SPONSOR:	Merck
TITLE:	Phase II trial of Lymphodepletion and Anti-PD-1 blockade to reduce relapse in high risk AML patients who are not eligible for allogeneic stem cell transplantation
IND NUMBER:	129899 Merck IND 118604
Protocol History	
Original	May 4, 2015
Revisions	October 20, 2015 December 29, 2015 March 22, 2016 March 25, 2016 March 29, 2016 September 9, 2016 November 11, 2016 January 16, 2017 December 12, 2017 July 6, 2021
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1.0 TRIAL SUMMARY

Abbreviated Title	Lymphodepletion and Anti-PD-1 blockade in AML
Trial Phase	*Phase II*
Clinical Indication	high risk AML patients not eligible for allogeneic stem cell transplantation
Trial Type	Single arm
Type of control	Historical
Route of administration	intravenous
Trial Blinding	none
Treatment Groups	Single arm
Number of trial subjects	20
Estimated enrollment period	*20 months*
Estimated duration of trial	*48 months*

2.0 TRIAL DESIGN

2.1 Trial Design:

Eligible patients:

1) Diagnosis of non-M3 AML

2) In CR1 with non-favorable risk disease (appendix 1) or subsequent CR defined as no evidence of residual leukemia by morphology, flow cytometry, cytogenetics, or FISH studies.

3) Completed at least one cycle of consolidation chemotherapy

4) Collection of at least 2x10e6/kg CD34+ cells, with negative immunophenotypic studies (no evidence of leukemia contamination by flow cytometric analysis) of the product

5) 18 - 78 years of age,

Preparative regimen / lymphodepletion:

Fludarabine 30mg/m^2/d x 3 days, days -4 to -2, and

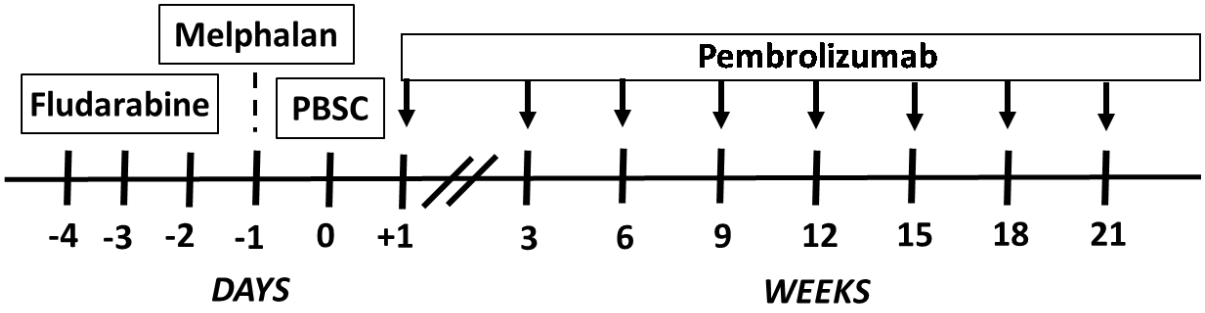
Melphalan 180mg/m^2 (age 18-60 years) or 140mg/m^2 (age 61-75 years), day -1

PBSC infusion Day 0

Anti-PD1 therapy:

Beginning day +1, pembrolizumab 200mg/dose will be administered q3weeks x 8 doses.

2.2 Trial Diagram



3.0 OBJECTIVES & HYPOTHESES

3.1 Primary Objective & Hypothesis

(1) **Objective:** To estimate the 2-yr relapse risk

Hypothesis: In patients with non-favorable risk AML in CR1 who are not candidates for allogeneic transplant, the risk of 2-yr relapse is estimated to be 60-80%. We hypothesize that following lymphodepleting chemotherapy and pembrolizumab, the 2-yr relapse risk will decrease to ≤35%.

3.2 Secondary Objective & Hypothesis

(1) **Objective**: To assess the safety of pembrolizumab in patients with AML following lymphodepleting chemotherapy

3.3 Exploratory Objective

(1) **Objective:** To assess the generation of anti-leukemic T cell responses in AML patients receiving pembrolizumab. Research blood samples will be drawn prior to lymphodepleting chemotherapy, prior to pembrolizumab dosing on each antibody dosing day, at 12 month, 18 month and 24 months following autologous transplantation (12 total samples).

4.0 BACKGROUND & RATIONALE

4.1 Background

Acute myeloid leukemia (AML) is the most common acute leukemia in adults. Treatment with modern chemotherapy regimens often induces complete remission, but a majority of patients will ultimately relapse and die of their disease. Results with conventional cytarabine-based post-remission therapy are unsatisfactory for the three-quarters of AML patients that do not fall in the favorable cytogenetic/molecular risk category. Five-year cumulative incidence of relapse following high-dose cytarabine is over 60% in intermediate risk AML and 90% in poor risk AML[3]. For many years, it has been recognized that allogeneic stem cell transplantation can be curative for some patients with AML[1,2], and as a result it remains the recommended consolidation approach for non-favorable risk AML patients in CR1 who are young, healthy and have suitable donors. The major therapeutic effect of allogeneic transplant is derived from the "graft-versus-leukemia" effect of allogeneic immune cells from the donor. Unfortunately, many patients with AML are not candidates for this procedure due to factors such as age, overall health, psychosocial limitations, or lack of an available donor. Therefore, cancer immunologists have sought approaches to stimulate anti-leukemic immunity within the host to promote immune-mediated elimination of AML.

In patients without an available donor, post-remission therapy with high-dose chemotherapy and autologous transplant has been utilized in an attempt to improve outcomes. Autologous transplant has consistently resulted in a significant reduction in relapse risk when compared with conventional chemotherapy, leading to improved event-free survival in a large number of clinical studies[4-9]. This has unfortunately not translated into improved overall survival in these patients, likely due to the ability to salvage relapse with allogeneic transplant in a subset of patients.

Cancer cells can express tumor antigens, rendering them susceptible to recognition and killing by cytotoxic T cells. However, spontaneous rejection of established cancers is a rare occurrence, in part due to negative regulatory mechanisms used by the tumor and its microenvironment. One such inhibitory mechanism is up-regulation of programmed death-ligand 1 (PD-L1) expressed on tumor cells which binds to programmed death-1 (PD-1) on activated T cells[10]. A wide variety of tumor cells express PD-L1, including AML cells[11]. PD-1/PD-L1 engagement results in diminished antitumor T cell responses and correlates with poor outcome in murine and human solid cancers[12-18]. The PD-1 molecule has been recognized as a hallmark for cell exhaustion, and PD-1 expressing antigen-specific T cells are dysfunctional in cytokine production and proliferation upon antigen restimulation[19].

Regulatory T cells (Tregs) are naturally occurring immunosuppressive T cell populations which are increased in frequency in cancer patients and have been correlated with cancer outcomes in some studies[17, 20-22]. Furthermore, depletion of Tregs in a number of transplantable cancer models results in significantly enhanced anti-tumor immune responses and control of tumor progression. In AML, several groups have observed elevated Treg frequencies in the blood and marrow of AML patients, and this appears to correlate negatively with chemotherapy response and survival[20-21]. In murine AML models, depletion

of Tregs alone or in combination with PD-L1 blockade resulted in enhanced anti-leukemic T cell responses[23-24].

Therefore, the obstacles of successful anti-leukemia immune responses in the clinical setting may include both suppressive factors in tumor environment that inhibit the function of a sufficient immune response (i.e. Tregs), as well as defeated immune effector components that are unable to control tumor growth (i.e. PD-1 expressing T cells). We propose to overcome these obstacles through a combination of lymphodepletion (high-dose chemotherapy and autologous transplantation) and anti-PD1 blockade. Chemotherapy-induced lymphodepletion may enhance the effectiveness of immunotherapy though several different mechanisms including increased availability of immune stimulatory cytokines and the creation of an environment conducive to disruption of T cell tolerance.[25] Adoptive cellular therapy after lymphodepleting chemotherapy is known to cause regression of established tumors in murine models.[26-28] More recently adoptive cellular therapy following nonmyeloablative conditioning has been shown to produce significant responses in patients with metastatic melanoma and have demonstrated the importance of modulating the host environment through lymphodepletion.[29-30]

In this study, we will be utilizing a high-dose chemotherapy approach rather than traditional consolidative therapy in order to achieve both maximal myeloablation and lymphodepletion. We believe appropriate myeloablation is important for optimally reducing the leukemic burden, which may be critical given the slower kinetics of response to immune checkpoint inhibitors[31-34]. Furthermore, high-dose chemotherapy is predicted to provide optimal lymphodepletion. A lymphopenic environment can be caused by irradiation or chemotherapy drugs including cyclophosphamide, fludarabine, and melphalan[35-37]. After lymphodepletion, lymphocytes undergo spontaneous, antigen-independent expansion called homeostatic proliferation that restores the pre-lymphodepletion lymphocyte compartment. In addition to endogenous lymphocytes, adoptively transferred T cells undergo homeostatic proliferation when placed in a lymphopenic environment[38]. Lymphodepletion also disrupts immunologic tolerance mechanisms, thus favoring the induction of anti-tumor immune responses[39-41].

In non-favorable risk AML patients that don't receive allogeneic transplant, the vast majority of patients will relapse and die of their disease. In such a context, exploration of effective adjuvant therapies that may reduce this high relapse risk is appropriate. We hypothesize that immune checkpoint blockade with the PD-1 inhibitor, pembrolizumab, will decrease the risk of relapse in high risk AML patients. In an analogous approach, the FDA recently expanded the approval of ipilimumab (Yervoy), another immune checkpoint inhibitor, in melanoma to include adjuvant treatment of patients with stage III melanoma with pathologic involvement of regional lymph nodes >1 mm who have undergone complete resection including total lymphadenectomy.

4.1.1 Pharmaceutical and Therapeutic Background

The importance of intact immune surveillance in controlling outgrowth of neoplastic transformation has been known for decades. Accumulating evidence shows a correlation between tumor-infiltrating lymphocytes (TILs) in cancer tissue and favorable prognosis in various malignancies. In particular, the presence of CD8+ T-cells and the ratio of CD8+ effector T-cells / FoxP3+ Tregs 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, Tregs and natural killer cells. Expression has also been shown during thymic development on CD4-CD8- (double negative) T-cells as well as subsets of macrophages and dendritic cells. The ligands for PD-1 (PD-L1 and PD-L2) are constitutively expressed or can be induced in a variety of cell types, including non-hematopoietic tissues as well as in various tumors. Both ligands are type I transmembrane receptors containing both IgV- and IgC-like domains in the extracellular region and contain short cytoplasmic regions with no known signaling motifs. Binding of either PD-1 ligand to PD-1 inhibits T-cell activation triggered through the T-cell receptor. PD-L1 is expressed at low levels on various non-hematopoietic tissues, most notably on vascular endothelium, whereas PD-L2 protein is only detectably expressed on antigen-presenting cells found in lymphoid tissue or chronic inflammatory environments. PD-L2 is thought to control immune T-cell activation in lymphoid organs, whereas PD-L1 serves to dampen unwarranted T-cell function in peripheral tissues. Although healthy organs express little (if any) PD-L1, a variety of cancers were demonstrated to express abundant levels of this T-cell inhibitor. PD-1 has been suggested to regulate tumor-specific T-cell expansion in subjects with melanoma (MEL). This suggests that the PD-1/PD-L1 pathway plays a critical role in tumor immune evasion and should be considered as an attractive target for therapeutic intervention.

Pembrolizumab is a potent and highly selective humanized monoclonal antibody (mAb) of the IgG4/kappa isotype designed to directly block the interaction between PD-1 and its ligands,

PD-L1 and PD-L2. Keytruda™ (pembrolizumab) has recently been approved in the United Stated for the treatment of patients with unresectable or metastatic melanoma and disease progression following ipilumumab and, if BRAF V600 mutation positive, a BRAF inhibitor.

4.1.2 Clinical Trial Data

In a prospective phase I study, 411 patients with advanced melanoma were treated with pembrolizumab on one of three dose schedules (10 mg/kg every two weeks, 10 mg/kg every three weeks, or 2 mg/kg every three weeks)[42]. Seventy-seven percent of patients had received prior systemic therapies for metastatic disease. The study included 190 patients who were ipilimumab naïve (46 percent) and 221 who had been previously treated with ipilimumab (54 percent). Included in the study was a cohort of 276 patients who were randomly assigned to either 2 or 10 mg/kg given every two weeks[43]. Results from this study were updated at the 2014 ASCO meeting. The overall response rate using RECIST criteria and central review was 34 percent, including 40 percent in those who were ipilimumab naïve and 28 percent in those who had been treated with ipilimumab. Similar response rates were seen using immune-related response criteria. On multivariate analysis of the entire study population, there were no significant differences in outcomes between the three dose schedules; however there was a trend to better responses in the q2week arm:

	IPI-N				IPI-T			
	2 Q3W n = 73	10 Q3W n = 76	10 Q2W n = 41	Total n = 190	2 Q3W n = 89	10 Q3W n = 116	10 Q2W n = 16	Total n = 221
RECIST								
ORR in pts with measurable disease, %	37	39	46	40	26	26	57	28
Median PFS, wk (95% CI)	36 (12-NR)	23 (12-36)	50 (14-NR)	24 (16-48)	22 (12-36)	17 (12-24)	NR (12-NR)	23 (14-24)
24-wk PFS, %	52	46	57	51	45	40	67	44
irRC								
ORR, %	37	41	59	43	27	30	56	31
Median PFS, wk (95% CI)	36 (15-NR)	28 (13-NR)	84 (24-NR)	37 (24-84)	31 (22-48)	30 (24-NR)	NR (12-NR)	36 (24-54)
24-wk PFS, %	57	52	61	56	57	56	73	58

Overall survival at 12 months was 69 percent and 62 percent at 18 months. The median progression-free survival was 5.5 months, and 45 percent of patients remained progression free at six months. Treatment toxicity was manageable. The most common toxicities were fatigue, pruritus, rash, diarrhea, and arthralgia (36, 24, 20, 16, and 16 percent, respectively). Overall

12 percent of patients experienced grade 3 or 4 toxicity, the most common being fatigue (2 percent), and there were no treatment-related deaths. There were similar safety profiles in those previously treated with ipilimumab and in those who were ipilimumab naïve.

The phase II KEYNOTE-002 trial randomized 540 patients with ipilimumab-refractory advanced melanoma to pembrolizumab (2 mg/kg every three weeks), pembrolizumab (10 mg/kg every three weeks) or chemotherapy (carboplatin plus paclitaxel, paclitaxel alone, dacarbazine, or temozolomide per institutional standard)[44]. Treatment continued on this schedule until progressive disease. Progression-free survival assessed by central review, the primary endpoint of the trial, was significantly improved with both pembrolizumab treatment regimens compared with chemotherapy. The six-month progression-free rates were 34, 38, and 16 percent for pembrolizumab 2 mg/kg, pembrolizumab 10 mg/kg, and chemotherapy, respectively (pembrolizumab 2 mg/kg versus chemotherapy hazard ratio 0.57, 95% CI 0.45-0.73, and pembrolizumab 10 mg/kg versus chemotherapy hazard ratio 0.50, 95% CI 0.39-0.64).

The objective response rates (complete plus partial) were 21, 26, and 4 percent, respectively, for pembrolizumab 2 mg/kg, pembrolizumab 10 mg/kg, and chemotherapy, respectively. Treatment was relatively well tolerated, with grade 3-5 adverse events reported in 11 and 14 percent of the pembrolizumab treatment arms, and 26 percent of those managed with chemotherapy. The most common pembrolizumab-related adverse events were fatigue, pruritus, and rash. Grade 3 immune related toxicity was reported in two patients treated with pembrolizumab 2 mg/kg (hepatitis, hypophysitis), and in eight patients given pembrolizumab 10 mg/kg (hepatitis, colitis, pneumonitis, and iritis or uveitis.

4.2 Rationale

4.2.1 Rationale for the Trial and Selected Subject Population

We hypothesize that the use of high-dose chemotherapy to induce lymphodepletion followed by anti-PD-1 antibody therapy to further break immune tolerance to AML cells will improve outcomes in patients with non-favorable risk AML. Historically, the vast majority of patients with non-favorable risk AML, who are not candidates for allogeneic transplant, relapse and die of their disease. It is currently estimated that 60-80% of patients with non-favorable risk AML will have disease recurrence. In this study, we hope to decrease the recurrence rate to 35% or less. There is now increasing in vitro and pre-clinical in vivo data supporting an important role for PD1-PDL1 interactions in AML (see Background, section 4.1). Although anti-PD1 therapy has not been formally tested in AML, it has been successfully used in other hematologic malignancies with 53-87% response rate (CR + PR) seen in Hodgkin lymphoma[45-46], 36% and 40% in diffuse large B cell and follicular lymphoma, respectively[47].

Eligible patients must be deemed medically fit to undergo Melphalan-based high-dose chemotherapy, and therefore must meet all inclusion/exclusion criteria as defined in the study protocol. Eligible patients must also be deemed “not eligible” for allogeneic transplant. Patients may meet this criteria for multiple reasons, including 1) lack of suitable donor (HLA-matched related, HLA-matched unrelated, haploidentical, or cord blood unit), 2) patient refusal of allogeneic transplant, 3) lack of appropriate psychosocial support, or 4) perceived high risk

of treatment-related mortality with allogeneic transplant due to patient comorbidities or other factors.

4.2.2 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. 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.

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

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

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

The choice of the 200 mg Q3W as an appropriate dose for the switch to fixed dosing is based on simulations performed using the population PK model of pembrolizumab showing that the

fixed dose of 200 mg every 3 weeks will provide exposures that 1) are optimally consistent with those obtained with the 2 mg/kg dose every 3 weeks, 2) will maintain individual patient exposures in the exposure range established in melanoma as associated with maximal efficacy response and 3) will maintain individual patients exposure in the exposure range established in melanoma that are well tolerated and safe.

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

5.0 METHODOLOGY

5.1 Entry Criteria

5.1.1 Subject Inclusion Criteria

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

1. Be willing and able to provide written informed consent/assent for the trial.
2. Be 18 - 78 years of age on day of signing informed consent.
3. Diagnosis of non-M3 AML
4. In CR1 with non-favorable risk disease (appendix 1) or subsequent CR defined as with no evidence of residual leukemia by morphology, flow cytometry, cytogenetics, or FISH studies.
5. Not eligible for allogeneic transplant for any reason, including
    a. lack of suitable donor
    b. patient refusal of allogeneic transplant,
    c. lack of appropriate psychosocial support,
    d. perceived high risk of treatment-related mortality with allogeneic transplant due to patient comorbidities or other factors.
6. Completed at least one cycle of consolidation chemotherapy.
7. Collection of at least $2x10^6$/kg CD34+ cells, with negative immunophenotypic studies on product.
8. Have a Karnofsky performance status of 70% or greater.

9. Demonstrate adequate organ function as defined in Table 1.

Table 1 Adequate Organ Function Laboratory Values

System	Laboratory Value
Renal	
Serum creatinine **OR** Measured or calculated creatinine clearance (GFR can also be used in place of creatinine or CrCl)	≤2mg/dl **OR** ≥40 mL/min for subject with creatinine levels > 2mg/dl
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)	≤ 3 X ULN

10. Female subject of childbearing potential (all women with a uterus <50 and women >50 but <1 year without a menstrual cycle) should have a negative urine or serum pregnancy within one week 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.

11. Female subjects of childbearing potential should be willing to use 2 methods of birth control or be surgically sterile, or abstain from heterosexual activity for the course of the study through 120 days after the last dose of study medication (Reference Section 5.7.2). Subjects of childbearing potential are those who have not been surgically sterilized or have not been free from menses for > 1 year.

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

5.1.2 Subject Exclusion Criteria

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

1. Is currently participating and receiving study therapy or has participated in a study of an investigational agent and received study therapy or used an investigational device within 4 weeks of the first dose of treatment.

2. Hypersensitivity to pembrolizumab or any of its excipients.

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

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

5. Has known active central nervous system (CNS) involvement.

6. 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.

7. Has an uncontrolled infection.

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

9. 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.

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

11. 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.

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

13. Has a history of Human Immunodeficiency Virus (HIV).

14. Has known active Hepatitis B (e.g., HBsAg reactive) or Hepatitis C (e.g., HCV RNA is detected).

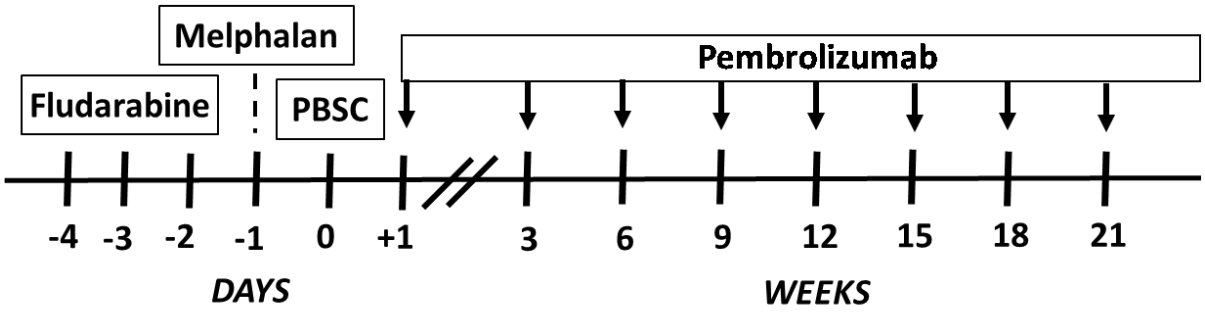
15. Has received a live vaccine or live-attenuated vaccine within 30 days of planned start of study therapy. Administration of killed vaccines is allowed.

16. Ejection fraction less than 40% or NYHA class II symptoms or higher

17. Has a history of (non-infectious) pneumonitis/interstitial lung disease that required steroids or current pneumonitis/interstitial lung disease

5.2 Trial Treatments

The treatment to be used in this trial is outlined below:



Preparative regimen / lymphodepletion:

Fludarabine 30mg/m^2/d x 3 days, days -4 to -2, and

Melphalan 180mg/m^2 (age 18-60 years) or 140mg/m^2 (age 61-75 years), day -1

PBSC Infusion Day 0

Anti-PD1 therapy:

Beginning day +1, pembrolizumab 200mg/dose will be administered q3weeks x 8 doses.

5.2.1 Chemotherapy Dosing:

All chemotherapy should be dosed based on ideal body weight (IBW) for patients who weigh 100-130% of their IBW. For patients who weigh less than 100% of their IBW, dosing should be based on actual body weight (ABW). For patients who weigh more than 130% of their IBW, dosing should be based on the adjusted ideal body weight (AIBW).

1. Ideal Body Weight (IBW) Formulas:

   Males IBW = 50 kg + 2.3 kg/inch over 5 feet

   Females IBW = 45.5 + 2.3 kg/inch over 5 feet

   For patients less than 5 feet, subtract 2.3 kg/inch

2. Adjusted Ideal Body Weight (AIBW) Formula:

   AIBW = IBW + [(0.25) x (ABW – IBW)]

Doses of Fludarabine will be adjusted as needed according to creatinine clearance:

Creatinine Clearance = (140-Age) x IBW (x 0.85 for females)

72 x Serum Creatinine

CHEMOTHERAPEUTIC AGENT	Calculated Creatinine Clearance (measured or calculated) 30-60
Fludarabine	80% of total dose

5.2.2 Stem Cell Collection

Peripheral blood stem cells (PBSC) are to be collected within 30 days of study treatment initiation. Peripheral blood stem cells will be collected by standard apheresis techniques following either chemotherapy-based or growth factor-based mobilization regimens per institutional standards. An acceptable PBSC product will contain a minimum of 2 x 10^6 CD34+ cells/kg body weight and have no evidence of leukemia contamination by flow cytometric analysis of the product.

5.2.3 Pembrolizumab Dose Modifications

Adverse events (both non-serious and serious) associated with pembrolizumab exposure may represent an immunologic etiology. These adverse events may occur shortly after the first dose or several months after the last dose of treatment. Pembrolizumab must be withheld for drug-related toxicities and severe or life-threatening AEs as per Table 2 below. See Section 5.4.1 for supportive care guidelines, including use of corticosteroids.

Table 2

Dose Modification Guidelines for Immune Related Adverse Events Associated with Pembrolizumab

General instructions:

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

Immune-related AEs	**Toxicity grade or conditions (CTCAEv4.0)**	**Action taken to pembrolizumab**	**irAE management with corticosteroid and/or other therapies**	**Monitor and follow-up**
Pneumonitis	Grade 2	Withhold	• Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper • Add prophylactic antibiotics for opportunistic infections	• Monitor participants for signs and symptoms of pneumonitis • Evaluate participants with suspected pneumonitis with radiographic imaging and initiate corticosteroid treatment •
	Grade 3 or 4, or recurrent Grade 2	Permanently discontinue		
Diarrhea / Colitis	Grade 2 or 3	Withhold	• Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper	• Monitor participants for signs and symptoms of enterocolitis (ie, diarrhea, abdominal pain, blood or mucus in stool with or without fever) and of bowel perforation (ie, peritoneal signs and ileus).

	Recurrent Grade 3 or Grade 4	Permanently discontinue		• Participants with ≥ Grade 2 diarrhea suspecting colitis should consider GI consultation and performing endoscopy to rule out colitis. • Participants with diarrhea/colitis should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion.
AST / ALT elevation or Increased bilirubin	Grade 2	Withhold	• Administer corticosteroids (initial dose of 0.5- 1 mg/kg prednisone or equivalent) followed by taper	• Monitor with liver function tests (consider weekly or more frequently until liver enzyme value returned to baseline or is stable
	Grade 3 or 4	Permanently discontinue	• Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper	
Type 1 diabetes mellitus (T1DM) or Hyperglycemia	Newly onset T1DM or Grade 3 or 4 hyperglycemia associated with evidence of β-cell failure	Withhold	• Initiate insulin replacement therapy for participants with T1DM • Administer anti-hyperglycemic in participants with hyperglycemia	• Monitor participants for hyperglycemia or other signs and symptoms of diabetes.
Hypophysitis	Grade 2	Withhold	• Administer corticosteroids and initiate hormonal replacements as clinically indicated.	• Monitor for signs and symptoms of hypophysitis (including hypopituitarism and adrenal insufficiency)
	Grade 3 or 4	Withhold or permanently discontinue[1]		
Hyperthyroidism	Grade 2	Continue	• Treat with non-selective beta-blockers (eg, propranolol) or thionamides as appropriate	• Monitor for signs and symptoms of thyroid disorders.
	Grade 3 or 4	Withhold or permanently discontinue[1]		
Hypothyroidism	Grade 2-4	Continue	• Initiate thyroid replacement hormones (eg, levothyroxine or liothyroinine) per standard of care	• Monitor for signs and symptoms of thyroid disorders.

Nephritis grading according to increased creatinine or acute kidney injury	Grade 2	Withhold	• Administer corticosteroids (prednisone 1-2 mg/kg or equivalent) followed by taper.	• Monitor changes of renal function
	Grade 3 or 4	Permanently discontinue		
Neurological Toxicities	Grade 2	Withold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grace 3 or 4	Permanently discontinue		
Myocarditis	Grade 1	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 2, 3 or 4	Permanently discontinue		
All other immune-related AEs	Intolerable/ persistent Grade 2	Withhold	• Based on type and severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 3	Withhold or discontinue based on the type of event. Events that require discontinuation include and not limited to: Gullain-Barre Syndrome, encephalitis		
	Grade 4 or recurrent Grade 3	Permanently discontinue		

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

NOTE:

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

Dosing interruptions are permitted in the case of medical / surgical events or logistical reasons not related to study therapy (e.g., elective surgery, unrelated medical events). Subjects should be placed back on study therapy within 1 week of the scheduled interruption, unless otherwise discussed with the Sponsor. The reason for interruption should be documented in the patient's study record.

5.2.4 Timing of Dose Administration

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

All trial treatments will be administered on an outpatient basis.

Beginning day +1, pembrolizumab 200mg/dose will be administered q3weeks x 8 doses.

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

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.

5.3.2 Prohibited Concomitant Medications

Subjects are prohibited from receiving the following therapies during the Screening and Treatment Phase of this trial:

- Immunotherapy not specified in this protocol
- Chemotherapy not specified in this protocol
- Investigational agents other than pembrolizumab
- 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 (1) as an antiemetic prior to chemotherapy or (2) to modulate symptoms from an event of clinical interest of suspected immunologic etiology. The use of physiologic doses of corticosteroids may be approved after consultation with the Sponsor.

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

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

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

5.4 Rescue Medications & Supportive Care

5.4.1 Supportive Care Guidelines

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

Note: if after the evaluation the event is determined not to be related, the investigator is instructed to follow the ECI reporting guidance but does not need to follow the treatment guidance (as outlined in the ECI guidance document). Refer to Section 5.2.1 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. Suggested conditional procedures, as appropriate, can be found in the ECI guidance document.

- **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**, felt related to study drug, that persists > 1 week, administer oral corticosteroids.
  - For **Grade 3 or 4 diarrhea/colitis**, felt related to study drug, that persists > 3 days, 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, felt related to study drug, monitor liver function tests more frequently until returned to baseline values (consider weekly).
    - Treat with IV or oral corticosteroids
  - For **Grade 3-4** events, felt related to study drug, 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.

- **Acute kidney injury**:
  - For **Grade 2** events, felt related to study drug, administer oral corticosteroids.
  - For **Grade 3-4** events, felt related to study drug, 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.

- **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 3 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	**Stop Infusion and monitor symptoms.**	Subject may be premedicated 30 min (± 30

NCI CTCAE Grade	Treatment	Premedication at subsequent dosing
Requires infusion interruption but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDS, narcotics, IV fluids); prophylactic medications indicated for < =24 hrs	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.**	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).
<u>Grades 3 or 4</u> Grade 3: Prolonged (i.e., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (e.g., renal impairment, pulmonary infiltrates) Grade 4: Life-threatening; pressor or ventilatory support indicated	**Stop Infusion.** Additional appropriate medical therapy may include but is not limited to: IV fluids Antihistamines NSAIDS Acetaminophen Narcotics Oxygen Pressors Corticosteroids Epinephrine Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator. Hospitalization may be indicated. **Subject is permanently discontinued from further trial treatment administration.**	No subsequent dosing
Appropriate resuscitation equipment should be available in the room and a physician readily available during the period of drug administration.		

5.5 Other Considerations

5.5.1 Contraception

Pembrolizumab may have adverse effects on a fetus in utero. Furthermore, it is not known if pembrolizumab has transient adverse effects on the composition of sperm. Non-pregnant, non-breast-feeding women may be enrolled if they are willing to use 2 methods of birth control or are considered highly unlikely to conceive. Highly unlikely to conceive is defined as 1) surgically sterilized, or 2) postmenopausal (a woman who is ≥50 years of age and has not had menses for greater than 1 year will be considered postmenopausal), or 3) not heterosexually active for the duration of the study. The two birth control methods can be either two barrier methods or a barrier method plus a hormonal method to prevent pregnancy. Subjects should start using birth control from study Visit 1 throughout the study period up to 120 days after the last dose of study therapy.

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

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

5.5.2 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.

5.5.3 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.
- Confirmed disease progression

  Note: A subject may be granted an exception to continue on treatment with confirmed disease progression if clinically stable or clinically improved.
- 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

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

If a subject is unable to complete at least 4 doses of pembrolizumab due to any reason (i.e. disease progression, toxicity, noncompliance, etc.), then accrual will be increased accordingly to replace these patients. We will replace a maximum of 5 patients which is equal to 25% of the total study enrollment.

5.8 Clinical Criteria for Early Trial Termination

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

Non-relapse mortality (NRM):

The incidence of NRM following autologous transplantation for patients with AML is predicted to be 5% or less. Consequently, an incidence of NRM convincingly greater than 10% would raise concerns for excessive toxicity and would trigger early trial termination. This trigger would be met if NRM occurs in 2 of the first 5 patients, 3 of the first 10 patients, 4 of the first 15 patients, and 5 of the first 20 patients.

Drug-related grade ≥3 adverse events (AEs):

The incidence of drug-related grade ≥3 AEs following treatment with pembrolizumab is predicted to be 15% or less. Consequently, an incidence of drug-related grade ≥3 AEs convincingly greater than 20% would raise concerns for excessive toxicity. This trigger would be met if a grade ≥3 AE, deemed to be related to study drug, occurs in 3 out of the first 5 patients, 5 of the first 10 patients, 6 of the first 15 patients, or 8 of the first 20 patients. If this stopping criterion is met, accrual to the trial will be temporarily halted, until a decision regarding either modification or termination of the trial could be made.

6.0 TRIAL FLOW CHART

6.1 Study Flow Chart

Trial Period:	Screening Visit	Treatment weeks												End of Treatment	Post-Treatment	
		Within 24 hours of high-dose chemo	0	1	2	3	6	9	12	15	18	21	24			
Scheduling Window (Days):	-28 to -5		Day +1	Days 2-7	Days 8-14	Days 15-21	± 3	± 3	± 3	± 3	± 3	± 3		At time of Discontinuation	30 days post discontinuation	Post-BMT month 12, 18, and 24
Informed Consent	x															
Inclusion/Exclusion Criteria	x															
Demographics and Medical History	x															
Prior and Concomitant Medication Review	x															
Trial Treatment Administration			x			x[6]	x	x	x	x	x	x				
Post-study anticancer therapy status															x	X
Survival Status															x	X
Review Adverse Events			x	x	x	x	x	x	x	x	x	x	x	x	x	
Full Physical Examination	x		x	x	x	X	x	x	x	x	x	x				
Directed Physical Examination			x						x				x	x		X
Vital Signs and Weight	x		x	x	x	X	x	x	x	x	x	x	x	x		
Karnofsky Performance Status	x		x	x	x	X	x	x	x	x	x	x				X
Pregnancy Test – Serum β-HCG	x	x														
CBC with Differential	x	x	x[1]	x	x	X	x	x	x	x	x	x	x	x		X
Comprehensive Serum Chemistry Panel	x	x	x[1]	x	x	X	x	x	x	x	x	x	x	x		X
Urinalysis	x															

Trial Period:	Screening Visit	Treatment weeks												End of Treatment	Post-Treatment	
		Within 24 hours of high-dose chemo	0	1	2	3	6	9	12	15	18	21	24			
Scheduling Window (Days):	-28 to -5		Day +1	Days 2-7	Days 8-14	Days 15-21	± 3	± 3	± 3	± 3	± 3	± 3		At time of Discontinuation	30 days post discontinuation	Post-BMT month 12, 18, and 24
PT/PTT/INR	x															
T3, FT4 and TSH	x								x				x			x
Bone Marrow Biopsy	X[2]					X[4]	X[4]		X[4]		x		X[4]			X[4]
Bone Marrow Collection						X[4]	X[4]		X[4]							
Correlative Studies Blood Collection[3]		x	X			x	x	x	x	x	x	x				x
Stem Cell Collection[5]	X															

[1]CBC, chemistry, vital signs & physical examinations will be done according to standard of care treatment following autologous stem cell transplant

2Screening & disease restaging will consist of bone marrow biopsy, aspirate, cytogenetics, flow and molecular studies and will be done according to institutional standards pre-transplant, at 3, 6, 12 and 24 months post-transplant.

[3]Research blood samples (30-60ml) will be drawn prior to lymphodepleting chemotherapy, prior to pembrolizumab dosing on each antibody dosing day, and at 12, 18 and 24 months following autologous transplantation.

[4] A bone marrow biopsy will be performed for research purposes only at one and two months post autologous transplant. Additional research marrow samples will be also collected at standard disease assessment times (3, 6, 12, 18 and 24 months post-transplant)

[5]Stem cells will be collected per institutional standard within 30 days of study treatment initiation

[6]Week 3 treatment administration will be given on Day 21 $\pm$ 3 days

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 or designee 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 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 approval in advance of use. The subject 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 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, and any condition diagnosed within the prior 10 years that are considered to be clinically significant by the Investigator. Details regarding the disease for which the subject has enrolled in this study will be recorded separately and not listed as medical history.

7.1.1.4 Prior Medications

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

7.1.1.5 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. If a subject initiates a new anti-cancer therapy within 30 days after the last dose of trial treatment, the 30 day Safety Follow-up visit must occur before the first dose of the new therapy. Once new anti-cancer therapy has been initiated the subject will move into survival follow-up.

7.1.1.6 Assignment of Study Number

Patients will be assigned a study number in chronological order including the IRB number - 001, 002, 003, etc along with the patient's initials.

7.1.2 Clinical Procedures/Assessments

7.1.2.1 Adverse Event (AE) Monitoring

The investigator or qualified designee will assess each subject to evaluate for potential new or worsening AEs as specified in the Trial Flow Chart and more frequently if clinically indicated. Adverse experiences will be graded and recorded throughout the study and during the follow-up period according to NCI CTCAE Version 4.0. 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 Karnofsky performance 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.

7.1.2.6 Assessment of Disease

Assessment of AML disease status will be performed at the following time points after autologous transplant: 3 months, 6 months, 12 months, 18 months and 24 months. A bone marrow biopsy will be performed and evaluated by morphology, flow cytometry, cytogenetics, and FISH studies (when applicable). Complete remission (CR) is defined by the absence of residual leukemia in the bone marrow (less than 5% blasts by morphology and no definitive evidence of disease by flow cytometry), absence of extramedullary disease and adequate peripheral blood counts (absolute neutrophil count >1,000/microL and platelet count > 100,000/microL). Patients fulfilling the criteria for CR, but who do not achieve adequate peripheral blood counts, will be denoted as CR with insufficient hematologic recovery (CRi). Relapse is defined as the reappearance of leukemia blasts in the peripheral blood; or > 5% blasts in the bone marrow not attributable to another cause (e.g., recovery of normal cells following chemotherapy-induced aplasia); or appearance or reappearance of extramedullary disease.

7.1.2.7 Correlative Studies Blood and Marrow Sampling

Research blood samples (30-60ml) will be drawn prior to lymphodepleting chemotherapy, prior to pembrolizumab dosing on each antibody dosing day, and at 12, 18 and 24 months following autologous transplantation (12 total samples). From each blood sample, peripheral blood mononuclear cells (PBMCs) and serum will be collected and cryopreserved for correlative studies. A bone marrow biopsy will be performed for research purposes only at one and two months post autologous transplant. Additional research marrow samples will be also collected at standard disease assessment times (3, 6, 12, 18 and 24 months post-transplant; 7 total samples). From each marrow sample, cells will be processed and cryopreserved for correlative studies.

7.1.3 Laboratory Procedures/Assessments

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

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

Table 5 Laboratory Tests

Hematology	Chemistry	Urinalysis	Other
Hematocrit	Albumin	Blood	Serum β-human chorionic gonadotropin†
Hemoglobin	Alkaline phosphatase	Glucose	(β-hCG)†
Platelet count	Alanine aminotransferase (ALT)	Protein	PT (INR)
WBC (total and differential)	Aspartate aminotransferase (AST)	Specific gravity	aPTT
Red Blood Cell Count	Lactate dehydrogenase (LDH)	Microscopic exam *(If abnormal results are noted)*	Total thriiodothyronine (T3)
Absolute Neutrophil Count	Carbon Dioxide ‡		Free tyroxine (T4)
Absolute Lymphocyte Count	*(CO_2 or biocarbonate)*		Thyroid stimulating hormone (TSH)
	Blood Urea Nitrogen		
	Calcium		
	Chloride		Blood for correlative studies
	Glucose		
	Creatinine		
	Potassium		
	Sodium		
	Magnesium		
	Total Bilirubin		
	Direct Bilirubin *(If total bilirubin is elevated above the upper limit of normal)*		
	Total protein		
† Perform on women of childbearing potential only.			

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

7.1.4 Other Procedures

Bone marrow biopsy, using standard techniques, will be performed at the following time points post-transplant: 1, 2, 3, 6, 12, 18, and 24 months.

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. After discontinuing treatment, these subjects should return to the site for a Safety Follow-up Visit (described in Section 7.1.5.3.1) and then proceed to the Follow-Up Period of the study (described in Section 7.1.5.4).

7.1.5 Visit Requirements

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

7.1.5.1 Screening

The screening visit will occur between 28 and 5 days prior to the start of high dose chemotherapy in preparation for stem cell transplantation. The screening procedures will include standard pre-bmt workup and are fully outlined in Section 6.0 Trial Flow Chart.

7.1.5.2 Treatment Period

The treatment period may continue every 3 weeks for up to 8 doses. If a subject withdraws from the trial early, end of study evaluations will occur. Refer to the Trial Flow Chart for specific study related evaluations.

7.1.5.3 Post-Treatment Visits

The patient will be evaluated 30 days after the discontinuation of treatment and then at 12, 18 & 24 months post-transplant. Refer to the Trial Flow Chart for specific post-treatment evaluations.

7.1.5.3.1 Safety Follow-up Visit

The mandatory Safety Follow-Up Visit should be conducted approximately 30 days after the last dose of trial treatment or before the initiation of a new anti-cancer treatment, whichever

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

7.1.5.1 Follow-up Visits

Subjects who discontinue trial treatment for a reason other than disease progression will move into the Follow-Up Phase and should be assessed according to institutional standards. 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.

7.1.5.1.1 Survival Follow-up

Once a subject experiences confirmed disease progression or starts a new anti-cancer therapy, the subject moves into the survival follow-up phase and should be contacted by telephone every 12 weeks to assess for survival status until death, withdrawal of consent, or the end of the study, whichever occurs first.

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 within the follow-up period specified by the protocol, or prescribed in clinical practice, from overdose (whether accidental or intentional), from abuse and from withdrawal.

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

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

All adverse events will be recorded from the time the first dose of study drug is administered through 30 days following cessation of treatment and at each examination on the Adverse Event case report forms/worksheets. The reporting timeframe for adverse events meeting any serious criteria is described in section 7.2.3.1.

7.2.1 Definition of an Overdose for this Protocol and Reporting of Overdose to the Sponsor 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), including the pregnancy of a male subject's female partner that occurs during the trial or within 120 days of completing the trial completing the trial, or 30 days following cessation of treatment if the subject initiates new anticancer therapy, whichever is earlier. All subjects and female partners of male subjects who become pregnant must be followed to the completion/termination of the pregnancy. Pregnancy outcomes of spontaneous abortion,

missed abortion, benign hydatidiform mole, blighted ovum, fetal death, intrauterine death, miscarriage and stillbirth must be reported as serious events (Important Medical Events). If the pregnancy continues to term, the outcome (health of infant) must also be reported.

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

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

7.2.3.1 Serious Adverse Events

A serious adverse event is any adverse event occurring at any dose or during any use of 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 a new cancer (that is not a condition of the study);
- Is associated with an overdose;
- Is an other important medical event

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

Any serious adverse event, or follow up to a serious adverse event, including death due to any cause other than progression of the cancer under study that occurs to any subject from the time the consent is signed through 90 days following cessation of treatment, or the initiation of new anti-cancer therapy, whichever is earlier, whether or not related to Merck product, must be reported within 24 hours to the Sponsor and within 2 working days to Merck Global Safety.

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

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

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.

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

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

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

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 [including hospitalization for an elective procedure] for a preexisting condition which has not worsened does not constitute a serious adverse event.); or	
	†**Is a congenital anomaly/birth defect** (in offspring of subject taking the product regardless of time to diagnosis);or	
	Is a new **cancer;** (that is not a condition of the study) **or**	
	Is an overdose (whether accidental or intentional). Any adverse event associated with an overdose is considered a serious adverse event. An overdose that is not associated with an adverse event is considered a non-serious event of clinical interest and must be reported within 24 hours.	
	Other important medical events that may not result in death, not be life threatening, or not require hospitalization may be considered a serious adverse event when, based upon appropriate medical judgment, the event may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed previously (designated above by a †).	
Duration	Record the start and stop dates of the adverse event. If less than 1 day, indicate the appropriate length of time and units	
Action taken	Did the adverse event cause the Merck product to be discontinued?	
Relationship to test drug	Did the Merck product cause the adverse event? The determination of the likelihood that the Merck product caused the adverse event will be provided by an investigator who is a qualified physician. The investigator's signed/dated initials on the source document or worksheet that supports the causality noted on the AE form, ensures that a medically qualified assessment of causality was done. This initialed document must be retained for the required regulatory time frame. The criteria below are intended as reference guidelines to assist the investigator in assessing the likelihood of a relationship between the test drug and the adverse event based upon the available information. **The following components are to be used to assess the relationship between the Merck product and the AE**; the greater the correlation with the components and their respective elements (in number and/or intensity), the more likely the Merck product caused the adverse event (AE):	
	Exposure	Is there evidence that the subject was actually exposed to the Merck product such as: reliable history, acceptable compliance assessment (pill count, diary, etc.), expected pharmacologic effect, or measurement of drug/metabolite in bodily specimen?
	Time Course	Did the AE follow in a reasonable temporal sequence from administration of the Merck product? Is the time of onset of the AE compatible with a drug-induced effect (applies to trials with investigational medicinal product)?
	Likely Cause	Is the AE not reasonably explained by another etiology such as underlying disease, other drug(s)/vaccine(s), or other host or environmental factors

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

7.2.5 Sponsor Responsibility for Reporting Adverse Events

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

8.0 STATISTICAL ANALYSIS PLAN

8.1 Patient Recruitment

Accrual will continue until 20 patients are transplanted. It is estimated that one patient will be enrolled per month and about 20 months of accrual will be necessary to reach the required sample size**.**

8.2 Sample Size Calculation

The objective of this study is to show that the 2-year cumulative incidence of relapse is less than 70%. Experience from the literature, suggests that following chemotherapy-based consolidation for high-risk AML, the rate of relapse is approximately 60-80%. It is hoped that under this protocol, this rate will be at most 35%. The 2-year cumulative incidence of NRM is about 5%. The 2-year leukemia-free survival (LFS) is the primary endpoint and tested against the reference value 25%. We frame the objective to the hypotheses H_0: $S(t)=0.25$ versus H_a: $S(t)>0.25$ for $t = 2$, where $S(t)$ denotes the LFS probability at t. The Kaplan-Meier method and Greenwood's formula are used to estimate the LFS probability and its precision. The one-sided Wald test at 5% significance level is used to test the hypotheses and we determine to analyze the data at the 3 years since the first patient is transplanted. The size of 20 patients yields the power of 90.5% assuming that the actual 2-year LFS is 60%.

The power was estimated based on 5000 simulated replicates. Assume that LFS time follows the exponential distribution. Under the condition that the 2-year LFS is 60% the hazard rate is calculated to be 0.255. The LFS time was generated from exponential with rate=0.255. The censoring time was generated by the accrual estimate of one per month and the duration of study of 3 years. The following table shows the estimated powers for a few sizes.

Sample size	Test	N=20	N=23	N=26
Estimated power	1-sided	0.905	0.915	0.924
Estimated power	2-sided	0.840	0.863	0.876

8.3 Analysis Plan

The primary endpoint is 2-year LFS and the secondary endpoints include 2-year overall survival (OS), cumulative incidences of relapse and NRM. We decided the duration of study to be 3 years since the first transplant. The analysis will be performed when the study ends. The duration of 3 years was chosen to ensure sufficient follow-up of the participants so that

we can precisely estimate the 2-year survival outcomes. For N=20, the duration of 3 years leads to a median follow-up of 2.2 years given that censoring is caused by administrative loss-to-follow up only.

The Kaplan-Meier method will be used to estimate LFS and OS. Their precisions will be evaluated by the Greenwood's formula. Relapse and NRM are considered as competing risks for defining LFS. The cumulative incidences of relapse and NRM will be estimated to accommodate competing risks. For each endpoint, the one-sample test for the 2-year outcome will be evaluated by the one-sided Wald test of 5% significance level.

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 trial site.

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

9.5 Returns and Reconciliation

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

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

10.0 ADMINISTRATIVE AND REGULATORY DETAILS

10.1 Good Clinical Practice

The study will be conducted in accordance with the International Conference on Harmonisation (ICH) for Good Clinical Practice (GCP) and the appropriate regulatory requirement(s). The investigator will be thoroughly familiar with the appropriate use of the study drug as described in the protocol and Investigator's Brochure. Essential clinical documents will be maintained to demonstrate the validity of the study and the integrity of the data collected. Master files should be established at the beginning of the study, maintained for the duration of the study and retained according to the appropriate regulations.

10.2 Ethical Considerations

The study will be conducted in accordance with applicable regulatory requirement(s) and will adhere to GCP standards. The IRB/IEC will review all appropriate study documentation in

order to safeguard the rights, safety and well-being of the patients. The study will be conducted only at sites where IRB/IEC approval has been obtained. The protocol, Investigator's Brochure, informed consent form, advertisements (if applicable), written information given to the patients (including diary cards), safety updates, annual progress reports, and any revisions to these documents will be provided to the IRB/IEC by the investigator.

10.3 Investigator Compliance

The investigator will conduct the study in compliance with the protocol given approval/favorable opinion by the IRB/IEC and the appropriate regulatory authority(ies). . The IRB/IEC may provide, if applicable regulatory authority(ies) permit, expedited review and approval/favorable opinion for minor change(s) in ongoing studies that have the approval /favorable opinion of the IRB/IEC. The investigator will submit all protocol modifications to the regulatory authority(ies) in accordance with the governing regulations.

Any departures from the protocol must be fully documented in the source documents.

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 Data Management

Data will be collected per standard of care for patients enrolled on this study. Shadow charts will be kept by the research administration team and will contain data specific to the clinical trial including screening and eligibility source documents, treatment information, adverse event/serious adverse event information and restaging/disease evaluation. Routine stem cell transplantation information including laboratory results, medications and hospitalization information will be house in the BMT application, Northside Hospital medical record and

BMTGA electronic medical record. This information is available to the research and clinical teams and can be viewed upon request.

10.6 References

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10.7 Appendices

Appendix 1: Favorable Cytogenetic/Molecular Risk Abnormalities

Favorable cytogenetic/molecular risk abnormalities:

1. T(15;17)
2. T(8;21) with wild-type c-kit
3. Inversion 16 with wild-type c-kit
4. Normal cytogenetics with mutated NPM-1 and wild-type FLT3
5. Normal cytogenetics with mutated CEBPA and wild-type FLT3

Appendix 2: Karnofsky Performance Status Scale

Index	Specific Criteria	General
100	Normal, no complaints, no evidence of disease.	Able to carry on normal activity; no special care needed.
90	Able to carry on normal activity, minor signs or symptoms of disease.	
80	Normal activity with effort, some signs or symptoms of disease.	
70	Care for self, unable to carry on normal activity or to do work.	Unable to work, able to live at home and care for most personal needs, varying amount of assistance needed.
60	Requires occasional assistance from others but able to care for most needs.	
50	Requires considerable assistance from others and frequent medical care	
40	Disabled, requires special care and assistance.	Unable to care for self, requires institutional or hospital care or equivalent, disease may be rapidly progressing.
30	Severely disabled, hospitalization indicated, but death not imminent.	
20	Very sick, hospitalization necessary, active supportive treatment necessary.	
10	Moribund	
0	Dead	