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TITLE: Augmentation of the Graft vs. Leukemia Effect via Checkpoint Blockade with Pembrolizumab for Relapse of Primary Malignancy after Allogeneic Hematopoietic Stem Cell Transplant: A Feasibility Study.

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1.0 TRIAL SUMMARY

Abbreviated Title	Pembrolizumab for Relapsed Disease after Allogeneic Hematopoietic Stem Cell Transplant
Trial Phase	Phase 1b
Clinical Indication	Relapsed myelodysplastic syndrome, acute myeloid leukemia and acute lymphoblastic leukemia after allogeneic hematopoietic stem cell transplant
Trial Type	Single center, Investigator-Initiated
Type of control	N/A
Route of administration	IV
Trial Blinding	none
Treatment Groups	Single treatment group
Number of trial subjects	20 subjects
Estimated enrollment period	2 years
Estimated duration of trial	3 years
Duration of Participation	14 months
Estimated average length of treatment per patient	12 months

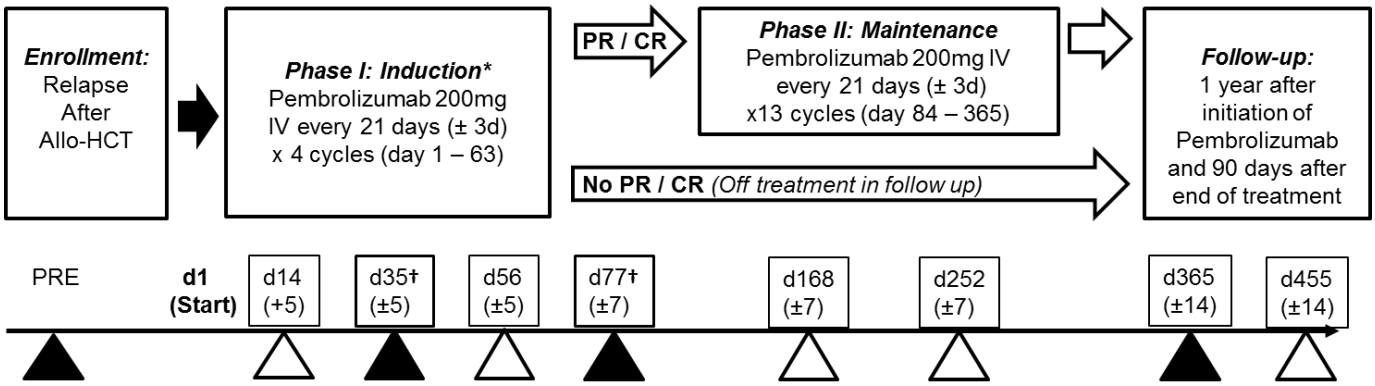
2.0 TRIAL DESIGN

2.1 Trial Design

Single-arm open label phase 1b clinical trial of pembrolizumab (Merck) to the determine the feasibility and immunologic correlates for treating relapse of primary malignancy after allogeneic stem cell transplantation.

2.2 Trial Diagram

Study Schema: Checkpoint Blockade to Induce GVL for Relapsed Disease After Allo-Transplantation



▲ Bone Marrow Aspirate and Biopsy for Tumor Sample and Disease Assessment
Research sample from peripheral blood and bone marrow

△ Research sample from peripheral blood ± bone marrow (if clinically indicated)

* standard induction chemotherapy may be administered during induction at investigators discretion if concern for rapid clinical progression of malignancy (see 5.2.1.2).

† Primary study endpoint (s) are ORR (PR+CR) at day 35 and day 77

3.0 OBJECTIVE(S) & HYPOTHESIS(ES)

3.1 Primary Objective(s) & Hypothesis(es)

3.1.1 Primary Objectives

1) To establish the safety of delivering single agent pembrolizumab ± chemotherapy to patients with relapse of ALL, AML or MDS after allogeneic transplantation.

2) To determine the overall response rate (ORR) to single agent pembrolizumab ± chemotherapy in patients with relapsed ALL, AML or MDS after allogeneic transplantation.

3) To describe the incidence of Graft vs. Host Disease (GvHD) and/or other clinically significant immune mediated toxicities after pembrolizumab ± chemotherapy.

3.1.2 Hypotheses for Primary Objectives

Blockade of PD-1 with pembrolizumab will enhance (induce) the Graft vs. Leukemia (GvL) effect resulting in objective clinical responses without excessive toxicity (GvHD) in patients who experience relapse of primary malignancy after allogeneic transplantation.

3.2 Secondary Objective(s) & Hypothesis(es)

3.2.1 Secondary Objectives

1) Estimate the one-year overall and disease-free survival in patients administered pembrolizumab for relapse after HCT

3.2.1.1 Exploratory Objectives

1) Determine the immunologic correlates of response to checkpoint blockade in patients with hematologic malignancies who have relapsed after allogeneic transplantation via assessment of PD1-PDL1 axis with a well-defined focus on T and NK cell phenotypes, functions and leukemia specific responses.

2) Determine the antigenic peptide repertoire of relapsed MDS and AML by whole exome sequencing (WES), bioinformatically nominate the most immunogenic antigens from the WES analyses and then functionally validate the top predicted peptides in silico and in vitro.

3) Determine if PD-L1 expression at relapse serves as a biomarker for response to pembrolizumab in hematologic malignancies as has been reported in solid malignancies[31].

4) Identify responsive and resistant malignant clones and assess kinetics and depth of response to treatment with ultrasensitive mutation detection (droplet digital PCR [ddPCR] and single-molecule/real-time sequencing [SMRT])

3.2.2 Hypotheses for Secondary and exploratory Objectives

Blockade of PD-1 with pembrolizumab can reverse the putative immunobiologic mechanisms reported to play a significant role in contributing to relapse after allogeneic transplantation via the development of ‘adaptive resistance’ determined by analyses of immune peptide repertoire by WES and specific expression of PD-LI and other immune inhibitory markers on (Galectin 9, HVEM, CD48, CD155) leukemic cells and characterize the ‘senescent/exhausted’ CD8/4+ immunophenotype (PD1, LAG3, TIM3).

4.0 BACKGROUND & RATIONALE

Allogeneic stem cell transplantation provides the only modality with curative potential for many patients with life-limiting hematologic malignancies, particularly those with acute myelogenous leukemia (AML).

Relapse After Allo-HCT: According to the Center for International Bone Marrow Transplant Registry (CIBMTR), approximately 40% of mortality after allogeneic hematopoietic cell transplantation (HCT) occurs from relapse[1]. To our knowledge, there have been no successful approaches for reducing relapse after HCT. In AML, relapse rates range from 25% to 65% depending on HCT and disease specific risk factors including conditioning intensity, T cell depletion, cytogenetic profile and status of disease at the

time of HCT. Refractory or relapsed AML, not in remission at time of HCT, has the highest relapse, approximately 60% or greater.

Management of relapse has been unfortunately met with little success and the proportion of patients with long term survival after relapse HCT remains unacceptably low. Although the use of Donor Lymphocyte Infusion (DLI), often in combination with chemotherapy has become a commonly utilized treatment approach, the long term outcomes remain poor and the incidence of Graft vs. Host Disease (GvHD) after DLI is a significant limitation to its overall success[2-6]. For example, 13% of patients with AML survived one-year if relapse occurred 6 months after HCT (Bejanyan et al. BBMT 2015).

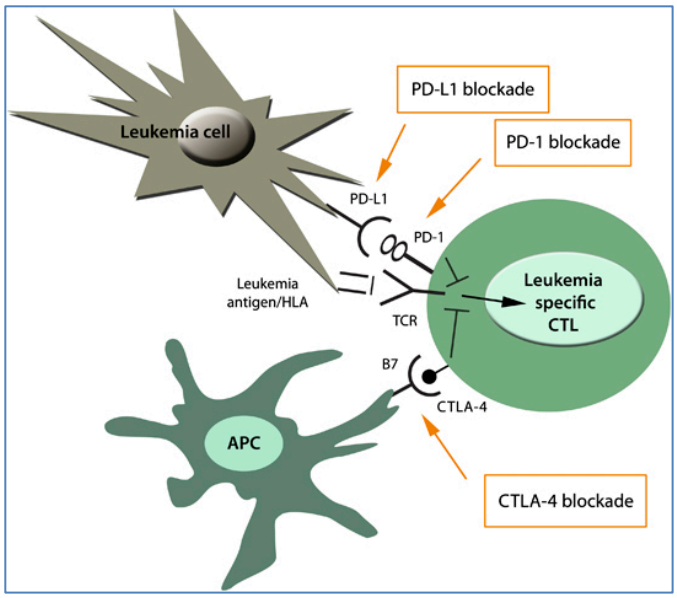
Although multi-factorial, one of the primary mechanisms by which HCT achieves anti-tumor control is via an immune-mediated 'Graft vs. Leukemia' (GvL) effect [2,7]. The mechanisms by which the host and donor hematopoietic and non-hematopoietic cells and tissues interact to achieve successful disease control and immune surveillance are complex and difficult to study in humans[8-10]. Over the last decade, there has been extraordinary progress in our understanding of these mechanisms, not only those involved in the activation of the immune effectors to enhance cytotoxicity, but in particular, the numerous pathways involved in inhibition of the immune system that otherwise protect healthy tissues from autoimmune reactions, but can paradoxically lead to immune escape by malignant cells[11], culminating in clinical relapse. Included among the multiple negative regulatory mechanisms which appear to contribute to the inhibition of sufficiently primed anti-leukemic (tumor) T cell responses are 1) suppression of conventional T-cell function by regulatory T-cells[12], 2) up-regulation of CTLA-4 on T-cells[13], 3) tryptophan catabolism by IDO[14-16], 4) T-cell anergy due to poor co-stimulation by tumor cells[17], 5) functional senescence or exhaustion of antigen specific CD8+ T-cells after allotransplantation[18] and 6) engagement of PD-1 on activated T-cells with PD-L1 [Figure 1][19,20]. Although interfering with any one of these pathways might enhance the GvT effect, this proposal focuses on the latter via blockade of PD-1 with pembrolizumab in relapsed AML or MDS after HCT.

Several murine and human studies have established that PD-1/PD-L1 interactions play a critical role in immune evasion[21-27] and provide strong rationale for enhancing GvL via PD-1 blockade post-HCT.

PD-L1 expression has been confirmed in several hematologic malignancies, including AML, providing the rationale for exploring both the impact of PD-1 blockade via pembrolizumab and the correlation of surface expression and response among disease subtypes. In addition, there are no published data exploring Pembrolizumab post allogeneic HCT in which a potentially 'healthy' immune effector system from the donor can be exploited to re-establish immune surveillance and cancer 'immuno-editing'[9]. A unique aspect of this study is that instead of 'activating' autologous T cells from a cancer patient with long-standing exposure to the tumor, the potential target are the 'normal' donor T-cells previously infused (and still persistent) after allogeneic HCT which have potentially become senescent/exhausted[18]. Although there is precedent for the 'inhibition of inhibitory pathways' via CTLA-4 blockade with ipilimumab, suggesting an enhancement in T-cell response against AML [28] without increasing GvHD in the post-HCT setting[29,30], this trial will focus on PD-1 blockade via pembrolizumab.

By targeting established immunoregulatory pathways with pembrolizumab, we postulate that we can overcome inhibition mediated by PD-1 binding with PD-L1 and PD-L2, thereby inducing or restoring the immune-mediated GvL effect without undue toxicity in a patient population with very limited treatment options.

When compared to the extensive data regarding the potential role of checkpoint blockade in solid tumors, there has been a relative paucity in hematologic malignancies. This proposal will investigate PD-1 based check-point blockade (pembrolizumab) in the post-HCT setting, and will provide an important 'proof of principle' for understanding key mechanisms of immune escape after HCT, reversal of



senescence/exhausted immunophenotype, and potential impact on re-establishing GvL and leukemic response. If successful, these clinical and laboratory data would provide compelling rationale for further definitive lines of investigation of pembrolizumab in this or related settings.

FIGURE 1. Immune checkpoint blockade as an immunotherapeutic modality. T-cell receptor binding to an human leukocyte antigen/peptide complex is a central event in cytotoxic T lymphocyte (CTL) mediated elimination of leukemia cells as it induces an activation signal within the CTL. Immune checkpoints refer to a number of inhibitory pathways that are crucial for maintaining self-tolerance and modulating the duration and amplitude of immune responses in peripheral tissues in order to minimize collateral tissue damage. It is well described that tumors use different immune checkpoint pathways as a major mechanism of immune resistance against leukemia-specific CTL. PD-1 is mainly expressed on antigen-experienced memory T cells in peripheral tissues (effector phase). Leukemia cells use this regulatory mechanism to evade a leukemia-directed CTL response by upregulating PD-L1, which is the ligand for PD-1, on its surface. Blocking monoclonal antibodies (orange squares) directed at the inhibitory immune receptors CTLA-4, PD-1 and PD-L1 have all emerged as promising novel treatment approaches for cancer patients. Figure and caption from MH Andersen, Leukemia 2014.

4.1 Pharmaceutical and Therapeutic Background

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

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. Keytruda is also approved for patients with metastatic NSCLC whose tumors express PD-L1 as determined by an FDA-approved test and who have disease progression on or after platinum-containing chemotherapy.

4.2 Rationale

4.2.1 Rationale for Dose Selection/Regimen/Modification

An open-label Phase I trial (Protocol 001) was conducted to evaluate the safety and clinical activity of single agent MK-3475 (Keytruda™, pembrolizumab). The dose escalation portion of this trial evaluated three dose levels, 1 mg/kg, 3 mg/kg, and 10 mg/kg, administered every 2 weeks (Q2W) in subjects with advanced solid tumors. All three dose levels were well tolerated and no dose-limiting toxicities were observed. This first in human study of 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. 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 Q3W dosing schedule in this study.

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 was 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 current study will employ pembrolizumab at a fixed dosage of 200mg every 3 weeks, which is the FDA approved standard dosing. 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.

4.2.2 Rationale for Endpoints

4.2.2.1 Efficacy Endpoints

This feasibility study addresses a cohort of patients with established resistance to chemotherapy and HCT by virtue of having relapsed after HCT. We are seeking to identify a signal for clinical benefit by assessing the ORR to pembrolizumab ± chemotherapy while providing additional insights into the mechanisms of check-point inhibition in the immune biology of post-HCT relapse. These efficacy endpoints will be assessed by serial CBC, bone marrow biopsies / aspirate, assessing peripheral blast percentages, absolute blast counts (ABC), and marrow blasts.

The time to response in this disease cohort is unknown. The first marrow assessment of disease response will be at day 35 after initiation of study treatment. If disease is stable (SD) or improved (CR or PR) at day 35, clinicians will continue single agent therapy every 3 weeks for a total of 4 doses. A second marrow assessment will be performed on day 77. If CR or PR is attained subjects may proceed to phase II (maintenance) (see section 5.2).

If there is a concern for rapid disease progression or clinical instability, chemotherapy may be added per investigators discretion after the day 35 marrow results (two doses of pembrolizumab) (See section 5.2.1.2).. Subjects may continue study drug in the absence of toxicity attributable to pembrolizumab per Table 3.

Primary objective endpoints:

Efficacy:

- ORR at days 35 and 77 in subjects receiving pembrolizumab monotherapy

- ORR at day 77 in subjects receiving pembrolizumab ± standard induction chemotherapy

- Clinical Benefit Rate (CBR) at days 35 and 77 in subjects receiving pembrolizumab monotherapy

Safety:

- Incidence and severity of GvHD after administration of pembrolizumab

- Grade 3-5 Regimen-related toxicities (RRT) per CTCAE v4

- Incidence of immune mediated toxicities attributable to pembrolizumab

Secondary objective endpoints:

- Estimate overall survival (OS) and disease-free survival (DFS) at one year in patients who receive pembrolizumab for relapse after allogeneic HCT.

5.0 METHODOLOGY

5.1 Entry Criteria

5.1.1 Diagnosis/Condition for Entry into the Trial

Please refer to section 5.1.2.

5.1.2 Subject Inclusion Criteria

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

1. Acute Myeloid Leukemia (AML), Acute Lymphoblastic Leukemia (ALL) or Myelodysplastic Syndrome (MDS) in confirmed relapse based on bone marrow examination after allogeneic HCT. Biopsy confirmed myeloid sarcoma or extramedullary AML may also be considered.

2. Confirmation of 'measurable disease' by blast % will be defined as a marrow blast percentage of > 5% by morphologic assessment on bone marrow examination. This criterion does not apply to myeloid sarcoma, or extramedullary leukemia, which must also show measurable lesion by CT, MRI, PET/CT or photograph (i.e. Leukemia cutis). If marrow blasts of ≤ 5% blasts are enumerated the patient may be eligible only if there is clear (probable or definite) flow cytometric, cytogenetic or molecular aberrations (e.g. FLT3-ITD, NPM1, etc.) documenting relapse of the leukemia associated clone defined prior to HCT.

3. Patient may not have received definitive salvage chemotherapy for their post-transplant relapse within the past 21 days. Use of hydroxyurea is permitted.

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

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

6. Be willing to provide tissue from bone marrow biopsies

7. Have a performance status of 0, to 1 on the ECOG Performance Scale. For purposes of HCT, this will correspond to a Karnofsky Performance status of ≥ 80%

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
Renal	
Serum creatinine **OR** Measured or calculated[a] creatinine clearance (GFR can also be used in place of creatinine or CrCl)	≤1.5 X upper limit of normal (ULN) **OR** ≥60 mL/min for subject with creatinine levels > 1.5 X institutional ULN
Hepatic	
Serum total bilirubin	≤ 1.5 X ULN **OR**
	Direct bilirubin ≤ ULN for subjects with total bilirubin levels > 1.5 ULN
AST (SGOT) and ALT (SGPT)	**≤** 5 X ULN for subjects
Coagulation	
International Normalized Ratio (INR) or Prothrombin Time (PT) Activated Partial Thromboplastin Time (aPTT)	≤1.5 X ULN unless subject is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants ≤1.5 X ULN unless subject is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants
Pulmonary	Pox >90% on Room Air
[a]Creatinine clearance should be calculated per institutional standard.	
Hematology (Blood Counts): Must have an absolute blast count (ABC) of < 15 K/ul in the peripheral blood prior to initiating study treatment. Use of hydroxyurea to control blast counts prior to initiating study treatment is acceptable.	

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

10. Female subjects of childbearing potential (Section 5.7.2) must be willing to use an adequate method of contraception as outlined in Section 5.7.2 – Contraception, for the course of the study through 120 days after the last dose of study medication.

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

11. Male subjects of childbearing potential (Section 5.7.1) must agree to use an adequate method of contraception as outlined in Section 5.7.1- Contraception, starting with the first dose of study therapy through 120 days after the last dose of study therapy.

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

5.1.3 Subject Exclusion Criteria

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

1. Has had relapse prior to primary neutrophil engraftment or ≤21 days post HCT.

2. Has received >1 line of chemotherapy or other treatment directed towards post-transplant relapse prior to study entry

3. Rapidly progressive relapse requiring urgent chemotherapy as determined by treating physician

4. Is currently participating and receiving study therapy of an investigational agent and received study therapy within 2 weeks of the first dose of treatment. This 2 week washout period would not apply to investigational food ingredients.

5. Has a diagnosis of active GvHD (≥ Grade I). Patients with prior active GvHD that is quiescent (Grade 0) at time of entry may be considered.

6. Receiving systemic steroid therapy of > 10mg prednisone daily or equivalent*

7. Has received GM-CSF within 14 days of first dose of pembrolizumab

8. Has a known history of active TB (Bacillus Tuberculosis)Hypersensitivity to pembrolizumab or any of its excipients

9. 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

10. Has had prior chemotherapy within 21 days, or radiation therapy within 14 days 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

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

b. Note: If subject received major surgery, they must have recovered adequately from the toxicity and/or complications from the intervention prior to starting therapy.

11. Has a known additional (secondary) 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.

12. Has known or suspected active central nervous system (CNS) metastases and/or carcinomatous meningitis. Patients with suspected CNS disease should have lumbar puncture performed to exclude this possibility. Subjects with previously treated brain metastases may participate provided they are stable (without evidence of progression by imaging for at least four weeks prior to the first dose of trial treatment and any neurologic symptoms have returned to baseline), have no evidence of new or enlarging brain metastases, and are not using steroids for at least 7 days prior to trial treatment. This exception does not include carcinomatous meningitis which is excluded regardless of clinical stability.

13. 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.

14. Has a history of (non-infectious) pneumonitis that required steroids, or current pneumonitis

15. 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.

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

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

18. Has received prior therapy with an anti-PD-1, anti-PD-L1, or anti-PD-L2 agent

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

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

21. 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.

**Note:*
a. Corticosteroid use on study after Cycle 1 for management of adverse events, serious adverse events, and events of clinical interest, as a premedication for IV contrast allergies/reactions, or if considered necessary for a subject's welfare is allowed.
b. Subjects who receive daily steroid replacement therapy are an exception. Daily prednisone at doses of 5 to 7.5 mg is an example of replacement therapy.
c. Equivalent hydrocortisone doses are also permitted if administered as replacement therapy.

Subject Screening and Registration Procedure

Subject registration for this study will be centrally managed by the Oncology Clinical Trials Support Unit (OCTSU) of The University of Michigan Comprehensive Cancer Center as described below:

All potential study subjects who are screened for the study and have signed the Informed Consent document will be assigned a study number.

It is the responsibility of the local site investigator to determine subject eligibility prior to submitting subject registration request to the OCTSU. After subject eligibility has been determined, the patient will be enrolled by the OCTSU study coordinator. The informed consent and eligibility checklist must be completed before subjects can receive the first study treatment of MK-3475 (pembrolizumab®).

Subjects found to be ineligible for participation after being consented will be considered screen failures, and documented as such. These subjects will not will not receive study treatment.

5.2 Trial Treatments

The treatment to be used in this trial is outlined below in Table 2 (see also Trial Diagram in section 2.2).

Table 2 Trial Treatment

Drug	Dose/Potency	Dose Frequency	Route of Administration	Regimen/Treatment Period	Use
Pembrolizumab (Phase I: Induction)	200 mg	Every 3 weeks	IV infusion	Day 1 of each 3 week cycle x 4 doses	Experimental
Pembrolizumab (Phase II: Maintenance)	200 mg	Every 3 weeks	IV infusion	Day 1 of each 3 week cycle up to 13 doses	Experimental

Description of Trial Treatment: Eligible subjects will be initiated on pembrolizumab (phase I) for up to 4 doses with response assessments at day 35 (after 2 doses) and day 77 (after 4 doses). Subjects who are tolerating therapy without drug related adverse events (Table 3) AND who have disease in PR or CR on day 77 response assessment may be continued on pembrolizumab maintenance (phase II). Phase II treatment will continue for up to an additional 13 doses or until either toxicity or progression of malignancy at which time the subject will be placed into follow-up.

Subjects initiated on systemic induction chemotherapy: due to progression will receive no additional or concomitant phase I (induction) doses of pembrolizumab but may be considered for phase II maintenance pembrolizumab if disease assessment at day 77 (following chemotherapy) indicates PR or CR. Pembrolizumab may have synergistic effects with chemotherapy and/or facilitate augmention of GVL after reduction of high leukemic burden.

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 (Escalation/Titration/Other)

After initiated study treatment, the use of chemotherapy prior to day 35 bone marrow biopsy (or two cycles of pembrolizumab) is discouraged.

- Systemic Chemotherapy may be instituted in the following scenarios:

    - Evidence for progressive AML or MDS on day 35 bone marrow biopsy. Progression will be defined as a minimum of > 5% increase in the absolute marrow blasts from pre-treatment biopsy. For example, increase in bone marrow blast from 10% on pretreatment biopsy to 25% on day 35 marrow examination OR

- At the discretion of the treating physician for impending rapidly progressive relapse (e.g. rapid increase in peripheral blast % or hematologic instability. These situations should be discussed in consultation with the study PIs OR

- Alternatively, subjects with minimal progression may remain on monotherapy if deemed there may be potential for subsequent clinical response or deemed poor candidates for systemic chemotherapy. For example, a subject who is tolerating pembrolizumab at day 35 of treatment with increase in bone marrow blasts to 15% at day 35 from 9% at pre-treatment will be recorded as progression but may remain on monotherapy to complete four dose of induction (phase I) at investigator's discretion.

- The chemotherapy regimen will be at the discretion of the treating physician and may include hypomethylation therapy or cytotoxic chemotherapy including high dose ara-C (e.g. FLAG) and/or anthracycline-based regimens. Other investigational agents are not permitted or the subject will be removed from further pembrolizumab and placed into follow-up.

Adverse events (both non-serious and serious) associated with pembrolizumab exposure may represent an immunologic etiology. These adverse events may occur shortly after the first dose or several weeks after the last dose of treatment. Pembrolizumab must be withheld for drug-related toxicities and severe or life-threatening adverse events (AEs) as per Table 3 below. Pembrolizumab must also be permanently discontinued in patients who develop ≥ Grade 3 acute GvHD requiring systemic corticosteroids. Pembrolizumab should be temporarily held if acute GVHD grade II occurs. Pembrolizumab may be re-initiated once acute GVHD improves to < grade II. See Section 5.4 for supportive care guidelines, including use of corticosteroids.

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

Toxicity	Hold Treatment For Grade	Timing for Restarting Treatment	Treatment Discontinuation
Diarrhea/Colitis	2-3	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks
	4	Permanently discontinue	Permanently discontinue
AST, ALT, or Increased Bilirubin	2	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose
	3-4	Permanently discontinue (see exception below)[a]	Permanently discontinue
Type 1 diabetes mellitus (if new onset) or Hyperglycemia	T1DM or 3-4	Hold pembrolizumab for new onset Type 1 diabetes mellitus or Grade 3-4 hyperglycemia associated with evidence of beta cell failure	Resume pembrolizumab when patients are clinically and metabolically stable
Hypophysitis	2-4	Toxicity resolves to Grade 0-1. Therapy with pembrolizumab can be continued while endocrine replacement therapy is instituted	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks
Hyperthyroidism	3	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks
	4	Permanently discontinue	Permanently discontinue

Toxicity	Hold Treatment For Grade	Timing for Restarting Treatment	Treatment Discontinuation
Hypothyroidism		Therapy with pembrolizumab can be continued while thyroid replacement therapy is instituted	Therapy with pembrolizumab can be continued while thyroid replacement therapy is instituted
Infusion Reaction	2[b]	Toxicity resolves to Grade 0-1	Permanently discontinue if toxicity develops despite adequate premedication
	3-4	Permanently discontinue	Permanently discontinue
Pneumonitis	2	Permanently discontinue	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks
	3-4	Permanently discontinue	Permanently discontinue
Renal Failure or Nephritis	2	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks
	3-4	Permanently discontinue	Permanently discontinue
All Other Drug-Related Toxicity[c]	3 or Severe	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks
	4	Permanently discontinue	Permanently discontinue

Note: Permanently discontinue for any severe or Grade 3 drug-related AE that recurs or any life-threatening event.

[a] For patients with liver metastasis who begin treatment with Grade 2 AST or ALT, if AST or ALT increases by greater than or equal to 50% relative to baseline and lasts for at least 1 week then patients should be discontinued.

[b] 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; – Infusion Treatment Guidelines for further management details.

[c] Patients with intolerable or persistent Grade 2 drug-related AE may hold study medication at physician discretion. Permanently discontinue study drug for persistent Grade 2 adverse reactions for which treatment with study drug has been held, that do not recover to Grade 0-1 within 12 weeks of the last dose.

Dosing interruptions are permitted in the case of medical / surgical events or logistical reasons not related to study therapy (e.g., elective surgery, unrelated medical events, patient vacation, and/or holidays). Subjects should be placed back on study therapy within 3 weeks of the scheduled interruption, unless otherwise discussed with the Sponsor. 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.

Pembrolizumab 200 mg (flat dose) will be administered as a 30 minute IV infusion every 3 weeks x 4 doses. 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 Sponsor, investigator and subject will know the treatment administered.

5.3 Concomitant Medications/Vaccinations (allowed & prohibited)

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

5.3.1 Acceptable Concomitant Medications

Patients may receive hydroxyurea at the discretion of their treating hematology physician as a temporary bridge to chemotherapy. 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 14 days before the first dose of trial treatment and 30 days after the last dose of trial treatment should be recorded. Concomitant medications administered after 30 days after the last dose of trial treatment should be recorded for SAEs and ECIs as defined in Section 7.2.

FLT-3 inhibitors and tyrosine kinase inhibitors which are resumed as part of usual care after HCT are permissible.

5.3.2 Prohibited Concomitant Medications

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

- Immunotherapy not specified in this protocol
- No GM-CSFwill be used during the trial
- 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 (e.g. hydrocortisone for adrenal replacement or premedication for blood transfusion) or continuation of low dosages of corticosteroids as specified in the protocol eligibility (≤ 10mg prednisone / day).

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

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

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

5.4 Rescue Medications & Supportive Care

5.4.1 Supportive Care Guidelines

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

Note: if after the evaluation the event is determined not to be related, the investigator does not need to follow the treatment guidance (as outlined below). 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,** administer oral corticosteroids.
    - For **Grade 3 or 4 diarrhea/colitis,** 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 Infusion Reactions**: Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion.

  Table 3 below shows treatment guidelines for subjects who experience an infusion reaction associated with administration of pembrolizumab (MK-3475).

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

NCI CTCAE Grade	Treatment	Premedication at subsequent dosing
renal impairment, pulmonary infiltrates) Grade 4: Life-threatening; pressor or ventilatory support indicated	Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator. Hospitalization may be indicated. **Subject is permanently discontinued from further trial treatment administration.**	
Appropriate resuscitation equipment should be available in the room and a physician readily available during the period of drug administration.		

5.5 Diet/Activity/Other Considerations

5.5.1 Diet

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

5.5.2 Contraception

Pembrolizumab may have adverse effects on a fetus in utero. Furthermore, it is not known if pembrolizumab has transient adverse effects on the composition of sperm.

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

Female subjects will be considered of non-reproductive potential if they are either:

(1) postmenopausal (defined as at least 12 months with no menses without an alternative medical cause; in women < 45 years of age a high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a post-menopausal state in women not using hormonal contraception or hormonal replacement therapy. In the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.);

OR

(2) have had a hysterectomy and/or bilateral oophorectomy, bilateral salpingectomy or bilateral tubal ligation/occlusion, at least 6 weeks prior to screening;

OR

(3) has a congenital or acquired condition that prevents childbearing.

Female and male subjects of reproductive potential must agree to avoid becoming pregnant or impregnating a partner, respectively, while receiving study drug and for 120 days after the last dose of study drug by complying with one of the following:

(1) practice abstinence[†] from heterosexual activity;

OR

(2) use (or have their partner use) acceptable contraception during heterosexual activity.

Acceptable methods of contraception are‡:

Single method (one of the following is acceptable):

- intrauterine device (IUD)
- vasectomy of a female subject's male partner
- contraceptive rod implanted into the skin

Combination method (requires use of two of the following):

- diaphragm with spermicide (cannot be used in conjunction with cervical cap/spermicide)
- cervical cap with spermicide (nulliparous women only)
- contraceptive sponge (nulliparous women only)
- male condom or female condom (cannot be used together)
- hormonal contraceptive: oral contraceptive pill (estrogen/progestin pill or progestin-only pill), contraceptive skin patch, vaginal contraceptive ring, or subcutaneous contraceptive injection

†Abstinence (relative to heterosexual activity) can be used as the sole method of contraception if it is consistently employed as the subject's preferred and usual lifestyle and if considered acceptable by local regulatory agencies and ERCs/IRBs. Periodic abstinence (e.g., calendar, ovulation, sympto-thermal, post-ovulation methods, etc.) and withdrawal are not acceptable methods of contraception.

‡If a contraceptive method listed above is restricted by local regulations/guidelines, then it does not qualify as an acceptable method of contraception for subjects participating at sites in this country/region.

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 subjects of childbearing potential must adhere to the contraception requirement (described above) from the day of study medication initiation (or 14 days prior to the initiation of study medication for oral contraception) throughout the study period up to 120 days after the last dose of trial therapy. If there is any question that a subject of childbearing potential will not reliably comply with the requirements for contraception, that subject should not be entered into the study.

5.5.3 Use in Pregnancy

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

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

5.5.4 Use in Nursing Women

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

5.6 Subject Withdrawal/Discontinuation Criteria

Subjects may withdraw consent at any time for any reason or be dropped from the trial at the discretion of the investigator should any untoward effect occur. In addition, a subject may be withdrawn by the investigator or the Sponsor if enrollment into the trial is inappropriate, the trial plan is violated, or for administrative and/or other safety reasons. Specific details regarding discontinuation or withdrawal are provided in Section 7.1.4 – 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.
- Unacceptable adverse experiences as described in Section 5.2.1.2
- Intercurrent illness that prevents further administration of treatment
- Investigator's decision to withdraw the subject
- The subject has a confirmed positive serum pregnancy test
- Noncompliance with trial treatment or procedure requirements
- The subject is lost to follow-up
- 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 telephone for overall survival until death, withdrawal of consent, or the end of the study, whichever occurs first.

5.7 Subject Replacement Strategy

Subjects receiving less than 2 doses of pembrolizumab may be replaced but will be monitored for study specified outcomes. Subjects removed from the trial for toxicities / SAEs probably or definitely related to pembrolizumab will not be replaced.

5.8 Clinical Criteria for Early Trial Termination

As a feasibility trial in which patients may receive the standard of care in addition to pembrolizumab therapy at the discretion of the treating physician, stopping rules for FUTILITY are not indicated.

Stopping rules for TOXICITY are outlined in section 8

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

Study Period:	**Screening Phase**		**Treatment Cycles Phase I: Induction**				**Response Post-Induction**	**Treatment Cycles Phase II: Maintenance**	**Response Post-Maintenance**	**Post-Treatment**	
Treatment Dose/Title Day (D)	Pre-screening	Main Study Screening	1 (D1)	2 (D22)	3 (D43)	4 (D64)	(D77)	Doses 5 – 17 (D85 - D365)*	End of Treatment (D365)	Follow-up: 30 and 90 Days After Treatment up to D455†	Relapse‡
Scheduling Window (Days):	Days -21 to -1	Days -21 to -1	± 3	± 3	± 3	± 3	±7	± 3	± 14	± 14	n/a
		Administrative Procedures									
Informed Consent		X									
Inclusion/Exclusion Criteria	X	X									
Subject Identification Card		X									
Demographics and Medical History		X									
Prior and Concomitant Medication Review		X					X				
Study Treatment Administration			X	X	X	X		X			
Post-study Therapy Response Status									X		
Survival Status									X	X	
		Clinical Procedures/Assessments									
Review Adverse Events		X	X	X	X	X	X	X	X	X	
Full Physical Examination		X	X	X	X	X	X				
Directed Physical Examination								X	X	X	
Vital Signs and Weight		X	X	X	X	X	X	X	X	X	
ECOG OR Karnofsky Performance Status		X	X	X	X	X	X	X			
		Laboratory Procedures/Assessments: analysis performed by LOCAL laboratory									
Pregnancy Test – Urine or Serum b-HCG		X	X	X	X	X	X				
PT/INR and aPTT		X	X	X	X	X					
CBC with Differential		X	X	X	X	X	X	X	X	X	
Comprehensive Serum Chemistry Panel‖		X	X	X	X	X	X	X	X	X	
LDH and Uric acid		X	X	X	X	X					
Urinalysis		X	X	X	X	X		X			

Study Period:	**Screening Phase**		**Treatment Cycles Phase I: Induction**				**Response Post-Induction**	**Treatment Cycles Phase II: Maintenance**	**Response Post-Maintenance**	**Post-Treatment**	
Treatment Dose/Title Day (D)	Pre-screening	Main Study Screening	1 (D1)	2 (D22)	3 (D43)	4 (D64)	(D77)	Doses 5 – 17 (D85 - D365)*	End of Treatment (D365)	Follow-up: 30 and 90 Days After Treatment up to D455†	Relapse‡
Scheduling Window (Days):	Days -21 to -1	Days -21 to -1	± 3	± 3	± 3	± 3	±7	± 3	± 14	± 14	n/a
T3, FT4 and TSH		X	X	X	X	X		X			
		Efficacy Measurements									
Bone Marrow Morphology§				D35 (±5)			X		X		X
Bone Marrow Flow Cytometry§				D35 (±5)			X		X		X
Bone Marrow Cytogenetics§				D35 (±5)			X		X		X
		Tumor Biopsies/Archival Tissue Collection/Correlative Studies Blood									
Pre-transplant Bone Marrow Biopsy Specimen Collection		X									
Correlative Studies: Bone Marrow Aspirate§		X		D35 (±5)			X		X		X
Correlative Studies: Blood Collection§,¶		X	D14 (+5)	D35 (±5)	D56 (±5)		X	D168 (±7) D252 (±7)	X	D425 (±14)†	X
Correlative Studies: Buccal Swabs		X									
Chimerism Analysis (VNTR) (Peripheral Blood)**		X		X			X		X		X

*Phase II Maintenance treatment: For subjects achieving CR / PR as determined by day 77 response post-induction without significant pembrolizumab related toxicity. Subjects without CR / PR at day 77, relapse / progression after day 77 or clinically significant toxicity during the treatment will be considered off treatment and will be placed into follow-up.

†Follow up: Toxicity assessments will be for 30 days after last dose of pembrolizumab. Longer follow-up for up to 90 days, if applicable, based on continuing SAE / AE that was observed in the treatment period or an events of clinical interest (ECI). Follow up for survival will be up to 90 days after pembrolizumab or D455 (±14) for subjects completing

maintenance and a research blood collection will be obtained. Subjects not initiating or completing maintenance will complete 30 day toxicity assessments and then be followed only for survival (through D365 after initiating pembrolizumab). Subjects in CR/PR not completing maintenance for toxicity may have additional research specimens collected per investigators discretion (see below note). ‡ Relapse denotes collection of unplanned / unscheduled bone marrow aspirate, biopsy and correlative studies at time of clinical suspicion of relapse (if CR) or progression of malignancy at any time during treatment and follow-up periods.

§Bone marrow morphology based on aspirate and/or core biopsy, flow cytometry and ± cytogenetics will be performed on day 35 (+5) after dose #2, day 77 (±7) after dose #4, day 365 (±14) after completing maintenance. An end of treatment bone marrow may be performed prior to day 365 in subjects in CR/PR who do not complete full maintenance therapy due to toxicity. Subjects removed from further treatment due to documented relapse are not required to undergo further bone marrow studies for research purposes. Cytogenetic analysis may be omitted if there are not pre-treatment cytogenetic anomalies of clinical interest.

‖Comprehensive Serum Chemistry Panel should include Magnesium and Phosphorus.

¶ PK and anti-pembrolizumab Ab testing may be performed as a component of the research lab testing, as indicated. These studies will be performed after collaboration with the sponsor (Merck)

** Chimerism studies (lineage specific) when sent as part of routine care will be recorded as percentage of donor cells (CD3 and CD33).

Note: Every effort will be made to collect bone marrow and blood samples for efficacy and correlative specimens for research purposes. Efficacy and correlative studies not obtained during the treatment and post-treatment for clinical reasons (e.g. intercurrent illness, leukemia progression receiving concomitant chemotherapy, myeloid sarcoma) will not constitute a protocol deviation.

7.0 TRIAL PROCEDURES

7.1 Trial Procedures

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

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

7.1.1 Administrative Procedures

7.1.1.1 Informed Consent

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

7.1.1.1.1 General Informed Consent

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

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

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

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

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

7.1.1.2 Inclusion/Exclusion Criteria

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

7.1.1.3 Medical History

A medical history will be obtained by the investigator or qualified designee. Medical history will include all active conditions. 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 7 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

The investigator or qualified designee will review all new anti-neoplastic therapy initiated after the last dose of trial treatment. Once new anti-cancer therapy has been initiated the subject will move into survival follow-up.

7.1.1.6 Assignment of Screening Number

A screening number will be assigned to all subjected being screened.

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 treatment and during the safety follow-up period (30 days after the last dose of pembrolizumab) according to NCI CTCAE Version 4.0 (see Section 11.3. Adverse events in the post-treatment follow up period will not be recorded or reported unless they represent continuing adverse events from the treatment period related to pembrolizumab therapy.

Toxicities will be characterized in terms regarding seriousness, causality, toxicity grading, and action taken with regard to trial treatment.

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

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

7.1.2.2 Full Physical Exam

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

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. Height will be measured at screening only.

7.1.2.5 Eastern Cooperative Oncology Group (ECOG) Performance Scale

The investigator or qualified designee will assess ECOG status (see Section 11.1) at screening, prior to the administration of each dose of trial treatment and discontinuation of trial treatment as specified in the Trial Flow Chart. As Karnofsky performance score is commonplace in BMT clinical practice and research, this scale is acceptable in place of ECOG (Appendix 11.2)

7.1.2.6 Tumor Tissue Collection and Correlative Studies Blood Sampling

See section **7.1.3.1.3**

7.1.3 Laboratory Procedures/Assessments

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

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

Table 5 Laboratory Tests

Hematology	Chemistry	Urinalysis	Other
Hematocrit	Albumin	Blood	Serum β-human chorionic gonadotropin†
Hemoglobin	Alkaline phosphatase	Glucose	(β-hCG)†
Platelet count	Alanine aminotransferase (ALT)	Protein	PT (INR)
WBC (total and differential)	Aspartate aminotransferase (AST)	Specific gravity	aPTT
Red Blood Cell Count	Lactate dehydrogenase (LDH)	Microscopic exam *(If abnormal)*	Total thriiodothyronine (T3)
Absolute Neutrophil Count	Carbon Dioxide ‡	results are noted	Free tyroxine (T4)
Absolute Lymphocyte Count	*(CO_2 or biocarbonate)*	Urine pregnancy test †	Thyroid stimulating hormone (TSH)
	Uric Acid		PK
	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.

‡ If considered standard of care in your region.

7.1.3.1 Pharmacokinetic/Pharmacodynamic and Laboratory correlation Evaluations

7.1.3.1.1 Blood Collection for Serum pembrolizumab

Sample collection, storage and shipment instructions for serum samples will be provided in the Laboratory Manual.

The time points for PK blood sampling are described in Section 6 – Trial Flow Chart.

7.1.3.1.2 Blood Collection for Anti-pembrolizumab Antibodies

Sample collection, storage and shipment instructions for blood samples will be provided in the Laboratory Manual.

7.1.3.1.3 Laboratory Correlates

The immunobiologic, neoantigen analyses, advanced studies for minimal residual studies, and flow and ex vivo studies will be performed in collaboration by Drs. Pavan Reddy's and Brian Parkin's labs with additional support from Dr. Arul Chinnaiyan's lab.

Lab correlates	**Assays**	**Tissue/Body Fluid Tested and Timing of Assay**
Immune-antigen repertoire and inhibitory receptor analyses of AML cells and donor T cell exhaustion and functional analyses	Whole exome sequencing of AML at relapse, Flow cytometry, tetramer analyses, cellular killing assays, MHC-peptide binding affinity studies, PCR	PBMC and BM: day 1 (pre-treatment), ±14, 35, 77, ±168, ±252, 365, ±425 , and at relapse/progression
Functional T cell subtypes and cytokine profiles	Flow cytometry: Quantify activated and effector $CD4^+$ and $CD8^+$ cells, NK cells, senescent, exhaustion and regulatory T cells (CD45RA, CD45RO, CD127, CD25, CCR7, CD57, CD28, CD62L, CTLA4, LAG3 and Foxp3) Cytokine profiling: Intracellular IFN-γ (Th1), IL-4 (Th2), IL-17 (Th17), IL-2, and transcription factor profiling with Q-PCR for T-bet, Gata-3, RORγT, Foxp3	PBMC and BM: day 1 (pre-treatment), ±14, 35, 77, ±168, ±252, 365, ±425 , and at relapse/progression
AML immune peptide repertoire analyses	• Whole exome sequencing (WES) of relapsed AML blasts • Characterize neoantigens • Bioinformatically nominate most immunogenic peptides • Functionally validate in silico the immunogenic potential of the peptides in the context of the donor MHC	
Characterization of T cell exhaustion	• Functionally validate in vitro the bioinformatically nominated	

Antigen specific T cell expansion Functional Antigen presenting cells subtypes and cytokine profiles	immunogenic AML peptides by performing MHC-peptide binding affinity assays PD1, CTLA4, LAG3, TIM3, TIGIT Tetramer staining for leukemia specific (HLA-$A2^+$ restricted WT1, PRAME, proteinase-3), hematologic cell specific minor antigen specific (HLA-B7 restricted LRH-1), and CMV (pp65). Quantify CD11c, CD1a, CD14, BDCA3, HLADR, CD40, CD80, CD86 and intracellular IL-1β, TNFα, IL-10, IL-6	
T cell and NK cell cytotoxicity Plasma cytokines	Intracellular CD107a, granzymeB (flow cytometry), flow cytometric analysis of tumor cell death TNFα, IL-6, IL-1β, IL-10, Reg3α, ST-2, TNFR1	PBMC: day 1 (pre-treatment), ~d14 [before 2nd dose of anti-PD-1], 35, 56, 77, ±168, ±252, ±365, ±425 and at relapse/progression
Ex-vivo stimulation analyses	Ex-vivo stimulation with specific peptides and DCs with ELISPOT, CFSE and CD107a	PBMC: day 1 (pre-treatment), ~d14 [before 2nd dose of anti-PD-1], 35, 56, 77, ±168, ±252, ±365, ±425 and at relapse/progression
AML and MDS post-therapy clonal selection analysis High-sensitivity response assessment (genomic minimal residual disease detection)	Droplet digital PCR (ddPCR) and single-molecule/real-time (SMRT) sequencing of AML- and MDS-associated mutations in BM, PBMC, and cell-free DNA to: • Define and distinguish responsive and resistant AML clones via longitudinal analysis • Assess kinetics and depth of response to therapy at serial timepoints	PBMC and BM: day 1 (pre-treatment), ±14, 35, 77, ±168, ±252, 365, ±425 , and at relapse/progression

Sample collection: We will obtain 4 heparinized (green top) and 1 EDTA (purple top) blood samples (or approximately 35 mL total/sample) as well as bone marrow aspirates per schedule shown in the schema above. Buccal swabs will also be collected once prior to initiation of therapy for use as a normal DNA control for each patient. Plasma will be banked and frozen for analysis of anti-PD-1 antibody titers, cytokine analyses, and cell-free DNA as indicated. Leukocytes will be isolated by Ficoll gradient centrifugation and used for phenotypic and functional analyses described below. AML blasts will be analyzed for immune peptide repertoire analyses and as targets for ex vivo studies. For the purposes of this study, day 1 is defined as the first day of pembrolizumab.

Statistics for correlative studies: The statistics will be descriptive in nature and hypothesis generating. However the analyses of leukemia from the bone marrow (BM) and both peripheral blood and BM derived

T cells analyses at the time of relapse after allo-HSCT, post treatment with pembrolizumab at at 35, 77 and 365 days will nonetheless serve as internal controls for assessing the impact of treatment on relapse, T cell functionality, immune neoantigen repertoire analyses, and depth and kinetics of response. However, the association of the laboratory values and percentage change of each variable and their relation to primary and secondary clinical outcomes will be descriptive and estimated with Cox regression (for response rate and PFS) and competing risks regression (TRM, relapse/progression).

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. 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.

7.1.4.2 Screening

A subject will be considered to be in the “Screening” period from the time he/she signs consent until the date the subject is determined as either “eligible” or “ineligible” (screen failure) by PI or a Co-I. Patients may be consented to this study based on disease eligibility and other criteria at the time of consent, but later removed from the study if the change of disease status makes the subject “ineligible”. In the event that this occurs, the subject will be replaced.

7.1.4.3 Treatment Period

“Treatment Period” is defined as the first day of pembrolizumab through 30 days after the last dose of pembrolizumab – from 1st to 4th doses (or 17th dose if receiving maintnenance). The assessment and reporting period for **adverse events (AE) related to the pembrolizumab** will start from the first pembrolizumab administration until 30 days after the last pembrolizumab administration.

“Follow-up Period” is defined as the first day the subject is no longer within the treatment period (e.g. 31 days after last administration of pembrolizumab) until six months after date of initiating study treatment.

7.1.4.4 Post-Treatment Visits

7.1.4.4.1 Safety Follow-Up Visit

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

7.1.4.5 Follow-up Visits

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 7.1.4.5.1.

Subjects in this trial will not be eligible for retreatment with pembrolizumab beyond the initial study phase.

7.1.4.5.1 Survival Follow-up

If a subject experiences a treatment related adverse event that necessitates their removal from further study treatment , starts a new anti-cancer therapy (non-protocol defined therapy), does not achieve after induction (phase I), develops progression during maintenance (phase II) or or completes planned treatment phase the subject moves from treatment into the survival follow-up phase and will be followed at a minimum of every 8 weeks to assess for survival status until death, withdrawal of consent, or the end of the study (1 year after initiation of pembrolizumab or 90 days after last maintenance dose of pembrolizumab), whichever occurs first (please reference section 5.2.1.2 of this protocol regarding permitted chemotherapies on-protocol). These visits will be coordinated with routine BMT follow-up. If follow-up is not feasible (e.g. patient leaves center) phone contacts will be made every 12 weeks.

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 the 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, teething, typical crying in infants and children and onset of menses or 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 as prescribed in clinical practice, from overdose (whether accidental or intentional), from abuse and from withdrawal.

Progression of the cancer under study is not considered an adverse event.

All adverse events that occur **after subject eligibility is confirmed** but before treatment allocation/randomization must be reported by the investigator if they ultimately cause the subject to be excluded from initiating treatment on 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.

From the time of treatment allocation/randomization through 30 days following cessation of treatment, **all non-hematologic grade ≥ III adverse events must be reported by the investigator**. **Investigators will monitor patients carefully for early evidence of transplant-related complications, such as hyperacute graft-versus-host disease (GVHD), severe acute GVHD, steroid-requiring febrile syndrome, hepatic veno-occlusive disease, and other immune-mediated adverse reactions.** Such events will be recorded 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. The investigator will make every attempt to follow all subjects with non-serious adverse events for outcome.

Adverse events will not be collected for subjects during the pre-screening period (for determination of archival tissue status) as long as that subject has not undergone any protocol-specified procedure or intervention. If the subject requires a blood draw, fresh tumor biopsy etc., the subject is first required to provide consent to the main study and AEs will be captured according to guidelines for standard AE reporting.

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

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

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

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

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

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

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

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

Pregnancies and lactations that occur from the time of treatment allocation/randomization through 120 days following cessation of Sponsor's product, or 30 days following cessation of treatment if the subject

initiates new anticancer therapy, whichever is earlier, must be reported by the investigator. All reported pregnancies must be followed to the completion/termination of the pregnancy. Pregnancy outcomes of spontaneous abortion, missed abortion, benign hydatidiform mole, blighted ovum, fetal death, intrauterine death, miscarriage and stillbirth must be reported as serious events (Important Medical Events). If the pregnancy continues to term, the outcome (health of infant) must also be reported.

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

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

7.2.3.1 Serious Adverse Events

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

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

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

Refer to Table 6 for additional details regarding each of the above criteria. For the time period beginning when the subject is enrolled until treatment is initiated, any serious adverse event, or follow up to a serious adverse event, including death due to any cause other than progression of the cancer under study (reference Section 7.2.3.3 for additional details) that occurs to any subject must be reported within 24 hours to the Sponsor and within 2 working days to Merck Global Safety if it causes the subject 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.

NOTE: for the purposes of this protocol planned hospitalizations solely for administration of protocol-specified chemotherapy for tumor progression will not require expedited reporting. For the time period beginning at treatment allocation/randomization through 30 days following cessation of treatment, any serious adverse event, or follow up to a serious adverse event, including death due to any cause other than progression of the cancer under study (reference Section 7.2.3.3 for additional details), 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 the Sponsor and to Merck Global Safety.

All subjects 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: +1-215-993-1220

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

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 subject must be reported within 24 hours to the Sponsor and within 2 working days to Merck Global Safety if it causes the subject 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 subject 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 24 hours to the Sponsor and within 24 hours to Merck Global Safety.

Events of clinical interest for this trial include:

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, that is not associated with clinical symptoms or abnormal laboratory results.

2. When **NOT** deemed to be related to underlying leukemia, an elevated AST or ALT lab value that is **greater than or equal to 5X** the upper limit of normal and an elevated total bilirubin lab value that is greater than or equal to 2X the upper limit of normal and, at the same time, an alkaline phosphatase lab value that is less than 2X the upper limit of normal, as determined by way of protocol-specified laboratory testing or unscheduled laboratory testing.*

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

7.2.4 Evaluating Adverse Events

An investigator who is a qualified physician will evaluate all adverse events according to the NCI Common Terminology for Adverse Events (CTCAE), version 4.0. Any adverse event which changes CTCAE grade

over the course of a given episode will have each change of grade recorded on the adverse event case report forms/worksheets.

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:

V4.0 CTCAE Grading	**Grade 1**	**Mild; asymptomatic or mid symptoms; clinical or diagnostic observations only; intervention not indicated.**
	Grade 2	**Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL.**
	Grade 3	**Severe or medically significant but not immediately life-threatening; hospitalization or prolongation or hospitalization indicated; disabling; limiting self-care ADL.**
	Grade 4	**Life threatening consequences; urgent intervention indicated.**
	Grade 5	**Death related to AE**
Seriousness	A serious adverse event is any adverse event occurring at any dose or during any use of Merck product that:	
	†**Results in death**; or	
	†**Is life threatening; or** places the 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 for an elective procedure to treat a pre-existing condition that has not worsened is not a serious adverse event. A pre-existing condition is a clinical condition that is diagnosed prior to the use of a Merck product and is documented in the patient's medical history.); or	
	†**Is a congenital anomaly/birth defect** (in offspring of subject taking the product regardless of time to diagnosis);or	

	Is a new **cancer** (that is not a condition of the study) **(**although not serious per ICH definition, is reportable to the Sponsor within 24 hours and to Merck within 2 working days to meet certain local requirements); **or**	
	Is an overdose (whether accidental or intentional). Any adverse event associated with an overdose is considered a serious adverse event for collection purposes. An overdose that is not associated with an adverse event is considered a non-serious event of clinical interest and must be reported within 24 hours to the Sponsor and to Merck within 2 working days..	
	Other important medical events that may not result in death, not be life threatening, or not require hospitalization may be considered a serious adverse event when, based upon appropriate medical judgment, the event may jeopardize the 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 Merck product to be discontinued?	
Relationship to Merck Product	Did Merck product cause the adverse event? The determination of the likelihood that Merck product caused the adverse event will be provided by an investigator who is a qualified physician. The investigator's signed/dated initials on the source document or worksheet that supports the causality noted on the AE form, ensures that a medically qualified assessment of causality was done. This initialed document must be retained for the required regulatory time frame. The criteria below are intended as reference guidelines to assist the investigator in assessing the likelihood of a relationship between the test drug and the adverse event based upon the available information. **The following components are to be used to assess the relationship between Merck product and the AE**; the greater the correlation with the components and their respective elements (in number and/or intensity), the more likely Merck product caused the adverse event (AE):	
	Exposure	Is there evidence that the subject was actually exposed to Merck product such as: reliable history, acceptable compliance assessment (pill count, diary, etc.), expected pharmacologic effect, or measurement of drug/metabolite in bodily specimen?

	Time Course	Did the AE follow in a reasonable temporal sequence from administration of Merck product? Is the time of onset of the AE compatible with a drug-induced effect (applies to trials with investigational medicinal product)?
	Likely Cause	Is the AE not reasonably explained by another etiology such as underlying disease, other drug(s)/vaccine(s), or other host or environmental factors

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

Record one of the following	**Use the following scale of criteria as guidance (not all criteria must be present to be indicative of Merck product relationship).**
Yes, there is a reasonable possibility of Merck product relationship.	There is evidence of exposure to Merck product. The temporal sequence of the AE onset relative to the administration of Merck product is reasonable. The AE is more likely explained by Merck product than by another cause.
No, there is not a reasonable possibility of Merck product relationship	Subject did not receive the Merck product OR temporal sequence of the AE onset relative to administration of Merck product is not reasonable OR the AE is more likely explained by another cause than the Merck product. (Also entered for a subject with overdose without an associated AE.)

7.2.5 Sponsor Responsibility for Reporting Adverse Events

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

8.0 STATISTICAL ANALYSIS PLAN

8.1 Statistical Analysis Plan Summary

The statistical plan for this feasibility study of pembrolizumab for relapse after HCT is primarily directed toward the primary objective of safety and feasibility after HCT. The trial will additionally estimate the proportion of patients responding to pembrolizumab monotherapy by overall response rate (ORR). The ORR (CR+PR) will also be estimated at day 35 and 77 for subjects receiving ≥ one dose of single agent pembrolizumab. If progression is noted subjects may receive standard induction chemotherapy. Subjects who are administered standard induction chemotherapy prior to day 77 (for any reason) will be considered non-responders for ORR of pembrolizumab monotherapy. However, we will perform a planned subset analysis to determine the ORR at day 77 for subjects receiving pembrolizumab followed by systemic chemotherapy.

The incidence of grade 3-4 acute GvHD and significant (≥ grade 3) immune mediated toxicities will be estimated at the conclusion of the treatment period which is 30 days after the last dose of pembrolizumab. Overall survival (OS) and Disease Free Survival (DFS) at 12 months will be calculated by Kaplan Meier methods. The observation period for OS and DFS will begin at the confirmed date of relapse after HCT until death or last scheduled clinical follow up. These observations will assist in determining whether further investigations are warranted after HCT.

8.2 Statistical Analysis Plan

8.2.1 As a phase 1b study, the analysis of results will be descriptive in nature. This study will estimate:

- ORR at days 35 and 77 in subjects receiving pembrolizumab monotherapy

- ORR at day 77 in subjects receiving pembrolizumab ± standard induction chemotherapy

- Clinical Benefit Rate (CBR) at days 35 and 77 in subjects receiving pembrolizumab monotherapy

Safety:

- Incidence and severity of GvHD after administration of pembrolizumab to include analysis of:

  a) incidence of severe acute GvHD events (grade 3-4) during induction treatment treatment and within 30 days of last pembrolizumab infusion during induction treatment (as described in sections 7.2 and 8.1).

  b) incidence of total GvHD events (acute GVHD grade 2-4, new onset chronic GVHD) that occur in subjects during treatment (both induction and maintenance) and in follow up through 90 days after last pembrolizumab infusion. Subjects taken “off-study” will be censored if they receive other immune therapies (e.g. DLI).

- Grade 3-5 Regimen-related toxicities (RRT) per CTCAE v4

- Incidence of immune mediated toxicities attributable to pembrolizumab

8.2.2 Sample size estimate to assess if study drug is promising for further study

Considering the highly refractory nature of the subjects to be enrolled in this study and our lack of understanding of the kinetics of response to pembrolizumab in the post HCT setting, the investigators will be cautious about the potential underestimation of response of this novel agent. In addition, several, but not all patients are expected to receive standard chemotherapy at some point during their on-study therapy, thereby potentially confounding interpretation of the response rate to study drug. Therefore, the following criteria will be used to assess if the study drug is promising for further study:

(a) if ≥ 4 subjects demonstrate evidence of clinical benefit the drug will be considered promising. With 20 subjects we would be 90% confident that the true clinical benefit rate (CBR) lies between 7% and 40%. The CBR will be assessed on both day 35 and day 77 as determined by the proportion of subjects who receive pembrolizumab monotherapy who achieve either stable disease (SD) or ORR prior to the addition of standard chemotherapy

(b) the observation of any CRs seen in subjects not receiving standard chemotherapy will be considered promising.

8.2.2.1 Definition of Response.

For the purposes of this study, complete remission (CR) will be defined as achieving a morphologic leukemia free state by achieving all of the following criteria: bone marrow myeloblasts < 5% by morphologic assessment; AND absence of circulating blasts with phenotypic or morphologic features of leukemia (e.g. Auer rods) AND no evidence of extramedulary disease. For subjects with ≤ 5% blasts but possessing flow cytometric, cytogenetic or molecular aberration (Sec 5.1); CR will also require resolution (absence) of that aberration. Partial remission (PR) will be defined as a ≥ 50% reduction in bone marrow blast percentage to 5-25% or marrow blasts < 5% with persistent Auer rods, flow cytometric or cytogenetic disease. PR is not possible response designation for indivuals entering with ≤ 5% blasts. SD will be defined as ≤ 5% increase in blasts or decreased blast percentage in the bone marrow that does not meet the criteria for PR. Progression will be defined as >5% increase in bone marrow blast percentage from prior bone marrow aspirate. NOTE Given these patients have relapsed after allogeneic HCT blood count recovery is not considered at criteria for response in this protocol.

8.2.3 Stopping rules for futility: Study subjects will receive pembrolizumab ± the addition of standard chemotherapy, therefore stopping rules for futility are not indicated. The primary endpoint of this study is safety and feasibility.

8.2.4 Stopping rules for toxicity: Patients will be monitored closely for the development of immune-mediated toxicity that may be attributable to pembrolizumab. For the purposes of this trial, we will consider the development of acute GvHD as a distinct entity from the known immune-mediated toxicity profile associated with PD1 blockade, though there may be clinical overlap. The impact of PD1 blockade on the development of acute GvHD following allogeneic HCT has not been studied in human subjects. Therefore, a rational approach will focus on whether there is an **increase** in the rates and severity of

acute GvHD and other immune mediated toxicities **over the expected baseline**. The following assumptions will be used to assess potential toxicities associated with this trial:

- All subjects will be inherently at risk for the development of GvHD as this study is limited to patients who have relapsed post-HCT. Although screening will exclude patients with active GvHD requiring immunosuppression, subjects will remain at risk independent of whether they receive study drug. The expected incidence of clinically significant grade 2 to 4 acute GvHD (requiring therapy) without Pembrolizumab is estimated to be 40-50%.

- Patients who relapse (without GVHD present) may still be receiving standard immunosuppression post-HCT to reduce the risk of inciting GVHD. Immunosuppressive medications (IS)may be withdrawn or tapered per usual care. Because patients are at risk for the development of GVHD within several weeks after IS withdrawal tapering may occur during administration of pembrolizumab at a rate determined by the treating physician. Due to timing of IS withdrawal overlapping with the treatment period for pembrolizumab, potentially confounding its relationship to the study drug, an aggregate summary of toxicity will be used to determine whether PD1 blockade is potentially associated with an increase in the severity of acute GvHD.

- For the purposes of this study, toxicity will be deemed as excessive if 12 of 20 subjects (60%) develop severe acute GvHD (≥ grade 3-4) OR ≥ grade 3 immune related adverse events that do not improve to grade 1 after systemic corticosteroid treatment for 14 days. This study specific stopping rule is intended to capture excessive rates of severe acute GvHD (grades 3-4) as an adverse safety signal. We have set this threshold because some degree of GvHD is an anticipated consequence of usual withdrawal of immune-suppression and chemotherapy which is a current treatment standard for relapse. Grade 2 GvHD is associated with less morbidity and mortality compared to grades 3-4 and may be a potential surrogate of a beneficial anti-leukemic response (GvL), thus grade 2 GvHD will be recorded but not included in the stopping definition. The occurrence of severe acute GvHD for this toxicity rule will be monitored during the induction treatment period until 30 days after the last induction treatment dose of pembrolizumab given for the induction phase (doses 1-4).

- We will also make interim assessments after 10 and 15 patients have been observed for 30 days after the last induction dose of pembrolizumab. Specifically, further accrual will be halted if we observe at least 6 of 10 or 9 of 15 patients developing severe acute GvHD. If the true rates of severe acute GvHD are 30%, 40%, 50% or 60%, the study has respective probabilities of 0.05, 0.18, 0.43, and 0.71 of stopping early.

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9.0 LABELING, PACKAGING, STORAGE AND RETURN OF CLINICAL SUPPLIES

9.1 Investigational Product

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

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

Table 7 Product Descriptions

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

9.2 Packaging and Labeling Information

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

9.3 Clinical Supplies Disclosure

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

9.4 Storage and Handling Requirements

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

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

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

9.5 Returns and Reconciliation

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

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

10.0 ADMINISTRATIVE AND REGULATORY DETAILS

10.1 Confidentiality

Subject medical information obtained as part of this study is confidential, and must not be disclosed to third parties, except as noted below. The subject may request in writing that medical information be given to his/her personal physician.

The Investigator will permit direct access to source data and documents by the FDA and/or other applicable regulatory authority. The access may consist of study-related monitoring, audits, IRB or Ethics

Committee reviews, and FDA inspections. Release of research results should preserve the privacy of medical information and must be carried out in accordance with Department of Health and Human Services Standards for Privacy of Individually Identifiable Health Information, 45 CFR 164.508.

10.2 Compliance with Financial Disclosure Requirements

The sponsor, investigator and members of the study team will comply with all applicable regulations regarding financial disclosure requirements.

10.3 Compliance with Law, Audit and Debarment

The study will be conducted in accordance with U.S. Food and Drug Administration (FDA) and International Conference on Harmonization (ICH) Guidelines for Good Clinical Practice (GCP), the Declaration of Helsinki, Health Canada, any applicable local health authority, and Institutional Review Board (IRB) or Ethics Committee requirements.

This study must have the approval of a properly constituted IRB or Ethics Committee. Before the investigational drug is shipped to the Investigator, the Investigator or designee will provide Merck with a copy of the IRB or Ethics Committee approval letter stating that the study protocol and any subsequent amendments and informed consent form have been reviewed and approved.

The Investigator or designee will be responsible for obtaining annual IRB or Ethics Committee re-approval throughout the duration of the study.

The Investigator is also responsible for notifying their IRB or Ethics Committee of any significant adverse events that are serious and/or unexpected. The Investigator is also required to notify the FDA in writing of any SAE that is both unexpected and related to the study drug, within 15 days of knowledge of the event, and within 7 days of a death related to the study drug.

10.4 Compliance with Trial Registration and Results Posting Requirements

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

10.5 Quality Management System

The following quality management systems at the University of Michigan will be performed in the conduct of this clinical trial.

10.5.1 Data Safety Monitoring Plan

The following are the procedures for data and safety monitoring of this clinical trial to be conducted at the University of Michigan Blood and Marrow Transplant program and sponsored by Merck, Inc. This is to ensure the safety of participants, the validity of research data, and the appropriate termination of studies for which significant benefits or risks have been uncovered or when it appears that the trial cannot be

concluded successfully. This protocol will conduct a data and safety monitoring process as described in the plan below.

10.5.2 Clinical Monitoring Plan

This trial will be monitored in accordance with the NCI approved University of Michigan Comprehensive Cancer Center Data and Safety Monitoring Plan.

The study team will provide continuous review of the data and patient safety and meet monthly or more frequently depending on the activity of the protocol. The discussion will include matters related to the safety of study participants (SAE/UaP reporting), validity and integrity of the data, enrollment rate relative to expectations, characteristics of participants, retention of participants, adherence to the protocol (potential or real protocol deviations) and data completeness. At these regular meetings, the protocol specific Data and Safety Monitoring Report form will be completed and signed by the Principal Investigator or by one of the co-investigators.

Data and Safety Monitoring Reports will be submitted to the University of Michigan Comprehensive Cancer Center Data and Safety Monitoring Committee on a monthly basis for independent review.

The University of Michigan Comprehensive Cancer Center Data and Safety Monitoring Committee can request a 'for cause' audit of the study if the committee identifies a need for a more rigorous evaluation of study-related issues. A "for cause" audit would be conducted by the Quality Assurance Review Core (QARC) of the University of Michigan Comprehensive Cancer Center.

A regulatory authority (e.g. FDA) may also wish to conduct an inspection of the study, during its conduct or even after its completion. If an inspection has been requested by a regulatory authority, the site investigator must immediately inform the Clinical Trials Office that such a request has been made.

10.5.3 Trained and Certified Personnel

All of the research protocol personnel who will work with study subjects, study subject data or subjects' research samples have completed training in the protection of human research participants per guidelines issued by the U. S. Department of Health and Human Services, Office of Human Research Protections. The documentation of completion of the certification is maintained in the Oncology Clinical Trials Support Unit (OCTSU). The investigator and designated associates have attended an IRB sponsored HIPAA research presentation in accordance with the policy of the study site. Each participant in this research trial will be listed by study specific numbers, without initials or date of birth; however, the date of transplant may be included when corresponding with the IRB or outside agencies.

Designation of Responsibilities: The Principal investigator is solely responsible for the implementation, conduct and safety of human subjects enrolled in this trial. The principal investigator has however, designated associates to assist with the protocol implementation which includes but is not limited to the following:

1. BMT Physicians – have been designated to assist with participant education, informed consent process, study implementation and compliance, recording of primary source documentation, AE assessment and reporting, adherence to all regulations.

2. BMT Research Nurse(s) - have been designated to assist with participant education, informed consent process, study implementation and compliance, recording of primary source documentation and adherence to all regulations.
3. BMT Data Manager(s) - have been designated to assist with patient enrollment/eligibility, verification of protocol compliance, all data collection and recording from primary source, AE reporting, DSM reports and adherence to all regulations.
4. BMT Clinical Team - The members of the BMT clinical team that have been designated to assist the investigator in any aspect of this protocol will be listed on the protocol specific designation log.
5. The BMT program's internal Data and Safety Monitoring Committee (BMT DSMC) will meet monthly to review the data, safety and monitoring reports and all SAEs that have been filed.

Storage and Dissemination of Reports

The Oncology Clinical Trials Support Unit (OCTSU) at the University of Michigan is responsible for collating all the Data and Safety Monitoring Reports and providing this information to Data Safety Monitoring Committee. The OCTSU will coordinate the reporting process between the Investigators, the Sponsor, the IRB and UMCCC DSMC as well as other applicable reporting agencies (FDA and study sponsors). Copies of all related correspondence and reporting documents will be maintained in a locked file by the OCTSU regulatory team and the research data file will be maintained in a file by the BMT data management team.

Quality Assurance and Audits

The Quality Assurance Review Committee (QARC) of the UMCCC performs quality assurance audits of investigator-initiated clinical trials. Audits provide assurance that trials are conducted in compliance with the protocol. Further, they ensure that study data are collected, documented and reported in compliance with Good Clinical Practices (GCP) Guidelines and regulatory requirements. A QARC audit of each clinical trial is conducted annually. All audit findings are reported by QARC to the UMCCC DSMB and the sponsor. The DSMB can also request QARC for a 'for cause' audit of the trial if the board identifies a need for a more rigorous evaluation of study-related issues. A regulatory authority (e.g. FDA) may also wish to conduct an inspection of the study, during its conduct or even after its completion. If an inspection has been requested by a regulatory authority, the investigator must immediately inform the OCTSU QA Team that such a request has been made. Audits of conduct of the clinical trial will also be conducted by the CRO to be determined by the sponsor.

10.6 Data Management

All information will be recorded locally and entered into Case Report Forms (CRFs) on the web-based Velos data management system of the University of Michigan.

11.0 APPENDICES

11.1 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.	

11.2 KARNOFSKY PERFORMANCE SCALE (KPS)

%	Description
100	Normal, no complaints, no evidence of disease
90	Able to carry on normal activity, minor symptoms of disease
80	Normal activity with effort, some signs of symptoms of disease
70	Cares for self (consistent with age), unable to carry on normal activity or do active work/school/play
60	Requires occasional assistance (beyond age-appropriate care), but is able to care for most of their needs
50	Requires considerable assistance and frequent medical care
40	Disabled, requires special care and assistance
30	Severely disabled, hospitalization is indicated although death is not imminent
20	Hospitalization is necessary, very sick, active support treatment is necessary
10	Moribund, fatal processes progressing rapidly

11.3 Common Terminology Criteria for Adverse Events V4.0 (CTCAE)

The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for adverse event reporting. (http://ctep.cancer.gov/reporting/ctc.html)

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