TITLE: Phase I/II study of pembrolizumab in patients failing to respond to or relapsing after anti-CD19 chimeric antigen receptor modified T cell therapy for relapsed or refractory CD19+ lymphomas

IND NUMBER: IND Exemption provided by FDA

Penn UPCC Protocol Number: 46415
IRB Protocol Number: 823486
Clinical trials.gov number: NCT02650999

Principal Investigator: Stephen J. Schuster, MD
Professor of Medicine
Director, Lymphoma Program, Abramson Cancer Center
University of Pennsylvania

Co-Investigators: Elise A. Chong, MD
Sunita D. Nasta, MD
Jakub Svoboda, MD
Daniel J. Landsburg, MD

Statistician: Wei-Ting Hwang, PhD

REGULATORY SPONSOR: Stephen J. Schuster, MD

TABLE OF CONTENTS

1.0 TRIAL SUMMARY

Title	Phase I/II study of pembrolizumab in patients failing to respond to or relapsing after anti-CD19 chimeric antigen receptor modified T cell therapy for relapsed or refractory CD19+ lymphomas
Abbreviated Title	Pembrolizumab after CTL019/CTL119 for relapsed/refractory CD19+ lymphomas
Trial Phase	Phase I / II
Clinical Indication	Relapsed / refractory CD19+ B cell lymphomas after CTL019/CTL119
Trial Type	Investigator-initiated
Type of control	None. Enrollment will be offered to subjects with an unmet medical need, which is no available effective, standard therapy for relapsed / refractory CD19+ lymphomas
Route of administration	Intravenous
Trial drug, dose, route, regimen	Pembrolizumab (Keytruda®) 200mg fixed dose IV every 3 weeks
Trial Blinding	None
Treatment Groups	Single group
Number of trial subjects	12 evaluable subjects
Estimated enrollment period	12 months (approximately January 2016-January 2017)
Estimated duration of trial	36 months (approximately January 2016-January 2019)
Duration of Participation	24 months (12 months treatment + 12 months follow-up)
Objectives	Primary Endpoints: 1. Determine safety of pembrolizumab after CTL019/CTL119. This endpoint will be met if ≤ 30% of patients develop toxicity resulting discontinuation of pembrolizumab. 2. Determine efficacy of pembrolizumab after CTL019/CTL119. This endpoint will be met if the ORR at 3 months is ≥ 35%.
Statistical methodology	Primary Endpoints: 1. Safety endpoint will be assessed using a Bayesian monitoring rule to ensure probability of a patient developing toxicity resulting in discontinuation of pembrolizumab ≤ 30% Secondary Endpoints: 1. ORR will be assessed using a one-sided binomial test 2. PFS, EFS, RD, and OS will be assessed using Kaplan Maier survival analysis. PFS after pembrolizumab will be compared to PFS after CTL019/CTL119 using a log rank test.

2.0 TRIAL DESIGN

2.1 Trial Design

This is a single center, open label trial of pembrolizumab in patients failing to respond to or relapsing after anti-CD19 chimeric antigen receptor modified T cell therapy (CTL019/CTL119) for relapsed or refractory CD19+ lymphomas.

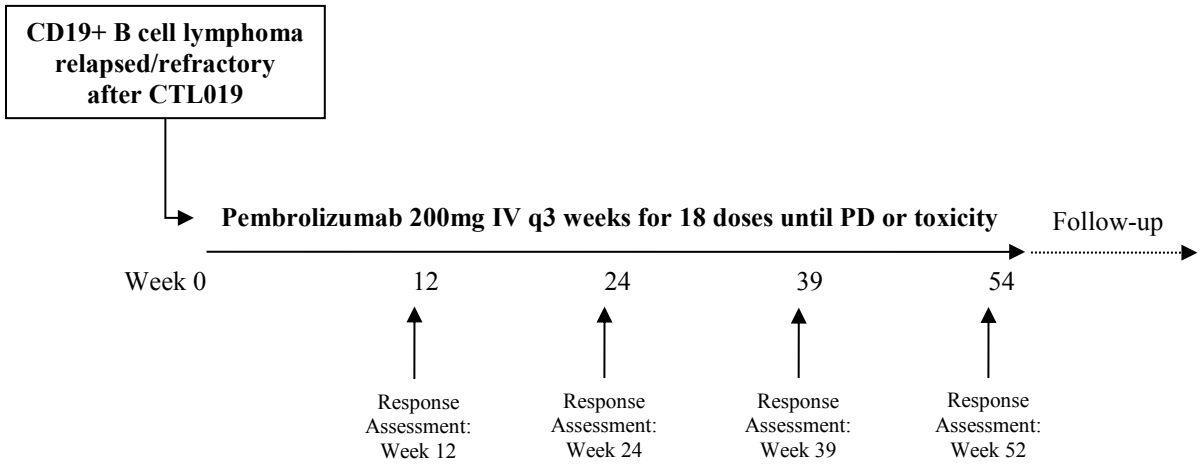
Eligible patients will have CD19+ diffuse large B-cell, follicular, or mantle cell lymphomas with no available curative treatment options, a limited prognosis of several months to <2 years anticipated survival with currently available therapies, and progressive or relapsed disease after a single intravenous dose of 5 x 10^8 ± 20% CTL019/CTL119 administered on our currently enrolling clinical trial (NCT02030834). We anticipate enrollment of 12 total patients onto the present trial for patients not responding to, or relapsing after, CTL019/CTL119.

The safety and efficacy of pembrolizumab in this group of patients will be determined using a fixed dose of 200mg IV. This dose was previously well-tolerated and effective for treatment of patients with metastatic melanoma and NSCLC. The primary safety endpoint will be determined by assessing the rate of pembrolizumab discontinuation as well as the rate of occurrence of treatment-related adverse events (AEs), defined as NCI CTCAE version 5 grade ≥ 3 AEs are possibly, probably, or definitely related to study treatment or grade 4 cytokine release syndrome. Secondary efficacy endpoints will be assessed, including overall response rate (ORR) and progression-free survival (PFS).

History (adverse events), physical examination, assessment of performance status, and routine laboratory studies will be performed prior to first pembrolizumab dose and every 3 weeks prior to pembrolizumab administration. Baseline tumor assessment by radiologic imaging will be performed within 6 weeks of starting pembrolizumab and then prior to week 12 after first dose of pembrolizumab, and then should be performed every 12 weeks from most recent imaging PET/CT, CT of chest/abdomen/pelvis, or MRI chest/abdomen/pelvis ± 2 weeks until 24 months after first dose of pembrolizumab. The duration of pembrolizumab administration will be one year; however, we plan to continue data collection regarding: (1) engraftment as long as patients are at risk (until evidence of loss of detectable transduced T cells); (2) disease-free survival until disease progression; (3) survival until time of death; or (4) until the patient withdraws consent for clinical data collection, as part of the follow-up data collection specified for the FDA for gene modified cell therapy clinical trials.

Peripheral blood, and when possible tumor biopsies, will be obtained prior to pembrolizumab and during therapy with pembrolizumab for correlative studies (see collateral research below).

2.2 Trial Diagram



- Assessment for adverse events every 3 weeks prior to pembrolizumab

3.0 TRIAL OBJECTIVES & HYPOTHESES

3.1 Primary Objectives & Hypotheses

(1) Objective: To determine the safety of pembrolizumab in patients failing to respond to or relapsing after CTL019/CTL119 for relapsed or refractory CD19+ lymphomas.

Hypothesis: Pembrolizumab will be safely tolerated with ≤ 30% of patients experiencing toxicities resulting in discontinuation of pembrolizumab

3.2 Secondary Objectives & Hypotheses

(1) Objective: To describe the overall response rate (ORR) at 3 months to pembrolizumab in patients failing to respond to or relapsing after CTL019/CTL119 for relapsed or refractory CD19+ lymphomas To describe the clinical efficacy of pembrolizumab, including progression-free survival, disease-free survival, event-free survival, response duration, and overall survival (Cheson, 2007) in patients failing to respond to or

relapsing after CTL019/CTL119. Efficacy comparisons will be made for ORR between CTL019/CTL119 and pembrolizumab.

Hypothesis: Pembrolizumab will enhance the efficacy of CTL019/CTL119 in patients failing to respond to or relapsing after CTL019/CTL119 for relapsed or refractory CD19+ lymphomas (John, 2013).

(2) **Objective**: To describe the immunophenotypic and cytokine profiles of chimeric antigen receptor modified T cells in these patients before and after therapy with pembrolizumab

Hypothesis: Immunophenotypic profiles of tumor cells and chimeric antigen receptor modified T cells obtained pre and post pembrolizumab therapy will identify patients for whom pembrolizumab will enhance efficacy.

3.3 Exploratory Objective

(1) **Objective:** To describe the baseline immunophenotypic profiles of tumor cells in these patients (see below chart).

Panels for polychromatic flow cytometry

Tumor: CD19 quant.	Tumor: inhibitory ligands	Tumor: costim & immune escape	T-cells: function (post Ag stimulation)	T-cells: inhibitory receptors, differentiation	T-cells: inhibitory receptors 2	T-cells: inhibitory receptors 3	T-cells: activation, HSC	T-cells: T-helper subsets, T-reg
8 colours	10 colours	13 colours	12 colours	13 colours	9 colours	7 colours	15 colours	12 colours
CD19	CD19	CD19	CAR19	CAR19	CAR19	CAR19	CAR19	CAR19
			CD3	CD3	CD3	CD3	CD3	CD3
CD20	CD20	CD20	CD4	CD4	CD4	CD4	CD4	CD4
CD5 or CD10	CD5 or CD10	CD5 or CD10	CD8	CD8	CD8	CD8	CD8	CD8
Ig λ		CD34		CCR7			CD34	
Ig κ				CD45RO			CD45RO	CD25
CD45	CD45	CD45		CD28			CD27	CD127
	CD200/Ox2	CD80/B7.1	CD107a	CD57	CD160	CD200R	CD134/Ox40	CCR4
CD3	CD270/HVEM	CD86/B7.2	GM-CSF	CD95	CD258/LIGHT	CD244/2B4	CD137/4-1BB	CCR6
	CD273/PD-L2	CD54/ICAM-1	IFN-γ	CTLA-4	CD272/BTLA		CD154/CD40L	CCR10
	CD274/PD-L1	CD162/PSGL-1	IL-2	PD-1	LAG-3		CD278/ICOS	CXCR3
		HLA-A,B,C	MIP-1α	TIM-3			HLA-DR	CXCR5
	Galectin-9	HLA-DR	MIP-1β				Ki67	
		HLA-G	TNF				Perforin	
dead/CD16	dead/CD16	dead/CD16	dead/CD14	dead/CD14	dead/CD14	dead/CD14	dead/CD14	dead/CD14

4.0 BACKGROUND & RATIONAL

4.1 Background

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

4.1.1 Pharmaceutical and Therapeutic Background

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

The PD-1 receptor-ligand interaction is a major pathway hijacked by tumors to suppress immune control. The normal function of PD-1, expressed on the cell surface of activated T-cells under healthy conditions, is to down-modulate unwanted or excessive immune responses, including autoimmune reactions. PD-1 (encoded by the gene Pdcd1) is an Ig superfamily member related to CD28 and CTLA-4 which has been shown to negatively regulate antigen receptor signaling upon engagement of its ligands (PD-L1 and/or PD-L2). The structure of murine PD-1 has been resolved. PD-1 and family members are type I transmembrane glycoproteins containing an Ig Variable-type (V-type) domain responsible for ligand binding and a cytoplasmic tail which is responsible for the binding of signaling molecules. The cytoplasmic tail of PD-1 contains 2 tyrosine-based signaling motifs, an immunoreceptor tyrosine-based inhibition motif (ITIM) and an immunoreceptor tyrosine-based switch motif (ITSM). Following T-cell stimulation, PD-1 recruits the tyrosine phosphatases SHP-1 and SHP-2 to the ITSM motif within its cytoplasmic tail, leading to the dephosphorylation of effector molecules such as CD3ζ, PKCθ and ZAP70 which are involved in the CD3 T-cell signaling cascade. The mechanism by which PD-1 down modulates T-cell responses is similar to, but distinct from that of CTLA-4 as both molecules regulate an overlapping set of signaling proteins. PD-1 was shown to be expressed on activated lymphocytes including peripheral CD4+ and CD8+ T-cells, B-cells, T regs and Natural Killer cells. Expression has also been shown during thymic development on CD4-CD8- (double negative) T-cells as well as subsets of macrophages and dendritic cells. The ligands for PD-1 (PD-L1 and PD-L2) are constitutively expressed or can be induced in a variety of cell types, including non-hematopoietic tissues as well as in various tumors. Both ligands are type I transmembrane receptors containing both IgV- and IgC-like domains in the extracellular region and contain short cytoplasmic regions with no known signaling motifs. Binding of either PD-1 ligand to PD-1 inhibits T-cell activation triggered through the T-cell receptor. PD-L1 is expressed at low levels on various non-hematopoietic tissues, most notably on vascular endothelium,

whereas PD-L2 protein is only detectably expressed on antigen-presenting cells found in lymphoid tissue or chronic inflammatory environments. PD-L2 is thought to control immune T-cell activation in lymphoid organs, whereas PD-L1 serves to dampen unwarranted T-cell function in peripheral tissues. Although healthy organs express little (if any) PD-L1, a variety of cancers were demonstrated to express abundant levels of this T-cell inhibitor. PD-1 has been suggested to regulate tumor-specific T-cell expansion in subjects with melanoma. This suggests that the PD-1/PD-L1 pathway plays a critical role in tumor immune evasion and should be considered as an attractive target for therapeutic intervention.

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

4.1.2 Preclinical and Clinical Trial Data

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

4.2 Rationale

4.2.1 Rationale for the Trial and Selected Subject Population

We are currently conducting a phase IIA clinical trial of redirected autologous T cells, engineered to contain anti-CD19 attached to 4-1BB and TCRζ signaling domains, in patients with chemotherapy relapsed or refractory CD19+ lymphomas (NCT02030834). Briefly, autologous T cells collected from eligible patients with diffuse large B cell, follicular, and mantle cell lymphomas are transduced using a lentiviral vector to express a chimeric antigen receptor comprised of an extracellular single chain antibody (scFv) with specificity for CD19 in tandem with an intracellular signaling domain comprised of 4-1BB and TCRζ signaling molecules. The transduced T cells have specificity for cells expressing CD19, a molecule that is restricted in expression to the surface of B cell lymphoma cells as well as normal B cells. Therapy with anti-CD19 chimeric antigen receptor modified T cells has shown efficacy in chronic lymphocytic and acute lymphoblastic leukemias (Porter, 2011; Grupp, 2013; Maude, 2014). On our lymphoma trial, to date, 7 of 7 evaluable patients with relapsed or refractory follicular lymphoma have responded to anti-CD19 chimeric antigen receptor modified T cell therapy (100% response rate and at a median follow-up of 290 days, only one patient has had progression of disease [*S. Schuster, preliminary data*]), while only 6 of 12 evaluable patients with relapsed or refractory diffuse large B cell lymphoma have responded to therapy (50% response rate; 5 of 6 patients have ongoing complete responses at median follow-up of 274 days [*S. Schuster, preliminary data*]). We have preliminary evidence that the PD-1 receptor-ligand pathway may have a role in patients failing to respond to chimeric antigen receptor

modified T cell therapy, since we have observed increased expression of PD-1 on CTL019/CTL119 with decreased TNF-α and IFN-γ levels in the setting of progressive disease. This has also been demonstrated in a laboratory model of CAR T cells in combination with PD-1 blockade (John, 2013).

Based on this data, we have written this phase I/II clinical trial of pembrolizumab in patients failing to respond to or relapsing after anti-CD19 chimeric antigen receptor modified T cell therapy for relapsed or refractory CD19+ lymphomas.

4.2.2 Rationale for Dose Selection/Regimen/Modification

An open-label Phase I trial evaluated the safety and clinical activity of single agent pembrolizumab (Hamid, et al., 2013; Garon, et al., 2015). The dose escalation portion of this trial evaluated three dose levels, 1 mg/kg, 3 mg/kg, and 10 mg/kg, administered every 2 weeks (Q2W) in subjects with advanced solid tumors. All three dose levels were well tolerated and no dose-limiting toxicities were observed. This first in human study of pembrolizumab showed evidence of target engagement and objective evidence of tumor size reduction at all dose levels.

PK data analysis of pembrolizumab administered Q2W and every three week (Q3W) showed slow systemic clearance, limited volume of distribution, and a long half-life (refer to Investigator's Brochure). Pharmacodynamic data (IL-2 release assay) suggested that peripheral target engagement is durable (>21 days). This PK and pharmacodynamic data provides scientific rationale for the FDA-approved Q3W dosing schedule.

A population pharmacokinetic analysis has been performed using serum concentration time data from 476 patients. Within the resulting population PK model, clearance and volume parameters of pembrolizumab were found to be dependent on body weight. The relationship between clearance and body weight, with an allometric exponent of 0.59, is within the range observed for other antibodies and would support both body weight normalized dosing or a fixed dose across all body weights. Pembrolizumab has been found to have a wide therapeutic range based on the melanoma indication. The differences in exposure for a 200 mg fixed dose regimen relative to a 2 mg/kg Q3W body weight based regimen are anticipated to remain well within the established exposure margins of 0.5 – 5.0 for pembrolizumab in the melanoma indication. The exposure margins are based on the notion of similar efficacy and safety in melanoma at 10 mg/kg Q3W vs. the proposed dose regimen of 2 mg/kg Q3W (i.e. 5-fold higher dose and exposure). The population PK evaluation revealed that there was no significant impact of tumor burden on exposure. In addition, exposure was similar between the NSCLC and melanoma indications. Therefore, there are no anticipated changes in exposure between different the FDA-approved indications and non-Hodgkin lymphoma.

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

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

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

It is possible that cytokine release syndrome may occur given that these patients have received prior treatment with CLT019; thus, if cytokine release syndrome occurs, we have planned for dosing hold parameters and dosing modifications (see Section 5.2.1.2 and Section 5.4.2).

4.2.3 Rationale for Endpoints

4.2.3.1 Rationale for Efficacy Endpoints

1) **Primary Objective:** To determine the safety of pembrolizumab in patients failing to respond to or relapsing after anti-CD19 chimeric antigen receptor modified T cell therapy for relapsed or refractory CD19+ lymphomas.

   Although pembrolizumab has been approved for use in melanoma, there have been no studies in non-Hodgkin lymphoma and the transition to a fixed dose has not been well-studied. In previous studies of pembrolizumab, the rates of drug discontinuation due to an adverse event were 4.2% in melanoma and 2.6%% in non-small cell lung cancer and the rates of drug discontinuation for any reason were 9.4% in melanoma and 21.1% in non-small cell lung cancer (see Investigator's Brochure). Additionally, given that we hypothesize that pembrolizumab may re-activate quiescent chimeric antigen receptor T cells, there is the potential for additional toxicity in patients who have previously received chimeric antigen receptor T cells. Thus, we will define safety as ≤ 30% of patients experiencing toxicities resulting in discontinuation of pembrolizumab.

5.0 METHODOLOGY

5.1 Entry Criteria

5.1.1 Diagnosis/Condition for Entry into the Trial

1. Histologically confirmed follicular lymphoma grade 1-3A, diffuse large B cell lymphoma, or mantle cell lymphoma by WHO 2009 classification

2. Relapsed/refractory lymphoma after CTL019/CTL119

3. No available curative treatment options, a limited prognosis of several months to <2 years anticipated survival with currently available therapies, and progressive or relapsed disease

5.1.2 Subject Inclusion Criteria

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

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

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

3. Have baseline imaging within 6 weeks of enrollment (CT, MR or PET/CT imaging) and have measurable disease on physical examination or imaging studies. Any lesion ≥1.5 cm in **long axis** dimension is considered measurable.

4. Have a performance status of 0-1 on the ECOG Performance Scale (Appendix 12.1).

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

Table 1 Adequate Organ Function Laboratory Values

System	Laboratory Value
Hematological	
Absolute neutrophil count (ANC)	≥1,000 /mcL
Platelets	≥50,000 / mcL
Hemoglobin	≥8 g/dL without transfusion or EPO dependency (within 7 days of assessment). Subject must demonstrate Hgb 8.0g/dL within 14 days of treatment initiation and have a Hgb of ≥ 8g/dL 7 days or more from last PRBC transfusion
Renal	
Serum creatinine **OR** Measured or calculated[a] creatinine clearance (GFR can also be used in place of creatinine or CrCl)	≤1.5 X upper limit of normal (ULN) **OR** ≥60 mL/min for subject with creatinine levels > 1.5 X institutional ULN
Hepatic	
Serum total bilirubin	≤ 1.5 X ULN **OR**
	Direct bilirubin ≤ ULN for subjects with total bilirubin levels > 1.5 ULN
AST (SGOT) and ALT (SGPT)	≤ 2.5 X ULN **OR** ≤ 5 X ULN for subjects with liver metastases
Coagulation	
International Normalized Ratio (INR) or Prothrombin Time (PT) Activated Partial Thromboplastin Time (aPTT)	≤1.5 X ULN unless subject is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants ≤1.5 X ULN unless subject is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants
[a]Creatinine clearance should be estimated per institutional standard.	

6. 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.

7. Female subjects of childbearing potential should be willing to use 2 methods of birth control or be surgically sterile, or abstain from heterosexual activity for the course of the study through 120 days after the last dose of study medication (Reference Section5.5.2). Subjects of childbearing potential are those who have not been surgically sterilized or have not been free from menses for > 1 year.

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

5.1.3 Subject Exclusion Criteria

The subject must be excluded from participating in the trial if the subject:

1. Is currently participating and receiving study therapy or has participated in a study of an investigational agent and received study therapy or used an investigational device within 4 weeks of the first dose of treatment. An exception will be made for patients who have received CTL019/CTL119 on experimental protocol; these patients will be eligible to enroll once progression of disease or failure to respond is documented by clinical or radiologic assessment.

2. Patient has received intervening therapy for lymphoma after CTL019/CTL119 infusion.

3. Has active cytokine release syndrome from CTL019/CTL119 infusion.

4. Has a known history of active TB (Bacillus Tuberculosis).

5. Hypersensitivity to pembrolizumab or any of its excipients.

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

7. Has had prior chemotherapy, targeted small molecule therapy, or radiation therapy within 2 weeks prior to study Day 1 or who has not recovered (i.e., ≤ Grade 1 or at baseline) from adverse events due to a previously administered agent.

    - Note: Subjects with ≤ Grade 2 neuropathy are an exception to this criterion and may qualify for the study.

    - Note: If subject received major surgery, they must have recovered adequately from the toxicity and/or complications from the intervention in the opinion of the Principal Investigator prior to starting therapy.

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

9. Has known active central nervous system (CNS) metastases and/or carcinomatous meningitis. Subjects with previously treated brain metastases may participate provided

they are stable (without evidence of progression by imaging for at least four weeks prior to the first dose of trial treatment and any neurologic symptoms have returned to baseline), have no evidence of new or enlarging brain metastases, and are not using steroids for at least 7 days prior to trial treatment.

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

11. Has known history of non-infectious pneumonitis that required steroids or has any evidence of active non-infectious pneumonitis.

12. Has an active infection requiring systemic therapy.

13. Has a history or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the trial, interfere with the subject's participation for the full duration of the trial, or is not in the best interest of the subject to participate, in the opinion of the treating investigator.

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

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

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

17. Has known active Hepatitis B (e.g., HBsAg reactive) or Hepatitis C (e.g., HCV RNA [qualitative] is detected).

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

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

5.2 Trial Treatments

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

Table 2 Trial Treatment

Drug	Dose	Dose Frequency	Route of Administration	Regimen/Treatment Period	Use
Pembrolizumab	200 mg	Q3 weeks	IV infusion	Day 1 of each 3 week cycle	Experimental

Trial treatment should begin on the day of enrollment or as close as possible to this date.

5.2.1 Dose Selection/Modification

5.2.1.1 Dose Selection

The rationale for selection of the dose to be used in this trial is provided in Section 4.2.2– Background and Rationale.

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

5.2.1.2 Dose Modification

Adverse events (both non-serious and serious) associated with pembrolizumab exposure may represent an immunologic etiology. These adverse events may occur shortly after the first dose or several months after the last dose of treatment. Pembrolizumab must be withheld for drug-related toxicities and severe or life-threatening AEs as per Table 3 below. See Section 5.4 and Events of Clinical Interest Guidance Document for supportive care guidelines, including use of corticosteroids.

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

General instructions:

1. Corticosteroid taper should be initiated upon AE improving to Grade 1 or less and continue to taper over at least 4 weeks.
2. For situations where pembrolizumab has been withheld, pembrolizumab can be resumed after AE has been reduced to Grade 1 or 0 and corticosteroid has been tapered. Pembrolizumab should be permanently discontinued if AE does not resolve within 12 weeks of last dose or corticosteroids cannot be reduced to ≤10 mg prednisone or equivalent per day within 12 weeks.
3. For severe and life-threatening irAEs, IV corticosteroid should be initiated first, followed by oral steroid. Other immunosuppressive treatment should be initiated if irAEs cannot be controlled by corticosteroids.

Immune-related AEs	Toxicity grade or conditions (CTCAEv5.0)	Action taken to pembrolizumab	irAE management with corticosteroid and/or other therapies	Monitor and follow-up
Pneumonitis	Grade 2	Withhold	• Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper	• Monitor participants for signs and symptoms of pneumonitis • Evaluate participants with suspected pneumonitis with radiographic imaging and initiate corticosteroid treatment • Add prophylactic antibiotics for opportunistic infections
	Grade 3 or 4, or recurrent Grade 2	Permanently discontinue		
Diarrhea / Colitis	Grade 2 or 3	Withhold	• Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper	• Monitor participants for signs and symptoms of enterocolitis (ie, diarrhea, abdominal pain, blood or mucus in stool with or without fever) and of bowel perforation (ie, peritoneal signs and ileus).

	Grade 4	Permanently discontinue		• 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 / ALT elevation or Increased bilirubin	Grade 2	Withhold[1]	• Administer corticosteroids (initial dose of 0.5- 1 mg/kg prednisone or equivalent) followed by taper	• Monitor with liver function tests (consider weekly or more frequently until liver enzyme value returned to baseline or is stable
	Grade 3 or 4	Permanently discontinue[1]	• Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper	
Type 1 diabetes mellitus (T1DM) or Hyperglycemia	Newly onset T1DM or Grade 3 or 4 hyperglycemia associated with evidence of β-cell failure	Withhold	• Initiate insulin replacement therapy for participants with T1DM • Administer anti-hyperglycemic in participants with hyperglycemia	• Monitor participants for hyperglycemia or other signs and symptoms of diabetes.
Hypophysitis	Grade 2	Withhold	• Administer corticosteroids and initiate hormonal replacements as clinically indicated.	• Monitor for signs and symptoms of hypophysitis (including hypopituitarism and adrenal insufficiency)
	Grade 3 or 4	Withhold or permanently discontinue[2]		
Hyperthyroidism	Grade 2	Continue	• Treat with non-selective beta-blockers (eg, propranolol) or thionamides as appropriate	• Monitor for signs and symptoms of thyroid disorders.
	Grade 3 or 4	Withhold or permanently discontinue[2]		

Hypothyroidism	Grade 2-4	Continue	• Initiate thyroid replacement hormones (eg, levothyroxine or liothyroinine) per standard of care	• Monitor for signs and symptoms of thyroid disorders.
Nephritis and Renal dysfunction	Grade 2	Withhold	• Administer corticosteroids (prednisone 1-2 mg/kg or equivalent) followed by taper.	• Monitor changes of renal function
	Grade 3 or 4	Permanently discontinue		
Myocarditis	Grade 1 or 2	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 3 or 4	Permanently discontinue		
All other immune-related AEs[3]	Intolerable/ persistent Grade 2	Withhold	• Based on type and severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 3	Withhold or discontinue based on the type of event. Events that require discontinuation include and not limited to: Gullain-Barre Syndrome, encephalitis		
	Grade 4 or recurrent Grade 3	Permanently discontinue		

[1] For patients with liver metastasis who begin treatment with Grade 2 AST or ALT, if AST or ALT increases by greater than or equal to 50% relative to baseline and lasts for at least 1 week then patients should be discontinued.
[2] Withhold or permanently discontinue pembrolizumab is at the discretion of the investigator or treating physician.

[3] "All other immune-related AEs" excludes hematologic AEs given that hematologic changes are not considered reportable AEs or treatment-limiting toxicity (Section 7.3, Section 8.1). For grade 3-4 hematologic toxicity at least possibly related to therapy, therapy will be held until toxicity resolves to grade 0-1 or subject's baseline.

NOTE:

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

Dose modification for cytokine release syndrome:

If patients develop cytokine release syndrome grades 1-3 after pembrolizumab, then pembrolizumab will be held until cytokine release syndrome resolves. Once cytokine release syndrome has fully resolved, the clinical investigator has the option of restarting pembrolizumab at ½ dose (100mg) every 3 weeks. If patients develop grade 4 cytokine release syndrome or require administration of tocilizumab, pembrolizumab will be stopped due to drug toxicity.

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

5.2.2 Timing of Dose Administration

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

All trial treatments will be administered on an outpatient basis.

Pembrolizumab 200 mg will be administered as a 30 minute IV infusion every 3 weeks. Sites should make every effort to target infusion timing to be as close to 30 minutes as possible. However, given the variability of infusion pumps from site to site, a window of -5 minutes and +10 minutes is permitted (i.e., infusion time is 30 minutes: -5 min/+10 min).

The Pharmacy Manual contains specific instructions for the preparation of pembrolizumab infusion fluid and administration of infusion solution.

5.2.3 Trial Blinding/Masking

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

5.3 Concomitant Medications/Vaccinations (allowed & prohibited)

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

5.3.1 Acceptable Concomitant Medications

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

All concomitant medications received within 28 days before the first dose of trial treatment and 30 days after the last dose of trial treatment should be recorded. Concomitant medications administered after 30 days after the last dose of trial treatment should be recorded for SAEs and ECIs as defined in Section 7.2 and 7.3.

5.3.2 Prohibited Concomitant Medications

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

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

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

Subjects who, in the assessment by the investigator, require the use of any of the aforementioned treatments for clinical management should be removed from the trial. Subjects may receive other medications that the investigator deems to be medically necessary.

The Exclusion Criteria describes other medications which are prohibited in this trial.

There are no prohibited therapies during the Post-Treatment Follow-up Phase.

5.4 Rescue Medications & Supportive Care

5.4.1 Supportive Care Guidelines

Subjects should receive appropriate supportive care measures as deemed necessary by the treating investigator. Suggested supportive care measures for the management of adverse events with potential immunologic etiology are outlined below and in greater detail in the ECI guidance document. Where appropriate, these guidelines include the use of oral or intravenous treatment with corticosteroids as

well as additional anti-inflammatory agents if symptoms do not improve with administration of corticosteroids. Note that several courses of steroid tapering may be necessary as symptoms may worsen when the steroid dose is decreased. For each disorder, attempts should be made to rule out other causes such as metastatic disease or bacterial or viral infection, which might require additional supportive care. The treatment guidelines are intended to be applied when the investigator determines the events to be related to pembrolizumab.

Note: if after the evaluation the event is determined not to be related, the investigator is instructed to follow the ECI reporting guidance but does not need to follow the treatment guidance (as outlined in the ECI guidance document). Refer to Section 5.2.1.2 for dose modification.

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

Table

~~Table~~ 4 below shows treatment guidelines for subjects who experience an infusion reaction associated with administration of pembrolizumab.

Table 4 Infusion Reaction Treatment Guidelines

NCI CTCAE Grade	Treatment	Premedication at subsequent dosing
Grade 1 Mild transient reaction; infusion interruption not indicated; intervention not indicated	Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator.	None
Grade 2 Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDS, narcotics, IV fluids); prophylactic medications indicated for < =24 hrs	**Stop Infusion and monitor symptoms.** Additional appropriate medical therapy may include but is not limited to: IV fluids Antihistamines NSAIDS Acetaminophen Narcotics	Subject may be premedicated 1.5h (± 30 minutes) prior to infusion of pembrolizumab with, but is not limited to: Diphenhydramine 50 mg po (or equivalent dose of antihistamine).

NCI CTCAE Grade	Treatment	Premedication at subsequent dosing
	Corticosteroids Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator. If symptoms resolve within one hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (e.g., from 100 mL/hr to 50 mL/hr). Otherwise dosing will be held until symptoms resolve and the subject should be premedicated for the next scheduled dose. **Participants who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further trial treatment administration.**	Acetaminophen 500-1000 mg po (or equivalent dose of antipyretic).
Grades 3 or 4 Grade 3: Prolonged (e.g., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae (e.g., renal impairment, pulmonary infiltrates) Grade 4: Life-threatening consequences; urgent intervention indicated	**Stop Infusion.** Additional appropriate medical therapy may include but is not limited to: IV fluids Antihistamines NSAIDS Acetaminophen Narcotics Oxygen Pressors Corticosteroids Epinephrine** Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator. Hospitalization may be indicated. **In cases of anaphylaxis, epinephrine should be used immediately **Participant is permanently discontinued from further further study drug treatment.**	No subsequent dosing
Appropriate resuscitation equipment should be available in the room and a physician readily available during the period of drug administration.		

NCI CTCAE Grade	Treatment	Premedication at subsequent dosing
For further information, please refer to the Common Terminology Criteria for Adverse Events v5 (CTCAE)		

5.4.2 Cytokine release syndrome and macrophage activation syndrome

Given that pembrolizumab will be administered after patients have received CART-19 therapy, the possibility of re-activating CART-19 cells with subsequent development of cytokine release syndrome exists.

Overview and Clinical Manifestations: Patients treated with pembrolizumab who have previously received CART-19 may experience a cytokine release syndrome (CRS), which has correlated with disease response. Clinical manifestations have included high fevers, fatigue, anorexia, nausea, vomiting, headache, rash, hypotension (occasionally requiring pressor support) tachypnea, hypoxia (occasionally requiring ventilator support), delirium and confusion (in several patients), evidence of disseminated intravascular coagulation as well as macrophage activation syndrome (MAS). In some cases CRS, TLS and hypotension have led to acute kidney injury and several patients have required at least transient dialysis. The CRS has been effectively abrogated with anti-cytokine directed therapy including tocilizumab in most patients. As of July 2014, three patients on another CART-19 trial have died of complications related to refractory CRS and intercurrent infections. It is unclear if treating the CRS adversely impacts the anti-tumor response.

Features consistent with MAS or HLH have been observed in patients treated with CART 19, coincident with clinical manifestations of the CRS. MAS appears to be a reaction to immune activation that occurs from the CRS, and therefore should be considered a manifestation of CRS.

Macrophage activation syndrome (MAS) is similar to Hemophagocytic lymphohistiocytosis (HLH); it is a reaction to immune stimulation by infection, autoimmune diseases or other precipitants, but is distinguished from familial or genetically mediated HLH. There are no definitive diagnostic criteria for MAS, but it is typically diagnosed by meeting HLH criteria.

Some but not all features of MAS are typically observed. The clinical syndrome of MAS is characterized by high grade non-remitting fever, cytopenias affecting at least two of three lineages, and hepatosplenomegaly. It is associated with biochemical abnormalities, such as high circulating levels of serum ferritin, soluble interleukin-2 receptor (sCD25), and triglycerides, together with a decrease of

circulating NK activity. Other findings include variable levels of transaminases up to signs of acute liver failure and coagulopathy with findings consistent with DIC. A pathologic feature of MAS is the presence of hemophagocytic CD163+ macrophages (HPC) in bone marrow or lymph-node aspirates.

Diagnosis of HLH is based on the fulfillment of criteria established in 2004[101] for HLH associated with autosomal recessive disorders (familial HLH, fHLH).

A diagnosis of non-familial HLH/MAS is made by having 5/8 criteria:

- Fever
- Splenomegaly
- Cytopenias (affecting 2 or more lineages in the peripheral blood; hemoglobin <9 g/dL, platelets <100,000/μL, Absolute neutrophil count <1000/μL)
- Fasting triglycerides >265 mg/dL , Fibrinogen < 1.5 g/L
- Hemophagocytosis in bone marrow or spleen or lymph nodes
- Low or absent NK-cell activity
- Ferritin > 500 g/L
- Soluble CD25R > 2400 U/L

Supportive clinical criteria include neurologic symptoms and cerebrospinal fluid pleocytosis, conjugated hyperbilirubinemia, and transaminitis, hypoalbuminemia and hyponatremia. Typically, high fevers, cytopenias, and when performed, hemophagocytosis in the bone marrow is observed (though marrow specimens at the time of the reaction are not often taken). Soluble CD25R and NK cell activity are not standard tests, though samples are taken for retrospective CD25R analysis. Therefore, patients may not meet strict definition of HLH/MAS, but given the constellation of findings, and the consistent dramatic elevation in Ferritin, this is indeed the reaction associated with the CRS.

At this time it is still unknown whether CRS/MAS is beneficial or harmful to the antitumor response. Research monitoring data showed that IL6 levels were extraordinarily high during the CRS, prompting us to use an anti-IL6 receptor antibody tocilizumab to treat the CRS/MAS. The majority of patients treated with tocilizumab for CRS and MAS had rapid (within hours) resolution of dramatic fevers, and continuous improvement in hypotension and hypoxia over hours to several days, and showed improvement in biochemical evidence of CRS and MAS within 48 hours. Adult patients were treated with tocilizumab 4mg/kg or 8mg/kg. It is unclear if early treatment will negate the antitumor response. Treatment and timing of treatment of this toxicity will be at the discretion of the patient's physician and the study principal investigator, and occur in the setting of hemodynamic instability.

Management of cytokine release syndrome

Some patients who have responded to CART-19 cells have experienced a CRS. Cytokine production is required for the activation, expansion and cytolytic function of T cells and for CART-19 T cells. Therefore some degree of CRS may be a desired clinical outcome. Premature or early intervention with anti-cytokine therapy may therefore abrogate the anti-tumor efficacy of CART-19. Subsequent to this experience, selective tocilizumab (an anti-IL6-receptor antibody) therapy has been utilized (described below) with effective toxicity management and successful ongoing CART-19 T cell expansion in patients. Please note, steroids or other immunosuppressant drugs should **NOT** be used as pre-medication for pembrolizumab but may be considered in the management of CRS.

The moderate to severe cases of CRS observed required intervention with tocilizumab, with or without high dose corticosteroids, between 2 and 9 days after T cell infusion. This resulted in rapid reversal of the high persistent fevers associated with CRS in most but not all patients.

Given the dramatic clinical improvement of most patients treated with anti-cytokine therapy, patients with moderate to severe cytokine toxicities should be first managed with administration of tocilizumab.

Tocilizumab should be used as a weight-based dose of 8 mg/kg at the time of hemodynamic instability. This management approach is designed to avoid life-threatening toxicities, while attempting to allow the CART-19 cells to establish a proliferative phase that appears to correlate with anti-tumor efficacy. Thus, the timing of the tocilizumab should be individualized, in close consultation with the Principal Investigator and/or expert consultants for the trial. Steroids have not always been effective in this setting and may not be

necessary given the rapid response to tocilizumab. Because steroids will interfere with CART-19 function and efficacy, if used, they should be rapidly tapered.

Upon developing the prodrome of high-persistent fevers following CART-19 infusion, patients should then be followed closely. Infection and tumor lysis syndrome work up should be immediately undertaken. The pharmacy should be notified of the potential need for tocilizumab. Patient management in an intensive care unit may be required and the timing is dependent upon local institutional practice. In addition to supportive care, tocilizumab may be administered in cases of moderate to severe CRS, especially if the patient exhibits any of the following:

- Hemodynamic instability despite intravenous fluid challenges and moderate stable vasopressor support
- Worsening respiratory distress, including pulmonary infiltrates, increasing oxygen requirement including high-flow O2, and/or need for mechanical ventilation.
- Any other signs or symptoms of rapid deterioration despite medical management

The recommended dosing for tocilizumab is 8 mg/kg i.v. single dose. Not all Grade 4 CRS reactions following CART-19 have been immediately treated with tocilizumab and decisions are, in part, based upon the rapidity of the syndrome onset and underlying patient reserve.

Other anti-cytokine therapies, such as repeat administration of tocilizumab or use of siltuximab or etanercept, may also be considered if the patient does not respond to the initial dose of tocilizumab. If the patient experiences ongoing CRS despite administration of anti-cytokine directed therapies, anti T-cell therapies such as Cytoxan, ATG, Campath may be considered.

CRS has been associated with biochemical and physiologic abnormalities consistent with MAS. Moderate to extreme elevations in serum C-reactive protein (CRP) and ferritin have been seen with CART-19 associated CRS, however the magnitude and kinetics vary greatly between individual patients. CRS management decisions should be based upon clinical signs and symptoms and response to interventions, not these laboratory values *per se*.

CTCAE grading of CRS relates to its occurrence with acute infusional toxicities, whereas the CRS associated with CART-19 therapy is not acute, but rather delayed. Refer to Section 7.3.3 for modified definitions of grading of CART-19 delayed CRS events.

5.5 Diet/Activity/Other Considerations

5.5.1 Diet

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

5.5.2 Contraception

Pembrolizumab may have adverse effects on a fetus in utero. Furthermore, it is not known if pembrolizumab has transient adverse effects on the composition of sperm. Non-pregnant, non-breast-feeding women may be enrolled if they are willing to use 2 methods of birth control or are considered highly unlikely to conceive. Highly unlikely to conceive is defined as 1) surgically sterilized, or 2) postmenopausal (a woman who is ≥45 years of age and has not had menses for greater than 1 year will be considered postmenopausal), or 3) not heterosexually active for the duration of the study. The two birth control methods can be either two barrier methods or a barrier method plus a hormonal method to prevent pregnancy. Subjects should start using birth control from study Visit 1 throughout the study period up to 120 days after the last dose of study therapy.

The following are considered adequate barrier methods of contraception: diaphragm, condom (by the partner), copper intrauterine device, sponge, or spermicide. Appropriate hormonal contraceptives will include any registered and marketed contraceptive agent that contains an estrogen and/or a progestational agent (including oral, subcutaneous, intrauterine, or intramuscular agents).

Subjects should be informed that taking the study medication may involve unknown risks to the fetus (unborn baby) if pregnancy were to occur during the study. In order to participate in the study they must adhere to the contraception requirement (described above) for the duration of the study and during the follow-up period defined in section 7.2.2-Reporting of Pregnancy and Lactation to the Sponsor and to Merck. If there is any question that a subject will not reliably comply with the requirements for contraception, that subject should not be entered into the study.

5.5.3 Use in Pregnancy

If a subject inadvertently becomes pregnant while on treatment with pembrolizumab, the subject will immediately be removed from the study. The site will contact the subject at least monthly and document the subject's status until the pregnancy has been completed or terminated. The outcome of the pregnancy will be reported to the Sponsor and to Merck without delay and within 24 hours to the Sponsor and within 2 working days to Merck if the outcome is a serious adverse experience (e.g., death, abortion, congenital anomaly, or other disabling or life-threatening complication to the mother or newborn).

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

5.5.4 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, subjects who are breast-feeding are not eligible for enrollment.

5.6 Subject Withdrawal/Discontinuation Criteria

Subjects may withdraw consent at any time for any reason or be dropped from the trial at the discretion of the investigator should any untoward effect occur. In addition, a subject may be withdrawn by the investigator or the Sponsor if enrollment into the trial is inappropriate, the trial plan is violated, or for administrative and/or other safety reasons. Specific details regarding discontinuation or withdrawal are provided in Section 7.1.3– Other Procedures.

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

- The subject or legal representative (such as a parent or legal guardian) withdraws consent.
- Confirmed radiographic disease progression

Note: For unconfirmed radiographic disease progression, if a biopsy is felt clinically necessary, patients may continue pembrolizumab until progression is biopsy confirmed.

Progressive disease (PD): Immunotherapeutic agents such as pembrolizumab may produce antitumor effects by potentiating endogenous cancer-specific immune responses. The response patterns with immunotherapy may extend beyond the typical course of responses seen with cytotoxic agents and can manifest as a clinical response preceded by initial increase in tumor burden, the appearance of new lesions, or a mixed response with some enlarging lesions while other lesions are regressing. Therefore, if the investigator feels the patient has clinical benefit, subjects may continue pembrolizumab until progression is 1) confirmed at follow-up imaging at next response assessment unless clinically indicated to perform sooner and 2) found to have progressive disease at a subsequent imaging evaluation.

Evidence of PD will be based on a comparison with baseline (or nadir) scans or other evaluations.

Subjects with PD on imaging should be managed as follows:

Subjects will be permitted to continue pembrolizumab beyond first confirmed progressive disease as measured by the 2007 Revised response criteria for malignant lymphoma as long as the following are true:

• Investigator assessed clinical benefit

AND

• Subject is tolerating pembrolizumab

Subjects that meet the above criteria and continue pembrolizumab must discontinue pembrolizumab upon the next documented event of PD. The assessment of clinical benefit should be balanced by clinical judgment as to whether the subject is clinically deteriorating and unlikely to receive any benefit from continued treatment. The decision to continue treatment should be discussed with the Principal Investigator and Medical Monitor and documented in the study records.

- Unacceptable adverse experiences as described in Section 5.2.1.2
- Intercurrent illness that prevents further administration of treatment
- Investigator's decision to withdraw the subject
- The subject has a confirmed positive serum pregnancy test
- Noncompliance with trial treatment or procedure requirements
- The subject is lost to follow-up
- Completed 12 months of uninterrupted treatment with pembrolizumab or 18 administrations of study medication, whichever is later.

  Note: 12 months of study medication is calculated from the date of first dose. Subjects who stop pembrolizumab after 12 months may be eligible for up to one year of additional study treatment if they progress after stopping study treatment provided they meet the requirements detailed in Section 7.1.3.5

- Administrative reasons

The End of Treatment and Follow-up visit procedures are listed in Section 7.1.3 Visit Requirements. After the end of treatment, each subject will be followed for 30 days for adverse event monitoring (serious adverse events will be collected for 90 days after the end of treatment as described in Section 7.2.3.1).

5.7 Second Course

Additional details are provided in Section 7.1.3.5.

5.8 Subject Replacement Strategy

1. If a subject is enrolled, but does not receive any doses of pembrolizumab, they may be replaced, to allow for a total of 12 subjects treated with pembrolizumab who are assessed for response rate

2. If a subject receives one dose of pembrolizumab but is removed from study for a reason aside from toxicity prior to receiving 4 doses of pembrolizumab, this patient may be replaced to allow for a total of 12 subjects treated with pembrolizumab who are assessed for response rate. Patients removed prior to 3 months who have not experienced toxicity will be included for efficacy analyses but will not be included in toxicity analysis.

5.9 Clinical Criteria for Early Trial Termination

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

1. Quality or quantity of data recording is inaccurate or incomplete

2. Poor adherence to protocol and regulatory requirements

3. Incidence or severity of adverse drug reaction in this or other studies indicates a potential health hazard to subjects

4. Plans to modify or discontinue the development of the study drug

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

6.0 TRIAL FLOW CHART

6.1 Study Flow Chart

Trial Period:	**Screening**	**Treatment cycles and week #**									**End of Treatment**		
Treatment Cycle^^:	Main Study Screening	C1				C2			C3 to C8	C9 onwards	Discon	Safety Follow-up Visit	Follow-up
Day (relative to each cycle):	-28 to -1	D0 (W0)	D3	D7	D14	D0	D7	D14	D0	D0			
Scheduling Window (Days):		-3[B]	±1	± 3	± 3	± 3	± 3	±3	± 3	± 7	At time of Discon	30 days post discon	± 2 weeks
Informed Consent	x												
Inclusion/Exclusion Criteria	x												
Demographics and Medical History	x												
Prior and Concomitant Medication Review	x	x				x			x	x	x		
Trial Treatment Administration		x				x			x	x			
Post-study anticancer therapy status											x	x	x
Survival Status											x	x	
Review Adverse Events		x				x			x	x	x	x	
Full Physical Examination	x	x				x			x	x	x	x	

Trial Period:	**Screening**	**Treatment cycles and week #**									**End of Treatment**		
Treatment Cycle^^:	Main Study Screening	C1				C2			C3 to C8	C9 onwards	Discon	Safety Follow-up Visit	Follow-up
Day (relative to each cycle):	-28 to -1	D0 (W0)	D3	D7	D14	D0	D7	D14	D0	D0			
Scheduling Window (Days):		-3[B]	±1	± 3	± 3	± 3	± 3	±3	± 3	± 7	At time of Discon	30 days post discon	± 2 weeks
Vital Signs	x	x				x			x	x	x	x	
ECOG Performance Status (Appendix 12.1)	x	x				x			x	x	x	x	
Electocardiogram (EKG)	x												
Pregnancy Test – Urine or Serum β-HCG	x	x[B]				x			x[E]	x		x	
PT/INR and aPTT	x												
CBC with Differential	x	x[B]	x[C]	x[D]	x[D]	x	x[D]	x[D]	x[E]	x		x	
Comprehensive Serum Chemistry Panel,, LDH	x	x[B]	x[C]	x[D]	x[D]	x	x[D]	x[D]	x[E]	x		x	
Uric acid, phosphate	x	x[BD]	x[C]	x[D]	x[D]	x	x[D]	x[D]	x[I]				
Urinalysis	x												
TSH with reflex to T4	x	x[B]				x			x	x[F]		x	
Tumor Imaging	x[A]	Week 12 then every 12 weeks from most recent imaging PET/CT, CT of chest/abdomen/pelvis, or MRI chest/abdomen/pelvis ± 2 wk for 24 months									x[A]		x[A]
HIV, Hep B sAg/sAb/cAb, HCV Ab	x[G]												

Trial Period:	**Screening**	**Treatment cycles and week #**									**End of Treatment**		
Treatment Cycle^^:	Main Study Screening	C1				C2			C3 to C8	C9 onwards	Discon	Safety Follow-up Visit	Follow-up
Day (relative to each cycle):	-28 to -1	D0 (W0)	D3	D7	D14	D0	D7	D14	D0	D0			
Scheduling Window (Days):		-3[B]	±1	± 3	± 3	± 3	± 3	±3	± 3	± 7	At time of Discon	30 days post discon	± 2 weeks
Archival or Newly Obtained Tissue Collection (optional)	x										x		
Correlative Studies Blood Collection[H] (optional)	x	x[B]	x[H]	x[D]	x[D]	x	x[D]	x[D]	through C4		x		

^^Please note that for study purposes, Day 0 / Week 0 / Cycle 1 refers to the date of the first infusion

[A] See Section 6.3

[B]Cycle 1, Day 0 labs will be drawn within 3 days prior to infusion; screening labs may double as Cycle 1, Day 0 labs if they are performed within this timeframe

[C]Labs will be drawn Day 3 ± 1 day after Cycle 1 infusion

[D]For Cycles 1 and 2, labs will be drawn weekly ± 3 days at one week and two weeks after each infusion

[E]From Cycle 3-8, labs will be drawn ± 3 days prior to each dose of pembrolizumab

[F]Beginning with Cycle 9 of pembrolizumab), labs may be drawn every odd-numbered cycle (i.e. prior to every other dose) ± 1 week until drug discontinuation.

[G]Within 3 months of enrollment

[H]See Section 6.5

[I]Only for Cycle 3

6.2 Physical examination and adverse events

Physical examination including vital signs, as well as determination of ECOG performance status will be obtained prior to start of each cycle of pembrolizumab.

Review of adverse events will be performed prior to start of each cycle of pembrolizumab.

Review of concomitant medications will be performed prior to the start of each cycle of pembrolizumab.

6.3 Imaging studies

[A]Baseline imaging must be performed within 6 weeks of first dose of pembrolizumab. This may be obtained by contrast-enhanced CT, contrast-enhanced MRI, or PET/CT. Imaging for response assessment should be performed at week 12 after first dose of pembrolizumab, and then should be performed every 12 weeks from most recent imaging PET/CT, CT of chest/abdomen/pelvis, or MRI chest/abdomen/pelvis ± 2 weeks until 24 months after first dose of pembrolizumab. After 24 months, subjects who did not discontinue study due to progression of lymphoma or toxicity will transition to the follow-up period and be followed with imaging every 6 months ± 2 weeks until 60 months after first dose of pembrolizumab.

Subjects will be reimaged at the time of pembrolizumab discontinuation ± 2 weeks unless they are coming off study for toxicity, coming off study with recently documented complete response (within 8 weeks), or coming off study after > 1 year of follow-up.

6.4 Laboratory studies

Screening tests (within 28 days prior to enrollment): CBC with differential, CMP, uric acid, phosphate, TSH with reflex to T4, PT/PTT, HIV (to be performed within 3 months of enrollment), Hepatitis B surface antibody / surface antigen, core antibody (to be performed within 3 months of enrollment), Hepatitis C antibody (to be performed within 3 months of enrollment) urinalysis, urine or serum pregnancy test if the subject is a woman whose last menstrual period was < 18 months ago. EKG will also be obtained.

Cycle 1, Day 0 (labs within 3 days prior to infusion; screening labs may double as Cycle 1, Day 0 labs if they are performed within this timeframe): CBC with differential, CMP, LDH, uric acid, phosphate, TSH with reflex to T4, urine or serum pregnancy test if the subject is a woman whose last menstrual period was < 18 months ago.

Cycle 1, day 3 ± 1 day: CBC with differential, CMP, LDH, uric acid, phosphate

Cycle 1 (labs one week and two weeks after cycle 1 infusion ± 3 days): CBC with differential, CMP, LDH, uric acid, phosphate

Cycle 2 (labs within 3 days prior to the infusion): CBC with differential, CMP, LDH, uric acid, phosphate, TSH with reflex to T4, urine or serum pregnancy test if the subject is a woman whose last menstrual period was < 18 months ago.

Cycle 2 (labs one week and two weeks after cycle 2 infusion ± 3 days): CBC with differential, CMP, LDH, uric acid, phosphate

Cycles 3-8 (labs every 3 weeks within 3 days prior to each cycle): CBC with differential, CMP, LDH, uric acid (only for cycle 3), phosphate (only for cycle 3), TSH with reflex to T4, urine or serum pregnancy test if the subject is a woman whose last menstrual period was < 18 months ago.

Cycles 9-onwards, labs prior to every cycle of pembrolizumab within 1 week prior to each cycle: CBC with differential, CMP, LDH, urine or serum pregnancy test if the subject is a woman whose last menstrual period was < 18 months ago.

Cycles 9-onwards (labs prior to each odd cycle of pembrolizumab within 1 week prior to each cycle): TSH with reflex to T4

6.5 Optional correlative studies

Subjects will have blood drawn prior to the first infusion, then at 24 hours, 48 hours, and 72 hours, as well as day 7, day 14, day 21, then prior to each successive dose of pembrolizumab through cycle 4. Given that these are exploratory studies, the timing of these labs may be flexible. The total amount of blood drawn at a single time will not exceed 30cc and the maximum volume drawn will not exceed 330cc.

7.0 TRIAL PROCEDURES

7.1 Trial Procedures

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

Furthermore, additional evaluations/testing may be deemed necessary by the Sponsor and/or Merck for reasons related to subject safety. In some cases, such evaluation/testing may be potentially sensitive in nature (e.g., HIV, Hepatitis C, etc.), and thus local regulations may

require that additional informed consent be obtained from the subject. In these cases, such evaluations/testing will be performed in accordance with those regulations.

7.1.1 Administrative Procedures

7.1.1.1 Informed Consent

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

7.1.1.1.1 General Informed Consent

The consent process will be documented for every subject. This process will involve a) documentation of the consent discussion and obtaining consent via the b) IRB approved Informed Consent Form.

Documentation of the consent discussion will record that the study was explained to the subject along with the risks and benefits and that the subjects had no questions or all questions were answered and both the subject and person obtaining consent signed the consent form on "X" date and a signed copy was given to the subject for his/her records.

Only designated members of the study team, who are qualified through education and experience and who have completed CITI certification will obtain consent from subjects.

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

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

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

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

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

7.1.1.2 Adult subjects not competent to give consent

This will be approached on a case-by-case basis by the Principal Investigator in consultation with the IRB, DSMB, and study supporter.

Adult subjects who are deemed by informal assessment by the investigator to have concern for inability to give informed consent will be further evaluated for medical decision-making capacity to give consent by a study investigator. In the event the patient is unable to give informed consent, a "legally responsible party", will be advised when the patient's primary oncologist is considering enrollment on this clinical trial. The patient's legally responsible party, must give informed consent prior to participation. The following individuals may be considered legally authorized representatives of the subject and capable of providing surrogate consent (or surrogate HIPAA Authorization):

- A court-appointed guardian authorized to consent to the subject's participation in the protocol in a current court order issued within the subject's jurisdiction
- A health care agent appointed by the subject in a power of attorney
- A "health care representative" when the subject cannot speak for themselves and where there has been no guardian appointed by the court or health care power of attorney designated by the patient

Any member of the following classes, in descending order of priority, who is reasonably available may act as the subject’s health care representative:

- The spouse (unless an action for divorce is pending) and adult child or children of another relationship.
- Adult children (18 years of age or older).
- A parent.
- An adult sibling.
- An adult grandchild
- An adult who has knowledge of the patient’s preferences and values, including but not limited to religious and moral beliefs

Assent, will be obtained from the subject, if they are able to provide it, prior to participation.

7.1.1.3 Inclusion/Exclusion Criteria

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

7.1.1.4 Medical History

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

7.1.1.5 Prior and Concomitant Medications Review

7.1.1.5.1 Prior Medications

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

7.1.1.5.2 Concomitant Medications

The investigator or qualified designee will record medication, if any, taken by the subject during the trial. All medications related to reportable SAEs and ECIs should be recorded as defined in Section 7.2.

7.1.1.6 Disease Details and Treatments

7.1.1.6.1 Disease Details

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

7.1.1.6.2 Prior Treatment Details

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

7.1.1.6.3 Subsequent Anti-Cancer Therapy Status

The investigator or qualified designee will review all new anti-neoplastic therapy initiated after the last dose of trial treatment. If a subject initiates a new anti-cancer therapy within 30 days after the last dose of trial treatment, the 30 day Safety Follow-up visit must occur before the first dose of the new therapy. Once new anti-cancer therapy has been initiated the subject will move into survival follow-up (see Section 7.1.3.4).

7.2 Clinical Procedures/Assessments

7.1.1.7 Adverse Event (AE) Monitoring

The investigator or qualified designee will assess each subject to evaluate for potential new or worsening AEs as specified in the Trial Flow Chart and more frequently if clinically indicated. Adverse experiences will be graded and recorded throughout the study and during the follow-up period according to NCI CTCAE Version 5.0 (see Section 12.2). Toxicities will be characterized in terms regarding seriousness, causality, toxicity grading, and action taken with regard to trial treatment.

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

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

7.1.1.8 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,

7.1.1.9 Directed Physical Exam

For cycles that do not require a full physical exam per the Trial Flow Chart (i.e., cycles with an even number beginning with Cycle 4), the investigator or qualified designee will perform a directed physical exam as clinically indicated prior to trial treatment administration.

7.1.1.10 Vital Signs

The investigator or qualified designee will take vital signs at screening, prior to and at the conclusion of the administration of each dose of trial treatment and at the time patient is removed from study as specified in the Trial Flow Chart (Section 6.0). Vital signs should include temperature, pulse, and blood pressure.

7.1.1.11 Eastern Cooperative Oncology Group (ECOG) Performance Scale

The investigator or qualified designee will assess ECOG status (Appendix 12.1) at screening, prior to the administration of each dose of trial treatment and discontinuation of trial treatment as specified in the Trial Flow Chart.

7.1.1.12 Tumor Imaging and Assessment of Disease

Baseline imaging must be performed within 6 weeks of first dose of pembrolizumab. This may be obtained by contrast-enhanced CT, contrast-enhanced MRI, or PET/CT. Imaging for response assessment (Cheson, 2007) should be performed prior to week 12 after first dose of pembrolizumab, and then should be performed every 12 weeks from most recent imaging PET/CT, CT of chest/abdomen/pelvis, or MRI chest/abdomen/pelvis ± 2 weeks until 24 months after first dose of pembrolizumab.

At time of pembrolizumab discontinuation ± 2 weeks, subjects will be reimaged unless they are coming off study for toxicity, coming off study with recently documented complete response (within 8 weeks of most recent imaging), or coming off study after > 1 year of follow-up.

7.1.1.13 Tumor Tissue Collection and Correlative Studies Blood Sampling

Blood may be optionally collected for correlative studies up to 3 days before pembrolizumab administration during cycles 1, 2, 3, and 4. Further optional blood draws may occur at time of routine laboratory study blood draws scheduled near time of imaging. These labs may be collected within 7 days before that week's dose of pembrolizumab.

7.1.1.14 Laboratory Procedures/Assessments

Details regarding specific laboratory procedures/assessments to be performed in this trial are provided below in the table: Laboratory Safety Evaluations (Hematology, Chemistry and Urinalysis)

Laboratory tests for hematology, chemistry, urinalysis, and others are specified in Table 5.

Table 5 Laboratory Tests

Hematology	Chemistry	Urinalysis	Other
Hematocrit	Albumin	Blood	Serum β-human chorionic gonadotropin†
Hemoglobin	Alkaline phosphatase	Glucose	(β-hCG)†
Platelet count	Alanine aminotransferase (ALT)	Protein	PT (INR)
WBC (total and differential)	Aspartate aminotransferase (AST)		aPTT
Red Blood Cell Count	Lactate dehydrogenase (LDH)	Microscopic exam *(If abnormal)*	
Absolute Neutrophil Count		results are noted	Thyroxine (T4)
Absolute Lymphocyte Count		Urine pregnancy test †	Thyroid stimulating hormone (TSH)
	Uric Acid		
	Calcium		
	Chloride		Blood for correlative studies
	Glucose		
	Phosphorus		
	Potassium		
	Sodium		
	Total Bilirubin		
	Direct Bilirubin *(If total bilirubin is elevated above the upper limit of normal)*		
	Total protein		
	Blood Urea Nitrogen		

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

‡ If considered standard of care in your region.

Laboratory tests for screening or entry into the Second Course Phase should be performed within 10 days prior to the first dose of treatment. Results must be reviewed by the investigator or qualified designee and found to be acceptable prior to each dose of trial treatment.

7.1.2 Other Procedures

7.1.2.1 Withdrawal/Discontinuation

When a subject discontinues/withdraws prior to trial completion, all applicable activities scheduled for the final trial visit should be performed at the time of discontinuation. Any adverse events which are present at the time of discontinuation/withdrawal should be followed in accordance with the safety requirements outlined in Section 7.2 - Assessing and Recording Adverse Events. Subjects who a) attain a CR or b) complete 12 months of treatment with pembrolizumab may discontinue treatment with the option of restarting treatment if they meet the criteria specified in Section 7.1.5.5. After discontinuing treatment following assessment of CR, these subjects should return to the site for a Safety Follow-up Visit (described in Section 7.1.5.3.1) and then proceed to the Follow-Up Period of the study (described in Section 7.1.5.4).

7.1.3 Visit Requirements

Visit requirements are outlined in Section 6.0 - Trial Flow Chart. Specific procedure-related details are provided above in Section 7.1 - Trial Procedures.

7.1.3.1 Screening Period

Baseline imaging must be obtained within 6 weeks of first dose of pembrolizumab. Laboratory requirements for enrollment eligibility are listed in the study flow chart (Section 6.1) and entry criteria (Section 5.1).

7.1.3.2 Treatment Period

Subjects will receive pembrolizumab every 3 weeks for up to 18 cycles or 54 weeks, whichever is later.

7.1.3.3 Safety Follow-Up Visit

The mandatory Safety Follow-Up Visit should be conducted approximately 30 days ± 1 week after the last dose of trial treatment or before the initiation of a new anti-cancer treatment, whichever comes first. If it is not medically safe to delay initiation of a new anti-cancer therapy until a safety follow-up visit is performed, it is permissible to have the safety visit soon after initiation of new anti-cancer therapy, but this should be noted in the patient's record.

All AEs that occur prior to the Safety Follow-Up Visit should be recorded. Subjects with an AE of Grade > 1 will be followed until the resolution of the AE to Grade 0-1 or until the beginning of a new anti-neoplastic therapy, whichever occurs first. SAEs that occur within 90

days of the end of treatment or before initiation of a new anti-cancer treatment should also be followed and recorded. Subjects who are eligible for retreatment with pembrolizumab (as described in Section 7.1.3.5) may have up to two safety follow-up visits, one after the Treatment Period and one after the Second Course Phase.

7.1.3.4 Follow-up Visits

Subjects who discontinue trial treatment for toxicity will be followed at least monthly or more frequently at the discretion of the study investigator until stabilization, return to baseline, resolution of toxicity, or initiation of a new cancer treatment.

Subjects who discontinue trial treatment for a reason other than disease progression or toxicity (i.e., elective discontinuation of therapy) will move into the Follow-Up Phase and should be assessed depending upon time from first dose of pembrolizumab. If the patient is within 24 months from first dose of pembrolizumab, follow-up imaging will occur every 12 weeks from most recent imaging PET/CT, CT of chest/abdomen/pelvis, or MRI chest/abdomen/pelvis ± 2 weeks until 24 months after first dose of pembrolizumab. After 24 months, subjects will be followed with imaging every 6 months ± 2 weeks until 60 months after first dose of pembrolizumab. Adverse events will be collected and reported per adverse event sections 7.2.3.1 and 7.3. Information regarding post-study anti-neoplastic treatment will be collected if new treatment is initiated.

Subjects who are eligible to receive retreatment with pembrolizumab according to the criteria in Section 7.1.3.5 will move from the follow-up phase to the Second Course Phase when they experience disease progression. Details are provided in Section 6.2 – Trial Flow Chart for Retreatment.

7.1.3.5 Second Course Phase (Retreatment Period)

Subjects who stop pembrolizumab with SD or better may be eligible for up to an additional 17 cycles (approximately one year) pembrolizumab treatment if they progress after stopping study treatment from the initial treatment phase. This retreatment is termed the Second Course Phase of this study and is only available if the study remains open and the subject meets the following conditions:

- **Either**
    - Stopped initial treatment with pembrolizumab after attaining an investigator-determined confirmed CR, and
        - Was treated for at least 8 cycles with pembrolizumab before discontinuing treatment, and

- Received at least two treatments with pembrolizumab beyond the date when the initial CR was declared

OR

- Had SD, PR or CR and stopped pembrolizumab treatment after 12 months of study therapy for reasons other than disease progression or intolerability

AND

- Experienced an investigator-determined confirmed radiographic disease progression after stopping their initial treatment with pembrolizumab
- Did not receive any anti-cancer treatment since the last dose of study treatment
- The subject meets all of the safety parameters listed in the inclusion criteria and none of the safety parameters listed in the exclusion criteria
- The study is ongoing

A drug-related toxicity, objective response or disease progression that occurs during the Second Course Phase for a subject will not be counted as an event for safety or efficacy analyses in this study.

*Note: patients must have measurable disease at the start of re-treatment to be eligible for this provision.

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

7.2 Adverse Events

An adverse event is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product or protocol-specified procedure, whether or not considered related to the medicinal product or protocol-specified procedure. Any worsening (i.e., any clinically significant adverse change in frequency and/or intensity) of a preexisting condition that is temporally associated with the use of pembrolizumab, is also an adverse event.

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

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

Adverse events may occur during the course of the use of pembrolizumab in clinical trials or within the follow-up period specified by the protocol, or prescribed in clinical practice, from overdose (whether accidental or intentional), from abuse and from withdrawal.

Adverse events will not occur in screened subjects prior to receiving ANY dose of pembrolizumab.

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

All adverse events will be recorded from the time of first dose of pembrolizumab through completion of the Safety Follow Up Visit, and at each examination on the Adverse Event case report forms/worksheets. The reporting timeframe for adverse events meeting any serious criteria is described in sections 7.2 and 7.3.

Hospitalization, Prolonged Hospitalization or Surgery
Any adverse event that results in hospitalization or prolonged hospitalization should be documented and reported as a serious adverse event unless specifically instructed otherwise in this protocol. Any condition responsible for surgery should be documented as an adverse event if the condition meets the criteria for an adverse event. As was noted above, events related to the cytotoxic chemotherapy will be excluded from adverse event reporting.

Neither the condition, hospitalization, prolonged hospitalization, nor surgery are reported as an adverse event in the following circumstances:

- Hospitalization or prolonged hospitalization for diagnostic or elective surgical procedures for a preexisting condition. Surgery should ***not*** be reported as an outcome of an adverse event if the purpose of the surgery was elective or diagnostic and the outcome was uneventful.

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

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

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

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

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

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

Although pregnancy and lactation are not considered adverse events, it is the responsibility of investigators or their designees to report any pregnancy or lactation in a subject (spontaneously reported to them), including the pregnancy of a male subject's female partner that occurs during the trial or within 120 days of completing the trial completing the trial, or 30 days following cessation of treatment if the subject initiates new anticancer therapy, whichever is earlier. All subjects and female partners of male subjects who become pregnant must be followed to the completion/termination of the pregnancy. Pregnancy outcomes of spontaneous abortion, missed abortion, benign hydatidiform mole, blighted ovum, fetal death, intrauterine death, miscarriage and stillbirth must be reported as serious events (Important Medical Events). If the pregnancy continues to term, the outcome (health of infant) must also be reported.

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

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

7.2.3.1 Serious Adverse Events

A serious adverse event is any adverse event occurring at any dose or during any use of pembrolizumab that:

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

- Is associated with an overdose;
- Is an other important medical event

Refer to Table 6 for additional details regarding each of the above criteria.

Any serious adverse event, or follow up to a serious adverse event, including death due to any cause other than progression of the cancer under study that occurs to any subject from the time the consent is signed through 90 days following cessation of treatment (i.e. last dose of pembrolizumab), or the initiation of new anti-cancer therapy, whichever is earlier, whether or not related to pembrolizumab, must be reported within 24 hours of discovery to the Sponsor (SJ Schuster, schustes@mail.med.upenn.edu or 215-662-400 / page Dr. Schuster). Dr. Schuster and the study team will be responsible for reporting SAEs to the University of Pennsylvania IRB, the medical monitor, and the DSMC per reporting of Adverse Events Section 7.3 below. Any serious adverse event must also be reported within 2 working days to Merck Global Safety in the form of a completed CIOMS I/Medwatch. All information shall contain the reporter's name and the Study subject identifier code.

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

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

7.3 Reporting of Adverse events

HEMATOLOGIC GRADE 3 OR GREATER ADVERSE EVENTS WILL **NOT** BE REPORTED unless they are determined by the Principal Investigator to be unanticipated and clinically significant.**Penn IRB Reporting:**

(1) Unanticipated problems including suspected adverse reactions and adverse reactions
- An event is considered a "suspected adverse reaction" when there is *reasonable possibility* that the drug/investigational product caused the adverse event. For these reporting purposes, *reasonable possibility* means there is evidence to suggest a causal relationship between the drug/investigational product and the event.
- An event is considered *probably or definitely related to the research procedures.*

(2) In addition to unanticipated problems, the IRB also requires prompt reporting of the following events:
- Complaint of a participant when the complaint indicates unexpected risks or the complaint cannot be resolved by the research team.

- Violation or deviation (meaning an accidental or unintentional change to the IRB approved protocol) only when: one or more participants were placed at increased risk of harm, or, the event has the potential to occur again, the event represents serious or continuing noncompliance.
- Breach of confidentiality.
- Incarceration of a participant when the research was not previously approved under Subpart C and the investigator believes it is in the best interest of the subject to remain on the study.

REPORTS MUST BE SUBMITTED ELECTRONICALLY at:
https:\\medley.isc-seo.upenn.edu\hsProtocol\jsp\fast.do

The IRB requires investigators to submit reports within 10 working days (with one exception) of events that meet the definition of an unanticipated problem involving risks to subjects or others. Exception: If the adverse event involved a death and indicates that participants or others are at increased risk of harm, investigators are required to submit a report to the IRB within 3 days.

Penn DSMC Reporting:

- All grade 3 or higher events (unless listed as exclusionary) within ten business days of knowledge
- All unexpected deaths within two business days of knowledge
- All others deaths within 30 days of knowledge. Deaths of subjects off-study for greater than 90 days from the last study treatment/intervention are not reportable

REPORTS MUST BE SUBMITTED ELECTRONICALLY VIA VELOS.

Events will be reported for 30 days following the last study intervention (i.e., last dose of pembrolizumab), or for the protocol defined follow-up if greater than 30 days after the last study intervention.

Penn Medical Monitor Reporting:

- All events reported to the Penn DSMC or non-serious Events of Clinical Interest reported to Merck Global safety will be reported within the same required timeframes as for the Penn DSMC and Merck reporting requirements, respectively. If there are conflicting timeframes, the shorter timeframe will be used.

- A summary of SAEs and therapy-limiting toxicities will be forwarded to the medical monitor for review after every 3 patients are enrolled and receive at least 4 doses of therapy or every 3 months, whichever occurs first.

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

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

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

7.3.1.1 Events of Clinical Interest

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

Events of clinical interest for this trial include:

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

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

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

1. Additional adverse events:

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

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

Subjects should be assessed for possible ECIs prior to each dose. Lab results should be evaluated and subjects should be asked for signs and symptoms suggestive of an immune-related event. Subjects who develop an ECI thought to be immune-related should have additional testing to rule out other etiologic causes. If lab results or symptoms indicate a possible immune-related ECI, then additional testing should be performed to rule out other etiologic causes. If no other cause is found, then it is assumed to be immune-related.

7.3.2 Evaluating Adverse Events

An investigator who is a qualified physician will evaluate all adverse events according to the NCI Common Terminology for Adverse Events (CTCAE), version 5.0. Any adverse event which changes CTCAE grade over the course of a given episode will have each change of grade recorded on the adverse event case report forms/worksheets.

If CTCAE grading does not exist for an adverse event, the severity of mild, moderate, severe, and life-threatening, corresponding to Grades 1-4, will be used. Subjects will be monitored by medical histories, physical examinations, and blood studies to detect potential toxicities from the treatment.

Table 6 Evaluating Adverse Events

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

V5.0 CTCAE Grading	**Grade 1**	**Mild; asymptomatic or mild 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 of hospitalization indicated; 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 pembrolizumab that:	
	†**Results in death**; or	
	†**Is life threatening; or** places the subject, in the view of the investigator, at immediate risk of death from the event as it occurred (Note: This does not include an adverse event that, had it occurred in a more severe form, might have caused death.); or	
	†**Results in a persistent or significant disability/incapacity** (substantial disruption of one's ability to conduct normal life functions); or	
	†**Results in or prolongs an existing inpatient hospitalization** (hospitalization is defined as an inpatient admission, regardless of length of stay, even if the hospitalization is a precautionary measure for continued observation. (Note: Hospitalization [including hospitalization for an elective procedure] for a preexisting condition which has not worsened does not constitute a serious adverse event.); or	
	†**Is a congenital anomaly/birth defect** (in offspring of subject taking the product regardless of time to diagnosis);or	

	Is a new **cancer;** (that is not a condition of the study) **or**	
	Is an overdose (whether accidental or intentional). Any adverse event associated with an overdose is considered a serious adverse event. An overdose that is not associated with an adverse event is considered a non-serious event of clinical interest and must be reported within 24 hours.	
	Other important medical events that may not result in death, not be life threatening, or not require hospitalization may be considered a serious adverse event when, based upon appropriate medical judgment, the event may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed previously (designated above by a †).	
Duration	Record the start and stop dates of the adverse event. If less than 1 day, indicate the appropriate length of time and units	
Action taken	Did the adverse event cause pembrolizumab to be discontinued?	
Relationship to test drug	Did pembrolizumab cause the adverse event? The determination of the likelihood that pembrolizumab 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 pembrolizumab and the AE**; the greater the correlation with the components and their respective elements (in number and/or intensity), the more likely pembrolizumab caused the adverse event (AE):	
	Exposure	Is there evidence that the subject was actually exposed to pembrolizumab 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 pembrolizumab? 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 Pembrolizumab (continued)	**The following components are to be used to assess the relationship between the test drug and the AE: (continued)**	
	Dechallenge	Was pembrolizumab 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 pembrolizumab; or (3) the trial is a single-dose drug trial); or (4) pembrolizumab is/are only used one time.)
	Rechallenge	Was the subject re-exposed to pembrolizumab 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) pembrolizumab is used only one time).

		NOTE: IF A RECHALLENGE IS PLANNED FOR AN ADVERSE EVENT WHICH WAS SERIOUS AND WHICH MAY HAVE BEEN CAUSED BY PEMBROLIZUMAB, OR IF REEXPOSURE TO PEMBROLIZUMAB POSES ADDITIONAL POTENTIAL SIGNIFICANT RISK TO THE SUBJECT, THEN THE RECHALLENGE MUST BE APPROVED IN ADVANCE BY THE U.S. CLINICAL MONITOR AS PER DOSE MODIFICATION GUIDELINES IN THE PROTOCOL.
	Consistency with Trial Treatment Profile	Is the clinical/pathological presentation of the AE consistent with previous knowledge regarding pembrolizumab or drug class pharmacology or toxicology?
The assessment of relationship will be reported on the case report forms /worksheets by an investigator who is a qualified physician according to his/her best clinical judgment, including consideration of the above elements.		
Record one of the following		**Use the following scale of criteria as guidance (not all criteria must be present to be indicative of a pembrolizumab relationship).**
Yes, there is a reasonable possibility of pembrolizumab relationship.		There is evidence of exposure to pembrolizumab. The temporal sequence of the AE onset relative to the administration of pembrolizumab is reasonable. The AE is more likely explained by pembrolizumab than by another cause.
No, there is not a reasonable possibility pembrolizumab relationship		Subject did not receive pembrolizumab OR temporal sequence of the AE onset relative to administration of pembrolizumab is not reasonable OR there is another obvious cause of the AE. (Also entered for a subject with overdose without an associated AE.)

7.3.3 Modification of CTC Grading scale for Cytokine Release Syndrome (CRS)

The CTCAE grading system was developed to capture a cytokine release syndrome occurring during infusional therapy and is inadequate to capture the delayed CRS that occurs after CART-19 infusions. We propose to modify the CTC grading specifically to capture toxicity for protocols using CART-19 cells (Table 7.2.5a). Related definitions can be found in **Table 7.2.5b**.

Recipients of CART-19 cells may develop a cytokine release syndrome. Data from small numbers of patients show marked elevations in IL6, IFN-g, and less intensely TNF among other cytokines. Elevations in clinically available markers of inflammation including ferritin and CRP have also been observed to correlate with the clinical CRS syndrome.

Symptoms usually occur 1-14 days after cell infusion, but the syndrome is not defined by the timing of the reaction. Patients developing any symptoms attributable by the investigator as related to cytokine release should be reported as having had a CRS. Symptoms may include:

- High fevers
- Rigors
- Sweating
- Nausea
- Vomiting
- Anorexia
- Fatigue
- Headache
- Myalgia/arthralgia
- Hypotension
- Dyspnea
- Tachypnea
- Hypoxia
- Altered mental status
- End organ dysfunction
- Signs of macrophage activation syndrome including hemophagocytosis and hemolysis

For the purposes of reporting and grading on clinical trials using CART-19 cells, we will use the following grading for CRS Toxicity. The start date of CRS is a retrospective assessment of the date of onset of persistent fevers and/or myalgia consistent with CRS and not explained by other events (i.e. sepsis). The stop date of CRS is defined as the date when the patient has been afebrile for 24 hours and off vasopressors for 24 hours.

Table 7.2.5a - CRS Toxicity Grading				
1	2	3	4	5
Mild reaction: Treated with supportive care such as anti-pyretics, anti-emetics	Moderate reaction requiring IV fluids or parenteral nutrition; some signs of organ dysfunction (i.e. grade 2 creatinine or grade 3 liver function tests ([LFTs] related to CRS and not attributable to any other condition). Hospitalization for management of CRS related symptoms including fevers with associated neutropenia.	More severe reaction: Hospitalization required for management of symptoms related to organ dysfunction including: • grade 4 LFTs • grade 3 creatinine related to CRS and not attributable to any other conditions • hypotension requiring multiple fluid boluses for blood pressure support or low-dose pressors (see Table 7.2.5b) • coagulopathy requiring fresh frozen plasma or cryoprecipitate • hypoxia requiring supplemental oxygen (nasal cannula oxygen, high flow oxygen, Continuous Positive Airway Pressure [CPAP] or Bilateral Positive Airway Pressure [BiPAP]) Patients admitted for management of suspected infection due to fevers and/or neutropenia may have grade 2	Life-threatening complications such as hypotension requiring high-dose pressors (see Table 7.2.5b) or hypoxia requiring mechanical ventilation	Death

Table 7.2.5a - CRS Toxicity Grading				
		CRS and this excludes management of fever or myalgias		

Table 7.2.5b High Dose Vasopressor Use

Definition of "High-Dose" Vasopressors	
Vasopressor	Dose for ≥ 3 hours
Norepinephrine monotherapy	≥ 20 mcg/kg/min
Dopamine monotherapy	≥ 10 mcg/kg/min
Phenylephrine monotherapy	≥ 200mcg/min
Epinephrine monotherapy	≥ 10 mcg/min
If on vasopressin	High-dose if vaso + Norepinephrine Equivalent (NE) of >10 mcg/min (using Vasopressin and Septic Shock Trial (VASST) formula)
If on combination vasopressors (not vasopressin)	Norepinephrine equivalent of ≥ 20 mcg/min (using VASST formula)

Vasopressin and Septic Shock Trial (VASST) Equivalent Equation:

Norepinephrine equivalent dose = [norepinephrine (mcg/min)] + [dopamine (mcg/kg/min) ÷ 2] + [epinephrine (mcg/min)] + [phenylephrine (mcg/min) ÷10]

7.3.4 Sponsor Responsibility for Reporting Adverse Events including Deviations and Exceptions

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

Reportable Events:
Any accidental or unintentional deviation from the approved protocol, identified retrospectively, that in the opinion of the investigator or as defined by the protocol, placed one or more participants at increased risk, compromises the rights or welfare of subjects, and/or disrupts the study design, is considered a reportable event and must be reported to the Study Principal Investigator, Study Medical Monitor, IRB, and ACC DSMC within 10 working days of notification. Principal Investigator and Medical Monitor approval/acknowledgement must be received first and included in with the IRB/DSMC submission. Deviations to protect subjects from immediate harm/danger should be reported immediately following the event to the entities outlined above.

Exceptions (Prospective action):
An exception is defined as a one-time, intentional action or process that departs from the IRB and CTSRMC approved study protocol, intended for one occurrence. If this action disrupts the study progress, such that the study design or outcome (endpoints) may be compromised, or the action compromises the safety and welfare of study subjects (i.e., requests to enroll and/or treat subjects outside of the current protocol criteria), **advance documentation of Medical Monitor, IRB, and DSMC approval is required**. Principal Investigator and Medical Monitor approval must be received first and included in with the IRB/DSMC submission. All entities should be given sufficient time to evaluate this request.

Deviations (Retrospective action):

A one time, **un**intentional action or process that departs from the IRB and CTSRMC approved study protocol, involving one incident and identified retrospectively, after the event occurred. If the impact on the protocol disrupts the study design, may affect the outcome (endpoints) or compromises the safety and welfare of the subjects, the deviation must be reported to the DSMC within 5 business days and the IRB within 10 business days.

For reportable deviations, documentation of the Medical Monitor response must be submitted to the DSMC **with** the report.

Deviations that do not meet the definition above of "reportable" will be explained in a memo to file or recorded on a deviation log and will contain documentation of the **PI's assessment** of the impact of the deviation on safety and study outcomes.

8.0 STATISTICAL ANALYSIS PLAN

8.1 Statistical Analysis Plan

8.1.1 Primary Objectives & Hypotheses

(1) Objective: To determine the safety of pembrolizumab in patients failing to respond to or relapsing after anti-CD19 chimeric antigen receptor modified T cell therapy for relapsed or refractory CD19+ lymphomas. Safety will be assessed by adverse event monitoring. Patients who have received at least one dose of pembrolizumab will be considered evaluable for safety. In this trial, success will be defined as receiving at least one dose of pembrolizumab and the lack at least possibly related adverse events leading to permanent discontinuation of pembrolizumab. Patients who experience Grade 3 or higher non-hematologic toxicity leading to permanent pembrolizumab discontinuation or any Grade 4 non-hematologic toxicity or cytokine release syndrome at least possibly related to pembrolizumab will be considered toxicity failures.

Methodology: We will use a Bayesian monitoring rule to assure that the failure rate is no greater than 30%. Monitoring will begin with the first patient. Because little information is available on the safety of this drug in lymphoma, we will assume a non-informative Beta(1, 1) prior distribution for the failure rate. We will denote the rate of pembrolizumab discontinuation as failure rate, FR, and will use the following monitoring rule in the interest of patient safety: we will stop the trial if at any time: Pr[FR > 0.30 | data from the trial] >= 97.5%

That is, if at any time during the study, we can conclude that there is at least a 97.5% chance that the failure rate is greater than 30%, we will stop the study. The stopping boundaries corresponding to this probability criterion are to terminate the trial if:

(# of patients that experience failure) / (# of patients evaluated) ≥ 3/3, 3/4, 4/5, 4/6, 5/7, 5/8, 6/9, 6/10, 7/11, 7/12. Any patient who has received at least one dose of pembrolizumab will be included in this denominator for evaluable patients if they have received at least 4 doses of pembrolizumab and not experienced toxicity OR if they have experienced any toxicity with any dose of pembrolizumab.

If the study is not terminated early, it will continue until all patients have been treated with pembrolizumab and completed all follow up evaluations.

Hypothesis: Pembrolizumab will be safely tolerated with ≤ 30% of patients experiencing toxicities resulting in discontinuation of pembrolizumab

8.1.2 Secondary Objectives & Hypotheses

Any patient who receives at least one dose of pembrolizumab will be included in efficacy analyses.

(1) Objective: To describe the overall response rate (ORR) to pembrolizumab in patients failing to respond to or relapsing after anti-CD19 chimeric antigen receptor modified T cell therapy for relapsed or refractory CD19+ lymphomas.

Methodology: For efficacy, a sample size of 12 patients achieves an 80% power to detect a difference (P1 0.35 – P0 0.05) of 0.30 using a one-sided binomial test for ORR. The target of significance level is 0.05. This response rate prediction of 35% is based on the reported 28% response rate reported for nivolumab, another anti-PD1 blocking antibody, in patients with B cell lymphoma. This also assumes that a 5% response rate would be seen if pembrolizumab does not have efficacy in this population. If the response rate is 3 or more, the hypothesis that the ORR is ≤ 0.05 is rejected. If the number of responses is 2 or less, the hypothesis that ORR is ≥ 0.35.

Hypothesis: The response rate after pembrolizumab will be 3 or more, allowing us to reject the null hypothesis that pembrolizumab after CTL019/CTL119 has an ORR ≤ 0.05

(2) Objective: To describe the clinical efficacy of pembrolizumab, including progression-free survival, disease-free survival, event-free survival, response duration, and overall survival (Cheson, 2007) in patients failing to respond to or relapsing after anti-CD19 chimeric antigen receptor modified T cell therapy for relapsed or refractory CD19+ lymphomas. Efficacy comparisons will be made with both most recent prior therapy as well as with CTL019/CTL119.

Methodology: Kaplan Meier survival analysis will be used to estimate progression-free survival, event-free survival, response duration, and overall survival. For patients with initial responses to both CTL 019 and pembrolizumab, progression-free survival, event-free survival, and response duration, patients' response to CTL 019 therapy will be compared to their response to pembrolizumab using the log-rank test, with $p \leq 0.05$ considered statistically significant.

Hypothesis: Pembrolizumab will enhance the efficacy of CTL019/CTL119 in patients failing to respond to or relapsing after chimeric antigen receptor modified T cell therapy for relapsed or refractory CD19+ lymphomas.

8.1.3 Exploratory Objectives

(1) Objective: To describe the immunophenotypic and cytokine profiles of chimeric antigen receptor modified T cells in these patients before and after therapy with pembrolizumab

Hypothesis: Immunophenotypic profiles of tumor cells and chimeric antigen receptor modified T cells obtained pre and post pembrolizumab therapy will identify patients for whom pembrolizumab will enhance efficacy.

(2) Objective: For immunologic correlative studies, within subject comparisons of baseline to post pembrolizumab measures will be conducted. These analyses will be descriptive and considered exploratory; thus, power will not be considered for these paired comparisons.

9.0 LABELING, PACKAGING, STORAGE AND RETURN OF CLINICAL SUPPLIES

9.1 Investigational Product

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

Clinical Supplies will be provided by Merck as summarized in Table 7.

Table 7 Product Descriptions

Product Name & Potency	Dosage Form
Pembrolizumab 50 mg	Lyophilized Powder for Injection
Pembrolizumab 100 mg/ 4mL	Solution for Injection

9.2 Packaging and Labeling Information

Clinical supplies will be affixed with a clinical label in accordance with regulatory requirements.

9.3 Clinical Supplies Disclosure

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

9.4 Storage and Handling Requirements

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

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

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

9.5 Returns and Reconciliation

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

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

10.0 ADMINISTRATIVE AND REGULATORY DETAILS

10.1 Confidentiality

Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Those regulations require a signed subject authorization informing the subject of the following:

- What protected health information (PHI) will be collected from subjects in this study
- Who will have access to that information and why
- Who will use or disclose that information

- The rights of a research subject to revoke their authorization for use of their PHI.

In the event that a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For subjects that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (i.e. that the subject is alive) at the end of their scheduled study period.

10.2 Compliance with Law and Audits

The investigator will permit study-related monitoring, audits, and inspections by the EC/IRB, the supporter, government regulatory bodies, and University compliance and quality assurance groups of all study related documents (e.g. source documents, regulatory documents, data collection instruments, study data etc.). The investigator will ensure the capability for inspections of applicable study-related facilities (e.g. pharmacy, diagnostic laboratory, etc.).

Participation as an investigator in this study implies acceptance of potential inspection by government regulatory authorities and applicable University compliance and quality assurance offices.

10.3 Compliance with Trial Registration and Results Posting Requirements

Under the terms of the Food and Drug Administration Modernization Act (FDAMA) and the Food and Drug Administration Amendments Act (FDAAA), the Sponsor of the trial is solely responsible for determining whether the trial and its results are subject to the requirements for submission to the Clinical Trials Data Bank, http://www.clinicaltrials.gov. Information posted will allow subjects to identify potentially appropriate trials for their disease conditions and pursue participation by calling a central contact number for further information on appropriate trial locations and trial site contact information.

10.4 Quality and Safety Management

It is the responsibility of the Principal Investigator to oversee the safety of the study at his/her site. This safety monitoring will include careful assessment and appropriate reporting of adverse events as noted above, as well as the construction and implementation of a site data and safety-monitoring plan. This will include a regular assessment of the number and type of serious adverse events.

The investigator will permit study-related monitoring, audits, and inspections by the DSMC, IRB, government regulatory bodies, and University compliance and quality assurance groups of all study related documents (e.g. source documents, regulatory documents, data collection

instruments, study data etc.). The investigator will ensure the capability for inspections of applicable study-related facilities (e.g. pharmacy, diagnostic laboratory, etc.).

Interim analyses of toxicity are to be performed quarterly or every three patients on-study. The Abramson Cancer Center Data and Safety Monitoring Committee will conduct in-house safety audits as per their guidelines.

During the course of the trial, safety and data quality monitoring will be performed in an on-going manner by the Principal Investigator. The principal investigator will monitor data integrity. This includes ensuring that all source documents exist for the data on the case report forms, ensuring that all fields are competed appropriately, all corrections are done according to GCPs and any inconsistencies / deviations are documented. The Principal Investigator will also review all Adverse Event forms in "real-time" to ensure appropriateness of the data and timeliness of reporting.

The Medical monitor for this study will be Alfred L. Garfall, M.D., who is not directly involved in the trial and is not collaborating with the sponsor or study supported in any other trial. In this role, the medical monitor will review all AEs including grading, toxicity assignments, all other safety data and activity data. The medical monitor may recommend reporting of adverse events and relevant safety data not previously reported and may recommend suspension or termination of the trial. The Medical Monitor will be asked to review study data at least quarterly (every 3 months) or more frequently depending on enrollment.

10.5 Ethical Considerations

The protocol for this study has been designed in accordance with the general ethical principles outlined in the Declaration of Helsinki. This study is to be conducted according to US and international standards of Good Clinical Practice (FDA Title 21 part 312 and International Conference on Harmonization guidelines), applicable government regulations and Institutional research policies and procedures.

All subjects for this study will be provided a consent form describing this study and providing sufficient information for subjects to make an informed decision about their participation in this study. See Appendix I for a copy of the Subject Informed Consent Form. This consent form will be submitted with the protocol for review and approval by the EC/IRB for the study. The formal consent of a subject, using the EC/IRB-approved consent form, must be obtained before that subject is submitted to any study procedure. This consent form must be signed by the subject or legally acceptable surrogate, and the investigator-designated research professional obtaining the consent. Documentation of the informed consent process should be

recorded in the subject's source documents. The original consent form signed and dated by the subject and by the person consenting the subject prior to the subject's entry into the study, must be maintained in the Investigator's study files.

10.6 Conflict of Interest

Any investigator who has a conflict of interest with this study (patent ownership, royalties, or financial gain greater than the minimum allowable by their institution, etc.) must have the conflict reviewed by a properly constituted Conflict of Interest Committee with a Committee-sanctioned conflict management plan that has been reviewed and approved by the study supporter prior to participation in this study. All University of Pennsylvania investigators will follow the University conflict of interest policy.

10.7 Records Retention

It is the investigator's responsibility to retain study essential documents for at least 2 years after the last approval of a marketing application in their country and until there are no pending or contemplated marketing applications in their country or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period if required by an agreement. In such an instance, it is the responsibility of the sponsor to inform the institution as to when these documents no longer need to be retained. The Investigator agrees to adhere to the document/records retention procedures by signing the protocol.

11.0 REFERENCES

Cheson, B. P. (2007). Revised response criteria for malignant lymphoma. *Journal of Clinical Oncology, 25*, 579-586.

Garon, E., Rizvi, N., Hui, R., Leighl, N., Balmanoukian, A., & al, e. (2015). Pembrolizumab for the treatment of non-small cell lung cancer. *New England Journal of Medicine*, 1-11.

Grupp, S. K. (2013). Chimeric antigen receptor-modified T cells for acute lymphoid leukemia. *New England Journal of Medicine, 368*(16), 1509-1518.

Hamid, O., Robert, C., Daud, A., Hodi, S., Hwu, W., & al, e. (2013). Safety and tumor responses with lambrolizumab (anti-PD-1) in melanoma. *New England Journal of Medicine, 369*(2), 134-144.

John, L. D. (2013). Anti-PD-1 antibody therapy potently enhances the eradication of established tumors by gene-modified T cells. *Clinical Cancer Research, 19*(20), 5636-5646.

Lesokhin, A., Ansell, S., Armand, P., Scott, E., Halwani, A., & al, e. (2014). Preliminary Results of a Phase I Study of Nivolumab (BMS-936558) in Patients with Relapsed or Refractory Lymphoid Malignancies. *Blood, 124*(21), Abstract #291.

Maude, S. F. (2014). Chimeric antigen receptor T cells for sustained remissions in leukemia. *New England Journal of Medicine, 371*(16), 1507-1517.

Porter, D. L. (2011). Chimeric antigen receptor-modified T cells in chronic lymphocytic leukemia. *New England Journal of Medicine, 365*(8), 725-733.

12.0 APPENDICES

12.1 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.	

12.2 Common Terminology Criteria for Adverse Events V5.0 (CTCAE)

The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for adverse event reporting. (http://ctep.cancer.gov/reporting/ctc.html)

12.3 Response Evaluation Criteria

The Revised Response Criteria for Malignant Lymphoma will be utilized for response assessment in this study (Cheson, 2007).

12.4 Events of Clinical Interest Guidance Document

Events of Clinical Interest (ECI) Guidance Document Version 5 will guide pembrolizumab administration, discontinuation, and specific event reporting. Please refer to attached document.