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Phase II Trial of Pembrolizumab in Combination with ICE Salvage Chemotherapy for Relapsed/Refractory Hodgkin Lymphoma

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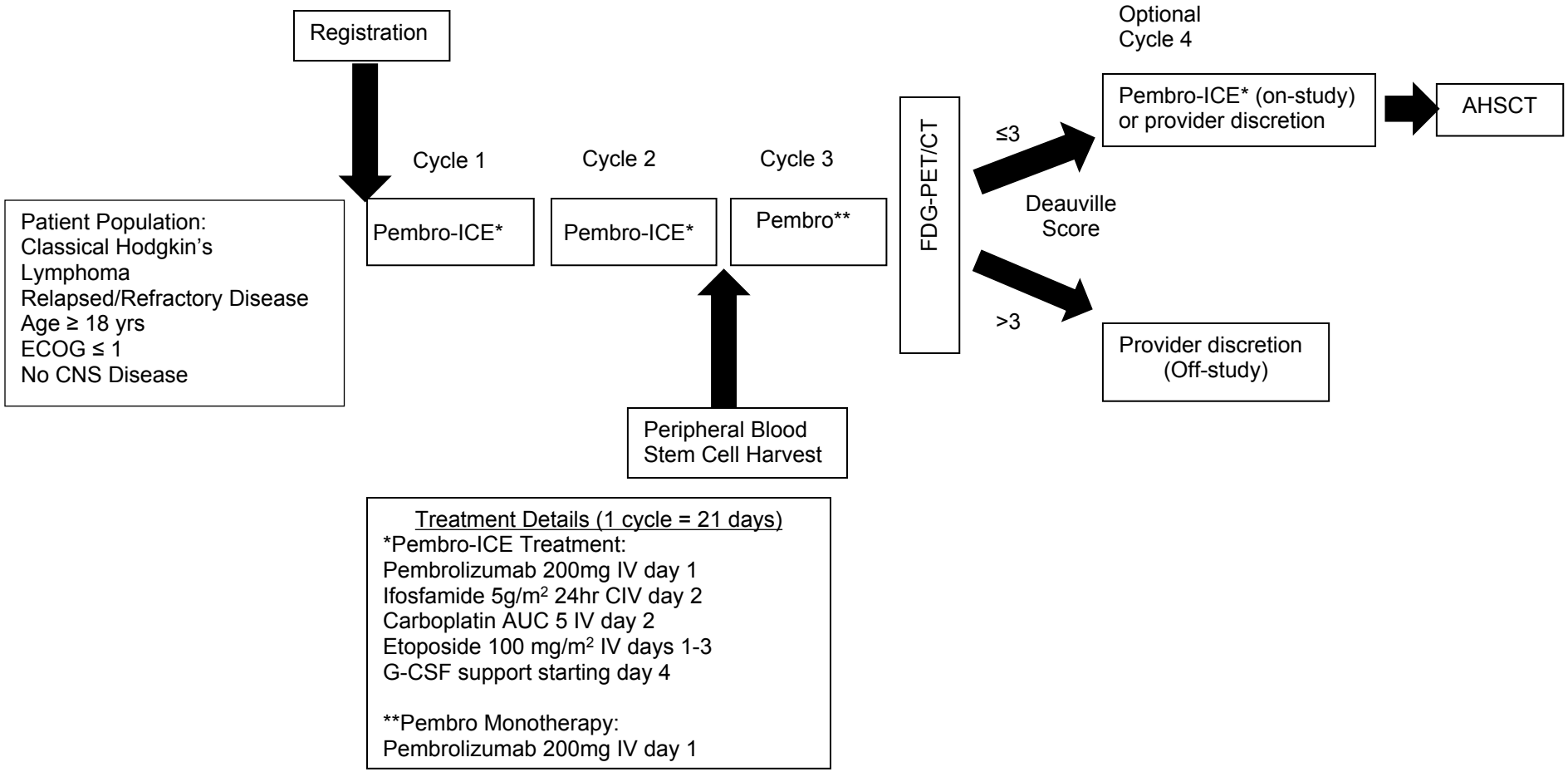
LIST OF ABBREVIATIONS

ABVD	Adriamycin, Bleomycin, Vinblastine, Dacarbazine
ADC	Antibody-Drug Conjugate
AE	Adverse Event
AHSCT	Autologous Hematopoietic Stem Cell Transplant
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
AUC	Area Under the Curve
BEACOPP	Bleomycin, Etoposide, Adriamycin, Cyclophosphamide, Oncovin, Procarbazine, Prednisone
BUN	Blood Urea Nitrogen
CBC	Complete Blood Count
CIV	Continuous IV Infusion
CMP	Comprehensive Metabolic Panel
CNS	Central Nervous System
CR	Complete Response
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Events
DLBCL	Diffuse Large B-cell Lymphoma
DLCO	Diffusing Capacity of the Lungs for Carbon Monoxide
DLT	Dose Limiting Toxicity
DSMC	Data and Safety Monitoring Committee
ECOG	Eastern Cooperative Oncology Group
EFS	Event Free Survival
FDG	Fluorodeoxyglucose
FISH	Fluorescence In Situ Hybridization
FOCBP	Female of Child Bearing Potential
G-CSF	Granulocyte Colony Stimulating Factor
H&P	History & Physical Exam
HL	Hodgkin’s Lymphoma

ICE	Ifosfamide, Carboplatin, Etoposide Chemotherapy
IPS	International Prognostic Score
IV (or iv)	Intravenously
MDS	Myelodysplastic Syndrome
MTD	Maximum Tolerated Dose
MUGA	Multigated Acquisition Scan
NCI	National Cancer Institute
NOTIS	Northwestern Oncology Trial System
ORR	Overall Response Rate
OS	Overall Survival
PCM	Plasma Cell Myeloma
PD-1	Programmed death-1
PET/CT	Positron Emission Tomography–Computed Tomography
PD	Progressive Disease
PD-1	Programmed Death-1
PFS	Progression Free Survival
PFT's	Pulmonary Function Tests
PO (or p.o.)	Per os/by mouth/orally
PR	Partial Response
QA	Quality Assurance
RR-HL	Relapsed/Refractory Hodgkin's Lymphoma
SAE	Serious Adverse Event
SD	Stable Disease
SGOT	Serum Glutamic Oxaloacetic Transaminase
SPGT	Serum Glutamic Pyruvic Transaminase
WBC	White Blood Cells
WHO	World Health Organization

STUDY SCHEMA



STUDY SUMMARY

Title	Phase II Trial of Pembrolizumab in Combination with ICE Salvage Chemotherapy for Relapsed/Refractory Hodgkin Lymphoma
Version	02/21/2022 (Amendment 9)
Study Design	A single-stage Phase II, prospective, open-label, single-arm, multi-centered clinical trial.
Study Center(s)	Northwestern University, Chicago, IL Augusta University, Augusta, GA Loyola University, Maywood, IL University of Rochester, Rochester, NY Emory University, Atlanta, GA
Concept and Rationale	Therapy for advanced stage Hodgkin's lymphoma (HL) continues to improve however up to 10% of patients have refractory disease never achieving a complete remission. Another 20-30% of advanced stage HL patients will ultimately relapse after initial treatment. In the event of relapsed or refractory HL (RR-HL), patients are treated with salvage chemotherapy. While salvage chemotherapy has demonstrated good overall response rates, the risk of relapse remains high and AHSCT remains the standard of care for transplant eligible patients. Programmed death-1 (PD-1) is a member of the B7 receptor family that plays an important role in the regulation of the immune response. The PD-1 receptor in conjunction with receptor ligands, PD-LI and PD-L2, functions to regulate the immune response primarily by down regulating T-cell receptor signaling. Suppression of the immune response by the PD-1 pathway functions as a mechanism for malignant cells to escape immune surveillance. A broad spectrum of malignancies including Hodgkin's lymphoma mitigate anti-tumor immune response through the PD-1 pathway. Pembrolizumab is a humanized IgG-4 kappa isotype monoclonal antibody currently FDA approved in unresectable or metastatic melanoma. The target for pembrolizumab is PD-1 receptor on human T-cells. Hodgkin’s lymphoma have been demonstrated to carry a recurrent genetic abnormality in chromosome 9p24.1. The amplification of chromosome 9p24.1 results in overexpression of the PD-1 ligands, PD-L1 and PD-L2. Twenty-three patients with HL enrolled on the Keynote-013 trial were treated with pembrolizumab resulting in responses including 22% CR and 43% PR for a 65% ORR. Important clinical responses with nivolumab, a different anti-PD-1 antibody, were demonstrated in RR-HL following AHSCT. The study included 23 patients with an overall response rate of 87% including 17% complete responses and 70% with partial responses. Anti-PD-1 therapy for HL has thus emerged as a promising option. We propose using the combination of pembrolizumab with ICE salvage chemotherapy for relapsed/refractory HL. We hypothesize that the addition of PD-1 blockade to standard ICE chemotherapy will enhance the efficacy of treatment for RR-HL. We expect an improvement in the CR rate as defined by a negative FDG-

	PET/CT, a measure that is correlated with improvement in both EFS and OS. The protocol will also evaluate the toxicity and tolerability of combining pembrolizumab with high-dose chemotherapy. We feel this therapy represents an important step in improving management of this aggressive lymphoma and will ultimately be incorporated into future treatment algorithms.
Objectives	Primary Objective: • To determine the CR rate by FDG-PET/CT prior to AHSCT with the combination of pembrolizumab and ICE salvage chemotherapy for relapsed/refractory Hodgkin lymphoma Secondary Objectives: • To determine the safety and tolerability of pembrolizumab in combination with salvage high-dose chemotherapy • To estimate the event free survival (EFS) at 2 years • To estimate the overall survival (OS) at 2 years Exploratory Objectives: • To characterize PD-1 pathway specific expression and correlate with response • To characterize T-lymphocyte subset changes to treatment with pembrolizumab • To investigate the prevalence and clinical correlation of chromosome 9p24.1 mutations for this population • To evaluate the effect on stem cell harvest following treatment with pembrolizumab
Sample Size	Up to 43 patients for 37 evaluable
Diagnosis & Key Eligibility Criteria	Inclusion criteria include: • Relapsed/refractory classical Hodgkin lymphoma; • Previously completed at least one line of chemotherapy for their Hodgkin lymphoma (but ≤ 2 lines); • Measurable FDG-PET/CT avid disease; • Age ≥ 18 yrs; • Performance status ECOG 0 or 1. Exclusion criteria include: • Known CNS involvement; • Known HIV, HBV, HCV infection; • Prior exposure to anti-PD-1 or anti-PD-L1 agents; • Prior autologous or allogeneic stem cell transplant; • Concurrent immunosuppressive therapy.
Treatment Plan	Patients with relapsed/refractory classical Hodgkin lymphoma following standard up-front chemotherapy will be eligible for participation. Patients with FDG-PET/CT avid disease will be treated with combination pembrolizumab and ICE (ifosphamide, carboplatin, etoposide)* salvage chemotherapy for 2 cycles (1 cycle = 21 days). On cycle 3 day 1, patients will receive pembrolizumab monotherapy. A FDG-PET/CT will be obtained 14-22 days after pembrolizumab monotherapy to assess response by Deauville criteria. Patients with Deauville ≤3 will proceed to AHSCT which may include a fourth optional cycle of Pembro-ICE

	prior to transplant per investigator discretion. Patients with Deauville >3 will be treated per provider's discretion which may also include stem cell transplant. *Pembrolizumab 200 mg IV will be administered on day 1. Standard ICE salvage chemotherapy includes ifosfamide 5 g/m2 with equivalent dose of MESNA given over 24 hours by CIV on day 2, carboplatin AUC 5 IV with a maximum of 800 mg on day 2, and etoposide 100 mg/m^2/day IV on days 1 to 3. G-CSF support will be administered 24 hours following completion of chemotherapy.
Statistical Methodology	The standard response rate is assumed to be 0.5 (under the null hypothesis) by historical controls; and the new therapy is considered worthy of further research if we can reject the null hypothesis in favor of the alternative hypothesis, where the response rate is 0.7. The consequent decision rule provides the sample size (n=37) and minimum number of responders (r) as ≥24 thus warranting further investigation of the new therapy, such that statistical significance is achieved. If r<24, then this is the maximum number of responders for which statistical significance is not achieved. This design yields a type I error rate of 0.05 and power of 0.80 when the true response rate is 0.70. For our secondary objectives, we will tabulate the number and percentage of toxicities by type, grade, severity, and attribution. We will generate Kaplan-Meier curves of EFS and OS including lifetables of point estimates and associated standard errors, which would include the presentation of the 2-year estimate.

4.2 INTRODUCTION - BACKGROUND & RATIONALE

1.1 Disease Background

Hodgkin's lymphoma (HL) is a neoplasm of lymphoid tissue defined by the presence of malignant Hodgkin Reed-Sternberg cells in a background of inflammatory cells[1]. Approximately 9050 new cases of HL are diagnosed in the United States annually and 1,150 people will die of their disease[2]. Advanced stage HL, defined as Ann Arbor stage III or IV disease, is characterized by widespread involvement and is associated with diminished survival. From the International Hodgkin Lymphoma Database, the median overall survival (OS) is approximately 18 years for stage III patients and only 9 years for stage IV patients. The median age of diagnosis is only 38 thus these projected rates of OS are unacceptable.

Prognosis is predicted using the international prognostic score (IPS) developed for advanced stage HL[3]. The treatment goal remains curative therapy often using a combination of chemotherapy and radiation. Patients with advanced stage HL are treated with combination chemotherapy that includes an anthracycline and an alkylating agent. ABVD has been defined as the most preferred front-line regimen with alternative regimens including BEACOPP and Standford V[4].

1.2 Treatment of Relapsed/Refractory Hodgkin's Lymphoma

Therapy for advance stage HL continues to improve however up to 10% of patients have refractory disease never achieving a complete remission. Another 20-30% of advanced stage HL patients will ultimately relapse after initial treatment[5]. In the event of relapsed or refractory HL (RR-HL), patients are treated with salvage chemotherapy. While salvage chemotherapy has demonstrated high overall response rates, the risk of relapse remains high and AHSCT remains the standard of care for transplant eligible patients[6,7].

There are multiple salvage chemotherapy regimens supported by Phase II clinical trials however no direct comparison exists to provide a census recommendation on the best therapy[8]. The goal of salvage chemotherapy remains a balance of high response rates with acceptable toxicity profiles and uncompromised stem cell mobilization at the time of harvest. Likewise, the optimal number of cycles of salvage chemotherapy is poorly defined but most institutions give 2-3 cycles with disease assessment following cycle 2 at the time of stem cell harvest.

A commonly utilized salvage regimen is ICE which includes a combination of ifosfamide, carboplatin, and etoposide. The previously reported overall response rate (ORR) is 85% and includes a 26% complete response rate (CR) when response was assessed by CT imaging[9]. Similarly, two sequential prospective trials reported 23% complete response with ICE chemotherapy[10]. Although the regimen has anticipated side effects, ICE is well tolerated in comparison to other salvage options. ICE chemotherapy is administered as 14 or 21 day cycles. The addition of G-CSF support has made the 14 day cycle feasible without worsening the rate of hematologic adverse events.

Brentuximab vendotin (SGN-35) is a promising antibody-drug conjugate (ADC) that selectively delivers a toxic agent to CD30-expressing cells. Several clinical

trials have now demonstrated efficacy and safety in heavily pre-treated patients with RR-HL patients. An international, open-label, Phase II study evaluated brentuximab in RR-HL patients following AHSCT with ORR of 75% including CR of 34%[11,12]. These results and emerging data from ongoing clinical trials may support the use of brentuximab vendotin in RR-HL patients preceding AHSCT.

1.3 Role of FDG-PET/CT in Hodgkin's Lymphoma

Functional imaging by FDG-PET/CT has increasingly become a tool for response assessment prior to AHSCT. Disease response is measured by Deauville criteria, a defined radiographic guideline for interpreting functional imaging. Utilization of functional imaging with FDG-PET/CT defines complete response by Deauville criteria ≤3[13,14]. Updated guidelines for management of HL have recently incorporated the use of Deauville criteria for disease assessment by FDG-PET/CT[15].

A positive FDG-PET/CT following salvage chemotherapy entering AHSCT is predictive of poorer outcomes. The 3-year OS is reduced to 58% from 87% in those with a positive FDG-PET/CT[16]. In a series here at Northwestern, the complete responses by FDG-PET/CT correlated with improved outcomes following AHSCT including a 5-year PFS and OS of 85% and 100%, respectively[17]. Similarly a smaller series reported the 2 year PFS of 10% for pre-AHSCT FDG-PET/CT positive disease compared to 93% for FDG-PET/CT negative disease[18]. The use of ICE as a salvage regimen prior to AHSCT has demonstrated a 5-year event free survival (EFS) of 31% if the pre-AHSCT FDG-PET/CT is negative compared to 75% if the pre-AHSCT FDG-PET/CT is positive[19].

The use of functional imaging to evaluate the response to ICE chemotherapy has been defined in several series. Moskowitz, et al reported a complete response rate at 60% in 97 patients treated with ICE/augmentedICE[20]. The enrolled patients were younger with good performance status and lower risk disease. We reported a 50% complete response rate by FDG-PET/CT with salvage chemotherapy in a retrospective analysis of 51 patients at our institution[17]. This patient population was more representative of a typical clinical practice including patients with higher risk disease.

1.4 The PD-1 Pathway

Programmed death-1 (PD-1) is a member of the B7 receptor family that plays an important role in the regulation of the immune response. The PD-1 receptor is a 288 amino acid type I transmembrane protein that is part of the immunoglobulin superfamily[21,22]. The PD-1 receptor in conjunction with receptor ligands, PD-LI and PD-L2, functions to regulate the immune response primarily by down regulating T-cell receptor signaling processes called immune checkpoints. Immune checkpoints are key elements in the physiologic process that limits autoimmunity in the normal host but that also limits immune surveillance in cancer, allowing tumor escape.

The interaction of PD-1 and the receptor ligands induce processes resulting in apoptosis of activated T lymphocytes[23-26]. PD-1 is expressed on progenitor T-cells, activated T and B lymphocytes, natural killer cells, and myeloid cells. While PD-1 has broad expression across multiple immune cell types, the primary

function of PD-1 is on effector/memory T lymphocytes resulting in regulation of T-cell activation and apoptotic pathways[22,27]. The end result of the PD-1 pathway is a regulatory role in peripheral tolerance[28].

Co-optation of the PD-1 pathway by malignant cells was first described in the early 2000s, leading to investigations into PD-1 blockade as a possible mechanism for cancer therapy[29,30]. The pathway has been demonstrated in a broad spectrum of solid malignancies including breast, colon, esophageal, lung, pancreatic, renal cell, and skin cancers. Furthermore, hematologic malignancies including lymphomas and leukemia have adopted the PD-1 pathway to mitigate anti-tumor immune response. The aberrant expression of PD-L1 has been demonstrated on tumor-infiltrating lymphocytes of lymphomas[31]. The result of stimulation through the PD-1 pathway is T-cell exhaustion thus inhibition of the anti-tumor response. Blockade of the PD-1 pathway through the use of PD-1 or PD-1 ligand (PD-L1) antibodies releases this brake on the immune response.

Hodgkin's lymphoma has been demonstrated to carry a recurrent genetic abnormality in chromosome 9p24.1. Mutations of chromosome 9p24.1 result in amplification of the PD-1 ligands, PD-L1 and PD-L2[32]. The Epstein-Barr virus (EBV) is associated with HL and also will increase the expression of the PD-1 ligands[33]. Important clinical responses with anti-PD-1 blockade by nivolumab were demonstrated in RR-HL following AHSCT with a majority of patients who has also previously received brentuximab vendotin. The study included 23 patients with an overall response rate of 87% including 17% complete responses and 70% with partial responses[34].

1.5 Pembrolizumab

Pembrolizumab is a humanized IgG-4 kappa isotype monoclonal antibody[35]. The drug was developed by Merck and currently has FDA approval in unresectable or metastatic melanoma and disease progression following ipilimumab and, if BRAF V600 mutation positive, a BRAF inhibitor. The target for pembrolizumab is PD-1 receptor on human T-cells. The variable region sequences of a very-high-affinity mouse antihuman PD-1 antibody were grafted into a human IgG-4 immunoglobulin with a stabilizing S228P Fc alteration. The IgG-4 immunoglobulin subtype does not engage Fc receptors or activate complement, thus avoiding cytotoxic effects of the antibody when binding to T-cells.

1.6 Clinical Investigations with Pembrolizumab

Pembrolizumab has been studied in solid malignancies including melanoma, renal cell cancer, and lung cancer with promising results. Pembrolizumab is an emerging therapy for treatment of advanced melanoma with noted durable response rates of 38% in patients with prior exposure to immunotherapy including ipilimumab[35]. Pembrolizumab currently has FDA approval for the treatment of patients with unresectable or metastatic melanoma and disease progression following ipilimumab and, if BRAF V600 mutation positive, a BRAF inhibitor. Additionally, pembrolizumab has received "breakthrough status" by the FDA for the treatment of non-small cell lung cancers and likely will be approved in the near future[36].

Merck is currently pursuing clinical trials with pembrolizumab in hematologic malignancies. An international Phase Ib trial is currently registered on

clinicaltrials.gov for study of pembrolizumab in blood cancers (NCT01953692). Eligible patients are those with relapsed/refractory malignancies including myelodysplastic syndrome (MDS), plasma cell myeloma (PCM), nodular sclerosis or mixed cellularity Hodgkin lymphoma, primary mediastinal large B-cell lymphoma, or other non-Hodgkin lymphomas. The study has completed though final published results remain pending. Preliminary findings were presented at the ASH 54th Annual Meeting in 2014 in abstract form. There was 31 patients with HL enrolled and of the 23 evaluable patients, 22% had CR, 43% had PR, and there was a 65% ORR[37]. A second clinical trial recently opened to investigate use of pembrolizumab follow AHSCT in patients with HL and DLBCL (NCT02362997). A third clinical trial is combining pembrolizumab with chemotherapy for advanced lymphomas (NCT02408042).

1.7 Pembrolizumab Safety and Tolerability

Out of a total of 479 patients treated on clinical trials, 466 (97.3%) experienced treatment emergent AEs of which 368 (76.8%) were considered drug-related. SAEs were reported in 0.1% of patients, but SAEs that were attributed as potentially (possibly, probably, or definitely) drug-related by investigators were reported in 6.7% of patients overall. Five patients died within 30 days of the last dose of pembrolizumab; none of the deaths were considered drug-related.

The most prevalent (>30% frequency) adverse events that have occurred in prior clinical trials include fatigue, cough, diarrhea, nausea/vomiting, rash, headache, and pruritis. Immune-mediated adverse events are possible particularly pneumonitis, colitis, hepatitis, endocrinopathies (hypopituitarism, hyper/hypothyroidism), and nephritis. Immune-mediated adverse events represent <5% of those from clinical trials. The overall AE summary suggests that pembrolizumab is generally tolerable and AEs are generally manageable.

There is currently no published data on the safety and tolerability of combining pembrolizumab with chemotherapy. Several active clinical trials in melanoma, non-small lung cancer, urothelial cancers, and hematologic malignancies include pembrolizumab given concurrently with chemotherapy. Chemotherapy agents include carboplatin, cisplatin, docetaxel, etoposide, gemcitabine, ifosfamide, nab-paclitaxel, oxaliplatin, paclitaxel, and pemetrexed. No study has been closed to date related to adverse events. The current clinical experience is that pembrolizumab can be safely administered concurrently with cytotoxic agents.

1.8 Concept and Rationale for the Current Study

Hodgkin's lymphoma remains a disease with a high cure rate however the response to further treatment at disease relapse dramatically declines and patients require salvage chemotherapy followed by AHSCT. The PD-1 pathway is an adaptive strategy by tumors to suppress the anti-tumor immune response. Co-optation of the PD-1 pathway by HL has been demonstrated with impressive responses in heavily pretreated patients with nivolumab, an anti-PD-1 antibody within the same class as pembrolizumab.

We propose using the combination of pembrolizumab with ICE salvage chemotherapy for relapsed/refractory HL. The addition of PD-1 blockade will enhance the efficacy of salvage chemotherapy. We expect an improvement in CR rate as defined by a negative FDG-PET/CT, a measure that is correlated with

improvement in both EFS and OS. The protocol will also evaluate the toxicity and tolerability of combining pembrolizumab with high-dose chemotherapy. We feel this therapy represents an important step in improving management of this aggressive lymphoma and will ultimately be incorporated into future treatment algorithms.

The treatment population will include patients ≥ 18 years of age with advanced stage RR-HL with measurable disease confirmed by FDG-PET/CT. Patients will be treated with pembrolizumab 200 mg IV concurrently with ICE combination chemotherapy every 21 days (+/-2) for 2 cycles. Pembrolizumab dosing is based on prior clinical experience and recent standardization of dosing by the manufacturer, Merck. Following 2 cycles of therapy, a third dose of pembrolizumab monotherapy will be administered. Disease response will then be assessed by FDG-PET/CT. Our primary objective is to determine the complete response rate by functional imaging. We expect an improvement in complete response as compared to historical controls.

Our secondary objectives will evaluate EFS and OS in this population. The proposed therapy is expected to improve the EFS and OS for patients with RR-HL. The safety and tolerability of pembrolizumab given concurrently with ICE salvage chemotherapy will be determined. The use of pembrolizumab has a limited toxicity profile and we expect limited adverse effects over those anticipated with ICE chemotherapy.

1.9 Rationale for Pembrolizumab 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 Pembrolizumab. The dose escalation portion of this trial evaluated three dose levels, 1 mg/kg, 3 mg/kg, and 10 mg/kg, administered every 2 weeks (Q2W) in subjects with advanced solid tumors. All three dose levels were well tolerated and no dose-limiting toxicities were observed. This first in human study of Pembrolizumab showed evidence of target engagement and objective evidence of tumor size reduction at all dose levels (1 mg/kg, 3 mg/kg, and 10 mg/kg Q2W). No MTD has been identified to date. Recent data from other clinical studies within the Pembrolizumab program has shown that a lower dose of Pembrolizumab and a less frequent schedule may be sufficient for target engagement and clinical activity.

PK data analysis of Pembrolizumab administered Q2W and Q3W showed slow systemic clearance, limited volume of distribution, and a long half-life (Merck Pembrolizumab Investigators Brochure). 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 subjects. Within the resulting population PK model, clearance and volume parameters of pembrolizumab were found to be dependent on body weight. The relationship between clearance and body weight, with an allometric exponent of 0.59, is within the range observed for other antibodies and would support both body weight normalized dosing or a fixed dose across all body weights. Pembrolizumab has been found to have a wide

therapeutic range based on the melanoma indication. The differences in exposure for a 200 mg fixed dose regimen relative to a 2 mg/kg Q3W body weight based regimen are anticipated to remain well within the established exposure margins of 0.5 – 5.0 for pembrolizumab in the melanoma indication. The exposure margins are based on the notion of similar efficacy and safety in melanoma at 10 mg/kg Q3W vs. the alternate 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 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 subject exposures in the exposure range established in melanoma as associated with maximal efficacy response and 3) will maintain individual subject 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.

1.10 Exploratory 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[38]. We will analyze the previously obtained biopsy specimens from patients' diagnostic samples to determine PD-1 and PD-L1 expression. 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 lead to amplification of gene expression of PD-L1 and PD-L2[34]. We will perform FISH analysis 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[39]. The correlative investigations will determine lymphocyte subset changes during treatment with pembrolizumab.

4.3 STUDY OBJECTIVES

2.1 Primary Objective

To determine the complete response rate by FDG-PET/CT prior to AHSCT with the combination of pembrolizumab and ICE salvage chemotherapy for relapsed/refractory Hodgkin lymphoma. Response will be assessed using Lugano criteria 2014.

2.2 Secondary Objectives

2.2.1 To determine the safety and tolerability of pembrolizumab in combination with salvage high-dose chemotherapy according to CTCAE v4.03.

2.2.2 To estimate the event free survival (EFS) at 2 years from start of treatment.

2.2.3 To estimate the overall survival (OS) at 2 years from start of treatment.

2.3 Exploratory Objectives

2.3.1 To characterize PD-1 pathway specific expression and correlate with response

2.3.2 To characterize T-lymphocyte subset changes to treatment with pembrolizumab

2.3.3 To investigate the prevalence and clinical correlation of chromosome 9p24.1 mutations for this population

2.3.4 To evaluate the effect on stem cell harvest following treatment with pembrolizumab

3.0 PATIENT ELIGIBILITY

The target population for this study is patients with relapsed/refractory Hodgkin's lymphoma with intention to proceed to autologous stem cell transplant following salvage chemotherapy. This will be a multicenter trial. Northwestern University will serve as the lead site and coordinating center for this study. Participating sites will include Augusta University, Loyola University, University of Rochester, and Emory.

A total of 40 subjects will be needed for this trial given the low incidence of RR-HL, this will be a multi-institutional clinical trial. Potential patients may be referred to the Principal Investigator (PI) at Northwestern University, Dr. Jane N. Winter, at (312) 695-6180, 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 for complete instructions regarding registration procedures.

3.1 Inclusion Criteria

3.1.1 Patients must have 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.[40]

3.1.2 Patients must have disease with FDG-PET/CT avidity.

3.1.3 Patients must have relapsed/refractory disease, with at least one line of prior chemotherapy, but ≤ 2 prior lines of treatment, for Hodgkin lymphoma.
NOTE: Patients must not have had prior immune checkpoint inhibitors. However, there are no other limitations to prior agent or regimen types.

3.1.4 Patients must be ≥ 18 years of age.

3.1.5 Patients must have ECOG performance status 0 or 1 (**Appendix A**)

3.1.6 Patients must have adequate organ and bone marrow function prior to registration, as defined below:

- absolute neutrophil count — ≥ 1,000/mcL (in the absence of GCSF for ≥14 days)
- platelets — ≥ 75,000/mcl (in the absence of platelet transfusion for ≥14 days)
- hemoglobin — ≥ 7g/dL (transfusion permitted)
- total bilirubin — ≤ 2 x institutional upper limit of normal (ULN); if total bilirubin is >2 x ULN, direct bilirubin must be normal
- AST(SGOT)/ALT(SPGT) — ≤ 2.5 x institutional ULN
- creatinine — ≤ 2 x ULN or CrCl > 30 ml/min

3.1.7 Female subjects of childbearing potential should have a negative urine or serum pregnancy within 72 hours prior to registration. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required.

3.1.8 Females of childbearing potential (FOCBP) should be willing to use 2 methods of birth control or be surgically sterile, or abstain from heterosexual activity for the course of the study through 120 days after the last dose of study medication.
NOTE: A FOCBP is *any woman* (regardless of sexual orientation, having undergone a tubal ligation, or remaining celibate by choice) who meets the following criteria:

- *Has not* undergone a hysterectomy or bilateral oophorectomy
- *Has had* menses at any time in the preceding 12 consecutive months (and therefore has not been naturally postmenopausal for > 12 months)

NOTE: Abstinence is acceptable if this is the usual lifestyle and preferred contraception for the subject.

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

3.1.10 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 who have had chemotherapy, radiotherapy, monoclonal antibody (mAb), or targeted small molecule therapy within 4 weeks of study registration are not eligible. Those who have not recovered from adverse events (Grade 1 or baseline) due to such agents administered more than 4 weeks earlier are not eligible.

3.2.2 Patients may not be currently receiving any other investigational agents within 4 weeks of study registration.

3.2.3 Patients must not have had prior exposure to any immune checkpoint inhibitors including anti-PD-1, anti-PD-L1 agents, anti-PD-L2 agents, or anti-CTLA-4 monoclonal antibodies.

3.2.4 Patients must not have known central nervous system (CNS) involvement.

3.2.5 Patients must not have had prior stem cell transplantation (autologous or allogeneic).

3.2.6 Patients must not have persistent diarrhea greater than NCI CTCAE grade 2 at the time of study registration, despite medical management.

3.2.7 Patients must not have a history of (non-infectious) pneumonitis that required steroids, evidence of interstitial lung disease or active, non-infectious pneumonitis.

3.2.8 Patients with known immunodeficiency, known autoimmune disease, or concurrent use of immunomodulatory agents including systemic steroids within 7 days prior to registration, are ineligible

3.2.9 Patients must not have co-morbid systemic illnesses or other severe concurrent disease which, in the judgment of the investigator, would make the patient inappropriate for entry into this study or interfere significantly with the proper assessment of safety and toxicity of the prescribed regimens. This includes, but not limited to, ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements.

3.2.10 Patients must not have a known additional malignancy that is progressing or requires active treatment. Exceptions include basal cell carcinoma of

the skin or squamous cell carcinoma of the skin that has undergone potentially curative therapy or in situ cervical cancer.

3.2.11 Patients with known HIV infection or active TB (Bacillus Tuberculosis) are not eligible.

3.2.12 Patients with known active HBV or HCV infection are not eligible.

3.2.13 Patients must not have a hypersensitivity to pembrolizumab or any of its excipients

3.2.14 Patients must not have received a live vaccine within 30 days of registration
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.

3.2.15 Patients must not be pregnant or breastfeeding, or expecting to conceive or father children within the projected duration of the trial, starting with the pre-screening or screening visit through 120 days after the last dose of trial treatment.

3.2.16 Patients who are unwilling or unable to comply with the protocol or have known psychiatric or substance abuse disorders that would interfere with cooperation with the requirements of the trial are not eligible.

4.0 TREATMENT PLAN

4.1 Overview

Patients with relapsed/refractory classical Hodgkin lymphoma following standard up-front chemotherapy will be eligible for participation. Patients will be treated with combination intravenous pembrolizumab and ICE (ifosfamide, carboplatin, etoposide) salvage chemotherapy for two cycles (1 cycle = 21 days) followed by a third dose of pembrolizumab monotherapy. During combination treatment, pembrolizumab 200 mg IV will be administered on Day 1. Standard ICE salvage chemotherapy will begin on Day 1 and includes ifosfamide 5 g/m^2 with equivalent dose of MESNA given over 24 hours by CIV on Day 2, carboplatin AUC 5 IV with a maximum of 800 mg Day 2, and etoposide 100 mg/m^2/day IV on Days 1 to 3. G-CSF support per institutional protocol will be administered 24 hours following completion of chemotherapy. Pembrolizumab monotherapy will then be administered on Day 1 of Cycle 3. A FDG-PET/CT will be obtained 14-22 days after Cycle 3 pembrolizumab treatment to assess response by Deauville criteria. See section 4.7 for central review requirements for this PET/CT. Patients with Deauville ≤3 will proceed to AHSCT which may include an optional third cycle of Pembro-ICE (Cycle 4 on study) prior to transplant per investigator discretion. Patients with Deauville >3 will be treated off trial, per provider's discretion which may include stem cell transplant.

4.2 Treatment Administration

Table 4.1: Treatment Administration Summary

Agent	Pre-medications[1]	Dose	Route	Schedule	Cycle Length
Pembrolizumab	Acetaminophen 650 mg po; diphenhydramine 50 mg po	200 mg	IV over 30 minutes (-5 / + 10 minutes)	Day 1	21 days (+/-2 days)
Ifosfamide + Mesna	Anti-emetics[3]	5 gm/m2 + 5 gm/m2	Continuous IV infusion x 24 hrs	Day 2	
Carboplatin	Anti-emetics[3]	AUC 5 (800 mg max dose)	IV over approximately 60 minutes	Day 2	
Etoposide	Anti-emetics[3]	100 mg/m2	IV over approximately 60 minutes	Days 1 to 3[4]	
G-CSF[2]	N/A	variable	SQ	Starts Day 4	

[1] Pre-medications for pembrolizumab are required on protocol. The remaining pre-medications listed are recommendations for ICE chemotherapy but may vary per institutional standard.
[2] G-CSF support will start following completion of chemotherapy per institutional standards. Drug selection per institutional protocol for ICE chemotherapy.
[3] It is recommended that steroids be omitted from the pre-medications for PEM-ICE. Institutional guidelines should prevail for alternative pre-medications. One option is as follows:

Day 1	Ondansetron 16 mg IV prior to chemotherapy
Day 2	Ondansetron 16 mg IV prior to chemotherapy, followed by 8 mg PO every 8 hours
Day 2, 3, & PRN at discharge	Aprepitant 125 mg PO prior to chemotherapy on D2 then aprepitant 80 mg PO D3, D4 (alternative: fosaprepitant)

[4] Etoposide will be given approximately 1 hour after pembrolizumab on day 1.

The pre-medications listed are a guidelines for anti-emetic therapy and may vary per institutional preference and formulary. Substitutions are allowed per treating provider discretion. The only required pre-medications on the protocol are acetaminophen 650 mg po and diphenhydramine 50 mg po prior to administration of pembrolizumab.

4.2.1 Day 1 of Treatment

For both combination and monotherapy cycles, pembrolizumab will be administered on Day 1. Patients will receive pre-treatment with acetaminophen 650 mg po and diphenhydramine 50 mg po given approximately 30 minutes prior to the pembrolizumab infusion. Pembrolizumab 200 mg IV will be infused over approximately 30 minutes. See section 8.1 for preparation instructions.

During combination therapy, etoposide will be administered approximately 1 hour following pembrolizumab dose on Day 1. A suggested anti-emetic premedication regimen includes ondansetron 16 mg IV prior to chemotherapy on Day 1 given approximately 30 minutes prior to chemotherapy. Etoposide 100 mg/m^2 IV will be infused over approximately 60 minutes.

4.2.2 Day 2 of Combination Treatment

Etoposide, carboplatin, and ifosfamide with mesna will be administered on Day 2. A suggested anti-emetic premedication regimen includes ondansetron 16 mg IVP and aprepitant (or fosaprepitant) 125 mg PO prior to chemotherapy followed by ondansetron 8 mg PO every 8 hours.

Carboplatin AUC 5 IV will be infused first over approximately 60 minutes. Once the carboplatin infusion is complete, then etoposide 100 mg/m2 IV will be infused over approximately 60 minutes. Ifosfamide 5 g/m2 IV mixed with mesna 5 g/m2 IV will be administered as a continuous infusion over approximately 24 hours. The ifosfamide with mesna can be started concurrently with the etoposide.

4.2.3 Day 3 of Combination Treatment

Etoposide will be administered on Day 3. A suggested anti-emetic premedication regimen includes aprepitant 80 mg PO prior to chemotherapy and ondansetron 8 mg po every 8 hours. Etoposide 100 mg/m2 IV will be infused over approximately 60 minutes.

4.2.4 Day 4 of Combination Treatment

Patients will receive G-CSF support starting after completion of chemotherapy per institutional standards. G-CSF (filgastrim, tbo-filgrastim, or pegfilgastrim) will be given as a subcutaneous injection per institutional protocol.

4.2.5 Mobilization and Stem Cell Collection

Patients are to have a Peripheral Blood Stem Cell Harvest (PBSCH) preferably within 10-20 days after the second pembro-ICE combination treatment (C2D10-21). If delayed for medical, insurance, or scheduling reasons, harvest may be performed after pembrolizumab monotherapy Cycle 3 or after the optional additional cycle of pembrolizumab- ICE. Per institutional guidelines, patients will receive growth factor as indicated for mobilization of peripheral blood progenitor cells (filgrastim / tbo-filgrastim). Additional growth factor support with plerixafor may be given per institutional guidelines.

Patients must have ≥2.0x10^6 CD34+ cells/kg to move forward with stem cell transplant. If the initial collection is inadequate, PBSCH may be collected after the study PET/CT either with growth factor stimulation alone (within 30 days of C3 pembrolizumab monotherapy for patients who do not have additional pembro-ICE), or 10-20 days after the (optional) third pembro-ICE combination treatment.

4.2.6 Pembrolizumab Monotherapy Cycle

Only pembrolizumab will be administered on Day 1 of Cycle 3, following two cycles of Pembro-ICE chemotherapy. Patients will receive pre-treatment with acetaminophen 650 mg po and diphenhydramine 50 mg po given approximately 30 minutes prior to the pembrolizumab infusion. Pembrolizumab 200 mg IV will be infused over approximately 30 minutes.

4.3 Toxicity Management & Dose Delays/Modifications

Any patient who receives at least one dose of pembrolizumab will be evaluable for toxicity endpoints. Toxicity will be assessed according to the timeframe referenced in the Schedule Procedures Table that can be found in Section 7.0.

Toxicity will be assessed according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE), version 4.03, which is available on the NCI website at http://evs.nci.nih.gov/ftp1/CTCAE/About.html.

4.3.1 Pembrolizumab

4.3.1.1 Dose Delays

Adverse events (both non-serious and serious) associated with pembrolizumab exposure may represent an immunologic etiology. These adverse events may occur shortly after the first dose or several months after the last dose of treatment. Pembrolizumab must be withheld for drug-related toxicities and severe or life-threatening AEs as per Table 3 below. See Section 4.3.1.2 for supportive care guidelines, including use of corticosteroids.

For patients who miss a treatment for a reason unrelated to toxicity, treatment may be resumed within 7 days of the originally planned treatment. If a delay of more than 21 days from the planned treatment occurs for reasons of toxicity, the patient will be taken off study. If removal from study is secondary to toxicity from pembrolizumab, the patient should receive further treatment per provider discretion which could include continuation of ICE chemotherapy without combination pembrolizumab.

Table 4.2: Pembrolizumab Dose Delays for Toxicity

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 (CTCAEv4.0)	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
	Grade 3 or 4, or recurrent Grade 2	Permanently discontinue		

				for opportunistic infections
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).

Pembrolizumab will be withheld for drug-related toxicities, including SAEs. There are no dose modifications for pembrolizumab on the study protocol.

4.3.1.2 Rescue Medications & Supportive Care

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

Diarrhea: Subjects should be carefully monitored for signs and symptoms of enterocolitis (such as diarrhea, abdominal pain, blood or mucus in stool, with or without fever) and of bowel perforation (such as peritoneal signs and ileus). In symptomatic subjects, infectious etiologies should be ruled out, and if symptoms are persistent and/or severe, endoscopic evaluation should be considered.

In subjects with severe enterocolitis (Grade 4), pembrolizumab will be permanently discontinued and treatment with systemic corticosteroids should be initiated at a dose of 1 to 2 mg/kg/day of prednisone or equivalent. When symptoms improve to Grade 1 or less, corticosteroid taper should be started and continued over at least 1 month.

In subjects with moderate enterocolitis (Grade 2 or 3), pembrolizumab should be held per Table 4.2 and anti-diarrheal treatment should be started. If symptoms are persistent for more than one week, systemic corticosteroids should be initiated (e.g., 1-2 mg/kg/day of prednisone or equivalent). When symptoms improve to Grade 1 or less, corticosteroid taper should be started and continued over at least 1 month.

All subjects who experience diarrhea should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion.

Nausea/vomiting: Nausea and vomiting should be treated aggressively, and consideration should be given in subsequent cycles to the administration of prophylactic antiemetic therapy according to standard institutional practice. Subjects should be strongly encouraged to maintain liberal oral fluid intake.

Anti-infectives: Subjects with a documented infectious complication should receive oral or IV antibiotics or other anti-infective agents as considered appropriate by the treating investigator for a given infectious condition, according to standard institutional practice.

4.3.1.3 Management of Immune-Related Adverse Events

Non-inflammatory causes must be ruled out for each suspected immune-related adverse event. If an immune-related adverse event is confirmed, treatment of moderate or severe immune-related adverse events requires interruption or permanent discontinuation of treatment with pembrolizumab and the use of corticosteroid immunosuppression. Use of mycophenolic acid or infliximab may be appropriate in specific circumstances.

Treatment is based on the severity of the observed toxicity. When corticosteroids are indicated, the following points should be considered:

- Treatment with prophylactic antibiotics to prevent opportunistic infections, in particular Pneumocystis jiroveci pneumonia, should be considered, particularly if treatment with corticosteroids will last for more than 5 weeks.
- IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g., prednisone) at the start of tapering or earlier after sustained clinical improvement is observed.
- Standard IV to oral corticosteroid conversion should be used to account for the lower bioavailability of oral corticosteroids when switching to the equivalent dose of oral corticosteroids. Steroid tapers should be gradual and the case should be followed closely to monitor for adrenal insufficiency.

Pembrolizumab should be permanently discontinued under the following circumstances:

- Grade 4 anaphylaxis
- A grade 4 immune-related adverse event, with the exception of endocrinopathies stabilized on replacement hormonal therapy
- A grade 3 immune-related adverse event that does not improve to grade 0 or 1 within 10 days after the last dose of pembrolizumab, with the exception of endocrinopathies that can be treated with replacement hormonal therapy
- Any grade 3 or 4 immune-related adverse event that recurs at grade 2 or higher after resuming pembrolizumab
- Any uveitis event
- Grade 4 enterocolitis

4.3.1.4 Management of Infusion Reactions

Acute infusion reactions (which can include cytokine release syndrome, angioedema, or anaphylaxis) are different from allergic/hypersensitive reactions, although some of the manifestations are common to both AEs. Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion. Signs/symptoms may include: Allergic reaction/hypersensitivity (including drug fever); Arthralgia (joint pain); Bronchospasm; Cough; Dizziness; Dyspnea (shortness of breath); Fatigue (asthenia, lethargy, malaise); Headache; Hypertension; Hypotension; Myalgia (muscle pain); Nausea; Pruritis/itching; Rash/desquamation; Rigors/chills; Sweating (diaphoresis); Tachycardia; Tumor pain (onset or exacerbation of tumor pain due to treatment); Urticaria (hives, welts, wheals); Vomiting.

Treatment for infusion reactions includes methylprednisolone, acetaminophen, diphenhydramine, epinephrine, and supportive measures with IV fluids or pressors support when needed. Table 4.3 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	**Stop Infusion.** Additional appropriate medical therapy may include but is not limited to: • IV fluids • Antihistamines • NSAIDS	No subsequent dosing

NCI CTCAE Grade	Treatment	Premedication at subsequent dosing
symptoms following initial improvement; hospitalization indicated for other clinical sequelae (e.g., renal impairment, pulmonary infiltrates) Grade 4: Life-threatening; pressor or ventilatory support indicated	• 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.**	
Appropriate resuscitation equipment should be available in the room and a physician readily available during the period of drug administration.		

4.3.1.5 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 4.4.

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.	

4.3.2 Recommended ICE Chemotherapy Dose Management

The standard salvage regimen ICE includes a combination of ifosfamide, carboplatin, and etoposide. Management of these commonly used agents should be guided by standard institutional practice. Included here are management recommendations for more common or severe adverse events. In general, there are no dose reductions recommended for hematologic toxicities.

Table 4.5: Guidelines for Dose Modification for Toxicity

	Ifosfamide	Carboplatin	Etoposide
Original Dose	5 g/m2 CIV	AUC 5 IV	100 mg/m2 IV
1st Dose Reduction	4 g/m2 CIV	AUC 4 IV*	80 mg/m2 IV
2nd Dose Reduction	3 g/m2 CIV	AUC 3 IV*	60 mg/m2 IV

*AUC 4 maximum dose = 640mg; AUC 3 maximum dose = 480mg

Patients experiencing significant (Grade 3-4) ifosfamide-related hematuria should have the dose of ifosfamide reduced 1 level. If hematuria persists on the urinalysis prior to the next cycle, reduce one additional level. If symptoms persist, remove patient from study therapy.

If Grade 2 ifosfamide-related neurologic symptoms develop (e.g., confusion), reduce ifosfamide dose 1 level. If Grade 3 or 4 neurologic symptoms develop, remove patient from study therapy.

Grade 3 (or greater) hepatic toxicity with elevations in SGOT (AST), SGPT (ALT), alkaline phosphatase or bilirubin requires reduction of one dose level of the agent felt to be responsible for the elevation and delay in subsequent therapy for a maximum of 14 days until recovered to Grade 1.

4.3.3 Treatment Stopping Criteria

4.3.3.1 Pembrolizumab Stopping Criteria:

Treatment with pembrolizumab must be discontinued for the following toxicities:

Adverse Event	Severity
Infusion reaction	Grade 3 or 4
Anaphylaxis	Grade 4
Immune-related AE	Grade 4* Grade 3* that does not improve to grade 0 or 1 within 10 days of last dose of pembrolizumab Grade 3 or 4 that recurs at grade 2 or higher after resuming pembrolizumab *with the exception of endocrinopathies stabilized on replacement hormonal therapy
Uveitis	Any grade
Enterocolitis	Grade 3 or 4
AST, ALT, or Increased Bilirubin	Grade 3 or 4 (For patients with liver metastasis who begin treatment with Grade 2 AST or ALT, if AST or ALT increases by greater than or equal to 50% relative to baseline and lasts for at least 1 week then patients should be discontinued
Hypophysitis	Grade 4
Hyperthyroidism	Grade 4
Pneumonitis	Grade 3 or 4
Renal failure / Nephritis	Grade 3 or 4
All other drug-related toxicities	Grade 4
Any drug-related toxicity requiring drug to be held >21 days	Any grade
Cardiac toxicity	Grade 2 with confirmed myocarditis, Grade 3 or 4
Confirmed Stevens-Johnson Syndrome (SJS)	Any grade
Confirmed Toxic Epidermal Necrolysis (TEN)	Any grade

4.3.3.2 Combination (Pembrolizumab-ICE) Stopping Criteria:
Treatment with combination pembrolizumab-ICE must be discontinued for the following toxicities:

Adverse Event	Severity
Ifosfamide-related hematuria	Grade 3 or 4 and persisting after dose reduction
Neurologic symptoms	Grade 3 or 4

4.3.3.3 Stopping rules for engraftment delays/failure and transplantation related toxicity:
Engraftment and transplantation-related toxicity will be monitored monthly. The stopping guidelines serve as a trigger for consultation with all investigators and the DSMC for additional review and are not formal stopping rules that would mandate automatic closure of study enrollment.

- >1 patients have engraftment delay/failure >28 days post-transplant based on CIBMTR engraftment definitions for ANC and platelets. (https://www.cibmtr.org/manuals/fim/1/en/topic/2450)
- >2 patients experience Grade 4 non-hematologic toxicity excluding alopecia, fatigue, anorexia, dysphagia, mucositis, vomiting or diarrhea.
- >1 patient experiences any Grade 5 toxicity.

4.4 Concomitant Medications/Treatments

4.4.1 Permitted 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 and the protocol. All concomitant medication will be recorded on the case report form (CRF) including all prescription, over-the-counter (OTC), herbal supplements, and IV medications and fluids. If changes occur during the trial period, documentation of drug dosage, frequency, route, and date may also be included on the CRF. All concomitant medications received within 28 days before the first dose of trial treatment and 30 days after the last dose of trial treatment should be recorded.

4.4.2 Cautionary Medications
Caution should be taken with anticoagulation, aspirin, and NSAIDs during

4.4.3 Prohibited Medications
Patients should not be on other investigational agents, immunomodulatory drugs, or other cancer directed therapies as outlined in the exclusion criteria for study eligibility. Patients should also not receive any live vaccines within 30 days of starting treatment. If there is a clinical indication for one of these or other medications or vaccinations specifically prohibited during the trial, discontinuation from trial therapy or vaccination may be required. The investigator should discuss any questions regarding this with

the PI/QAM. The final decision on any supportive therapy or vaccination rests with the investigator and/or the subject's primary physician.

4.5 Autologous Stem Cell Transplant

Following completion of therapy, patients with a FDG-PET/CT that has a Deauville score ≤ 3 will proceed to autologous stem cell transplant (AHSCT). Conditioning regimens prior to AHSCT may include an additional cycle of pembrolizumab-ICE combination on-study, or may be based on institutional standards and not be regulated by the study protocol. Details of conditioning regimen including dosing must be clearly detailed in the patient's medical record. Details of the stem cell pre-treatments or modifications and the stem cell amounts for reinfusion must be included in the medical record. A minimum of $2.0x10^6$ CD34+ cells/kg must have been collected during stem cell harvest to proceed with stem cell transplant (see section 4.2.5 for details). Patients are recommended to meet the following criteria before initiating autologous stem cell transplant, however institutional practice will take precedence:

- Corrected DLCO of 60%
- FEV1 or FVC >60%
- Ejection fraction 5% less than institutional lower limits of normal
- Calculated creatinine clearance > 30mL/min (using Cockcroft-Gault formula; see Appendix D)
- Liver function <2.5 x ULN (unless related to neoplastic involvement)

4.6 Provider Discretion

Following completion of therapy, patients with a FDG-PET/CT that has a Deauville score >3 will be treated by provider discretion. Anticipated options include other combination chemotherapy, brentuximab vendotin, AHSCT, allogeneic stem cell transplant, vs some combination of these therapies. Any treatments including details about dosing must be clearly documented in the medical record.

4.7 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 Northwestern and to Merck without delay and within 24 hours to Northwestern and within 2 working days to Merck if the outcome is a serious adverse experience (e.g., death, abortion, congenital anomaly, or other disabling or life-threatening complication to the mother or newborn).

The study investigator will make every effort to obtain permission to follow the outcome of the pregnancy and report the condition of the fetus or newborn to Merck. If a male subject impregnates his female partner the study personnel at the site must be informed immediately and the pregnancy reported to the Northwestern and to Merck and followed as described above and in Section 7.7.

4.8 Duration of Therapy

Patients will be treated with 2 cycles of combination pembrolizumab and ICE salvage chemotherapy (Pembro-ICE) on protocol followed by a third dose of pembrolizumab monotherapy. All patients will have a FDG-PET/CT 14-22 days after the pembrolizumab monotherapy dose. Patients with a Deauville score ≤3 may proceed to further treatment with Pembro-ICE combination (Cycle #4), if appropriate. Cycle #4 is not required on the study protocol. If the AHSCT can be arranged preferably within 21-35 days of the third pembrolizumab dose (but 21-42 days will be acceptable), the patient may proceed directly to transplant otherwise cycle #4 will be administered per protocol. Alternatively, if the patient's FDG-PET/CT has a Deauville score >3, they will come off protocol, receive no further study agent, and be treated per investigator discretion.

4.9 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. Patients who complete the protocol regimen will have an off-treatment visit approximately 30 days after stem cell transplant as well as visits at 60, 90, and 180 days (±14 days) post-transplant. Thereafter, they will be followed with at least one clinic visit every 3 months for to 2 years and then annually for 2 years (one visit at 3rd year and one visit at 4th year of follow up) for 4 years total post-transplant or post-study treatment. Patients removed from treatment for unacceptable adverse events will be followed until resolution or stabilization of the adverse event.

Adverse events will be followed for 30 days after last dose of study therapy or final stem cell transplant. Serious adverse events will be followed for 90 days after the last dose of pembrolizumab (or 30 days after starting subsequent therapy, whichever occurs first). Immune-related AE's will be recorded for 90 days after the last dose of pembrolizumab - these may include pneumonitis, colitis, hepatitis, endocrinopathies (hypopituitarism, hyper/hypothyroidism), and nephritis. For patients who undergo ASCT, AE's ≥ Grade 3 will be recorded for 180 days post-transplant. See section 7.7.1 for reporting requirements.

4.10 Removal of Subjects from Study Treatment and/or Study as a Whole

Patients can be taken off the study treatment and/or study as a whole at any time at their own request, or they may be withdrawn at the discretion of the investigator for safety, behavioral or administrative reasons. The reason(s) for discontinuation must be clearly documented on the appropriate eCRF and may include:

- Patient voluntarily withdraws from treatment (follow-up permitted)
- Patient withdraws consent (no follow-up permitted)
- Patient is unable to comply with protocol requirements
- Patient demonstrates disease progression
- Patient experiences unacceptable toxicity
- Treating physician determines that continuation on the study would not be in the patient's best interest
- Patient becomes pregnant
- Patient develops a second malignancy that requires treatment which would interfere with this study
- Patient becomes lost to follow-up (LTF)

4.11 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 POD or toxicity will still be considered evaluable for toxicity endpoints; however, for the purpose of efficacy endpoints, another patient may be added to the accrual goal 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.

4.12 Suspension of Accrual

This study will be monitored in accordance with the Data Safety Monitoring Plan (DSMP) of the Robert H. Lurie Comprehensive Cancer Center of Northwestern University. The DSMC will review all toxicity data, and in the event of an excessive toxicity, the DSMC may require suspension of accrual.

5 STUDY PROCEDURES

Trial Period:	**Screening**	**Treatment Cycles[1]**									**Post-Treatment**	
Treatment Cycle/Title:	Main Study Screening	Cycle 1		Cycle 2			Cycle 3		Optional Cycle 4[2]	ASCT[3]	30 days post Transplant	Follow up
		D1	D2-4	D1	D2-4	D10-21	D1	D14-22	D1			
Cumulative Days on Study	Within 28 days of registration[18]	1	2-4	22	23-25	32-42	43	59-64	64	64-85[20]		
Scheduling Window (Days):		--		± 2		--	± 2	± 2	± 2		± 3	
Administrative Procedures												
Informed Consent	X											
Inclusion/Exclusion Criteria	X											
Demographics and Medical History	X											
Prior/Concomitant Medication Review	X	X		X			X		X	X	X	
Survival Status												X[17]
Clinical Procedures/Assessments												
Review Adverse Events		X		X			X		X	X	X[17]	X[17]
Physical Examination[4]	X	X		X			X		X	X	X	X[17]
IPS Score[5]	X											
ECOG Performance Status[6]	X	X		X			X		X	X	X	
ECHO/MUGA	X[19]									X		
ECG	X[19]									X		
PFT's with DLCO										X		
Laboratory Procedures/Assessments												
Pregnancy Test[7]	X											
CBC with differential and Chemistry panel[8]	X[8]	X		X			X		X	X	X	
Urinalysis[9]			X[9]		X[9]				X[9]			
Quantiferon-gold TB blood test	X											
Study labs[10]		X		X			X			X	X	
Study Treatment												
Pembrolizumab[14]		X		X			X		X[2]			
ICE Chemotherapy[15]		X	X	X	X				X[2]			
PBSCH[16]						X[16]		X[16]				
Efficacy Measurements												
CT Scans[11]	X[11]									X[11]		
FDG-PET/CT[12]	X[12]							X[12]				
Tumor Biopsies/Archival Tissue Collection												

Archival Tissue Collection[13]	X											

		[1] A cycle is defined as 21 days (+/- 2 days) depending on CBC recovery as defined by ANC>1.5 and platelet count >75K [2] Cycle #4 is not required on the study protocol. Patients with a Deauville score ≤3 may proceed directly to AHSCT per provider discretion if the procedure can be arranged within 21-35 days after cycle #3. Alternatively, if the patient's FDG-PET/CT has a Deauville score >3, they will come off protocol, receive no further study agent, and be treated per investigator discretion. [3] Autologous Stem Cell Transplant will take place 21-42 days after the final study regimen pembrolizumab dose (optional pembro-ICE combination or otherwise, per provider discretion). Transplant visit parameters should be obtained on the initial day of induction chemotherapy or within 21-42 days following final study regimen but prior to the autologous stem cell transplant procedure [4] Patients will have a physical exam, including vital signs, weight and height (screening only) at each treatment visit. [5] See Appendix C [6] See Appendix A [7] Required for all FOCBP at baseline (within 72 hours of registration) and only as clinically indicated thereafter. [8] Labs must be completed within 10 days of study registration. Labs include a CBC w/ differential and CMP (Na, K, Cl, CO2, Glucose, Calcium, BUN, Cr, AST, ALT, Alkaline Phosphatase, Total Bilirubin) [9] Urinalysis will be performed on Day 2 of ICE chemotherapy to evaluate for hematuria (prior to ifosfamide treatment and per institutional standard thereafter). [10] Study labs will be collected pre-dose at each of the specified time points and will include (2) 5ml sodium heparin tubes for FlowCore See section 6.4 and 9.0 for specific analysis. [11] Diagnostic quality CT scan of the chest/abdomen/pelvis is required at baseline (within 6 weeks / 42 days prior to study registration). CT scan (with or without diagnostic quality) prior to ASCT is optional at the discretion of the treating investigator. If completed it should be preferably within 7 days prior to autologous stem cell transplant but 2-3 weeks prior to transplant will be acceptable. If there is involvement of the neck, then a CT Neck should be completed at the discretion of the treating investigator. [12] FDG-PET/CT is required for eligibility (within 6 weeks / 42 days prior to study registration) and interim tumor assessment for the primary endpoint analysis. The interim assessment FDG-PET/CT must be obtained on day 14-22 of cycle 3 (at least 14 days after the pembrolizumab monotherapy dose) and uploaded into LifeImage within 30 days for central review as outlined in section 6.1.1 (see NOTIS for LifeImage Submission Manual). [13] Tumor biopsy specimens are required for correlative analysis (if available). Patients are not required to have a repeat biopsy for eligibility unless no prior tissue is available. Tumor specimen can be from their biopsy at diagnosis or from a repeat biopsy at relapse. The most recent biopsy is preferred. [14] Pembrolizumab will be administered at 200mg on day 1 of cycle 1, 2, and 3 for all patients (cycle 1 and 2 in combination with ICE chemotherapy, cycle 3 as monotherapy). For patients with a Deauville score ≤3, pembrolizumab may be given cycle 4 day 1 in combination with ICE therapy at physician's discretion. [15] Patients will receive pembrolizumab in combination with ICE chemotherapy during cycle 1 and 2, as well as cycle 4 if applicable (see footnote 2). The ICE regimen will be given over days 1-4 and consists of ifosfamide + mesna, carboplatin, etoposide and G-CSF as detailed in section 6.2 of the protocol. [16] Patients who will undergo ASCT are required to have a Peripheral Blood Stem Cell Harvest (PBSCH) preferably 10-20 days after the second pembro-ICE combination treatment See Section 4.2.5 for details. If stem cell collection is inadequate (<$2x10^6$ cells/kg) or there are issues with coordination and/or insurance verification, PBSCH may be collected after the study PET/CT either with growth factor stimulation alone (within 30 days of C3 pembrolizumab monotherapy dose for patients who do not have additional pembro-ICE), or 10-20 days after the (optional) third pembro-ICE combination treatment. [17] Patients will have follow-up clinic visits at 60, 90, and 180 days (±14 days) post-transplant (or post-study treatment) to assess adverse events according to the table in section 7.7.1. Engraftment will also be assessed as per section 4.3.3.3. Thereafter patients will be followed (either by routine clinic visit or by phone call) every 3 months for 2 years and then annually for 2 years (one visit at 3rd year and one visit at 4th year of follow up) for 4 years total post-transplant or post-study treatment to document survival and disease progression. [18] Unless otherwise noted [19] Echocardiogram and/or ECG should be performed as clinically indicated for patients with a history of congestive heart failure or at risk because of underlying

		cardiovascular disease or exposure to cardiotoxic drugs Cardiac toxicities should be closely monitored and managed per section 4.3.1.5. [20] If optional Cycle 4 of PEM-ICE is completed the window for Autogous Stem Cell Transplant and study related procedures will be Days 85-106.

6.0 RESPONSE ASSESSMENT

6.1 Deauville Criteria for FDG-PET/CT Interpretation

Deauville criteria is an internationally recommended scale for assessment of treatment response in Hodgkin's lymphoma. Deauville criteria will be used to assess treatment response in participants following treatment with combination pembrolizumab and ICE salvage chemotherapy. Deauville criteria is a tool based on interpretation of FDG uptake in comparison to two reference organs, the mediastinum and the liver. The scale ranges from 1 to 5 and **Appendix B** defines the Deauville scoring criteria. Scores of 1 to 3 are considered a complete response. Scores 4 and 5 may represent partial response, stable disease, or progressive disease.

6.1.1 Central Review of PET/CT

All patients will have a retrospective central review of the interim PET/CT for research purposes. As scans are performed in real time, a de-identified image of the PET should be uploaded within 30 days to LifeImage to be reviewed at the Northwestern University Imaging Core. A copy of the diagnostic CT scan may be requested if needed for further interpretation, but only the PET is routinely required. The LifeImage Submission Manual is located in NOTIS.

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.

In the event that a site is unable to upload PET/CT scans to LifeImage, contact QAM at Northwestern for an alternative method of providing PET/CT scans for central review.

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]

6.2 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.

6.3 Efficacy Endpoints

Response and progression will be evaluated using the Lugano criteria 2014[15]. See Appendix E for specific response assessment criteria. All patients who undergo the interim assessment during Cycle 3 will be evaluable for response. For patients who discontinue the study prior to this point for any reason other than PD or toxicity, another patient may be added to the accrual goal with the approval of the Data and Safety Monitoring Committee (DSMC).

6.3.1 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 (e.g., 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.

6.3.2 Event Free Survival (EFS)

EFS 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.

6.3.3 Overall Survival (OS)

OS will be defined as time from study enrollment until death, or until last contact if the patient did not die.

6.4 Exploratory Endpoints

Each enrolled patient's most recent diagnostic biopsy sample will be obtained for additional marker expression analysis. Peripheral blood will be obtained at specified time points for flow analysis

6.4.1 PD-1 Pathway Marker Expression

Tissue sample slides from the most recent diagnostic 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.
NOTE: If a patient does not have tissue available, they are not required to have a fresh biopsy.

6.4.2 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 that will be evaluated as the primary endpoint and include CD4+CD25+PD-L1+ T lymphocytes and CD4+CD62L+CD127+ T lymphocytes. Lymphocyte subsets are continuous measurements in cells/μL.

6.4.3 Chromosome 9p24.1 Mutation

Tissue sample slides from the most recent diagnostic biopsy will be evaluated by FISH break-apart probes for mutations at chromosome 9p24.1. Samples will be deemed either positive or negative. Presence/absence (binary) of chromosome 9p24.1 mutations will be correlated with response to pembrolizumab and clinical outcomes.

6.4.4 Stem Cell Harvest

Patients will proceed to the stem cell harvest, per institutional guidelines, preferably within 10-20 days following cycle #2 pembrolizumab-ICE treatment (See Section 4.2.5 for details). The number of required pheresis sessions and total amount of stem cells collected will be correlated with institutional experience.

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 NOTIS for additional information). The level of risk attributed to this study requires High Intensity 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 time points). 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.

For subjects receiving treatment with pembrolizumab all Aes of unknown etiology associated with pembrolizumab exposure should be evaluated to determine if it is possibly an event of a potentially immunologic etiology (termed immune-related adverse events, or irAEs). See section 7.7.1 for further details.

7.2 Definitions & Descriptions

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.

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).

7.3 Severity of AEs

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.

7.4 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, or 30 days after patient starts new anti-cancer therapy, whichever occurs first, 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.

7.5 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.

7.6 Events of Clinical Interest

Selected non-serious and serious adverse events are also known as Events of Clinical Interest (ECI) and must be recorded as such on the NU CTO SAE Form and reported within 24 hours to the assigned QAM and within 2 working days to Merck Global Safety. (Attn: Worldwide Product Safety; FAX 215 993-1220) Events of clinical interest for this trial include:

- an overdose of Merck product, as defined as any dose of 1,000 mg or greater (≥5 times the indicated dose), that is not associated with clinical symptoms or abnormal laboratory results.
- 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.

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

Although pregnancy and lactation are not considered adverse events, it is the responsibility of investigators or their designees to report any pregnancy or lactation in a subject (spontaneously reported to them) 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 study treatment, or 30 days following cessation of treatment if the subject initiates new anticancer therapy, whichever is earlier, must be reported by the investigator. All reported pregnancies must be followed to the completion/termination of the pregnancy. Pregnancy outcomes of spontaneous abortion, missed abortion, benign hydatidiform mole, blighted ovum, fetal death, intrauterine death, miscarriage and stillbirth must be reported as serious events (Important Medical Events). If the pregnancy continues to term, the outcome (health of infant) must also be reported.

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

7.8 Adverse Event Reporting

7.8.1 Overall Adverse Event Reporting Schedule

All adverse events will be monitored and recorded from the time of consent until 30 days after stem cell transplant or study treatment. Other types of adverse events will be recorded according to the following schedule:

Adverse Event Type	Duration of Reporting
Serious adverse events (SAE's)	90 days after last dose of pembrolizumab
Immune-mediated adverse events*	90 days after last dose of pembrolizumab
≥Grade 3 adverse events	180 days after stem cell transplant

*Examples of immune-mediated adverse events are pneumonitis, colitis, hepatitis, endocrinopathies (hypopituitarism, hyper/hypothyroidism), and nephritis.

7.8.2 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.

7.8.3 Determining if Expedited Reporting is Required

This includes all events that occur within 30 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 a 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

7.8.4 Expedited Reporting of SAEs/Other Event

7.8.4.1 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.

7.8.4.2 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 10 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.

7.8.4.3 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.

7.8.4.4 Reporting to Merck

Any serious adverse event, or follow up to a serious adverse event, including death due to any cause other than progression of the cancer under study that occurs to any subject from the time the consent is signed through 90 days following cessation of treatment, or 30 days after patient starts subsequent therapy, whichever occurs first, whether or not related to Merck product, must be reported to Merck within one business day. The NU SAE form is to be used for reporting to Merck. SAE reports and any other relevant safety information are to be forwarded to the Merck Global Safety facsimilie number: +1-215-993-1220.

8 DRUG INFORMATION

8.1 Pembrolizumab

8.1.1 Other names

MK-3475; Keytruda®

8.1.2 Classification - type of agent
Immunotherapy; Humanized X PD-1_mAb (H409A11) IgG4

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
Pembrolizumab injection (solution): carton containing one 100 mg/4 mL (25 mg/mL), single-use vial (NDC 006-3026-02) Store vials under refrigeration at 2°C to 8°C (36°F to 46°F) in original carton to protect from light. Do not freeze. Do not shake. Store the diluted solution from the pembrolizumab 100 mg/4 mL vial either:

- At room temperature for no more than 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.
- Under refrigeration at 2°C to 8°C (36°F to 46°F) for no more than 20 hours. If refrigerated, allow the diluted solution to come to room temperature prior to administration.

8.1.5 Protocol dose specifics
For the clinical trial there will be a set dose of 200 mg IV for all cycles regardless of weight. There are no dose modifications for toxicity.

8.1.6 Preparation
Pembrolizumab is provided as a liquid solution (100 mg/vial) in Type I glass vials intended for single use only. Pembrolizumab is formulated with L-histidine as buffering agent, polysorbate 80 as surfactant, sucrose as stabilizer/tonicity modifier, and hydrochloric acid (HCl) and/or sodium hydroxide (NaOH) for pH adjustment (if necessary).

The product ***after reconstitution with sterile water for injection*** and the liquid drug product is a clear to opalescent solution, which may contain extraneous and proteinaceous particulates. The reconstituted drug product solution and liquid drug product are to be further diluted with normal saline in polyvinyl chloride (PVC) or non-PVC IV bags to achieve final concentration between 1 mg/mL and 10 mg/mL.

Reconstituted vials and infusion solutions should be immediately administered after preparation. If not used immediately, reconstituted vials and/or IV bags may be stored at 2-8 °C for up to a cumulative time of 20 hours. If refrigerated, the vials and/or IV bags should be allowed to equilibrate to room temperature prior to subsequent use. Pembrolizumab solutions may be stored at room temperature for a cumulative time of up to 4 hours. This includes room temperature storage of reconstituted drug product solution and liquid drug product in vials, storage of infusion solution in the IV bag and the duration of infusion.

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 pembroliuzmab (investigational / clinical supply) directly to the NU Investigational Pharmacy and affiliate sites 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 an 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 the most prevalent (>30% frequency) adverse events that have occurred in prior clinical trials.

- Fatigue
- Cough
- Diarrhea
- Nausea/Vomiting
- Rash
- Headache
- Pruritis

Special attention should be made to immune-related adverse events (<5% frequency), particularly dermatitis, pneumonitis, colitis, hepatitis, endocrinopathies (hypopituitarism, hypothyroidism), and nephritis. Please see the current IB for a comprehensive list of side effects and known frequencies of occurrence.

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.

8.1.12 Return and Retention of Study Drug

Pembrolizumab will be supplied at no charge by Merck for patients on the protocol. In the event of patient has dosing delays, the study agent will remain at the treating institution per storage guidelines (8.1.4). The drug will be returned to Merck if a patient withdraws from the trial.

8.2 Ifosfamide

8.2.1 Other names

IFEX

8.2.2 Classification - type of agent

Alkylating Agents: Nitrogen Mustards

8.2.3 Mode of action

Ifosfamide is classified as an alkylating agent of the nitrogen mustard type. After metabolic activation, active metabolites of ifosfamide alkylate or bind with many intracellular molecular structures, including nucleic acids. The cytotoxic action is primarily due to cross-linking of strands of DNA and RNA, as well as inhibition of protein synthesis.

8.2.4 Storage and stability

IFEX (ifosfamide for injection, USP) is available in single-dose vials as follows:

- NDC 0338-3991-01 1-gram Single-Dose Vial
- NDC 0338-3993-01 3-gram Single-Dose Vial

Store at controlled room temperature 20°C to 25°C (68°F to 77°F). Protect from temperatures above 30°C (86°F). Constituted or constituted and further diluted solutions of ifosfamide should be refrigerated and used within 24 hours.

8.2.5 Protocol dose specifics

For the clinical trial there will be a set dose of 5 g/m^2 CIV over 24hrs on day 2 for all cycles. Dose modifications are outlined in Section 4.3; Table 2 and Table 3.

8.2.6 Preparation

Injections are prepared for parenteral use by adding Sterile Water for Injection, USP, or Sterile Bacteriostatic Water for Injection, USP (benzyl alcohol or parabens preserved), to the vial and shaking to dissolve. Use the quantity of diluent shown below to constitute the product:

Dosage Strength	Quantity of Diluent	Final Concentration
1 gram	20 mL	50 mg/mL
3 grams	60 mL	50 mg/mL

Solutions of ifosfamide may be diluted further to achieve concentrations of 0.6 to 20 mg/mL in the following fluids:

- 5% Dextrose Injection, USP
- 0.9% Sodium Chloride Injection, USP
- Lactated Ringer's Injection, USP
- Sterile Water for Injection, USP

Because essentially identical stability results were obtained for Sterile Water admixtures as for the other admixtures (5% Dextrose Injection, 0.9% Sodium Chloride Injection, and Lactated Ringer's Injection), the use of large volume parenteral glass bottles, Viaflex bags or PAB™ bags that contain intermediate concentrations or mixtures of excipients (eg, 2.5% Dextrose Injection, 0.45% Sodium Chloride Injection, or 5% Dextrose and 0.9% Sodium Chloride Injection) is also acceptable. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration.

8.2.7 Route of administration for this study

Administer ifosfamide at 5 g/m2 IV mixed with equal dose of mesna via continuous intravenous infusion over 24 hours beginning on day 2 of each cycle.

8.2.8 Incompatibilities

Ifosfamide is incompatible with diazepam, pantoprazole, and potassium phosphate. Do not co-administer these drugs through the same infusion line.

8.2.9 Availability & Supply

Ifosfamide is commercially available from multiple manufacturers and not supplied by the study.

8.2.10 Side effects

In patients receiving ifosfamide as a single agent, the dose-limiting toxicities are myelosuppression and urotoxicity. Dose fractionation, vigorous hydration, and a protector such as mesna can significantly reduce the incidence of hematuria, especially gross hematuria, associated with hemorrhagic cystitis. Leukopenia, when it occurs, is usually mild to moderate. Other significant side effects include alopecia, nausea, vomiting, and central nervous system toxicities. The most commonly reported adverse events include:

Adverse Reaction	Incidence (%)
Alopecia	83
Nausea-Vomiting	58
Hematuria	46
Gross Hematuria	12
CNS Toxicity	12
Infection	8
Renal Impairment	6
Liver Dysfunction	3
Phlebitis	2
Fever	1

8.2.11 Nursing implications

Procedures for proper handling and disposal of anticancer drugs should be considered. Skin reactions associated with accidental exposure to ifosfamide may occur. The use of gloves is recommended. If ifosfamide solution contacts the skin or mucosa, immediately wash the skin thoroughly with soap and water or rinse the mucosa with copious amounts of water. Several guidelines on this subject have been published. There is no general agreement that all of the procedures recommended in the guidelines are necessary or appropriate.

Advise patients on the possible side effect profile. Follow infusion rate protocol with vigilant monitoring for possible infusion-related effects. At least 2 L/day of oral or IV fluids should be given to prevent bladder toxicity. Patients require a urinalysis to evaluate for hematuria prior to administration of ifosfamide then monitoring per institutional standard.

8.3 Carboplatin

8.3.1 Other names

CBDCA; Paraplatin®

8.3.2 Classification - type of agent

Antineoplastic Agent: Alkylating Agent, Platinum Compound

8.3.3 Mode of action

Carboplatin cytotoxic activity is a result of DNA binding to form intrastrand crosslinks and adducts that cause changes in the conformation of the DNA and affect DNA replication. Carboplatin readily crosses the cell membrane. Once inside the cell, the ring structure of carboplatin is hydroxylated by water to form the active moiety. Once in the active form, carboplatin binds with DNA, RNA, or other macromolecules at two sites to form interstrand and intrastrand links. Carboplatin forms irreversible covalent bonds which inhibit DNA replication, RNA transcription, and protein synthesis.

8.3.4 Storage and Stability

Product is stable for up to 14 days at 77 ^{o}F following multiple uses
Protect from light. Store at 77 ^{o}F; excursions permitted to 59-86 ^{o}F.

Reconstituted vials are stable for 24 hours at room temperature (25 ^{o}C). Paraplatin multidose (10 mg/ml) vials are stable for up to 14 days following initial entry into the vial.

Carboplatin solutions further diluted with D5W or NS are stable for 8 hours at room temperature (25 ^{o}C). Since carboplatin solutions are preservative-free the manufacturer recommends discarding any unused carboplatin solution after 8 hours.

8.3.5 Protocol dose specifics

For the clinical trial there will be a set dose carboplatin AUC 5 IV on day 2 (maximum of 800 mg). Dose modifications are outlined in Section 4.3.2, Table 4.5.

8.3.6 Preparation

Aluminum needles, or IV sets containing aluminum should not be used for carboplatin preparation or administration because aluminum reacts with carboplatin to form a precipitate, causing loss of potency.

Reconstitution of vials:

- Reconstitute carboplatin 50, 150, or 450 mg vials with 5, 15, or 45 ml, respectively, of sterile water for injection, D5W, or sodium chloride injection. The reconstituted vials should have a concentration of 10 mg/ml of carboplatin.

Further dilution for infusion:

- Further dilute carboplatin solution (10 mg/ml) with D5W or NS to concentrations of 0.5-4 mg/ml.

8.3.7 Route of administration for this study

Carboplatin will be given IV at a dose of AUC 5 (max 800 mg) over 60 minutes on day 2 of each cycle.

8.3.8 Incompatibilities

Carboplatin is incompatible with diazepam and lansoprazole. Do not co-administer these drugs through the same infusion line.

8.3.9 Availability & Supply

Carboplatin is commercially available from multiple manufacturers and is not supply by the study.

8.3.10 Side effects

Most likely (>30%) side effects are myelosuppression, alopecia, nausea/vomiting, taste changes, weakness, and low magnesium. Less likely (10-29%) side effects include abdominal pain, diarrhea/constipation, mouth sores, increased risk of infections, peripheral neuropathy, ototoxicity, electrolyte imbalances, abnormal LFTs, nephrotoxicity, and allergic reactions. Rare side effects are life-threatening cardiovascular events.

8.3.11 Nursing implications

Administer pre-treatment medications per protocol. Advise patients on the possible side effect profile. Routine hydration is not required with carboplatin therapy. Hydration should be considered in patients with renal impairment or in those receiving concurrent nephrotoxic agents. Visually inspect parenteral products for particulate matter and discoloration prior to administration whenever solution and container permit.

8.4 Etoposide

8.4.1 Other names

VP-16, Vepesid®

8.4.2 Classification - type of agent

Antineoplastic Agents: Natural and Semi-synthetic Antineoplastics: Epipodophyllotoxin

8.4.3 Mode of action

Etoposide inhibits the enzyme topoisomerase II, nucleoside transport, and incorporation, and causes DNA breakage.

8.4.4 Storage and stability

The injection should be stored at room temperature. Following dilution in 0/9% sodium chloride or 5% dextrose to concentrations of 0.2-0.4 mg/ml the drug is chemically stable for 48 and 96 hrs at room temperature, respectively.

8.4.5 Protocol dose specifics

For the clinical trial, there will be a set dose etoposide of 100 mg/m^2 on days 1 to 3 of each cycle. Dose modifications are outlined in Section 4.3.2, Table 4.5.

8.4.6 Preparation

The desired dose is diluted to a concentration of <0.4 mg/ml in normal saline or 5% dextrose to a volume of 250-500 ml.

8.4.7 Route of administration for this study

Etoposide will be given IV at a dose of 100 mg/m^2 over 60 minutes daily on days 1 to 3 of each cycle. The dose on day 1 will be administered 1 hour following completion of pembrolizumab.

8.4.8 Availability & Supply

Etoposide is commercially available from multiple manufacturers and is not supply by the study.

8.4.9 Side effects

Most likely (>30%) side effects include myelosuppression, alopecia, nausea/vomiting, and infertility. Less likely (10-29%) side effects include mouth sores, diarrhea, anorexia,

and skin reactions. Other rare side effects include metallic taste, peripheral neuropathy, and a slight increase risk of blood cancers.

8.4.10 Nursing implications

Administer pre-treatment medications per protocol. Advise patients on the possible side effect profile. Visually inspect parenteral products for particulate matter and discoloration prior to administration whenever solution and container permit.

Etoposide is administered by IV infusion. Avoid any contact with skin. Use Luer Lok fittings to prevent accidental leakage of etoposide during administration. If contact with skin occurs, wash immediately with soap and water.

Monitor blood pressure every 15 minutes during IV infusion of etoposide concentrate. If hypotension occurs, stop the infusion and notify physician. Infusion may be restarted at a slower rate after stabilization of blood pressure with IV fluids and supportive measures. Epinephrine, an antihistamine, and resuscitation equipment should be readily available in case of an anaphylactic reaction.

Plastic devices made of acrylic or ABS (a polymer composed of acrylonitrile, butadiene and styrene) have been reported to crack and leak when used with undiluted etoposide for injection.

8.5 Mesna

8.5.1 Other names

Mesnex®

8.5.2 Classification - type of agent

Detoxifying agent.

8.5.3 Mode of action

Binds to urotoxic ifosfamide metabolites thereby acting as a detoxifying agent.

8.5.4 Storage and stability

When mesna is exposed to oxygen, mesna is oxidized. Any unused drug remaining in the ampules after dosing should be discarded and new ampules used for each administration. Store ampules and vials at room temperature. Multidose vials may be stored and used for up to 8 days after initial entry. Syringes prepared for oral administration are stable for 9 days at room temperature and under refrigeration. Diluted solution is sterile for 24 hours at 25°C (77°F). It is recommended that solutions of mesna be refrigerated and used within six hours.

8.5.5 Protocol dose specifics

The mesna dose must equal the calculated dose of ifosfamide for each cycle, starting at $5g/m^2$.

8.5.6 Preparation

For IV administration, the drug can be diluted by adding the contents of a mesna ampule to any of the following solutions: 5% D/W, 5% D/NaCl injection, 0.9% NaCl injection, and lactated ingers injection. The vial should be inspected visually for particulate matter and discoloration prior to administration.

8.5.7 Route of administration for this study
Administer mesna at 5 g/m2 IV mixed with equal dose of ifosfamide via continuous intravenous infusion over 24 hours beginning on day 2 of each cycle.

8.5.8 Availability & Supply
Mesna is commercially available from multiple manufacturers and not supplied by the study.

8.5.9 Side effects
Mesna should not be given to patients known to be hypersensitive to mesna or other thiol compounds. Mesna in high doses can cause acetone in the urine, occasional irritation at the infusion site, and nausea and vomiting.

8.5.10 Nursing Implications
Visually inspect parenteral products for particulate matter and discoloration prior to administration whenever solution and container permit.

8.6 G-CSF

8.6.1 Other names
Filgastrim; Neupogen®; tbo-Filgastrim; Granix®; peg-filgastrim; Neulasta®

8.6.2 Classification - type of agent
Colony Stimulating Factor

8.6.3 Mode of action
Binds to receptors on hematopoietic cells, increasing neutrophil production and activation.

8.6.4 Storage and stability
The intact vials of filgrastim should be stored under refrigeration (2-8ºC). Avoid shaking.

8.6.5 Protocol dose specifics
Filgastrim 5 mcg/kg/day will be administered. Pre-filled syringes of 300 mcg and 480 mcg are available. Round up to the closest dispensed dose. Alternatively, peg-filgastrim 6 mg can be administered as a single dose on day 4. Doses may be altered during stem cell mobilization per institutional protocol.

8.6.6 Preparation
Filgrastim will be given subcutaneously directly from the vial.

8.6.7 Route of administration for this study
G-CSF will be administered as a subcutaneous injection starting day 4 per institutional protocol. G-CSF will start 24hrs after and within 48 hrs of completing chemotherapy with each cycle.

8.6.8 Availability & Supply
Filgastrim is commercially available Amgen and not supplied by the study.

8.6.9 Side effects

The most prevalent (>10% frequency) adverse events include nausea/vomiting and abnormal lab elevations (AST, Alk Phos, LDH, and uric acid). Common (1-10%) adverse events include fatigue, generalized weakness, headache, constipation/diarrhea, anorexia, chest pain, musculoskeletal pain, alopecia, and skin rash.

9 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[38]. We will analyze the previously obtained biopsy specimens from patients' most recent samples to determine PD-1 and PD-L1 expression. 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[34]. 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[39]. The correlative investigations will determine lymphocyte subset changes during treatment with pembrolizumab.

9.1 Archival Tissue Biopsy

An archival biopsy sample (preferably from the patient's most recent biopsy) will be obtained for each patient for PD-1 pathway marker analysis, if available. For each biopsy specimen, 5 unstained slides from a formalin-fixed, paraffin-embedded (FFPE) samples are required for immunohistochemical (IHC) analysis of PD-1 and PD-L1 expression (at QualTek Molecular Laboratories). A FFPE block section is also required to complete FISH analysis for alterations at chromosome 9p24.1 (at Northwestern University). See separate lab manual for processing and shipping details.

9.2 Flow Cytometry

Lymphocyte subsets will be evaluated by flow cytometry on peripheral blood obtained on Day 1 of Cycles 1-3, at the time of ASCT, and at the 30-day follow-up visit. For each specified time point, peripheral blood sampling will require 5 mL in a sodium heparin tube. See separate lab manual for processing details.

9.2.1 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.

10 STATISTICAL CONSIDERATIONS

This is a Phase II trial to estimate a clinical response (complete response rate) following administration of pembrolizumab with salvage ICE chemotherapy for patients with relapsed/refractory 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 dose of pembrolizumab
  AND
- have a FDG-PET/CT scan following cycle #3

10.2 Study Design and Study Endpoints

The trial design is a single-stage Phase II, prospective, open-label, single-arm, multi-centered clinical trial. The standard response rate is assumed to be 0.5 (under the null hypothesis) by historical controls; and the new therapy is considered worthy of further research if we can reject the null hypothesis in favour of the one-sided alternative hypothesis, where the response rate is 0.7. The consequent decision rule provides the sample size (n=37) and minimum number of responders (r) as ≥24 thus warranting further investigation of the new therapy, such that statistical significance is achieved. If r<24, then this number is the maximum number of responders for which statistical significance is not achieved. This design yields a type I error rate of 0.05 and power of 0.80 when the true response rate is 0.70.

Study endpoints are further defined in **Section 6**. For the primary objective, the endpoint will be complete response as defined by PET/CT with a Deauville score ≤3. For the secondary objectives, the endpoints will include the frequency, grade, timing, and attribution of AEs according to the NCI-CAE version 4.03. Efficacy endpoints for response and disease progression will be evaluated by the 2007 Revised Response Criteria for Malignant Lymphoma (RRCML).

For the exploratory endpoints, patient's tumor biopsy will be evaluated for PD-1 and PD-L1 expression by immunohistochemistry. Samples will be deemed either positive or negative for marker expression. Tumors will also be analyzed by FISH to determine presence or absence of chromosomal abnormalities at chromosome 9p24.1. Peripheral blood obtained at specific time points through treatment will be used to test serum levels for immune markers and soluble PD-L1. The immune marker and soluble PD-L1 assays include standardized reference ranges.

10.3 Sample Size and Accrual

Per the sample size calculations, 37 patients will be required. At Northwestern University, we see ~30 patients with RR-HL annually. We expect at least 20 patients will meet eligibility criteria. Given the low incidence of RR-HL, this will be a multi-institutional clinical trial. Accrual rate will include 6 patients per year at Northwestern and 15 patients per year at participating sites. The required patient accrual will be met by 2 years with the total study duration within 3 years.

Statistical sample size calculations and definitions[41]:

- P_0 = 0.5 = Historical complete response rate of salvage chemotherapy by FDG-PET/CT in RR-HL.
- P_1 = 0.7 = Proposed improvement in complete response rate by addition of pembrolizumab to salvage chemotherapy in RR-HL.
- *n* = Number of patients needed for enrollment
- *r* = Number patients with complete response needed to reject the null hypothesis.
- α = Probability of making a Type I error.
- P = Power

Sample sizes based on exact binomial test

		Target α=5% (+3%)			Target α=10% (+3%)		
P_0	P_1	Exact α (%)	Exact Power	$r\backslash n$	Exact α (%)	Exact Power	$r\backslash n$
0.50	**0.70**	**4.94**	**80.70**	**24\37**	**9.24**	**80.86**	**18\28**
		6.80	77.08	19\29	10.50	77.09	15\23
		7.48	80.76	20\31	11.48	81.06	16\25
		5.51	77.17	21\32	12.39	84.34	17\27
		6.07	80.71	22\34			
		6.62	83.73	23\36			

10.4 Stopping Rule for Toxicity

There is no planned interim analysis of toxicity. Ongoing review by the treating investigators for unexpected toxicity is required. Participants will be closely monitored for grade ≥ 3 AEs, high rates of autoimmune SAEs, and inability to obtain adequate stem cell harvest.

10.5 Data Analyses Plans

10.5.1 Analytic Plan for Primary Objective

To address the primary aim, we will calculate the proportion of patients with complete responses (defined as FDG-PET/CT Deauville score ≤ 3) as (number of responders) / (number of evaluable patients). We will place a 95% confidence interval on this proportion.

10.5.2 Analytic Plan for Secondary Objectives

To address the secondary objective 2.2.1, we will tabulate the number and percentage of toxicities by type, grade, severity, and attribution.

To address the secondary objectives 2.2.2 and 2.2.3, we will generate Kaplan-Meier curves of EFS, OS, and TSLC, including lifetables of point estimates and associated standard errors, which would include the presentation of the 2-year estimate.

10.5.3 Analytic Plan for Exploratory Objectives

To address the exploratory objective 2.3.1, we will perform a Fisher's exact test of patients achieving complete remission (yes/no) versus presence/absence of expression of (a) PD-1 and (b) PD-L1. Kaplan-Meier curves of EFS and OS for presence versus absence of expression, will be generated, and a log rank test will be performed, for (a) PD-1 and (b) PD-L1.

To address the exploratory objective 2.3.4, we will perform a Fisher's exact test of patients achieving complete remission (yes/no) versus (a) CD4+CD25+PD-L1+ T lymphocytes and (b) CD4+CD62L+CD127+ T lymphocytes responders (yes/no). Kaplan-Meier curves of EFS and OS for presence versus absence of response, will be generated, and a log rank test will be performed, for (a) CD4+CD25+PD-L1+ T lymphocytes and (b) CD4+CD62L+CD127+ T lymphocytes.

To address the exploratory objective 2.3.5, we will perform a Fisher's exact test of patients achieving complete remission (yes/no) versus presence/absence chromosome

9p24.1 mutation. Kaplan-Meier curves of EFS and OS for presence versus absence of chromosome 9p24.1 mutation, will be generated, and a log rank test will be performed.

To address the exploratory objective 2.3.6, descriptive statistics will be generated to describe the ability to collect stem cells at the time of harvest as defined by number of pheresis sessions and amount of cells collected.

11 STUDY MANAGEMENT

11.2 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.

11.2.1 Protected Health Information (PHI and HIPAA)

HIPAA authorization will be discussed with the participants during the consenting process and participant agreement will be documented by signature on the IRB approved consent form. The participants' PHI that will be collected for this study will be from their medical record (EMR), information collected from lab tests, procedures, imaging, and research samples (blood, tumor tissue) as well as information from the participants medical history related to their disease. PHI that may be collected from the medical record includes the patient date of birth, MRN, initials, address, phone number and elements of diagnosis treatment and death dates.

Data will be stored per the Feinberg School of Medicine IT Data Security Plan. Any data abstracted from the EMR will be entered directly into a password protected database. Only those with training and access to the database approved through the study may enter and review the data. Data entered into the databases are de-identified, and only patient initials and study numbers (study ID) are included. In cases where data is captured on paper case report forms, patient initials and study numbers are used on these forms. Paper case report forms and any printed source are kept in a patient specific research folder that is stored in a locked file cabinet.

11.3 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 Merck. Amendments will be distributed by the lead institution (Northwestern) to all affiliate sites upon approval by the Northwestern University IRB.

11.4 Registration Procedures

Patients may not begin protocol treatment prior to registration. All patient registrations will be registered centrally through the Clinical Research 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.fsm.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.

Training on eCRF completion will be provided prior to 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.

11.5 Instructions for Participating Sites

Before the study can be initiated at any site, the following documentation must be provided to the Clinical Research 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.

11.6 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.

11.7 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.

11.7.1 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.

11.7.2 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.

11.8 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.

11.9 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.

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APPENDIX A

ECOG Performance Status

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

APPENDIX B

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 C

International Prognostic Score (IPS) for Advanced Hodgkin's Lymphoma

Component	Description	Points
Age ≥ 45	No	0
	Yes	1
Sex	Female	0
	Male	1
Albumin < 40 g/L	No	0
	Yes	1
Hemoglobin < 105 g/L	No	0
	Yes	1
Stage	Stage III	0
	Stage IV	1
Leukocytosis > 15,000 per mm^3	No	0
	Yes	1
Lymphopenia	Lymphocyte ct > 600/mm3 and ≥ 8% of WBC ct	0
	Lymphocyte ct ≤ 600/mm3 and < 8% of WBC ct	1
	Total	

The Hasenclever International Prognostic Score (IPS) was designed to predict five-year freedom from progression of disease[3]. With each additional adverse prognostic factor, the predicted rate is reduced by approximately 8%. The score was developed and validated based on a set of patients being treated in the 1980s with regimens including ABVD, MOPP and ABVD, and similar hybrid regimens. Treatment variations did not appear to affect the validity of the prognostic score.

APPENDIX D

Cockcroft-Gault Formula for Creatinine Clearance

$$\text{Female CrCl} = \frac{(140 - \text{age in years}) \times \text{weight in kg} \times 0.85}{72 \times \text{serum creatinine in mg/dL}}$$

$$\text{Male CrCl} = \frac{(140 - \text{age in years}) \times \text{weight in kg} \times 1.00}{72 \times \text{serum creatinine in mg/dL}}$$

APPENDIX E - Lugano 2014 Response Criteria

Response and Site	PET-CT–Based Response	CT-Based Response
Complete Lymph nodes and extralymphatic sites	**Complete metabolic response** 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	**Radiologic CR (all of following)** 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 Lymph nodes and extralymphatic sites	**Partial metabolic response** 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	**PR (all of the following)** ≥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 Spleen must have regressed by > 50% in length beyond normal
Organ enlargement	Not applicable	None
New lesions	None	Not applicable
Bone marrow	Residual uptake higher than uptake in normal marrow but reduced compared with baseline (diffuse uptake compatible with reactive changes from chemotherapy allowed). If there are persistent focal changes in the marrow in the context of a nodal	

	response, consideration should be given to further evaluation with MRI or biopsy or an interval scan	
No response or stable disease Target nodes/nodal masses, extranodal lesions	**No metabolic response** Score 4 or 5 with no significant change in FDG uptake from baseline at interim or end of treatment	**Stable disease** < 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 Individual target nodes/nodal masses	**Progressive metabolic disease** Score 4 or 5 with an increase in intensity of uptake from baseline and/or	**PD (at least 1 of the following)** 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 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
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	any axis, its presence must be unequivocal and must be attributable to lymphoma Assessable disease of any size unequivocally attributable to Lymphoma New or recurrent involvement
Bone marrow	New or recurrent FDG-avid foci	

APPENDIX F – PROTOCOL SUMMARY OF CHANGES

Amendment 1 – September 23, 2016 (FDA Response Part-1)			
Section(s) Affected	***Prior Version***	***Amendment 1 Changes***	***Rationale***
Cover Page	Locke Bryan listed as Co-Primary Investigator	Lists Locke Bryan as Co-Sub Investigator	Administrative – there cannot be more than one PI on the study
Cover Page	n/a	Adds IND Number/Holder information (131946 / Jane Winter, M.D.)	New information provided by FDA
Abbreviations	n/a	Adds DLCO, MUGA, and PFT's as expanded abbreviations	New procedures added that require abbreviation expansion
Study Summary	Listed short title of study	Removes short title	Administrative – no longer required
2.1 (Primary Objective); 6.3 (Efficacy Endpoints)	Lugano classification	Lugano criteria	Administrative wording preference
4.2.5 (Mobilization and Stem Cell Collection); 5.0 (Study Procedures #15)	n/a	Adds two paragraphs to describe the mobilization regimens and requirements for stem cell collection. Also clarifies stipulation that if the first collection during Cycle 2 is inadequate, patients may have another collection after the study PET/CT	FDA requested a description of mobilization regimens and collection procedures for stem cell harvest
4.3.1.1 (Dose Delays)	Pembrolizumab could be delayed a maximum of 35 days	Changes maximum delay for pembrolizumab to 21 days	The PI feels that a delay of 21 days is more appropriate as it allows for recovery of immune-mediated adverse events without unreasonably delaying treatment and disease control.
4.3.1.1 (Dose Delays)	"Pembrolizumab will be withheld for drug-related toxicities and SAEs"	Pembrolizumab will be withheld for drug-related toxicities, including SAE's"	Clarification – pembrolizumab is to be held for drug-related SAE's rather than all SAE's
4.3.3 (Treatment Stopping Criteria)	n/a	Compiles criteria for discontinuing treatment into two tables specifically for "stopping criteria" – one for stopping pembrozlizumab alone and one for stopping combination pembro-ICE	The FDA requested clearly outlined stopping rules for treatment related toxicity for ICE plus pembrolizumab
4.5 (Autologous Stem Cell Transplant)	n/a	Adds the following criteria required to initiate stem cell transplant: • ≥ $2x10^6$ cells/kg collected • Corrected DLCO of 60% • FEV1 or FVC >60% • Ejection fraction 5% less than institutional limits of normal • Calculated creatinine	The FDA requested that explicit requirements, that include end organ function, be listed for patients to initiate stem cell transplant

		clearance > 30mL/min (using Cockcroft-Gault formula; see Appendix D) • Liver function <2.5 x ULN	
4.8 (Duration of Follow Up); 7.7.1 (Overall Adverse Event Reporting Schedule)	n/a	Adds additional instructions for monitoring and recording adverse events: • Immune-mediated adverse events are to be followed for 90 days after last dose of pembrolizumab • ≥ Grade 3 adverse events are to be followed for 180 days after stem cell transplant	The FDA requested additional monitoring since immune effects are expected and it is unknown how pembrolizumab will impact toxicity in the peri-transplantation period
5.0 (Study Procedures)	n/a	Adds ECHO/MUGA and Pulmonary Functions Tests (PFT's) at the time of transplant	Procedures have been added to obtain recommended values for ejection fraction, DLCO, and FEV1/FVC in order for patients to proceed with transplant.
5.0 (Study Procedures)	Patients were to be followed every 3 and then 6 months months after stopping treatment for survival only	Adds follow-up visits at 60, 90, and 180 days post-transplant or study treatment with adverse event monitoring	To account for additional adverse event monitoring requested by the FDA
7.1 (Adverse Event Monitoring)	Refers to immune-mediated adverse events as Events of Clinical Interest (ECI's) and refers to section 8.6	Removes reference to ECI's and replaces reference to section 8.6 to 7.7.1	Immune-mediated AE's are not listed as ECI's, and there is more information in section 7.7.1
Appendix D	n/a	Adds Cockcroft Gault formulas for creatinine clearance	Added concurrently with the recommended creatinine clearance value prior to transplant
Amendment 1 – September 30, 2016 (FDA Response Part 2)			
Section(s) Affected	***Prior Version***	***Amendment 1 Changes***	***Rationale***
4.3.3.3 (Stopping Rules for Transplant-Related Toxicity); 5.0 (Study Procedures #16)	n/a	Adds criteria for which transplant-related toxicities (for example, failure or delayed engraftment) would require a re-evaluation of study effectiveness	It is unknown how the addition of pembrolizumab will impact the function of the hematopoietic stem cell graft, the preparative regimen, or transplantation. Therefore, the FDA requested more intensive monitoring and consideration for toxicities related to transplant and engraftment.
IRB Response – November 30, 2016			
Section(s) Affected	***Prior Version***	***Amendment 1 Changes***	***Rationale***
5.0 Study Procedures Footnote 16	Patients will have follow-up clinic visits at 60, 90, and	Patients will have follow-up clinic visits at 60, 90, and	Follow-up is only up to two years.

	180 days (±7 days) post-transplant (or post-study treatment) to assess adverse events according to the table in section 7.7.1. Engraftment will also be assessed as per section 4.3.3.3. Thereafter patients will be followed (either by routine clinic visit or by phone call) every 3 months for 2 years and then every 6 months up to 5 years total from start of study treatment to document survival and disease progression.	180 days (±7 days) post-transplant (or post-study treatment) to assess adverse events according to the table in section 7.7.1. Engraftment will also be assessed as per section 4.3.3.3. Thereafter patients will be followed (either by routine clinic visit or by phone call) every 3 months for 2 years from start of study treatment to document survival and disease progression.	
Study Schema diagram	Stem Cell Harvest	Peripheral Blood Stem Cell Harvest	For clarity.
Amendment 2 – February 15, 2017 *Approved by Scientific Review Committee – March 9, 2017*			
Section(s) Affected	***Prior Version***	***Amendment 2 Changes***	***Rationale***
Cover Page	n/a	Adds Reem Karmali as sub-investigator	Administrative; new disease team faculty
	Listed Yanming Zhang and Derek Wainwright as collaborators	Removes Yanming Zhang and replaces with Xinyan Lu; removes Derek Wainwright	Yanming Zhang no longer works at the university and Xinyan Lu is the new pathologist in that department; the Wainwright laboratory is currently at capacity for new studies
Study Schema	n/a	Adds cycle length of 21 days	Clarification
Study Summary; 2.3 (Exploratory Objectives); 5.0 (Study Procedures, #10); 6.4 (Exploratory Endpoints); 9.0 (Correlatives/ Special Studies); 10.5.3 (Analytic Plan for Exploratory Objectives)	Included exploratory objectives for serum biomarkers of immune and inflammatory response and soluble PD-L1	Removes serum biomarkers and soluble PD-L1 as exploratory objectives and correlative samples	Since the Wainwright laboratory is at capacity, these samples cannot be analyzed
1.9 (Exploratory Studies)	Included rationale for studying serum biomarkers and soluble PD-L1 in this study	Removes rationale	These correlative samples are no longer being collected
4.2 (Treatment Administration)	Numbered tables 1, 2, 3…)	Re-numbers tables by section (4.1, 4.2, 4.3…)	Administrative clarification
4.2.5 (Mobilization and Stem Cell Collection)	PBSCH was to take place 10-20 days after the second pembro-ICE treatment	PBSCH is to take place **within** 10-20 days after the second pembro-ICE treatment	Clarification to allow more flexibility
4.3.1.1 (Dose Delays); 4.3.3.1 (Pembrolizumab Stopping Criteria)	n/a	Adds pembrolizumab dose delay guidelines for cardiac dysfunction (related to	Additional guidelines provided by Merck as a result of new safety events

		myocarditis), Stevens-Johnson Syndrome, and Toxic Epidermal Necrolysis	
4.3.1.1 (Dose Delays)	"There are no dose modifications on the study protocol"	"There are no dose modifications **for pembrolizumab** on the study protocol"	Clarification; ICE may be modified per standard practice
4.3.1.5 (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)	n/a	#9: Adds urinalysis on day 2 of ICE chemotherapy	To assess for hematuria as part of standard of care related to ifosfamide treatment
	#12: Interim FDG-PET/CT to be obtained on day 14 (+/- 2 days), 14 days after pembrolizumab monotherapy	#12: Interim FDG-PET/CT to be obtained on day 14-22, at least 14 days after pembrolizumab monotherapy.	Clarification; the intention was for the PET/CT to take place at least two weeks after pembrolizumab
	Follow up visits at 60, 90, and 180 days had a window of ±7 days	Follow up visits now have a window of ±14 days	To allow flexibility in visit timing
	n/a	#19: Adds ECHO and/or ECG as clinically indicated at baselined for patients with history of CHF, and references section 4.3.1.5	Guidelines provided by CTEP as a result of myocarditis safety events related to nivolumab, an immunotherapy agent similar to pembrolizumab
8.3.4 (Storage and Stability); 8.5.5 (Protocol Dose Specifics); 8.5.9 (Side Effects); 11.10 (Publication Policy)	Missing section title	Adds appropriate section titles	Correction of typographical errors
Amendment 3 – August 8, 2017 *Approved by Scientific Review Committee – August 14 ,2017*			
Section(s) Affected	***Prior Version***	***Amendment 3 Changes***	***Rationale***
Cover Page; Study Summary; 3.0 (Patient Eligibility)	Included Hackensack University as an affiliate site (Andre Goy as sub-investigator)	Removes Hackensack University as affiliate site, and adds Emory University School of Medicine	Administrative
5.0 (Study Procedures)	Cycle 3, Day 14 was listed as a time point with PBSCH and FDG-PET/CT as relevant procedures	Changes time point to Day 14-22	Revised for clarity; FDG-PET/CT is to take place Day 14-22 of Cycle 3. PBSCH may also take place at this time if the initial collection is inadequate.
5.0 (Study Procedures)	Echocardiogram (+ECG) was listed as a procedure with time points at baseline (as indicated) and EOT	Moves ECG to be a separate procedure with a single time point at baseline (as indicated)	Revised for clarity; Echo/MUGA is required as part of the ASCT, but ECG should only be listed as a baseline procedure for patients with history of

			congestive heart failure
Amendment 4 – February 26th, 2018 Approved by Scientific Review Committee –			
Section(s) Affected	***Prior Version***	***Amendment 4 Changes***	***Rationale***
Cover Page	Included Jason Kaplan as Northwestern sub-I and Jonathon Cohen as the sub-I at Emory	Removes Jason Kaplan and Jonathon Cohen, and adds Pamela Allen as the sub-I at Emory	Administrative updates; Jason Kaplan has left Northwestern. Pamela Allen will be the new PI at Emory
Cover Page; 7.7.4.1 (Reporting to the Northwestern University QAM/DSMC); 11.4 (Registration Procedures)	Coordinating Center was listed as the Clinical Research Office at Northwestern University	Updates to "Clinical Trials Office" with appropriate contact information	Administrative update
3.0 (Patient Eligibility)	Listed accrual projections, estimating 6 patients per year would be accrued at Northwestern and 16 across all sites over 3 years	Removes accrual projection language.	Language is not necessary and has potential to conflict with internal contractual numbers, which may change over time.
3.1.6 (Inclusion Criteria)	Organ and bone marrow function was to be "adequate" within 10 days of registration	Removes specific window and just states that levels must be adequate prior to registration	To avoid deviations in eligibility, window for labs will be stated only in the study procedures
4.2 (Treatment Administration); 4.2.1 (Day 1 of Treatment); 4.2.2 (Day 2 of Combination Treatment); 4.2.3 (Day 3 of Combination Treatment)	Listed dexamethasone 10 mg IVP as a recommended pre-medication for ICE.	Removes dexamethasone as a pre-med and lists anti-emetics, with general recommendations for ondansetron and aprepitant	Dexamethasone acts to suppress immune activity, which counteracts the mechanism of the study drug.
4.3.1.1 (Dose Delays)	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.
4.3.1.2 (Rescue Medications & Supportive Care); 4.3.1.3 (Management of Immune-Related Adverse Events)	Regarding enterocolitis, patients with Grade 3 or 4 were to be permanently discontinued, and patinets with Grade 2 were to be held with corticosteroids recommended at 0.5 mg/kg/day prednisone	Enterocolitis should only cause discontinuation at Grade 4. Patients with Grade 2 or 3 enterocolitis should be held with corticosteroids at 1-2 mg/kg/day prednisone	Updated to reflect new dose delay table in 4.3.1.1
4.3.1.3 (Management of Immune-Related Adverse Events)	"Pneumocystis carinii"	Updated to "Pneumocystis jiroveci"	To align with updated terminilogy
4.3.1.4 (Management of Infusion Reactions)	Table reference contained an "Error! Reference source not found.	Updated to reference Table 4.3	Administrative to correct error
4.3.2 (Recommended ICE Chemotherapy Dose Management)	Guidelines for dose modifications were located as a table in section 4.3, and included a column for pembrolizumab. Ifosfasmide reductions were: Original dose: 5 g/m2 1st reduction: 3 g/m2	Moves table to section 4.3.2 and removes column for pembrolizumab. Ifosfamide reductions are changed to be more stepwise: Original dose: 5 g/m2 1st reduction: 4 g/m2 2nd reduction: 3 g/m2	The table portrays modifications only for the ICE regimen, so it is more appropriate in the section referencing ICE modifications. Clinical clarification

	2nd reduction: discontinue	Adds statement "In general there are no dose reductions recommended for hematologic toxicities"	
4.3.3 (Treatment Stopping Criteria); 4.10 (Patient Replacement); 4.11 (Suspension of Accrual); 6.3 (Efficacy Endpoints); 7.7.2 (Routine Reporting); 7.7.4 (Expedited Reporting of SAE's); 11.5 (Instructions for Participating Sites); 11.10 (Publication Policy)	Referenced NU's internal Data Monitoring Committee (DMC)	Updates references to the Data and Safety Monitoring Committee (DSMC)	Administrative update to align with new internal policies
4.7 (Duration of Therapy); 5.0 (Study Procedures, #2,3)	AHSCT was to be arranged within 21 days of the third pembrolizumab dose.	Updates to within 21-35 days of the third pembrolizumab dose	A larger window is more realistic and clinically appropriate
4.8 (Duration of Follow-Up)	Only referred to off-treatment visit 30 days after stem cell transplant	Adds follow-up visits at 60, 90, and 180 days post-transplant	To match requirements in study procedures table
5.0 (Study Procedures)	n/a	Adds quantiferon-gold TB blood test	Patients with active TB are excluded due to immune suppression; adds baseline lab for consistency
	#2 & 3: AHSCT was to take place within 21 days after cycle 3	#2 & 3: AHSCT should take place within 21-35 days after cycle 3	Previous window was too tight in the PI's opinion
	#10: Referenced section 10.0 for correlative sample details	#10: Updates reference to sections 6.4 and 9.0	Updated for accuracy
	#11: Diagnostic CT's were required at all time points. Baseline scan was required within 28 days prior to study registration.	#11: CT's no longer have to be diagnostic quality prior to ASCT. Baseline scans can be within 6 weeks / 42 days prior to study registration.	Broadens scan allowance to benefit patients with recent scans; this is clinically appropriate and allowable per PI.
	#12: PET/CT was required within 28 days prior to registration	#12: Updates baseline window to 6 weeks / 42 days	
5.0 (Study Procedures #9); 8.2.11 (Ifosfamide Nursing Implications)	#9: Required urinalysis every 8 hours for 24 hours after ifosfamide	#9: changes urinalysis to "per institutional standards" after ifosfamide	To allow investigator discretion in monitoring for hematuria post-chemo
7.6 (Events of Clinical Interest)	ECI's were to be reported to the "Sponsor" using "Adverse Event case report forms / worksheets"	ECI's should be reported to the assigned QAM using the NU CTO SAE Form	Updated to align with internal policies and SAE reporting procedures
8.1.4 (Storage and Stability); 8.1.6 (Preparation)	Referenced instructions for both lyophilized powder and solution constitutions	Removes reference to lyophilized powder	Merck only provides pembrolizumab as a solution
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
8.1.9 (Availability & Supply)	Listed Sloan Stribling and Tammy Moll as drug	Removes contacts and instead refers to the drug	Contacts were out of date, and reference to drug order

	ordering contacts	order form where contacts are listed.	form avoids the need for unnecessary amendment in the case of staff changes
8.1.12 (Return and Retention of Study Drug)	Referenced 9.1.4 for storage guidelines	Updates reference to 8.1.4	To fix discrepancy
8.3.5; 8.4.5 (Protocol dose specifics: Carboplatin; Etoposide)	Referenced Section 4.3, Table 2 and Table 3 for ICE dose modifications	Updates reference to Section 4.3.2, Table 4.5	To fix discrepancy
10.2 (Study Design and Study Endpoints	Referenced Section 3 for study endpoints	Updates reference to Section 6	To fix discrepancy
11.4 (Registration Procedures)	Referenced outdated NOTIS hyperlink	Updates hyperlink for NOTIS and adds instructions for eCRF training	Administrative update
11.6 (Data Management and Monitoring/Auditing)	Referenced NOTIS for Data Safety Monitoring Plan (DSMP)	Removes references to NOTIS and adds a relevant hyperlink to our "DSMP". Adds that data is generally due within 10 days of completion of every cycle	Administrative clarifications
Amendment 5 – May 25, 2018 *Approved by Scientific Review Committee –*			
Section(s) Affected	***Prior Version***	***Amendment 5 Changes***	***Rationale***
Cover Page	n/a	Adds Hatice Savas as a collaborator from Northwestern radiology	Central reviews of PET/CT's have been added to the study, which will be performed by Dr. Savas
4.1 (Overview); 5.0 (Study Procedures #12); 6.1.1 (Central Review of PET/CT)	n/a	Adds a central review of PET imaging at the interim analysis	To provide an unbiased research analysis of PET results
4.7 (Use in Pregnancy); 7.7 (Reporting of Pregnancy and Lactation to the Sponsor and to Merck)	n/a	Adds pregnancy requirements from the Merck standard template. Patients should be removed from the study if they become pregnant, and the investigator must follow and report outcomes of such pregnancies	To align with Merck and pembrolizumab requirements in case of pregnancy. Patients should not become pregnant while taking pembrolizumab due to likely side effects
Amendment 6– May 29, 2019 *Approved by Scientific Review Committee –*			
Section(s) Affected	***Prior Version***	***Amendment 6 Changes***	***Rationale***
Coverpage	Fred Rademaker listed as Biostatistician	Removes Fred Rademaker and adds Denise Scholtens.	Change in biostatistician for the study
List of Abbreviations	DSMB Data and Safety Monitoring Board	DSMC Data and Safety Monitoring Committee	Updated to reflect current abbreviation and name
4.2.5 (Mobilization and Stem Cell Harvest) 5.0 (Study Procedures #16) 6.4.4 (Stem Cell Harvest)	N/A States that PBCSH will be	Adds language to make timing of PBSCH more general with delays permitted. Changes to PBCSH to be collected within 30 days of	Provides flexibility of timing of PBSCH. Clarification

	collected within 30 days of PET/CT'	C3 pembrolizumab monotherapy dose	
4.8 (Duration of Therapy) 5.0 (Study Procedures #3)	AHSCT can be arranged preferably within 21-35 days of C3 PEM monotherapy dose	Updates to allow AHSCT to be arranged up to 42 days of C3 pembrolizumab monotherapy dose	To provide more flexibility in timing and match timing changes in 5.0 ASCT timing
5.0 (Study Procedures)	ECG completed at screening only	ECG completed at screening and prior to ASCT	Added for safety monitoring
5.0 (Study Procedures)	Timing of ASCT referenced in table as D85-D99	Changed to D64-85	Updated to agree with timing being within 21-42 days of C3 pembrolizumab monotherapy dose
5.0 (Study Procedures #3 and #11)	Transplant visit parameters should be obtained on the initial day or induction chemotherapy and CT scan within 7 days of ASCT	Adds that parameters can be obtained any time after final study regimen but prior to ASCT and that loosens the timeframe for CT to allow for it to be completed 2-3 weeks prior to ASCT	Provide flexibility in scheduling
5.0 (Study Procedures #11)	CT required prior to ASCT	Changes this to make the CT scan optional prior to ASCT	Updated due to change in practice and insurance approval
5.0 (Study Procedures #20)	N/A	Added footnote to clarify timeframe of ASCT if optional Cycle 4 is completed	Clarification
6.1.1 (Central Review of PET/CT)	N/A	Adds alternative option for providing scans for central review	Updated information.
6.1.1.1 (Analysis Using Total Metabolic Volume)	Contained specific methods for analysis.	Removes specific methods and adds general methodology.	Provides more general overview of how TMTV analysis.
6.4.4 (Stem Cell Harvest)	Inferred Stem Cell Harvest was optional.	Removes the word '*optional*'	Updates section to be consistent with other sections of the protocol.
8.1.10 (Side Effects) Pembrolizumab	N/A	Adds '*Please see the current IB for a comprehensive list of side effects and known frequencies of occurrence*'	Provides reference to IB for known side effects
Amendment 7– March 4, 2020			
Section(s) Affected	***Prior Version***	***Amendment Changes***	***Rationale***
Coverpage	Denise Scholtens listed as Biostatistician	Removes Denise Scholtens and adds Joan Chmiel.	Change in biostatistician for the study
Study Summary	States "*up to 40 patients for 37 evaluable*"	Updates to "*up to **43** patients for 37 evaluable*"	Increases accrual to ensure 37 evaluable patients for analysis.
Amendment 8– June 10, 2021			
Section(s) Affected	***Prior Version***	***Amendment Changes***	***Rationale***
4.9 (Duration of Follow Up); 5.0 (Study Procedures)	Sections stated that "…*patients will be followed (either by routine clinic visit or by phone call) every 3*	Section updated to "…*patients will be followed (either by routine clinic visit or by phone call) at least*	Increase the length of time patients are followed for progression and survival and to clarify that the follow

	months for 2 years total from start of study treatment..."	*one clinic visit every 3 months for to 2 years and then annually for 2 years (one visit at 3rd year and one visit at 4th year of follow up) for 4 years total post-transplant or post-study treatment."*	up period does not include time on study treatment.

Amendment 9– February 21, 2022

Section(s) Affected	***Prior Version***	***Amendment Changes***	***Rationale***
Coverpage	June 10th, 2021 (Amendment 8)	Changed to: *February 21st, 2022 (Amendment 9)*	Administrative revision
Table of Contents	N/A	Updates to page numbers and to include missing section headings to reflect current protocol content.	Administrative revision
11.2.1 (Protected Health Information)	N/A	Section added as follows: *"HIPAA authorization will be discussed with the participants during the consenting process and participant agreement will be documented by signature on the IRB approved consent form. The participants' PHI that will be collected for this study will be from their medical record (EMR), information collected from lab tests, procedures, imaging, and research samples (blood, tumor tissue) as well as information from the participants medical history related to their disease. PHI that may be collected from the medical record includes the patient date of birth, MRN, initials, address, phone number and elements of diagnosis treatment and death dates.* *Data will be stored per the Feinberg School of Medicine IT Data Security Plan. Any data abstracted from the EMR will be entered directly into a password protected database. Only those with training and access to the database approved through the study may enter and review the data. Data entered into the databases are de-identified, and only patient initials and study numbers (study ID) are included. In cases where data is captured on paper case report forms, patient initials and study numbers are used on these forms. Paper case report forms and any printed source are kept in a patient specific research folder that is stored in a locked file cabinet. "*	Updated to conform with data security plan language, current informed consent addendum and institutional requirements.