Clin Trials.* 2008;5(2):93-106.
51. Ivanova A, Qaqish BF, Schell MJ. Continuous toxicity monitoring in phase II trials in oncology. *Biometrics.* 2005;61(2):540-545.
52. Wolchok JD, Hoos A, O'Day S, et al. Guidelines for the evaluation of immune therapy activity in solid tumors: immune-related response criteria. *Clin Cancer Res.* 2009;15(23):7412-7420.

APPENDIX A: ECOG PERFORMANCE STATUS

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

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

APPENDIX B: COMMON TERMINOLOGY CRITERIA FOR ADVERSE EVENTS V4.03 (CTCAE)

The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 will be utilized for adverse event reporting. (https://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf)

APPENDIX C: 2007 REVISED RESPONSE CRITERIA FOR MALIGNANT LYMPHOMA

LUGANO 2014 RESPONSE CRITERIA

Lugano 2014 response criteria will be used in this study for assessment of tumor response. While either CT or MRI may be utilized, PET-CT is the preferred imaging technique in this study.

Response and Site	PET-CT–Based Response	CT-Based Response
Complete	**Complete metabolic response**	**Complete radiologic response (all of the following)**
Lymph nodes and extralymphatic sites	Score 1, 2, or 3* with or without a residual mass on 5PS† It is recognized that in Waldeyer's ring or extranodal sites with high physiologic uptake or with activation within spleen or marrow (eg, with chemotherapy or myeloid colony-stimulating factors), uptake may be greater than normal mediastinum and/or liver. In this circumstance, complete metabolic response may be inferred if uptake at sites of initial involvement is no greater than surrounding normal tissue even if the tissue has high physiologic uptake	Target nodes/nodal masses must regress to < 1.5 cm in LDi No extralymphatic sites of disease
Nonmeasured lesion	Not applicable	Absent
Organ enlargement	Not applicable	Regress to normal
New lesions	None	None
Bone marrow	No evidence of FDG-avid disease in marrow	Normal by morphology; if indeterminate, IHC negative
Partial	**Partial metabolic response**	**Partial remission (all of the following)**
Lymph nodes and extralymphatic sites	Score 4 or 5† with reduced uptake compared with baseline and residual mass(es) of any size At interim, these findings suggest responding disease At end of treatment, these findings indicate residual disease	≥50% decrease in SPD of up to 6 target measurable nodes and extranodal sites When a lesion is too small to measure on CT, assign 5 mm x 5 mm as the default value When no longer visible, 0 x 0 mm For a node > 5 mm x 5 mm, but smaller than normal, use actual measurement for calculation
Nonmeasured lesions	Not applicable	Absent/normal, regressed, but no increase
Organ enlargement	Not applicable	Spleen must have regressed by > 50% in length beyond normal

New lesions		None
Bone marrow	None Residual uptake higher than uptake in normal marrow but reduced compared with baseline (diffuse uptake compatible with reactive changes from chemotherapy allowed). If there are persistent focal changes in the marrow in the context of a nodal response, consideration should be given to further evaluation with MRI or biopsy or an interval scan	Not applicable
No response or stable disease	**No metabolic response**	**Stable disease**
Target nodes/nodal masses, extranodal lesions	Score 4 or 5 with no significant change in FDG uptake from baseline at interim or end of treatment	< 50% decrease from baseline in SPD of up to 6 dominant, measurable nodes and extranodal sites; no criteria for progressive disease are met
Nonmeasured lesions	Not applicable	No increase consistent with progression
Organ enlargement	Not applicable	No increase consistent with progression
New lesions	None	None
Bone marrow	No change from baseline	Not applicable
Progressive disease	**Progressive metabolic disease**	**Progressive disease requires at least 1 of the following**
Individual target nodes/nodal masses	Score 4 or 5 with an increase in intensity of uptake from baseline and/or	PPD progression:
Extranodal lesions	New FDG-avid foci consistent with lymphoma at interim or end-of-treatment assessment	An individual node/lesion must be abnormal with: LDi > 1.5 cm and Increase by ≥ 50% from PPD nadir and An increase in LDi or SDi from nadir 0.5 cm for lesions < 2 cm 1.0 cm for lesions > 2 cm In the setting of splenomegaly, the splenic length must increase by > 50% of the extent of its prior increase beyond baseline (eg, a 15-cm spleen must increase to > 16 cm). If no prior splenomegaly, must increase by at least 2 cm from baseline New or recurrent splenomegaly

Nonmeasured lesions	None	New or clear progression of preexisting nonmeasured lesions
New lesions	New FDG-avid foci consistent with lymphoma rather than another etiology (eg, infection, inflammation). If uncertain regarding etiology of new lesions, biopsy or interval scan may be considered	Regrowth of previously resolved lesions A new node _ 1.5 cm in any axis A new extranodal site _ 1.0 cm in any axis; if _ 1.0 cm in any axis, its presence must be unequivocal and must be attributable to lymphoma Assessable disease of any size unequivocally attributable to Lymphoma
Bone marrow	New or recurrent FDG-avid foci	New or recurrent involvement

APPENDIX D: UNFAVORABLE RISK FACTORS - NCCN GUIDELINES

Unfavorable Risk Factors for Stage I-II Classic Hodgkin Lymphoma (NCCN)

Risk Factor	NCCN
Age	
Histology	
ESR and B symptoms	≥50 or any B symptoms
Mediastinal mass	MMR > .33
# Nodal sites	>3
E lesion	
Bulky	>10 cm

MMR = Mediastinal mass ratio, maximum width of mass/maximum intrathoracic diameter

NOTE: Under NCCN criteria, lymph node regions are defined using Ann Arbor definitions listed below.

Definitions of Lymph Node Regions*

	Ann Arbor	EORTC	GHSG
R Cervical/SCL			
R ICL/Subpec			
R Axilla			
L Cervical/SCL			
L ICL/Subpec			
L Axilla			
Mediastinum			
R Hilum			
L Hilum			
Total	9	5	5

*Note that the EORTC includes the infraclavicular/subpectoral area with the axilla while the GHSG includes it with the cervical. Both EORTC and GHSG combine the mediastinum and bilateral hila as a single region.

APPENDIX E: DEAUVILLE CRITERIA

Deauville Criteria for Evaluating FDG-PET/CT Imaging

Score	Description
1	No residual uptake
2	Slight uptake, but below blood pool (mediastinum)
3	Uptake above mediastinum, but below or equal to uptake in the liver
4	Uptake slightly to moderately higher than liver
5	Markedly increased uptake or any new lesions

APPENDIX F: IMMUNE RESPONSE CRITERIA

Immune response criteria will also be assessed in all patients who receive consolidation with pembrolizumab in addition to standard assessments with Lugano response criteria.

Response designation	Definition
irCR (complete remission)	Complete disappearance of all lesions (whether measureable or not, and no new lesions), confirmed by a repeat, consecutive assessment no less than 4 weeks from the date first documented
irPR (partial remission)	Decrease in tumor burden ≥50% relative to baseline confirmed by a consecutive assessment at least 4 weeks after first documentation
irSD (stable disease)	Not meeting criteria for irCR or irPR, in absence of irPD
irPD (progressive disease)	Increase in tumor burden ≥25% relative to nadir (minimum recorded tumor burden), confirmed by a repeat, consecutive assessment no less than 4 weeks from the date first documented

Adapted from Wolchok et al. ir, immune response [52].

APPENDIX G: PROTOCOL SUMMARY OF CHANGES

Amendment 1 (Pre-IRB) – December 16, 2016 ***Approved by Scientific Review Committee: January 23, 2017***			
Section(s) Affected	***Prior Version***	***Amendment 1 Changes***	***Rationale***
Cover Page	n/a	Adds Reem Karmali as a sub-investigator	Administrative; new faculty member to be involved in study
Cover Page	IND Number/Holder listed as "TBD"	Includes IND Number (132372) and Holder (Jane Winter, MD)	Administrative; IND information is now available
Study Schema	Diagram included two arms after PET#3: Stage I/II and Stage III/IV	Diagram now includes separate treatment plans for two age cohorts (Ages <60 and ≥60), and the options for different stages (Stage I-II vs III/IV) within those,	Clarifications; new diagram is more inclusive of the two age cohorts and clearly lays out the treatment plan for each possible situation.
Study Schema; Study Summary; 4.1 (Overview); 4.2.2 (AVD); 4.6.1 (Duration of Therapy); 5.0 (Study Procedures)	Pembrolizumab consolidation was to be given for a maximum of one year	Pembrolizumab consolidation can continue for up to two years for patients ≥60 who do not achieve a CR after AVD	To align with Merck's standard regimen for pembrolizumab after discussion between Merck and study PI.
Study Summary	Included short title: "Frontline PD-1 and Hodgkin Lymphoma"	Removes short title	To align with current NU protocol template; short title is no longer required
Study Summary	Listed objectives of PFS and OS separately by age and disease stage	Lists two separate objectives for PFS and OS; one is for the overall study population, and one separates the patients by age cohort (patients <60 and ≥60 years old)	Clarification requested by Merck. It was previously unclear whether the age cohorts also included separate assessments of PFS, OS and response.
Study Summary; 3.1.6 (Inclusion Criteria)	n/a	Adds inclusion criteria "All stages and International Prognostic Score (IPS) risk groups"	Clarification to verify that all stages of lymphoma are eligible
Study Summary; 10.2 (Sample Size and Accrual)	The treatment paradigm of this trial will be considered worthy of further evaluation if at least **50%** of patients achieve CR at PET#2 (defined as Deauville 1-3). In order to have **at least a 78% chance of detection at the 10% alpha level**, and increase from the historical control of 20% rates of CR for patients with rel/ref cHL	The treatment paradigm of this trial will be considered worthy of further evaluation if at least **40%** of patients achieve CR at PET#2 (defined as Deauville 1-3). In order to have **84% power to detect an** increase from the historical control of 20% rates of CR for patients with rel/ref cHL treated with pembrolizumab, **at a one-tailed alpha of 10%,** approximately 26 evaluable patients will be required total.	Statistical clarifications for accuracy

	treated with pembrolizumab approximately 26 evaluable patients will be required total.		
2.2 (Secondary Objectives); 6.3 (FDG-PET/CT Guidelines)	References A(B)VD	Removes B, referencing AVD	Bleomycin is part of the standard chemotherapy regimen but is omitted from this study due to possible toxicities
2.3 (Exploratory Objectives)	• Peripheral blood will be tested for serum levels of TNF-α, IFN-γ, IL-2, **IL-7, IL-9, and** galectin-1. • Referenced lymphocyte subsets as the primary objective	• Peripheral blood will be tested for serum levels of TNF-α, IFN-γ, IL-2, galectin-1, **TGF-β, IL-10, IL-13, and indoleamine 2 3-dioxygenase (IDO)**. • Removes reference to primary objective	• To account for additional analysis of correlative samples. • Correction of error; lymphocytes are being analyzed as an exploratory, rather than primary, objective.
3.1.8 (Inclusion Criteria)	Definition for Females of child-bearing potential was taken from the Northwestern template	Replaces language to match section 4.5.2	Clarification to align with Merck requirements and definitions
3.2.9 (Exclusion Criteria)	"Patients who have a known history of, or any evidence of active, non-infectious pneumonitis are not eligible."	"Patients who have a history of (non-infectious) pneumonitis that required steroids or current pneumonitis are not eligible."	To align with Merck's required language for pneumonitis.
4.1 (Overview); 4.2.1 (Pembrolizumab)	Consolidation was to be given to patients ≥60 with: • Stage III/IV disease who receive **<6 cycles** of AVD • DV score of 4 or 5 on interim PET	Consolidation will take place for patients ≥60: • With stage III/IV disease who receive **≤6 cycles** of AVD • Who are not in CR at the completion of chemotherapy	Clarifications;
4.3.1 (Pembrolizumab Dose Modifications)	n/a	Adds note to pneumonitis to specify that recurrent grade 2 pneumonitis should lead to discontinuation of pembrolizumab.	Clarification requested by Merck.
4.6.2 (Duration of Follow Up); 4.6.3 (Subject Withdrawal / Discontinuation Criteria from Treatment and/or Overall Study); 5.0 (Study Procedures #7,18)	n/a	Adds additional monitoring of patients who undergo allogeneic stem cell transplant within 24 months of study treatment. Specific adverse events and transplant parameters will be collected for 18 months from the date of the transplant.	Additional safety parameters requested by Merck.

5.0 (Study Procedures #17); 9.4 (Specimen Banking)	n/a	Adds specimens for banking to correlative blood samples	Future studies may be valuable in this study population, and extra blood will be collected for this possibility.
6.2 (Lymphoma Response Criteria); 6.4.2 (Secondary Endpoints); Appendix G	n/a	"Patients who receive consolidation with pembrolizumab will also have disease assessed by the Immune Response Criteria (Appendix G)"	Additional response criteria included for exploratory response assessment for immune response
6.4.2 (Secondary Endpoints)	Patients were to be evaluated using 2007 Revised Response Criteria for Malignant Lymphoma (RRCML)	Patients will be evaluated using Lugano 2014 Response Criteria	To align with current criteria for assessing response in lymphoma
10.2 (Sample Size and Accrual)	Included a sample size of 20 patients and analysis of patients by age cohort after PET #3	Changes sample size to 30 patients and includes power calculations for the probability that response rate is > 40%. Clarifies that patients will be analyzed as a total population as well as by age cohort, and this includes PFS, OS, and response.	Clarifications requested by Merck and to be consistent with prior sections

Amendment 2 (Pre-IRB) – March 10, 2017
Approved by Scientific Review Committee: March 27, 2017

Section(s) Affected	***Prior Version***	***Amendment 2 Changes***	***Rationale***
Cover Page; Study Summary (Centers)	Included Memorial Sloan Kettering Cancer Center as affiliate site with Paul Hamlin as PI	Removes Memorial Sloan Kettering and adds Stanford Cancer Institute as affiliate site, with Ranjana Advani as the PI	Administrative, changes in affiliates
Cover Page	Included Derek Wainwright as a study collaborator	Removes Derek Wainwright as study collaborator	Administrative; the Wainwright laboratory is currently at capacity for new studies
Study Schema; Study Summary (Study Design, Treatment Plan); 4.1 (Overview); 4.2.3 (Pembrolizumab Consolidation); 4.6.1 (Duration of Therapy)	Pembrolizumab consolidation was to take place for 1 or 2 years for certain patients ≥60	Adds that pemrolizumab consolidation should take place for 1 or 2 years **total** (where total treatment = 3 cycles of induction pembro + 14 or 32 cycles of consolidation pembro)	Clarification requested by Merck; it was previously unclear whether the induction doses were to be counted among the 1 or 2 years of pembrolizumab treatment.
Study Schema; 4.1 (Overview)	Pembrolizumab consolidation was reserved for patients who did not achieve a CR during chemotherapy	Pembrolizumab consolidation will now be based on PET#3 results, and response to AVD will not be accounted for. Patients >60 who are PET(+) and those who are PET(-) and	The protocol is intended to be PET-driven. A positive early PET (#3, following two cycles of AVD) generally predicts for treatment failure. Consequently, for

		receive <6 cycles of AVD will proceed to pembrolizumab consolidation	the elderly, the results of PET #3 will determine which patients get PEM consolidation in an attempt to improve outcomes. Rather than limiting PEM consolidation to those patients who have a positive PET at the conclusion of chemotherapy (AVD), all elderly patients with a positive PET#3 will have PEM consolidation
Study Schema; 4.2.2.2.3 (Repeat Imaging (PET#4 or CT Scan)); 6.3 (FDG-PET/CT Guidelines)	An end of treatment PET-CT or CT was listed as a vague recommendation	All patients will have imaging 2-6 weeks after completing chemotherapy to establish treatment response. Imaging will be a PET-CT (PET#4), except for patients who have Stage I/II disease and a negative PET#3, who will have a diagnostic CT scan.	To be sure of disease status at the completion of chemotherapy, patients will be reimaged.
Study Schema	Patients could receive 2 years of consolidation or 2 cycles beyond PET-CR	Removes option for 2 cycles beyond PET-CR	Requested by Merck; patients should receive the full two years pembrolizumab even after achieving a CR
Study Summary (Objectives)	n/a	Re-words third secondary objective for clarity	Grammatical clarification
Study Summary (Treatment Plan)	Listed treatment options into three groups of patients (Stage I/II vs Stage III/IV vs elderly).	Separates treatment options into four groups of patients by age (younger patients Stage I/II vs Stage III/IV and elderly patients Stage I/II vs Stage III/IV) Re-words treatment plan to make it very clear which patients receive what treatment. Also rewords descriptions of treatment for clarity.	Previous language was unclear and inaccurate. New language clearly delineates which patients should receive what treatment.
2.3 (Exploratory Objectives); 9.0 (Correlative/ Special Studies)	Included serum biomarkers of immune and inflammatory response as an exploratory study	Removes serum biomarkers as an exploratory study	Dr. Wainwright's lab will no longer be able to run the analysis for this study since it is at capacity
4.0 (Treatment Plan)	Tables were numbered 1, 2, 3 etc.	Re-numbers tables 4.1, 4.2, 4.3 etc.	Clarification
4.2 (Treatment Administration)	n/a	Re-orders treatment descriptions and sections to align with the order in which they are given (Pembrolizumab Induction → Chemotherapy → AVD or escBEACOPP → Pembro Consolidation); also adds	Revised for clarity

		"Cycle numbers" to section titles	
4.2.2.1 (Cycle 1 & 2: AVD Chemotherapy post pembrolizumab induction)	States that all trial treatments will be administered on an outpatient basis.	Removes statement that all trial treatments will be administered on an outpatient basis.	Clarification; if needed, chemotherapy or pembrolizumab may be given inpatient.
	n/a	Adds specific timing for PET#3 (day 117-120 / day 26-29 of AVD cycle 2)	Clarification
	Listed specific recommendations for prophylactic antibiotics (oral thrush and PCP prophylaxis)	Removes specific recommendations and states that antibiotic use is at the discretion of the treating physician	It is clinically appropriate to leave antibiotic prophylactic at the discretion of the treating physician
4.2.2.2 (Cycle 3-6: AVD (or escBEACOPP))	Contained language for both AVD and escBEACOPP treatment in the same section	Separates treatment details by patients with a negative (4.2.2.2.1) vs positive (4.2.2.2.2) PET #3; Clarifies *total* cycles of AVD received by each set of patients	Clarification; previous language was unclear
4.2.3 (Pembrolizumab Consolidation); 5.0 (Study Procedures #14); 6.3 (FDG-PET/CT Guidelines)	Patients were to have CT's every 3 months during consolidation	Patients are recommended to have PET/CT every 3 months during consolidation, and CT's once the PET is negative	Additional imaging will be obtained every three months during consolidation to determine duration of response for those beginning consolidation with a negative PET/CT, and to identify patients who convert from PET-positive to PET-negative during consolidation.
4.2.3 (Pembrolizumab Consolidation)	Contained redundant language about patients with PET-CR vs not PET-CR.	Removes language to distinguish between PET-CR and no PET-CR	Clarification
4.3.1 (Pembrolizumab Dose Modifications)	n/a	Adds pembrolizumab dose modification guidelines for cardiac dysfunction (related to myocarditis), Stevens-Johnson Syndrome, and Toxic Epidermal Necrolysis	Additional guidelines provided by Merck as a result of new safety events
4.5.2 (Management of Cardiac Toxicities)	n/a	Adds language for managing cardiac toxicities, specifically related to myocarditis	Guidelines provided by CTEP as a result of myocarditis safety events related to nivolumab, an immunotherapy agent similar to pembrolizumab
5.0 (Study Procedures)	Pembrolizumab consolidation cycles were listed as 1-34	Re-numbers consolidation cycles as 4-35	Clarification; total pembrolizumab treatment should be up to 35 cycles *including* pembrolizumab induction (Cycles 1-3)
	#5: Pembrolizumab for 2 years in elderly patients	#5: Elderly patients may receive consolidation for a	Clarifications

	with DV score >3 on PET #3 or elderly patients with stage III/IV disease receiving < the intended 6 cycles of AVD	total of up to 1 or 2 years pembrolizumab treatment. Elderly patients who do not achieve CR after additional AVD will have pembrolizumab consolidation for up to 32 additional doses. Elderly patients with Stage III/IV disease who achieve CR after <6 cycles AVD will receive pembrolizumab consolidation for up to 14 additional doses. See section 4.2.3 for details.	
	#14: Language on PET/CT timing was vague, referring to the primary endpoint.	#14: Clarifies timing of PET#2 and PET#3. Also adds that PET/CT will be performed 2-6 weeks after the completion of chemotherapy and every 3 months until PET-negative.	Clarifications
IRB Comments – June 29th, 2017 *Approved by Scientific Review Committee: July 3, 2017*			
Section(s) Affected	***Prior Version***	***Changes***	***Rationale***
5.0 (Study Procedures, #14, 16, 17)	n/a	Adds designations for "Research" vs "Standard of Care" procedures (PET/CT's, correlative tissue and correlative blood)	Clarification requested by the IRB
Amendment 3 – June 29th, 2017 *Approved by Scientific Review Committee: July 3, 2017*			
Section(s) Affected	***Prior Version***	***Amendment 3 Changes***	***Rationale***
5.0 (Study Procedures, #17)	Listed blood volumes for correlatives and "specimens for banking" as a separate blood draw	Removes blood volumes, adds "SST for CCL17", purpose of each SST tube (Inflammatory and Immune Markers, Soluble PD-L1) and removes "Specimens for banking"	Details for correlatives will be kept in the study lab manual and not the protocol to avoid unnecessary protocol deviations and amendments. Also corrects discrepancies.
6.2 (Lymphoma Response Criteria); 9.3.5 (Soluble PD-L1); Appendix F; Appendix G	Included Appendix F with details on processing the DuoSet ELISA assay for soluble PD-L1	Removes Appendix F, any references to Appendix F and renumbers subsequent appendices	Details for correlatives, including processing details, will be kept in the study lab manual
9.2 (Biopsy Specimen Analysis)	FISH was to be performed at the Northwestern PathCore facility	FISH will be performed in the Northwestern pathology department	To correct discrepancy; PathCore facility no longer performs FISH analysis
9.3 (Peripheral Blood Correlatives)	Section included specific language on sample collection, processing, and storage.	Removes all details on sample collection, processing, and storage.	Details for correlatives, including collection, processing, and storage, will be kept in the study lab manual
Amendment 4 – March 8th, 2018			

Approved by Scientific Review Committee: May 2, 2018			
Section(s) Affected	***Prior Version***	***Amendment 4 Changes***	***Rationale***
Cover Page	Listed Pamela Allen and Jason Kaplan as Northwestern sub-I's	Removes Jason Kaplan and adds Pamela Allen as the sub-I at Emory University	Administrative faculty changes
Cover Page; Study Summary; 3.0 (Patient Eligibility)	Affiliate sites were Tufts and Stanford	Removes Tufts, adds Rutgers Cancer Institute and Emory University	Andrew Evens transferred from Tufts to Rutgers and remains sub-I. Pam Allen transferred from Northwestern to Emory and remains sub-I
Study Schema	n/a	Clarifies that patients who receive escBEACOPP will be in follow-up at that stage Adds cycle duration throughout Adds follow-up after pembrolizumab consolidation Clarifies that consolidation is for 1 year total	Clarifications
Study Schema; Study Summary 4.1 (Overview); 4.2.2.2 (Cycle 3-6 AVD)	Patients with Stage I/II disease and a negative PET #3 were to receive 2 cycles of AVD	Adds an exception; patients with bulky disease at baseline may receive 4-6 cycles of AVD per physician discretion	Patients with bulky disease may require additional treatment. The PI feels it is clinically appropriate to allow for additional treatment as needed.
Study Summary; 2.2 (Secondary Objectives); 10.3.2 (Analytic Plan for Secondary Objective)	Included an objective to look specifically at PFS and OS by age (Cohort 1: < 60 years old; Cohort 2: ≥ 60 years old)	Removes analysis of separate cohorts. PFS and OS will be analyzed in the study population as a whole.	To avoid enrollment barriers, patient accrual goals are no longer evenly stratified by age groups
Study Summary; 3.1.6, 3.1.7 (Inclusion Criteria)	Allowed for all stages and International Prognostic Score (IPS) risk groups	Specifies that Stage III and IV disease may have any IPS, but Stage I and II must have at least one NCCN unfavorable risk factor	Clarification of allowable disease stages using updated NCCN guidelines
3.2.1 (Exclusion Criteria)	Patients were not eligible who had received prior therapy within 2 weeks prior to registration or who have not recovered from adverse events.	Patients are not eligible who have had any prior therapy. Removes window.	To address discrepancy; study aims to treat patients with no prior treatment as a frontline therapy.
3.2.5 (Exclusion Criteria)	Patients with congestive heart failure, unstable angina pectoris or cardiac arrhythmia were not eligible.	Adds that ejection fraction must be above institutional lower limit of normal.	Clinical clarification
4.2.2.2 (Cycle 3-6: AVD or escBEACOPP)	Referred to positive PET #3 as DV score 1,2, or 3	Changes to state that DV score 4 or 5 is considered positive for PET#3	To fix typographical error

4.3.1 (Pembrolizumab Dose Modifications)	Contained a table for pembrolizumab dose delays that was provided by Merck	Replaces table for pembrolizumab dose delays.	Response to action letter from Merck due to updated safety information.
4.4.2 (Prohibited Concomitant Medications)	The use of corticosteroids may be approved after consultation with the Sponsor	Changes Sponsor to PI	The PI should be consulted for such issues since this is an investigator-initiated study, and NU is the sponsor
4.3 (Toxicity Management & Dose Delay); 4.6.4 (Patient Replacement); 7.3 (Adverse Event Reporting); 11.8 (Publication Policy)	Referred to Data Monitoring Committee (DSMC)	Updates to Data and Safety Monitoring Committee (DSMC)	To align with internal policies
5.0 (Study Procedures); Appendix D	Patients' NCCN IPI score was to be collected at baseline	Updates to "Unfavorable risk factors" referencing Appendix D	To align with current practice for evaluating disease factors
5.0 (Study Procedures)	Off treatment visit was to take place 30 days after last dose	Adds clarification that this can be 30 days after pembrolizumab or AVD	Clarification
	n/a	Adds Quantiferon-gold TB blood test at baseline	Patients with active TB are excluded from the study; adds screening requirement for consistency
	#3: Physical exam was required on Day 1 and 15 of each cycle of AVD	#3: Removes Day 15 requirement	Does not follow standard practice and is not clinically necessary
	#14 & 15: Diagnostic CT and PET/CT were required within 5 weeks prior to patient registration	#14 & 15: Extends window to 6 weeks	Broadens scan allowance to benefit patients with recent scans; this is clinically appropriate and allowable per PI.
5.0 (Study Procedures #16); 9.0 (Correlative / Special Studies)	#16: Tissue collection was listed at AVD Cycle 1-2 and not listed in 9.0	#16: Moves tissue collection to pembrolizumab monotherapy with footnote to state that it will be collected 2-4 weeks after first dose of pembrolizumab (optional). Adds optional sample to section 9.0	Revised for clarity and to ensure tissue is collected
6.2 (Lymphoma Response Criteria); 6.4.2 (Secondary Endpoints);	Patients who receive consolidation treatment will be evaluated using Immune Response Criteria	Clarifies that Immune Response Criteria is only being used as an exploratory assessment	Clarification
7.2.2 (Severity of AE's); 7.3.2 (Determining if Expedited Reporting is	Referenced CTCAE version 4.0	Updates to CTCAE version 4.03	Administrative update

Required); Appendix B			
8.1.4 (Storage and Stability)	Storage was allowed for 6 hours at room temperature and 24 hours refrigerated.	Updates storage allowance to 4 hours at room temperature and 20 hours refrigerated.	Updated to align with most current pharmacy manual.
8.1.6 (Preparation)	Contained instructions for pembrolizumab as both a lyophilized powder and a solution	Removes references to lyophilized powder	Pembrolizumab is being supplied as a solution
8.1.9 (Availability & Supply)	Listed Sloan Stribling and Tammy Moll as drug ordering contacts	Removes contacts and instead refers to the drug order form where contacts are listed.	Contacts were out of date, and reference to drug order form avoids the need for unnecessary amendment in the case of staff changes
10.3 (Data Analyses Plan)	Analytic plans were inconsistent for primary and secondary endpoints.	• Updates analytic plans to match intended primary and secondary endpoints. • Adds further detail on evaluability and analysis methods • Adds futility monitoring after 10 patients and an interim safety analysis after 12 patients	Requests resulting from Emory University internal review

Amendment 5 – October 15th, 2018

Section(s) Affected	***Prior Version***	***Amendment 5 Changes***	***Rationale***
Cover Page; 7.3 (Adverse Event Reporting); 7.4 (Other Events Requiring Reporting); 11.3 (Registration Procedures)	Referred to Northwestern University's Clinical Research Office (CRO)	Updates references to Clinical Trials Office (CTO)	Administrative update
Cover Page	Contained outdated hyperlink for the Cancer Center (www.cancertrials.northwestern.edu)	Updates hyperlink to the following: www.cancer.norhtwestern.edu /research/clinical-trials-office/index.html	Administrative update
3.0 (Patient Eligibility)	Contained statement about accrual rates (approximating 4 patients accrued per month)	Removes accrual rate information	Language was not lining up with actual accrual rate and is not required
4.4.2 (Prohibited Concomitant Medications)	Dexamethasone was a required pre-medication for AVD but glucocorticoids were prohibited. Glucocorticoids were prohibited "within 1 week of treatment'	Adds clarifying language that dexamethasone is a permitted glucocorticoid when used as a pre-medication for AVD. Also clarifies that glucocorticoids are not permitted within 1 week of treatment and throughout treatment	Clarification to address discrepancy

5.0 (Study Procedures)	Timing of PET/CT's was unclear: • "PET/CT within 6 weeks **of** registration" • PET#2 and PET#3 were listed within the columns for AVD treatment, when footnote 14 stated that they would take place before and after AVD • PET/CT was not marked at the "Discontinuation" visit, making it unclear whether patients not undergoing consolidation needed a final PET/CT	Clarifies PET/CT timing: • "PET/CT within 6 weeks **prior to** registration" • Adds separate columns clearly indicating PET#2 and PET#3 before and after AVD with specific timing listed in footnote 14 • Adds a column for "Post-Chemo Assessment", an X for PET/CT at "Discontinuation" and a clarifying footnote to state that all patients will have this scan and that it may fall before consolidation or as part of the procedures for discontinuation	Clarifications for study team. • Avoids ambiguous language • PET#2 and PET#3 are more clearly indicated to avoid being missed by the study team • The final PET/CT is more clearly indicated to avoid being missed by the study team.
	n/a	Updates footnote numbering	To account for additional footnote clarifying PET/CT timing
Appendix D	Included multiple categories for unfavorable risk factors and did not specify how to count nodal sites	Lists only NCCN unfavorable risk factors and adds a chart for definition of lymph node regions, using Ann Arbor	Clarifications; we will only use NCCN unfavorable risk factors and Ann Arbor is the designated definition of lymph node regions under NCCN
Amendment 6 – March 29th, 2019			
Section(s) Affected	***Prior Version***	***Amendment 6 Changes***	***Rationale***
Cover Page	n/a	Adds Hatice Savas as a collaborator from Northwestern radiology	Central review information of PET/CT's have been added to the study, which will be performed by Dr. Savas
Cover Page	Fred Rademaker listed as Biostatistician	Removes Fred Rademaker and adds Denise Scholtens	Change in biostatistician for the study
4.1 (Overview); 5.0 (Study Procedures #14); 6.3.1 (Central	n/a	Adds a central review information of PET imaging for the study	To provide an unbiased research analysis of PET results

Review of PET/CT)			
11.7.2 (Other Protocol Deviations	"Promptly reportable non-compliance"	Changed to "Reportable new information"	Semantic administrative update