CC9805

A Pilot Trial of Adriamycin, Pembrolizumab, Vinblastine and Dacarbazine (APVD) for patients with Untreated Classical Hodgkin Lymphoma

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1.0 TRIAL SUMMARY

Abbreviated Title	Adriamycin, Pembrolizumab, Vinblastine and Dacarbazine (APVD) in Untreated cHL
Trial Phase	Pilot
Clinical Indication	Untreated Classical Hodgkin Lymphoma
Trial Type	Nonrandomized, single arm prospective clinical trial
Type of control	N/A
Route of administration	IV
Trial Blinding	N/A
Treatment Groups	Untreated Classical Hodgkin Lymphoma
Number of trial participants	Part A: 30 Part B: 20
Estimated enrollment period	36 months
Estimated duration of trial	48 months
Duration of Participation	48 months
Estimated average length of treatment per patient	2 months

2.0 TRIAL DESIGN

2.1 Trial Design

This is a nonrandomized, single-arm pilot study designed to evaluate Adriamycin, Pembrolizumab, Vinblastine, and Dacarbazine for 2 cycles (28 day cycle length) in patients with untreated Classical Hodgkin Lymphoma. Patients can receive an additional 4 cycles, up to a total of 6 cycles of APVD at the discretion of the treating provider (Part A only). All subjects should receive 6 total cycles in Part B.

2.2 Trial Diagram

Part A

Registration (any stage untreated Hodgkin lymphoma)

↓

Adriamycin, Vinblastine and Dacarbazine given on days 1 and 15 for 2 cycles (28 day cycle length).
Pembrolizumab given on cycle 1 day 1, cycle 1 day 22, and cycle 2 day 15.

Dosing Schema (Cycles 1-2) (Part A and Part B)

	Cycle 1			Cycle 2	
	Day 1	**Day 15**	**Day 22**	**Day 1**	**Day 15**
Doxorubicin 25mg/m^2	X	X		X	X
Pembrolizumab 200 mg (fixed dose)	X		X		X
Vinblastine 6 mg/m^2	X	X		X	X
Dacarbazine (DTIC) 375 mg/m^2	X	X		X	X

Continuing treatment after the initial 2 cycles will be at the discretion of the treating physician up to a maximum of 6 cycles (Part A). The primary endpoint of this trial is to evaluate the safety of 2 cycles of APVD (Part A).

Optional dosing schema for treatment cycle 3-6

	Cycle 3			Cycle 4			Cycle 5		Cycle 6		
	Day 1	**Day 8**	**Day 15**	**Day 1**	**Day 15**	**Day 22**	**Day 1**	**Day 15**	**Day 1**	**Day 8**	**Day 15**
Doxorubicin 25mg/m^2	X		X	X	X		X	X	X		X
Pembrolizumab 200 mg (fixed dose)		X		X		X		X		X	
Vinblastine 6 mg/m^2	X		X	X	X		X	X	X		X
Dacarbazine (DTIC) 375 mg/m^2	X		X	X	X		X	X	X		X

Part B

Registration (Stage III or IV untreated Hodgkin lymphoma)

	Cycle 1			Cycle 2		Cycle 3			Cycle 4			Cycle 5		Cycle 6		
	Day 1	**Day 15**	**Day 22**	**Day 1**	**Day 15**	**Day 1**	**Day 8**	**Day 15**	**Day 1**	**Day 15**	**Day 22**	**Day 1**	**Day 15**	**Day 1**	**Day 8**	**Day 15**
Doxorubicin 25mg/m^2	X	X		X	X	X		X	X	X		X	X	X		X
Pembrolizumab 200 mg (fixed dose)	X		X		X		X		X		X		X		X	
Vinblastine 6 mg/m^2	X	X		X	X	X		X	X	X		X	X	X		X
Dacarbazine (DTIC) 375 mg/m^2	X	X		X	X	X		X	X	X		X	X	X		X

Primary endpoint for Part B to estimate the 1-year event free survival (EFS) for advanced stage patients treated with APVD. An event will be defined as progression, biopsy proven recurrence, initiation of next line of chemotherapy, or death.

3.0 OBJECTIVES & HYPOTHESES

3.1 Primary Objectives & Hypotheses

Objective: Part A: To estimate the safety of delivering 2 cycles APVD to patients with previously untreated cHL. Part B: To estimate the 1-year event free survival (EFS) for advanced stage patients treated with APVD. An event will be defined as progression, biopsy proven recurrence, initiation of next line of chemotherapy, or death.

Hypothesis: We hypothesize that a combination of pembrolizumab with AVD chemotherapy (Doxorubicin, Vinblastine and Dacarbazine) for use in the front line setting for chemotherapy naïve patients with cHL will be safe and potentially efficacious.

3.2 Secondary Objective & Hypotheses

Objective: To estimate the FDG-PET2 negative (Deauville score 1-3) after 2 cycles of APVD.

3.3 Exploratory Objective

Objective: Overall survival, association of biomarkers with early CR. Predictive capacity of PET2 after APVD. To evaluate the impact of APVD on T-cell repertoire and diversity. To evaluate the ability of this regimen to attain minimal residual disease as measured by NGS.

3.4 Background

Efficacy and limitations of ABVD

ABVD (Doxorubicin, Bleomycin, Vinblastine, and Dacarbazine) is a component of a standard regimen in North America for treatment of classical Hodgkin's lymphoma (cHL) regardless of disease stage. It was originally developed in 1970, showed similar efficacy compared with MOPP regimen (Mechlorethamine, Vincristine, Procarbazine, and Prednisone) and more importantly had an improved tolerability and toxicity profile[1]. In the advanced cHL setting, ABVD use offers up to 70% long term tumor control rate[2]. However, up to 25% of patients do not respond completely to ABVD[3]. Additionally, of the initial responders relapse occurs in a significant proportion of patients who then require salvage chemotherapy, high dose chemotherapy, autologous stem cell transplant, brentuximab-vedotin, nivolumab or pembrolizumab[4]. Nevertheless, ABVD is still considered a standard frontline regimen for classical cHL despite the fact that up to one-third of patients will not be cured with this approach.

Toxicity of Bleomycin

ABVD use is associated with toxicities, both acute and long term. Bleomycin is most commonly implicated for causing severe toxicity, specifically, acute pulmonary toxicity - dyspnea on exertion, cough with dyspnea and decline in pulmonary function tests [5,6]. These can be potentiated

with concomitant use of G-CSF, hence the limited use of growth factor to abrogate the frequent neutropenia induced with this regimen. Bleomycin can also induce long-term pulmonary toxicity. Elderly patients and those receiving radiation therapy are at a higher risk of this toxicity including mortality and for this reason it is typically omitted from ABVD when treating older patients[7]. Recent data indicate that bleomycin may be safely discontinued in select early patients with early complete remissions to mitigate and prevent further damage[8,9]..

Efficacy and Safety of PD-1 inhibition in cHL.

Besides cytotoxic chemotherapy, promising results have been seen with checkpoint blockade based cancer immunotherapy in cHL. Tumors evade the T cell anti-tumor activity by blocking the PD-1/PD-L1/PD-L2 pathway. In cHL overexpression of PD-1 ligands in the RS cells[10] and the tumor associated macrophages[11] is seen. These cells engage the PD-1 receptor on the T cells, thus inducing immune tolerance. This allows tumor to evade the immune surveillance[10]. Pembrolizumab is a humanized IgG4 anti-PD-1 antibodies which blocks T cell inhibition, thereby enhancing anti-tumor T cell activity[12]. Pembrolizumab and the anti-PD-1 are both FDA approved for treatment of relapsed/refractory cHL patients based on 4 studies[13], though pembrolizumab has a broader label of approval. Pembrolizumab demonstrated a 65% overall response rate (KETNOTE 13) in the first trial at a dose of 10mg/kg every 2 weeks and an overall response rate of 69% in the KEYNOTE-87 trial at a dose of 200mg every 3 weeks [14, 15]. The patients in these studies were heavily pre-treated with chemotherapy, autologous stem cell transplant and novel antibody drug conjugate, Brentuximab-Vedotin. Pembrolizumab was overall well tolerated, no grade 4-5 drug related toxicities were noted in ≥5% of the patients.

Front Line Use and Combinations of anti-PD1 and chemotherapy:

Both Pembrolizumab and Nivolumab have been successfully used as part of intial therapy and combined with chemotherapy further improve the response rates [15, 16, 17, 18]. It is postulated that chemotherapy causes release of tumor antigens and in this setting the immune response can be further potentiated by using checkpoint inhibition. In a phase I study the safety and efficacy of Nivolumab combined with platinum based doublet chemotherapy for first line treatment of advanced NSLC was reported. Among the 95 patients treated in this study, no dose limiting occurred in the first 6 weeks of therapy. 45% patients reported grade 3 or 4 treatment related adverse effects. The safety profile was felt to be consistent with that expected for the agents.[19] Similar results have been observed using pembrolizumab as part of initial therapy [20-22]. For example, the large KEYNOTE-21 showed no higher rates of AEs ≥ grade 3 in the chemo alone or chemo+pembrolizumab groups[22]. In further support of this approach in patients with lymphoma we are currently carrying out a phase II trial of pembrolizumab + R-CHOP in patients with untreated DLBCL with no apparent increase in toxicity over R-CHOP alone (Smith et al- unpublished data).

Pembrolizumab is a potent humanized immunoglobulin G4 (IgG4) monoclonal antibody (mAb) with high specificity of binding to the programmed cell death 1 (PD-1) receptor, thus inhibiting its interaction with programmed cell death ligand 1 (PD-L1) and

programmed cell death ligand 2 (PD-L2). Based on preclinical in vitro data, pembrolizumab has high affinity and potent receptor blocking activity for PD-1. Pembrolizumab has an acceptable preclinical safety profile and is in clinical development as an intravenous (IV) immunotherapy for advanced malignancies. Keytruda® (pembrolizumab) is indicated for the treatment of patients across a number of indications because of its mechanism of action to bind the PD-1 receptor on the T cell. For more details on specific indications refer to the Investigator brochure.

3.4.1 Pharmaceutical and Therapeutic Background

The importance of intact immune surveillance function in controlling outgrowth of neoplastic transformations has been known for decades[1]. Accumulating evidence shows a correlation between tumor-infiltrating lymphocytes in cancer tissue and favorable prognosis in various malignancies. In particular, the presence of CD8+ T-cells and the ratio of CD8+ effector T-cells/FoxP3+ regulatory T-cells (T-regs) correlates with improved prognosis and long-term survival in solid malignancies, such as ovarian, colorectal, and pancreatic cancer; hepatocellular carcinoma; malignant melanoma; and renal cell carcinoma. Tumor-infiltrating lymphocytes can be expanded ex vivo and reinfused, inducing durable objective tumor responses in cancers such as melanoma [Dudley et al., 2005; Hunder et al., 2008].

The PD-1 receptor-ligand interaction is a major pathway hijacked by tumors to suppress immune control. The normal function of PD-1, expressed on the cell surface of activated T-cells under healthy conditions, is to down-modulate unwanted or excessive immune responses, including autoimmune reactions. PD-1 (encoded by the gene *Pdcd1*) is an immunoglobulin (Ig) superfamily member related to cluster of differentiation 28 (CD28) and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) that has been shown to negatively regulate antigen receptor signaling upon engagement of its ligands (PD-L1 and/or PD-L2) [Greenwald et al., 2005; Okazaki et al., 2001].

The structure of murine PD-1 has been resolved [Zhang et al., 2004]. PD-1 and its family members are type I transmembrane glycoproteins containing an Ig-variable–type (IgV-type) domain responsible for ligand binding and a cytoplasmic tail responsible for the binding of signaling molecules. The cytoplasmic tail of PD-1 contains 2 tyrosine-based signaling motifs, an immunoreceptor tyrosine-based inhibition motif, and an immunoreceptor tyrosine-based switch motif. Following T-cell stimulation, PD-1 recruits the tyrosine phosphatases, SHP-1 and SHP-2, to the immunoreceptor tyrosine-based switch motif within its cytoplasmic tail, leading to the dephosphorylation of effector molecules such as CD3 zeta (CD3ζ), protein kinase C-theta (PKCθ), and zeta-chain-associated protein kinase (ZAP70), which are involved in the CD3 T-cell signaling cascade [Okazaki et al., 2001; Chemnitz et al., 2004; Sheppard et al., 2004; and Riley, 2009]. The mechanism by which PD-1 down-modulates T-cell responses is similar to, but distinct from, that of CTLA-4, because both molecules regulate an overlapping set of signaling proteins [Parry et al., 2005; Francisco, 2010]. As a consequence, the PD-1/PD-L1 pathway is an attractive target for therapeutic intervention in [disease under study].

3.4.2 Preclinical and Clinical Trial Data

Refer to the Investigator's Brochure for Preclinical and Clinical data.

3.5 Rationale

3.5.1 Rationale for the Trial and Selected Population

The selected patient population is patients with untreated Classical Hodgkin Lymphoma. Pembrolizumab can be safely combined with a variety of chemotherapeutic agents in the front line setting, has a >60% response rate as a single agent in patients with highly-refractory cHL and a toxicity profile that is non-overlapping with AVD chemotherapy. Though not compared in a head-to head fashion, the clinical activity of pembrolizumab appears superior to what one would expect with single agent bleomycin and potentially brentuximab-vedotin. Recent data also suggest that omitting bleomycin in responding patients is safe and retains efficacy and is a standard of care in select patients. We hypothesize that the proposed APVD regimen may offer better efficacy and better tolerability in the front line setting for treatment of classical cHL. This study will address the safety of a minimum of 2 cycles of APVD as a first step toward incorporating PD1 blockade as part of front line therapy.

Early activity of APVD

Accrual on this study began in February 2020, and as of May 21, 2021, 29 of the original 30 planned patients have been enrolled (unpublished data). We noted a CR rate of 65% on interim PET (slightly lower than previously presented in standard ABVD[2]). 5 patients so far have had a positive PET at end of treatment, but only one patient so far has had evidence of progressive CHL. 80% (4/5) of patients with FDG uptake post treatment never progressed at 8, 9, 18, and 19 months. These patients were either followed with serial imaging with resolution or underwent a biopsy.

These findings raise concerns that traditional methods of PET response assessment may be prone to false positives in patients treated with checkpoint inhibitor combinations. For this reason, we will plan to treat an additional 20 advanced stage patients with this regimen in order to better assess the activity of this regimen using a 1-year EFS endpoint.

3.5.2 Dosing Justification for Dose

The planned dose of pembrolizumab for this study is 200 mg every 3 weeks (Q3W). Based on the totality of data generated in the Keytruda development program, 200 mg Q3W is the appropriate dose of pembrolizumab for adults across all indications and regardless of tumor type. As outlined below, this dose is justified by:

- Clinical data from 8 randomized studies demonstrating flat dose- and exposure-efficacy relationships from 2 mg/kg Q3W to 10 mg/kg every 2 weeks (Q2W),

- Clinical data showing meaningful improvement in benefit-risk including overall survival at 200 mg Q3W across multiple indications, and
- Pharmacology data showing full target saturation in both systemic circulation (inferred from pharmacokinetic [PK] data) and tumor (inferred from physiologically-based PK [PBPK] analysis) at 200 mg Q3W

Among the 8 randomized dose-comparison studies, a total of 2262 participants were enrolled with melanoma and non-small cell lung cancer (NSCLC), covering different disease settings (treatment naïve, previously treated, PD-L1 enriched, and all-comers) and different treatment settings (monotherapy and in combination with chemotherapy). Five studies compared 2 mg/kg Q3W versus 10 mg/kg Q2W (KN001 Cohort B2, KN001 Cohort D, KN002, KN010, and KN021), and 3 studies compared 10 mg/kg Q3W versus 10 mg/kg Q2W (KN001 Cohort B3, KN001 Cohort F2 and KN006). All of these studies demonstrated flat dose- and exposure-response relationships across the doses studied representing an approximate 5- to 7.5-fold difference in exposure. The 2 mg/kg (or 200 mg fixed-dose) Q3W provided similar responses to the highest doses studied. Subsequently, flat dose-exposure-response relationships were also observed in other tumor types including head and neck cancer, bladder cancer, gastric cancer and classical Hodgkin Lymphoma, confirming 200 mg Q3W as the appropriate dose independent of the tumor type. These findings are consistent with the mechanism of action of pembrolizumab, which acts by interaction with immune cells, and not via direct binding to cancer cells.

Additionally, pharmacology data clearly show target saturation at 200 mg Q3W. First, PK data in KN001 evaluating target-mediated drug disposition (TMDD) conclusively demonstrated saturation of PD-1 in systemic circulation at doses much lower than 200 mg Q3W. Second, a PBPK analysis was conducted to predict tumor PD-1 saturation over a wide range of tumor penetration and PD-1 expression. This evaluation concluded that pembrolizumab at 200 mg Q3W achieves full PD-1 saturation in both blood and tumor.

Finally, population PK analysis of pembrolizumab, which characterized the influence of body weight and other participant covariates on exposure, has shown that the fixed-dosing provides similar control of PK variability as weight based dosing, with considerable overlap in the distribution of exposures from the 200 mg Q3W fixed dose and 2 mg/kg Q3W dose. Supported by these PK characteristics, and given that fixed-dose has advantages of reduced dosing complexity and reduced potential of dosing errors, the 200 mg Q3W fixed-dose was selected for evaluation across all pembrolizumab protocols.

3.5.3 Rationale for Endpoints

Definitions of Disease, Criteria for Evaluation and Endpoint Definitions – response will be defined by standard NCI criteria (Lugano 2014) for lymphoid malignancies.

Primary endpoint (Part A): The primary objective of this study is to estimate the safety of 2 cycles of APVD. Historical data regarding the tolerability of 2 cycles of ABVD are limited. In a recent trial of AVD+ brentuximab vedotin, 4 of 26 (~15%) patients were reported to be unable to complete treatment. We will be more conservatively scoring treatment delay due to toxicity rather than inability to complete the entire treatment course. Thus, we will deem this regimen safe if >85% of patients are able to complete

2 cycles of APVD without a dose delay of >3 weeks. This will be employed as a stopping rule and serve as the primary endpoint.

Part B: We plan to estimate the efficacy of this regimen using advanced stage patients (who are at higher risk of recurrence) with a projection that 1-year EFS will be at least as good as the 85% demonstrated in the ECHELON-1 study between the two arms[3]. See statistical section for detail.

3.5.4 Efficacy Endpoints

Secondary and Exploratory endpoints will examine the efficacy of this regimen. Our secondary endpoint is to estimate the proportion of FDG-PET2 negative (Deauville score 1-3) patients after 2 cycles of APVD. Exploratory endpoints will estimate overall and progression free survival.

3.5.5 Biomarker Research

Correlative studies may be conducted whenever possible and may include PD1/PLDL1/PDL2 expression, MRD (e.g. Adaptive Clonoseq or similar) and cytokine monitoring. Tissue-based assays for tumor and immune infiltrate may be conducted when archival tissue is available.

4.0 METHODOLOGY

4.1 Study Population

4.1.1 Eligibility Criteria

4.1.1.1 Participant Inclusion Criteria

Participants are eligible to be included in the study only if all of the following criteria apply:

1. Patients must have cHL that has not been previously treated
   - Part A: Any stage
   - Part B: Must be stage 3 or 4
2. Patients must be appropriate candidates for at least 2 cycles of ABVD (6 cycles for Part B patients) or AVD (this could include patients ranging from favorable risk early stage disease to poor prognosis advanced stage disease).
3. Patients must have measurable FDG-avid disease defined by standard criteria (Lugano 2014) and a minimum of 1.0 cm in diameter.
4. Patients should not have evidence of active central nervous system lymphoma.
5. Patients must have an ECOG performance status of 0 or 1.
6. Patients must be 18 years of age or older.
7. Patients must have a LVEF ≥50% within 56 days of enrollment.
9. Patients must have adequate labs within 10 days of treatment.

Bone Marrow Function: ANC $\geq 500/mm^3$, platelets $\geq 25{,}000/mm^3$ (without transfusion or growth factor support), hemoglobin ≥ 8 g/dL. Growth factor and/or transfusion support is permissible to stabilize participant prior to study treatment if needed. There is no lower limit to cytopenias if related to bone marrow involvement.

Renal Function: serum creatinine < 1.5 x ULN or creatinine clearance greater than 30/ml per minute by Cockcroft Gault formula

Hepatic function: total bilirubin ≤ 1.5 times upper limit of normal OR direct bilirubin $\leq$ULN for participants with total bilirubin levels $>1.5 \times$ ULN), AST and ALT ≤ 2.5 times upper limit of normal ($\leq 5 \times$ ULN for participants with liver metastases)

10. All patients must be informed of the investigational nature of this study and have given written consent in accordance with institutional and federal guidelines.

11. Patients must be anticipated to complete all planned study therapy.

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

13. Female subject of childbearing potential should have a negative urine or serum pregnancy within 72 hours prior to receiving the first dose of study medication. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required.

14. Female subjects of childbearing potential should be willing to use 2 methods of birth control or be surgically sterile or abstain from heterosexual activity for the course of the study through 120 days after the last dose of study medication. Subjects of childbearing potential are those who have not been surgically sterilized or have not been free from menses for > 1 year.

4.1.1.2 Participant Exclusion Criteria:

Participants are excluded from the study if any of the following criteria apply:

1. Patients known positive for HIV, or infectious hepatitis type B or C.
2. Pregnant or nursing women. Men or women of reproductive potential may not participate unless they have agreed to use an effective contraceptive method.
3. Patients with other prior malignancies except for adequately treated basal cell carcinoma, squamous cell carcinoma of the skin, breast or cervical cancer *in*

situ, or other cancer from which the patient has been disease-free for 5 years or greater, unless approved by the protocol Chair or Co-Chair.

4. Patients who have other medical conditions that would contraindicate treatment with aggressive chemotherapy (including active infection, uncontrolled hypertension, congestive heart failure, unstable angina pectoris, or myocardial infarction within the past 6 months, uncontrolled arrhythmia, severe pulmonary disease or requirement of supplemental oxygen).
5. Active ischemic heart disease or congestive heart failure.
6. Concurrent use of other anti-cancer agents or experimental treatments.
7. Known current or prior autoimmune disease with the exception of vitiligo.
8. Active or prior history of pneumonitis/interstitial lung disease that required corticosteroids.
9. Current use of supplemental oxygen.
10. Is known to have received a live vaccine or live-attenuated vaccine within 30 days prior to the first dose of trial treatment. Administration of killed vaccines is allowed.

4.1.2 Lifestyle Restrictions

4.1.2.1 Meals and Dietary Restrictions

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

4.1.2.2 Contraception

Pembrolizumab may have adverse effects on a fetus in utero. Refer to Appendix 4 for approved methods of contraception.

For this study, male participants will be considered to be of non-reproductive potential if they have azoospermia (whether due to having had a vasectomy or due to an underlying medical condition).

4.1.3 Pregnancy

If a participant inadvertently becomes pregnant while on treatment with pembrolizumab, the participant will be immediately discontinued from study treatment. The site will contact the participant at least monthly and document the participant's status until the pregnancy has been completed or terminated. The outcome of the pregnancy will be reported to Merck within 2 working days if the outcome is a serious adverse experience (eg, death, abortion, congenital anomaly, or other disabling or life-threatening complication to the mother or newborn). The study Investigator will make every effort to obtain permission to follow the outcome of the pregnancy and report the condition of the fetus or newborn to Merck. If a male participant impregnates his female partner, the study personnel at the site must be

informed immediately and the pregnancy must be reported to Merck and followed as described in Section 6.3.1.

4.1.4 Use in Nursing Women

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

4.2 Trial Treatments

The treatment to be used in this trial is outlined below in Table below. Administration of APVD: Each cycle of therapy is given every 28 days with doses of doxorubicin, vinblastine, and dacarbazine on days 1 and 15. Pembrolizumab will be given on cycle 1 day 1, cycle 1 day 22, and cycle 2 day 15. Two cycles should be given per protocol. Administration may be +/-2 days. Infusion details should be as per institutional standard of care. Dates for optional (mandatory for part B) cycles 3-6 are outlined in section 2.2. Pembrolizumab will be administered first, followed by Doxorubicin, Vinblastine and Dacarbazine.

Drug	**Dose**	**Route**	**Days**
Doxorubicin	25mg/m2	IV	1 and 15
Vinblastine	6mg/m2	IV	1 and 15
Dacarbazine	375 mg/m2	IV	1 and 15

Drug	**Dose**	**Route**	**Cycle/Days**
Pembrolizumab*	200mg	IV	Cycle 1 days 1 and 22, Cycle 2 day 15 (and cycles 3-6 at outlined in section 2.2)

Trial treatment should begin on the day of enrollment or as close as possible to the date on which treatment is allocated/assigned.

4.2.1 Timing of Dose Administration

Trial treatment of doxorubicin, vinblastine, and dacarbazine should be administered on Day 1 and 15 of each cycle after all procedures/assessments have been completed as detailed on the Trial Flow Chart (Section 5.0). Pembrolizumab 200 mg will be administered as a 30 minute IV infusion every 3 weeks starting on cycle 1 day 1. Sites should make every effort to target infusion timing to be as close to 30 minutes as possible. However, given the variability of infusion pumps from site to site, a window of -5 minutes and +10 minutes is permitted (i.e., infusion time is 30 minutes: -5 min/+10 min).

Each cycle of therapy is given every 28 days. Two cycles should be given per protocol. Administration may be +/-2 days. All other infusion details should be as per institutional standard of care. Pembrolizumab will be administered first, followed by Doxorubicin, Vinblastine and Dacarbazine.

All trial treatments will be administered on an outpatient basis.

Growth factor support will be at the discretion of the treating team. Growth factors should be avoided whenever possible within 10 days of FDG-PET imaging. Antibiotic and antiemetic prophylaxis will be per institutional standard of care.

4.2.2 Dose Modification and toxicity management for immune-related AEs associated with pembrolizumab

AEs associated with pembrolizumab exposure may represent an immunologic etiology. These immune-related AEs (irAEs) may occur shortly after the first dose or several months after the last dose of pembrolizumab treatment and may affect more than one body system simultaneously. Therefore, early recognition and initiation of treatment is critical to reduce complications. Based on existing clinical study data, most irAEs were reversible and could be managed with interruptions of pembrolizumab, administration of corticosteroids and/or other supportive care. For suspected irAEs, ensure adequate evaluation to confirm etiology or exclude other causes. Additional procedures or tests such as bronchoscopy, endoscopy, skin biopsy may be included as part of the evaluation. Based on the severity of irAEs, withhold or permanently discontinue pembrolizumab and administer corticosteroids. Dose modification and toxicity management guidelines for irAEs associated with pembrolizumab are provided in Table 3.

Table 3 Dose modification and toxicity management guidelines for immune-related AEs associated with pembrolizumab

General instructions:

1. Severe and life-threatening irAEs should be treated with IV corticosteroids followed by oral steroids. Other immunosuppressive treatment should begin if the irAEs are not controlled by corticosteroids.
2. Study intervention must be permanently discontinued if the irAE does not resolve or the corticosteroid dose is not ≤10 mg/day within 12 weeks of the last study intervention treatment.
3. The corticosteroid taper should begin when the irAE is ≤ Grade 1 and continue at least 4 weeks.
4. If study intervention has been withheld, study intervention may resume after the irAE decreased to ≤ Grade 1 after corticosteroid taper.

irAEs	Toxicity Grade (CTCAE v5.0)	Action With Pembrolizumab	Corticosteroid and/or Other Therapies	Monitoring and Follow-up
Pneumonitis	Grade 2	Withhold	• Administer corticosteroids (initial dose of 1 to 2 mg/kg prednisone or equivalent) followed by taper • Add prophylactic antibiotics for opportunistic infections	• Monitor participants for signs and symptoms of pneumonitis • Evaluate participants with suspected pneumonitis with radiographic imaging and initiate corticosteroid treatment
	Recurrent Grade 2, Grade 3 or 4	Permanently discontinue		
Diarrhea/Colitis	Grade 2 or 3	Withhold	• Administer corticosteroids (initial dose of 1 to 2 mg/kg prednisone or equivalent) followed by taper	• Monitor participants for signs and symptoms of enterocolitis (ie, diarrhea, abdominal pain, blood or mucus in stool with or without fever)

irAEs	Toxicity Grade (CTCAE v5.0)	Action With Pembrolizumab	Corticosteroid and/or Other Therapies	Monitoring and Follow-up
	Recurrent Grade 3 or Grade 4	Permanently discontinue		and of bowel perforation (ie, peritoneal signs and ileus) • Participants with ≥Grade 2 diarrhea suspecting colitis should consider GI consultation and performing endoscopy to rule out colitis • Participants with diarrhea/colitis should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion
AST or ALT Elevation or Increased Bilirubin	Grade 2 [a]	Withhold	• Administer corticosteroids (initial dose of 0.5 to 1 mg/kg prednisone or equivalent) followed by taper	• Monitor with liver function tests (consider weekly or more frequently until liver enzyme value returned to baseline or is stable)
	Grade 3 [b] or 4 [c]	Permanently discontinue	• Administer corticosteroids (initial dose of 1 to 2 mg/kg prednisone or equivalent) followed by taper	
T1DM or Hyperglycemia	New onset T1DM or Grade 3 or 4 hyperglycemia associated with	Withhold [d]	• Initiate insulin replacement therapy for participants with T1DM	• Monitor participants for hyperglycemia or other signs and symptoms of diabetes

irAEs	Toxicity Grade (CTCAE v5.0)	Action With Pembrolizumab	Corticosteroid and/or Other Therapies	Monitoring and Follow-up
	evidence of β-cell failure		• Administer antihyperglycemic in participants with hyperglycemia	
Hypophysitis	Grade 2	Withhold	• Administer corticosteroids and initiate hormonal replacements as clinically indicated	• Monitor for signs and symptoms of hypophysitis (including hypopituitarism and adrenal insufficiency)
	Grade 3 or 4	Withhold or permanently discontinue [d]		
Hyperthyroidism	Grade 2	Continue	• Treat with nonselective beta-blockers (eg, propranolol) or thionamides as appropriate	• Monitor for signs and symptoms of thyroid disorders
	Grade 3 or 4	Withhold or permanently discontinue [d]		
Hypothyroidism	Grade 2, 3 or 4	Continue	• Initiate thyroid replacement hormones (eg, levothyroxine or liothyronine) per standard of care	• Monitor for signs and symptoms of thyroid disorders
Nephritis: grading according to increased creatinine or acute kidney injury	Grade 2	Withhold	• Administer corticosteroids (prednisone 1 to 2 mg/kg or equivalent) followed by taper	• Monitor changes of renal function
	Grade 3 or 4	Permanently discontinue		
Neurological	Grade 2	Withhold	• Based on severity of AE administer	• Ensure adequate evaluation to confirm etiology

irAEs	Toxicity Grade (CTCAE v5.0)	Action With Pembrolizumab	Corticosteroid and/or Other Therapies	Monitoring and Follow-up
Toxicities	Grade 3 or 4	Permanently discontinue	corticosteroids	and/or exclude other causes
Myocarditis	Grade 1	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 2, 3 or 4	Permanently discontinue		
Exfoliative Dermatologic Conditions	Suspected SJS, TEN, or DRESS	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology or exclude other causes
	Confirmed SJS, TEN, or DRESS	Permanently discontinue		
All Other irAEs	Persistent Grade 2	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology or exclude other causes
	Grade 3	Withhold or discontinue based on the event [e]		
	Recurrent Grade 3 or Grade 4	Permanently discontinue		

AE(s)=adverse event(s); ALT= alanine aminotransferase; AST=aspartate aminotransferase; CTCAE=Common Terminology Criteria for Adverse Events; DRESS=Drug Rash with Eosinophilia and Systemic Symptom; GI=gastrointestinal; IO=immuno-oncology; ir=immune related; IV=intravenous; SJS=Stevens-Johnson Syndrome; T1DM=type 1 diabetes mellitus; TEN=Toxic Epidermal Necrolysis; ULN=upper limit of normal.

Note: Non-irAE will be managed as appropriate, following clinical practice recommendations.

[a] AST/ALT: >3.0 to5.0 x ULN if baseline normal; >3.0 to 5.0 x baseline, if baseline abnormal; bilirubin:>1.5 to 3.0 x ULN if baseline normal; >1.5 to 3.0 x baseline if baseline abnormal

[b] AST/ALT: >5.0 to 20.0 x ULN, if baseline normal; >5.0 to 20.0 x baseline, if baseline abnormal; bilirubin:>3.0 to 10.0 x ULN if baseline normal; >3.0 to 10.0 x baseline if baseline abnormal

[c] AST/ALT: >20.0 x ULN, if baseline normal; >20.0 x baseline, if baseline abnormal; bilirubin: >10.0 x ULN if baseline normal; >10.0 x baseline if baseline abnormal

irAEs	Toxicity Grade (CTCAE v5.0)	Action With Pembrolizumab	Corticosteroid and/or Other Therapies	Monitoring and Follow-up

[d] The decision to withhold or permanently discontinue pembrolizumab is at the discretion of the investigator or treating physician. If control achieved or ≤ Grade 2, pembrolizumab may be resumed.

[e] Events that require discontinuation include, but are not limited to: encephalitis and other clinically important irAEs (eg, vasculitis and sclerosing cholangitis).

Dose modification and toxicity management of infusion-reactions related to pembrolizumab

Pembrolizumab may cause severe or life threatening infusion-reactions including severe hypersensitivity or anaphylaxis. Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion. Dose modification and toxicity management guidelines on pembrolizumab associated infusion reaction are provided in Table 4.

NCI CTCAE Grade	Treatment	Premedication at Subsequent Dosing
Grade 1 Mild reaction; infusion interruption not indicated; intervention not indicated	Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator.	None
Grade 2 Requires therapy or infusion interruption but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for ≤24 hrs	**Stop Infusion.** Additional appropriate medical therapy may include but is not limited to: IV fluids Antihistamines NSAIDs Acetaminophen Narcotics Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator. If symptoms resolve within 1 hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (e.g. from 100 mL/hr to 50 mL/hr). Otherwise dosing will be held until symptoms resolve and the participant should be premedicated for the next scheduled dose. **Participants who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further study drug treatment**	Participant may be premedicated 1.5h (± 30 minutes) prior to infusion of _____ with: Diphenhydramine 50 mg po (or equivalent dose of antihistamine). Acetaminophen 500-1000 mg po (or equivalent dose of analgesic).
Grades 3 or 4 Grade 3: Prolonged (i.e., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (e.g., renal impairment, pulmonary infiltrates) Grade 4:	**Stop Infusion.** Additional appropriate medical therapy may include but is not limited to: Epinephrine** IV fluids Antihistamines NSAIDs Acetaminophen Narcotics Oxygen Pressors Corticosteroids Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator.	No subsequent dosing

Life-threatening; pressor or ventilatory support indicated	Hospitalization may be indicated. **In cases of anaphylaxis, epinephrine should be used immediately. **Participant is permanently discontinued from further study drug treatment.**	
Appropriate resuscitation equipment should be available at the bedside and a physician readily available during the period of drug administration. For further information, please refer to the Common Terminology Criteria for Adverse Events v4.0 (CTCAE)		

Table 4 Pembrolizumab Infusion Reaction Dose modification and Treatment Guidelines

Other allowed dose interruption for pembrolizumab

Pembrolizumab may be interrupted for situations other than treatment-related AEs such as medical / surgical events or logistical reasons not related to study therapy. Participants should be placed back on study therapy within 3 weeks of the scheduled interruption, unless otherwise discussed with the Sponsor. The reason for interruption should be documented in the patient's study record.

4.2.3 Randomization or Treatment Allocation

Patients will not be randomized and will receive APVD.

4.3 Stratification

- The Ann Arbor staging criteria will be utilized;
- The GHLSG Risk Stratification will be used for all patients with early stage disease.
- The Hasenclever score will be used for all patients with advanced disease.
- Bulk will be defined as the long axis of the single largest nodal mass.

Concomitant Medications/Vaccinations (allowed & prohibited) Medications used during the course of the study should be documented.

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

4.3.1 Acceptable Concomitant Medications

All treatments that the investigator considers necessary for a participant's welfare may be administered at the discretion of the investigator in keeping with the community standards of medical care. All concomitant medication will be recorded on the case report form (CRF) including all prescription, over-the-counter (OTC), herbal supplements, and IV medications and fluids. If changes occur during the trial period, documentation of drug dosage, frequency, route, and date may also be included on the CRF.

All concomitant medications received within 28 days before the first dose of trial treatment and 30 days after the last dose of trial treatment should be recorded. Concomitant medications administered after 30 days after the last dose of trial treatment should be recorded for SAEs and ECIs as defined in Section 6.1.2.1.

4.3.2 Prohibited Concomitant Medications

The administration of concurrent medications intended to treat the primary cancer is not allowed during protocol therapy. This includes any chemotherapy, investigational agent, biologic agent or other anti-tumor agents. Radiation therapy is also prohibited.

Patients should be strongly discouraged from taking any "alternative" or "naturopathic" medications since these agents may interact with APVD.

4.3.3 Rescue Medications & Supportive Care

Participants should receive appropriate supportive care measures as deemed necessary by the treating investigator. Suggested supportive care measures for the management of AEs with potential immunologic etiology are outlined along with the dose modification guidelines in Section 4.2.2, [Table 3]. Where appropriate, these guidelines include the use of oral or IV treatment with corticosteroids, as well as additional anti-inflammatory agents if symptoms do not improve with administration of corticosteroids. Note that several courses of steroid tapering may be necessary as symptoms may worsen when the steroid dose is decreased. For each disorder, attempts should be made to rule out other causes such as metastatic disease or bacterial or viral infection, which might require additional supportive care. The treatment guidelines are intended to be applied when the Investigator determines the events to be related to pembrolizumab.

Note: If after the evaluation of the event, it is determined not to be related to pembrolizumab, the Investigator does not need to follow the treatment guidance. Refer to [Table 3] in Section 5.2.2 for guidelines regarding dose modification and supportive care.

It may be necessary to perform conditional procedures such as bronchoscopy, endoscopy, or skin photography as part of evaluation of the event.

When study interventions are administered in combination, attribution of an adverse event to a single component is likely to be difficult. Therefore, while the investigator may attribute a toxicity event to pembrolizumab alone, or to the combination of other chemo drugs, for adverse events listed below, all interventions must be held according to the criteria below.

When study interventions are administered in combination, if the AE is considered immune-related, all interventions should be held according to recommended dose modifications.

Participants may not have any dose modifications (no change in dose or schedule) of pembrolizumab in this study.

- If the toxicity does not resolve or the criteria for resuming treatment are not met, the participant must be discontinued from all study interventions.

- If the toxicities do resolve and conditions are aligned with what is defined below, the combination of study therapies may be restarted at the discretion of the investigator. In these cases where the toxicity is attributed to the other chemotherapy combination or individual drugs, re-initiation of pembrolizumab as a monotherapy may be considered at the investigator's discretion.

4.4 Participant Withdrawal/Discontinuation Criteria

Participants may discontinue study treatment at any time for any reason or be dropped from the study treatment at the discretion of the investigator should any untoward effect occur. In addition, a participant may be discontinued from study treatment by the investigator or the Sponsor if study treatment is inappropriate, the trial plan is violated, or for administrative and/or other safety reasons.

Specific details regarding procedures to be performed at study treatment discontinuation are provided in Section 7.1.4 – Other Procedures.

A participant must be discontinued from study treatment but continue to be monitored in the study for any of the following reasons:

- The participant or participant's legally acceptable representative requests to discontinue study treatment
- Confirmed radiographic disease progression outlined in Appendix 3
- Any progression or recurrence of any malignancy, or any occurrence of another malignancy that requires active treatment
- Unacceptable adverse experiences as described in Section 6.2.
- The participant has a medical condition or personal circumstance which, in the opinion of the investigator and/or sponsor, placed the participant at unnecessary risk from continued administration of study treatment.
- The participant has a confirmed positive serum pregnancy test
- Noncompliance with study treatment or procedure requirements
- Recurrent Grade 2 pneumonitis
- Completion of protocol treatment
- The participant is lost to follow-up
- Administrative reasons

4.5 Participant Replacement Strategy

Subjects who fail to complete study therapy will not be replaced.

4.6 Clinical Criteria for Early Trial Termination

Early trial termination will be the result of the criteria specified below:

1. Quality or quantity of data recording is inaccurate or incomplete
2. Poor adherence to protocol and regulatory requirements
3. Incidence or severity of adverse drug reaction in this or other studies indicates a potential health hazard to participants
4. Plans to modify or discontinue the development of the study drug

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

5.0 STUDY FLOW CHART – PART A AND PART B

Required Studies	Pre-Entry (within 4 weeks unless indicated otherwise)	Within 2 days prior to each dose[8]	Post Therapy[4]	Safety Follow-up Visit[5]	Follow-up[6]
Physical					
History and Physical (H&P)	X	X[1]	X	X	
Performance Status	X	X[1]	X	X	
Clinical Disease Assessment	X	X[1]	X		
Adverse Event Assessment	X	X[1]	X	X	
Lab					
ESR, TSH, T3, T4, LDH	X[7]		X[10]	X	
Complete blood count with differential[9]	X	X[1]	X	X	
Comprehensive metabolic panel[9]	X	X[1]	X	X	
Pregnancy test	X[2]				
Radiology					
Left Ventricular Ejection Fraction (LVEF)	X[3]				
PET/CT	X[11]		X		
Correlative Studies[12]	X		X		

1. For Cycle 1 Day 1, pre-entry H&P, performance status, disease assessment and adverse event assessment may be used (these do not need to be repeated within 2 days) and labs done within 10 days are acceptable.
2. Pregnancy test in women of childbearing potential.
3. EF must be ≥50% within 56 days.
4. Post therapy (interim PET for patients planning on receiving more than 2 total cycles) studies should be done as early as day 16 of cycle 2 but prior to any additional antineoplastic therapy unless other objective evidence of progressive disease. For patients who proceed with more than 2 cycles of therapy (Optional part A, mandatory 6 cycles for part B), an additional post therapy visit with additional PET/CT should be performed 28-35 days after the expected last dose of chemotherapy, which may also serve as the post treatment safety visit.
5. A safety follow up visit should be performed 28-35 days after last dose of study therapy is administered. This may be an additional visit depending on the date of the post-therapy visit, but may be combined with the post-therapy visit if the windows overlap.
6. Follow-up after cycle 2 will be standard of care. Patient will be tracked for subsequent therapy, response, progression-free, and overall survival after completion of 2 cycles of therapy up to 5 years.
7. Patients must have an ESR, TSH, T3 and T4 performed within 14 days prior to registration.
8. Dose is defined as a day in which one receives any of the medications outlined in section 4.2
9. See Table 6 for list of components
10. LDH and ESR not required at Post Therapy or Safety follow up visit
11. PET/CT may be performed within 42 days.
12. Correlative studies may be carried out whenever possible and include PD1/PLDL1/PDL2 expression, MRD (e.g. Adaptive Clonoseq or similar) and cytokine monitoring. This may include up to 10 unstained slides of diagnostic tissue or tissue block as well as up to 20 cc of whole blood and serum at the following (but not limited to) timepoints: baseline, cycle 2 day 1, cycle 3 day 1, and end of treatment.

6.0 TRIAL PROCEDURES

6.1 Trial Procedures

The Trial Flow Chart - Section 5.0 summarizes the trial procedures to be performed at each visit. Individual trial procedures are described in detail below. It may be necessary to perform these procedures at unscheduled time points if deemed clinically necessary by the investigator.

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

6.1.1 Informed Consent

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

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

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

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

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

6.1.1.1 Inclusion/Exclusion Criteria

All inclusion and exclusion criteria will be reviewed by the investigator or qualified designee to ensure that the participant qualifies for the trial.

6.1.1.2 Medical History

A medical history will be obtained by the investigator or qualified designee. Medical history will include all active conditions, and any condition diagnosed within the prior 10 years that are considered to be clinically significant by the Investigator. Details regarding the disease for which the participant has enrolled in this study will be recorded separately and not listed as medical history.

6.1.1.3 Prior and Concomitant Medications Review

6.1.1.3.1 Prior Medications

The investigator or qualified designee will review prior medication use, including any protocol-specified washout requirement, and record prior medication taken by the participant within 28 days before starting the trial. Treatment for the disease for which the participant has enrolled in this study will be recorded separately and not listed as a prior medication.

6.1.1.3.2 Concomitant Medications

The investigator or qualified designee will record medication, if any, taken by the participant during the trial. All medications related to reportable SAEs and ECIs should be recorded as defined in Section 6.1.2.1.

6.1.1.4 Disease Details and Treatments

6.1.1.4.1 Disease Details

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

6.1.1.4.2 Prior Treatment Details

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

6.1.1.4.3 Subsequent Anti-Cancer Therapy Status

The investigator or qualified designee will review all new anti-neoplastic therapy initiated after the last dose of trial treatment.

6.1.1.5 Assignment of Subject Number

Each subject will be assigned a unique subject identifier.

6.1.2 Clinical Procedures/Assessments

6.1.2.1 Adverse Event (AE) Monitoring

Complete and timely reporting of adverse events (AEs) is required to ensure the safety of patients. Reporting requirements are determined by the characteristics of the adverse event including the *grade* (severity), the *relationship to the study therapy* (attribution), and the *prior experience* (expectedness) of the adverse event. The guidelines outlined in this section, as well as the specific direction on each report form must be followed. The NCI Common Terminology Criteria for Adverse Events v4.0 (CTCAE) will be used to classify and grade toxicities.

The investigator or qualified designee will assess each participant to evaluate for potential new or worsening AEs as specified in the Trial Flow Chart and more frequently if clinically indicated. Adverse experiences will be graded and recorded throughout the study and during the follow-up period according to NCI CTCAE Version 4.0 (see Appendix 2). Toxicities will be characterized in terms regarding seriousness, causality, toxicity grading, and action taken with regard to trial treatment.

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

6.1.2.2 Full Physical Exam

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

6.1.2.3 Directed Physical Exam

For cycles that do not require a full physical exam per the Trial Flow Chart, the investigator or qualified designee will perform a directed physical exam as clinically indicated prior to trial treatment administration.

6.1.2.4 Vital Signs

The investigator or qualified designee will take vital signs at screening, prior to the administration of each dose of trial treatment and at treatment discontinuation as specified in the Trial Flow Chart (Section 5.0). Vital signs should include temperature, pulse, respiratory rate, weight and blood pressure. Height will be measured at screening only.

6.1.2.5 Eastern Cooperative Oncology Group (ECOG) Performance Scale

The investigator or qualified designee will assess ECOG status (see Appendix 1) at screening, prior to the administration of each dose of trial treatment and discontinuation of trial treatment as specified in the Trial Flow Chart.

6.1.2.6 Tumor Imaging and Assessment of Disease

Tumor imaging consists of standard of care FDG-PET/CT of the chest, abdomen, and pelvis at baseline within 42 days of day 1 of cycle 1. Post therapy (interim PET for those receiving more than 2 total cycles) imaging will consist of FDG-PET/CT of the chest, abdomen, and pelvis and should be performed as early as day 16 of cycle 2, but prior to any additional antineoplastic therapy. Additional imaging studies may per performed at the discretion of the treating provider.

Assessment of Disease

Definitions of Disease, Criteria for Evaluation and Endpoint Definitions – response will be defined by standard NCI criteria (Lugano 2014) for lymphoid malignancies.

6.1.2.7 Tumor Tissue Collection and Correlative Studies Blood Sampling

Correlative studies may be carried out whenever possible for ctDNA testing. Blood samples will be collected in two to four 10 mL K2EDTA tubes at baseline, on cycle 2 day 1, and after cycle 2. Additional blood draws can be collected at the investigator's discretion. Additionally, up to 10 unstained slides of diagnostic tissue or tissue block may also be collected.

6.1.3 Laboratory Procedures/Assessments

Details regarding specific laboratory procedures/assessments to be performed in this trial are provided below.

Laboratory tests for hematology, chemistry, and others are specified in Table 6.

Table 6 Laboratory Tests

Complete blood count (CBC) with differential	**Comprehensive metabolic panel**	**Other**
Hematocrit	Albumin	Serum or urine β-human chorionic gonadotropin(β-hCG)†
Hemoglobin	Alkaline phosphatase	Total thriiodothyronine (T3)
Platelet count	Alanine aminotransferase (ALT)	Free tyroxine (T4)
WBC (total and differential)	Aspartate aminotransferase (AST)	Thyroid stimulating hormone (TSH)
Red Blood Cell Count	Lactate dehydrogenase (LDH)	Erythrocyte Sedimentation Rate (ESR)
Absolute Neutrophil Count	Carbon Dioxide ‡	
Absolute Lymphocyte Count	*(CO_2 or biocarbonate)*	
	Uric Acid	
	Calcium	
	Chloride	Blood for correlative studies
	Glucose	
	Sodium	
	Total Bilirubin	
	Direct Bilirubin *(If total bilirubin is elevated above the upper limit of normal)*	
	Total protein	
	Blood Urea Nitrogen	

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

6.1.4 Other Procedures

6.1.4.1 Withdrawal/Discontinuation/Visit Requirements

When a subject discontinues/withdraws prior to trial completion, all applicable activities scheduled for the final trial visit should be performed at the time of discontinuation. Any adverse events which are present at the time of discontinuation/withdrawal should be followed in accordance with the safety requirements outlined in Section 6.2 - Assessing and Recording Adverse Events. Visit requirements are outlined in Section 5.0 - Trial Flow Chart. Specific procedure-related details are provided above in Section 6.0 - Trial Procedures.

6.1.4.2 Screening

6.1.4.2.1 Screening Period

The screening period begins upon signing consent and prior to Cycle 1 Day 1 of study therapy. The screening period may last up to 42 days, which may be extended provided the patients re-signs a consent form.

6.1.4.3 Treatment Period

The treatment period includes APVD, administered every 28 days. Administration of study medications may be +/- 2 days of the expected date as outlined in section 2.2. All other procedures should be performed per the Study Flow Chart.

6.1.4.4 Post-Therapy Visit

Post therapy procedures should be performed per the Study Flow Chart and include Physical Exam, Laboratory assessments, and imaging studies.

6.1.4.5 Safety Follow-Up Visit

The mandatory Safety Follow-Up Visit should be conducted approximately 30 days after the last dose of study treatment or before the initiation of a new anti-cancer treatment, whichever comes first. All AEs that occur prior to the Safety Follow-Up Visit should be recorded. Participants with an AE of Grade > 1 will be followed until the resolution of the AE to Grade 0-1 or until the beginning of a new anti-cancer therapy, whichever occurs first. SAEs that occur within 90 days of the end of treatment or before initiation of a new anti-cancer treatment should also be followed and recorded. \

6.1.4.6 Follow-up Visits

Follow-up after Cycle 2 (Cycle 6 for part B) will be conducted per Standard of Care. Patients will be tracked for subsequent therapy, response, progression-free, and overall survival up to 5 years.

6.2 Assessing and Recording Adverse Events

Routine reporting is required for all grade 3, 4 and 5 adverse events. Grade 1 or 2 AEs will not be captured or reported with the exception of ANC, platelet nadirs, or immune related adverse events. Routine reports include data after each cycle of therapy and 30 days after the last dose of study drugs, or until the patient receives an alternative anti-cancer therapy, whichever date comes first.

Routine reporting will be conducted in accordance with FHCRC/Cancer Consortium IRB policies, applicable FDA regulations, and agreements with Merck.

6.2.1 Expedited Reporting

Expedited reporting will be conducted in accordance with FHCRC/Cancer Consortium IRB policies, applicable FDA regulations.

6.3 Overdose and Reporting Requirements

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

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

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

All reports of overdose with and without an adverse event must be reported within 24 hours to the Sponsor and within 2 working days hours to Merck Global Safety. (Attn: Worldwide Product Safety; FAX 215-661-6229)

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

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

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

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

Such events must be reported within 24 hours to the Sponsor and within 2 working days to Merck Global Safety. (Attn: Worldwide Product Safety; FAX 215-661-6229)

6.3.1.1 Events of Clinical Interest

Selected non-serious and serious adverse events are also known as Events of Clinical Interest (ECI) and must be reported within 2 working days to Merck Global Safety. (Attn: Worldwide Product Safety; FAX 215-661-6229).

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

For the time period beginning at treatment allocation/randomization through 90 days following cessation of treatment, or 30 days following cessation of treatment if the participant initiates new anticancer therapy, whichever is earlier, any ECI, or follow up to an ECI, whether or not related to Merck product, must be reported within 2 working days to Merck Global Safety.

Events of clinical interest for this trial include:

1. an overdose of Merck product, as defined in Section 6.3- Definition of an Overdose for This Protocol and Reporting of Overdose to the Sponsor, that is not associated with clinical symptoms or abnormal laboratory results.

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

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

6.3.1.1.1 Evaluating Adverse Events

Table 7 Evaluating Adverse Events

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

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

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

Relationship to Merck Product (continued)	**The following components are to be used to assess the relationship between the test drug and the AE: (continued)**	
	Dechallenge	Was Merck product discontinued or dose/exposure/frequency reduced? If yes, did the AE resolve or improve? If yes, this is a positive dechallenge. If no, this is a negative dechallenge. (Note: This criterion is not applicable if: (1) the AE resulted in death or permanent disability; (2) the AE resolved/improved despite continuation of the Sponsor's product; or (3) the trial is a single-dose drug trial); or (4) Sponsor's product(s) is/are only used one time.)
	Rechallenge	Was the participant re-exposed to Merck product in this study? If yes, did the AE recur or worsen? If yes, this is a positive rechallenge. If no, this is a negative rechallenge. (Note: This criterion is not applicable if: (1) the initial AE resulted in death or permanent disability, or (2) the trial is a single-dose drug trial); or (3) Sponsor's product(s) is/are used only one time). NOTE: IF A RECHALLENGE IS PLANNED FOR AN ADVERSE EVENT WHICH WAS SERIOUS AND WHICH MAY HAVE BEEN CAUSED BY MERCK PRODUCT, OR IF REEXPOSURE TO MERCK PRODUCT POSES ADDITIONAL POTENTIAL SIGNIFICANT RISK TO THE PARTICIPANT, THEN THE RECHALLENGE MUST BE APPROVED IN ADVANCE BY THE SPONSOR AS PER DOSE MODIFICATION GUIDELINES IN THE PROTOCOL.
	Consistency with Trial Treatment Profile	Is the clinical/pathological presentation of the AE consistent with previous knowledge regarding Merck product or drug class pharmacology or toxicology?
The assessment of relationship will be reported on the case report forms /worksheets by an investigator who is a qualified physician according to his/her best clinical judgment, including consideration of the above elements.		
Record one of the following	**Use the following scale of criteria as guidance (not all criteria must be present to be indicative of Merck product relationship).**	
Yes, there is a reasonable possibility of Merck product relationship.	There is evidence of exposure to Merck product. The temporal sequence of the AE onset relative to the administration of Merck product is reasonable. The AE is more likely explained by Merck product than by another cause.	

No, there is not a reasonable possibility of Merck product relationship	Participant did not receive the Merck product OR temporal sequence of the AE onset relative to administration of Merck product is not reasonable OR the AE is more likely explained by another cause than the Merck product. (Also entered for a participant with overdose without an associated AE.)

6.3.2 Sponsor Responsibility for Reporting Adverse Events

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

- Results in death;
- Is life threatening;
- Results in persistent or significant disability/incapacity;
- Results in or prolongs an existing inpatient hospitalization;
- Is a congenital anomaly/birth defect;
- Is another important medical event

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

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

For the time period beginning at treatment allocation/randomization through 90 days following cessation of treatment, or 30 days following cessation of treatment if the participant initiates new anticancer therapy, whichever is earlier, any serious adverse event, or follow up to a serious adverse event, including death due to any cause whether or not related to the Merck product, must be reported within 24 hours to the Sponsor and within 2 working days to Merck Global Safety.

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

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

SAE reports and any other relevant safety information are to be forwarded to the Merck Global Safety facsimile number: +1-215-661-6229

A copy of all 15 Day Reports and Annual Progress Reports is submitted as required by FDA, European Union (EU), Pharmaceutical and Medical Devices agency (PMDA) or other local regulators. Investigators will cross reference this submission according to local regulations to the Merck Investigational Compound Number (IND, CSA, etc.) at the time of submission. Additionally, investigators will submit a copy of these reports to Merck & Co., Inc. (Attn: Worldwide Product Safety; FAX 215-661-6229) at the time of submission to FDA.

7.0 STATISTICAL ANALYSIS PLAN

7.1 Statistical Analysis Plan

Part A:

The primary objective of this study is to estimate the safety of 2 cycles of APVD. Historical data regarding the tolerability of 2 cycles of ABVD are limited. In a recent trial of AVD+ brentuximab vedotin, 4 of 26 (~15%) patients were reported to be unable to complete treatment [Connors et al. 2017]. treatment18. We will be more conservatively scoring treatment delay due to toxicity rather than inability to complete the entire treatment course. Thus, we will deem this regimen safe if >85% of patients are able to complete 2 cycles of APVD without a dose delay of >3 weeks. This will be employed as a stopping rule and serve as the primary endpoint.

Operationally, the stopping rule will be activated if the lower limit of the 95% confidence interval of toxicity crosses 15%. Thus, the trial would stop if 4/10, 7/20, 8/25, or 9 of 30 had a dose delay of >3 weeks due to toxicity.

If the stopping rule is activated the trial will be paused and the data reviewed to determine if the results can be explained by the patient population (e.g., older, more comorbidities) or by the toxicity of the regimen. A report will be drafted for IRB review to either close the trial, modify and continue the trial, or continue the trial in an unmodified fashion. Since the study is not statistically powered for efficacy evaluation, the sample size justification is based on clinical evaluation on safety. If we use the stopping rule if 30% patients were unable to complete treatment, then the 95% confidence interval for the assumed toxicity rate with 30 patients are 17% to 48%, which excluded 15% assumed rate. With smaller sample size, the width of the 95% CI will be larger, e.g. 15% to 52% for 20 patients, 16% to 50% for 25 patients, etc. The larger sample size will also lead to stable point estimation, so it will increase the chance for a more accurate observation. We anticipate that 30 patients will be required to reasonably estimate the safety of this regimen as defined above. Furthermore, assume the incidence rate of toxicity is around 15%, with sample size N=30, we will have more than 85% chance of observing more than two patients not finishing the trial and 99% chance of observing at least one such patient (see table 1) Probability to observe at least 1 or 3 events having a dose delay due to toxicity, estimated for different incidence rates and sample size

Sample Size	Incidence rate of toxicity	PR (observe at least one events had a dose delay)	PR (observe at least three events had a dose delay)
30	0.1	96%	59%
30	0.15	99%	85%
25	0.1	93%	46%
25	0.15	98%	75%
20	0.1	88%	32%
20	0.15	96%	60%

In unpublished data, 28 patients have completed 2 cycles of APVD, and there were no delays in treatments of greater than 21 days in any of these patients. Therefore, even without information on the final 2 patients, it can be determined that the primary endpoint for part A of the study has been met.

Part B:

Based on the rationale outlined in the background section, we plan to enroll 20 additional patients in part B (for a total of 50 between part A and B). We will only accrue advanced stage patients (stage 3 or 4) for this portion of the study.

In part A, we have enrolled 29 patients, of whom 18 were stage 3 or 4. We expect the final patient in part A will be advanced stage, and therefore we expect to have 19 total advanced stage patients in Part A. When combined with expected accrual of 20 patients in Part B, we expect to have 39 total advanced stage patients that are evaluable for efficacy data.

Given our concerns with PET-based assessments, we will analyze the 39 advanced patients for efficacy by estimating 1-year EFS. An event will be defined as progression, biopsy proven recurrence, initiation of next line of chemotherapy, or death. The benchmark to deem this regimen as potentially efficacious will be 1-year EFS of 85% for this population[3] (intermediate between the more commonly used ABVD and the more toxic but less commonly used brentuximab vedotin + AVD). Towards this end, we shall consider an observed 1-year EFS among the 39 patients of at least 0.85 (33 or more of 39) to be potentially efficacious and warrant further study of the current regimen (note that this will not necessarily imply a statistically significant improvement on this benchmark). The decision will also take into consideration secondary endpoints. The table below summarizes the probability of observing a 1-year EFS of at least 85% under a variety of assumed-true 1-year EFS values.

Assumed-true 1-year EFS	Probability of observed 1-year EFS of at least 85%
75%	0.11
80%	0.31
85%	0.63
90%	0.91

8.0 LABELING, PACKAGING, STORAGE AND RETURN OF CLINICAL SUPPLIES

8.1 Investigational Product

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

Pembrolizumab will be provided by Merck as summarized in Table 8.

Table 8 Product Descriptions

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

8.2 Packaging and Labeling Information

Supplies will be labeled in accordance with regulatory requirements.

8.3 Clinical Supplies Disclosure

This trial is open-label; therefore, the participant, the trial site personnel, the Sponsor and/or designee are not blinded to treatment. Drug identity (name, strength) is included in the label text; random code/disclosure envelopes or lists are not provided.

8.4 Storage and Handling Requirements

Clinical supplies must be stored in a secure, limited-access location under the storage conditions specified on the label.

Receipt and dispensing of trial medication must be recorded by an authorized person at the trial site.

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

8.5 Returns and Reconciliation

The investigator is responsible for keeping accurate records of the clinical supplies received from Merck or designee, the amount dispensed to and returned by the participants and the amount remaining at the conclusion of the trial.

Upon completion or termination of the study, all unused and/or partially used investigational product will be destroyed at the site per institutional policy. It is the Investigator's responsibility to arrange for disposal of all empty containers, provided that procedures for proper disposal have been established according to applicable federal, state, local and institutional guidelines and procedures, and provided that appropriate records of disposal are kept.

9.0 DATA AND SAFETY MONITORING PLAN

Ongoing trial oversight is carried out by the Principal Investigator and study staff. These individuals will communicate on a regular basis to review recently acquired data and adverse events. The data recorded within the research charts and protocol database is compared with the actual data that is available from the medical record and/or clinical histories. Data detailed in the research case report forms includes the nature and severity of all toxicities, which are also reported as described above.

Institutional support of trial monitoring will be in accordance with the FHCRC/UW Cancer Consortium Institutional Data and Safety Monitoring Plan. Under the provisions of this plan, FHCRC Clinical Research Support coordinates monitoring for data accuracy and compliance by consultants, contract research organizations, or FHCRC employees unaffiliated with the conduct of the study. Independent monitoring visits occur at specified intervals determined by the assessed risk level of the study and the findings of previous visits per the institutional DSMP.

In addition, protocols are reviewed at least annually and as needed by a the Consortium Data Safety Monitoring Committee (DSMC), FHCRC Scientific Review Committee (SRC) and the FHCRC/Cancer Consortium Institutional Review Board (IRB). The review committees evaluate accrual, adverse events, stopping rules, and adherence to the applicable data and safety monitoring plan for studies actively enrolling or treating patients. The IRB reviews the study progress and safety information to assess continued acceptability of the risk-benefit ratio for human subjects. Approval of committees as applicable is necessary to continue the study.

The trial will comply with the standard guidelines set forth by these regulatory committees and other institutional, state and federal guidelines.

The IRB has the authority to suspend or terminate the study should it be deemed necessary.

9.1 RECORDS

Research staff under the supervision of the investigators will maintain case report forms and secured databases on the relevant clinical and laboratory data. Records maintained in investigators' offices will be secured with access limited to study personnel. Authorization for access to medical records will be obtained from all patients in accordance with provisions of the Health Insurance Portability and Accountability Act (HIPAA).

9.2 REGULATORY RESPONSIBILITIES OF SPONSOR-INVESTIGATOR

The Sponsor-Investigator will ensure that the study is conducted in accordance with all applicable institutional, state, and federal regulatory requirements, including, but not limited to: compliance with requirements for IRB and other regulatory approvals, monitoring responsibilities, reporting obligations, and compliance with standards for written informed consent from all patients entering the study. In addition, the sponsor will ensure oversight of the study via data and safety monitoring as described above.

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11.0 APPENDICES

Appendix 1: ECOG Performance Status

Grade	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.
* As published in Am. J. Clin. Oncol.: *Oken, M.M., Creech, R.H., Tormey, D.C., Horton, J., Davis, T.E., McFadden, E.T., Carbone, P.P.: Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. Am J Clin Oncol 5:649-655, 1982.* The Eastern Cooperative Oncology Group, Robert Comis M.D., Group Chair.	

Appendix 2: Common Terminology Criteria for Adverse Events V4.0 (CTCAE)

The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for adverse event reporting.

Appendix 3: Response Criteria: "The Lugano Classification" [38]

Response and Site	PET-CT–Based Response	CT-Based Response
Complete	**Complete metabolic response**	Complete radiologic response (all of the following)
Lymph nodes and extralymphatic sites	Score 1, 2, or 3* with or without a residual mass on 5PS‡	Target nodes/nodal masses must regress to ≤ 1.5 cm in LDi
	It is recognized that in Waldeyer's ring or extranodal sites with high physiologic uptake or with activation within spleen or marrow (eg, with chemotherapy or myeloid colony-stimulating factors), uptake may be greater than normal mediastinum and/or liver. In this circumstance, complete metabolic response may be inferred if uptake at sites of initial involvement is no greater than surrounding normal tissue even if the tissue has high physiologic uptake	No extralymphatic sites of disease
Nonmeasured lesion	Not applicable	Absent
Organ enlargement	Not applicable	Regress to normal
New lesions	None	None
Bone marrow	No evidence of FDG-avid disease in marrow	Normal by morphology; if indeterminate, IHC negative
Partial	**Partial metabolic response**	**Partial remission (all of the following)**
Lymph nodes and extralymphatic sites	Score 4 or 5‡ with reduced uptake compared with baseline and residual mass(es) of any size	≥ 50% decrease in SPD of up to 6 target measurable nodes and extranodal sites

Response and Site	**PET-CT–Based Response**	CT-Based Response
	At interim, these findings suggest responding disease	When a lesion is too small to measure on CT, assign 5 mm × 5 mm as the default value
	At end of treatment, these findings indicate residual disease	When no longer visible, 0 × 0 mm
		For a node > 5 mm × 5 mm, but smaller than normal, use actual measurement for calculation
Nonmeasured lesions	Not applicable	Absent/normal, regressed, but no increase
Organ enlargement	Not applicable	Spleen must have regressed by > 50% in length beyond normal
New lesions	None	None
Bone marrow	Residual uptake higher than uptake in normal marrow but reduced compared with baseline (diffuse uptake compatible with reactive changes from chemotherapy allowed). If there are persistent focal changes in the marrow in the context of a nodal response, consideration should be given to further evaluation with MRI or biopsy or an interval scan	Not applicable
No response or stable disease	**No metabolic response**	**Stable disease**
Target nodes/nodal masses, extranodal lesions	Score 4 or 5 with no significant change in FDG uptake from baseline at interim or end of treatment	< 50% decrease from baseline in SPD of up to 6 dominant, measurable nodes and extranodal sites; no criteria for progressive disease are met

Response and Site	**PET-CT–Based Response**	CT-Based Response
Nonmeasured lesions	Not applicable	No increase consistent with progression
Organ enlargement	Not applicable	No increase consistent with progression
New lesions	None	None
Bone marrow	No change from baseline	Not applicable
Progressive disease	**Progressive metabolic disease**	**Progressive disease requires at least 1 of the following**
Individual target nodes/nodal masses	Score 4 or 5 with an increase in intensity of uptake from baseline and/or	PPD progression:
Extranodal lesions	New FDG-avid foci consistent with lymphoma at interim or end-of-treatment assessment	An individual node/lesion must be abnormal with: LDi > 1.5 cm and Increase by ≥ 50% from PPD nadir and An increase in LDi or SDi from nadir 0.5 cm for lesions ≤ 2 cm 1.0 cm for lesions > 2 cm In the setting of splenomegaly, the splenic length must increase by > 50% of the extent of its prior increase beyond baseline (eg, a 15-cm spleen must increase to > 16 cm). If no prior splenomegaly, must increase by at least 2 cm from baseline New or recurrent splenomegaly

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

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

- ↵* A score of 3 in many patients indicates a good prognosis with standard treatment, especially if at the time of an interim scan. However, in trials involving PET where de-escalation is investigated, it may be preferable to consider a score of 3 as inadequate response (to avoid undertreatment). Measured dominant lesions: Up to six of the largest dominant nodes, nodal masses, and extranodal lesions selected to be clearly measurable in two diameters. Nodes should preferably be from disparate regions of the body and should include, where applicable, mediastinal and retroperitoneal areas. Non-nodal lesions include those in solid organs (eg, liver, spleen, kidneys, lungs), GI involvement, cutaneous lesions, or those noted on palpation. Nonmeasured lesions: Any disease not selected as measured, dominant disease and truly assessable disease should be considered not measured. These sites include any nodes, nodal masses, and extranodal sites not selected as dominant or measurable or that do not meet the requirements for measurability but are still considered abnormal, as well as truly assessable disease, which is any site of suspected disease that would be difficult to follow quantitatively with measurement, including pleural effusions, ascites, bone lesions, leptomeningeal disease, abdominal masses, and other lesions that cannot be confirmed and followed by imaging. In Waldeyer's ring or in extranodal sites (eg, GI tract, liver, bone marrow), FDG uptake may be greater than in the mediastinum

with complete metabolic response, but should be no higher than surrounding normal physiologic uptake (eg, with marrow activation as a result of chemotherapy or myeloid growth factors).

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

Appendix 4: Contraceptive Guidance and Pregnancy Testing

Woman of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming post-menopausal unless permanently sterile (see below)

Women in the following categories are not considered WOCBP:

- Premenarchal
- Premenopausal female with 1 of the following:
  - Documented hysterectomy
  - Documented bilateral salpingectomy
  - Documented bilateral oophorectomy

  Note: Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.

- Postmenopausal female
  - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
    - A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, confirmation with two FSH measurements in the postmenopausal range is required.
  - Females on HRT and whose menopausal status is in doubt will be required to use one of the non-hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

Contraception Requirements

Male Participants:

Male participants with female partners of childbearing potential are eligible to participate if they agree to one of the following during protocol treatment and for 120 days after last dose:

- Be abstinent from penile-vaginal intercourse as their usual and preferred lifestyle (abstinent on a long term and persistent basis) and agree to remain abstinent
- Use a male condom plus partner use of a contraceptive method with a failure rate of <1% per year as described in Table 9 when having penile-vaginal intercourse with a woman of childbearing potential who is not currently pregnant.
  - Note: Men with a pregnant or breastfeeding partner must agree to remain abstinent from penile-vaginal intercourse or use a male condom during each episode of penile penetration.

Female Participants:

Female participants of childbearing potential are eligible to participate if they agree to use two forms of birth control consistently and correctly during the protocol treatment and for 120 days after last dose. Subjects may use hormonal contraception, the barrier method or a highly effective method of contraception that has a low user dependency as outlined in Table 9 below.

Table 9 Highly Effective Contraceptive Methods That Have Low User Dependency

Highly Effective Methods That Have Low User Dependency *Failure rate of <1% per year when used consistently and correctly.*
● Progestogen- only contraceptive implant [a, b] ● Intrauterine hormone-releasing system (IUS) [b] ● Intrauterine device (IUD) ● Bilateral tubal occlusion
● **Vasectomized partner** A vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.
● **Sexual abstinence** Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatment. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.
Notes: Use should be consistent with local regulations regarding the use of contraceptive methods for participants of clinical studies. a) If locally required, in accordance with Clinical Trial Facilitation Group (CTFG) guidelines, acceptable contraceptive implants are limited to those which inhibit ovulation. b) If hormonal contraception efficacy is potentially decreased due to interaction with study treatment, condoms must be used in addition to the hormonal contraception during the treatment period and for at least [120 days, corresponding to time needed to eliminate study treatment plus 30 days for study treatments with genotoxic potential] after the last dose of study treatment.

Pregnancy Testing

WOCBP should only be included after a negative highly sensitive urine or serum pregnancy test and in accordance with local requirements. When applicable this test should be repeated a maximum of 24-hours before the first dose/vaccination.

Pregnancy testing will be performed whenever an expected menstrual cycle is missed or when pregnancy is otherwise suspected.

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