Nivolumab with standard of care chemotherapy for the first line treatment of peripheral T cell lymphoma

Protocol Number:	CA209-8J6
COMIRB Number:	18-0708
Principal Investigator:	Bradley Haverkos, MD
IND/IDE:	139751
Coordinating Center and Lead Principal Investigator:	University of Colorado, Bradley Haverkos
Funded by:	Bristol-Myers Squibb
Version Date:	Version 7.0, Dated October 8, 2020

STATEMENT OF COMPLIANCE

This is an investigator-initiated study. The principal investigator (PI), Bradley Haverkos, MD, is conducting the study and acting as the sponsor. As the sponsor-investigator, both the legal/ethical obligations of a PI and those of a sponsor will be followed.

The trial will be carried out in accordance with Good Clinical Practice (GCP) as required by applicable United States (US) laws and applications, including but not limited to United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, 21 CFR Part 312, and/or 21 CFR Part 812).

The PI will assure that no changes to the protocol will take place without documented approval from the Institutional Review Board (IRB). All personnel involved in the conduct of this study have completed Human Subjects Protection Training.

I agree to ensure that all staff members involved in the conduct of this study are informed about their obligations in meeting the above commitments.

Sponsor-Lead Principal Investigator: Bradley Haverkos, MD
Print/Type Name

Signed: _____ **Date:** _____

Site Principal Investigator: _____
Print/Type Name

Signed: _____ **Date:** _____

LIST OF ABBREVIATIONS

ACRONYM	DESCRIPTION
AITL	angioimmunoblastic T cell lymphoma
BEAM	BCNU, etoposide, cytarabine, melphalan
BMS	Bristol-Meyers Squibb
CHOP	cyclophosphamide, doxorubicin, vincristine, prednisone
CHOEP	CHOP with etoposide
CNSL	central nervous system lymphoma
CTL	cytotoxic T lymphocytes
CTX	cyclophosphamide
DA-EPOCH	dose adjusted, continuous infusion etoposide, prednisone, vincristine, doxorubicin, and bolus dosing of cyclophosphamide
DLBCL	diffuse large B-cell lymphoma
EPOCH	etoposide, prednisone, vincristine, doxorubicin, cyclophosphamide
PJP	Pneumocystis Jiroveci Pneumonia
PTCL	peripheral T cell lymphoma
R-CHOP	CHOP with rituximab
SJS	Stevens-Johnson syndrome
TEN	toxic epidermal necrolysis
VCR	vincristine

PROTOCOL SUMMARY / SYNOPSIS

Protocol Title: Nivolumab with standard of care chemotherapy for the first line treatment of peripheral T cell lymphoma

Objectives:

- **Primary Objectives:**
  A pilot/feasibility study to evaluate the efficacy of nivolumab when given in combination with dose adjusted EPOCH for the first line management of peripheral T cell lymphoma.

- **Secondary Objectives:**
  Progression free survival, duration of response, overall response rate (CR + PR), toxicity.

  Correlative analysis: Determine immune-related predictors of response to nivolumab + EPOCH chemotherapy using blood and tumor tissue specimens.

Endpoint:

- **Primary Endpoints:**
  Efficacy (Complete response rate)

- **Secondary Endpoint:**
  2year progression free survival (Maurer et al. JCO 2017), duration of response, overall response rate (CR+PR), safety/toxicity.

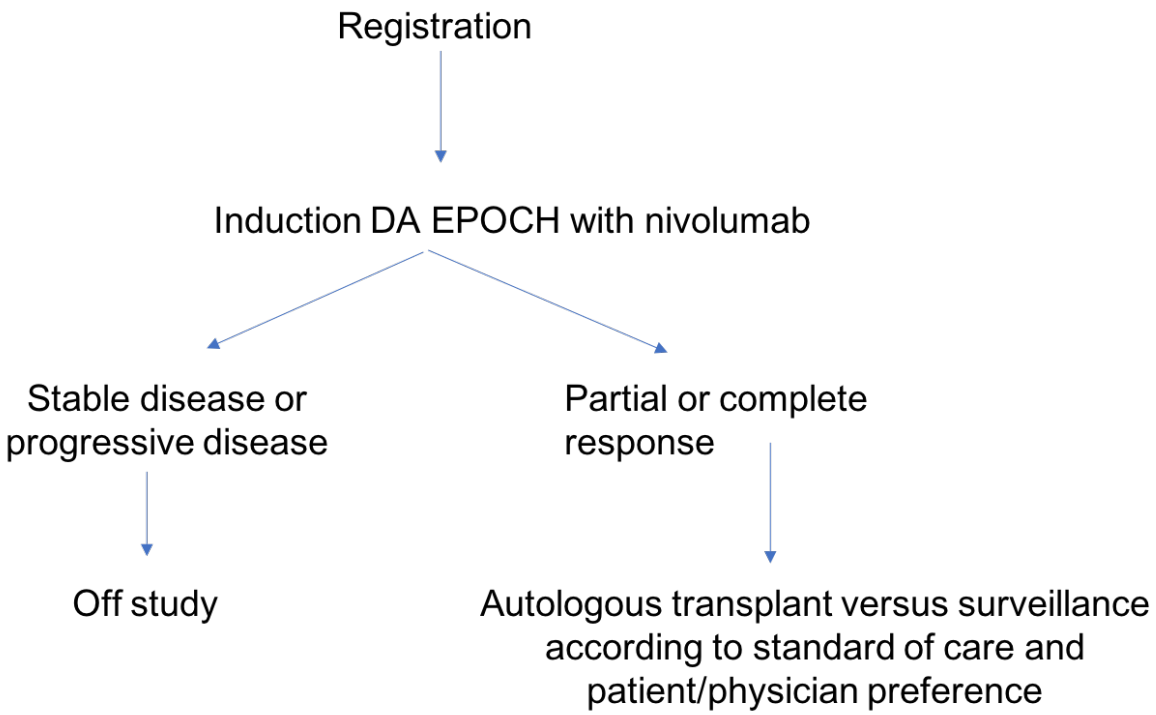
Population:

- **Sample size**
  - Maximum number of participants that can be enrolled is 18 (not including screen failures)
  - Minimum number of participants to be enrolled 12 (number of participants needed to answer scientific question/aims)
- **Gender** Male or Female
- **Age Range** 18-80 years old.
- **Demographic group** Any
- **General health status** ECOG 0-2
- **Geographic location** Participating medical center

Phase: I/II

Number of Participating Sites:	3
Description of Study Agent:	PD-1 checkpoint antibody
Study Duration:	Patient enrollment is expected to last for 2 years. Patients will be followed for outcome measures for up to 2 years after enrollment in study.

SCHEMATIC OF STUDY DESIGN



1 PARTICIPATING SITES

A complete and current listing of investigators, research personnel, research facilities and other study centers (if applicable) participating in this study will be maintained throughout the duration of this study on a **Protocol Contact List** form, incorporated herein by reference.

Thomas Jefferson University, Pierluigi Porcu MD

City of Hope, Jasmine Zain MD

2 INTRODUCTION: BACKGROUND INFORMATION AND SCIENTIFIC RATIONALE

2.1 BACKGROUND INFORMATION

Peripheral T cell lymphomas (PTCL) comprise a heterogeneous group of non-Hodgkin lymphomas that have consistently demonstrated poor outcomes when treated with anthracycline based chemotherapy regimens (e.g. CHOP). When treated with CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone), the overall response rate (ORR) for PTCL is 50-70%, with a progression free survival (PFS) of 30-40% at 12 months (1, 2) and long term disease free survival rates of 20-30% (2). In an attempt to improve upon these outcomes, more intensive combination chemotherapy approaches, such as CHOEP (CHOP with etoposide) or DA-EPOCH (dose adjusted, continuous infusion etoposide, prednisone, vincristine, doxorubicin, and bolus dosing of cyclophosphamide), have been used. Based on retrospective and post-hoc analysis, outcomes appear improved in PTCL patients treated with etoposide containing regimens (1, 3, 4). As a result, EPOCH has emerged as a first line chemotherapeutic option for patients with PTCL at the University of Colorado, as well as other centers (5-8). Nevertheless, long term outcomes in patients with PTCL continue to be sub-optimal with current estimates of 5-year survival of 10-30% (9).

Checkpoint blockade is an exciting new therapeutic approach in oncology that has improved the standard of care in multiple hematologic and solid tumor malignancies. Less is known about the use of checkpoint blockade for the treatment of T cell lymphomas relative to other malignancies. Nivolumab had a response rate of 40% in PTCL in a phase 1 study (10). In a heavily pretreated advanced stage cutaneous T-cell lymphoma cohort, pembrolizumab showed an ORR of ~40% with meaningful durable responses (11). Additionally, 5 out of 7 patients with relapsed/refractory NK/T-cell lymphoma after L-asparaginase based therapy had a complete response to pembrolizumab (2 PRs) (12).

Mechanistically, there is reason to believe that PD-1 inhibition will be effective for the treatment of PTCL. In lung cancer, increased PD-L1 expression is associated with increased response rates to PD-1/PD-L1 antibodies (13). In T-cell lymphomas, PD-1 expression on tumor cells is frequent. For instance, 93% of angioimmunoblastic T cell lymphomas (AITL) and 62% of PTCL-NOS have

increased number of extrafollicular PD-1 positive cells. PD-1 expression can also be used to aid in the diagnosis of PTCL (14).

Furthermore, the microenvironment is expected to play a significant role in the etiopathogenesis of PTCL (15). The programmed death (PD) pathway serves as a checkpoint to limit T-cell mediated immune responses. Blocking the PD-1 receptor on T-cell results in T-cell activation and proliferation, inducing a potent immunotherapeutic antitumor effect. Nivolumab inhibits the ligation of PD-1 and PD-L1 and would be expected to alter the microenvironment stimulating T-cell mediated anti-tumor immune responses (16).

2.2 RATIONALE

Unfortunately, checkpoint blockade as a single treatment modality produces durable responses only in a minority of patients with PTCL. As a result, a current major area of interest lies in determining how to improve responses to this novel class of therapeutics. One approach that has demonstrated promise is via rational combination with other therapeutics with distinct yet complementary mechanisms of action. As chemotherapy regimens like EPOCH are effective (albeit with modest long-term success) for patients with PTCL, approaches that combine chemotherapy with PD-1/PD-L1 antibodies are appealing. Mechanistically, it has been demonstrated that chemotherapy-induced apoptotic cells behave as a potent source of immunogenic tumor antigens for the stimulation of cytotoxic T lymphocytes (CTL) (17). It has subsequently been demonstrated that multiple components of the EPOCH regimen, including etoposide, cyclophosphamide, and vincristine increase antigen presentation and MHC expression, thus triggering an immune response (18, 19). Further, chemotherapy may increase the activity of immune effector cells such as NK cells, while also suppressing the effects of negative regulators of an immune response such as T-regulatory cells and myeloid derived suppressor cells (20). These immune-modulating effects of chemotherapy may allow for synergism with checkpoint blockade. Of note, it has been demonstrated that increased expression of antigens via MHC II has been correlated with response to checkpoint blockade in melanoma (21). Similarly, loss of function mutations in JAK/STAT and beta-2-microglobulin proteins leading to decreased expression of MHC I has been associated with acquired resistance to checkpoint blockade (22).

Patients receiving checkpoint blockade in later lines of therapy tend to be more de-conditioned and have weakened immunity after failing prior lines of chemotherapy. In solid tumors, checkpoint blockade in combination with standard first line chemotherapy regimens appears to be a safe and potentially synergistic combination. For instance, the response rate for pembrolizumab plus standard of care pemetrexed/carboplatin in first line lung cancer is 57%; the response rate for chemotherapy alone was 30% (23). Of note, the response rate for second line checkpoint blockade in unselected non-small cell lung cancer is about 19% (24). Despite a 75% crossover rate to PD-1 blockade in the chemotherapy alone arm, the hazard ratio for survival in this randomized study was 0.69, favoring combination PD-1 blockade with chemotherapy in the first line setting. This study led to FDA approval for pembrolizumab plus chemotherapy in the first line treatment of non-small cell lung cancer.

There are currently two ongoing studies combining checkpoint blockade with standard first line R-CHOP in B cell lymphomas (Clinicaltrials.gov NCT02541565; and NCT03003520). We are not aware of any concerning safety signals that have emerged from these studies; however, there are no trials on clinicaltrials.gov combining checkpoint blockade with EPOCH.

Thus, we are conducting a multi-center phase I/II study of standard of care EPOCH in combination with nivolumab for the first-line treatment of PTCL.

2.3 POTENTIAL RISKS AND BENEFITS

Patients in this study will be offered standard of care first-line chemotherapy (i.e. EPOCH) in addition to an experimental drug, nivolumab. As discussed in sections 2.1 and 2.2, nivolumab and other checkpoint inhibitors have demonstrated activity in relatively small early studies of patients with relapsed refractory T-cell lymphoma. Further, multiple trials are being conducted combining PD-1 checkpoint antibodies with first line chemotherapy, including trials in lung cancer (23), gastric cancer (25), as well as diffuse large B-cell lymphoma (DLBCL) (26). Importantly, all of these studies have demonstrated evidence of therapeutic activity, as well as reasonable toxicity profiles when combining chemotherapy with PD-1 antibody immunotherapy. Thus, PD-1 immunotherapy in combination with first line chemotherapy appears to be an effective and tolerable approach in multiple tumor types in preliminary investigations.

Nivolumab has been given to a large number of patients with diverse malignancies. As a result, nivolumab has a well characterized toxicity profile, outlined below. Nevertheless, the toxicity profile of nivolumab specifically in patients with peripheral T cell lymphoma (PTCL) has not been completely characterized given the small number of patients with PTCL who have received nivolumab. Further, few if any prior patients with PTCL have been treated with DA-EPOCH in combination with nivolumab. Thus, potential interactions of the drug components of DA-EPOCH with nivolumab are not yet completely characterized.

Of note, a recent pre-clinical study found that PD-1 may act as a tumor suppressor and PD-1 inhibition may lead to proliferation of lymphoma cells in a genetic PTCL mouse model (27). This pre-clinical model relied on translocation of ITK-SYK, which has been observed in 5/46 cases of PTCL (28). Similarly, a recent clinical study of PD-1 immunotherapy for T-cell leukemia lymphoma was stopped prematurely due to rapid progression of the initial enrolled patients(29). T-cell lymphomas are a heterogenous group of malignancies, and the subset of T-cell leukemia lymphoma that demonstrated rapid progression in response to PD-1 immunotherapy will not be enrolled in this study. Nevertheless, while it has not been observed clinically to date, it remains possible that PD-1 inhibition may lead to rapid progression in other subtypes of T-cell lymphoma. Importantly, if PD-1 treatment does lead to enhanced proliferation of malignant cells, the tumor would theoretically have increased sensitivity to the intensive chemotherapy component of our treatment protocol. Nevertheless, careful stopping rules and patient monitoring have been integrated into our protocol to ensure the safety of the enrolled patients.

2.3.1 KNOWN POTENTIAL RISKS

Nivolumab Monotherapy

MDX1106-01 was a Phase 1, open-label, multicenter, safety and pharmacokinetic dose-escalation study of nivolumab (0.3, 1, 3, or 10 mg/kg) in subjects with selected refractory or relapsed malignancies. 27 of 39 subjects received a single dose of nivolumab and 15 of those 27 received 10 mg/kg. All subjects were followed for up to 84 days after the dose of study drug.

The following are the key safety findings(30):

24 of 27 (88.9%) subjects had a drug-related AE. The most commonly reported (≥5%) drug-related AEs were: fatigue, lymphopenia, proteinuria, dry mouth, fever, decreased weight, pruritus, hypocalcemia, anemia, nausea, vomiting, TSH increased, TSH decreased, hypokalemia, myalgia, and rash. No drug-related AEs were serious. Most drug-related AEs were Grade 1 or 2. Nine (33.3%) subjects had Grade 3 or 4 drug-related AEs; the most commonly reported drug-related AEs were CD4 lymphocytes decreased (N=4) and lymphocyte count decreased (N=2)(30).

7 of 27 (25.9%) subjects had an immune-mediated adverse event. These included rash/erythema (N=4), pruritus (N=3), arthritis (N=1), melena (N=1), hypersensitivity (N=1), blood bilirubin increased (N=1). No immune-mediated adverse events were serious. All immune-mediated adverse events were Grade 1 except for the case of hypersensitivity which was Grade 2(30).

There was no apparent dose-related pattern with regard to the incidence, severity, or relationship of AEs(30).

Nivolumab in Combination with Chemotherapy:
In CA209012, a completed, multi-arm, Phase 1 safety study of nivolumab in chemotherapy-naive NSCLC subjects, 56 subjects were administered nivolumab in combination with chemotherapy (gemcitabine/cisplatin, pemetrexed/cisplatin, or carboplatin/paclitaxel)(31).

The maximum evaluated dose was 10 mg/kg of nivolumab in combination with chemotherapy. No dose-limiting toxicities (DLTs) were reported in any subjects receiving nivolumab + platinum-based chemotherapy during the protocol-defined evaluation period (first 6 weeks of treatment) and, thus, no MTD was defined. The safety profile of nivolumab in combination with chemotherapy was manageable and consistent with that reported for nivolumab monotherapy and platinum-based doublet chemotherapy alone. No new safety concerns were identified.

The following were the key safety findings:

The most frequently reported drug-related AE with nivolumab + chemotherapy was fatigue (71.4%)(31).

Drug-related SAEs reported in more than 2 subjects treated with nivolumab in combination with chemotherapy included pneumonitis (7.1%), anemia (5.4%), febrile neutropenia (3.6%), and rash maculo-papular (3.6%)(31).
Drug-related AEs leading to discontinuation reported in more than 2 subjects treated with nivolumab in combination with chemotherapy included pneumonitis (5.4%) and hypersensitivity (3.6%)(31).

Most deaths in CA209012 were due to disease progression. There were no deaths reported due to study drug toxicity in subjects treated with nivolumab + chemotherapy(31).

PD-1 Immunotherapy in Combination with R-CHOP:

An ongoing study is evaluating the safety of pembrolizumab in combination with R-CHOP chemotherapy. The preliminary safety results were presented at ASH 2017(26). Safety results were available for the initial 14 patients. Of these, median age is 62 (range 38-72); NCCN-IPI is low, low-int, and high-int, and high in 2,6,6, and 0 pts respectively. 2/9 tested are double-expressers (MYC IHC >40%, BCL2 IHC>50%), and no patients have double hit (now high-grade B-cell) lymphoma.

Eleven grade 3-5 clinically significant adverse have occurred, in 7 unique patients (7/14 patients, 50%). Eight serious adverse events occurred in 5 patients; none met criteria for reporting as an unanticipated event. One death occurred in the first accrued patient who had extensive gastric involvement by DLBCL and died during cycle 1 of RCHOP of bleeding from the responding tumor bed despite maximal inpatient intervention. Two probable immune-related adverse events were seen: grade 3 rash, resolving with steroid and not recurring on continuation of pembrolizumab and grade 1 hyperthyroidism. No instances of pneumonitis were observed, and no serious immune-related adverse events were seen.

2.3.2 KNOWN POTENTIAL BENEFITS

Nivolumab has demonstrated evidence of clinical activity in multiple malignancies, including in early phase studies of PTCL (10, 12). Nivolumab may increase the likelihood of improved outcomes in patients with PTCL, though further studies are needed.

The risks to participants are reasonable in relation to the anticipated benefits to participants and/or society, and in relation to the importance of the knowledge that may reasonably be expected to result, thereby falling in favor of performing the study:

- To Participant: Potential to improve management of malignancy.
- To Society: Improved understanding of the role of nivolumab in the management of PTCL.
- Justify the importance of the knowledge gained: PD-1 immunotherapy has led to improved outcomes in patients with a large number of malignancies, including melanoma, non-small cell lung cancer, Hodgkin's disease, and others. However, there is a relative paucity of information regarding the efficacy of PD-1 immunotherapy in patients with PTCL. This protocol will provide

valuable insights into the potential role of nivolumab in the management of PTCL.

3 OBJECTIVES AND PURPOSE

Primary objectives:
Pilot/feasibility study to measure the efficacy of nivolumab when given in combination with dose adjusted EPOCH for the first line management of peripheral T cell lymphoma.

Secondary objectives:
Progression free survival (PFS), overall response rate (CR + PR), toxicity/safety and duration of response.

Correlative analysis:
Determine immune-related predictors of response to nivolumab plus EPOCH chemotherapy.

Rationale for correlative analysis: Data is rapidly accumulating on baseline factors that predict response to checkpoint blockade in patients with solid tumors. Further, dynamic changes in peripheral blood and tumor immune profiling also associate with response to immunotherapy; however, less is known about predictive correlates associated with T-cell lymphomas, especially in patients receiving checkpoint blockade in combination with chemotherapy.

4 STUDY DESIGN AND ENDPOINTS

4.1 DESCRIPTION OF THE STUDY DESIGN

Single arm, open-label, Phase I/II interventional study in order to assess the safety and efficacy of nivolumab with dose adjusted EPOCH for the treatment of peripheral T cell lymphoma.

The planned accrual for this study is 18 patients. Patients will all receive nivolumab in combination with standard dose-adjusted EPOCH for a planned 6 cycles unless treatment is stopped early for disease progression or toxicity. Patients that have already received up to 1 cycle of standard of care chemotherapy will also be eligible for this study. Patients that had already received 1 cycle of standard of care chemotherapy will receive 5 cycles of experimental nivolumab + DA-EPOCH for a total of 6 cycles of chemotherapy. After completion of 6 cycles, patients that had a response will have the option of autologous stem cell transplant versus surveillance. This decision will be made according to standard of care (e.g. patient and physician preference).

Study enrollment will continue until stopping endpoints as described below.

Stopping rules for efficacy: If 3 or fewer complete responses are observed in initial 10 patients trial will be stopped for lack of efficacy. See section 8.5 for statistical calculations.

Treatment-related mortality: If any patient experiences death due to an adverse event that is assessed as related to study treatment (by investigator and/or Sponsor), it will lead to temporary hold of study pending review by study team. The study will be terminated prematurely if at any point 2 patients experience treatment-related death during induction chemotherapy with study regimen.

Toxicities of special interest: The study will be halted prematurely if 3 out of the initial 10 patients experience the following toxicities:

Grade 3 or higher pneumonitis
Grade 3 or higher colitis
Rapid progression, at discretion of investigator, upon initiation of treatment
Grade 4 hepatitis
Grade 4 rash
Grade 4 encephalitis
Grade 3 or higher myocarditis
Other grade 4 or unmanageable immune related events attributable to the study treatment.

Transplant-related adverse events of special interest: For patients undergoing auto-transplant the study will be halted prematurely if 3 out of initial 10 patients undergoing auto-transplant experience the following toxicities of special interest during period from start of conditioning regimen (e.g. BEAM) through 60 days post-transplant:

Non-relapse related death,
grade 4 or higher hepatotoxicity
autograft mobilization failure.

Of note, the study will accrue continuously, and will not stop enrollment of patients while analysis of stopping endpoints are underway.

Patients will continue to receive study therapy until disease progression according to RECIL, unacceptable toxicity, death, patient or physician decision to withdraw, pregnancy or completion of induction chemotherapy, whichever occurs first.

The study will end when all patients enrolled have been followed until death, have withdrawn consent, have been lost to follow-up, until 2-year follow up, or the Sponsor decides to end the trial, whichever occurs first.

4.2 STUDY ENDPOINTS

4.2.1 PRIMARY ENDPOINTS

Efficacy: Complete responses will be assessed by investigator and will be based on PET/CT scan to be obtained after 6 cycles of induction chemotherapy (overall response rate, complete response

rate, partial response rate, rate of stable disease, and rate of progressive disease according to RECIL). We anticipate a complete response rate > 56% for the treatment of nivolumab with DA-EPOCH for PTCL. Responses will be assessed by the investigator and will be based on PET/CT scan to be obtained after 6 cycles of induction chemotherapy. Patients with rapid progression after completion of induction chemotherapy, e.g. within 6 weeks following CR, will not be considered to have achieved a complete remission but will be considered non-responders.

4.2.2 SECONDARY ENDPOINTS

Two-year PFS (32). PFS is defined as time from enrollment to PD or death of any cause. Living patients without PD who are lost to follow up will have their information censored at date of most recent tumor assessment. Overall response rate is defined as the rate of complete responses + partial responses. Minor responses will not count towards the overall response rate. Duration of response is defined as time elapsed from initial evidence of either a PR or CR, until patient is found to have disease progression or death. Toxicity and tolerability will be monitored, and adverse events will be quantified.

5 STUDY ENROLLMENT AND WITHDRAWAL

5.1 PARTICIPANT INCLUSION CRITERIA

In order to be eligible to participate in this study, an individual must meet all of the following criteria:

1. Ability to sign and date the consent form.
2. Stated willingness to comply with all study procedures and be available for the duration of the study.
3. Be a male or female aged 18-80.
4. Histologically confirmed new diagnosis of Stage II, III or IV Peripheral T-cell Non-Hodgkin's lymphoma not otherwise specified (NOS), Anaplastic large cell lymphoma (ALK negative) (ALK positive if IPI 3, 4, or 5), Angioimmunoblastic T-cell lymphoma, Enteropathy associated T-cell lymphoma (MEITL and EATL), Hepatosplenic T-cell lymphoma, γ/δ T-cell lymphoma, Subcutaneous panniculitis like T-cell lymphoma, and Nodal T-cell lymphomas with T-follicular helper phenotype.
5. Available pathology material (fine needle aspirate is inadequate) for review at University of Colorado -- see section 7.3.1 for further information.
6. No prior therapy with the exception of prior radiation therapy and/or 1 cycle of chemotherapy (may be any chemotherapy regimen or even prednisone alone) based on current diagnosis and clinical condition. If given cytotoxic chemotherapy (one cycle only, e.g. CHOP), this cycle of treatment will count toward the 6 cycles of treatment given in the study.

7. ECOG performance status 0 - 2.
8. Laboratory status as follows:
   - ANC > 1000 cells/mm^3, unless cytopenias due to lymphoma (i.e., bone marrow involvement or splenomegaly)
   - Platelet Count > 100,000 /μL, or > 50,000 /μL if bone marrow involvement or splenomegaly
   - Total bilirubin ≤1.5 x upper normal limit, or ≤ 3 x upper normal limit if documented hepatic involvement with lymphoma, or ≤ 5 x upper normal limit if history of Gilbert's Disease.
   - Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤ 2.5 x upper normal limit (≤ 5 x upper normal limit if documented hepatic involvement with lymphoma).
   - Serum creatinine < 2.0 mg/dL or calculated creatinine clearance (CrCl) > 45 mL/min (Cockcroft-Gault, Appendix)
   - PT or INR, and PTT ≤ 1.5 x upper limit of normal unless patient is receiving anticoagulants. If patient is on warfarin therapy, levels should be within therapeutic range.
9. Patients with measurable disease. Measurable disease is defined as having at least one objective measurable disease parameter. A clearly defined, bi-dimensionally measurable defect or mass measuring at least 1.5 cm in diameter on the CT portion of a PET/CT or CT scan or MRI (if appropriate) will constitute measurable disease. Proof of lymphoma in the liver is required by a confirmation biopsy unless there is measurable disease by imaging. Skin lesions can be used as measurable disease provided bi-dimensional measurements are possible. Patients with non-measurable but evaluable disease may be eligible after discussion with the PI. Abnormal PET/CT scans will not constitute evaluable disease, unless verified by the CT scan portion, CT scan, or other appropriate imaging.
10. For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use of contraceptive methods that result in a failure rate of < 1% per year during the treatment period and for at least 180 days after the last study treatment. A woman is considered to be of childbearing potential if she is post-menarchal, has not reached a postmenopausal state (≥ 12 continuous months of amenorrhea with no identified cause other than menopause), and has not undergone surgical sterilization (removal of ovaries and/or uterus). Examples of contraceptive methods with a failure rate of < 1% per year include bilateral tubal ligation, male sterilization, hormonal contraceptives that inhibit ovulation, hormone-releasing intrauterine devices and copper intrauterine devices. The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g. calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of contraception.

11. Patient must be able to adhere to the study visit schedule and other protocol requirements.

5.2 PARTICIPANT EXCLUSION CRITERIA

An individual who meets any of the following criteria will be excluded from participation in this study:

1. An additional malignancy treated with palliative intent within the past 2 years. Malignancies in patients who have completed definitive treatment with curative intent >1 year will be permitted after discussion with the PI. Adequately treated basal cell, squamous cell skin cancer, or thyroid cancer; carcinoma in situ of the cervix or breast; prostate cancer of Gleason Grade 6 or less with stable PSA levels are allowed.
2. Patients with a diagnosis of other PTCL histologies other than those specified in the inclusion criteria.
3. Primary T-cell CNS lymphoma; however, secondary CNS disease is not an exclusion criteria.
4. Pregnant or breastfeeding females.
5. Contraindication to any of the required concomitant drugs or supportive treatments.
6. Any other clinically significant medical disease or condition laboratory abnormality or psychiatric illness that, in the investigator's opinion, may interfere with protocol adherence or a subject's ability to give informed consent.
7. Ejection fraction of <45% by either MUGA or ECHO.
8. Has immunodeficiency or is being treated with immuno-suppressive therapy (aside from medications used to treat lymphoma) within 7 days of first dose of study treatment. Inhaled or topical steroids are accepted. Prednisone used to treat adrenal insufficiency in the absence of auto-immune disease is also acceptable.
9. Auto-immune condition requiring immuno-suppressive disease modifying therapy within the prior 2 years. Replacement therapy, e.g. levothyroxine for thyroiditis or insulin for diabetes are acceptable.
10. History of non-infectious pneumonitis requiring immuno-suppressive therapy.
11. Active hepatitis B or C (with measurable virus or antigen in serum) or HIV. Patients who are seropositive because of hepatitis B virus vaccine or have a history of hepatitis B (with no measurable virus or antigen in serum) are eligible.
12. Prior PD-1 or PD-L1 antibody treatment.
13. Has received a live virus vaccine in 30 days preceding start of therapy.

5.3 STRATEGIES FOR RECRUITMENT AND RETENTION

Newly diagnosed patients with PTCL at participating institutions will be presented with the options of standard of care chemotherapy versus study participation. The study will also be posted on clinicaltrials.gov. Given the benefit observed for PD-1 immunotherapy in multiple disease types, we anticipate that patients may be referred to participating institutions specifically to enroll in this trial.

5.4 PARTICIPANT WITHDRAWAL OR TERMINATION

5.4.1 REASONS FOR WITHDRAWAL OR TERMINATION

The subject may withdraw consent at any time for all or certain aspects of the study as follows:

- Withdraw consent for study treatment, but allow follow-up period assessments and data collection on subsequent anti-lymphoma therapy and PFS
- Withdraw consent for study treatment and follow-up period assessments, but allow data collection on subsequent anti-lymphoma therapy and overall survival
- Withdraw all consent

Note: if a patient chooses to voluntarily withdraw from study, then documentation must be made regarding if patient chooses to simply discontinue study treatment, or if patient also no longer wants to be followed for treatment outcomes (and thus opts out of study related follow up).
Investigational study drug MUST be terminated for any of the following reasons:

- Subject's request to stop study treatment
- Any clinical adverse event (AE), laboratory abnormality or intercurrent illness, which, in the opinion of the investigator, indicates that continued participation in the study is not in the best interest of the subject.
- Termination of the study by the study sponsor
- Loss of ability to freely provide consent through imprisonment or involuntarily incarceration for treatment of either a psychiatric or physical (e.g., infectious disease) illness
- Disease progression assessed by RECIL criteria
- Pregnancy or intention to become pregnant
- Patient non-adherence
- Initiation of an alternative anti-cancer therapy

5.4.2 HANDLING OF PARTICIPANT WITHDRAWALS OR TERMINATION

Should a patient choose to withdraw voluntarily from the study at any time, study drug will be terminated, and the patient will proceed to treatment according to standard of care. Study-related information accumulated prior to the patient's withdrawal of consent will be analyzed according to intention to treat analysis.

Subjects that discontinue study drug will remain on study and continue to follow specified follow-up procedures. If a subject wishes to withdraw consent for all study-related follow up, then the patient should notify the investigator of this request. The patient's request should be in writing if possible. The investigator should document in the medical records in detail if the patient's withdrawal is from study treatment or also from all study-related follow up. However, an investigator may consult public records, such as those establishing survival status.

5.5 PREMATURE TERMINATION OR SUSPENSION OF STUDY (STUDY STOPPING RULES)

Monthly teleconferences will be held with all participating sites to exchange findings and unexpected results that may occur in patients participating in this study. Stopping criteria are outlined in section 4.1. Efficacy and toxicity will be monitored closely, and study will be terminated if criteria for continuation are not met.

Any new information suggesting the study intervention (addition of nivolumab to standard of care chemotherapy for first line treatment of PTCL) may be harmful in study population will be shared with IRB of participating sites. The participating principal investigators will discuss any such new information via conference, and if warranted may choose to terminate study.

6 STUDY AGENT

6.1 STUDY AGENT AND CONTROL DESCRIPTION

Nivolumab is currently FDA approved for the management of a variety of solid and hematologic malignancies. Other drugs will be administered according to standard of care.

Nivolumab

Preparation and storage:
Vials of nivolumab injection must be stored at 2°C to 8°C (36°F to 46°F) and protected from light and freezing. Nivolumab injection is to be administered as an IV infusion through a 0.2-micron to 1.2-micronpore size, low-protein binding (polyethersulfone membrane) in-line filter at the protocol-specified doses and infusion times. It is not to be administered as an IV push or bolus injection. When the dose is based on patient weight (i.e., mg/kg), nivolumab injection can be infused undiluted (10 mg/mL) or diluted with 0.9% Sodium Chloride Injection, or 5% Dextrose Injection, to concentrations as low as 0.35 mg/mL. When the dose is fixed (e.g., 240 mg, 360 mg, or 480 mg flat dose), nivolumab injection can be infused undiluted or diluted so as not to exceed a total infusion volume of 120 mL. During drug product preparation and handling, vigorous mixing or shaking is to be avoided. Instructions for dilution and infusion of nivolumab injection may be provided in the clinical protocol, pharmacy binder, pharmacy manual, or pharmacy reference sheet. Care must be taken to ensure sterility of the prepared solution as the product does not contain any antimicrobial preservative or bacteriostatic agent. Nivolumab infusions are compatible with polyvinyl chloride (PVC) or polyolefin containers and infusion sets, and glass bottles. Further details regarding preparation and administration of Nivolumab can be located in the current investigator brochure or package insert.

Known potential toxicities:
See section 2.3.1.

Drug procurement:

Nivolumab vials of 100mg, 10 mg/mL (10 mL), will be supplied by Bristol-Meyers Squibb (BMS).

Nursing guidelines:

- Severe infusion reactions have been reported in clinical trials of nivolumab. In case of a severe or life-threatening infusion reaction, the nivolumab infusion must be discontinued and appropriate medical therapy administered. Patients with mild or moderate infusion reaction may receive nivolumab with close monitoring and use of premedication according to local treatment guidelines for prophylaxis of infusion reactions. Instruct patient to take prednisone after and close to meals. To prevent sleep disruption and restlessness, avoid taking prednisone at bedtime. A mild sedative may be needed.
- Monitor for signs/symptoms of adrenal insufficiency, hypophysitis, thyroid disorders, immune-mediated colitis, pneumonitis, rash/dermatologic toxicity, and encephalitis (changes in neurologic function).

Concurrent drug therapy issues:

- Drug-drug interactions: Potentially significant interactions may exist, requiring dose or frequency adjustment, additional monitoring, and/or selection of alternative therapy. Consult drug interactions database for more detailed information.
- Potential lack of benefit in treating PTCL, or the addition of nivolumab to standard of care chemotherapy may even lead to inferior outcomes.
- Patients undergoing allogeneic transplant after receiving nivolumab may have complications, some of which could be fatal. Such complications including severe graft versus host disease, sinusoidal obstructive syndrome, lymphocytic encephalitis, and others have occurred.
- Patients with pre-existing auto-immune conditions may experience flares as a result of receiving nivolumab. Such flares may be severe and irreversible, or mild and reversible.

Dose Adjusted EPOCH:

Please refer to CALGB 50303 protocol for detailed instructions regarding preparation and administration of EPOCH

Body Surface Area (BSA) Calculations*:*
Dosage calculations will be based on the patient's BSA at baseline, recommend using Mosteller formula. Actual height and weight should be used in determining body surface area. Dose adjustments at the beginning of each cycle do not need to be made unless there has been a >10% weight gain or loss.

Requirement for Venous Access:
Central venous access is required for protocol participation. A previously placed central venous access device that is functioning properly (free infusion of saline, unimpeded blood return, good condition of external appliance, no recent history of device infection or thrombosis) can be used. Should the patient need a new central venous access device, an implanted port central venous

access device should be placed (e.g. Power Port) or peripherally inserted central venous catheter (PICC) after appropriate informed consent has been obtained. Other aspects of catheter/port management will be in accordance with standard nursing clinic central venous port procedures.

Prophylaxis:
Pre and post medications as prescribed by the treating physician.

Intrathecal chemotherapy:
Treatment or prophylaxis for secondary CNSL is not required by the protocol. Patients should be treated per institutional guidelines.

Tumor lysis precaution, per institutional guidelines:
Patients considered to be at risk for tumor lysis should be well hydrated and treated with allopurinol or a suitable alternative for 12-24 hours prior to the first infusion of chemotherapy.

Prophylactic Anti-Emetic Premedication:
Standard antiemetic prophylaxis will be given per institutional guidelines. Note: EPOCH is considered moderately ematogenic and nivolumab has minimal ematogenicity.

Cyclophosphamide

Preparation and storage:
Injectable powder is stored at room temperature. The temperature is not to exceed 90°F. Reconstituted parenteral solutions are stable for 24 hours at room temperature or six days if refrigerated. Dissolve the 100 mg, 200 mg, 500 mg, 1 gm, and 2 gm vials in 5, 10, 25, 50, and 100 mL of sterile water, respectively, resulting in a solution of 20 mg/mL. Shake vials vigorously. The lyophilized form is more easily solubilized. Further details regarding preparation and administration of cyclophosphamide can be located in the current investigator brochure or package insert.

Known potential toxicities:
Myelosuppression, hemorrhagic cystitis (higher incidence at doses >1250 mg/m2), alopecia, nausea, and vomiting are all common; SIADH is dose-related (more common with single doses > 2 gm/m^2) as well as cardiac (if dose level ≥2 gm/m^2). Secondary leukemia, liver dysfunction, headaches, dizziness, interstitial pulmonary fibrosis, cardiac necrosis may occur. Anaphylaxis is rare.

Drug procurement:
Commercially available for injection in 100 mg, 200 mg, 500 mg, 1 gm and 2 gm vials.

Nursing guidelines:
- Leukopenia nadir occurs 8-14 days after administration and recovery is usually 18-25 days. Monitor CBC.
- Instruct patient to drink 2-3 liters of fluid per day for 2-3 days following treatment and to void frequently, not greater than every three hours to facilitate emptying the bladder of

drug.
- Instruct patient to report any urinary urgency, frequency, dysuria, or hematuria.
- Advise patient of possible strong metallic taste associated with cyclophosphamide and suggest hard candy with a strong flavor (cinnamon, peppermint) to alleviate it.
- Administer antiemetics as necessary to minimize nausea and vomiting, which usually occurs 6-8 hours after administration and can continue up to 5 days.
- Report and record any complaint of lightheadedness, facial "heat sensation", or diaphoresis during administration.
- Corticosteroids, phenothiazine, imipramine, and allopurinol may inhibit Cytoxan metabolism and modify its effect. They may also increase bone marrow suppression.

Etoposide

Background:
Etoposide has been shown to delay transit of cells through the S phase and arrest cells in late S or early G2 phase. The drug may inhibit mitochondrial transport at the NADH dehydrogenase level or inhibit uptake of nucleosides into HeLa cells. It is a topoisomerase II inhibitor and appears to cause DNA strand breaks. Etoposide does not inhibit microtubular assembly.

Formulation:
Commercially available for injection as: Injection, solution: 20 mg/mL (5 mL, 25 mL, 50 mL)

Preparation, storage, and stability:
Refer to package insert for complete preparation and dispensing instructions. Store intact vials at room temperature of 25ºC (77ºF); do not freeze. Protect from light. Etoposide should be diluted to a concentration of 0.2-0.4 mg/mL in D5W or NS for administration (avoid concentrations >0.4 mg/mL). Diluted solutions have concentration-dependent stability; more concentrated solutions have shorter stability times. Precipitation may occur with concentrations >0.4 mg/mL. Following dilution 0.9% Sodium Chloride or D5W to concentrations of 0.2-0.4 mg/mL, drug is chemically stable for 96 and 24 hours at room temperature, respectively.

Pharmacokinetic information:
Distribution: V_d: 7-171 L/m^2; poor penetration across the blood-brain barrier; CSF concentrations <5% of plasma concentrations
Protein binding: 94% to 98%
Metabolism: Hepatic via CYP3A4 and 3A5, to various metabolites.
Half-life elimination: Terminal 4-11 hours
Excretion: Urine (56%; 45% as unchanged drug) within 120 hours; feces (44%) within 120 hours

Potential Drug Interactions:
- Metabolism/Transport Effects: Substrate of CYP1A2 (minor), CYP2E1 (minor), CYP3A4 (major), P-glycoprotein; Inhibits CYP2C9 (weak), 3A4 (weak)
- Ethanol/Herb/Nutraceutical Interactions: Avoid ethanol (may increase GI irritation). Avoid concurrent St John's wort; may decrease etoposide levels.

- Known potential adverse events: Consult the package insert for the most current and complete information.

U.S. boxed warning:
Severe dose-limiting and dose-related myelosuppression with resulting infection or bleeding may occur.

Known potential toxicities:
- Common known potential toxicities, > 10%:
    - Dermatologic: Alopecia
    - Gastrointestinal: Nausea/vomiting, anorexia, diarrhea
    - Hematologic: Leukopenia, thrombocytopenia, anemia
- Less common known potential toxicities, 1% - 10%:
    - Cardiovascular: Hypotension
    - Gastrointestinal: Stomatitis, abdominal pain
    - Hepatic: Hepatic toxicity
    - Neuromuscular & skeletal: Peripheral neuropathy
    - Miscellaneous: Anaphylactic-like reaction
- Rare known potential toxicities, <1% (Limited to important or life-threatening):
  Amenorrhea, blindness (transient/cortical), cyanosis, extravasation, facial swelling, hypersensitivity, hypersensitivity-associated apnea, interstitial pneumonitis, laryngospasm, maculopapular rash, metabolic acidosis, MI, mucositis, optic neuritis, perivasculitis, pruritus, pulmonary fibrosis, radiation-recall dermatitis, rash, seizure, Stevens-Johnson syndrome, tongue swelling, toxic epidermal necrolysis, weakness

Drug procurement:
Commercial supplies. Pharmacies or clinics shall obtain supplies from normal commercial supply chain or wholesaler.

Nursing guidelines:
- Monitor CBC. Neutropenia may be severe. Instruct patients to report any sign/symptoms of infection to the health care team.
- Rare myocardial infarctions have been reported in patients who have received prior mediastinal XRT. Instruct patient to report any chest pain, or racing of the pulse to the health care team immediately.
- Advise patient of possible mild, reversible alopecia.
- A rapid infusion may cause hypotension and/or allergic reaction; administer medication over at least 30-60 minutes and monitor vital signs during administration.
- Drug is a radiosensitizer and irritant. Assess IV patency before and throughout infusion. Patients who have received prior radiation may experience radiation recall. Assess skin in these areas and monitor closely. Instruct patient to report any rash or skin changes to the health care team immediately.
- Anaphylaxis is rare but has been observed. Symptoms may include hypotension, bronchospasm, fever, or chills. Have the anaphylaxis tray available.

- Nausea and vomiting are usually mild; however, the incidence is increased with oral administration. Pre-medicate with antiemetics as ordered and monitor for their effectiveness.
- Instruct patient in importance of maintaining adequate hydration to avoid hyperuricemia.
- Monitor liver function tests.
- Etoposide solution is oil based and settles to bottom of bag or drip chamber. Be sure to agitate bag to avoid reaction to concentrated solution. Reaction would include flushing, shortness of breath, back pain, and anxiety.
- Advise patient that facial flushing is common and may occur even after administration.
- Monitor INR closely in patients on warfarin therapy, as etoposide may increase prothrombin (PT) time.
- May increase the toxicity of methotrexate or cyclosporine when given concurrently.

Doxorubicin

Preparation and storage:
Doxorubicin vials must be protected from light and kept at room temperature. Doxorubicin PFS vials must be refrigerated, 2-8°C. Reconstituted solutions are stable for 24 hours at room temperature and 48 hours under refrigeration. The doxorubicin 150 mg multi-dose vial is stable after reconstitution for 7 days at room temperatures or 15 days if refrigerated and protected from sunlight. It is not necessary to further dilute. This avoids long infusion times and the risk of extravasation. Dilution takes place when administered through a rapidly flowing IV line. Doxorubicin should be administered according to standard EPOCH regimen. Further details regarding preparation and administration of doxorubicin can be located in the current investigator brochure or package insert.

Known potential toxicities:
- Hematologic: Leukopenia (dose-limiting), also thrombocytopenia and anemia. This treatment nadir is usually 10-14 days with recovery in 21 days.
- Dermatologic: Alopecia, usually complete, hyperpigmentation of nail beds and dermal creases, radiation recall.
- Gastrointestinal: Nausea and vomiting, sometimes severe, anorexia, diarrhea, mucositis.
- Cardiovascular: Arrhythmias, thrombosis/embolism, ECG changes, rarely sudden death. Congestive heart failure due to cardiomyopathy related to total cumulative dose, risk is greater with doses greater than 550 mg/m2, mediastinal irradiation, preexisting cardiac disease, advanced age, risk is reduced with weekly or continuous infusion regimens.
- Other: Red discoloration of urine, fever, anaphylactoid reaction, may enhance cyclophosphamide cystitis or mercaptopurine hepatotoxicity, secondary AML/MDS (risk is uncommon, but may be increased when given in combination with an alkylating agent, especially if one or both are given at higher than standard doses.
- Local effects: Vesicant if extravasated; flush along vein, facial flush.

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

Nursing guidelines:

- Check CBC and platelet counts. Monitor for signs of infection, bleeding, and anemia.
- Advise patient that their urine may turn pink in color for approximately 24 hours after administration of the drug.
- Doxorubicin is a vesicant. Check IV potency before and frequently during administration. If extravasation occurs, refer to institutional extravasation policy.
- Hair loss occurs 2-4 weeks after initial injection and can be complete. Regrowth begins 2-3 months after discontinuation.
- Beware of doxorubicin "flare" that can occur during administration. The reaction consists of an erythematous streak up the vein receiving the infusion. Adjacent veins may also demonstrate red streaks. Urticaria and pruritus can be associated with the reaction. The use of corticosteroids and/or antihistamines has been helpful.
- Administer antiemetics to minimize nausea and vomiting.
- Assess for alterations in mucous membranes. Stomatitis occurs within 7-10 days after injection. It begins with burning sensation and can progress to ulceration, which can last 3 days. Carafate slurry may be useful. Adequate nutritional counseling is important. Topical anesthetics such as viscous lidocaine can be used symptomatically. Advise patient that there is often significant malaise and fatigue 1-2 weeks after injection.
- Doxorubicin may potentiate toxicity of other antineoplastic therapies. It has reportedly exacerbated cyclophosphamide- induced hemorrhagic cystitis.
- Assess heart and lung sounds. Monitor vital signs (resting pulse). Be alert to early signs of cardiotoxicity (i.e., dyspnea, steady weight gain, nonproductive cough, arrhythmias, tachycardia, and pulmonary rales).
- Document doses, total should not exceed maximum cumulative dose (550 mg/m2 or 450 mg/m2 if history of mediastinal radiation).
- Advise patient of probable facial flushing for several hours after drug administration, especially if given quickly.

Vincristine (VCR)

Preparation and storage:

Vincristine is stored under refrigeration, 2-8°C. No dilution is required. Vincristine should be administered according to the standard EPOCH regimen. Further details regarding preparation and administration of vincristine can be located in the current investigator brochure or package insert.

Known potential toxicities:

- Hematologic: Rarely leukopenia (mild), rarely thrombocytopenia, and anemia.
- Dermatologic: Alopecia, skin and soft tissue damage if extravasated (the manufacturer recommends subcutaneous injection of hyaluronidase and application of heat to help disperse the drug), rash.
- Gastrointestinal: Nausea, rarely vomiting, constipation, abdominal cramps, anorexia, and diarrhea. Fatal ascending paralysis follows intrathecal administration.
- Hepatic: Elevation of AST and ALT (mild and transient).

- Neurologic: Peripheral neuropathy (loss of deep tendon reflexes, paresthesias, paralysis), autonomic neuropathy (constipation, paralytic ileus, urinary retention, orthostasis), ataxia, myalgias, cortical blindness, headache, seizures.
- Pulmonary: Bronchospasm (acute shortness of breath), more common when administered with mitomycin.
- Ocular: Diplopia, ptosis, photophobia, cortical blindness (see neurologic), and optic atrophy.
- Other: Severe pain in the jaw, pharynx, bones, back, and limbs following injection, syndrome of inappropriate antidiuretic hormone (SIADH), fever, rarely pancreatitis.
- Cardiovascular: Thrombosis/embolism.

Availability:
Commercially available in a concentration of 1 mg/ml in 1, 2, and 5 mg vials and 1 mg and 2 mg syringes.

Nursing guidelines:
- Check IV patency before and frequently during administration. Vincristine is a vesicant. If extravasation occurs, refer to agency extravasation policy.
- Evaluate the patient for numbness and tingling in fingertips and toes, clumsiness of hands, and difficulty walking.
- Monitor bowel function and encourage use of stool softeners.
- Symptoms of cranial nerve neuropathy may develop several weeks after drug administration and take 10–12 months to resolve.

Prednisone

Storage and Administration:
The drug is a commercially available table that is intended for oral use and should be stored at room temperature in a dry place. Further details regarding administration of prednisone can be located in the current investigator brochure or package insert.

Known potential toxicities:
- Hematologic: Leukocytosis.
- Gastrointestinal: Nausea, vomiting, anorexia, increased appetite and weight gain, peptic ulcer.
- Dermatologic: Rash, skin atrophy, facial hair growth, acne, facial erythema, and ecchymosis.
- Genitourinary: Menstrual changes (amenorrhea, menstrual irregularities)
- Neurologic: Insomnia, muscle weakness, euphoria, psychosis, depression, headache, vertigo, and seizures.
- Cardiovascular: Fluid retention and edema, hypertension, hyperkalemia.
- Ocular: Cataracts, increased intraocular pressure, and exophthalmos.
- Metabolic: Hyperglycemia decreased glucose tolerance, aggravation or precipitation of diabetes mellitus, adrenal suppression, and cushingoid syndrome.

- Other: Osteoporosis (and resulting back pain), serious infections including herpes zoster, varicella zoster, fungal infections, pneumocystis carinii, tuberculosis, muscle wasting.

Availability:
Commercially available in 1, 2.5, 5, 10, 20, 25, and 50 mg tablets.

Nursing guidelines:
- Instruct patient to report any abdominal pain, GI bleeding (i.e., tarry stools, vomiting coffee-ground material, etc.) to health care team immediately since active peptic ulceration is a toxicity that requires dose modification. Antacid therapy may be employed.
- Instruct patient to take prednisone after and close to meals. To prevent sleep disruption and restlessness, avoid taking prednisone at bedtime. A mild sedative may be needed.
- Monitor CBC and glucose levels.
- Educate patient concerning potential mood changes.
- Gradual tapering of doses should be employed after long-term use.

6.1.1 DOSING SCHEDULES

INDUCTION

Patients will receive a planned 6 cycles of therapy (or 5 cycles if patient received a cycle of chemotherapy prior to enrollment) before having an autologous stem cell transplant or surveillance.

Each cycle is 21 days, +/- 3 days. Nivolumab (360 mg) will be given on day 1 concurrently with chemotherapy, including for cycles that are delayed beyond 21 days. Unless there is a planned delay (e.g. for low blood counts), the start of chemotherapy should be within 3 days of day 1 of each 21-day cycle. Note that the dose of 360 mg of nivolumab was chosen because nivolumab is FDA approved at a dose of 240 mg every 2 weeks and 480 mg every 4 weeks. Because the cycles of DA EPOCH are every 3 weeks, we will be giving nivolumab 360 mg.

DA-EPOCH will be given according to standard protocols derived from CALGB 50303 with the exceptions outlined in this protocol.

All patients will begin treatment at dose level -1.

DRUG	***DOSE***	***FREQUENCY[5]***						***# of CYCLES***	***Administration***
		Day 1	**Day 2**	**Day 3**	**Day 4**	**Day 5**	**Day 6**		
Cyclophosphamide[1]	750 mg/m^2					X		6 cycles	IV
Doxorubicin[2]	10 mg/m^2/day	X	X	X	X			6 cycles	IV
Vincristine[3]	0.4 mg/m^2/day	X	X	X	X			6 cycles	IV

Etoposide[4]	50 mg/m^2/day	X	X	X	X			6 cycles	IV
Prednisone	60 mg/m^2 /day	X	X	X	X	X		6 cycles	PO
Nivolumab[7]	360 mg	X						6 cycles[5]	IV
Pegfilgrastim (Neulasta or OnPro)[6]	6 mg						X	6 cycles	SQ

1. Cyclophosphamide dose may be rounded to nearest 50 mg.
2. Doxorubicin dose may be rounded to nearest 5 mg.
3. Vincristine has no cap.
4. Etoposide dose may be rounded to nearest 5 mg.
5. Each "day" of the chemotherapy regimen EPOCH represents an approximate 24 hour infusion; however, each day may not finish until the subsequent day. (i.e. day 2 chemo may end on day 3, day 3 on day 4, etc.). These alterations from schedule should not be considered protocol deviations and are expected.
6. Within 24-72 hours after completing chemotherapy. Alternatively, can administer filgrastim 480 mcg subcutaneous daily from Day 6 until ANC > 5000 after the nadir (nadir usually between Days 10-12) *or* for 10 days (Days 6-15) if the ANC is not being monitored, during every cycle. Substitutions with generic or biosimilar growth factors are permitted.
7. Nivolumab treatment will always be administered first, followed by EPOCH. There is no study-directed window between completion of Nivolumab administration and start of EPOCH administration.

Dose adjustments listed in table below (and modified from CALGB 50303) for subsequent cycles of EPOCH will be determined by the absolute neutrophil (ANC) or platelet nadir (below adjustments are based on twice weekly CBC).

- If nadir ANC is greater or equal to 500, increase the EPOCH dose level by 20%.
- If nadir ANC is less than 500 on 1 or 2 measurements, then continue EPOCH at the same dose level.
- If nadir ANC is less than 500 on at least 3 measurements (3-4 days apart), then decrease the EPOCH dose level 20%.

OR

- If nadir platelet count is less than 25,000 on 1 measurement, then decrease the EPOCH dose level by 20%.

Begin each cycle of EPCOH chemotherapy when ANC is greater than or equal to 1000 and platelets are greater than or equal to 100,000 (unless low due to bone marrow infiltration secondary to disease).

For patients whose blood counts are not recovered to ANC $\geq$ 1000 and platelets $\geq$ 100,000 by start of subsequent cycle:

- If patient's counts recover by day 28 or sooner, dose adjustments for EPOCH should be made as outlined above.
- If patient's counts recover on day 29 or later, reduce DA-EPOCH to next lower dose level and hold nivolumab for subsequent cycle. Then, may resume nivolumab with subsequent cycle at the same lower dose level of EPOCH. If delayed count recovery (e.g. by day 29 or

later) occurs a second time after patient resumed nivolumab, make standard dose adjustments to DA-EPOCH and permanently discontinue nivolumab.
- If patient's counts are low (eg. ANC <1000 or platelets <100 at day 21) due to marrow involvement by disease, next cycle can resume without delay or dose reduction. EPOCH can be delayed or reduced per investigator discretion.

Additional adjustments for severe cytopenias attributed to nivolumab and not EPOCH: For hematologic nadirs: ANC<500 for ≥7 days or PLT<25,000 for ≥7 days: For first occurrence hold nivolumab with next cycle and make necessary standard dose reductions. If hematologic recovery is not delayed with this cycle, then may resume nivolumab with subsequent cycle. If this occurs a second time after patient resumed nivolumab, make standard dose adjustments and permanently discontinue nivolumab.

Dose levels, as originally described in CALGB 50303.

	Dose Levels									
Adjusted Agents	**-3**	**-2**	**-1**	**1**	**2**	**3**	**4**	**5**	**6**	**7**
Doxorubicin (mg/m^2/day)	10	10	10	**10**	12	14.4	17.3	20.7	24.8	29.8
Etoposide (mg/m^2/day)	50	50	50	**50**	60	72	86.4	103.7	124.4	149.3
Cyclophosphamide (mg/m^2)	384	480	600	**750**	900	1080	1296	1555	1866	2239
Non-Adjusted Agents										
Vincristine (mg/m^2/day) (No cap)	0.4	0.4	0.4	**0.4**	0.4	0.4	0.4	0.4	0.4	0.4
Prednisone (mg/m^2/day)	60	60	60	**60**	60	60	60	60	60	60

*Dose adjustments for dose levels -1, -2, -3 and below apply to cyclophosphamide only. Dose adjustment to dose level -4 and -5 will each include ~20% reduction in cyclophosphamide (i.e. DL-4 = 307 and DL-5 = 245 mg/m^2).

Recommendations outlined above are consistent with protocol CALGB 50303 section 9.2. However, while rituximab was given in CALGB 50303, no rituximab is given in the current protocol.

AUTOLOGOUS STEM CELL TRANSPLANTATION

Administration of standard preparative regimen (in patients who have a CR or PR, as per investigator's discretion) followed by HSCT (as per institutional guidelines). The choice of the conditioning regimen is optional (ex: BEAM).

Hematopoietic Stem Cell Collection:
Peripheral blood stem cells will be collected as per the discretion of the treating physician until an adequate number of CD34+ cells/kg have been collected (as per existing institutional guidelines). The timing of stem cell collection will be at the discretion of the treating physician and as per institutional guidelines.

Suggested Optional Preparative Regimen – BEAM:

Day – 6	Day – 5	Day - 4	Day - 3	Day - 2	Day - 1	Day 0
BCNU 300mg/m^2	Etoposide 100mg/m^2 BID Cytarabine 100mg/m^2 BID	Etoposide 100mg/m^2 BID Cytarabine 100mg/m^2 BID	Etoposide 100mg/m^2 BID Cytarabine 100mg/m^2 BID	Etoposide 100mg/m^2 BID Cytarabine 100mg/m^2 BID	Melphalan 140mg/m^2	Stem Cell Infusion

Dose Modifications for Suggested Optional BEAM Regimen:
The dose of BEAM will remain constant for each subject throughout the study. No adjustments in doses for post-screening changes in body surface area will be made.
NOTE: The preparative regimen above is a suggested option. The exact combination and dosing should be as per institutional standards.

Reason as to why patients do not proceed to transplant:
Physicians will be required to document the reason why patients did not proceed to an autologous transplant – i.e., comorbidities, advanced age, inability to mobilize, patient decision, and physician decision.

6.1.2 DOSE ADJUSTMENTS FOR TOXICITY

After the initial two cycles, if it's felt by the investigator that a dose increase of EPOCH would be detrimental to the patient, chemotherapy doses can be maintained without dose escalation. Similarly, if the investigator feels it is in the best interest of the patient dose levels can be decreased.

If multiple adverse events are seen, administer dose based on greatest reduction required for any single adverse event observed.

Omit = The current dose(s) during a cycle is skipped. The patient does not make up the omitted dose(s) at a later time.

Hold = Refers to decision made at the beginning of the cycle to delay the start of the cycle until the patient meets the protocol criteria to restart drug.

NOTE: Patients in whom one or more DA-EPOCH plus nivolumab study treatment agents have been discontinued will remain on study unless all DA-EPOCH plus nivolumab study treatment agents are discontinued. Patients in whom all the study treatment agents were discontinued will proceed to event monitoring.

NOTE: For adverse events associated with Nivolumab, based on the severity of the adverse reaction, withhold nivolumab and administer systemic corticosteroids. Consider increasing the corticosteroid dose (and/or other immunosuppressants) if there is no improvement or if toxicity worsens. Begin corticosteroid taper when adverse reaction improves to below grade 1 and continue taper over approximately 1 month. For adverse reactions that do not result in permanent discontinuation, when improved to grade 1 (or lower) and the corticosteroid dose is reduced to ≤10 mg/day prednisone (or equivalent), resume nivolumab with subsequent cycles.

NIVOLUMAB dose modifications :

Adverse Event	Severity	Dose Modification
Colitis	Grade 2 or 3 diarrhea or colitis	Delay or discontinue dose
	Grade 4 diarrhea or colitis	Permanently discontinue
Pneumonitis	Grade 2	Delay dose
	Grade 3 or 4	Discontinue
Hepatitis	Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) >3 and ≤5 x the upper limit of normal (ULN) *or* total bilirubin >1.5 and ≤3 x ULN	Delay dose
	AST or ALT >5 x ULN *or* total bilirubin >3 x ULN	Delay dose or discontinue
Hypophysitis	Grade 2 or 3	Withhold dose
	Grade 4	Permanently discontinue
Adrenal insufficiency	Grade 2	Withhold dose
	Grade 3 or 4	Permanently discontinue
Type 1 diabetes mellitus	Grade 3 hyperglycemia	Withhold dose
	Grade 4 hyperglycemia	Permanently discontinue
Nephritis and renal dysfunction	Serum creatinine >1.5 and ≤6 x ULN	Delay dose
	Serum creatinine >6 x ULN	Discontinue dose

Adverse Event	Severity	Dose Modification
Skin	Grade 3 rash or suspected Stevens-Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN)	Withhold dose
	Grade 4 rash or confirmed SJS or TEN	Permanently discontinue
Encephalitis	New onset moderate or severe neurologic symptoms	Withhold dose
	Immune-mediated encephalitis	Permanently discontinue
Cardiac	Grade 3 myocarditis	Permanently discontinue
Infusion reactions	Grade 1 or 2 Grade 3 or 4	Interrupt or slow infusion Permanently discontinue

- For all immune-related adverse reactions, consider administering systemic glucocorticoids per institutional guidelines.

- For neurological adverse reactions of any grade, discontinue for myasthenia gravis, Guillain-Barre syndrome, treatment-related myelitis, or encephalitis.

- For suspected Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), or Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS), withhold immune-oncology treatment and refer patient for specialized care.

- For other Grade 3 adverse reactions suspected to be attributable to nivolumab: First occurrence, withhold dose. For recurrence of same Grade 3 adverse reactions, permanently discontinue.

- For other life-threatening or Grade 4 adverse reactions attributable to nivolumab, permanently discontinue nivolumab.

- Discontinue nivolumab for requirement of 10 mg per day or greater prednisone or equivalent for more than 12 weeks.

- Permanently discontinue nivolumab for persistent Grade 2 or 3 adverse reactions that last for at least 12 weeks.

Dose modifications for adverse events associated with chemotherapy:

Use Common Terminology Criteria for Adverse Events (CTCAE) v5.0 unless otherwise specified			
CTCAE CATEGORY	ADVERSE EVENT	AGENT	DOSAGE CHANGE
BASED ON INTERVAL ADVERSE EVENT			
Cardiac General	Left ventricular systolic dysfunction ≥ grade 3	doxorubicin	Discontinue doxorubicin.
Renal/ Genitourinary	Cystitis ≥ grade 2	cyclophosphamide	Omit until resolution of cystitis. Decrease 50% of preceding dose for next cycle of treatment. If subsequent cycle is well tolerated and there is no grade ≥2 renal/GU adverse events, increase to 100% of the original dose.
Neurology	Neuropathy – motor Grade 2 Neuropathy – motor Grade ≥ 3 Neuropathy – sensory Grade 2 Neuropathy – sensory Grade 3 Neuropathy – sensory Grade 4	VCR	Omit VCR until neuropathy < grade 2 and resume at 50% dose reduction. Discontinue VCR. Reduce VCR by 25%. Omit VCR until neuropathy <grade 2 and resume at 50% dose reduction. Discontinue VCR.
Gastrointestinal	Nausea/Vomiting ≥ Grade 3	Nivolumab DA-EPOCH	Maximize antiemetic therapy; if maximized antiemetic treatment ineffective, reduce doses at physician discretion.
	Mucositis/Stomatitis ≥ Grade 2	doxorubicin	If attributable to prolonged cytopenias, follow dose reduction according to section 6.1.1 If not due to prolonged cytopenias, decrease doxorubicin by 25% of preceding dose for next cycle. If no grade ≥3 GI toxicities in subsequent cycle, increase doxorubicin to 100% of original dose.
	Constipation grade 2 Constipation ≥ grade 3	VCR	Initiate bowel regimen and continue VCR. Decrease VCR by 25%.

Use Common Terminology Criteria for Adverse Events (CTCAE) v5.0 unless otherwise specified			
CTCAE CATEGORY	ADVERSE EVENT	AGENT	DOSAGE CHANGE
BASED ON INTERVAL ADVERSE EVENT			
Infection	Infection with ANC ≥ 1,000/μL	Nivolumab DA-EPOCH	Hold drugs in case of an infection requiring IV antibiotics or hospitalization and restart when infection is controlled. If dosing is held ≥ 21 days call study chair. If adverse event recurs on subsequent cycles, decrease DA-EPOCH to next lower dose level and consider prophylactic antibiotics. If AE recurs at this dose level call study chair.
	Infection with ANC < 1,000/μL		Hold drugs in case of an infection requiring IV antibiotics or hospitalization and restart when infection is controlled. Decrease DA-EPOCH to next lower dose level and consider prophylactic antibiotics. If AE re-occurs at this dose level call study chair.
	New or reactivation of viral hepatitis		Discontinue treatment, treat hepatitis.

VCR = vincristine

Dose modifications for adverse events associated with chemotherapy or nivolumab (and not due to bone marrow infiltration secondary to disease):

Use Common Terminology Criteria for Adverse Events (CTCAE) v5.0 unless otherwise specified			
CTCAE CATEGORY	ADVERSE EVENT	AGENT	DOSAGE CHANGE
BASED ON INTERVAL ADVERSE EVENT			
Blood/Bone marrow	Hematologic nadirs: ANC<500 for ≥7 days or PLT<25,000 for ≥7 days Or delayed count recovery to ANC > 1000 and platelets > 100,000 on day 29 or later	cyclophosphamide / doxorubicin / etoposide/ nivolumab	Dose adjustments as described in section 6.1.1.

Note: For other adverse events, or where attribution of cause of adverse event is unclear, please discuss with study chair for guidance with dose modifications. In general, maintenance of adequate dose intensity of DA-EPOCH will be prioritized given the uncertain benefit of nivolumab in management of PTCL.

6.2 STUDY AGENT ACCOUNTABILITY PROCEDURES

Nivolumab will be provided by BMS to the participating institution. The investigator, or a responsible party designated by the investigator, must maintain a careful record of the receipt, dispensing and final disposition of all agents received from BMS in a Drug Accountability Log. The Drug Accountability Log will record the study drugs received, dosages prepared, time prepared, doses dispensed and doses/vials destroyed. The Drug Accountability Log will be reviewed during any site visits and at the completion of the study.

Nivolumab will be kept in an appropriate, secure locked area and stored in accordance with the conditions specified on the label.

6.3 POST-STUDY ACCESS

At the end of the study period, Bristol-Myers Squibb Company will not continue to supply study drug to subjects/investigators unless the Sponsor-Investigator chooses to extend their study. The investigator is responsible to ensure that the subject receives appropriate standard of care or other appropriate treatment in the independent medical judgement of the Investigator to treat the condition under study.

7 STUDY PROCEDURES AND SCHEDULE

7.1 STUDY PROCEDURES/EVALUATIONS

- **PET/CT:** A PET/CT scan is done at baseline as part of the initial staging evaluation, and at the end of therapy to confirm the response. For patients that had already been treated with 1 cycle of standard of care chemotherapy prior to study enrollment, if the patient had baseline PET-CT within 6 weeks prior to C1D1 of standard of care chemotherapy then another PET-CT is not required prior to initial cycle of study therapy. Otherwise, repeat CT or PET/CT is required within 28 days of C1D1 of study therapy. A dedicated CT or PET/CT response assessment will also be done between cycle 2 and cycle 3 of EPOCH + nivolumab (if the patient received 1 cycle of standard of care chemotherapy prior to enrollment in the study, then the scan should be performed between the 3rd and 4th cycles of all chemotherapy, and between cycles 2 and 3 of EPOCH + nivolumab). PET-CT should also be performed within 6 weeks of cycle 6 day 1 of chemotherapy.

  If the patient elects to undergo autologous transplant, response evaluation is required with CT or PET/CT (per investigator's discretion) at D+100 (+/- 14 days), but PET/CT would be preferred if not in a CR after cycle 6.

- **Bone Marrow Biopsy:** A restaging bone marrow biopsy may be done if a staging bone marrow biopsy was previously positive or if symptoms suggest involvement. Restaging may also include MRI, if clinically indicated.

- **Autologous Hematopoietic Cell Transplantation:** After 6 courses, and if transplant eligible, patients can proceed to autologous hematopoietic cell transplantation per investigator's discretion. Auto-HCT will be performed per institutional guidelines.

- **Post-Trial Assessments:** Patients who go off study treatment at any time during the trial will complete end of treatment assessments per section 7.3.6. For all patients, drug-related SAEs and AEs will be followed until baseline or ≤ grade 1 levels. Patients who responded or maintained stable disease during the study will be followed for date of disease progression. Patients will be assessed after cycle 2 and 6 as outlined in treatment plan as well as at 100 days post-transplant according to standard of care for patients undergoing transplant. Patients may refuse to participate in the post-trial assessments.

- **Clinical Evaluations:** Patients should be seen and evaluated by provider no more than 7 days prior to start of every chemotherapy cycle, and patients should be evaluated by a provider or nurse no more than 48 hours prior to every chemotherapy cycle.

7.1.1 RESPONSE ASSESSMENT

Response to therapy will be classified as complete response (CR), partial response (PR), stable disease (SD), progressive disease (PD), early death, or not evaluable. Response assessment will be obtained between cycle 2 and cycle 3 of EPOCH + nivolumab and after cycle 6 as outlined in

treatment plan (For patients that got 1 cycle of standard of care chemotherapy prior to enrolling in study, then response assessment is between cycles 3 and 4 of all induction chemotherapy and between cycles 2 and 3 of study EPOCH + nivolumab). If patients discontinue therapy due to a toxic event this will not also be counted towards the efficacy endpoint unless objective progressive disease is documented. Patients with a complete response based on end of treatment imaging assessment, but subsequently develop rapid progression within 6 weeks, will not be considered a complete responder, rather instead progressive disease.

Definitions for clinical response for patients with lymphoma are from the Younes et al, Annals of Oncology, 2017, the RECIL criteria. Measurable disease lesions will be determined from CT, CT portion of the PET/CT if possible, or MRI scans where applicable. Measurement of disease burden will be from sum of longest diameters (SLD). A maximum of three target lesions will be followed. Measurable extranodal disease should be assessed in a manner similar to that for nodal disease. For these recommendations, the spleen is considered nodal disease. Disease that is only assessable – but not measurable by RECIL criteria (e.g., pleural effusions, bone lesions) – will be recorded as present or absent only, unless, while an abnormality is still noted by imaging studies or physical examination it is found to be histologically negative. Response is based on the CT component of PET/CT (as below), CT alone, or MRI where applicable. Response assessment will be performed by treating provider and will not be performed centrally at the University of Colorado.

Response Category	Definition	PET-CT	New Lesions	Bone Marrow
Complete Response	Complete disappearance of all target lesions. All nodes have long diameter <10 mm. ≥30% decrease in the sum of longest diameters of target lesions (PR) with normalization of FDG-PET	Normalization of FDG-PET (Deauvile score 1-3)	No	Infiltrate cleared on repeat biopsy; if indeterminate by morphology, immunohistochemistry should be negative
Partial Response	≥30% decrease in the sum of longest diameters of target lesions but not a CR	Positive (Deauville score 4-5)	No	Irrelevant if positive prior to therapy; cell type should be specified
Stable Disease	<30% decrease or ≤ 20% increase in the sum of longest diameters of target lesions	Any	No	Any

Response Category	Definition	PET-CT	New Lesions	Bone Marrow
Progressive Disease	>20% increase in the sum of longest diameters of target lesions For small lymph nodes measuring < 15 mm post-therapy, a minimum of 5 mm increase in longest diameter to > 15 mm New lesion	Any	Yes or No	Any

FDG-PET, [18F]2-fluoro-2-deoxy-D-glucose
(All response criteria modified from Younes et al, Annals of Oncology, 2017)

Note: A minimum of 1 cm in largest diameter of new extra-nodal lesions is required to assign PD directly. New smaller but suspicious lesion should be designated as equivocal, and if later confirmed (by CT or biopsy) as being due to lymphoma, the documented date of progression should be the date of when it was first identified as equivocal.

Complete Response (CR)

CR is defined as a complete resolution of all target lesions by CT scans with complete normalization of FDG-PET uptake in all areas (Deauville score of 1–3), and bone marrow biopsy negativity (if it was positive or unknown at baseline). If pretreatment PET scan was negative, lymph nodes that measured 15 mm in the long axis should regress to < 10 mm. CR is also defined as achievement of a partial remission by CT scan criteria (reduction in sum of longest diameters by CT imaging by >30%) with normalization (Deauville score 1–3) of FDG-PET activity in FDG-avid lymphoma.

Normalizing of FDG-PET imaging alone is not sufficient by itself to determine CR status unless accompanied with a significant (>30%) decrease in the sum of diameters. Accordingly, a reduction in the sum of diameters by ≤ 30% with normalization of FDG-PET uptake should not be considered a CR unless documented by a negative tissue biopsy.

If the bone marrow was involved by lymphoma before treatment, the infiltrate must have cleared on repeat bone marrow biopsy. The biopsy sample on which this determination is made must be adequate (with a goal of > 20 mm unilateral core). If the sample is indeterminate by morphology, it should be negative by immunohistochemistry. A sample that is negative by immunohistochemistry but that demonstrates a small population of clonal lymphocytes by flow cytometry will

be considered a CR until data become available demonstrating a clear difference in patient outcome.

In cases where pretreatment baseline tumor burden is low, with only a few lesions measuring around 2 cm in longest diameter, treatment effect may shrink the long axis of a target lymph node to a normal value of <10 mm. However, even though the lymph node is now within normal size range, consistent with CR, the percentage of diameter reduction may be <30% (less than a PR). In these cases, a normalized diameter of "0, or resolved" should be used to calculate the sum of diameters, and therefore ensuring accurate response designation. Patients in CR but with rapid progression within 6 weeks of end of treatment scan will not be considered a CR, but rather will be considered a PD.

Criteria for Partial Response (PR) – *the designation of PR requires all of the following:*

PR is defined as a reduction of the sum of longest diameters of target lesions by 30%, but without meeting the definition of CR described above. If one or more target lesions grew in size but the sum of the diameters remains ≤ 30% of the baseline measurement, and no new lesions appear, the response should be designated PR. This definition will eliminate the false interpretation of disease progression due to treatment-related inflammatory flares. Patients in CR but with rapid progression within 6 weeks of end of treatment scan will not be considered a CR, but rather will be considered a PD.

Criteria for Stable Disease (SD)

A patient is considered to have SD when he or she fails to attain the criteria needed for a CR or PR (see above) but does not fulfill those for progressive disease (see below).

Progressive Disease (PD)

Consistent with Deauville criteria, and using a unidimensional tumor measurement, PD after initiating a new therapy is defined as an increase in the sum of longest diameters of target lesions by >20%, and/or appearance of a new lesion (lymph node or a soft tissue mass 10 mm of the longest diameter), irrespective of FDG-PET results. Whenever possible, questionable small FDG-PET avid lesions should be confirmed by a histologic or cytologic analysis. Appearance of a new FDG-PET avid lesion that is smaller than the above thresholds should be closely monitored, and whenever possible, a biopsy should be performed to determine its nature. An increase in the size of previously involved small lymph nodes by >20% while other lesions are decreasing, especially at the beginning of treatment with investigational agents, may represent a tumor flare and should not be designated a PD, unless there is continued increase in size on subsequent imaging studies. Patients should be allowed to remain on trial at investigators and patient discretion (eg if patient is not showing signs of symptomatic progression or deterioration) until the response or lack thereof is clarified on subsequent imaging. When treating clinicians are suspicious of tumor flare, repeat imaging should be obtained 4-8 weeks after initial indeterminate scan to help make the diagnosis of flare versus PD.

Relapsed Disease

After an initial response, and in the absence of appearance of new lesions, PD is defined as an increase of the nadir sum of diameters by >20%. Consistent with Deauville criteria, patients who achieve a CR (normalization of all lymph node measurements and disappearance of extranodal lesions), at least one previously involved lymph node should increase in size to measure 15 mm in the long diameter, with a minimum absolute increase of at least 5 mm from nadir. Accordingly, an increase in a lymph node longest diameter from 8 to 13 mm is not considered a PD, even though there is 38% increase in the measurement, since the lesion did not exceed 15 mm. Similarly, a change from 12 to 16 mm does not qualify as a PD even though the new measurement exceeds 15 mm, since the absolute increase was < 5 mm.

Patients will be analyzed with respect to progression-free survival (PFS). Progression-free survival is defined as time from therapy until relapse, progression, or death from any cause.

7.2 LABORATORY PROCEDURES/EVALUATIONS

Local laboratory assessments as specified on the schedule of events table will include the following:

- Hepatitis B virus (HBV) testing will include hepatitis B surface antigen (HBsAg), antibody to the hepatitis B surface antigen (anti-HBs), and antibody to the hepatitis B core antigen (anti-HBc). If a subject is anti-HBc or HBsAg positive, then a quantitative polymerase chain reaction test to measure viral DNA load will be done.
- Testing for HCV (testing for antibody; if positive then quantitative polymerase chain reaction test to measure viral DNA load), HIV, and HTLV will be performed per institutional guidelines.
- EBV PCR will be performed in EBV+ subset.
- Hematology: Complete Blood Count (CBC) with absolute differential, including hematocrit, hemoglobin, white blood cell count (WBC) with differential, and platelet count.
- Chemistry: Comprehensive Metabolic Panel including albumin, alkaline phosphatase, alanine aminotransferase (ALT/SGPT), aspartate transaminase (AST/SGOT), bilirubin (total and direct), calcium, chloride, creatinine, glucose, phosphorous, potassium, sodium, total protein, serum urea/blood urea nitrogen (BUN), LDH and uric acid.
- Thyroid function tests will include thyroid stimulating hormone (TSH) and free thyroxine (fT4).
- Calculated creatinine clearance (CrCl) will be estimated using the Cockcroft-Gault formula by central laboratory: CrCl (mL/min) = (140 – age) (weight [kg]) / 72 (serum creatinine [mg/dL]; for females, the formula is multiplied by 0.85 (Cockcroft, 1976).

  - Ideal body weight (IBW) will be used in the Cockroft-Gault equation to calculate estimated creatinine clearance for all patients with a total body weight ≤120% of their IBW.
  - Adjusted body weight will be used in the Cockroft-Gault equation for all patients with a total body weight >120% of their total body weight
- Coagulation tests will include prothrombin time, international normalized ratio (INR) and partial thromboplastin time (PTT or activated PTT).
- Urinalysis (a urine dipstick may be used) will include color, appearance, specific gravity, pH, glucose, ketones, blood, bilirubin, and protein. A microscopic examination will be performed if urinalysis result is abnormal.
- Pregnancy testing (serum or urine) will be performed for patients of child-bearing potential at screening only. Pregnancy test must be done ≤14 days of starting treatment.

7.2.1 CLINICAL LABORATORY EVALUATIONS (RESEARCH PROCEDURES)

Pathology

Baseline standard of care diagnostic pathology samples will be performed as clinically indicated. Pathological materials including H&E stain, all IHC slides, and any leftover FFPE tissue block along with the pathology report from initial diagnosis should be sent to be reviewed, and the diagnosis confirmed by the University of Colorado pathology department (retrospective diagnostic review: treatment may commence prior to the University of Colorado review).

Obtaining pathology samples is not required prior to enrollment, but confirmation of availability IS required prior to enrollment.

Initial diagnostic materials should be submitted within 30 days of patient registration. A copy of the pathology report should be sent when the sample is shipped.

Please refer to the Lab Manual for detailed instructions on acquisition and shipping.

The diagnostic slides and any leftover material will be returned after review.

7.2.2 OTHER ASSAYS OR PROCEDURES (RESEARCH)

Correlative analysis blood samples.

Peripheral blood will be collected at the following time points (see lab manual for specifics):

- Baseline—Within 28 days prior to first day of first cycle of study treatment.
- Prior to cycle 2 on study—within 7 days prior to C2D1 of nivolumab + EPOCH.
- Prior to cycle 3 on study—within 7 days prior to C3D1 of nivolumab + EPOCH.
- At the end of induction treatment—within 14 days of EOT imaging response assessment.
- At the end of treatment (D+100 post auto-transplant).
- At time of recurrence/progression, or if patient is taken off study.

Please refer to the Lab Manual for detailed instructions on acquisition and shipping.

7.2.3 SPECIMEN PREPARATION, HANDLING, AND STORAGE

Pathology

H&E stain, IHC slides, and any leftover FFPE tissue block along with the pathology report from initial diagnosis should be sent to be reviewed, and the diagnosis confirmed by the University of Colorado.

NOTE: the diagnostic H&E slide and IHC slides will be returned after review. Specimens from the tissue block will be stored in the Lymphoid Malignancy Tissue Bank (LTB) for potential further correlative studies at a later time.

Research Blood Samples

Research blood samples will be banked in the LTB and subject to further correlative analysis.

7.2.4 SPECIMEN SHIPMENT

Please reference Lab Manual for full details on specimen collection, requisition forms and details on shipment supplies and specifications.

7.3 STUDY SCHEDULE

7.3.1 SCREENING

Informed Consent must be obtained prior to beginning any assessments solely for the purpose of this study. Informed consent will be reviewed with patient in detail with the physician, with the physician addressing all questions and concerns of the patient. Informed consent will be signed by patient and authorized consenting personnel should risks/benefits be deemed acceptable to patient.

Screening evaluations will be performed for all subjects to determine study eligibility after signing the informed consent form. These evaluations must be completed within 28 days of administration of the first dose (Cycle 1 Day 1 [C1D1]) unless noted otherwise below.

The following will be performed or assessed at screening as specified in section 7.4:

- Complete medical history will be documented by a qualified clinician at the time of the Screening Visit. The medical history will be general enough to document common comorbid conditions as well as specific enough to confirm any condition against the eligibility criteria, and will document whether the identified conditions are active or

inactive at the time of enrollment. Disease history will include specific information regarding diagnosis and histology including grade.

- Physical examination including evaluation of lymph nodes, spleen and liver will be performed.
- Demographics will include date of birth, sex, race, and ethnicity (if allowed by local regulations).
- Adverse Event assessment (baseline AEs)
- Concomitant medications reviewed and documented
- ECOG performance status will be recorded.
- Vital signs will include blood pressure, pulse, and body temperature.
- Body weight and height (height at the screening only) will be measured.
- Body surface area (BSA) will be calculated using the subject's height and weight according to local pharmacy practice.
- Pregnancy testing (in WOCBP) ≥14 days of starting treatment
- Counseling about pregnancy precautions and the potential risks of fetal exposure will be given to patients of child-bearing potential.
- Tumor tissue sample for confirmation of diagnosis and correlative research (submitted within one month after registration – confirmation of *availability* is required). H&E stain and IHC slides or a representative FFPE tissue block along with the pathology report from initial diagnosis, should be sent to be reviewed and have the diagnosis confirmed at University of Colorado. Patients whose tissue is not available may still be eligible to go on trial only if they choose to have a SOC biopsy prior to treatment. In either case, patients may commence treatment prior to pathologic review of tissue and the diagnosis confirmed at the University of Colorado. Tissue must be a core needle, excisional, or incisional biopsy. Fine needle aspirations are not adequate. If patient does not have adequate tissue for biomarker analysis, then an additional biopsy may be performed as per standard of care.
- Hematology (as outlined in section 7.2)
- Chemistry (as outlined in section 7.2)
- Urinalysis (as outlined in section 7.2)
- TSH and free T4

- PT/INR and PTT
- HIV, HBV, HCV, HTLV screen (as outlined in section 7.2)*
- EBV PCR (in EBV+ subset)*
- PET-CT will be performed ≤ 6 weeks of C1D1 of treatment*
- 12-lead single electrocardiogram (ECG) will be recorded
- Left ventricular function assessment via MUGA or echocardiogram*
- Bone marrow biopsy and/or CSF analysis will be performed if clinically indicated (must be performed ≤6 weeks prior to study registration)*
- Research blood tubes will be collected for biomarker/correlative analysis

*For patients that received 1 cycle of standard of care chemotherapy prior to enrollment: If these tests were performed within 28 days prior to C1D1 of standard of care chemotherapy, they do not need to be repeated prior to first cycle of study nivolumab + EPOCH.

Inclusion/exclusion criteria will be reviewed in detail to ensure that the patient is a study candidate prior to enrollment and subsequent treatment. If it is not clear if patient qualifies for study, the principal investigator should be notified for review of patient candidacy.

7.3.2 INDUCTION TREATMENT WITH NIVOLUMAB + CHEMOTHERAPY

Cycle 1 – Cycle 6

Chemotherapy should be started within 3 days of day 1 for each 21-day cycle.

NOTE: If patient has been given one cycle of cytotoxic chemotherapy (e.g. CHOP) prior to enrollment, this cycle of treatment will count toward the 6 cycles of treatment given in the study, and thus would be starting at Cycle 2. Thus, patients will receive no more than 6 total cycles of induction treatment.

If screening assessments are performed within 48 hours of Cycle 1 Day 1, safety laboratory and physical examinations need not be repeated at Cycle 1 Day 1.

Upon starting treatment, patients will be seen and evaluated by treating provider within 7 days prior to day 1 of every cycle. All laboratory, safety, and physical examinations should be performed by a provider or nurse within 48 hours of the start of every cycle (e.g. within 48 hours of the start of chemotherapy).

The following evaluations will be performed at scheduled follow up visits:

- Physical examination with vital signs and weight
- Adverse Event assessment
- Concomitant medications
- Hematology (as outlined in section 7.2)
- Chemistry (as outlined in section 7.2)
- Urinalysis (as outlined in section 7.2)
- TSH and free T4 (as outlined in section 7.2)
- EBV PCR (as outlined in section 7.2)
- Tumor response assessment (PET/CT or CT according to investigator preference). Note that we generally recommend interim scan be performed between the 2nd and 3rd cycle of EPOCH + nivolumab. For patients that received 1 cycle of standard of care chemotherapy prior to enrollment in study, we suggest interim scan be performed between cycle 2 and cycle 3 of EPOCH + nivolumab (i.e. between the 3rd and 4th cycles of all chemotherapy).
- Bone marrow biopsy and/or CSF assessment (as clinically indicated) or to confirm CR.
- Research blood tubes will be collected for biomarker analysis prior to Cycle 2 and Cycle 3 of nivolumab + EPOCH.

Hematology Blood Collection between Induction Cycles

Hematology (as outlined in section 7.2) is to be collected 2 times per week during Cycles 1 through 6. These two hematology blood draws must be at least one day apart.

7.3.3 END OF INDUCTION VISIT

The End of Induction Visit will occur after completion of 6 cycles of chemotherapy (3-6 weeks after C6D1 of nivolumab + chemotherapy) and will include the following assessments:

- History and physical examination with vital signs and weight
- Adverse Event assessment
- Concomitant medications

- ECOG performance status will be recorded
- Hematology (as outlined in section 7.2)
- Chemistry (as outlined in section 7.2)
- Urinalysis (as outlined in section 7.2)
- TSH and free T4 (as outlined in section 7.2)
- EBV PCR (as outlined in section 7.2)
- End of induction treatment PET-CT (within 6 weeks of cycle 6 day 1 of chemotherapy) and tumor response assessment.
- If PET positive after the completion of cycle 6, a biopsy of PET positive area may be done at investigator discretion.
- Bone marrow biopsy and CSF assessment (as clinically indicated) or to confirm CR.
- Survival status will be assessed.
- Discussion of candidacy and risks/benefits of consolidation autologous transplant.
- Research blood tubes will be collected for biomarker analysis.

7.3.4 AUTOLOGOUS HEMOPOEITIC CELL TRANSPLANT & POST-TRANSPLANT

Patients undergoing autologous transplant will undergo clinical and laboratory evaluation according to standard of care subsequent to end of induction treatment visit. A CT or PET/CT should be obtained according to standard of care every 3 months (+/- 14 days) until 1 year post transplant. While encouraged, it is not mandatory to obtain imaging every 3 months if patients achieve complete metabolic response after completion of cycle 6. The end of treatment visit will be at D+100 (+/- 14 days) after the transplant date. Patients will then enter LTFU.

7.3.5 END OF TREATMENT (FOR PATIENTS UNDERGOING TRANSPLANT OR THOSE WHO DO NOT COMPLETE 6 CYCLES OF TREATMENT)

This visit will be completed for subjects who are **withdrawn** from treatment for any reason as soon as possible after the decision to permanently discontinue treatment has been made. This visit applies to patients who stop treatment for any reason prior to completing all treatment OR if a patient goes on to get an autologous stem cell transplant, then they would complete the End of

Treatment visit 100 days after their transplant (see calendar for details). If a patient decision to withdraw the patient from treatment occurs at a specific time point in the protocol (ex: at the scheduled End of Induction visit a patient comes off treatment due to PD) then that time point would be considered the EOT visit.

The following evaluations will be performed at the EOT visits:

- History and physical examination with vital signs and weight
- Adverse Event assessment
- Concomitant medications
- ECOG performance status
- Hematology (as outlined in section 7.2)
- Chemistry (as outlined in section 7.2)
- Urinalysis (as outlined in section 7.2)
- TSH and free T4 (as outlined in section 7.2)
- EBV PCR (as outlined in section 7.2)
- End of treatment PET-CT and tumor response assessment (unless patient has had a scan within the past 21 days).)
- Bone marrow biopsy and CSF assessment (as clinically indicated)
- Survival status will be assessed
- Research blood tubes will be collected for biomarker analysis

7.3.7 LONG-TERM FOLLOW-UP

The follow-up period begins upon all study treatment discontinuation or completion as per protocol. This includes subjects who complete the full course of treatment and who discontinue treatment due to toxicity. All subjects will be followed for AEs and concomitant medications/procedures for 100 days after the last dose of nivolumab. In addition, after end of induction or end of treatment visit/labs, patients will be contacted via telephone every 3 months (+/- 1 month) for 2 years for the following endpoints: death, first progression, and new anti-lymphoma treatment. If at any point a patient decides to withdraw from long term follow-up, there must be documentation of this decision by the provider, nurse or coordinator.

7.3.8 EARLY TERMINATION VISIT

Early termination visits will be performed with the same requirements as the end of treatment visit (see section 7.3.6).

Note that if a patient chooses to voluntarily withdraw from study, then documentation must be made regarding if patient chooses to simply discontinue study treatment, or if patient also no longer wants to be followed for treatment outcomes (and thus opts out of study related follow up).

7.3.9 UNSCHEDULED VISIT

The following evaluations will be performed all unscheduled visits:

- History and physical exam including vital signs
- Laboratory evaluation and imaging as clinically indicated

7.4 SCHEDULE OF EVENTS TABLE

	Active Monitoring Phase					Off Treatment	
Tests and procedures	**Screening ≤ 28 days prior to C1D1 (exceptions noted)**	**Induction Treatment with Nivolumab + Chemotherapy**		**Post-Induction**		**End of Treatment[26]**	**Long Term Follow-Up[28]**
		C1 – C6 Treatment[15, 16]	**Hematology during Induction[21]**	**End of Induction Visit (3-6 weeks after C6D1)**	**Autologous Transplant & Post-Transplant[24,26]**		
		+/-3 days					
History and exam	X	X[17]		X		X	
Adverse event assessment	X	X[17]		X		X	X[29]
Concomitant medications assessment	X	X[17]		X		X	X[29]
ECOG	X			X		X	
Vital signs[1] including weight and height[2]	X	X[17]		X		X	
Serum or urine pregnancy test[3]	X[3]						
Tumor tissue sample for confirmation of diagnosis and research purposes *or* SOC biopsy	X[4]			X[22]			
Hematology (see section 7.2)	X	X[17]	2x per week[21]	X		X	
Chemistry (see section 7.2)	X	X[17]		X		X	
Urinalysis	X			X		X	
TSH and free T4	X	X[17]		X		X	
PT/INR[5], PTT	X						
HIV, HBV, HCV, HTLV screen	X[6, 30]						
EBV PCR (in EBV+ subset)	X[30]			X	X	X	
Tumor Measurement/Evaluation of indicator lesions (CT chest, abdomen, pelvis; other CT and/or MRI when indicated)	X[8, 30]	Before C3[7, 18]		X	X[24,25]	X[27]	
PET/CT scan[7]	X[8, 30]	Before C3[7]		X[22]	X[24,25]	X[27]	
Bone marrow aspirate and biopsy (unilateral or bilateral)[9]	X[10, 30]	Before cycle 3[19]		X[19]		X[9]	
Electrocardiogram[11]	X						
Left ventricular function measurement[12]	X[30]						
Cerebrospinal fluid analysis[10,13]	X[30]	X		X		X[13]	
Research blood samples [14]	X	Before C2 ***and*** C3[14]		X	X[14,23]	X[14,23]	
Dosing[20]		X					
Survival status				X		X	X[28]

1. Vital signs include blood pressure, pulse and temperature.
2. Height will be measured at screening only.
3. Pregnancy tests for females of childbearing potential must be done ≤14 days of treatment start date. A female of childbearing potential (FCBP) is a sexually mature female who: 1) has not undergone a hysterectomy or bilateral oophorectomy; or 2) has not been naturally postmenopausal for at least 24 consecutive months (i.e., has had menses at any time in the preceding 24 consecutive months).
4. Central review of pathology is required for confirmation of diagnosis. Completion of central pathology review is not required prior to registration for patients; however, materials for central review must be submitted within 30 days after registration. Pathology material: H&E stain and IHC slides or a representative FFPE tissue block from initial diagnosis, including additional material for correlative analysis. Please NOTE: the diagnostic H&E slide and IHC slides will be returned after review. In addition, patients whose tissue is not available may still be eligible to go on trial if they choose to have an SOC biopsy prior to treatment.
5. PT/INR assessment frequency (for patients on Coumadin) is per investigator discretion to keep within therapeutic range.
6. Patients who are seropositive because of hepatitis B virus vaccine are eligible.
7. Imaging should be obtained per standard of care and NCCN guidelines. PET/CT is mandatory pre- and post-treatment. Interim CT may be adequate to assess disease response; however, PET/CT is preferred. Note that we generally recommend interim scan be performed prior to 3rd cycle of study chemotherapy; for patients that got 1 cycle of standard of care chemotherapy prior to enrollment in study, we suggest interim scan be performed prior to cycle 3 of EPOCH + nivolumab (Thus, for patients who received 1 cycle of standard of care chemotherapy prior to study enrollment, scan will be prior to 4^{th} cycle of all induction chemotherapy and prior to 3^{rd} cycle of nivolumab + EPOCH).
8. Imaging must be done ≤ 6 weeks prior to study registration, unless patient received 1 cycle of standard of care chemotherapy prior to enrollment in study, in which case imaging must have been obtained within 6 weeks of C1D1 of standard of care chemotherapy.
9. Bone marrow biopsies will be done according to standard of care and only mandatory in the setting of unexplained cytopenias. However, bone marrow biopsies are highly encouraged, especially in the setting of cytopenias. If screening bone marrow biopsy is indicated, it should be done ≤ 6 weeks prior to study registration.
10. Screening bone marrow biopsy and/or CSF analysis will be performed if clinically indicated (for screening: must be performed ≤6 weeks prior to study registration). Since the chemotherapy requires dose adjustment based on hematologic toxicity it is strongly encouraged to obtain a bone marrow biopsy prior to treatment but can be omitted in select situations after discussion with the study chair.
11. 12-lead single electrocardiogram (ECG) will be recorded.
12. MUGA or ECHO.
13. A lumbar puncture and cytologic examination of the cerebrospinal fluid is not required but should be performed if clinically indicated. (Secondary CNSL is not an exclusion criteria).
14. Research blood samples: Blood samples will be drawn at screening, prior to 2^{nd}, and 3^{rd} cycles of nivolumab + EPOCH (on trial), and at end of induction visit. See requisition form for further detail. For patients who have not progressed, the end of treatment samples will be D+100 post auto-transplant. End of treatment tubes should also be drawn for any patient that is taken off treatment early. See section 7.2.2 for full details of blood draws
15. If patient has been given one cycle of cytotoxic chemotherapy (e.g. CHOP) prior to enrollment, this cycle of treatment will count toward the 6 cycles of total treatment given, and thus would be starting at Cycle 2.
16. All assessments must be done prior to treatment – may be done up to 2 days prior.
17. If screening assessment are performed within 48 hours of C1D1, safety laboratory and physical examinations need not be repeated at Cycle 1.
18. Measurements can be done off the CT images of a PET/CT.
19. If bone marrow positive at diagnosis, a repeat bone marrow biopsy must be done to confirm CR. Can be delayed to end of treatment response assessment or done in parallel with interim response assessment. If interim bone marrow biopsy is negative for disease, it will be repeated at the discretion of the treating physician.
20. During the induction treatment, patients will dose according to section 6.1.1 Dosing Schedule.
21. Hematology blood draws must be done 2 times per week (i.e., twice during every 7-day period, starting with Day 1) at least one day apart, but ideally 2 days apart.
22. If PET positive after the completion of cycle 6, a biopsy of PET positive area may be done at investigator discretion. PET should be done within 6 weeks of cycle 6 day 1 of chemotherapy.
23. At relapse.
24. For patients who have undergone an autologous transplant, a CT or PET/CT should be obtained according to standard of care every 3 months (+/- 14 days) until 1-year post-transplant. While highly encouraged, it is not mandatory to obtain imaging every 3 months if patients achieve complete metabolic response after completion of cycle 6.
25. If the patient elects to undergo autologous transplant, at D+100 (+/- 14 days) response evaluation is required with CT or PET/CT (per investigator's discretion), but PET/CT would be preferred if not in a CR after cycle 6. This visit will also be

considered the end of treatment visit for patients who have undergone autologous transplant, and as such all assessments should be done accordingly.

26. An end of treatment visit will be completed for the subjects who are withdrawn from treatment early, for any reason, as soon as possible after the decision to permanently discontinue treatment has been made. For patients who undergo autologous transplant, the end of treatment visits will be D+100 (+/- 14 days) post auto-transplant.
27. Patients who have had a PET-CT within the last 21 days will not require a repeat scan.
28. The long-term follow-up (LTFU) period begins after the EOT visit. All patients on LTFU will be contacted via phone every 3 months (+/- one month) until first progression, subsequent anti-lymphoma therapy, and survival for up to 2 years after enrollment, unless they have withdrawn consent. Patients will also continue SOC follow-up as dictated by institutional guidelines.
29. All subjects will be followed for AEs and concomitant medications/procedures for 100 days after the last dose of nivolumab or until start of new anti-lymphoma treatment.
30. For patients that had 1 cycle of standard of care chemotherapy prior to enrollment in study: Patients that had these tests prior to cycle 1 of standard of care chemotherapy do not have to repeat these tests prior to start of nivolumab + EPOCH.

7.5 CONCOMITANT MEDICATIONS, TREATMENTS, AND PROCEDURES

All concomitant prescription medications taken during study participation will be recorded on the case report forms (CRFs). For this protocol, a prescription medication is defined as a medication that can be prescribed only by a properly authorized/licensed clinician. Medications reported in the CRF are concomitant prescription medications, over-the-counter medications, and non-prescription medications.

In addition, examples of acceptable methods of contraception include the following (also listed in section 5.1):

- Bilateral tube ligation
- Male sterilization
- Hormonal contraceptives that inhibit ovulation
- Hormone-releasing intrauterine devices
- Copper intrauterine devices

NOTE: Periodic abstinence (e.g. calendar, ovulation, symptothermal, or post-ovulation methods) and withdrawal are **NOT** acceptable methods of contraception.

Involved site radiation therapy (ISRT): ISRT does not have a proven role for the management of PTCL and will not be allowed during induction(33) or as consolidation for patients in complete response treated in this protocol. If patients have residual disease after induction chemotherapy and opt not to undergo an autologous transplant, consolidative radiation will be permitted after discussion with the study chair.

7.5.1 PRECAUTIONARY MEDICATIONS, TREATMENTS, AND PROCEDURES

- Antiemetics may be used at the discretion of the attending physician.
- Tumor lysis syndrome prophylaxis will be used at the discretion of the treating physician.
- Blood products and growth factors should be utilized as clinically warranted and following institutional policies and recommendations. Pegfilgrastim support will be given with each cycle. Treat as needed.
- Patients should receive full supportive care while on this study. This includes blood product support, antibiotic treatment, and treatment of other newly diagnosed or concurrent medical conditions.
- All blood products and concomitant medications such as anti-diarrheals, analgesics, and/or antiemetics received from the first day of study treatment administration until 30 days after the final dose will be recorded in the medical records.

7.6 PROHIBITED MEDICATIONS, TREATMENTS, AND PROCEDURES

The following medications are **prohibited** while on study treatment (exceptions noted):

- Treatment with immuno-suppressive medications, except as used to treat drug-related adverse events, will not be permitted unless discussed with and approved by the study principal investigator.
- Patients will also not be allowed to be treated with any concurrent anti-neoplastic therapy, including chemotherapy, non-palliative radiotherapy, and Chinese medications used for cancer treatment.
- Topical, inhaled, articular, intra-nasal corticosteroids are permitted. A brief (<3 weeks) course of steroids is permitted for purposes of prophylaxis (e.g. contrast) or treatment of non-auto-immune conditions (e.g. anaphylaxis).

Treatment needs to be administered in collaboration with an oncology trained pharmacist. Drugs that have interactions with standard of care EPOCH or nivolumab should be used with caution or avoided as per institutional guidelines.

7.7 PROPHYLACTIC MEDICATIONS, TREATMENTS, AND PROCEDURES

Prophylactic medications, treatments and procedures should be performed according to institutional guidelines. This includes prophylactic antibiotics, anti-fungals, or PJP prophylaxis. We strongly encourage prophylactic antibacterial and antifungal for 10 days after EPOCH (e.g. levofloxacin 500 mg daily and fluconazole 400 mg daily) and continuous antiviral prophylaxis (e.g. acyclovir 400 mg BID or valacyclovir 500 mg daily) for 6 months post induction.

7.8 RESCUE MEDICATIONS, TREATMENTS, AND PROCEDURES

Patients with adverse events while on study drug should be treated as indicated in section 6 of protocol. Other medical conditions that arise while patients are on study should be treated according to standard of care. The principal investigator should be made aware of serious adverse events occurring while patients are on study. Inquiries regarding handling of adverse events occurring while on study that are not described in this protocol should be directed towards the principal investigator.

7.9 PARTICIPANT ACCESS TO STUDY AGENT AT STUDY CLOSURE

At the end of the study period, Bristol-Myers Squibb Company will not continue to supply study drug to subjects/investigators unless the Sponsor-Investigator chooses to extend their study. The investigator is responsible to ensure that the subject receives appropriate standard of care or other appropriate treatment in the independent medical judgement of the Investigator to treat the condition under study.

8 ASSESSMENT OF SAFETY

8.1 SPECIFICATION OF SAFETY PARAMETERS

8.1.1 DEFINITION OF ADVERSE EVENTS (AE)

An Adverse Event (AE) is defined as any new untoward medical occurrence or worsening of a preexisting medical condition in a clinical investigation participant administered study drug and that 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, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

A ***non-serious adverse event*** is an AE not classified as serious.

Laboratory Test Abnormalities:

All laboratory test results captured as part of the study should be recorded following institutional procedures. Test results that constitute SAEs should be documented and reported to BMS as such.

The following laboratory abnormalities should be documented and reported appropriately:

- any laboratory test result that is clinically significant or meets the definition of an SAE
- any laboratory abnormality that required the participant to have study drug discontinued or interrupted
- any laboratory abnormality that required the subject to receive specific corrective therapy.

It is expected that wherever possible, the clinical rather than laboratory term would be used by the reporting investigator (e.g., anemia versus low hemoglobin value).

Overdose:

An overdose is defined as the accidental or intentional administration of any dose of a product that is considered both excessive and medically important. All occurrences of overdose must be reported as an SAE.

Other Safety Considerations:

Any significant worsening noted during interim or final physical examinations, electrocardiograms, X-rays, and any other potential safety assessments, whether or not these procedures are required by the protocol, should also be recorded as a non-serious or serious AE, as appropriate, and reported accordingly.

8.1.2 DEFINITION OF SERIOUS ADVERSE EVENTS (SAE)

A ***Serious Adverse Event (SAE)*** is any untoward medical occurrence that at any dose:

- results in death
- is life-threatening (defined as an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe)
- requires inpatient hospitalization or causes prolongation of existing hospitalization (see **NOTE** below)
- results in persistent or significant disability/incapacity
- is a congenital anomaly/birth defect
- is an important medical event (defined as a medical event(s) that may not be immediately life-threatening or result in death or hospitalization but, based upon appropriate medical and scientific judgment, may jeopardize the subject or may require intervention [eg, medical, surgical] to prevent one of the other serious outcomes listed in the definition above.) Examples of such events include, but are not limited to, intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization.)
- Suspected transmission of an infectious agent (e.g. pathogenic or nonpathogenic) via the study drug is an SAE.

Although pregnancy, overdose, potential drug-induced liver injury (DILI), and cancer are not always serious by regulatory definition, these events must be handled as SAEs.

Any component of a study endpoint that is considered related to study therapy should be reported as an SAE (e.g. death is an endpoint, if death occurred due to anaphylaxis, anaphylaxis must be reported).

The following are <u>NOT</u> considered serious adverse events:

- A visit to the emergency room or other hospital department < 24 hours, that does not result in admission (unless considered an important medical or life-threatening event)
- Elective surgery, planned prior to signing consent
- Admissions as per protocol for a planned medical/surgical procedure
- Routine health assessment requiring admission for baseline/trending of health status (eg, routine colonoscopy)
- Medical/surgical admission other than to remedy ill health and planned prior to entry into the study. Appropriate documentation is required in these cases.

- Admission encountered for another life circumstance that carries no bearing on health status and requires no medical/surgical intervention (e.g., lack of housing, economic inadequacy, caregiver respite, family circumstances, administrative reason).
- Admission for administration of anticancer therapy in the absence of any other SAEs

8.1.3 DEFINITION OF UNANTICIPATED PROBLEMS (UAP)

The Office of Human Research Protection (OHRP) considers unanticipated problems involving risks to participants or others to include, in general, any incident, experience, or outcome that meets **all** of the following criteria:

- Unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the participant population being studied.
- Related or possibly related to participation in the research ("possibly related" means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research).
- Suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

This study will use the OHRP definition of UAP.

8.2 CLASSIFICATION OF AN ADVERSE EVENT

8.2.1 SEVERITY OF EVENT

For AEs not included in the protocol-defined grading system, the following guidelines will be used to describe severity.

- **Mild** – Events require minimal or no treatment and do not interfere with the participant's daily activities.
- **Moderate** – Events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.
- **Severe** – Events interrupt a participant's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually potentially life-threatening or incapacitating.

8.2.2 RELATIONSHIP TO STUDY AGENT

The causal relationship to study drug is determined by a physician and should be used to assess all adverse events (AE). The casual relationship can be one of the following:

Related: There is a reasonable causal relationship between study drug administration and the AE.

Not related: There is not a reasonable causal relationship between study drug administration and the AE.

The term "reasonable causal relationship" means there is evidence to suggest a causal relationship.

Adverse events can be spontaneously reported or elicited during open-ended questioning, examination, or evaluation of a subject. (In order to prevent reporting bias, subjects should not be questioned regarding the specific occurrence of one or more AEs.)

8.2.3 EXPECTED ADVERSE EVENTS

The study investigators will be responsible for determining whether an AE is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the study agent.

8.3 TIME PERIOD AND FREQUENCY FOR EVENT ASSESSMENT AND FOLLOW-UP

The occurrence of an AE or SAE may come to the attention of study personnel during study visits and interviews of a study participant presenting for medical care, or upon review by a study monitor. All AEs including local and systemic reactions not meeting the criteria for SAEs will be captured on the appropriate CRF. Information to be collected includes event description, time of onset, clinician's assessment of severity, relationship to study product (assessed only by those with the training and authority to make a diagnosis), and time of resolution/ stabilization of the event. All AEs occurring while on study must be documented appropriately regardless of relationship. All AEs will be followed to adequate resolution.

Any medical condition that is present at the time that the participant is screened will be considered as baseline and not reported as an AE. However, if the study participant's condition deteriorates at any time during the study, it will be recorded as an AE. UAPs will be recorded in the data collection system throughout the study.

Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity to be performed. AEs characterized as intermittent require documentation of onset and duration of each episode.

The investigator will record all reportable events with start dates occurring any time after informed consent is obtained (for SAEs) *or* from initiation of study treatment (AEs) until 100 days after the last day of study treatment. At each study visit, the investigator will inquire about the occurrence of AE/ SAEs since the last visit. Events will be followed for outcome information until resolution or stabilization.

8.4 REPORTING PROCEDURES

8.4.1 ADVERSE EVENT REPORTING

ADVERSE EVENTS

Adverse events can be spontaneously reported or elicited during open-ended questioning, examination, or evaluation of a subject. (In order to prevent reporting bias, subjects should not be questioned regarding the specific occurrence of one or more AEs.)

Adverse events will be documented in clinic notes at all scheduled visits. Adverse events will be graded by investigator according to CTCAE v5.0.

NON-SERIOUS ADVERSE EVENTS

Non-serious Adverse Events (AE) are to be provided to BMS in aggregate via interim or final study reports as specified in the agreement or, if a regulatory requirement [e.g., IND US trial] as part of an annual reporting requirement. The collection of non-serious AE information should begin at initiation of the study. All non-serious adverse events (not only those deemed to be treatment-related) should be collected continuously during the treatment period and for a minimum of 100 days following the last dose of study treatment.

Non-serious AEs should be followed to resolution or stabilization, or reported as SAEs if they become serious. Follow-up is also required for non-serious AEs that cause interruption or discontinuation of study drug and for those present at the end of study treatment as appropriate.

8.4.2 SERIOUS ADVERSE EVENT REPORTING

Although pregnancy, overdose, potential drug-induced liver injury (DILI), and new cancer are not always serious by regulatory definition, these events must be handled as SAEs.

1) Potential drug induced liver injury is defined as:
    i) AT (ALT or AST) elevation > 3 times upper limit of normal (ULN)
    AND
    ii) Total bilirubin > 2 times ULN, without initial findings of cholestasis (elevated serum alkaline phosphatase)
    AND
    iii) No other immediately apparent possible causes of AT elevation and hyperbilirubinemia, including, but not limited to, viral hepatitis, pre-existing chronic or acute liver disease, or the administration of other drug(s) known to be hepatotoxic.

Any component of a study endpoint that is considered related to study therapy should be reported as an SAE (e.g., death is an endpoint, if death occurred due to anaphylaxis, anaphylaxis must be reported).

All Serious Adverse Events (SAEs) that occur following the subject's written consent to participate in the study through 100 days of discontinuation of dosing must be reported to BMS Worldwide Safety, whether related or not related to study drug. All SAEs must be collected that relate to participation in the study. This includes SAEs associated with study drug or other protocol-specified procedure (e.g., a follow-up skin biopsy).

SAEs, whether related or not related to study drug, and pregnancies must be reported to BMS within 24 hours / 1 Business Day of becoming aware of the event. SAEs must be recorded on either CIOMS, MedWatch, or approved site SAE form. BMS Protocol number must be included on the SAE form or on the cover sheet with the SAE form transmission.

- The CIOMS form is available at: *http://www.cioms.ch/index.php/cioms-form-i*

To submit an SAE (or other immediately reportable event):

- write in the expectedness, relationship and severity at the bottom of the CIOMS form
- have the investigator sign and date the bottom of the form
- then attach and email, including ALL of the following:

Email SAE Form To:	*Worldwide.Safety@BMS.com (or fax to +1 609-818-3804)* *CPDM.IIT@CUAnschutz.edu* *Bradley.Haverkos@CUAnschutz.edu* *DSMC@CUAnschutz.edu*
Subject:	**18-0708 SAE Report Form**
Body of Email:	List the following information as assessed by the Investigator • **whether the event is expected or unexpected** • **causality of events in relation to all study medications** • **whether the SAE is related to disease progression** • **CTCAE grade**

If an ongoing SAE changes in its intensity or relationship to study drug or if new information becomes available, a follow-up SAE report should be sent within 24 hours \ 1 Business Day to BMS using the same procedure used for transmitting the initial SAE report.

Following the subject's written consent, all SAEs including those thought to be associated with protocol-specified procedures, need to be reported to BMS and others as above. The investigator should report any SAE occurring after these aforementioned time periods which is believed to be related to study drug or protocol-specified procedure.

An SAE report should be completed for any event where doubt exists regarding its seriousness;

If the investigator believes that an SAE is not related to study drug, but is potentially related to the conditions of the study (such as withdrawal of previous therapy or a complication of a study procedure), the relationship should be specified in the narrative section of the SAE Report Form. The sponsor must notify FDA and all participating PIs in an IND safety report of potential serious risks as soon as possible, but in no case later than 15 calendar days after the sponsor determines that the information qualifies for reporting (21 CFR 312.32(c)(1)).

The sponsor must notify FDA of any unexpected fatal or life-threatening adverse reactions as soon as possible, but in no case later than 7 calendar days after the sponsor's initial receipt of the information (21 CFR 312.32(c)(2)).

The study clinician will complete an SAE Form within the following timelines:

- All deaths and immediately life-threatening events, whether related or unrelated, will be recorded on the SAE Form and submitted to the study sponsor within 24 hours of site awareness. See **Study Contact Listing** for contact information.
- Other SAEs, regardless of relationship, will be submitted to the study sponsor within 72 hours of site awareness.

All SAEs will be followed until satisfactory resolution or until the site PI deems the event to be chronic or the adherence to be stable. Other supporting documentation of the event may be requested by the study sponsor and should be provided as soon as possible.

The study sponsor will be responsible for notifying FDA of any unexpected fatal or life-threatening suspected adverse reaction as soon as possible but in no case later than 7 calendar days after the sponsor's initial receipt of the information.

Overdose:

An overdose is defined as the accidental or intentional administration of any dose of a product that is considered both excessive and medically important. All occurrences of overdose must be reported as an SAE.

8.4.3 UNANTICIPATED PROBLEM REPORTING

Incidents or events that meet the OHRP criteria for UAPs require the creation and completion of a UAP report form. It is the site PI's responsibility to report UAPs to their IRB, using the IRB's standard UAP form. The Lead PI is responsible for reporting the UAP to the UCCC DSMC, if applicable. If an IRB UAP form is not provided, the UAP report will include the following information:

- Protocol-identifying information: protocol title and number, PI's name, and the IRB project number;
- A detailed description of the event, incident, experience, or outcome;

- An explanation of the basis for determining that the event, incident, experience, or outcome represents a UAP;
- A description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the UAP.

To satisfy the requirement for prompt reporting, UAPs will be reported using the following timeline:

- UAPs that are SAEs will be reported to the IRB and to the DSMC within 5 calendar days of the investigator becoming aware of the event.
- Any other UAP will be reported to the IRB and to the DSMC within 5 calendar days of the investigator becoming aware of the problem.

8.4.4 REPORTING OF PREGNANCY

If following initiation of the investigational product, it is subsequently discovered that a study participant is pregnant or may have been pregnant at the time of investigational product exposure (including during at least 5 half-lives after the last dose of a potentially fetotoxic, non-genotoxic therapy) the investigational product will be permanently discontinued in an appropriate manner (e.g., dose tapering if necessary for participant).

The investigator must immediately notify Worldwide.Safety@bms.com of this event via either the CIOMS in accordance with SAE reporting procedures, as listed in section 8.4.2.

Protocol-required procedures for study discontinuation and follow-up must be performed on the participant.

Follow-up information regarding the course of the pregnancy, including perinatal and neonatal outcome and, where applicable, offspring information must be reported on the CIOMS, MedWatch, BMS Pregnancy Surveillance Form, or approved site SAE form. A BMS Pregnancy Surveillance Form may be provided upon request.

8.5 STUDY HALTING RULES

Toxicity
If any patient experiences death due to an adverse event that is assessed as related to study treatment (by investigator and/or Sponsor), it will lead to temporary hold of study pending review by study team.

Toxicities of special interest: The study will be halted prematurely if 3 out of the initial 10 patients experience the toxicities of special interest, listed in 4.1.

Transplant-related adverse events of special interest: For patients undergoing auto-transplant the study will be halted prematurely if 3 out of initial 10 patients undergoing auto-transplant

experience any of the following toxicities of special interest during period from start of conditioning regimen (e.g. BEAM) through 60 days post-transplant:

- Non-relapse related death
- grade 4 or higher hepatotoxicity
- autograft mobilization failure

Treatment-related mortality: If any patient experiences death due to an adverse event that is assessed as related to study treatment (by investigator and/or Sponsor), it will lead to temporary hold of study pending review by study team. The study will be terminated prematurely if at any point 2 patients experience treatment-related death during induction chemotherapy with study regimen.

Efficacy

The study will be suspended pending further review if, at any time, there is sufficient evidence to suggest that the true probability of achieving a complete response falls below 30% while assuming the treatment drug will elicit a 56% complete response rate. Statistically significant evidence for this low complete response rate is defined as an observed complete response rate whose upper one-sided 90% confidence limit is lower than 30%. Sample size calculations were made assuming 80% power. In practice, the study will be suspended if too few complete responses are observed in participants. Table 3 displays the total number of subjects needed for a complete response endpoint for this study and the number of subjects to be accrued in each of two stages in Simon's two-stage procedure (n1 and n2). If r1 or fewer complete responses are observed during stage 1, the trial is stopped early for futility. If r2 or fewer complete responses are observed by the end of stage 2, then no further investigation of this treatment regimen is warranted. While 17 samples are needed to achieve 80% power, 18 total patients will be enrolled in the study to account for possible drop-out/loss to follow-up.

Table 2. Simon Two-Stage Design Stopping Rules for Efficacy

n_1	r_1	n_2	n (Total Sample Size)	r_2	Assumed response rate of treatment drug	Type I error	Power
10	3	7	**17**	7	56%	0.096	0.813

8.6 SAFETY OVERSIGHT

Monitoring and Oversight

The sponsor investigator will be responsible for monitoring the trial per the trial monitoring plan, in addition to overseeing the safety and efficacy of the trial including any specimens collected, executing the data and safety monitoring (DSM) plan, and complying with all reporting requirements to local and federal authorities. This oversight will be accomplished through additional oversight from the Data and Safety Monitoring Committee (DSMC) at the University of Colorado Cancer Center (CU Cancer Center). The DSMC is responsible for ensuring data

quality and study participant safety for all clinical studies at the CU Cancer Center, which is the coordinating institution of this trial. A summary of the DSMC's activities is as follows:

• Conduct of internal audits
• Ongoing review of all serious adverse events (SAEs) and unanticipated problems (UAPs)
• Has the authority to suspend trials for safety or trial conduct issues
• May submit recommendations for corrective actions to the CU Cancer Center's Executive Committee

Per the CU Cancer Center Institutional DSM Plan, SAEs and UAPs are reported to the DSMC, IRB and the sponsor investigator per protocol. All SAEs and UAPs are to be reported to the DSMC within 7 (for fatal or life-threatening events) or 15 (non-life-threatening events) calendar days of the sponsor investigator receiving notification of the occurrence.

Each subject's treatment outcomes will be discussed by the site PI and appropriate staff at regularly scheduled meetings. Data regarding number of subjects, significant toxicities, dose modifications, and treatment responses will be discussed.

The sponsor investigator is responsible for organizing and conducting regularly scheduled teleconferences with all participating sites. The sponsor investigator will also be responsible for including data from all the participating sites to include the minutes from these regularly scheduled teleconferences between the sponsor investigator and the sites within the overall trial's DSM progress report.

The sponsor investigator will provide a DSM progress report to the CU Cancer Center DSMC on a recurring basis (either every six or twelve months based on DSMC vote). The DSM report will include a protocol summary, current enrollment numbers, summary of toxicity data to include specific SAEs, UAPs and AEs, any dose modifications, all protocol deviations, and protocol amendments. The DSM report submitted to the DSMC will also include, if applicable, the results of any efficacy data analysis conducted. Results and recommendations from the review of this progress report by the DSMC will then be provided to the sponsor investigator in a DSMC review letter. The sponsor investigator is then responsible for ensuring this letter is submitted to the site's IRB of record at the time of IRB continuing review.

Quality Control and Quality Assurance

Site monitoring visits will be performed by the sponsor investigator's authorized representative on a regular basis, pursuant to the Monitoring Plan. During these visits, information recorded on the CRFs will be verified against source documents. As necessary, requests for data clarification or correction will be sent to the appropriate site PI.

Independent auditors from the sponsor investigator's authorized representative will be allowed by the site's PI to audit. In addition, audits may be conducted at any time by appropriate regulatory authorities and/or the IRB.

9 CLINICAL MONITORING

Clinical site monitoring will be conducted to ensure that the rights and well-being of human participants are protected, that the reported trial data are accurate, complete, and verifiable, and that the conduct of the trial is in compliance with the currently approved protocol/ amendment(s), with GCP, and with applicable regulatory requirement(s).

Monitoring for this study will be performed by CU Cancer Center Clinical Monitor in accordance with the clinical monitoring plan (CMP), incorporated herein by reference. The CMP describes in detail who will conduct the monitoring, at what frequency monitoring will be done, at what level of detail monitoring will be performed, and the distribution of the monitoring reports.

Independent audits will be conducted by the CU Cancer Center DSMC to ensure monitoring practices are performed consistently across all participating sites, if applicable, and that monitors are following the CMP.

10 STATISTICAL CONSIDERATIONS

10.1 STATISTICAL AND ANALYTICAL PLANS

Using standard of care first-line treatment of PTCL, as low as 40% of patients will achieve a complete response. We hypothesize that treating patients with standard of care EPOCH in combination with nivolumab that we can improve complete response rate to 56% by combining standard of care treatment with nivolumab. Safety will be tested by noting the number of toxicities and SAEs experienced in the treatment cohort. Simon's two-stage design (Simon, 1989) will be used to test the efficacy of combination treatment. Efficacy will be assessed using the proportion of patients who achieve a complete response. See 8.5 for further details.

10.2 STATISTICAL HYPOTHESES

Primary endpoint

Complete response rates will be formally assessed as the primary endpoint. With standard of care treatment, the majority of studies suggest complete response rates of approximately 40% (Maeda et al. Haematologica. 2017; Gleesen et al. Leuk & Lymphoma. 2018; Schmitz et al. Blood & Vose et al. JCO). Of note, these prior studies include favorable subsets (low risk ALK+ ALCL and Stage I disease), which we have excluded from our study. Additionally, in our study we have included poor risk subsets (EATL, MEITL, γ/δ TCL, and secondary CNS disease), which are commonly excluded from PTCL studies. In this current study investigating nivolumab + EPOCH, we hope to achieve an observed complete response rate of >56% and if fewer than 30% of patients experience a complete response to treatment, then the treatment approach is considered a failure.

A sample size of 17 was determined assuming a Simon Two-Stage design with a Type I error of 0.096 and a power of 0.813—given an assumed complete response rate of 56% compared to a 30% complete response rate of the treatment population under standard of care (with realization that this treatment population excludes favorable subsets of the overall disease population). An additional patient will be enrolled to account for potential loss-to-follow-up, etc.

For the experimental treatment, we define failure as an observed complete response rate less than 30%, and we define the null hypothesis as follows: H_0: $p_0 \leq 0.30$. Under the assumption that standard of care in combination with nivolumab will result in an observed complete response rate of at least 56%, we define the following alternative hypothesis: H_1: $p_1 \geq 0.56$. Formal calculation of the p-value associated with the observed data (as well as calculation of a 90% two-sided confidence interval for the complete response rate) will be made using the method outlined by Koyama and Chen (2007).

Secondary endpoints

The following secondary endpoints will be descriptive in nature (no formal statistical analyses will be conducted.) They are:

2-year Progression-free survival
Toxicity/safety
Overall response rate (CR + PR)
Duration of response.
Correlative Analysis: determine immune-related predictors of response to nivolumab + EPOCH

10.3 ANALYSIS DATASETS

The primary efficacy analyses will be performed on the Intent-to-treat (ITT) population, which will include all subjects who have been enrolled for the study.

10.4 DESCRIPTION OF STATISTICAL METHODS

10.4.1 GENERAL APPROACH

To assess efficacy, this study will be guided by a Simon Two-stage design.

The proportion of patients achieving a complete response also will be calculated for the patients being treated in this study. This proportion will be formally compared to a null proportion of 30%. Calculation of the p-value for the observed data and a two-sided 90% confidence interval will be made using the method outlined by Koyama and Chen (2007).

10.4.2 ANALYSIS OF THE PRIMARY EFFICACY ENDPOINT

The proportion of patients achieving a complete response will be calculated for the patients being treated in this study. This proportion will be formally compared to a null proportion of 30%. The population proportion for complete response rate and associated p-value and 90% confidence intervals for the complete response rate will be calculated at study completion.

10.4.3 ANALYSIS OF THE SECONDARY ENDPOINTS

Secondary endpoints will be descriptive in nature, and no formal statistical analyses will be conducted on them.

Progression-free survival (PFS) will be summarized by the proportion of patients without objective or symptomatic progression or death within the first 24 months of therapy.

Overall response rate is defined as complete response rate + partial response rate.

Duration of response is defined as time from first evidence of response until progressive disease or death.

Safety and toxicity: Adverse events will be monitored and quantified.

Correlative Analysis will be descriptive in nature and will investigate immune-related predictors of response to nivolumab + EPOCH.

10.4.4 SAFETY ANALYSES

Regimen toxicities, as defined by CTCAE v5.0 will be summarized using tables and descriptive statistics.

10.4.5 ADHERENCE AND RETENTION ANALYSES

The PI will provide a DSM report to the UCCC DSMC on a six-month basis. The DSM report will include summaries of minutes taken at monthly meetings, the participants' demographic characteristics, expected versus actual recruitment rates, treatment retention rates, any quality assurance or regulatory issues (including a summary of any protocol deviations).

10.4.6 BASELINE DESCRIPTIVE STATISTICS

Demographic data will be compiled for participants in the study at baseline, including age, gender, ethnicity, disease status, and comorbid conditions.

10.4.7 PLANNED INTERIM ANALYSES

No interim analyses are planned for this study. A stopping rules are described in 4.1.

10.4.8 SAFETY REVIEW

10.4.8.1 TOXICITY REVIEW

Data will be monitored continuously, and study will be halted prematurely if at any point stopping criteria as described in 4.1 are met.

10.4.8.2 EFFICACY REVIEW

A Simon 2 stage design will be used to assess efficacy of the regimen using complete response rate as the primary outcome.

10.4.9 EXPLORATORY ANALYSES

Secondary endpoints may lead to exploratory analyses outlined in 10.4.3.

10.5 SAMPLE SIZE

The study will enroll 18 patients.

10.6 MEASURES TO MINIMIZE BIAS

In this non-blinded phase I-II study and outcomes will be assessed by investigators.

11 SOURCE DOCUMENTS AND ACCESS TO SOURCE DATA/DOCUMENTS

To ensure the privacy and confidentiality of data for this protocol, the data will be stored on a restricted access server. Access to the project directory containing the data will be limited to the investigators and research staff. Information about data security awareness is promoted through user training and education and supplemented by policies and procedures. Password protection will be used for all transactions that involve viewing, editing, and analyzing the data or that provide access to data fields derived from the original source documents.

12 QUALITY ASSURANCE AND QUALITY CONTROL

Quality Control (QC) procedures will be implemented beginning with the data entry system and data QC checks that will be run on the database will be generated. Any missing data or data anomalies will be communicated to the site(s) for clarification/ resolution.

Following written SOPs, the study monitor will verify that the clinical trial is conducted and data are generated, documented (recorded), and reported in compliance with the protocol, GCP, and the applicable regulatory requirements (e.g., Good Laboratory Practices (GLP), Good Manufacturing Practices (GMP)).

The investigational site will provide direct access to all trial-related sites, source data/ documents, and reports for the purpose of monitoring and auditing by the DSMC audit team, and inspection by local and regulatory authorities.

13 ETHICS/PROTECTION OF HUMAN SUBJECTS

13.1 ETHICAL STANDARD

The PI will ensure that this study is conducted in full conformity with regulations for the Protection of Human Subjects of Research codified in 45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56. ICH E6 may also be followed to the extent it has been adopted by and is in accordance with FDA regulations.

13.2 INSTITUTIONAL REVIEW BOARD

The protocol, informed consent form(s), recruitment materials, and all subject materials will be submitted to the Colorado Multiple Institutional Review Board (COMIRB) for review and approval. Approval of both the protocol and the consent form must be obtained before any subject is enrolled. Any amendment to the protocol will require review and approval by COMIRB before the changes are implemented to the study. All changes to the consent form will COMIRB approved; a determination will be made regarding whether previously consented participants need to be re-consented.

13.3 INFORMED CONSENT PROCESS

The Consent Forms must be signed and dated by the patient or the patient's legally authorized representative before his or her participation in the study. The case history or clinical records for each patient shall document the informed consent process and that written informed consent was obtained prior to participation in the study.

The Consent Forms should be revised whenever there are changes to study procedures or when new information becomes available that may affect the willingness of the patient to participate. The final revised IRB/EC-approved Consent Forms must be provided to BMS for review.

Patients must be re-consented to the most current version of the Consent Forms (or to a significant new information/findings addendum in accordance with applicable laws and IRB/EC policy) during their participation in the study. For any updated or revised Consent Forms, the case history or clinical records for each patient shall document the informed consent process and that written informed consent was obtained using the updated/revised Consent Forms for continued participation in the study.

A copy of each signed Consent Form must be provided to the patient or the patient's legally authorized representative. All signed and dated Consent Forms must remain in each patient's study file or in the site file and must be available for verification by study monitors at any time.

Consent Form may also include patient authorization to allow use and disclosure of personal health information in compliance with the U.S. Health Insurance Portability and Accountability Act (HIPAA) of 1996. If the site utilizes a separate Authorization Form for patient authorization for use and disclosure of personal health information under the HIPAA regulations, the review, approval, and other processes outlined above apply except that IRB review and approval may not be required per study site policies.

13.3.1 CONSENT/ASSENT AND OTHER INFORMATIONAL DOCUMENTS PROVIDED TO PARTICIPANTS

Consent forms describing in detail the study agent, study procedures, and risks are given to the participant and written documentation of informed consent is required prior to starting intervention/ administering study product.

13.3.2 CONSENT PROCEDURES AND DOCUMENTATION

Informed consent process will be initiated prior to the individual's agreeing to participate in the study and continues throughout the individual's study participation. Extensive discussion of risks and possible benefits of participation will be provided to the participants and their families.

Consent forms will be IRB-approved and the participant will be asked to read and review the document. The investigator will explain the research study to the participant and answer any questions that may arise. All participants will receive a verbal explanation in terms suited to their comprehension of the purposes, procedures, and potential risks of the study and of their rights as research participants. Participants will have the opportunity to carefully review the written consent form and ask questions prior to signing. The participants will have the opportunity to discuss the study with their surrogates or think about it prior to agreeing to participate. The participant will sign the informed consent document prior to any procedures being done specifically for the study.

The participants may withdraw consent at any time throughout the course of the trial. A copy of the informed consent document will be given to the participants for their records. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

The study allows the inclusion of non-English speaking and non-reading participants. Witnesses to these consent processes will be individuals not associated with the trial and will not have a conflict of interest.

13.4 PARTICIPANT AND DATA CONFIDENTIALITY

Participant confidentiality is strictly held in trust by the participating PIs, their staff, and the sponsor(s) and their agents. This confidentiality is extended to cover testing of biological samples and genetic tests in addition to the clinical information relating to participants. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor.

The study monitor, other authorized representatives of the sponsor, representatives of the IRB or pharmaceutical company supplying study product may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the participants in this study. The clinical study site will permit access to such records.

The study participant's contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by local IRB and Institutional regulations.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored at the University of Colorado Cancer Center. This will not include the participant's contact or identifying information. Rather, individual participants and their research data will be identified by a unique study identification number. The study data entry and study management systems used by clinical sites and by the University of Colorado Cancer Center research staff will be secured and password protected. At the end of the study, all study databases will be de-identified and archived at the University of Colorado Cancer Center.

13.4.1 RESEARCH USE OF STORED HUMAN SAMPLES, SPECIMENS OR DATA

Intended Use:
Samples and data collected under this protocol may be used to assess biomarkers associated with response to chemo-immunotherapy. No genetic testing will be performed.

Storage:
Access to stored samples will be limited to research personnel only. Samples and data will be stored using codes assigned by the investigators. Data will be kept in password-protected computers. Only investigators will have access to the samples and data.

Disposition at completion of the study:
Consent will be obtained from all patients for tumor tissue banking. Patients can withdraw consent for tumor banking at any time. All stored samples will be sent to the University of Colorado HCTU bank. Study subjects who request destruction of samples will be notified of compliance with such request and all supporting details will be maintained for tracking.

13.5 FUTURE USE OF STORED SPECIMENS

Data collected for this study will be analyzed and stored within the University of Colorado Hematology Clinical Trials Unit. After the study is completed, the de-identified, archived data will be transmitted to and stored at the, under the supervision of the primary investigator of Hematology Lymphoid Malignancy Tissue Bank (LTB) for use by other researchers including those outside of the study. Permission to transmit data to the LTB will be included in the informed consent.

With the participant's approval and as approved by local IRBs, de-identified biological samples will be stored at the LTB with the same goal as the sharing of data with the LTB. These samples could be used for research into the causes of PTCL its complications and other conditions for which individuals with PTCL are at increased risk, and to improve treatment. The LTB will also be provided with a code-link that will allow linking the biological specimens with the phenotypic data from each participant, maintaining the masking of the identity of the participant.

During the conduct of the study, and individual participant can choose to withdraw consent to have biological specimens stored for future research. However, withdrawal of consent with regard to biosample storage will not be possible after the study is completed.

When the study is completed, access to study data and/ or samples will be provided through the LTB.

14 DATA HANDLING AND RECORD KEEPING

14.1 DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site PI. The PI is responsible for ensuring the accuracy, completeness, legibility, and timelines of the data reported.

Source Documentation:
All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data. When making changes or corrections, cross out the original entry with a single line, and initial and date the change. DO NOT ERASE, OVERWRITE, OR USE CORRECTION FLUID OR TAPE ON THE ORIGINAL.

Source documents (paper or electronic) are those in which patient data are recorded and documented for the first time. They include, but are not limited to, hospital records, clinical and office charts, laboratory notes, memoranda, patient-reported outcomes, evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies of transcriptions that are certified after verification as being accurate and complete, microfiche, photographic negatives, microfilm or magnetic media, X-rays, patient files, and records kept at pharmacies, laboratories, and medico-technical departments involved in a clinical trial.

Before study initiation, the types of source documents that are to be generated will be clearly defined in the Clinical Monitoring Plan. This includes any protocol data to be entered directly into the eCRFs (i.e., no prior written or electronic record of the data) and considered source data.

Source documents that are required to verify the validity and completeness of data entered into the eCRFs must not be obliterated or destroyed and must be retained.

The study site must also allow inspection by applicable health authorities.

When clinical observations are entered directly into a study site's computerized medical record system (i.e., in lieu of original hardcopy records), the electronic record can serve as the source document if the system has been validated in accordance with health authority requirements pertaining to computerized systems used in clinical research.

An acceptable computerized data collection system allows preservation of the original entry of data. If original data are modified, the system should maintain a viewable audit trail that shows the original data as well as the reason for the change, name of the person making the change, and date of the change.

Electronic Case Report Forms (eCRF):
Clinical data (including AEs, concomitant medications, and expected adverse reactions data) and clinical laboratory data will be entered into an electronic data capture system provided by the University of Colorado.

eCRFs are to be completed through use of a Sponsor-Investigator designated EDC system. Sites will receive training and have access to a manual for appropriate eCRF completion. The data system includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate. Clinical data will be entered directly from the source documents. All eCRFs should be completed by designated, trained site staff.

At the end of the study, any hard copy of patient data received by the investigator for his or her site must be stored safely with the study records. Acknowledgement of receipt of the compact disc is required.

Copies of the electronic CRF (eCRF) will be provided for use as source documents and maintained for recording data for each subject enrolled in the study. Data reported in the eCRF derived from source documents should be consistent with the source documents or the discrepancies should be explained and captured in a progress note and maintained in the subject's official electronic study record.

Data Quality Assurance:
The Sponsor-Investigator will be responsible for data management of this study, including quality checking of the data. Data entered manually will be collected via EDC through use of eCRFs. Site will be responsible for data entry into the EDC system.

eCRFs and correction documentation will be maintained in the EDC system's audit trail. System backups for data stored by the Sponsor-Investigator and records retention for the study data will be consistent with the Sponsor-Investigator's standard procedures.

14.2 STUDY RECORDS RETENTION

Study documents should be retained for a minimum of 2 years after the last approval of an investigational marketing application and until there are no pending or contemplated marketing applications or until at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period, however, if required by local regulations, or institution policies. No records will be destroyed without the written consent of the sponsor, if applicable. It is the responsibility of the sponsor to inform the PI when these documents no longer need to be retained.

14.3 PROTOCOL DEVIATIONS

A protocol deviation is any noncompliance with the clinical trial protocol, GCP, or SOP requirements. The noncompliance may be either on the part of the subject, the investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly. These practices are consistent with ICH E6, sections:

- 4.5 Compliance with Protocol, sections 4.5.1, 4.5.2, and 4.5.3.
- 5.1 Quality Assurance and Quality Control, section 5.1.1.
- 5.20 Noncompliance, sections 5.20.1 and 5.20.2.

It is the responsibility of the study team to use continuous vigilance to identify and report deviations. Deviations will be reported to the DMSC and IRB according to UCCC DSM plan and institutional policy.

14.4 PUBLICATION AND DATA SHARING POLICY

This study will comply with the NIH Public Access Policy, which ensures that the public has access to the published results of NIH-funded research. It requires scientists to submit final peer-reviewed journal manuscripts that arise from NIH funds to the digital archive PubMed Central upon acceptance for publication.

The International Committee of Medical Journal Editors (ICMJE) member journals have adopted a clinical trials registration policy as a condition for publication. The ICMJE defines a clinical trial as any research project that prospectively assigns human participants to intervention or concurrent comparison or control groups to study the cause-and-effect relationship between a medical intervention and a health outcome. Medical interventions include drugs, surgical procedures, devices, behavioral treatments, process-of-care changes, and the like. Health outcomes include any biomedical or health-related measures obtained in patients or participants, including pharmacokinetic measures and adverse events. The ICMJE policy, and the Section 801 of the Food and Drug Administration Amendments Act of 2007 requires that all clinical trials be registered in a public trials registry such as ClinicalTrials.gov, which is sponsored by the National Library of Medicine. Other biomedical journals are considering adopting similar policies. For interventional clinical trials performed under NIH IC grants and cooperative agreements, it is the grantee's responsibility to register the trial in an acceptable registry, so the research results may be considered for publication in ICMJE member journals. The ICMJE does not review specific studies to determine whether registration is necessary; instead, the committee recommends that researchers who have questions about the need to register err on the side of registration or consult the editorial office of the journal in which they wish to publish.

FDAAA mandates that a "responsible party" (i.e., the sponsor or designated PI) register and report results of certain "applicable clinical trials".

- Trials of Drugs and Biologics: Controlled, clinical investigations, other than Phase I investigations, of a product subject to FDA regulation;
- Trials of Devices: Controlled trials with health outcomes of a product subject to FDA regulation (other than small feasibility studies) and pediatric post-market surveillance studies.

16 CONFLICT OF INTEREST POLICY

Independence of this study from any actual or perceived influence, such as by the pharmaceutical industry, is critical. Any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed.by the University of Colorado Denver's (UCD) Office of Regulatory Compliance Conflict of Interest and Commitment Management (COIC) program. Persons with a perceived conflict of interest will have such conflicts managed in a way that is appropriate to their participation in the trial. Conflict of

Interest management plans are project-specific and are reviewed at least annually. UCD has integrated the institutional conflict of interest management program with its existing program.

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COMIRB No: **18-0708**
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Study Title: **Nivolumab with standard of care chemotherapy for the first line treatment of peripheral T cell lymphoma**

You are being asked to participate in a research study. A member of the research team will explain what is involved in this study and how it will affect you. This consent form describes the study procedures, the risks and benefits of participation, as well as how your confidentiality will be maintained. Please take your time to ask questions and feel comfortable making a decision whether to participate or not. This process is called informed consent. If you decide to participate in this study, you will be asked to sign this form.

Why is this study being done?

The purpose of this study is to learn more about a combination of the standard chemotherapy regimen with one additional drug and how well they might work to treat peripheral T cell lymphoma (PTCL). The chemotherapy drugs together are commonly called DA-EPOCH and include the following: Etoposide, Prednisone, Vincristine, Doxorubicin, and Cyclosphosphamide. 'DA' stands for dose-adjusted. The additional drug that you will receive is called Nivolumab.

You are being asked to be in this research study because you have been newly diagnosed with PTCL.

The drugs in EPOCH regimen are approved by the U.S. Food and Drug Administration (FDA) to treat PTCL. Nivolumab is approved by the FDA to treat several different types of cancer, including other blood cancers, but is not approved to treat your specific type of cancer. This combination is therefore considered to be experimental.

Throughout the rest of this consent form, the DA-EPOCH regimen and Nivolumab will be called the "study drugs" when referenced together.

How many people will participate?

Up to 14 people from your area will participate in the study.
Up to 24 people from around the country will participate in the study.

What happens if I join this study?

If you join the study, you will be asked to sign this consent form. You will be given a copy to keep and the original form will be kept at the clinic. You can withdraw from the study at any time and without giving a reason. This will not affect the standard medical care you receive.

There are 3 parts to the study:

1. Screening (before beginning the study drugs)
2. Induction Phase (attempt to eliminate visible lymphoma in your body)
3. Follow-Up

The next section of this form lists what will be expected of you if you join this study.

Study Procedures

While you are taking part in this study, some of the tests and procedures are the same type that would be performed as part of your regular cancer care even if you did not join the study. Some of the tests and procedures are required only for the study, and are identified below as "**research**" procedures.

The screening tests and procedures will be done to see if you are eligible to join this study. You may have had some of these tests and procedures done recently as standard care for your cancer, and they may not need to be repeated.

- **Informed Consent (Research)**
  This informed consent form will be discussed with you and you will be given a copy of this document. If you join the study, you will be asked to sign this consent form before you receive any study related tests or procedures.

- **Medical and Cancer History (Standard of Care)**
  Before you start the study we will record your date of birth, race, ethnicity, and complete medical history. This history will look at the background and progress of your cancer and any treatments you have received for your disease.

- **Physical Examination (Standard of Care)**
  A physical examination will be completed as part of your standard of care. We will also assess if the study drug is affecting your body functions including lungs, heart, abdomen, extremities, skin, head (eyes, ears, nose, hair, etc.) and neurologically.

- **Vital Signs (Standard of Care)**
  We will take your blood pressure, heart rate, respiratory rate, body temperature and weight. Height will be measured only during screening.

- **Performance Status (Standard of Care)**
  We will assess how well you are performing your daily activities.

- **Review of Current Medications (Standard of Care)**
  Your study doctor will let you know which medications you can and cannot take while taking part in this study. From the time you first receive the study drugs through 30 days after the last dose, we will record medications you may be taking.

- **Review of Side Effects (Standard of Care)**
  Some risks have been identified because of the disease process or through use of the study drugs themselves and these will be followed very closely by the Principal Investigator and study staff. More information will be provided in the Risks section of this consent.

- **Blood and Urine Samples (Standard of Care)**
  These tests are sometimes called safety labs so the study doctor can be sure it is safe for you to take part in this study and to be given the study drugs.
  - Pregnancy test: Women who are able to become pregnant will be given either a urine or a blood pregnancy test. A positive pregnancy test prior to being given the study drugs will exclude you from starting or continuing to take part in the study. This test must be performed 14 days prior to starting treatment.
  - Complete blood count (CBC)
  - Comprehensive metabolic panel (CMP)
  - Blood clotting tests (PT/INR, and PTT)
  - Thyroid function tests (TSH)
  - Creatinine Clearance
  - Testing for HIV (human immunodeficiency virus), HBV (hepatitis B virus), HCV (hepatitis C virus), and EBV (Epstein-Barr virus)
  - Urinalysis

- **Blood Samples (Research)**
  These tests are being done specifically because you are participating in this study.
  - Blood testing: These tests will be done to understand better how the drug is working.

- **Electrocardiogram (ECG or EKG) (Standard of Care)**

This is a simple, noninvasive procedure that records the electrical activity of the heart. Electrodes are placed on the skin of the chest and connected in a specific order to a machine. Output usually appears on a long scroll of paper that displays a printed graph.

- **Echocardiogram (ECHO) or Multigated Acquisition (MUGA) Scan (Standard of Care)**
  This is a noninvasive scan of the heart using sound waves. This test will be used to see how well your heart pumps blood.

- **Bone Marrow Biopsy/Aspirate (Standard of Care, if necessary)**
  At various time points during the study, you will have bone marrow examined. This involves placing a hollow needle into your hip bone near the small of your back and taking a small sample of the bone (bone marrow biopsy) and 2-3 tablespoons of the liquid bone marrow inside the bone (bone marrow aspirate).

  If a screening bone marrow biopsy is required, it needs to be done within 6 weeks prior to study enrollment. A repeat bone marrow biopsy prior to Cycle 3 would only be required to assess response if initial biopsy was positive for disease.

- **Imaging (CT or MRI) (Standard of Care)**
  These tests will be performed to check the status of your disease. These tests must be performed 4 weeks prior to study enrollment.
  - CT: A computed tomography scan uses x-rays to make detailed pictures of parts of the body and the structures inside the body.
  - MRI: Magnetic resonance imaging is a test that uses a magnetic field and pulses of radio wave energy to make pictures of organs and structures inside the body.

- **Positron Emission Tomography (PET/CT) Scan (Standard of Care)**
  Positron emission tomography (PET) scan is a test that uses radioactive glucose (sugar) and a computer to create images of how organs and tissues in the body are functioning. Abnormal cells in the body use glucose at a different rate than normal cells and this allows the scanner to create a detailed picture of how your body is working. A PET/CT scan is mandatory before and after treatment. A CT scan may be performed in place of a PET/CT scan at other time points during the study, depending on your insurance carrier.

- **Tumor Tissue Samples (Standard of Care)**
  - Archived Tissue: If you had surgery for your cancer in the past, you must agree to allow us to contact the institution where you had your surgery and ask them to send us a portion of your tumor tissue that they have stored so

we may use it for this to confirm your diagnosis of PTCL and for future research.

- Tumor tissue biopsy during screening: If archived tissue is not available, we will ask you to allow us to take a fresh biopsy of your tumor tissue prior to treatment to confirm your diagnosis and to store it for optional future research. This biopsy may be core needle, excisional, or incisional since fine needle aspirations are typically inadequate to make a diagnosis of PTCL.

- **Lumbar Puncture (Standard of Care, if necessary)**
  A lumbar puncture (spinal tap) is performed in your lower back, in the lumbar region. During a lumbar puncture, a needle is inserted between two lumbar bones (vertebrae) to remove a sample of cerebrospinal fluid. This is the fluid that surrounds your brain and spinal cord to protect from injury. If this procedure is required, it will need to be performed 6 weeks prior to starting treatment.

- **Receiving the Study Drugs**
  EPOCH regimen (Standard of Care):
  You will receive these drugs through an intravenous infusion, using a central venous catheter. This involves the insertion of a catheter, or small tube, into a large vein in the arm, or into a vein under your collar bone. This may be done under local anesthesia. You will receive these drugs over 5 days including a continuous 96 hour infusion.

  Nivolumab (Research): You will also receive these drugs through an intravenous infusion, using a central venous catheter.

Study Visits
Please refer to Study Calendar for schedule of events. In addition, please note the following information.

Screening
If screening tests and procedures are performed within 48 hours of Cycle 1 Day 1, routine lab testing and physical exams do not need to be repeated.

Induction Cycles
All assessments must be done prior to treatment and may be performed up to 2 days prior to treatment.

If after your treatment during the Induction cycles, the PET/CT scan shows evidence of disease, a biopsy of that area may be done at the study doctor's discretion. The PET/CT scan should be within 6 weeks of cycle 6 day 1.

End of Treatment

Any subject that has had a PET/CT scan within 21 days of their end of treatment will not have to repeat that procedure.

For subjects that choose to have the stem cell transplant after the Induction phase, you will undergo a PET/CT scan or CT scan (PET preferred) approximately 3 months after the transplant. This will be considered your end of treatment visit for the study.

Follow-Up

The follow-up period starts after the end of treatment visit. Subjects will be contacted via phone every 3 months for 2 years for disease status and survival information.

*For subjects who have completed one cycle of chemotherapy prior to joining this study please note the following.

- These subjects are essentially starting at Cycle 2 of the induction phase.
- PET scan normally performed prior to cycle 3 would be performed prior to cycle 4 of all chemotherapy.
- Imaging must have been performed within 4 weeks of Cycle 1 Day 1 of chemotherapy.
- Subjects that underwent the following procedures prior to Cycle 1 of standard chemotherapy do NOT need to have them repeated:
    - Testing for HIV (human immunodeficiency virus), HBV (hepatitis B virus), HCV (hepatitis C virus), and EBV (Epstein-Barr virus)
    - CT/MRI
    - PET scan
    - Bone marrow biopsy/aspirate
    - ECHO or MUGA scan
    - Lumbar puncture

Tests and procedures	Screening ≤ 28 days prior to C1D1; 6 weeks prior for PET/CT	Induction Treatment with Nivolumab + Chemotherapy		Post-Induction			Long Term Follow-Up
		C1 – C6 Treatment	Hematology between Induction Cycles	End of Induction Visit (3-6 weeks after C6D1)	Autologous Transplant & Post-Transplant	End of Treatment	
Medical History, Physical Exam and Vital Signs	X	X		X		X	
Adverse Events	X	X		X		X	X
Medications	X	X		X		X	X
ECOG Performance Status	X			X		X	
Pregnancy Test (blood or urine)	X						
Tumor tissue sample for confirmation of diagnosis and research purposes *or* fresh tumor biopsy	X			X			
Hematology	X	X	2x per week	X		X	
Chemistry	X	X		X		X	
Urinalysis	X			X		X	
Thyroid Function Tests	X	X		X		X	
PT/INR, PTT	X						
HIV, HBV, HCV, HTLV testing	X						
EBV PCR (in EBV+ subset)	X			X	X	X	
Tumor Measurement/Evaluation (CT and/or MRI when indicated)	X	Before C3		X	X	X	
PET/CT scan	X	Before C3, C4, & C6			X	X	
Bone marrow aspirate and biopsy (unilateral or bilateral)	X	Before C3		X		X	
Electrocardiogram	X						
ECHO or MUGA scan	X						

Consent and Authorization Form

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Lumbar Puncture	X	X		X		X	
Research blood samples	X	Before C2 ***and*** C3		X	X	X	
Drug Administration		X					
Survival status				X		X	X

How long will I be in the study?

You may continue receiving study drugs for up to 6 cycles (approximately 6 months) and be followed every 3 months for the next 2 years.

What are the possible discomforts or risks?

You may have side effects while you are in this study, but you will be carefully checked by the study doctor for any problems. There may be risks or side effects of the study treatment that are unknown at this time. You should tell the study doctor about anything that is bothering you or any side effects you have, even if you do not think they are related to the study treatment. Many side effects go away shortly after the medications are stopped, but in some cases side effects can be serious, long lasting, or permanent.

Because this treatment is experimental, it is possible that the addition of a new drug, nivolumab, to standard of care may make the therapy either more or less effective.

Risks of the Study Drugs

What are the possible discomforts or risks?

You may have side effects while you are in this study, but you will be carefully checked by the study doctor for any problems. There may be risks or side effects of the study treatment that are unknown at this time. You should tell the study doctor about anything that is bothering you or any side effects you have, even if you do not think they are related to the study treatment. Many side effects go away shortly after the medications are stopped, but in some cases side effects can be serious, long lasting, permanent, or lead to **death**.

Risks of Nivolumab

Most Common:

- Fatigue
- Pain in Muscles, bones, and joints
- Diarrhea
- Cough
- Constipation
- Back pain
- Fever
- Rash
- Itchy Skin
- Nausea
- Shortness of breath

- Decreased appetite
- Upper respiratory tract infection
- Weakness

Less Common:

Lung problems (pneumonitis) Symptoms may include:
- new or worsening cough
- chest pain
- shortness of breath

Intestinal problems (colitis) that can lead to tears or holes in your intestine. Signs and symptoms of colitis may include:
- diarrhea or more bowel movements than usual
- blood in your stools or dark, tarry, sticky stools
- severe stomach-area pain or tenderness

Liver problems (hepatitis) Signs and symptoms may include:
- yellowing of your skin or the whites of your eyes
- severe nausea or vomiting
- pain on the right side of your stomach area (abdomen)
- drowsiness
- dark urine (tea colored)
- bleeding or bruising more easily than normal
- feeling less hungry than usual

Hormone gland problems (especially the thyroid, pituitary, adrenal glands, and pancreas) Signs and symptoms may include:
- headaches that will not go away or unusual headaches
- extreme tiredness
- weight gain or weight loss
- dizziness or fainting
- hair loss
- feeling cold
- constipation
- voice gets deeper
- excessive thirst or lots of urine
- changes in mood or behavior, such as decreased sex drive, irritability, or forgetfulness

Kidney problems, including nephritis and kidney failure**.** Signs of kidney problems may include:

- decrease in the amount of urine
- blood in your urine
- swelling in your ankles
- loss of appetite

Skin Problems. Signs of these problems may include:

- rash
- itching
- skin blistering
- ulcers in mouth or other mucous membranes

Inflammation of the brain (encephalitis) Signs and symptoms may include:

- headache
- fever
- tiredness or weakness
- confusion
- memory problems
- sleepiness
- seeing or hearing things that are not really there (hallucinations)
- seizures
- stiff neck

Rare but Serious:

Severe infusion reactions. Tell your doctor or nurse right away if you get these symptoms during an infusion of Nivolumab:

- chills or shaking
- itching or rash
- flushing
- difficulty breathing
- dizziness
- fever
- feeling like passing out

Risks of Etoposide
More common

- bad, unusual, or unpleasant (after) taste
- change in taste
- constipation
- cracked lips

- hair loss or thinning of the hair
- lack or loss of strength
- swelling or inflammation of the mouth
- weight loss
- black, tarry stools
- bleeding gums
- blood in the urine or stools
- chest pain
- chills
- cough
- fever
- painful or difficult urination
- pale skin
- pinpoint red spots on the skin
- shortness of breath
- sore throat
- sores, ulcers, or white spots on the lips or in the mouth
- swollen glands
- troubled breathing with exertion
- unusual bleeding or bruising
- unusual tiredness or weakness

Less common

- blurred vision
- confusion
- cough or hoarseness, accompanied by fever or chills
- difficulty with swallowing
- dizziness
- dizziness, faintness, or lightheadedness when getting up suddenly from a lying or sitting position
- face is warm or hot to touch
- fast heartbeat
- headache
- hives, itching, or skin rash
- lower back or side pain, accompanied by fever or chills
- nervousness
- numbness or tingling in the fingers or toes
- pain or redness at the site of injection
- pale skin at the site of injection

- pounding in the ears

- puffiness or swelling of the eyelids or around the eyes, face, lips, or tongue
- redness to face
- slow or fast heartbeat
- sweating
- tightness in the chest

Rare

- back pain
- difficulty with walking
- loss of consciousness
- swelling of the face or tongue
- tightness in the throat

Risks of Doxorubicin

More common

- hair loss, thinning of hair
- nausea and vomiting
- sores in the mouth and on the lips

Less common

- cough or hoarseness accompanied by fever or chills
- darkening or redness of the skin (if you recently had radiation treatment)
- fast or irregular heartbeat
- fever or chills
- joint pain
- lower back or side pain accompanied by fever or chills
- pain at the injection site
- painful or difficult urination accompanied by fever or chills
- red streaks along the injected vein
- shortness of breath
- stomach pain
- swelling of the feet and lower legs
- darkening of the soles, palms, or nails
- diarrhea

Rare

- black, tarry stools
- blood in the urine
- pinpoint red spots on the skin
- unusual bleeding or bruising

Risks of Vincristine

More common

- abdominal or stomach pain
- black, tarry stools
- bleeding gums
- blood in the urine or stools
- blurred vision
- burning, tingling, numbness or pain in the hands, arms, feet, or legs
- change in consciousness
- change in muscle reflexes
- chest pain
- chills
- confusion
- cough
- dizziness, faintness, or lightheadedness when getting up suddenly from a lying or sitting position
- fever
- increased sensitivity to pain or touch
- low blood pressure or pulse
- lower back or side pain
- nerve pain
- painful or difficult urination
- pale skin
- pinpoint red spots on the skin
- sensation of pins and needles
- severe constipation
- severe vomiting
- shortness of breath
- sneezing
- sore throat
- stabbing pain

- sweating
- tightness in the chest
- troubled breathing
- ulcers, sores, or white spots in the mouth
- unsteadiness or awkwardness
- unusual bleeding or bruising
- unusual tiredness or weakness

Less common

- blue lips, fingernails, or skin
- irregular, fast or slow, or shallow breathing
- Lack or loss of strength
- mental depression or anxiety
- muscle weakness
- nightmares or unusually vivid dreams

Risks of Prednisone

More common

- aggression
- agitation
- blurred vision
- decrease in the amount of urine
- dizziness
- fast, slow, pounding, or irregular heartbeat or pulse
- headache
- irritability
- mood changes
- noisy, rattling breathing
- numbness or tingling in the arms or legs
- pounding in the ears
- shortness of breath
- swelling of the fingers, hands, feet, or lower legs
- trouble thinking, speaking, or walking
- troubled breathing at rest
- weight gain

Risks of Cyclophosphamide

More common

- cough or hoarseness
- fever or chills
- lower back or side pain
- missing menstrual periods
- painful or difficult urination
- darkening of the skin and fingernails
- loss of appetite
- nausea or vomiting

Less common

- black, tarry stools
- pinpoint red spots on the skin
- unusual bleeding or bruising
- diarrhea
- flushing or redness of the face
- headache
- increased sweating
- skin rash, hives, or itching
- stomach pain
- swollen lips

Rare

- frequent urination
- redness, swelling, or pain at the injection site
- sores in the mouth and on the lips
- sudden shortness of breath
- unusual thirst
- yellow eyes or skin

Risks of the Study Procedures

Blood collection

Blood sampling and needle punctures carry some risk. Possible side effects include, but are not limited to, fainting, bleeding, bruising, discomfort, dizziness, infection and/ or pain at the puncture site.

Having an IV inserted in your vein

In this study we will insert a needle, connected to a plastic tube, into a vein in your arm. We will use the tube to take blood samples or give you fluids. You will feel some pain when we first insert the tube into your vein. You may have some redness, swelling, or bruising where the tube goes under your skin. In some cases, this type of tube can cause an infection where it goes under the skin. In rare cases, it can cause a blood clot in the vein. You will have this tube inserted for about four or five hours.

Bone marrow biopsy

In this study we will take four samples of bone marrow from your pelvic bone. Before we take each sample, we will give you some numbing medication on the skin outside your pelvic bone (on your hip). After your skin is numb, we will push a special needle into the center of your pelvic bone. Then, we will draw the bone marrow up into the syringe. When we do this, you will have a pulling feeling as the marrow leaves the bone and goes into the syringe. The area around the bone will be sore for a few days. There is a very small chance that you will be allergic to the numbing medicine. There is also a very small chance that you could bleed or develop an infection.

Tumor biopsy

In this study, an additional biopsy may be required from you. There are some risks to taking a biopsy. There is a small chance that you could get an infection where the needle goes in. You may also experience redness, swelling, minor bleeding or bruising at the site where the cut was made or the needle inserted. You may experience mild to moderate pain at the site of the needle puncture. There is also a small chance that you could have an allergic reaction to the numbing medicine. After your skin heals up, you may have a small scar where we take the samples. If an X-ray is used to help place the needle, you will be exposed to additional radiation. The amount of radiation you receive during each biopsy procedure is approximately equal to the radiation you would receive in about 4 years in your normal environment.

There may be some additional risks, depending on where your tumor is located. If you have a biopsy of a solid organ, like your liver or a kidney, or of a lymph node, there is a risk of pain, bleeding, and infection. There is a risk of damage to nearby structures or organs. There is a risk of injury due to positioning of the needle and a small risk of heart or lung problems. If you have a lung biopsy, there is a risk of air getting into the space around your lung that would require a tube to be placed in between your ribs to draw the air out. If this tube is placed, some additional risks include damage to other nearby structures, including the lung, a prolonged air leak, and a possible need for additional tubes or procedures. There is a small risk of death from complications of a biopsy.

Electrocardiogram (EKG)

An electrocardiogram (EKG) is a test that records the electrical activity of the heart. Skin irritation is rare but could occur during an EKG from the electrodes or the gel that is used.

Imaging (PET, CT scans)

Procedures such as CT scans, X-rays and/or radioactive drugs will be used during this research study to see how you are doing. The cumulative radiation exposure from these tests is considered small and is not likely to adversely affect you or your disease. However, the effects of radiation add up over a lifetime. It is possible that having several of these tests may add to your risk of injury or disease. When deciding to enter this study, think about your past and future contact with radiation. Examples of contact with radiation include x-rays taken for any reason or radiation therapy for cancer treatment.

MRI

Some people cannot have an MRI because they have some type of metal in their body. For instance, if you have a heart pacemaker, artificial heart valves, metal implants such as metal ear implants, bullet pieces, chemotherapy or insulin pumps or any other metal such as metal clips or rings, they cannot have an MRI. During this test, you will lie in a small closed area inside a large magnetic tube. Some people are scared or anxious in small places (claustrophobic). The MRI scanner makes loud banging noises while taking a measurement, so either ear plugs or specially designed headphones will be used to reduce the noise.

Lumbar Puncture

- **Post-lumbar puncture headache.** Up to 25 percent of people who have undergone a lumbar puncture develop a headache afterward due to a leak of fluid into nearby tissues.

  The headache typically starts several hours up to two days after the procedure and may be accompanied by nausea, vomiting and dizziness. The headaches are usually present when sitting or standing and resolve after lying down. Post-lumbar puncture headaches can last from a few hours to a week or more.

- **Back discomfort or pain.** You may feel pain or tenderness in your lower back after the procedure. The pain might radiate down the back of your legs.
- **Bleeding.** Bleeding may occur near the puncture site or, rarely, into the epidural space.
- **Brainstem herniation.** Increased pressure within the skull (intracranial), due to a brain tumor or other space-occupying lesion, can lead to compression of the brainstem after a sample of cerebrospinal fluid is removed.

A computerized tomography (CT) scan or MRI prior to a lumbar puncture can be obtained to determine if there is evidence of a space-occupying lesion that results in increased intracranial pressure. This complication is rare.

Reproductive Risks

While participating in this research study, you should not become pregnant, nurse a baby, or father a baby. Both men and women who are able to have children must use a highly effective means of birth control approved by your study doctor.

If you are a female who has stopped having menstrual periods for at least 1 year (menopause), please discuss with your study doctor the need for birth control. If you become pregnant, you must stop taking the study drugs at once and notify your doctor immediately. You will not be allowed to continue in the study. You may be asked questions about the outcome of your pregnancy and the baby.
You must continue the use of birth control during the entire time of your study participation and to at least 5 months after the last dose of nivolumab.

Risk of Loss of Confidentiality

There is a risk that people outside the research team will see your research information. We will do all that we can to protect your information, but it cannot be guaranteed.

There may be other risks that could arise which are not reasonably foreseeable. If new information becomes available which could influence your willingness to continue, this new information will be discussed with you.

What are the possible benefits of the study?

This study is designed for the researcher to learn more about a combination of the standard chemotherapy regimen with an additional drug (Nivolumab). However, there is no guarantee that your health will improve if you join this study. Also, there could be risks to being in this study. If there are risks, these are described in the section describing the discomforts or risks.

Are there alternative treatments?

There may be other ways of treating your cancer. Instead of taking part in this study:

- You may choose to receive treatment with an approved therapy.
- You may choose to participate in a different study with another experimental drug.
- You may choose to receive comfort/ palliative care.
- You may choose to get no treatment at all.

You should talk to your doctor about your choices. Make sure you understand all of your

choices before you decide to take part in this study. You may leave this study and still have these other choices available to you.

Who is paying for this study?

Bristol Meyers Squibb (BMS) is providing a grant of funding support for this study. BMS manufactures the study drug, Nivolumab, and will provide this drug for the study. This research is being conducted by Dr. Bradley Haverkos. The research study will only pay for procedures not considered standard of care.

Three of the investigators in this study, Dr. Tomer, Dr. Forsberg, and Dr. Pollyea, have a financial interest with Celgene Corporation (affiliated with Bristol Myers Squibb Pharmaceutical). Bristol Myers Squibb Pharmaceutical is the manufacturer of Nivolumab. Dr. Tomer and Dr. Forsberg are speakers for the company, and Dr. Pollyea is an advisory board member. Please feel free to ask any questions you may have about this matter.

Will I be paid for being in the study?

You will not be paid to be in the study.

Will I have to pay for anything?

The drug manufacturer, BMS, will pay for the cost of the study drug, Nivolumab. The funding for this study will also pay for any tests or procedures that are related to the research study.

The study drug regimen DA-EPOCH is considered standard treatment for your type of cancer. This drug will be obtained through your insurance, and you will be responsible for any applicable copays required by your insurance policy.

There are some medical procedures that you would get for your condition whether you were in this study or not, such as routine blood draws, imaging, drugs for the EPOCH regimen, and administration of nivolumab. These are considered standard of care. You and/or your health insurance may be billed for the costs of medical care during this study if these expenses are related to standard of care procedures. If you have health insurance, the cost of these services will be billed to your insurance company. If your insurance does not cover these costs, or you do not have insurance, these costs will be your responsibility.

Ask your study doctor to discuss the costs that will or will not be covered by this research study. This discussion should include the costs of treating possible side effect. Otherwise, you might have unexpected expenses from being in this study.

Is my participation voluntary?

Taking part in this study is voluntary. You have the right to choose not to take part in this study. If you choose to take part, you have the right to stop at any time. If you refuse or decide to withdraw later, you will not lose any benefits or rights to which you are entitled.

If you leave this study, you will still receive your normal medical care. The only medical care that you will lose is the medical care you are getting as part of this study. You might be able to get that same kind of medical care outside of the study. Ask your study doctor.

Can I be removed from this study?

The study doctor may decide to stop your participation without your permission if the study doctor thinks that being in the study may cause you harm, or for any other reason.

What happens if I am injured or hurt during the study?

If you have an injury while you are in this study, you should call Dr. Haverkos immediately. His phone number is720-848-8698 (office hours) or 720-848-0000 (24-hour contact number, and ask for HEME BMT Attending on-call).

We will arrange to get you medical care if you have an injury that is caused by this research. However, you or your insurance company will have to pay for that care.

Who do I call if I have questions?

The researcher carrying out this study is Bradley Haverkos, MD. You may ask any questions you have now. If you have questions, concerns, or complaints later, you may call Dr. Haverkos at 720-848-8698 (office hours) or 720-848-0000 (24-hour contact number, and ask for HEME BMT Attending on-call). You will be given a copy of this form to keep.

You may have questions about your rights as someone in this study. You can call Dr. Haverkos with questions. You can also call the responsible Institutional Review Board (COMIRB). You can call them at 303-724-1055.

A description of this clinical trial will be available on http://www.Clinical Trials.gov, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

Optional Consent for Specimen Banking for Future Research

Dr. Haverkos would like to keep some blood, tissue from biopsies, and/or archived tissue that was taken during previous biopsy procedures. If you agree, the samples will be kept and may be used in future research to learn more about cancer. The research that is done with your samples is not designed to specifically help you. It might help people who have cancer and other diseases in the future. Reports about research done with your samples will not be given to you or your doctor. These reports will not be put in your health records. The research using your samples will not affect your care.

The choice to let Dr. Haverkos keep the tissue samples for future research is up to you. No matter what you decide to do, it will not affect the care that you will receive as part of the study. If you decide now that your samples can be kept for research, you can change your mind at any time and contact your study doctor to let him know that you do not want Dr. Haverkos to use your samples any longer, and they will no longer be used for research. Otherwise, they may be kept until they are used up, or until Dr. Haverkos decides to destroy them.

When your samples are given to other researchers in the future, Dr. Haverkos will not give them your name, address, phone number or any other information that will let the researchers know who you are.

Sometimes samples are used for genetic research (about diseases that are passed on in families). If your samples are used for this kind of research, the results will not be told to you and will not be put in your health records. Your samples will only be used for research and will not be sold. The research done with your samples may help to develop new products in the future, but there is no plan for you to be paid.

We may share data from our research with other researchers or data banks. One such data bank is called dbGAP, which collects genetic and other data and is sponsored by the National Institutes of Health. By broadly sharing data in data banks like this, we can make our discoveries more accessible to other researchers. Information which directly identifies you will not be sent to these data banks.

Because your genetic information is unique to you, there is a small risk that someone could connect the information back to you. Also, genetic research and broadly sharing data may involve risks to you or people like yourself that are unknown at this time.

The possible benefits of research from your samples include learning more about what causes cancer and other diseases, how to prevent them and how to treat them. The greatest risk to you is the release of your private information. Dr. Haverkos will protect your records so that your name, address and phone number will be kept private. The chance that this information will be given to someone else is very small. There will be no cost to you for any data or sample collection and storage by Dr. Haverkos.

Please read each sentence below and think about your choice. After reading each sentence, circle “yes” or “no.” If you have questions, please talk to your doctor or nurse. Remember, no matter what you decide to do about the storage and future use of your samples, you may still take part in the study.

I give my permission for my blood and tissue to be stored in a central tissue bank for future use by the study investigators:

1. I give my permissions for my blood and tissue samples to be kept by Dr. Haverkos for use in future research to learn more about how to prevent, detect, or treat lymphoma.

   ☐ Yes ☐ No _____Initials

2. I give my permissions for my blood and tissue samples to be used for research about other health problems (for example: causes of heart disease, osteoporosis, diabetes).

   ☐ Yes ☐ No _____Initials

Who will see my research information?

The University of Colorado Denver (UCD) and its affiliated hospital(s) have rules to protect information about you. Federal and state laws including the Health Insurance Portability and Accountability Act (HIPAA) also protect your privacy. This part of the consent form tells you what information about you may be collected in this study and who might see or use it.

The institutions involved in this study include:

- University of Colorado Denver
- University of Colorado Hospital
- Thomas Jefferson University
- City of Hope Hospital

We cannot do this study without your permission to see, use and give out your information. You do not have to give us this permission. If you do not, then you may not join this study.

We will see, use and disclose your information only as described in this form and in our Notice of Privacy Practices; however, people outside the UCD and its affiliate hospitals may not be covered by this obligation.

We will do everything we can to maintain the confidentiality of your personal information but confidentiality cannot be guaranteed.

The use and disclosure of your information has no time limit. You can cancel your

permission to use and disclose your information at any time by writing to the study's Principal Investigator (PI), at the name and address listed below. If you do cancel your permission to use and disclose your information, your part in this study will end and no further information about you will be collected. Your cancellation would not affect information already collected in this study.

Bradley Haverkos, MD
Anschutz Medical Campus
1665 N. Aurora Court
Mail Stop F754
Aurora, CO 80045

Both the research records that identify you and the consent form signed by you may be looked at by others who have a legal right to see that information, such as:

- Federal offices such as the Food and Drug Administration (FDA) and the Office of Human Research Protections (OHRP) that protect research subjects like you.
- People at the Colorado Multiple Institutional Review Board (COMIRB).
- The study doctor and the rest of the study team.
- Bristol Meyers Squibb, Inc., manufacturer of Nivolumab who is also providing a grant of funding support.
- Officials at the institution where the research is conducted and officials at other institutions involved in this study who are in charge of making sure that we follow all of the rules for research.

We might talk about this research study at meetings. We might also print the results of this research study in relevant journals. But we will always keep the names of the research subjects, like you, private.

You have the right to request access to your personal health information from the Investigator.

Information about you that will be seen, collected, used and disclosed in this study:

- Name and demographic information (age, sex, ethnicity, address, phone number, etc.
- Portions of your previous and current medical records that are relevant to this study, including but not limited to diagnosis(es), history and physical, laboratory or tissue studies, radiology studies, procedure results.
- Research visit and research test records.
- Tissue samples and the data with the samples.
- Billing or financial information.

What happens to Data, Tissue, Blood and Specimens that are collected in this study?

Scientists at the University of Colorado Denver and the hospitals involved in this study work to find the causes and cures of disease. The data, tissue, blood and specimens collected from you during this study are important to this study and to future research. If you join this study:

- The data, tissue, blood, or other specimens given by you to the investigators for this research no longer belong to you.
- Both the investigators and any sponsor of this research may study your data, tissue, blood, or other specimens collected from you.
- If data, tissue, blood, or other specimens are in a form that identifies you, UCD or the hospitals involved in this study may use them for future research only with your consent or Institutional Review Board (IRB) approval.
- Any product or idea created by the researchers working on this study will not belong to you.
- There is no plan for you to receive any financial benefit from the creation, use or sale of such a product or idea.

HIPAA Authorization for Optional Additional Study Procedures –In this form, you were given the option to agree to additional, optional research procedures. You must also give us your permission, under HIPAA rules, to use and disclose the information collected from these optional procedures, as described above.

Some of these optional procedures may involve genetic testing or the use of your genetic information. Your genetic information will not be released to others. If you decline to give us permission to use and disclose your information, you cannot take part in these optional procedures, but you can still participate in the main study. Please initial next to your choice:

_____I give permission for my information, from the optional procedures I have agreed to above, to be used and disclosed as described in this section.

_____I **do not** give permission for my information for any optional procedures to be used and disclosed; I understand that I will not participate in any optional procedures.

Agreement to be in this study and use my data

The research project and the procedures associated with it have been explained to me.

The experimental procedures have been identified and no guarantee has been given about the possible results. I will receive a signed copy of this consent form for my records.

I agree to participate in this study. My participation is voluntary and I do not have to sign this form if I do not want to be part of this research study.

Subject Signature:_____ Date: _____

Subject Print Name:_____

Consent form explained by:_____ Date: _____

Print Name: _____

---------- ***Use Only if Applicable*** ----------

Signature Line for witness; required for consent of non-reading subjects and consent using a short form, if you requested such consent procedures

Witness of Signature ☐
Witness of consent process ☐

Witness Signature:_____ Date:_____

Witness Print Name: _____