TITLE: A phase II study of anti-PD-1 antibody (MK-3475; pembrolizumab) for the treatment of minimal residual disease in adults with acute lymphoblastic leukemia

Sponsor-Investigator:
Ryan Cassaday, MD
Assistant Professor, Department of Medicine, University of Washington School of Medicine
Assistant Member, Clinical Research Division, Fred Hutchinson Cancer Research Center
Phone: (206)606-1202
E-mail: cassaday@uw.edu

TABLE OF CONTENTS

1.0 TRIAL SUMMARY

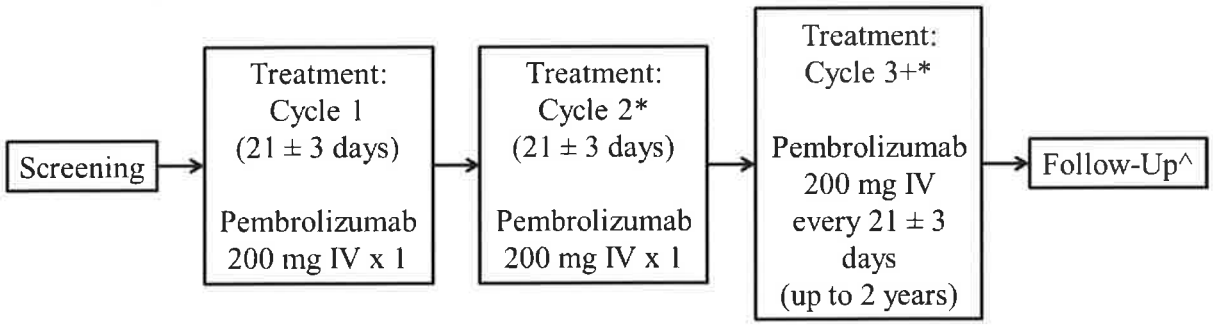
Abbreviated Title	Pembrolizumab for MRD in Adults with ALL
Trial Phase	II
Clinical Indication	Acute lymphoblastic leukemia/lymphoma
Trial Type	Single-arm, non-randomized
Type of control	None
Route of administration	Intravenous
Trial Blinding	None
Treatment Groups	1
Number of trial subjects	21
Estimated enrollment period	6/1/2016 – 10/1/2018
Estimated duration of trial	3 years
Duration of Participation	Up to 2 years

2.0 TRIAL DESIGN

2.1 Trial Design

This is a single-institution, non-randomized, prospective, phase II trial of pembrolizumab (MK-3475) in adult patients with acute lymphoblastic leukemia (ALL) with minimal residual disease (MRD), as defined by a bone marrow examination consistent with morphologic complete remission (i.e., less than 5% blasts) and no clinically-apparent extramedullary disease but quantifiable molecular or immunophenotypic evidence of disease by either polymerase chain reaction (PCR) or multiparameter flow cytometry (MFC), respectively.

2.2 Trial Diagram



* Subsequent cycles will be administered in the absence of morphologic relapse/progression or development of extramedullary disease (as defined in Section 7.1.2.6) or transition to alternative therapy at the discretion of the patient and treating investigator.
^. Long-term follow-up will occur for up to 2 years after completion of treatment or until relapse to determine duration of complete MRD response and overall survival.

3.0 OBJECTIVES & HYPOTHESES

3.1 Primary Objective & Hypothesis

(1) **Objective:** To evaluate the efficacy of pembrolizumab in MRD-positive ALL.

Hypothesis: Pembrolizumab will yield a complete MRD response rate of $\geq$ 50%.

3.2 Secondary Objectives & Hypotheses

(1) **Objective**: To describe the toxicity profile of pembrolizumab in patients with previously-treated ALL.

Hypothesis: Pembrolizumab will be safe and well-tolerated in this patient population.

(2) **Objective:** To gain a preliminary assessment of how MRD response translates into relapse-free and overall survival.

Hypothesis: Patients that experience a complete MRD response will have longer morphologic relapse-free and overall survival than those who do not.

3.3 Exploratory Objectives

(1) **Objective:** To compare disease assessments by MFC and PCR to a newly-developed and more sensitive next generation sequencing (NGS)-based platform.

Hypothesis: NGS will be able to detect MRD in a subset of patients that appear to have complete MRD response by MFC and/or PCR, and subsequent relapse will occur more frequently in these patients.

(2) **Objective:** To correlate response to pembrolizumab to immunologic markers in peripheral blood and bone marrow specimens.

Hypotheses: Patterns of changes in peripheral blood mononuclear cells (PBMC) and circulating cytokines will emerge as predictors of an immunologic response and anti-leukemia efficacy.

(3) **Objective:** To evaluate if treatment with pembrolizumab has a measurable impact on hematopoietic engraftment and graft-vs-host disease (GVHD) in patients who subsequently undergo allogeneic hematopoietic cell transplantation (HCT).

Hypothesis: Prior treatment with pembrolizumab will not increase the risk of graft rejection or acute GVHD (compared to historical data) in those patients that subsequently undergo HCT.

4.0 BACKGROUND & RATIONALE

4.1 Background

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

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

(MEL). This suggests that the PD-1/PD-L1 pathway plays a critical role in tumor immune evasion and should be considered as an attractive target for therapeutic intervention.

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

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

ALL is among the most common forms of cancer in children, and in this circumstance it is highly curable. However, treatment of ALL in adults is very challenging, and outcomes with standard approaches remain unsatisfactory. Apart from the use of ABL kinase inhibitors for patients with the Philadelphia chromosome (t[9;22], abbreviated Ph+), the treatment still relies primarily upon remission induction with intensive multiagent cytotoxic chemotherapy. This is a particular challenge in older adults diagnosed with ALL, as these regimens are (in general) prohibitively toxic for these patients.[1] Therefore, improvements in the treatment of ALL in adults are critically needed.

The importance of MRD in ALL is firmly established.[2] MRD is typically assessed by two different techniques: multiparameter flow cytometry (MFC) to detect the unique abnormal immunophenotype of the leukemic blasts, or polymerase chain reaction (PCR) for clonal DNA alterations (including immunoglobulin or T-cell receptor gene rearrangements or oncogenic chromosomal rearrangements like BCR-ABL). It is understood that the presence of MRD (either as persistence during therapy or reappearance afterward) confers a poor prognosis, as it almost inevitably heralds frank hematologic relapse without additional intervention.[3,4] Our center's experience also demonstrates the risk associated with MRD in the context of HCT. Its presence is associated with a significantly higher risk of relapse when detected before or after myeloablative HCT.[5] Qualitatively comparable results have been observed from patients undergoing nonmyeloablative conditioning, which may be the only option for HCT in older or medically-infirm patients (G. Georges, personal communication). Unfortunately, for those that have MRD, little is known about the optimal management of this high-risk scenario. However, it stands to reason that elimination of MRD could significantly improve their outcome.

4.2.2 Rationale for Dose Selection/Regimen/Modification

An open-label Phase I trial (Protocol 001) is being conducted to evaluate the safety and clinical activity of single agent MK-3475. The dose escalation portion of PN001 evaluated three dose levels, 1 mg/kg, 3 mg/kg, and 10 mg/kg, administered every 2 weeks (Q2W) in subjects with advanced solid tumors. All three dose levels were well tolerated and no dose-limiting toxicities were observed. This first in human study of MK-3475 showed evidence of target engagement

and objective evidence of tumor size reduction at all dose levels (1 mg/kg, 3 mg/kg and 10 mg/kg Q2W). No MTD has been identified to date. 10.0 mg/kg Q2W, the highest dose tested in PN001, will be the dose and schedule utilized in Cohorts A, B, C and D of PN001 to test for initial tumor activity. Recent data from other clinical studies within the MK-3475 program has shown that a lower dose of MK-3475 and a less frequent schedule may be sufficient for target engagement and clinical activity.

PK data analysis of MK-3475 administered Q2W and Q3W showed slow systemic clearance, limited volume of distribution, and a long half-life (refer to IB). Pharmacodynamic data (IL-2 release assay) suggested that peripheral target engagement is durable (>21 days). This early PK and pharmacodynamic data provides scientific rationale for testing a Q2W and Q3W dosing schedule.

A population pharmacokinetic analysis has been performed using serum concentration time data from 476 patients. Within the resulting population PK model, clearance and volume parameters of MK-3475 were found to be dependent on body weight. The relationship between clearance and body weight, with an allometric exponent of 0.59, is within the range observed for other antibodies and would support both body weight normalized dosing or a fixed dose across all body weights. MK-3475 has been found to have a wide therapeutic range based on the melanoma indication. The differences in exposure for a 200 mg fixed dose regimen relative to a 2 mg/kg Q3W body weight based regimen are anticipated to remain well within the established exposure margins of 0.5 – 5.0 for MK-3475 in the melanoma indication. The exposure margins are based on the notion of similar efficacy and safety in melanoma at 10 mg/kg Q3W vs. the proposed dose regimen of 2 mg/kg Q3W (i.e. 5-fold higher dose and exposure). The population PK evaluation revealed that there was no significant impact of tumor burden on exposure. In addition, exposure was similar between the NSCLC and melanoma indications. Therefore, there are no anticipated changes in exposure between different indication settings.

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

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

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

4.2.3 Rationale for Endpoints

4.2.3.1 Efficacy Endpoints

Immunotherapy is a particularly attractive approach to the problem of MRD persistence/reappearance: the disease burden by definition is very low; and when MRD is detected following multiple cytotoxic agents, additional cytotoxic therapy is unlikely to provide substantial efficacy but could lead to significant toxicity. Proof of this principle has been demonstrated with blinatumomab, a CD3-CD19 bispecific antibody that helps target the patient's endogenous CD3+ T cells to the CD19+ blasts in B-cell precursor ALL. Early in its development, this agent was shown to be efficacious against chemorefractory MRD in adults with ALL, with 16 of 20 patients remaining in hematologic remission at a median follow-up of 405 days (relapse-free survival of 78%).[6] Similar results were observed in a larger study from the German Multicenter ALL Study Group.[7] It is now being tested in a randomized Phase III study (ClinicalTrials.gov #NCT02013167), and it was granted accelerated approval by the Food and Drug Administration in December 2014. Unfortunately, blinatumomab must be administered as a 28-day continuous intravenous (IV) infusion, making it very inconvenient for the patient and the clinical staff. Furthermore, it is associated with significant toxicity, including serious neurologic side-effects and cytokine release syndrome. While it can be highly efficacious in this setting, blinatumomab is not universally effective. Further, due to its toxicity profile and need for 4-week continuous infusion (a portion of which must be administered in an inpatient setting), patients may not be eligible or willing to receive it. Immune checkpoint blockade through inhibition of the PD-1/PD-L1 axis could provide a similar benefit for a very high-risk clinical scenario with relatively low toxicity, a significantly easier mode of administration, and inclusion of both T- and B-cell ALL.

Thus, based on the ability of immunotherapy to eliminate MRD, the belief that this endpoint will translate into improved long-term outcomes in ALL, as well as a strong need for new treatments for this challenging disease, we will study pembrolizumab for the treatment of MRD in adults with ALL. This trial will offer an option to reduce the risk of frank relapse following either front-line or salvage therapy. Should this approach prove efficacious, it could create a novel method of treatment, in addition to providing a platform from which this agent could be tested either as a single-agent or in combination with other treatments as consolidation for patients in complete remission or for those with frankly relapsed/refractory ALL.

4.2.3.2 Biomarker Research

ALL is relatively unique in that frequent disease assessments are common, relatively safe and non-invasive, and involve direct evaluation of the leukemia microenvironment (i.e., bone marrow). This provides an attractive opportunity to explore changes in the cellular and immunologic composition of tumor microenvironment before and after treatment with pembrolizumab. For example, since it has been demonstrated previously that PD-1 and PD-L1 expression on tumor cells and the tumor microenvironment is associated with a higher likelihood of response to inhibition of the PD-1/PD-L1 axis,[8-10] we will be able to specifically evaluate the tumor microenvironment over time via bone marrow specimens. By definition, samples from patients on this study will have very little leukemia present, such that these analyses will be primarily reflective of the tumor microenvironment and not the malignancy *per se*.

Further, to evaluate the systemic immune response more broadly, we can study changes in circulating PBMC and serum cytokines and inflammatory markers that occur following exposure to pembrolizumab to draw correlations to disease response (or lack thereof). Using a flow cytometry platform available in the UW Hematopathology Laboratory, relative proportions of circulating T-cell subsets and other components of cellular immunity can be quantified and compared pre- and post-treatment with pembrolizumab. Additionally, the Immune Monitoring Laboratory (IML) at the Fred Hutchinson Cancer Research Center (FHCRC) can measure the levels of approximately 40 different cytokines from samples of peripheral blood. Such analyses may provide evidence of an on-target *in vivo* effect in responding patients. They can also advance our understanding of why some patients respond to these agents while others seemingly do not, a phenomenon which has been suggested previously.[11]

Lastly, while MFC and PCR remain the most widely-utilized methods of MRD detection in ALL, more sensitive methods are being developed. NGS platforms have been developed that can amplify and identify disease-specific index sequence from either the immunoglobulin heavy chain (IGH) or T-cell receptor (TCR) genes that are unique to individual B-cell and T-cell ALL (respectively).[12,13] This technique can detect MRD with a frequency below 10^{-5}, which is generally $\geq$ 2 orders of magnitude more sensitive than most clinically-available assays currently. Early studies suggest that detection even to this low level can impact outcomes in ALL.[14,15] As this clinical trial is designed specifically for patients with MRD, it will provide a unique opportunity to further evaluate NGS as a viable method of MRD detection in ALL.

5.0 METHODOLOGY

5.1 Entry Criteria

5.1.1 Diagnosis/Condition for Entry into the Trial

All subjects must have a diagnosis of ALL of either B-cell, T-cell, or mixed (i.e., B/T) lineage.

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 for the trial.
2. Be $\geq$ 18 years of age on day of signing informed consent.
3. Presence of MRD (defined as < 5% blasts in the bone marrow by morphologic assessment and no clinically-apparent extramedullary disease but with quantifiably-measurable disease as assessed by either MFC or PCR) under any of the following circumstances:
    a. MRD persistence $\geq$ 11 weeks after the start of initial therapy,
    b. MRD persistence $\geq$ 2 weeks after the start of salvage therapy, or
    c. MRD reappearance at any time.

4. For patients with Ph+ disease, have previously received treatment with ≥ 1 ABL kinase inhibitor (e.g., imatinib, dasatinib, etc.) or are ineligible for such treatment.

5. Have previously received or are ineligible for treatment with blinatumomab. Ineligibility will include (but not be limited to) CD19-negative disease, denial of insurance coverage, physician discretion, and/or patient refusal.

6. Be willing to provide tissue from a newly obtained bone marrow aspirate and/or biopsy. Newly-obtained is defined as a specimen obtained up 28 days prior to initiation of treatment on Day 1. Subjects for whom newly-obtained samples cannot be provided (e.g., inaccessible or subject safety concern) may submit an archived specimen only upon agreement from the PI.

7. Have a performance status of 0 to 1 on the ECOG Performance Scale.

8. Demonstrate adequate organ function as defined in Table 1, all screening labs should be performed within 10 days of treatment initiation.

Table 1: Adequate Organ Function Laboratory Values

System	Laboratory Value
Hematological	
Absolute neutrophil count (ANC)	≥1,000 /mcL
Hemoglobin	≥8 g/dL
Platelets	≥50,000 / mcL
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/1.73 m^2 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
Coagulation	
International Normalized Ratio (INR) or Prothrombin Time (PT)	≤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
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
[a]Creatinine clearance or glomerular filtration rate (GFR) should be calculated per the MDRD equation: GFR (mL/min/1.73 m^2) = 175 × $(S_{cr})^{-1.154}$ × $(Age)^{-0.203}$ × (0.742 if female) × (1.212 if African American)	

9. Female subjects of childbearing potential should have a negative urine or serum pregnancy within 3 days 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. (For this protocol, childbearing potential is defined in section 5.7.2.)

10. 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 Section 5.7.2).

11. Male subjects should agree to use an adequate method of contraception (as defined in section 5.7.2) 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 new drug and received study therapy or used an investigational device within 4 weeks of the first dose of treatment.

2. Has a diagnosis of immunodeficiency or is receiving systemic steroid therapy or any other form of immunosuppressive therapy within 7 days prior to the first dose of trial treatment.

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

4. Has a known hypersensitivity to pembrolizumab or any of its excipients.

5. 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.

6. 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 or with hematologic toxicity that has recovered to levels above that stated in Inclusion Criterion 6 are an exception to this criterion and may qualify for the study if all other inclusion/exclusion criteria are met.

    - Note: If subject received major surgery, they must have recovered adequately from the toxicity and/or complications from the intervention (i.e., ≤ Grade 1 or at baseline) prior to starting therapy.

7. 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.

8. Has known active central nervous system (CNS) leukemia and/or leukemic meningitis. Subjects with previously treated CNS leukemia may participate provided they are stable (e.g., without evidence of active disease by imaging for at least four weeks prior to the first

dose of trial treatment and any neurologic symptoms have returned to baseline) and have no evidence of leukemic blasts on analysis of cerebrospinal fluid (CSF).

9. Has active autoimmune disease that has required systemic treatment in the past 2 years (i.e. with 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.

10. Has known history of, or any evidence of active, non-infectious pneumonitis.

11. Has previously received an allogeneic hematopoietic cell transplant, unless the following criteria are met:

    - Detection of MRD occurred ≥ 21 days from stem cell infusion
    - No active GVHD
    - Receiving systemic steroid therapy of ≤ 10 mg of prednisone daily (or equivalent)
    - Has discontinued systemic immunosuppressant therapy ≥ 7 days prior to first dose of pembrolizumab

12. Has previously received other forms of cellular immunotherapy (e.g., chimeric antigen receptor-modified [CAR] T cells), unless the following criteria are met:

    -Detection of MRD occurred ≥ 21 days from cell infusion

    -Any specific manifestations of cytokine release syndrome or neurologic toxicity attributable to the cellular therapy have completely resolved (i.e., < Grade 1)

13. Has an active infection requiring systemic therapy. Antimicrobial prophylaxis will be permitted at the discretion of the treating investigator.

14. 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.

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

16. Is pregnant or breastfeeding, or expecting to conceive or father children within the projected duration of the trial, starting from the time of consent through 120 days after the last dose of trial treatment.

17. Has received prior therapy with any immune checkpoint inhibitor.

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

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

20. 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: Trial Treatment

Drug	Dose/Potency	Dose Frequency	Route of Administration	Regimen/Treatment Period	Use
Pembrolizumab	200 mg	Q 21±3 days	IV infusion	Day 1 of each 21-day cycle	Experimental

Trial treatment should begin within 28 days of signed informed consent.

5.2.1 Dose Selection/Modification

5.2.1.1 Dose Selection

The rationale for selection of doses to be used in this trial is provided in Section 4.0 – Background and Rationale.

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

5.2.1.2 Dose Modification

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

Table 3: Dose Modification Guidelines for Drug-Related Adverse Events

General instructions:

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

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). • Participants with ≥ Grade 2 diarrhea suspecting colitis should consider GI consultation and performing endoscopy to rule out colitis. • Participants with diarrhea/colitis should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion.
	Grade 4	Permanently discontinue		
AST / ALT elevation or Increased bilirubin	Grade 2	Withhold	• Administer corticosteroids (initial dose of 0.5- 1 mg/kg prednisone or equivalent) followed by taper	• Monitor with liver function tests (consider weekly or more frequently until liver enzyme value returned to baseline or is stable
	Grade 3 or 4	Permanently discontinue	• Administer corticosteroids (initial dose of 1-2 mg/kg	

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

	Grade 4 or recurrent Grade 3	Permanently discontinue		

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

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

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 Merck. 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 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 21 ± 3 days. Every effort should be made to target infusion timing to be as close to 30 minutes as possible. However, given the variability of infusion pumps, a window of -5 minutes and +10 minutes is permitted (i.e., infusion time is 30 minutes: -5 min/+10 min).

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

5.2.3 Trial Blinding/Masking

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

5.3 Randomization or Treatment Allocation

There will not be any randomization. All subjects will receive the same treatment.

5.4 Stratification

There will not be any formal stratification.

5.5 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 may be required. The investigator should discuss any questions regarding this with the Merck Clinical team. The final decision on any supportive therapy or vaccination rests with the investigator and/or the subject's primary physician.

5.5.1 Acceptable Concomitant Medications

All treatments that the investigator considers necessary for a subject's welfare may be administered at the discretion of the investigator in keeping with the community standards of medical care. All concomitant medication will be recorded on the 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 events of clinical interest (ECIs) as defined in Section 7.2.

5.5.2 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
- 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 approved after consultation with the PI.

Subjects who enroll in the context of persistent MRD following prior treatment will not be allowed to continue this prior treatment. 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.

5.6 Rescue Medications & Supportive Care

5.6.1 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. 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 relapsed 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 policies but does not need to follow the treatment guidance . Refer to Section 5.2.1 for dose modification.

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

- **Pneumonitis**:
  - For **Grade 2 events**, treat with systemic corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.
  - For **Grade 3-4 events**, immediately treat with intravenous steroids. Administer additional anti-inflammatory measures, as needed.
  - Add prophylactic antibiotics for opportunistic infections in the case of prolonged steroid administration.

- **Diarrhea/Colitis**:
  Subjects should be carefully monitored for signs and symptoms of enterocolitis (such as diarrhea, abdominal pain, blood or mucus in stool, with or without fever) and of bowel perforation (such as peritoneal signs and ileus).

  - All subjects who experience diarrhea/colitis should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion. For Grade 2 or higher diarrhea, consider GI consultation and endoscopy to confirm or rule out colitis.

- For **Grade 2 diarrhea/colitis** that persists greater than 3 days, administer oral corticosteroids.
- For **Grade 3 or 4 diarrhea/colitis** that persists > 1 week, treat with intravenous steroids followed by high dose oral steroids.
- When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.

- **Type 1 diabetes mellitus (if new onset, including diabetic ketoacidosis [DKA]) or ≥ Grade 3 Hyperglycemia, if associated with ketosis (ketonuria) or metabolic acidosis (DKA)**

  - For **T1DM** or **Grade 3-4** Hyperglycemia
    - Insulin replacement therapy is recommended for Type I diabetes mellitus and for Grade 3-4 hyperglycemia associated with metabolic acidosis or ketonuria.
    - Evaluate patients with serum glucose and a metabolic panel, urine ketones, glycosylated hemoglobin, and C-peptide.

- **Hypophysitis**:

  - For **Grade 2** events, treat with corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. Replacement of appropriate hormones may be required as the steroid dose is tapered.
  - For **Grade 3-4** events, treat with an initial dose of IV corticosteroids followed by oral corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. Replacement of appropriate hormones may be required as the steroid dose is tapered.

- **Hyperthyroidism or Hypothyroidism**:
  Thyroid disorders can occur at any time during treatment. Monitor patients for changes in thyroid function (at the start of treatment, periodically during treatment, and as indicated based on clinical evaluation) and for clinical signs and symptoms of thyroid disorders.

  - **Grade 2** hyperthyroidism events (and **Grade 2-4** hypothyroidism):
    - In hyperthyroidism, non-selective beta-blockers (e.g. propranolol) are suggested as initial therapy.
    - In hypothyroidism, thyroid hormone replacement therapy, with levothyroxine or liothyroinine, is indicated per standard of care.
  - **Grade 3-4** hyperthyroidism
    - Treat with an initial dose of IV corticosteroid followed by oral corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. Replacement of appropriate hormones may be required as the steroid dose is tapered.

- **Hepatic**:
  - For **Grade 2** events, monitor liver function tests more frequently until returned to baseline values (consider weekly).
    - Treat with IV or oral corticosteroids
  - For **Grade 3-4** events, treat with intravenous corticosteroids for 24 to 48 hours.
  - When symptoms improve to Grade 1 or less, a steroid taper should be started and continued over no less than 4 weeks.

- **Renal Failure or Nephritis**:
  - For **Grade 2** events, treat with corticosteroids.
  - For **Grade 3-4** events, treat with systemic corticosteroids.
  - When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.

- **Management of Complications Unique to HCT or Cellular Immunotherapy:** A potential risk of administering pembrolizumab to patients who have previously received HCT or other cellular immunotherapy modalities like CAR-T cells is a recrudescence of toxicities that are germane to these specific therapies, including GVHD, cytokine release syndrome (CRS), and neurologic toxicity. The manifestations of such events (e.g., diarrhea, pneumonitis, rash, hepatitis, etc.) are included in the specific guidelines above. As needed and on a case-by-case basis, best local practices and additional expert consultation can also be instituted as needed for management of these toxicities, should they develop. Recording and reporting of these adverse events will follow the same guidelines as those set out elsewhere in the protocol (Section 7.2).

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

  Minor deviations from these guidelines will be permitted, at the discretion of the treating investigator.

  Table 4 below shows treatment guidelines for subjects who experience an infusion reaction associated with administration of pembrolizumab (MK-3475). Minor deviations from these guidelines will be permitted, at the discretion of the treating investigator.

Table 4 Infusion Reaction Treatment Guidelines

NCI CTCAE Grade	Treatment	Premedication at subsequent dosing
Grade 1 Mild reaction; infusion interruption not indicated; intervention not indicated	Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator.	None

NCI CTCAE Grade	Treatment	Premedication at subsequent dosing
Grade 2 Requires therapy or infusion interruption but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDS, narcotics, IV fluids); prophylactic medications indicated for < =24 hrs	**Stop Infusion and monitor symptoms.** Additional appropriate medical therapy may include but is not limited to: IV fluids Antihistamines NSAIDS Acetaminophen Narcotics Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator. If symptoms resolve within one hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (e.g., from 100 mL/hr to 50 mL/hr). Otherwise dosing will be held until symptoms resolve and the subject should be premedicated for the next scheduled dose. **Subjects who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further trial treatment administration.**	Subject may be premedicated 1.5h (± 30 minutes) prior to infusion of pembrolizumab (MK-3475) with: Diphenhydramine 50 mg po (or equivalent dose of antihistamine). Acetaminophen 500-1000 mg po (or equivalent dose of antipyretic).
Grades 3 or 4 Grade 3: Prolonged (i.e., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (e.g., renal impairment, pulmonary infiltrates) Grade 4: Life-threatening; pressor or ventilatory support indicated	**Stop Infusion.** Additional appropriate medical therapy may include but is not limited to: IV fluids Antihistamines NSAIDS Acetaminophen Narcotics Oxygen Pressors Corticosteroids Epinephrine Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator. Hospitalization may be indicated. **Subject is permanently discontinued from further trial treatment administration.**	No subsequent dosing
Appropriate resuscitation equipment should be available and an adequately-trained medical provider/physician readily available during the period of drug administration.		

5.7 Diet/Activity/Other Considerations

5.7.1 Diet

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

5.7.2 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. Female 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).

Men may be enrolled if they are willing to use a condom or are considered highly unlikely to conceive. Highly unlikely to conceive is defined as 1) surgically sterilized, 2) previously known to have azoospermia, or 3) not heterosexually active for the duration of the study. Male subjects should start using condoms from study Visit 1 throughout the study period up to 120 days after the last dose of study therapy.

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-Investigator 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.

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

The 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-Investigator and Merck. If a male subject impregnates his female partner the study personnel at the site must be informed immediately and the pregnancy reported to the PI and to Merck and followed as described above and in Section 7.2.2.

5.7.4 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.

5.8 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 treating investigator or the PI 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 7.1.4 – 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 morphologic relapse/progression
- Radiologic studies highly suspicious for extramedullary relapse (biopsy confirmation is strongly recommended unless prohibitively risky or patient refuses)
- Unacceptable adverse experiences as described in Section 5.2.1.2
- Intercurrent illness that prevents further administration of treatment
- Treating investigator feels that alternative treatment (e.g., allogeneic HCT) would be more beneficial for the subject
- 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 24 months of uninterrupted treatment with pembrolizumab or 35 administrations of study medication, whichever is later.

  Note: 24 months of study medication is calculated from the date of first dose. Subjects who stop pembrolizumab after 24 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 7.1.5.5

- Administrative reasons

The End of Treatment and Follow-up visit procedures are listed in Section 6 (Protocol Flow Chart) and Section 7.1.5 (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). Subjects who discontinue for reasons other than progressive disease will have post-treatment follow-up for

disease status until disease progression, initiating a non-study cancer treatment, withdrawing consent or becoming lost to follow-up. After documented disease progression each subject will be followed by medical record review and/or telephone for overall survival until death, withdrawal of consent, or the end of the study, whichever occurs first.

5.8.1 Discontinuation of Study Therapy after Complete MRD Response

Discontinuation of treatment may be considered for subjects who have attained a confirmed complete MRD response that have been treated for at least 24 weeks with pembrolizumab and had at least two treatments with pembrolizumab beyond the date when the initial complete MRD response was declared. Subjects who then experience disease progression may be eligible for up to one year of additional treatment with pembrolizumab via the Second Course Phase at the discretion of the investigator if no cancer treatment was administered since the last dose of pembrolizumab, the subject meets the safety parameters listed in the Inclusion/Exclusion criteria, and the trial is open. Subjects will resume therapy at the same dose and schedule at the time of initial discontinuation. Additional details are provided in Section 7.1.5.5.

5.9 Subject Replacement Strategy

Subjects will be replaced only in the rare event that they are not evaluable, which will be defined as alive > 3 weeks after initiation of study treatment but without sufficient response data from bone marrow examination (refused response assessments, technical limitations precluding ability to review bone marrow status, etc.).

5.10 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 Phase	Treatment Cycles[a]								End of Treatment	Post-Treatment	
						To be repeated beyond 8 cycles						
Treatment Cycle/Title:	Screening Visit(s)	1	2	3	4	5	6	7	8	Discontinuation		Survival Follow-Up
Scheduling Window (Days):	-28 to -1		± 3	± 3	± 3	± 3	± 3	± 3	± 3	≤ 7 days post discontinuation		Every ~ 3 months
Administrative Procedures												
Informed Consent	X											
Inclusion/Exclusion Criteria	X											
Demographics and Medical History	X											
Prior and Concomitant Medication Review	X	X	X	X	X	X	X	X	X	X		
Pembrolizumab Administration		X	X	X	X	X	X	X	X			
Post-study anticancer therapy status												X
Survival Status												X
Clinical Procedures/Assessments												
Review Adverse Events	X	X[d]	X	X	X	X	X	X	X	X		
Full Physical Examination	X									X		
Directed Physical Examination		X[d]	X	X	X	X	X	X	X			
Vital Signs and Weight	X	X[d]	X	X	X	X	X	X	X	X		
ECOG Performance Status	X	X[d]	X	X	X	X	X	X	X	X		
Laboratory Procedures/Assessments: analysis performed by LOCAL laboratory												
Pregnancy Test – Urine or Serum β-HCG	X[b]											
PT/INR and aPTT	X[b]											
CBC with Differential	X[b]	X[d]	X	X	X	X	X	X	X	X		

Trial Period:	Screening Phase	Treatment Cycles[a]								End of Treatment	Post-Treatment	
						To be repeated beyond 8 cycles						
Treatment Cycle/Title:	Screening Visit(s)	1	2	3	4	5	6	7	8	Discontinuation		Survival Follow-Up
Scheduling Window (Days):	-28 to -1		± 3	± 3	± 3	± 3	± 3	± 3	± 3	≤ 7 days post discontinuation		Every ~ 3 months
Comprehensive Serum Chemistry Panel	X[b]	X[d]	X	X	X	X	X	X	X	X		
Urinalysis	X[b]									X		
T3, FT4 and TSH	X[b]									X		
Efficacy Measurements												
Bone Marrow Examination	X	X[e]	X[e]		X[e]		X[e,f]		X[e,f]	X[e]		
Tumor Imaging	X[c]									X[c]		
Tumor Biopsies/Archival Tissue Collection/Correlative Studies Blood												
Archival or Newly Obtained Tissue Collection	X[g]	X[g]	X[g]		X[g]					X[g]		
Correlative Studies Blood Collection	X[g]		X[g]		X[g]					X[g]		

[a] Treatment cycles will occur every 21 ± 3 days

[b] Screening laboratory assessments should be performed within 10 days prior to the first dose of pembrolizumab, while urine/serum pregnancy test must be performed within 3 days of the first dose of pembrolizumab.

[c] Tumor imaging is only required in patients suspected of having sites of extramedullary disease.

[d] In the event that adequate clinical and laboratory assessments performed for screening purposes occur within 3 days of the start of Cycle 1, they do not need to be repeated for Cycle 1.

[e] Bone marrow examinations should be performed 3 ± 1 days prior to the start of the subsequent cycle (i.e., Day 18-20) to provide adequate time for interpretation. At a minimum, bone marrow exams will include an evaluation of morphology as well as a repeat analysis of whatever study (or studies) detected MRD at the time of enrollment; other studies may be included as clinically indicated. An end-of-treatment bone marrow examination does not need to be repeated if morphologic relapse/progression is identified on a scheduled surveillance examination.

[f] For those eligible to continue beyond Cycle 8, the timing of subsequent bone marrow exams will be left to the treating investigator, though no less often than every 3 months while receiving study treatment will be recommended.

[g] Details regarding planned correlative analyses on bone marrow and blood are described in Section 7.1.2.7.

7.0 TRIAL PROCEDURES

7.1 Trial Procedures

The Trial Flow Chart - Section 6.0 summarizes the trial procedures to be performed during each cycle. 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 PI 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

Consent must be documented by the subject's dated signature or by the subject's legally authorized 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's approval/favorable opinion in advance of use. The subject or his/her legally authorized 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.

The informed consent will adhere to IRB requirements, applicable laws and regulations and Sponsor-Investigator requirements.

7.1.1.2 Inclusion/Exclusion Criteria

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

7.1.1.3 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.

7.1.1.4 Prior and Concomitant Medications Review

7.1.1.4.1 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.

7.1.1.4.2 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.

7.1.1.5 Disease Details and Treatments

7.1.1.5.1 Disease Details

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

7.1.1.5.2 Prior Treatment Details

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

7.1.1.5.3 Subsequent Anti-Cancer Therapy Status

Once new anti-cancer therapy has been initiated the subject will move into survival follow-up.

7.1.1.6 Assignment of Enrollment Number

Once a subject has enrolled, they will be assigned a unique identifying number for the purposes of tracking and collecting data.

7.1.1.7 Trial Compliance (Medication/Diet/Activity/Other)

The investigator or qualified designee will review compliance with study requirements at study visits and as deemed necessary.

7.1.2 Clinical Procedures/Assessments

7.1.2.1 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 the most current available version of the NCI CTCAE (see Section 12.2). Toxicities will be characterized in terms regarding seriousness, causality, toxicity grading, and action taken with regard to trial treatment.

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

7.1.2.2 Full Physical Exam

The investigator or qualified designee will perform a complete physical exam during the screening period (and at time points indicated in the Trial Flow Chart). Clinically significant abnormal findings should be recorded as medical history.

7.1.2.3 Directed Physical Exam

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

7.1.2.4 Vital Signs

The investigator or qualified designee will take vital signs at screening, prior to the administration of each dose of trial treatment and at treatment discontinuation as specified in the Trial Flow Chart (Section 6.0). Vital signs should include temperature, pulse, respiratory rate, weight and blood pressure.

7.1.2.5 Eastern Cooperative Oncology Group (ECOG) Performance Scale

The investigator or qualified designee will assess ECOG status (see Section 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.

7.1.2.6 Assessment of Disease

Bone marrow examinations will be the primary modality for disease assessments on this study. The bone marrow performed for screening/eligibility may be performed at an outside

institution, provided an assessment of morphology was performed that confirmed morphologic CR and MRD was detected by either MFC or PCR. If the marrow exam was performed > 28 days before the start of treatment or if either of these elements is not available, a repeat bone marrow exam will be required prior to enrollment.

Following the initiation of treatment, bone marrow exams will be repeated after each of the first 2 cycles of treatment. These should be performed 3 ± 1 days prior to the start of the subsequent cycle (i.e., Day 18-20) to provide adequate time for interpretation. At a minimum, bone marrow exams will include an evaluation of morphology as well as a repeat analysis of whatever study (or studies) detected MRD at the time of enrollment (e.g., if MRD was detected by MFC and PCR at enrollment, follow-up marrow exams should include both MFC and PCR); other studies may be included as clinically indicated.

If morphologic relapse (i.e., leukemic blasts in the peripheral blood or ≥ 5% blasts in the bone marrow not attributable to any other cause) is detected at any time, treatment will stop and the subject will be removed from the study. However, subjects with persistent MRD may continue, provided other criteria to continue study treatment are met.

As our institution's standard methods for MRD detection in ALL are either MFC or PCR for the *BCR-ABL* fusion product in patients that have Ph+ disease, it is anticipated that these will be the primary modalities by which MRD is monitored. That said, for patients from whom adequate baseline material is available, NGS performed in the UW Hematopathology Laboratory or at Adaptive Biotechnologies will be used as an additional method of MRD monitoring. These results, however, will not be available in real time, and thus clinical decision-making will rest entirely on the results of MFC and/or PCR.

For subjects who are eligible to proceed to Cycles 3 and beyond, bone marrow exams will be repeated after every other cycle (i.e., Cycle 4, 6, and 8) through Cycle 8. For those eligible to continue beyond Cycle 8, the timing of subsequent bone marrow exams will be left to the treating investigator, though every 3 months while receiving study treatment will be recommended.

A bone marrow exam will also be required at the end of treatment. If the decision to discontinue treatment coincides with the timing of one of the above follow-up assessments, a separate end-of-treatment examination will not be required (e.g., the post-cycle 4 bone marrow demonstrated morphologic relapse). Similarly, if morphologic relapse is detected after Cycle 1, no further bone marrow examinations will be required for this study.

For definitions of response categories, please see Section 12.3.

Imaging studies will only be performed if extramedullary disease is suspected based on the evaluation of the treating investigator. This may occur at screening (to ensure eligibility) or at end of treatment (to document relapse/progression). If extramedullary disease is identified, this will constitute disease relapse: study treatment will be discontinued, and the subject will be removed from the study.

7.1.2.7 Tissue Collection and Correlative Studies Blood Sampling

Subjects who enroll on this study will have the option to provide tissue and blood samples for correlative studies, as described above in Section 4.2.3.2. Subjects may enroll on this study and opt out of these additional tests.

Bone marrow samples available from screening, post-cycle 1, post-cycle 2, post-cycle 4, and end-of-treatment will undergo DNA extraction in order to perform NGS-based MRD assessments. As these assays require knowledge of the leukemia-specific sequence from a sample with relatively high disease burden (e.g., initial diagnosis or morphologic relapse), archived tissue will be requested in order to identify this. In the event that this baseline sample cannot be obtained, then collection of samples for these exploratory MRD assessments may be deferred at the discretion of the PI. Lastly, DNA will be extracted from bone marrow obtained post-cycle 4 (for those patients still enrolled at that time) to investigate for clonal changes in the immune microenvironment.

As close as feasible to the timing of these marrow examinations at screening, post-cycle 2, post-cycle 4, and end-of-treatment, peripheral blood will also be collected for additional correlative studies. Flow cytometry will be performed in the UW Hematopathology Laboratory to assess for changes in circulating T-cell subsets (e.g., cytotoxic T cells, regulatory T cells) and other markers of cellular immunologic response. DNA will also be extracted to investigate for clonal changes in the immune repertoire. Lastly, cytokine and inflammatory marker measurements will occur in the IML at FHCRC and can include (but not necessarily limited to) PD-L1, interleukin (IL)-2, IL-21, and tumor necrosis factor alpha.

7.1.3 Laboratory Procedures/Assessments

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

Laboratory tests for hematology, chemistry, 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)	Specific gravity	aPTT
Red Blood Cell Count	Lactate dehydrogenase (LDH)	Microscopic exam *(If abnormal, results are noted)*	Total thriiodothyronine (T3)
Absolute Neutrophil Count	Carbon Dioxide	Urine pregnancy test †	Free tyroxine (T4)
Absolute Lymphocyte Count	*(CO_2 or biocarbonate)*		Thyroid stimulating hormone (TSH)
	Uric Acid		
	Calcium		
	Chloride		Blood for correlative studies
	Glucose		
	Phosphorus		
	Potassium		
	Sodium		
	Magnesium		
	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.

Laboratory tests for screening or entry into the Second Course Phase should be performed within 10 days prior to the first dose of treatment. After Cycle 1, pre-dose laboratory procedures can be conducted up to 3 days prior to dosing. Results must be reviewed by the investigator or qualified designee and found to be acceptable prior to each dose of trial treatment.

7.1.3.1 Pharmacokinetic/Pharmacodynamic Evaluations

There will not be any formal pharmacokinetic/pharmacodynamic evaluations as part of this study, apart from those described in Section 7.1.2.7.

7.1.4 Other Procedures

7.1.4.1 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 24 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 proceed to the Follow-Up Period of the study (described in Section 7.1.5.4).

7.1.4.2 Blinding/Unblinding

No blinding will be performed on this trial.

7.1.5 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.

7.1.5.1 Screening

7.1.5.1.1 Screening Period

Screening evaluations as listed in Section 6.0 - Trial Flow Chart may occur within 28 days of initiation of treatment, with the following two exceptions: laboratory assessments (as mentioned above) should be obtained within 10 days, and urine/serum pregnancy test must be performed within 3 daysof the first dose of pembrolizumab.

7.1.5.2 Treatment Period

Treatment will occur every 3 weeks (21 ± 3 days). Clinical and laboratory procedures/assessments (as delineated in Section 6.0) should occur within 3 days of administration of pembrolizumab. In the event that these assessments performed for screening

purposes occur within 3 days of the start of Cycle 1, they do not need to be repeated for Cycle 1. Response assessments by bone marrow examination will be performed as described in Section 7.1.2.6.

7.1.5.3 Post-Treatment Visits

7.1.5.3.1 Safety Follow-Up

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 (whichever comes first) should also be followed and recorded.

7.1.5.3.2 Follow-up Visits

Subjects who discontinue trial treatment for a reason other than disease progression will move into the Follow-Up Phase and should be assessed approximately every 3 months for up to 2 years. These assessments may be performed by local or referring medical providers, provided appropriate medical records can be made available to research staff. Every effort should be made to collect information regarding disease status until the start of new anti-neoplastic therapy, disease progression, death, end of the study or if the subject begins retreatment with pembrolizumab as detailed in Section 7.1.5.5. Information regarding post-study anti-neoplastic treatment will be collected if new treatment is initiated. If this anti-neoplastic treatment includes allogeneic HCT, occurrence of graft rejection and/or grade 3 or higher acute GVHD according to section 12.4 will be noted.

Subjects who are eligible to receive retreatment with pembrolizumab according to the criteria in Section 7.1.5.5 will move from the follow-up phase to the Second Course Phase when they experience disease progression. Details are provided in Section 6.1 – Trial Flow Chart (i.e., Second Course Phase will be identical to initial treatment).

7.1.5.3.3 Survival Follow-up

Once a subject experiences confirmed disease progression or starts a new anti-cancer therapy, the subject moves into the survival follow-up phase and should be contacted (via medical record review and/or telephone) approximately every 3 months to assess for survival status until death, withdrawal of consent, or the end of the study, whichever occurs first.

7.1.5.4 Second Course Phase (Retreatment Period)

Subjects who stop pembrolizumab in a complete MRD response may be eligible for up to one year of additional pembrolizumab therapy if they experience MRD reappearance after stopping study treatment. 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:

- Stopped initial treatment with pembrolizumab after attaining an investigator-determined confirmed complete MRD response according to consensus criteria,[16] and

  - Was treated for at least 24 weeks with pembrolizumab before discontinuing therapy
  - Received at least two treatments with pembrolizumab beyond the date when the initial complete MRD response was declared

- Experienced an investigator-determined confirmed MRD reappearance after stopping their initial treatment with pembrolizumab
- Did not receive any anti-cancer treatment since the last dose of pembrolizumab
- Has a performance status of 0 or 1 on the ECOG Performance Scale
- Demonstrates adequate organ function as detailed in Section 5.1.2
- Female subject of childbearing potential should have a negative serum or urine pregnancy test within 3 days prior to receiving retreatment with study medication.
- Female subject 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 Section 5.7.2). Subjects of child bearing potential are those who have not been surgically sterilized or have been free from menses for > 1 year.
- Male subject should agree to use a condom starting with the first dose of study therapy through 120 days after the last dose of study therapy.
- Does not have a history or current evidence of any condition, therapy, or laboratory abnormality that might 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.

Subjects who restart treatment will be retreated at the same dose and dose interval as when they last received pembrolizumab. Treatment will be administered for up to one additional year.

Visit requirements are outlined in Section 6.1 – Trial Flow Chart.

7.2 Assessing and Recording 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 Merck's product is also an adverse event.

Changes resulting from normal growth and development that do not vary significantly in frequency or severity from expected levels are not to be considered adverse events. Examples of this may include, but are not limited to, menopause occurring at a physiologically appropriate time.

Merck product includes any pharmaceutical product, biological product, device, diagnostic agent or protocol-specified procedure, whether investigational (including placebo or active comparator medication) or marketed, manufactured by, licensed by, provided by or distributed by Merck for human use.

Adverse events may occur during the course of the use of Merck product in clinical trials or 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 may also occur in screened subjects during any pre-allocation baseline period as a result of a protocol-specified intervention, including washout or discontinuation of usual therapy, diet, placebo treatment or a procedure.

Relapse/progression of ALL is not considered an adverse event unless it is considered to be drug related by the investigator.

All ECIs (as defined in Section 7.2.3.2) and other grade 3 or higher adverse events will be recorded from the time the consent form is signed through 30 days following cessation of treatment 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 section 7.2.3.1.

7.2.1 Definition of an Overdose for This Protocol and Reporting of Overdose to the Sponsor-Investigator 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 a Merck product, the adverse event(s) is reported as a serious adverse event, even if no other seriousness criteria are met.

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

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

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

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

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

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

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

7.2.3 Immediate Reporting of Adverse Events to the PI 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 another important medical event

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

For the time period beginning when the consent form is signed until treatment allocation/randomization, any serious adverse event, or follow up to a serious adverse event,

including death due to any cause that occurs to any participant must be reported within 24 hours to the Sponsor and within 2 working days to Merck Global Safety if it causes the participant to be excluded from the trial, or is the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure.

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

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

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

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

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

7.2.3.2 Events of Clinical Interest

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

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

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

1. an overdose of Merck product, as defined in Section 7.2.1 - Definition of an Overdose for This Protocol and Reporting of Overdose to the Sponsor-Investigator, 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).

7.2.4 Evaluating Adverse Events

An investigator who is a qualified physician will evaluate all adverse events according to the most current available version of NCI Common Terminology for Adverse Events (CTCAE). 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.

All adverse events regardless of CTCAE grade must also be evaluated for seriousness.

Table 6: Evaluating Adverse Events

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

CTCAE Grading	**Grade 1**	**Mild; asymptomatic or mid symptoms; clinical or diagnostic observations only; intervention not indicated.**
	Grade 2	**Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL.**
	Grade 3	**Severe or medically significant but not immediately life-threatening; hospitalization or prolongation or hospitalization indicated; disabling; limiting self-care ADL.**
	Grade 4	**Life threatening consequences; urgent intervention indicated.**
	Grade 5	**Death related to AE**
Seriousness	A serious adverse event is any adverse event occurring at any dose or during any use of Merck product that:	
	†**Results in death**; or	
	†**Is life threatening; or** places the 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 the Merck product to be discontinued?	
Relationship to test drug	Did the Merck product cause the adverse event? The determination of the likelihood that the Merck product caused the adverse event will be provided by an investigator who is a qualified physician. The investigator's signed/dated initials on the source document or worksheet that supports the causality noted on the AE form, ensures that a medically qualified assessment of causality was done. This initialed document must be retained for the required regulatory time frame. The criteria below are intended as reference guidelines to assist the investigator in assessing the likelihood of a relationship between the test drug and the adverse event based upon the available information. **The following components are to be used to assess the relationship between the Merck product and the AE**; the greater the correlation with the components and their respective elements (in number and/or intensity), the more likely the Merck product caused the adverse event (AE):	
	Exposure	Is there evidence that the subject was actually exposed to the Merck product such as: reliable history, acceptable compliance assessment (pill count, diary, etc.), expected pharmacologic effect, or measurement of drug/metabolite in bodily specimen?
	Time Course	Did the AE follow in a reasonable temporal sequence from administration of the Merck product? Is the time of onset of the AE compatible with a drug-induced effect (applies to trials with investigational medicinal product)?
	Likely Cause	Is the AE not reasonably explained by another etiology such as underlying disease, other drug(s)/vaccine(s), or other host or environmental factors

Relationship to Merck product (continued)	**The following components are to be used to assess the relationship between the test drug and the AE: (continued)**	
	Dechallenge	Was the Merck product discontinued or dose/exposure/frequency reduced? If yes, did the AE resolve or improve? If yes, this is a positive dechallenge. If no, this is a negative dechallenge. (Note: This criterion is not applicable if: (1) the AE resulted in death or permanent disability; (2) the AE resolved/improved despite continuation of the Merck product; or (3) the trial is a single-dose drug trial); or (4) Merck product(s) is/are only used one time.)
	Rechallenge	Was the subject re-exposed to the Merck product in this study? If yes, did the AE recur or worsen? If yes, this is a positive rechallenge. If no, this is a negative rechallenge. (Note: This criterion is not applicable if: (1) the initial AE resulted in death or permanent disability, or (2) the trial is a single-dose drug trial); or (3) Merck product(s) is/are used only one time). NOTE: IF A RECHALLENGE IS PLANNED FOR AN ADVERSE EVENT WHICH WAS SERIOUS AND WHICH MAY HAVE BEEN CAUSED BY THE MERCK PRODUCT, OR IF REEXPOSURE TO THE MERCK PRODUCT 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 the Merck product or drug class pharmacology or toxicology?
The assessment of relationship will be reported on the case report forms /worksheets by an investigator who is a qualified physician according to his/her best clinical judgment, including consideration of the above elements.		
Record one of the following	**Use the following scale of criteria as guidance (not all criteria must be present to be indicative of a Merck product relationship).**	
Yes, there is a reasonable possibility of Merck product relationship.	There is evidence of exposure to the Merck product. The temporal sequence of the AE onset relative to the administration of the Merck product is reasonable. The AE is more likely explained by the Merck product than by another cause.	
No, there is not a reasonable possibility Merck product relationship	Subject did not receive the Merck product OR temporal sequence of the AE onset relative to administration of the Merck product is not reasonable OR there is another obvious cause of the AE. (Also entered for a subject with overdose without an associated AE.)	

8.0 DATA AND SAFETY MONITORING PLAN

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

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

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

9.0 STATISTICAL ANALYSIS PLAN

9.1 Statistical Analysis Plan Summary

The primary objective of this study is to evaluate the efficacy of pembrolizumab in MRD-positive ALL. To address this, a Simon two-stage minimax design will be used.

9.2 Statistical Analysis Plan

The primary endpoint of this phase II study will be the rate of complete MRD response, defined as the percentage of evaluable subjects who achieve a complete MRD response, as defined in Section 11.3. The study of blinatumomab for chemorefractory MRD cited previously assumed an historical rate of complete MRD response to standard chemotherapy of 5%.[6] Considering the fact that the current study will enroll patients that have previously received or are ineligible for treatment with blinatumomab, we feel it is reasonable to assume a similar historical rate of complete MRD response for subjects in this trial. The design will be based on Simon's two-stage minimax design with an historical response rate of 5% and an assumed-true response rate of 20% for patients receiving treatment on this protocol. The design also assumed a 10% type-I error rate and a 20% type-II error rate. Under these assumptions and parameters, the first stage will enroll 12 evaluable patients. If 0 responses are seen among these 12, the study will be paused for futility to consider alternative strategies to improve efficacy versus consideration of study closure (the probability of 0 responses among 12 under the alternative hypothesis of 20% response is 0.07). On the other hand, if at least 1 response is seen among the first 12 patients, an additional 9 will be enrolled for a total of 21. If at least 3 responses occur among the 21 (14.3% or more), this will be considered as sufficient evidence to conclude that the observed response rate is statistically better than the fixed historical rate of 5%. This yields a type-I error rate of .08 and power of 80% along with an expected sample size of 16.1.

Additionally, the study will be stopped early if there is a signal of unacceptably-high early morphologic relapse. For this stopping rule, the rate of morphologic relapse within the first 2 cycles of treatment will be assessed in cohorts of 5 for the first 15 patients enrolled. If the lower bound of the 80% confidence

interval of the morphologic relapse rate exceeds 50% at these assessments (i.e., ≥ 4 out of 5, ≥ 7 out of 10, and ≥ 10 out of 15), the study will close early.

Reporting of secondary endpoints, including toxicity profiles, OS, and impact of biomarkers, will be primarily descriptive.

10.0 LABELING, PACKAGING, STORAGE AND RETURN OF CLINICAL SUPPLIES

10.1 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

10.2 Packaging and Labeling Information

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

10.3 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; random code/disclosure envelopes or lists are not provided.

10.4 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.

10.5 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.

11.0 ADMINISTRATIVE AND REGULATORY DETAILS

11.1 Confidentiality

The investigator will assure that subjects' anonymity will be strictly maintained and that their identities are protected from unauthorized parties. Only subject initials, date of birth and a study identification code will be recorded on any form or biological sample submitted to Merck or applicable outside institutions/laboratories. Laboratory specimens will be labeled in such a way as to protect subject identity while allowing the results to be recorded to the proper subject. The investigator will keep a screening log showing study identification codes, names, date of birth and last known address for all subjects screened and for all subjects enrolled in the trial. Subject data will be processed in accordance with all applicable regulations.

11.2 Compliance with Financial Disclosure Requirements

The investigator and all applicable subinvestigators will comply with 21 CFR, Part 54, 1998, providing documentation of their financial interest or arrangements with Merck, or proprietary interests in the investigational drug under study. This documentation will be provided prior to the investigator's (and any subinvestigator's) participation in the study. The investigator and subinvestigator will notify applicable parties of any change in reportable interests during the study.

11.3 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.

11.4 Retention of Records and Study Files

The investigator will maintain adequate and accurate records to enable the conduct of the study to be fully documented and the study data to be subsequently verified. All clinical study documentation will be retained by the investigator according to local laws and regulatory requirements.

11.5 Data Management

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

12.0 ORIGINAL SIGNED INFORMED CONSENT FORMS WILL BE KEPT WITHIN THE SECURED STUDY TEAM OFFICE, ACCESS IS LIMITED TO STUDY PERSONNEL. A COPY OF THE SIGNED INFORMED CONSENT FORM IS GIVEN TO THE PARTICIPANT. DATA WILL BE COLLECTED ON PATIENT CHARACTERISTICS, DISEASE CHARACTERISTICS, PROTOCOL THERAPY, RESPONSE TO TREATMENT, ADVERSE EVENTS AND FOLLOW-UP FOR RELAPSE AND SURVIVAL. COPIES OF THE PATIENT'S MEDICAL RECORD INCLUDING HISTORY AND PHYSICAL EXAMS, DOCUMENTATION OF PROTOCOL THERAPY, LABS, SCANS, X-RAYS, HOSPITALIZATIONS, OPERATIVE REPORTS, PATHOLOGY REPORTS ETC. ARE REQUIRED.

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 (CTCAE)

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

12.3 Response Evaluation Criteria

Consensus guidelines regarding definitions of MRD were developed following the Second International Symposium on MRD Assessment.[16] To summarize, quantifiable MRD is required for eligibility for this study. Complete MRD response is defined as having achieved MRD negativity or no longer detectable. MRD persistence is defined as continuously quantifiable MRD positivity measurable at ≥ 2 time points with ≥ 1 relevant treatment element (e.g., a cycle of study treatment) in between. MRD reappearance is

conversion from MRD negativity to quantifiable MRD positivity. Low-level, non-quantifiable MRD positivity does not fit into any of these categories.

For the purposes of determining morphologic relapse/progression, this will be defined as the appearance of leukemic blasts in the peripheral blood or ≥ 5% blasts in the bone marrow not attributable to any other cause.[17]

When considering subject eligibility or signs of treatment failure, extramedullary disease will be suspected in the presence of lymph nodes > 1.5 cm in longest diameter, extranodal sites > 1.0 cm in longest diameter, or splenomegaly with an increase in length of > 50%. These definitions are adapted from international working group criteria for the evaluation of lymphoma (the Lugano classification).[18] For the purposes of this study, these parameters will not define the presence of extramedullary disease, but instead will be used as a guide to consider its presence; when feasible and if the results of imaging studies are equivocal, biopsy will be preferred to confirm or refute this suspicion.

12.4 Grading of Acute Graft-Versus-Host Disease[a]

Severity of Individual Organ Involvement		
Skin	+1	a maculopapular eruption involving less than 25% of the body surface
	+2	a maculopapular eruption involving 25-50% of the body surface
	+3	generalized erythroderma involving >50% of the body surface
	+4	generalized erythroderma with bullous formation and often with desquamation
Liver	+1	bilirubin (2.0-2.9 mg/100ml)
	+2	bilirubin (3-5.9 mg/100ml)
	+3	bilirubin (6-14.9 mg/100ml)
	+4	bilirubin > 15mg/100ml
Gut	Diarrhea is graded +1 to +4 in severity. Nausea and vomiting and/or anorexia caused by GVHD is assigned as +1 in severity. The severity of gut involvement is assigned to the most severe involvement noted. Patients with visible bloody diarrhea are at least stage +2 gut and grade +3 overall	
Diarrhea	+1	≤ 1000 ml of liquid stool/day*
	+2	>1,000 ml of stool/day*

	+3	>1,500 ml of stool/day*
	+4	2,000 ml of stool/day*

**In the absence of infectious/medical cause*

Severity of GVHD	
Grade I	+1 to +2 skin rash
	No gut or liver involvement
Grade II	+1 to +3 skin rash and/or
	+1 gastrointestinal involvement and/or +1 liver involvement
Grade III	+4 skin involvement and/or
	+2 to +4 gastrointestinal involvement and/or
	+2 to +4 liver involvement with or without a rash
Grade IV	Pattern and severity of GVHD similar to grade 3 with extreme constitutional symptoms or death

a. From "Graft-vs-host disease" Sullivan, Keith M. Hematopoietic Cell Transplantation Ed: D. Thomas, K. Blume, S. Forman, Blackwell Sciences; 1999, pages 518-519.

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