TITLE: Pilot study of pembrolizumab treatment for disease relapse after allogeneic stem cell transplantation

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1.0 TRIAL SUMMARY

Abbreviated Title	Pilot study of pembrolizumab treatment for disease relapse after allogeneic stem cell transplantation
Trial Phase	Pilot study
Clinical Indication	Classical Hodgkin lymphoma (cHL), B cell non-Hodgkin lymphoma (B-NHL), acute myeloid leukemia (AML), myelodysplastic syndromes (MDS)
Trial Type	Interventional
Type of control	None
Route of administration	Intravenous
Trial Blinding	None
Treatment Groups	1
Number of trial subjects	12-26
Estimated enrollment period	10-20 months
Estimated duration of trial	36-48 months
Duration of Participation	35 cycles (up to 2 years)

2.0 TRIAL DESIGN

2.1 TRIAL DESIGN

This pilot study has been designed to investigate the safety of pembrolizumab treatment for disease relapse following allogeneic stem cell transplant (alloSCT). Pembrolizumab will be administered at a fixed dose of 200 mg IV every 3 weeks. Approximately 12-26 patients with relapsed MDS, AML, or mature B cell (B-NHL, cHL) malignancies that

have relapsed following alloSCT will be enrolled on this trial. Pembrolizumab treatment will be administered for up to 24 months, provided that neither disease progression, nor development of a dose-limiting toxicity (DLT), has occurred. Adverse events will be monitored every three weeks throughout the trial and graded in severity according to the guidelines outlined in the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. This trial will be conducted in accordance with Good Clinical Practices.

Briefly, patients will undergo baseline eligibility screening within 2 weeks prior to enrollment, including a medical history, physical examination, and assessment of performance status and hematology and chemistry parameters. Baseline assessment of disease status will be based on results of a bone marrow aspirate and biopsy for patients with AML and MDS, and a CT/PET scan (with a bone marrow exam for history of disease involvement) for patients with lymphoma. Baseline and subsequent bone marrow and peripheral blood samples will be obtained for correlative assays. Disease response assessment (bone marrow aspirate and biopsy and/or CT/PET) will be performed at baseline, and then every 3 months for 2 years, as well as any time if relapse is suspected. Specific procedures to be performed during the trial, as well as their prescribed times and associated visit windows, are outlined in the trial flow chart – Section 7.0. Details of each procedure are provided in Section 8.0 – trial procedures. After 24 months, ongoing disease re-assessments will be performed at the discretion of the treating physician. Any patient who experiences biopsy-proven disease progression at any time will be removed from study, and alternative treatment can be recommended at the treating physician's discretion. Subjects are not eligible for re-treatment on with pembrolizumab in the setting of this protocol should they experience a disease relapse after completing 24 months of therapy. 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). Subjects who discontinue treatment for reasons other than disease progression will have post-treatment follow-up for disease status until disease progression, initiating a non-study cancer treatment, withdrawal of consent, or becoming lost to follow-up. All subjects will be followed by telephone contact for overall survival until death, withdrawal of consent or the end of the study, whichever comes first.

The primary objective of this trial is to determine whether administration of pembrolizumab is tolerable in patients who have experienced disease relapse following alloSCT. Secondary objectives include analysis of efficacy parameters (ORR, DOR, OS). Correlative studies to examine the effect of PD-1 blockade therapy on T cell parameters and clonality, as well as on donor chimerism are planned as exploratory analyses.

A DLT is defined as the development of grade 3 or 4 acute GVHD (defined by the Gluckenberg scale), graft rejection, the development of any unexpected grade > 2 toxicity felt to be related to pembrolizumab, or the development of > grade 2 dysfunction of a vital organ felt to be secondary to an immune-related adverse event within 90 days following the initiation of pembrolizumab treatment. For immune-related adverse events that do not meet criteria for a DLT, but do meet criteria for a treatment-limiting toxicity (TLT), for example grade 2 acute GVHD, pembrolizumab will held until the toxicity has

decreased to ≤ grade 1. It will be permanently discontinued if delayed for >12 weeks. For patients who develop GVHD or an immune-related adverse event while on pembrolizumab, corticosteroid therapy and potentially other immunomodulatory agents will be initiated.

If the safety and feasibility of pembrolizumab is confirmed in this patient cohort, a phase II expansion cohort may be considered, particularly for disease subtypes where objective responses have been observed.

2.2 TRIAL OVERVIEW

The trial overview is depicted in **Table 1**.

Table 1. Trial overview

Initial treatment	Pembrolizumab 200 mg IV on day 1 of each 21 day cycle
Treatment-limiting toxicity (TLT) (for example, grade 2 acute GVHD)	Hold treatment for up to 12 weeks.. For immune-related adverse events that do not meet criteria for a DLT, but do meet criteria for a treatment-limiting toxicity (TLT), for example grade 2 acute GVHD, pembrolizumab can be restarted provided that the toxicity has decreased to < grade 2. For patients who develop GVHD or an immune-related adverse event while on pembrolizumab, corticosteroid therapy and potentially other immunomodulatory agents will be initiated. Re-start treatment with pembrolizumab 200 mg IV on day 1 of each 21 day cycle, provided that the TLT has resolved to ≤ grade 1. Permanently discontinue if no improvement in toxicity to ≤ grade 1 in 12 weeks.
Dose-limiting toxicity (DLT)	Discontinue treatment. Remove patient from study

3.0 OBJECTIVES & HYPOTHESES

3.1 PRIMARY OBJECTIVE & HYPOTHESIS

Objective: To determine the tolerability of pembrolizumab treatment in the setting of relapsed myeloid malignancies and mature B cell lymphomas following alloSCT.

Hypothesis: Pembrolizumab administered for disease relapse following alloSCT will be

tolerable with an acceptable incidence of immune-related adverse events, including GVHD.

3.2 SECONDARY OBJECTIVES & HYPOTHESES

Objective 1: To determine the overall response rate (ORR) of patients treated with pembrolizumab in the setting of relapsed myeloid malignancies and mature B cell lymphomas following alloSCT, stratified by disease type. ORR is defined as the first documentation of CR or PR (by IRC) to the first documentation of disease progression or death by any cause.

Objective 2: To determine the duration of response (DOR) of patients treated with pembrolizumab in the setting of relapsed myeloid malignancies and mature B cell lymphomas following alloSCT. DOR is defined as the time between the initial response to therapy and subsequent disease progression or relapse.

Objective 3: To determine the overall survival (OS) of patients treated with pembrolizumab in the setting of relapsed myeloid malignancies and mature B cell lymphomas following alloSCT. OS is defined as the interval from the start of the study treatment to death from any cause.

Hypothesis 1: Pembrolizumab will have anti-tumor activity in the defined patient population as measured by ORR.

3.3 EXPLORATORY OBJECTIVES & HYPOTHESES

Objective 1: To determine the effect of pembrolizumab on restoring donor chimerism in patients with relapsed myeloid malignancies and mature B cell lymphomas following alloSCT.

Objective 2: To determine the effect of pembrolizumab on the numbers and activations status of peripheral blood T cells.

Objective 3: To compare PD-L1 expression on malignant cells at initial diagnosis and at disease relapse following alloSCT.

Objective 4: To examine the effect of pembrolizumab on the T cell receptor (TCR) repertoire in the peripheral blood, and where available, tumor environment, following alloSCT.

Hypothesis 1: Pembrolizumab treatment will restore donor chimerism when administered to patients with relapsed myeloid malignancies and mature B cell lymphomas following alloSCT.

Hypothesis 2: Pembrolizumab treatment will be associated with enhanced expression of activation markers on peripheral blood T cells in patients with relapsed myeloid malignancies and mature B cell lymphomas following alloSCT.

Hypothesis 3: PD-L1 expression will be increased on malignant cells following disease relapse after alloSCT compared to diagnosis.

Hypothesis 4: Pembrolizumab treatment will be associated with clonal expansion of conventional and regulatory T cell subsets in peripheral blood as measured by TCR-β deep sequencing and Simpson's index of diversity analysis.

4.0 BACKGROUND

4.1 DISEASE RELAPSE AFTER ALLOSCT.

AlloSCT remains the only curative treatment modality for many high-risk and relapsed hematological malignancies. The widespread use of reduced-intensity conditioning (RIC) regimens has expanded patient eligibility for alloSCT due to reduced rates of transplant-related mortality (TRM). However, disease relapse remains the major cause of mortality following alloSCT [1]. The infusion of T cell-depleted allografts, a common practice at some institutions to reduce the risk of graft-versus-host disease (GVHD), has also been associated with a higher risk of disease recurrence following alloSCT [2, 3, 4]. Prognosis of patients with aggressive hematological cancers that relapse following alloSCT is abysmal [5, 6, 7, 8, 9]. Treatment options for this patient population are extremely limited, and new therapeutic approaches are needed.

4.2 IMMUNE CHECKPOINT BLOCKADE IN HEMATOLOGICAL MALIGNANCIES.

PD-L1 expression on malignant and non-malignant cells in the tumor environment potently down-regulates the function of PD-1-expressing tumor antigen-specific T cells [10, 11, 12]. Interference with PD-1/PD-L1 interactions can "re-awaken" previously generated, but ineffective anti-tumor T cell responses. PD-1 blockade has demonstrated remarkable clinical efficacy in a number of solid tumors [13, 14], and has created a new paradigm for cancer treatment.

PD-1 blockade has also been effective in some hematological cancers, particularly Hodgkin lymphoma (HL) [15], in which the genetic loci that encode the PD-1 ligands are commonly amplified [16]. In patients with relapsed/refractory HL, treatment with the PD-1 blocking antibody, nivolumab, led to an objective response rate (ORR) of 87% (70% partial responses – PR, and 17% complete responses – CR). At 24 weeks, 86% of responding patients were progression-free [15]. Pembrolizumab, a similar PD-1 blocking antibody, induced ORR and CR rates of 53% and 20%, respectively, in a heavily pre-treated group of HL patients [17]. An updated abstract presented at ASCO 2016 showed that in patients refractory to brentuximab vedotin, pembrolizumab treatment was associated with a 65% ORR. Many of the responses observed were durable [18].

With regard to NHL, a phase II study of a third PD-1 blocking antibody, pidilizumab, in combination with the anti-CD20 antibody, rituximab, was conducted in patients with relapsed follicular lymphoma. ORR and CR rates were impressive at 66% and 52 % [19]. Preliminary results of a phase I study of nivolumab in patients with refractory

hematological malignancies demonstrated a 36% and 40% ORR in diffuse large B cell lymphoma and follicular lymphoma, respectively. There were also responses in patients with peripheral and cutaneous T cell lymphomas [20]. Therapy with anti-PD-1 antibodies has been generally safe, and only a few grade 3 or 4 toxicities were reported. Immune-related adverse events can occur following PD-1 blockade, but are less common and severe than what has been observed with the CTLA-4 blocking antibody, ipilimumab [21].

Clinical studies of PD-1 blockade are currently ongoing in other hematological cancers, such as AML and myelodysplastic syndrome (MDS) (MK3475 KEYNOTE 013; NCT01096602; NCT02532231), and the results are eagerly awaited. Our group has demonstrated that PD-1/PD-L1 interactions promote immune evasion in a pre-clinical AML model [22], and our preliminary data indicates that human AML blasts from a fraction of patients express PD-L1 when analyzed by flow cytometry, arguing that interfering with PD-1/PD-L1 interactions may be therapeutically efficacious in human myeloid malignancies as well.

4.3 PD-1/PD-L1 INTERACTIONS, GRAFT-VERSUS-HOST DISEASE (GVHD) AND THE GRAFT-VERSUS-TUMOR EFFECT (GVT).

Acute GVHD is influenced by factors that either positively or negatively modulate donor T cell activation, and the PD-1/PD-L1 pathway has been previously implicated in exacerbating acute GVHD in pre-clinical models. For example, in a MHC-mismatched murine alloSCT model, acute GVHD was enhanced in transplant recipients treated with a PD-L1 blocking antibody [23]. Additional studies in animals have found elevated expression of PD-L1 and PD-L2 in GVHD target organs following alloSCT. Interestingly, PD-1/PD-L1, but not PD-1/PD-L2 blockade markedly accelerated GVHD-related lethality [24]. Although PD-1 blockade has not formally been tested in humans in the post-transplant setting, results in animal models do raise concern that by attempting to harness a GVT effect via PD-1 blockade, GVHD could develop as a complicating factor. In addition, a recent presentation at the 2015 meeting of the American Society of Hematology, Herbeux and colleagues presented a retrospective analysis of nivolumab treatment for patients with Hodgkin lymphoma who had relapsed following alloSCT. Of 8 evaluable patients, acute GVHD occurred in 2 (grades 3 and 4 acute GVHD of the skin). Both patients had a history of acute GVHD in the 3 months prior to receiving nivolumab. Seven of 8 nivolumab-treated patients derived clinical benefit, with 4 achieving a partial response (PR), and 3 a complete response (CR). Furthermore, both patients who developed GVHD improved with treatment [25].

4.4 POST-ALLOSCT IMMUNOTHERAPY.

Unfortunately, patients who relapse after alloSCT have few treatment options and dismal outcomes. Withdrawal of immunosuppression to unleash a GVT effect has been effective in CML, but rarely in other diseases [26]. Chemotherapy may be an option, although responses are not often durable [27], and most patients do not have sufficient performance status or hematological reserve to tolerate cytotoxic therapies. Cellular-based immunotherapies, including donor lymphocyte infusion (DLI), as well as adoptive T and NK cell therapy, have been employed to treat disease relapse following allo-SCT with

variable efficacies [28, 29, 30], including a 2-year survival of only 21% following DLI in an EBMT study [31]. In addition, acute GVHD develops in up to 40–60% of patients who receive DLI, and pancytopenia, infections, current GVHD, and donor availability at the time of relapse are major impediments to its use [30, 31].

The anti-CTLA-4 antibody, ipilimumab, was administered in the context of a phase 1 study to 29 patients with relapsed malignancies after alloSCT [32]. No dose-limiting toxicities (DLT) or grade 3-4 GVHD were observed. Chronic GVHD, present in 2 patients at the time of anti-CTLA-4 therapy, did not flare. One patient developed grade 1 GVHD two months after receiving ipilimumab, which occurred only after a DLI was administered for progressive disease. A CR was achieved in 2 patients with HL, and a PR was observed in a patient with NHL. These results suggest that checkpoint blockade therapy can be safely administered to patients with disease relapse following alloSCT.

A prospective trial was recently published utilizing ipilimumab in 28 patients with various hematologic malignancies including relapsed AML, MDS, NHL, and HL following allogeneic transplant. Patients had no history of grade III or IV acute GVHD and were off immunosuppression. for at least 4 weeks 21% of patients had immune-related adverse events and 14% had GVHD precluding further treatment. ORR was 32% (23% CR) at the 10 mg/kg dose, with 18% of patients achieving a durable remission for more than 1 year [33].

4.5 PEMBROLIZUMAB (MK-3475).

Please refer to the IB / approved labeling for detailed background information on pembrolizumab (MK-3475).

4.6 PHARMACEUTICAL AND THERAPEUTIC BACKGROUND OF PEMBROLIZUMAB (MK-3475).

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

The PD-1 receptor-ligand interaction is a major pathway hijacked by tumors to suppress immune control [34, 35]. 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.

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 States for the treatment of patients with unresectable or metastatic melanoma and disease progression following ipilimumab and, if BRAF V600 mutation positive, a BRAF inhibitor. It has also been FDA approved for patients with metastatic non-small cell lung cancer (NSCLC) who have progressed on standard chemotherapy and whose tumor expresses PD-L1. It has also been FDA approved for patients with recurrent or metastatic head and neck squamous cell carcinoma (HNSCC) with disease progression on or after platinum-containing chemotherapy.

4.7 PRE-CLINICAL AND CLINICAL TRIAL DATA.

Refer to the IB for details.

5.0 RATIONALE

5.1 RATIONALE FOR THE TRIAL AND SELECTED SUBJECT POPULATION.

Checkpoint blockade therapy with anti-PD-1 antibodies has demonstrated remarkably broad therapeutic success as cancer immunotherapy. The efficacy of PD-1 blockade

appears to be greater in neo-antigen rich and "inflamed" tumors. However, in the post-alloSCT setting, immune-mediated elimination of malignant cells is driven by a mismatch in minor histocompatibility antigens (miHA) between donor and recipient. It is not known whether donor T cells recognize neo-antigens displayed on recipient-derived malignant cells.

Examining the safety of anti-PD-1 antibodies following disease relapse after alloSCT is critical for several reasons. First, the "off-protocol" use of anti-PD-1 antibodies following alloSCT will rise due to the general excitement around them and due to lack of other treatment options. Even a small study such as the one proposed here could go a long way in generating a safety signal for PD-1 blockade following alloSCT. Second, given that PD-1 expression is common on donor T cells following alloSCT [36, 37], and has been associated with leukemia relapse after transplantation [38], it is not unreasonable to speculate that the clinical activity of ant-PD-1 therapy post-alloSCT will be high.

5.2 RATIONALE FOR PEMBROLIZUMAB DOSE AND SCHEDULE.

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 DLTs 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 maximum-tolerated dose (MTD) has been identified to date; however, recent data from other clinical studies within the MK-3475 program has shown that a lower dose of MK-3475 and a less frequent schedule may be sufficient for target engagement and clinical activity.

PK data analysis of MK-3475 administered Q2W and Q3W showed slow systemic clearance, limited volume of distribution, and a long half-life (refer to IB). Pharmacodynamic data (IL-2 release assay) suggested that peripheral target engagement is durable (>21 days). This early PK and pharmacodynamic data has provided 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 was based on: 1) similar efficacy and safety of pembrolizumab when dosed at either 2 mg/kg or 10 mg/kg Q3W in melanoma patients, 2) the flat exposure-response relationships of pembrolizumab for both efficacy and safety in the dose ranges of 2 mg/kg Q3W to 10 mg/kg Q3W, 3) the lack of effect of tumor burden or indication on distribution behavior of pembrolizumab (as assessed by the population PK model) and 4) the assumption that the dynamics of pembrolizumab target engagement will not vary meaningfully with tumor type.

The 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. Therefore 200mg pembrolizumab Q3W will be used in the current study.

5.3 RATIONALE FOR TOLERABILITY ENDPOINTS.

The primary endpoint of this trial is to determine whether pembrolizumab administration is safe and tolerable in patients with relapsed AML, MDS, and mature B cell lymphomas following alloSCT. The safety analysis will be based on subjects who experience toxicities following treatment with pembrolizumab as defined by CTCAE criteria. Safety will be assessed by quantifying and grading the toxicities experienced by subjects who have received pembrolizumab, including serious adverse events (SAEs) and events of clinical interest (ECIs). Safety will be assessed by reported adverse events using CTCAE, version 4.0. The attribution to drug, timing of onset, event duration, event resolution, and any concomitant medications administered will be recorded. AEs will be analyzed, including but not limited to all AEs, SAEs, fatal AEs, and laboratory changes. Further, the occurrence of a grade 2 or higher immune-related AE will be collected and designated as an immune-related event of clinical interest (irAE) as well as veno-occlusive disease (VOD) and steroid-requiring febrile syndrome. Special attention will be paid in this patient population, to the development and severity of acute GVHD, which will be appropriately staged and graded according to accepted criteria (see Appendix, Section 13.6).

Given that a standard, phase I dose-escalation approach is not warranted given the discussion in Section 5.2, the investigators feel it is reasonable to perform a pilot study to

explore if the chosen pembrolizumab dose and schedule (i.e. 200 mg Q3W) is safe in this patient population.

5.4 RATIONALE FOR EFFICACY ENDPOINTS.

The secondary objective of this study (primary efficacy endpoints) is to determine the anti-tumor activity of pembrolizumab treatment in subjects with relapsed AML, MDS or mature B cell lymphomas following alloSCT. The overall response rate (ORR) will be the most valuable and primary efficacy endpoint. ORR for B cell lymphoma patients will be assessed according to the International Working Group criteria [39]. ORR for AML and MDS patients will be assessed according to the European Leukemia Net and International Working Group response criteria, respectively [40, 41]. ORR is defined as the proportion of subjects who achieve an objective disease response, as defined in Section 3.2.

Secondary efficacy endpoints include duration of response (DOR) and overall survival (OS). DOR is defined as the interval from the first documentation of an objective disease response, as defined in Section3.2, to the documentation of disease progression, as defined in Section 3.2. OS is defined as the interval from the date of study enrollment to death from any cause.

5.5 RATIONALE FOR BIOMARKER RESEARCH.

Effect of pembrolizumab treatment on restoring donor chimerism. Disease relapse following alloSCT is commonly associated with a decline in donor chimerism. By stimulating donor-derived T cells, it is hypothesized that pembrolizumab will improve or even completely restore full donor chimerism in patients will relapsed disease after alloSCT (where loss or decline in donor chimerism has been documented to occur). Donor chimerism in both the entire WBC population and in the CD3+ cell compartment will be analyzed by short tandem repeat analysis on 10 pre-defined loci by PCR and a capillary amplifier. Analyses on peripheral blood (all patients) and bone marrow aspirates (in AML and MDS patients only) will be performed at baseline (pre-treatment) and at 3, 6, 9, 12, 15, 18, 21 and 24 months of pembrolizumab treatment. It is expected that pembrolizumab treatment will improve or completely restore donor chimerism in treated patients. A correlation between donor chimerism status and objective response will be sought, although patient number may be too small to make any definitive conclusion.

Effect of pembrolizumab on T cell number and activation status. Pembrolizumab, by interrupting PD-1/PD-L1 interactions, may affect not only numbers of T cells present in peripheral blood (and bone marrow), but may also lead to upregulation of activation markers on peripheral blood T cells. To explore this hypothesis, the frequencies and absolute numbers of T cell subsets (conventional CD4+ and CD8+ and CD4+CD25+CD127- regulatory T cells (Tregs)) will be enumerated in the peripheral blood (all patients) and bone marrow (AML and MDS patients only) at several defined time points prior to and following pembrolizumab treatment (pre-treatment, and at 3, 6, 9, 12, 15, 18, and 24 months of treatment). Peripheral blood mononuclear cells (PBMC) or bone marrow cells will be stained with anti-CD3, anti-CD8, anti-CD4, anti-CD25, and

anti-CD127 antibodies and analyzed by flow cytometry to define specific T cell subsets. Conventional CD4+ T cells will be defined as CD3+CD4+CD25-/low cells, while conventional CD8+ T cells will be defined as CD3+CD8+ cells. Tregs will be defined as CD3+CD4+CD25hiCD127- cells. Frequencies will be calculated by sub-gating on the lymphocyte population as appropriate. Absolute numbers of T cells in each subset will be enumerated by multiplying the frequency of each T cell subset by the total white blood count from each sample. T cell activation status will be analyzed by co-staining cells with antibodies directed against the following markers: HLA-DR, CD69, ICOS and CD25 (others may be added). Descriptive statistics will be utilized to compare pre- and post-treatment frequencies, absolute numbers and activation status of T cells in enrolled patients. The goal would be to define potential biomarkers associated with responsiveness to pembrolizumab treatment that could be verified in larger studies in a similar patient population.

Detection of PD-L1 and PD-L2 expression. To determine whether expression of PD-1 ligands on malignant or non-malignant cells in the tumor environment may be a driver of disease relapse following alloSCT, PD-L1 and PD-L1 expression will be analyzed and compared between diagnostic samples and post-alloSCT relapse samples. This assay will be performed in collaboration with Merck using in-house protocols.

TCR sequencing. To investigate the hypothesis that pembrolizumab treatment will be associated with clonal expansion of antigen-specific T cells, the peripheral blood TCR repertoires will be compared in each patient prior to and at defined time points following pembrolizumab treatment (see above) using TCR-β deep sequencing. These studies will be performed by Adaptive Biotechnologies, and data analyzed internally. Simpson's index of diversity will be utilized to compare the diversity of TCR repertoires prior to and following pembrolizumab treatment

6.0 METHODOLOGY

6.1 ENTRY CRITERIA

6.1.1 DIAGNOSIS FOR STUDY ENTRY

Male or female subjects with AML, MDS or mature B cell lymphomas that have relapsed following matched-related donor (MRD) or matched unrelated donor (MUD) (HLA-A -B -C -DR -DQ) alloSCT are eligible for enrollment.

6.1.2 SUBJECT INCLUSION CRITERIA

1. Signed written informed consent

a) Subjects must have signed and dated an IRB-approved written informed consent form in accordance with regulatory and institutional guidelines. This must be obtained before the performance of any protocol-related procedures that are not part of normal subject care.

b) Subjects must be willing and able to comply with scheduled visits, treatment schedule, laboratory tests and other requirements of the study.

2. Target population

a) Subjects must be ≥ 18 years of age.

b) Subjects must have an ECOG performance status of 0-1 (Appendix).

c) Subjects have undergone alloSCT > 90 days prior to enrollment from a matched-related donor (MRD), matched-unrelated donor (MUD), cord blood donor, or haplo-identical and cord blood donor.

d) There must be histological confirmation of relapse after alloSCT of any of the following diseases: any mature B cell lymphoma (cHL or NHL), AML or MDS.

e) Subjects must be off of all immunosuppressive medications for a minimum of 2 weeks with the exception of physiologic doses of corticosteroids.

f) Subjects with B cell lymphoma must have measurable disease, defined as at least 1 lesion that can be accurately measured in at least 2 dimensions with CT scan. Minimum measurement must be > 15 mm in the longest diameter and > 10 mm in the short axis.

g) Subjects must not have had any prior investigational agents or devices within 4 weeks of beginning study drug

h) Subjects must have no prior history of VOD

i) Subjects must demonstrate adequate organ function as defined in **Table 2**. All screening labs should be performed within 10 days of treatment initiation.

Table 2. Adequate Organ Function Laboratory Values

System	**Laboratory Value**
Hematological	
Absolute neutrophil count (ANC)	≥ 500 /mcL
Platelets	≥ 20,000 /mcL
Hemoglobin	≥ 8 g/dL (RBC transfusions are OK)
Renal	
Serum creatinine **OR** Measured or calculated[a] creatinine clearance (GFR can also be used in place of creatinine or	≤ 1.5 X upper limit of normal (ULN) or ≥ 60 mL/min for subject with creatinine levels > 1.5 X institutional ULN

CrCl)	
Hepatic	
Serum total bilirubin	≤ 1.5 X ULN or direct bilirubin ≤ ULN for subjects with total bilirubin levels > 1.5X ULN
AST (SGOT) and ALT (SGPT)	≤ 2.5 X ULN
Albumin	≥ 2.0 mg/dL
Coagulation	
International Normalized Ratio (INR) or Prothrombin Time (PT)	≤ 1.5 X ULN unless subject is receiving anticoagulant therapy, in which case, the PT/INR should be within therapeutic range for intended use.
Activated Partial Thromboplastin Time (aPTT)	≤ 1.5 X ULN unless subject is receiving anticoagulant therapy, in which case, the PTT should be within therapeutic range for intended use.
[a]Creatinine clearance should be calculated per institutional standard.	

j) Female subjects of childbearing potential should have a negative urine or serum pregnancy test (β-hCG) within 72 hours prior to receiving the first dose of study medication.

k) Female subjects with childbearing potential should be willing to use 2 methods of contraception, be surgically sterile, or abstain from heterosexual activity throughout the course of the study, until 120 days after the final dose of study medication. Subjects with childbearing potential are those who have not been surgically sterilized or have not been free from menses for > 1 year. Abstinence is acceptable if this is the established and preferred contraceptive method for the subject (see Section 6.7.1).

l) Male subjects should agree to use an adequate method of contraception starting with the first dose of study medication until 120 days after the final dose of study medicine. Abstinence is acceptable if this is the established and preferred contraceptive method for the subject (see Section 6.7.1).

6.1.3 SUBJECT EXCLUSION CRITERIA

1. Target disease exclusions

a) Subjects must not have known central nervous system involvement by disease (parenchymal, meningeal or cerebrospinal fluid)

2. Medical history, concurrent diseases, and prior treatments

a) Subjects must not have a history of any positive test for hepatitis B or hepatitis

C indicating active disease or previous exposure.

b) Subjects must not have a history of human immunodeficiency virus (HIV) infection.

c) Subjects must not be receiving systemic steroid therapy or any other form of immunosuppressive therapy within 2 weeks prior to the first dose of study medication. The use of physiologic doses of corticosteroids is acceptable.

d) Subjects must not be concurrently receiving disease-modifying therapy in another therapeutic investigational study.

e) Subjects must not have received a prior monoclonal antibody within 4 weeks prior to the first dose of study medication, and must have recovered (≤ grade 1) from adverse events related to any anti-cancer agent administered > 4 weeks previous to the first dose of study medication.

f) Subjects must not have received chemotherapy or targeted small molecule therapy within 4 half-lives of the specific agent(s), or radiation therapy within 2 weeks prior to the first dose of study medication, and must have recovered (≤ grade 1) from adverse events related to a previously administered agent.

g) Subjects must not have received a donor lymphocyte infusion (DLI) within 8 weeks prior to the first dose of study medication.

h) Subjects must not have a history of severe (grade 3-4) acute GVHD, and/or current > grade 1 acute GHVD. Subjects must not have a history of active chronic GVHD (whether limited or extensive stage).

i) Subjects must not have 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 (e.g., thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency, etc.) is not considered a form of systemic treatment.

j) Subjects must not have a known history of congestive heart failure, unstable angina pectoris, or cardiac arrhythmia (with the exception of chronic and rate-controlled atrial fibrillation).

k) Subjects must not have a history of other serious underlying medical or psychiatric condition that, in the opinion of the investigator, would impair the ability to receive, tolerate and or comply with the planned treatment and follow-up.

l) Subjects must not have a history of a known secondary primary malignancy that is not in remission and/or that requires active therapy. Exceptions include non-melanoma skin cancers and in situ cervical cancer that has undergone

curative-intent local therapy.

m) Subjects must not have a known active infection requiring intravenous antibiotic therapy.

n) Subjects must not have a history of (non-infectious) pneumonitis that required steroid treatment, evidence of interstitial lung disease, or active, non-infectious pneumonitis. Subjects must not have active, non-infectious colitis.

o) Subjects must not be pregnant or breastfeeding, or expecting to conceive or father children within the projected duration of the trial, starting with the screening visit through 120 days after the final dose of study medication.

p) Subjects must not have received a live vaccine within 30 days prior to the first dose of study medication.

q) Subjects must not be or have an immediate family member (spouse, parent, legal guardian, sibling or child) who is an investigational site sponsor or staff directly involved with the trial, unless IRB approval is granted previously.

6.2 TRIAL TREATMENTS

The treatment to be used in this trial is outlined below in **Table 3**.

Table 3. Trial treatments

Study Drug	Dose	Cycle duration	Route of administration	Treatment period	Use
Pembrolizumab	200 mg in 100 mL of normal saline	21 days	IV infusion (0.2 micron in-line filter) over 30 minutes	Day 1 of each treatment cycle	Experimental

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 the study medication in accordance with the study protocol and any applicable laws and regulations.

6.2.1 DOSE SELECTION/MODIFICATION

6.2.1.1 DOSE SELECTION (PREPARATION)

All subjects will receive 200 mg of pembrolizumab via IV infusion every 21 days. Details on preparation and administration are provided in the pharmacy manual.

The rationale for selection of pembrolizumab dose to be used in this trial is provided in Section 5.2. There are no specific clarifications or evaluations required to be performed in order to administer the proper dose to each subject.

6.2.1.2 DOSE MODIFICATION

Pembrolizumab will be withheld for drug-related, grade 4 hematologic toxicities and drug-related ≥ grade 2 or 3 toxicities including laboratory abnormalities, as outlined in **Tables 4 and 5**. Attribution of events to drug will be per investigator/physician discretion.

Table 4. Dose modification guidelines for hematological drug-related adverse events

Toxicity	**Grade**	**Hold Treatment (Y/N)**	**Timing for restarting treatment**	**Discontinue Subject (after consultation with the Principal Investigator)**
Hematological Toxicity	1, 2, 3	No	N/A	N/A
	4	Yes	Toxicity resolves to Grade 0-1 or baseline	Toxicity does not resolve within 12 weeks of last infusion Permanent discontinuation should be considered for any life-threatening event

Table 5. Dose modification guidelines for non-hematological drug-related adverse events

Toxicity	**Hold Treatment For Grade**	**Timing for Restarting Treatment**	**Discontinue Subject**
Acute GVHD (as defined by the Gluckenberg scale - see appendix)	2[1]	Toxicity resolves to grade 0-1. Re-start pembrolizumab at 200 mg IV q21 days.	Toxicity does not resolved within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone equivalent per day within 12 weeks.
	3-4[1]	Permanently discontinue	Permanently discontinue

Toxicity	Hold Treatment For Grade	Timing for Restarting Treatment	Discontinue Subject
Diarrhea/Colitis	2[1]	Toxicity resolves to Grade 0-1. Re-start pembrolizumab at 200 mg IV q21 days.	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks.
	3-4[1]	Permanently discontinue	Permanently discontinue
Hypophysitis	2-3[1]	Toxicity resolves to Grade 0-1.	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks.
	4[1]	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks.
AST, ALT, or Increased Bilirubin	2[1]	Toxicity resolves to Grade 0-1. Re-start pembrolizumab at 200 mg IV q21 days.	Toxicity does not resolve within 12 weeks of last dose.
	3-4[1]	Permanently discontinue (see exception below)[2]	Permanently discontinue
Hyperthyroidism or Hypothyroidism	3[1]	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks.
	4[1]	Permanently	Permanently discontinue

Toxicity	Hold Treatment For Grade	Timing for Restarting Treatment	Discontinue Subject
		discontinue	
Infusion Reaction	3-4	Permanently discontinue	Permanently discontinue
Neurologic events (including myasthenia gravis)	2[1]	Toxicity resolves to Grade 0-1. Re-start pembrolizumab at 200 mg IV q21 days.	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks.
	3-4[1]	Permanently discontinue	Permanently discontinue
Pneumonitis	2[1]	Toxicity resolves to Grade 0-1. Re-start pembrolizumab at 200 mg IV q21 days.	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks.
	3-4[1]	Permanently discontinue	Permanently discontinue
Renal Failure or Nephritis	2[1]	Toxicity resolves to Grade 0-1. Re-start pembrolizumab at 200 mg IV q21 days.	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks.
	3-4[1]	Permanently discontinue	Permanently discontinue
All Other Drug-Related Toxicity[3]	3 or Severe[1]	Toxicity resolves to Grade 0-1. Re-start pembrolizumab at 200 mg IV q21 days.	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks.

Toxicity	Hold Treatment For Grade	Timing for Restarting Treatment	Discontinue Subject
	4	Permanently discontinue	Permanently discontinue

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

[1] Administer corticosteroid (See also Events of Clinical Interest Guidance Document and Section 8.2.3.2 Events of Clinical Interest).

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

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

* Attribution of events to drug will be per investigator/physician discretion; in case of DLT grade toxicity that is deemed to be unrelated to drug, patient can continue on trial with appropriate treatment

6.2.2 TIMING OF DOSE ADMINISTRATION

Trial treatment should be administered on day 1 of each treatment cycle after all procedures/assessments have been completed as detailed on the trial flow chart (Section 7.0). Trial treatment may be administered up to 3 days before or after the scheduled day 1 of each cycle due to administrative reasons. Interruptions from the treatment plan for > 3 days and up to 3 weeks may be allowed, but require consultation between the principal investigator and treating investigator, and written documentation of the collaborative decision on subject management.

Pembrolizumab will be administered as a 30 minute (+/- 5 minute) IV infusion every 21 days, unless a treatment-limiting toxicity (TLT), as defined in Section 6.2.1.2 and as outlined in **Table 5**, has occurred. In this case, provided that the patient has sufficiently recovered, pembrolizumab will be restarted as a 30 minute (+/- 5 minute) IV infusion every 21 days. All trial treatments will be administered on an outpatient basis.

In the setting where a subject assessment is consistent with progressive disease (PD) at the 3 month disease response assessment, study drug may be continued until next disease response assessment provided the subjects' clinical condition is stable**.** If progressive

disease is noted on imaging and patient is clinically stable or improved, repeat imaging should be obtained 4-6 weeks later. **This exception pertains to B cell lymphoma patients only.**

If a subject is noted to have progression of disease at a time point beyond the 3 month disease response assessment, a repeat assessment may not be performed and the subject should not receive further treatment with the study medication.

Subjects may only receive study treatment if the following criteria are met:

- Absence of signs and symptoms (including worsening of laboratory values indicative of disease progression)
- No decline in ECOG performance status
- Absence of rapid disease progression

6.2.3 EXTENT OF TRIAL TREATMENT

All subjects who experience a partial response or have stable disease may remain on treatment for up to 2 years, or until progression.

Subjects who achieve a complete response may choose to discontinue pembrolizumab therapy. However, they will not be eligible for re-treatment on this study should the disease recur before or after the planned 2 year treatment period.

6.2.4 TRIAL BLINDING/MASKING

This is an open-label trial. The investigator and subject will be aware of the study treatment administered.

6.3 RANDOMIZATION OR TREATMENT ALLOCATION

Subjects participating in this trial will be allocated by non-random assignment.

6.4 STRATIFICATION

No stratification based on age, sex or other characteristics will be used in this trial.

6.5 CONCOMITANT MEDICATIONS AND VACCINES.

Medications or vaccinations specifically prohibited in the exclusion criteria are not allowed. If there is a clinical indication for any medication or vaccination specifically prohibited during the trial, discontinuation from trial therapy or vaccination may be required. The treating investigator should discuss any questions regarding this with the principal investigator and drug manufacturer, Merck (as appropriate). The final decision on any supportive therapy or vaccination rests with the investigator and/or the subject's primary physician. However, the decision to continue the subject on trial therapy or

vaccination schedule requires the mutual agreement of the investigator, the principal investigator and the subject.

6.5.1 ACCEPTABLE CONCOMITANT MEDICATIONS

All treatments that the investigator considers necessary for a subject's welfare may be administered at the discretion of the investigator in keeping with the community standards of medical care. All concomitant medication will be recorded on the case report form (CRF) including all prescription, over-the-counter (OTC), herbal supplements, and IV medications and fluids. If changes occur during the trial period, documentation of drug dosage, frequency, route, and date may also be included on the CRF. Subject may remain on anti-coagulation therapy as long as the PT or PTT is within therapeutic range of the intended use of anticoagulants

All concomitant medications received within 28 days before the first dose of trial treatment and 30 days after the last dose of trial treatment should be recorded. Concomitant medications administered after 30 days after the last dose of trial treatment should be recorded for SAEs and ECIs as defined in Section 8.2.

6.5.2 PROHIBITED CONCOMITANT MEDICATIONS AND TREATMENTS

- Anti-neoplastic systemic chemotherapy or biological therapy
- GM-CSF
- Immunotherapy not specified in this protocol
- Investigational agents other than pembrolizumab
- Radiation therapy (Radiation therapy to a symptomatic solitary lesion may be allowed after consultation with the investigator.
- Live vaccines within 30 days prior to the first dose of pembrolizumab and through the duration of the study. Examples include, but are not limited to: measles, mumps, rubella, chicken pox, yellow fever, rabies, BCG, oral typhoid, and intranasal influenza vaccines (e.g. Flu-Mist®). Seasonal influenza vaccines for injection are generally acceptable.
- Immunosuppressive medications including, but not limited to, systemic corticosteroids (>10 mg/day prednisone or equivalent), methotrexate, azathioprine, and tumor necrosis factor alpha (TNF-α) blockers. Use of immunosuppressive medications for the management of investigational product-related AEs and in subjects with contrast allergies is permitted. The use of physiologic steroid replacement may be approved after consultation with the investigator, study PI, and sponsor. In addition, use of inhaled and intranasal corticosteroids is permitted.

- Other medications as outlined in the exclusion criteria (Section 6.1.3).

6.6 RESCUE MEDICATIONS AND SUPPORTIVE CARE

6.6.1 SUPPORTIVE CARE GUIDELINES

Subjects should receive appropriate supportive care measures as deemed necessary by the treating physician, including but not limited to the items outlined below:

- Diarrhea: 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 bowel perforation (such as peritoneal signs and ileus). Diarrhea in this particular patient population may be due either to acute GVHD or to classical pembrolizumab-induced enterocolitis, and the differentiation between the two may be difficult or impossible. In symptomatic subjects, infectious etiologies should be evaluated, and if symptoms are persistent and/or severe, endoscopic evaluation should be performed.

- In subjects with severe enterocolitis (grade 3 or 4) caused by acute GVHD or classical pembrolizumab-associated enterocolitis, pembrolizumab will be permanently discontinued, and treatment with systemic corticosteroids should be initiated at a dose of 1-2 mg/kg/day of prednisone or equivalent. When symptoms improve to ≤ grade 1, a corticosteroid taper should be started and continued for > 1 month.

- In subjects with moderate enterocolitis (grade 2) caused by acute GVHD or classical pembrolizumab-associated enterocolitis, pembrolizumab will be withheld and corticosteroids should be initiated at a dose of 1 mg/kg/day of prednisone or equivalent. When symptoms improve to ≤ grade 1, a corticosteroid taper should be started and continued for > 1 month. Pembrolizumab may be re-started at 200 mg IV every 21 days, as outlined in Section 6.2.1.2.

- All subjects who experience diarrhea should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolyte repletion (IV) is appropriate. Other treatments, including loperamide, oral non-absorbable corticosteroids and octreotide may be administered according to institutional guidelines for the treatment of acute GVHD.

- GVHD: Subjects should be carefully monitored for signs and symptoms of GVHD (including diarrhea, transaminitis, rash). These symptoms will be treated aggressively with topical and/or systemic steroids and additional immunosuppressants per institutional guidelines.

- Nausea/vomiting: These symptoms should be treated aggressively, and consideration should be given in subsequent cycles to the administration of prophylactic anti-emetics according to institutional practice.

- Antibiotics: Antibiotics, either prophylactic or therapeutic, are allowed as considered appropriate by the treating physician. **Appropriate antibiotics (i.e. PCP prophylaxis) should be initiated for patients who are on longer courses of corticosteroids.**

- Immune-related adverse events: Please see Table 5 above and separate guidance document regarding diagnosis and treatment of adverse events of a potential immunologic etiology.

- Infusion reactions: Acute infusion reactions (which include cytokine release syndrome, angioedema, or anaphylaxis) are unique from allergic/hypersensitive reactions, although some of the manifestations are common to both. Signs and symptoms usually develop during or shortly after pembrolizumab infusion and generally resolve completely within 24 hours of completion of infusion. Signs/symptoms may include: allergic reaction/hypersensitivity (including fever), arthralgia, bronchospasm, cough, dizziness, dyspnea, fatigue, headache, hypertension, hypotension, tachycardia, rigors or chills, myalgia, nausea, vomiting, pruritus, rash or urticaria, and tumor pain. See **Table 6** below for management guidelines for pembrolizumab-associated infusion reactions.

- Respiratory/Pulmonary adverse events: Investigators should maintain a high index of suspicion for pneumonitis and initiate treatment with corticosteroids in a timely manner. Additional supportive care guidance for pneumonitis can be found in Section 6.6.1.2.

Table 6. Infusion reaction treatment guidelines

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

NCI CTCAE Grade	Treatment	Premedication at subsequent dosing
≤ 24 hrs	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 pre-medicated for the next scheduled dose. Subjects who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further trial treatment administration.	antihistamine dose). Acetaminophen 500-1000 mg PO (or equivalent dose of antipyretic).
Grade 3 or 4 Grade 3: Prolonged (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)	Stop Infusion. Additional appropriate medical therapy may include but is not limited to: IV fluids Antihistamines NSAIDS Acetaminophen Narcotics Oxygen Corticosteroids Epinephrine Increase monitoring of vital	No subsequent dosing

NCI CTCAE Grade	Treatment	Premedication at subsequent dosing
Grade 4: Life-threatening; pressor or ventilatory support indicated	signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator. Hospitalization may be indicated. Subject is permanently discontinued from further trial treatment administration.	
Appropriate resuscitation equipment should be available in the room and a physician readily available during the period of drug administration. For further information, please refer to the Common Terminology Criteria for Adverse Events v4.0 (CTCAE) at http://ctep.cancer.gov		

6.6.1.1 SUPPORTIVE CARE GUIDELINES FOR ADVERSE EVENTS OF CLINICAL INTEREST WITH AN IMMUNE ETIOLOGY (IRAES) AND EVENTS OF CLINICAL INTEREST (ECI)

Immune-related adverse events (irAE)

irAEs are defined as an adverse event associated with pembrolizumab exposure and mediated through an immune mechanism. irAEs may be predicted based on the nature of the known mechanism of action of pembrolizumab, as well as experience with other immunotherapies with a similar mechanism of action. Special attention should be paid to AEs that are suggestive of potential irAEs. An irAE can occur shortly after the first dose, or several months after the final dose of pembrolizumab. If an irAE is suspected, effort should be made to rule out other potential etiologic causes prior to labeling an AE as an irAE. Information on how to identify and evaluate irAEs is included in the event of clinical interest and immune-related adverse event guidance document located in the administrative binder.

Events of clinical interest (ECI)

ECIs are non-serious and serious AEs that may or may not be irAEs. ECIs must be reported to Merck within 24 hours regardless of attribution to pembrolizumab.

Information on how to identify and report ECIs can be referenced in Section 8.2.3.2.

6.6.1.2 SUPPORTIVE CARE GUIDELINES FOR PNEUMONITIS

Pembrolizumab treatment should be immediately held in subjects with symptomatic pneumonitis, and a clinical evaluation should be performed. The evaluation may include bronchoscopy and pulmonary function tests to rule out other causes. If the subject is determined to have pembrolizumab-associated pneumonitis, a treatment plan is outlined in Table 7.

Table 7. Recommended approach to the management of pneumonitis

Study drug associated pneumonitis	**Withhold/Discontinue pembrolizumab?**	**Supportive Care**
Grade 1 Asymptomatic; clinical or diagnostic observations	No	Intervention not indicated
Grade 2 Symptomatic; medical intervention indicated; limiting instrumental ADL	Yes May re-treat with pembrolizumab 200 mg every 21 days if improves to grade ≤ 1 within 12 weeks	Systemic corticosteroids are indicated.
Grade 3 and 4 Grade 3- Severe symptoms; limiting self-care; oxygen indicated Grade 4 - Life-threatening respiratory compromise; urgent intervention indicated (e.g., tracheotomy or	Yes Discontinue pembrolizumab permanently	Systemic corticosteroids are indicated. The use of infliximab may be indicated as appropriate. Refer to the Event of Clinical Interest Guidance Document for additional recommendations.

intubation)		

For grade 2 pneumonitis that improves to ≤ 1 grade 1 within 12 weeks, the following rules should apply:

- First episode of pneumonitis
    - May return to treatment (pembrolizumab 200 mg IV every 21 days)
- Second episode of pneumonitis - permanently discontinue pembrolizumab if upon re-challenge, subject develops recurrent pneumonitis ≥ grade 2.

6.7 CONTRACEPTION, PREGNANCY AND NURSING MOTHERS

6.7.1 CONTRACEPTION

Pembrolizumab may have adverse effects on a fetus. It is not known if pembrolizumab has transient adverse effects on the composition of sperm. For this trial, male subjects will be considered to be of no reproductive potential if they are azospermic (whether due to having a vasectomy or an underlying medical condition).

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

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

OR

2. have had a hysterectomy and/or bilateral oppherectomy, bilateral salpingectomy or bilateral tubal ligation/occlusions, at least 6 weeks prior to screening;

OR

3. have a congentially-acquired condition that prevents childbearing.

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

1. practice abstinence from heterosexual activity;

OR

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

Acceptable methods of contraception are:

- Single method (one of the following is acceptable):
    - intrauterine device (IUD)
    - vasectomy of a female subject's male partner
    - contraceptive rod implanted into the skin
- Combination method (requires use of two of the following):
    - diaphragm with spermicide (cannot be used in conjunction with cervical cap/spermicide)
    - cervical cap with spermicide (nulliparous women only)
    - contraceptive sponge (nulliparous women only)
    - male condom or female condom (cannot be used together)
    - hormonal contraceptive: oral contracceptive pill (estrogen/progestin pill or rogestin-only pill), contraceptive skin patch, vaginal contraceptive ring, or subcutaneous contraceptive injection.

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

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

Subjects should be informed that taking the study medication may involve unknown risks to the fetus (unborn baby) if pregnancy were to occur during the study. In order to participate in the study, they must adhere to the contraception requirement (described above) from the day of study medication initiation (or 14 days prior to the initiation of a study medication for oral contraception) throughout the study period up to 120 days after the last dose of trial therapy. If there is any question that a subject will not reliably comply with the requirements for contraception, that subject should not be entered into the study.

6.7.2 USE DURING PREGNANCY

If a subject inadvertently becomes pregnant while on treatment with pembrolizumab, she 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 without delay and within 24 hours 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.

6.7.3 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.

6.8 SUBJECT WITHDRAWAL/DISCONTINUATION CRITERIA

Subjects may withdraw consent at any time for any reason or be removed 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.

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.

A subject must be discontinued from treatment (but may continue to be monitored in the trial) for any of the following reasons:

- The subject or legal representative withdraws consent for treatment
- Disease progression occurs
- Unacceptable AEs develop as described in Tables 5 and 6, and Sections 6.6.1.1 and 6.6.1.2
- Intercurrent illness develops that prevents further administration of pembrolizumab
- Investigator's decision
- The subject becomes pregnant
- The subject is non-compliant with the treatment or trial requirements

- The subject is lost to follow-up
- Administrative reasons

The end of treatment and follow-up visit procedures are listed in Section 7.0 (Trial flow chart) and Section 8.1.5 (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. 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 or the start of new anti-cancer therapy, each subject will be followed by telephone for overall survival until death, withdrawal of consent, or the end of the study, whichever occurs first.

6.8.1 DISCONTINUATION OF PEMBROLIZUMAB AFTER ACHIEVEMENT OF A COMPLETE RESPONSE (CR)

Per the discretion of the investigator (and patient), subjects who achieve a CR following pembrolizumab treatment after a minimum of 6 months of treatment with at least 2 doses of pembrolizumab after confirmation of CR status may elect to discontinue pembrolizumab treatment. However, subjects who are discontinued from pembrolizumab treatment are not eligible for re-treatment on this trial should disease relapse occur.

6.9 BEGINNING AND END OF TRIAL

The overall trial begins when the first subject signs the informed consent form. The overall trial ends when the last subject completes the last study-related phone-call or visit, discontinues from the trial or is lost to follow-up (unable to be contacted by the investigator).

6.10 CRITERIA FOR EARLY TRIAL TERMINATION

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

1. Quality or quantity of data recording is inaccurate or incomplete
2. Poor adherence to the protocol and regulatory requirements
3. Plans to modify or discontinue the development of the study drug
4. Early stopping rule(s) are met

7.0 TRIAL FLOW CHART

7.1 SCREENING AND CYCLES 1-4

Trial Period	**Screening Phase**						
Weeks of treatment/cycle#	**Main Study Screening Visit**	**1(D1C1)**	**2(D8C1)**	**3(D15C1)**	**4(D1C2)**	**7(D1C3)**	**10(D1C4)**
Scheduling Window (days):	**(Day -28 to -1)**	**(+/- 3)**	**(+/- 3)**	**(+/- 3)**	**(+/- 3)**	**(+/- 3)**	**(+/- 3)**
Administrative Procedures							
Informed Consent	X						
Inclusion/Exclusion Criteria	X						
Demographics and Medical History	X						
Prior and Concomitant Medication Review	X						
Trial Treatment Administration		X			X	X	X
Post-Study anticancer therapy status	X						
Survival status	X	X	X	X	X	X	X
Clinical Procedures/Assessments							
Review Adverse Events	X	X	X	X	X	X	X
Full Physical Examination	X						
Directed Physical Examination		X	X	X	X	X	X
Vital Signs and Weight	X	X	X	X	X	X	X
ECOG Performance Status	X	X	X	X	X	X	X

Trial Period	**Screening Phase**						
Weeks of treatment/cycle#	**Main Study Screening Visit**	**1(D1C1)**	**2(D8C1)**	**3(D15C1)**	**4(D1C2)**	**7(D1C3)**	**10(D1C4)**
Scheduling Window (days):	**(Day -28 to -1)**	**(+/- 3)**	**(+/- 3)**	**(+/- 3)**	**(+/- 3)**	**(+/- 3)**	**(+/- 3)**
Laboratory Procedures/Assessments: analysis performed by local laboratory							
Pregnancy Test- Urine or Serum b-HCG	X						
PT/INR and aPTT	X						
CBC with differential	X	X	X	X	X	X	X
Comprehensive Serum Chemistry Panel	X	X	X	X	X	X	X
Urinalysis	X						
T3, FT4, and TSH	X				X		X
HIV, CMV	X						
HBV core antibody, anti-HCV antibody	X						
Peripheral blood chimerism	X						
Efficacy Measurements							
Tumor Imaging*	X						
BM Biopsy**	X						
Tumor Biopsies/Archival Tissue Collection Correlative Studies Blood							
Archival or Newly Obtained Tissue Collection	X						
Correlative Studies Blood Collection	X						

*Tumor imaging only for HL and NHL

**BM biopsy only for AML, MDS patients. For HL and NHL patients, a bone marrow is required only in patients with a prior history of marrow involvement

7.2 CYCLES 5-12

Trial Period								
Weeks of treatment/cycle#	**13(D1C5)**	**16(D1C6)**	**19(D1C7)**	**22(D1C8)**	**25(D1C9)**	**28(D1C10)**	**31(D1C11)**	**34(D1C12)**
Scheduling Window (days):	**(+/- 3)**	**(+/- 3)**	**(+/- 3)**	**(+/- 3)**	**(+/- 3)**	**(+/- 3)**	**(+/- 3)**	**(+/- 3)**
Administrative Procedures								
Informed Consent								
Inclusion/Exclusion Criteria								
Demographics and Medical History								
Prior and Concomitant Medication Review								
Trial Treatment Administration	X	X	X	X	X	X	X	X
Post-Study anticancer therapy status								
Survival status	X	X	X	X	X	X	X	X
Clinical Procedures/Assessments								
Review Adverse Events	X	X	X	X	X	X	X	X
Full Physical Examination								
Directed Physical Examination	X	X	X	X	X	X	X	X
Vital signs and Weight	X	X	X	X	X	X	X	X
ECOG Performance Status	X	X	X	X	X	X	X	X
Laboratory Procedures/Assessments: analysis performed by local laboratory								
Pregnancy Test- Urine or Serum b-HCG								
PT/INR and aPTT								
CBC with differential	X	X	X	X	X	X	X	X
Comprehensive Serum Chemistry Panel	X	X	X	X	X	X	X	X
Urinalysis								
T3, FT4, and TSH		X		X		X		X
HIV, CMV								

Trial Period								
Weeks of treatment/cycle#	**13(D1C5)**	**16(D1C6)**	**19(D1C7)**	**22(D1C8)**	**25(D1C9)**	**28(D1C10)**	**31(D1C11)**	**34(D1C12)**
Scheduling Window (days):	**(+/- 3)**	**(+/- 3)**	**(+/- 3)**	**(+/- 3)**	**(+/- 3)**	**(+/- 3)**	**(+/- 3)**	**(+/- 3)**
HBV core antibody, anti-HCV antibody								
Peripheral blood chimerism	X				X			
Efficacy Measurements								
Tumor Imaging*	X				X			
BM Biopsy**	X				X			
Tumor Biopsies/Archival Tissue Collection Correlative Studies Blood								
Archival or Newly Obtained Tissue Collection	X				X			
Correlative Studies Blood Collection	X				X			

*Tumor imaging only for HL and NHL

**BM biopsy only for AML, MDS patients. For HL and NHL patients, a bone marrow is required only in patients with a prior history of marrow involvement

7.3 CYCLES 13-19

Trial Period							
Weeks of treatment/cycle#	**37(D1C13)**	**40(D1C14)**	**43(D1C15)**	**46(D1C16)**	**49(D1C17)**	**52(D1C18)**	**55(D1C19)**
Scheduling Window (days):	**(+/- 3)**	**(+/- 3)**	**(+/- 3)**	**(+/- 3)**	**(+/- 3)**	**(+/- 3)**	**(+/- 3)**
Administrative Procedures							
Informed Consent							
Inclusion/Exclusion Criteria							
Demographics and Medical History							
Prior and Concomitant Medication Review							
Trial Treatment Administration	X	X	X	X	X	X	X
Post-Study anticancer therapy status							
Survival status	X	X	X	X	X	X	X
Clinical Procedures/Assessments							
Review Adverse Events	X	X	X	X	X	X	X
Full Physical Examination							
Directed Physical Examination	X	X	X	X	X	X	X
Vital signs and Weight	X	X	X	X	X	X	X
ECOG Performance Status	X	X	X	X	X	X	X
Laboratory Procedures/Assessments: analysis performed by local laboratory							
Pregnancy Test- Urine or Serum b-HCG							
PT/INR and aPTT							
CBC with differential	X	X	X	X	X	X	X
Comprehensive Serum Chemistry Panel	X	X	X	X	X	X	X

Trial Period							
Weeks of treatment/cycle#	**37(D1C13)**	**40(D1C14)**	**43(D1C15)**	**46(D1C16)**	**49(D1C17)**	**52(D1C18)**	**55(D1C19)**
Scheduling Window (days):	**(+/- 3)**	**(+/- 3)**	**(+/- 3)**	**(+/- 3)**	**(+/- 3)**	**(+/- 3)**	**(+/- 3)**
Urinalysis							
T3, FT4, and TSH		X		X		X	
HIV, CMV							
HBV core antibody, anti-HCV antibody							
Peripheral blood chimerism	X				X		
Efficacy Measurements							
Tumor Imaging*	X				X		
BM Biopsy**	X				X		
Tumor Biopsies/Archival Tissue Collection Correlative Studies Blood							
Archival or Newly Obtained Tissue Collection	X				X		
Correlative Studies Blood Collection	X				X		

*Tumor imaging only for HL and NHL

**BM biopsy only for AML, MDS patients. For HL and NHL patients, a bone marrow is required only in patients with a prior history of marrow involvement

7.4 CYCLE 20-26

Trial Period							
Weeks of treatment/cycle#	**58(D1C20)**	**61(D1C21)**	**64(D1C22)**	**67(D1C23)**	**70(D1C24)**	**73(D1C25)**	**76(D1C26)**
Scheduling Window (days):	**(+/- 3)**	**(+/- 3)**	**(+/- 3)**	**(+/- 3)**	**(+/- 3)**	**(+/- 3)**	**(+/- 3)**
Administrative Procedures							
Informed Consent							
Inclusion/Exclusion Criteria							
Demographics and Medical History							
Prior and Concomitant Medication Review							
Trial Treatment Administration	X	X	X	X	X	X	X
Post-Study anticancer therapy status							
Survival status	X	X	X	X	X	X	X
Clinical Procedures/Assessments							
Review Adverse Events	X	X	X	X	X	X	X
Full Physical Examination							
Directed Physical Examination	X	X	X	X	X	X	X
Vital signs and Weight	X	X	X	X	X	X	X
ECOG Performance Status	X	X	X	X	X	X	X
Laboratory Procedures/Assessments: analysis performed by local laboratory							
Pregnancy Test- Urine or Serum b-HCG							
PT/INR and aPTT							
CBC with differential	X	X	X	X	X	X	X
Comprehensive Serum Chemistry Panel	X	X	X	X	X	X	X
Urinalysis							

Trial Period							
Weeks of treatment/cycle#	**58(D1C20)**	**61(D1C21)**	**64(D1C22)**	**67(D1C23)**	**70(D1C24)**	**73(D1C25)**	**76(D1C26)**
Scheduling Window (days):	**(+/- 3)**	**(+/- 3)**	**(+/- 3)**	**(+/- 3)**	**(+/- 3)**	**(+/- 3)**	**(+/- 3)**
T3, FT4, and TSH	X		X		X		X
HIV, CMV							
HBV core antibody, anti-HCV antibody							
Peripheral blood chimerism		X				X	
Efficacy Measurements							
Tumor Imaging*		X				X	
BM Biopsy**		X				X	
Tumor Biopsies/Archival Tissue Collection Correlative Studies Blood							
Archival or Newly Obtained Tissue Collection		X				X	
Correlative Studies Blood Collection		X				X	

*Tumor imaging only for HL and NHL

**BM biopsy only for AML, MDS patients. For HL and NHL patients, a bone marrow is required only in patients with a prior history of marrow involvement

7.5 CYCLE 27-33

Trial Period							
Weeks of treatment/cycle#	**79(D1C27)**	**82(D1C28)**	**85(D1C29)**	**88(D1C30)**	**91(D1C31)**	**94(D1C32)**	**97(D1C33)**
Scheduling Window (days):	**(+/- 3)**	**(+/- 3)**	**(+/- 3)**	**(+/- 3)**	**(+/- 3)**	**(+/- 3)**	**(+/- 3)**
Administrative Procedures							
Informed Consent							
Inclusion/Exclusion Criteria							
Demographics and Medical History							
Prior and Concomitant Medication Review							
Trial Treatment Administration	X	X	X	X	X	X	X
Post-Study anticancer therapy status							
Survival status	X	X	X	X	X	X	X
Clinical Procedures/Assessments							
Review Adverse Events	X	X	X	X	X	X	X
Full Physical Examination							
Directed Physical Examination	X	X	X	X	X	X	X
Vital signs and Weight	X	X	X	X	X	X	X
ECOG Performance Status	X	X	X	X	X	X	X
Laboratory Procedures/Assessments: analysis performed by local laboratory							
Pregnancy Test- Urine or Serum b-HCG							
PT/INR and aPTT							
CBC with differential	X	X	X	X	X	X	X
Comprehensive Serum Chemistry Panel	X	X	X	X	X	X	X
Urinalysis							

Trial Period							
Weeks of treatment/cycle#	**79(D1C27)**	**82(D1C28)**	**85(D1C29)**	**88(D1C30)**	**91(D1C31)**	**94(D1C32)**	**97(D1C33)**
Scheduling Window (days):	**(+/- 3)**	**(+/- 3)**	**(+/- 3)**	**(+/- 3)**	**(+/- 3)**	**(+/- 3)**	**(+/- 3)**
T3, FT4, and TSH		X		X		X	
HIV, CMV							
HBV core antibody, anti-HCV antibody							
Peripheral blood chimerism			X				X
Efficacy Measurements							
Tumor Imaging*			X				X
BM Biopsy**			X				X
Tumor Biopsies/Archival Tissue Collection Correlative Studies Blood							
Archival or Newly Obtained Tissue Collection			X				X
Correlative Studies Blood Collection			X				X

*Tumor imaging only for HL and NHL

**BM biopsy only for AML, MDS patients. For HL and NHL patients, a bone marrow is required only in patients with a prior history of marrow involvement

7.6 CYCLE 34 – POST TREATMENT

Trial Period				
Weeks of treatment/cycle#	**100(D1C34)**	**103(D1C35)**	**End of Treatment*** **	**Post-Treatment*** **
Scheduling Window (days):	**(+/- 3)**	**(+/- 3)**	**(+/- 7)**	**(+/- 7)**
Administrative Procedures				
Informed Consent				
Inclusion/Exclusion Criteria				
Demographics and Medical History				
Prior and Concomitant Medication Review				
Trial Treatment Administration	X	X		
Post-Study anticancer therapy status				X
Survival status	X	X	X	X
Clinical Procedures/Assessments				
Review Adverse Events	X	X	X	X
Full Physical Examination				
Directed Physical Examination	X	X	X	X
Vital signs and Weight	X	X	X	X
ECOG Performance Status	X	X	X	X
Laboratory Procedures/Assessments: analysis performed by local laboratory				
Pregnancy Test- Urine or Serum b-HCG				
PT/INR and aPTT				
CBC with differential	X	X	X	X
Comprehensive Serum Chemistry Panel	X	X	X	X
Urinalysis				

Trial Period				
Weeks of treatment/cycle#	**100(D1C34)**	**103(D1C35)**	**End of Treatment*** **	**Post-Treatment*** **
Scheduling Window (days):	**(+/- 3)**	**(+/- 3)**	**(+/- 7)**	**(+/- 7)**
T3, FT4, and TSH	X		X	X
HIV, CMV				
HBV core antibody, anti-HCV antibody				
Peripheral blood chimerism				X
Efficacy Measurements				
Tumor Imaging*				X
BM Biopsy**				X
Tumor Biopsies/Archival Tissue Collection Correlative Studies Blood				
Archival or Newly Obtained Tissue Collection				X
Correlative Studies Blood Collection				X

*Tumor imaging only for HL and NHL

**BM biopsy only for AML, MDS patients. For HL and NHL patients, a bone marrow is required only in patients with a prior history of marrow involvement

***The safety visit (Section 8.1.6.3) can be completed on the same date as the initial end of treatment or post-treatment visit. Follow-up visits should occur every 12 weeks until initiation of a new anti-cancer therapy, disease progression, withdrawal of consent or death, whichever comes first.

8.0 TRIAL PROCEDURES

8.1 TRIAL PROCEDURES

The trial flow chart (Section 7.0) 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 as unscheduled time points if deemed clinically necessary by the investigator.

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

8.1.1 ADMINISTRATIVE PROCEDURES

8.1.1.1 INFORMED CONSENT

The investigator or qualified designee must obtain documented consent from each potential subject or each subject's legal representative prior to his or her participation in this clinical trial.

8.1.1.1.1 GENERAL INFORMED CONSENT

Consent must be documented by the subject's dated signature or by the subject's legal representative's dated signature on a consent form along with the dated signature of the person conducting the consent discussion. A copy of the signed and dated consent form should be given to the subject before participation in the trial.

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

8.1.1.2 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.

8.1.1.3 MEDICAL HISTORY

A medical history will be obtained by the investigator or qualified designee.

8.1.1.4 PRIOR AND CONCOMITANT MEDICATION REVIEW

8.1.1.4.1 PRIOR MEDICATIONS

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

8.1.1.4.2 CONCOMITANT MEDICATIONS

The investigator or qualified designee will record medication, if any, taken by the subject during the trial.

8.1.1.5 DISEASE DETAILS AND TREATMENTS

8.1.1.5.1 DISEASE DETAILS

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

8.1.1.5.2 PRIOR TREATMENT DETAILS

The investigator or qualified designee will review all prior cancer treatments including systemic treatments, radiation, and surgeries and record in the trial database.

8.1.1.5.3 SUBSEQUENT ANTI-CANCER THERAPY STATUS

The investigator or qualified designee will review all new anti-cancer 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 antineoplastic therapy has been initiated the subject will move into survival follow-up.

8.1.1.6 ASSIGNMENT OF STUDY IDENTIFICATION NUMBER

All eligible subjects will be assigned a study identification number. The subject identification number identifies the subject for all procedures occurring after start of study. Once a subject identification number is assigned to a subject, it can never be re-assigned to another subject.

8.1.1.7 TRIAL COMPLIANCE (MEDICATION/DIET/ACTIVITY/OTHER)

Interruptions from the protocol specified treatment for > 12 weeks between

pembrolizumab doses due to toxicity require consultation between the principal and treating investigators and written documentation of the collaborative decision on subject management.

Administration of trial medication will be witnessed by the investigator and/or trial staff. The total volume of trial treatment infused will be compared to the total volume prepared to determine compliance with each dose administered. The instructions for preparing and administering pembrolizumab will be provided in the Pharmacy Manual.

8.1.2 CLINICAL PROCEDURES/ASSESSMENTS

8.1.2.1 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 events will be graded and recorded throughout the study and during the follow-up period according to NCI CTCAE Version 4.0. All AEs of unknown etiology associated with pembrolizumab exposure should be evaluated to determine if they are possibly events of clinical interest (ECI) of a potentially immunologic etiology (irAE). See Section 6.6.1.1 and the separate guidance document in the administrative binder regarding the identification, evaluation, and management of AEs of a potential immunological etiology. Please refer to Section 8.2 for detailed information regarding the assessment and recording of AEs.

8.1.2.2 PHYSICAL EXAMINATION

The investigator or qualified designee will perform a complete physical examination during the screening period. Clinically significant abnormal findings should be recorded as medical history. A complete physical examination should be performed during screening and repeated as per the frequency defined in the Study Flow Chart. After the first dose of trial treatment, new clinically significant abnormal findings should be recorded as AEs.

8.1.2.3 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 7.0). Vital signs should include temperature, pulse, respiratory rate, weight and blood pressure. Height will be measured at screening only.

8.1.2.4 ELECTROCARDIOGRAM

A standard 12-lead ECG will be performed using local standard procedures at screening. Clinically significant abnormal findings should be recorded as medical history.

8.1.2.5 EASTERN COOPERATIVE ONCOLOGY GROUP (ECOG) PERFORMANCE STATUS

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

8.1.2.6 ASSESSMENT OF DISEASE

8.1.2.6.1 CRITERIA FOR ASSESSMENT OF DISEASE

The efficacy of pembrolizumab will be evaluated using the following disease-specific criteria

- **B cell lymphomas** - The International Working Group response criteria will be utilized as the primary means to assess disease response to pembrolizumab in B cell lymphoma patients [39], and is the basis for all protocol guidelines related to disease status.

- **MDS -** The International Working Group response criteria in myelodysplasia will be utilized as the primary means to assess disease response to pembrolizumab in MDS patients [40], and is the basis for all protocol guidelines related to disease status.

- **AML -** The European LeukemiaNet guidelines will be utilized as the primary means to assess disease response to pembrolizumab in AML patients [41], and is the basis for all protocol guidelines related to disease status.

8.1.2.6.2 B CELL LYMPHOMA SUBJECT DISEASE RESPONSE ASSESSMENT

Response in B cell lymphoma patients using bone marrow analysis (where applicable), as well as PET/CT (aggressive B cell lymphomas and Hodgkin lymphoma) or CT (low-grade B cell lymphomas) is based on the International Working Group criteria [39]. Local reading (investigator assessment with site radiology reading) will be used to determine subject eligibility and for subject management. No central radiology review will be performed. Assessment of lymphoma-related B symptoms should occur with each disease response assessment.

8.1.2.6.3 DISEASE ASSESSMENT OF IMMUNOTHERAPEUTIC AGENTS

Note - this section pertains to subjects with B cell lymphomas only. Immunotherapeutic agents such as pembrolizumab may produce anti-tumor effects by potentiating endogenous cancer-specific immune responses, which may be functionally anergic. The response patterns seen with such an approach may extend beyond the typical time course of responses seen with cytotoxic agents, and can manifest a clinical response after an initial increase in tumor burden or even the appearance of new lesions.

Standard response assessment criteria may not provide a complete response assessment of immunotherapeutic agents such as pembrolizumab. Therefore in the setting where a subject assessment shows PD, study drug may be continued until next disease response assessment provided that the subjects' clinical condition is stable. Repeat scans after suspected "pseudoprogression" should be obtained in 4-6 weeks; if scans confirm progression, pembrolizumab will be discontinued. If progression is not confirmed on repeat imaging, the patient may continue on therapy. However, imaging should occur at any time where there is clinical suspicion of progression.

Note - with the next disease response assessment if the disease is clinically stable or clinically improved, an exception may be considered to continue treatment upon consultation with the principal investigator.

8.1.2.6.4 AML SUBJECT DISEASE RESPONSE ASSESSMENT

Response in AML patients using peripheral blood and bone marrow analysis is based on the European LeukemiaNet guidelines [41]. Local review by a site hematopathologist will be used to determine subject eligibility and management. No central pathology review will be performed.

8.1.2.6.5 MDS SUBJECT DISEASE RESPONSE ASSESSMENT

Response in MDS patients using peripheral blood and bone marrow analysis is based on the International Working Group response criteria in myelodysplasia [40]. Local review by a site hematopathologist will be used to determine subject eligibility and management. No central pathology review will be performed.

8.1.2.6.6 TIMING OF DISEASE ASSESSMENTS

Uniform disease response assessments in all subjects will occur every 12 weeks following the first disease response assessment at week 12 (see **Table 8**).

Table 8. Disease response assessments

Indication	Assessment Frequency
B cell lymphoma, AML and MDS	Every 12 weeks following first assessment at week 13 up to 12 months. Subsequent disease response assessments are at the discretion of the treating physician.

8.1.2.6.7 INITIAL DISEASE ASSESSMENT

Initial disease assessment must be performed within 28 days prior to the first dose of trial treatment. The site study team must review pre-trial images to confirm that the subject has measurable disease as defined in the inclusion criteria.

8.1.2.6.8 DISEASE ASSESSMENT DURING THE TRIAL

Disease assessments should be performed as outlined in Table 8. There is a +/- 7 day window for assessments performed after Day 1. For MDS and AML patients, bone marrow biopsy will be the method of assessing disease response (along with peripheral blood counts). For subjects with lymphoma, PET and diagnostic CT scans will be performed for aggressive B cell lymphoma and Hodgkin lymphoma subjects, while CT scans alone will be performed for subjects with low-grade lymphomas. Disease assessments and imaging should continue to be performed on protocol for 2 years after initiation of pembrolizumab treatment, and then until documented disease progression, the start of new anti-cancer treatment, withdrawal of consent, death, or the end of the study, whichever occurs first.

8.1.2.6.9 DISEASE PROGRESSION ASSESSMENTS

A subject with B cell lymphoma ONLY with evidence of progressive disease documented at the week 12 assessment may continue trial treatment until next response assessment provided the subjects' clinical condition is stable. However, imaging should occur at any time where there is clinical suspicion of progression. Repeat scans after suspected "pseudoprogression" should be obtained in 4-6 weeks; if scans confirm progression, pembrolizumab will be discontinued. If progression is not confirmed on repeat imaging, the patient may continue on therapy. Subjects may only receive treatment if the following criteria are met:

- Absence of signs and symptoms (including worsening of laboratory values) indicating disease progression
- No decline in ECOG performance status
- Absence of rapid progression of disease
- Absence of progressive tumor at critical anatomical sites (e.g. cord compression) requiring urgent alternative medical intervention

After the first disease response assessment, it is at the discretion of the investigator to keep a clinically stable subject on trial treatment or to stop trial treatment until a repeat assessment is performed. Subjects that are deemed clinically unstable after first disease response assessment at week 13 should not continue trial treatment and must be discontinued from the trial.

For subjects who have stable disease, partial response, or complete response following the first disease response assessment (at week 13), disease assessments and imaging should continue per the regular frequency every 12 weeks as outlined in the trial flow chart.

For subjects noted to have progression of disease at a time point beyond the week 13 initial disease response assessment, it is at the discretion of the investigator to keep a

clinically stable subject on trial treatment or to stop trial treatment until a repeat assessment is performed.

8.1.2.6.10 COLLECTION OF SAMPLES FOR COLLABORATIVE STUDIES

All subjects enrolled onto this trial must consent to provide extra samples of peripheral blood and bone marrow at screening and at the 3, 6, 9, 12, 15, 18, 21 and 24 month visits. See Table 9.

Table 9. Bone marrow and peripheral blood collection for correlative assays.

Subjects	Timing of correlative blood and bone marrow collection
B cell lymphoma, MDS and AML	At screening and 13 weeks, 25 weeks, 37 weeks, 49 weeks, 61 weeks, 73 weeks,, 85 weeks and post-treatment assessments. Blood will be collected from all subjects. Bone marrow aspirate samples will be collected from AML and MDS subjects at all time points. Bone marrow aspirate samples will be collected from B cell lymphoma patients at screening, and 3 month, 6 month, 9 month and 12 month assessments only for B cell lymphoma patients with marrow involvement at screening.

8.1.3 LABORATORY PROCEDURES/ASSESSMENTS

Samples will be drawn for our institutional lab. Local laboratory testing will include institutional standard tests for evaluating safety and making clinical decisions. The following laboratory assessments will be performed by the institutional lab to evaluate safety at scheduled timepoints during the course of the study. To contact the hematology lab for marrow/aspirate collection, dial 773-702-1314.

8.1.3.1 LABORATORY EVALUATIONS

Laboratory tests for hematology, chemistry and urinalysis are specified in Table 10.

Table 10. Laboratory tests

Hematology	Chemistry	Urinalysis	Other
Hematocrit	Albumin	Blood	Serum β-human

Hematology	Chemistry	Urinalysis	Other
			chorionic gonadotropin (β-hCG)
Hemoglobin	Alkaline phosphatase	Glucose	PT (INR)
CBC with differential [a]	Alanine aminotransferase (ALT)	Protein	aPTT
Platelet count	Aspartate aminotransferase (AST)	Specific gravity	Total Thriiodothyronine (T3) (or FT3) [b]
WBC (total and differential)	Lactate dehydrogenase (LDH)	Microscopic exam, if abnormal results are noted	Free thyroxine (T4)
Red Blood Cell Count	Carbon Dioxide (CO_2 or bicarbonate)	Urine pregnancy test[c]	Thyroid stimulating hormone (TSH)
Absolute Neutrophil Count	Creatinine		Anti-pembrolizumab Antibodies
Absolute Lymphocyte Count	Uric Acid		
	Calcium		Blood for FBR
	Chloride		Blood for correlative studies (donor chimerism, T cell receptor sequencing, T cell activation markers)
	Glucose		
	Phosphorus		
	Potassium		
	Sodium		

Hematology	Chemistry	Urinalysis	Other
	Magnesium		
	Total Bilirubin		
	Direct and Indirect Bilirubin, if total bilirubin is elevated above the upper limit of normal		
	Total protein		
	Blood Urea Nitrogen		

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

8.1.4 OTHER PROCEDURES

8.1.4.1 WITHDRAWAL/DISCONTINUATION

Subjects who discontinue/withdraw from treatment prior to completion of the treatment regimen should be encouraged to continue to be followed for all remaining study visits.

When a subject discontinues/withdraws from participation in the trial, 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 8.2 - Assessing and recording adverse events. Subjects who attain a CR may discontinue treatment without the option of restarting treatment. After discontinuing treatment following assessment of CR, these subjects should return to the site for a safety follow-up visit (Section 8.1.6.3), and then proceed to the follow-up period of the study (Section 8.1.6.4).

8.1.4.2 BLINDING/UNBLINDING

This is an open label trial; there is no blinding for this trial.

8.1.5 VISIT REQUIREMENTS

Visit requirements are outlined in Section 7.0 - trial flow chart. Specific procedure-related details are provided above in Section 8.1 - trial procedures.

8.1.5.1 SCREENING

Approximately 28 days prior to start of study drug dosing, potential subjects will be evaluated to determine that they fulfill the entry requirements as set forth in Section 6.1. Screening procedures may be repeated after consultation with the principal investigator.

Written consent for the main study must be obtained prior to performing any protocol specific procedure. Results of a test performed prior to the subject signing consent as part of routine clinical management are acceptable in lieu of a screening test if performed within the specified time frame. Screening procedures are to be completed within 28 days prior to the first dose of trial treatment except for the following:

Laboratory tests are to be performed within 10 days prior to the first dose of trial treatment.

For women of reproductive potential, a urine pregnancy test will be performed within 72 hours prior to the first dose of trial treatment. If urine pregnancy results cannot be confirmed as negative, a serum pregnancy test will be required (performed by the local study site laboratory).

Subjects may be rescreened after initially failing to meet the inclusion/exclusion criteria. Results from assessments performed during the initial screening period are acceptable in lieu of a repeat screening test if performed within the specified time frame and the inclusion/exclusion criteria is met.

8.1.5.2 TREATMENT PERIOD

Visit requirements are outlined in Section 7.0 – trial flow chart. Specific procedure-related details are provided above in Section 8.1 – trial Procedures. Each on-study visit will be scheduled based on the date of the week 0 (day 1) visit. Required visits are outlined below. The treatment period commences on the day of the first dose of pembrolizumab, and ends following a 21 day cycle. During the study treatment period, subjects will be regularly monitored to assess the safety and anti-tumor activity of the treatment.

Baseline/Week 0

Subjects who meet all of the inclusion criteria and none of the exclusion criteria will return to the clinic within 28 days after screening for baseline assessments.

The following baseline assessments will be completed prior to the first dose of pembrolizumab:

- Physical examination and vital signs, including ECOG performance status
- Laboratory assessments and blood sampling:
- Chemistry

- TSH, T3, FT4
- Hematology: CBC and differential
- Urine pregnancy test, if applicable
- Correlative studies
- Confirmation of Medical History
- Assessment of AEs
- Recording of concomitant medications

Weeks 1, 2, 3

Clinic/laboratory visits will occur every week through the Week 4 visit. The following procedures will be completed at each visit, unless otherwise specified:

- Physical examination and vital signs, including ECOG performance status
- Laboratory assessments and blood sampling:
- Chemistry
- Hematology: CBC and differential
- Assessment of AEs
- Recording of concomitant medications

Weeks 4, 7, 10, 13, 16, 19, 22, 25, 28, 31, 34, 37, 40, 43, 46, 49, 52, 55, 58, 61, 64, 67, 70, 73, 76, 79, 82, 85, 88, 91, 94, 97, 100, 103

Subjects continuing on study past Week 4 will have visits every 3 weeks through Week 49, and then at physician discretion. The following procedures will be completed at each visit, unless otherwise specified:

- Physical examination and vital signs, including ECOG performance status
- Laboratory assessments and blood sampling:
- Chemistry
- TSH, T3, FT4 (every 6 weeks)
- Hematology: CBC and differential

- Assessment of adverse events
- Recording of concomitant medications

Weeks 13, 25, 37, 49, 61, 73, 85, 97 - Disease assessments

- Bone marrow aspirate and biopsy for all patients with AML and MDS and B cell lymphoma patients with bone marrow involvement
- Correlative studies
- Radiology assessment (CT or CT/PET) for B cell lymphoma patients only

8.1.6 POST-TREATMENT ASSESSMENTS

8.1.6.1 END OF TREATMENT VISIT

If a subject permanently discontinues pembrolizumab, every attempt should be made to keep the subject in the study and continue to perform the required study-related follow-up and procedures.

The following procedures will be completed at the time of study treatment discontinuation for patients who elect to discontinue or are required to discontinue study treatment prior to the end of the planned study duration:

- Physical examination vital signs, including ECOG performance status
- Laboratory assessments and blood sampling:
- Chemistry
- TSH, T3, FT4
- Hematology: CBC and differential
- Assessment of adverse events
- Recording of concomitant medications
- Assessment of disease status if disease progression is suspected.

8.1.6.2 END OF STUDY VISIT (WEEK 104-105)

The following procedures will be completed at the end of study visit:

- Physical examination vital signs, including ECOG performance status
- Laboratory assessments and blood sampling:

- Chemistry
- TSH, T3, FT4
- Hematology: CBC and differential
- Assessment of adverse events
- Recording of concomitant medications

8.1.6.3 SAFETY FOLLOW-UP VISIT

The mandatory safety follow-up visit should be conducted approximately 30 days after the last dose of pembrolizumab treatment or before the initiation of a new anti-cancer treatment, whichever comes first. The safety follow-up visit can be done on the same day as the end of study visit (Section 8.1.6.2) or the end of treatment visit (Section 8.1.6.1). All AEs that occur prior to the safety follow-up visit should be recorded. Subjects with an AE of grade > 1 will be followed until the resolution of the AE to grade 0-1, or until the beginning of a new anti-cancer therapy, whichever occurs first. SAEs that occur within 90 days of the end of treatment or before initiation of a new anti-cancer treatment should also be followed and recorded.

8.1.6.4 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 every 12 weeks (+/- 7 days) to monitor disease status. Every effort should be made to collect information regarding disease status until the start of new anti-cancer therapy, disease progression, death, or end of the study. Information regarding post-study anti-cancer treatment will be collected if new treatment is initiated.

8.1.6.4.1 SURVIVAL FOLLOW-UP

Once a subject experiences confirmed disease progression or starts a new antineoplastic 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.

8.2 ASSESSING AND RECORDING ADVERSE EVENTS

The rate of subject entry and expansion will depend upon assessment of the safety profile of patients entered at the previous dose level. Toxicity will be evaluated according to the NCI Common Terminology Criteria for Adverse Events (CTCAE), Version 4.0 (see Appendix E). If at least 5 of the first 12 patients complete pembrolizumab treatment without developing a DLT, we will open an expansion cohort to enroll with plans to enroll 14 additional patients should DLT-associated stopping rule not be met in the first 12 patients. If at least 14 of the 26 patients remain DLT-free, we would have sufficient

evidence to warrant further study of pembrolizumab in a future trial.

This particular safety stopping rule is based on the expected 50% rate of GVHD that has been reported to develop after DLI therapy [30]. The inclusion of an expansion cohort will enable a further and more robust safety signal, as well as provide a larger cohort of patients in whom to assess clinical response, especially given the mixture of diseases that are being included in this study.

8.2.1 DEFINITION OF AN OVERDOSE FOR THIS PROTOCOL AND REPORTING OF OVERDOSE TO THE SPONSOR

For purposes of this trial, an overdose will be defined as any dose exceeding the prescribed dose for pembrolizumab will be defined as any dose of 1000 mg or greater. No specific information is available on the treatment of overdose of pembrolizumab. In the event of overdose, pembrolizumab should be discontinued and the subject should be observed closely for signs of toxicity. Appropriate supportive treatment should be provided if clinically indicated.

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

If a dose of pembrolizumab according to the definition of overdose is administered 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 either by electronic media or paper.

8.2.2 REPORTING OF PREGNANCY AND LACTATION

Although pregnancy and lactation are not considered adverse events, it is the responsibility of investigators or their designees to report any pregnancy or lactation in a subject (spontaneously reported to them) that occurs during the trial or within 120 days of completing the trial or 30 days following cessation of treatment if the subject initiates new anticancer therapy, whichever is earlier. All 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 principal investigator and Merck either by electronic media or paper.

8.2.3 IMMEDIATE REPORTING OF ADVERSE EVENTS

8.2.3.1 SERIOUS ADVERSE EVENTS

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

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

Refer to **Table 11** for additional details regarding each of the above criteria.

Progression of the cancer under study is not considered an adverse event unless it results in hospitalization or death.

Any serious adverse event, or follow up to a serious adverse event, including death due to any cause other than progression of the cancer under study (reference Section 7.2.3.3 for additional details) that occurs to any subject from the time the consent is signed through 90 days following cessation of treatment, or 30 days following cessation of treatment if the subject initiates new anticancer therapy, whichever is earlier, whether or not related to pembrolizumab, must be reported within 24 hours to the principal investigator and Merck either by electronic media or paper.

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

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

8.2.3.2 EVENTS OF CLINICAL INTEREST

Selected non-serious and serious adverse events are also known as Events of Clinical Interest (ECI) and must be recorded as such on the adverse event case report forms/worksheets and reported within 24 hours to the principal investigator and Merck

either by electronic media or paper.

Events of clinical interest for this trial include:

1. an overdose of pembrolizumab, as defined in Section 8.2.1, that is not associated with clinical symptoms or abnormal laboratory results.

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

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

3. Early transplant-related events such as veno-occlusive disease (VOD) and steroid-requiring febrile syndrome.

A separate guidance document has been provided entitled "Event of Clinical Interest Guidance Document." This document can be found in the administrative binder and provides guidance regarding identification, evaluation and management of ECIs and irAEs.

ECIs identified in this guidance document from the date of first dose through 90 days following cessation of treatment, or 30 days after the initiation of a new anticancer therapy, whichever is earlier need to be reported to the SPONSOR within 24 hours of the event consistent with standard SAE reporting guidelines and either by electronic media or paper. Sponsor Contact information can be found in the administrative binder.

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

8.2.3.3 PROTOCOL-SPECIFIC EXCEPTIONS TO SERIOUS ADVERSE EVENT REPORTING

Efficacy endpoints as outlined in this section will not be reported as described in Section 8.2.3, unless there is evidence suggesting a causal relationship between the drug and the event. Any such event will be submitted to the principal investigator and Merck.

Specifically, the suspected/actual events covered in this exception include disease progression of the cancer during the study period.

The principal investigator will monitor aggregated efficacy endpoint events and safety data to ensure the safety of the subjects in the trial.

8.2.4 EVALUATING ADVERSE EVENTS

A qualified investigator 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 11. Evaluating adverse events

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 pembrolizumab that:	
	†Results in death; or	
	†Is life threatening; or places the subject, in the view of the investigator, at immediate risk of death from the event as it occurred (Note: This does not include an adverse event that, had it occurred in a more severe form, might have caused death.); or	
	†Results in a persistent or significant disability/incapacity (substantial disruption of one's ability to conduct normal life functions); or	
	†Results in or prolongs an existing inpatient hospitalization (hospitalization is defined as an inpatient admission, regardless of length of stay, even if the hospitalization is a precautionary measure for continued observation. (Note: Hospitalization for an elective procedure to treat a pre-existing condition that has not worsened is not a serious adverse event. A pre-existing condition is a clinical condition that is diagnosed prior to the use of a Merck product and is documented in the patient's medical history.); or	

	†**Is a congenital anomaly/birth defect** (in offspring of subject taking the product regardless of time to diagnosis);or	
	Is a new **cancer;** (that is not a condition of the study) **or**	
	Is an overdose (whether accidental or intentional). Any adverse event associated with an overdose is considered a serious adverse event. An overdose that is not associated with an adverse event is considered a non-serious event of clinical interest and must be reported within 24 hours.	
	Other important medical events that may not result in death, not be life threatening, or not require hospitalization may be considered a serious adverse event when, based upon appropriate medical judgment, the event may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed previously (designated above by a †).	
Duration	Record the start and stop dates of the adverse event. If less than 1 day, indicate the appropriate length of time and units	
Action taken	Did the adverse event cause pembrolizumab to be discontinued?	
Relationship to test drug	Did pembrolizumab product cause the adverse event? The determination of the likelihood that pembrolizumab caused the adverse event will be provided by the investigator. The criteria below are intended as reference guidelines to assist the investigator in assessing the likelihood of a relationship between the test drug and the adverse event based upon the available information. **The following components are to be used to assess the relationship between pembrolizumab and the AE**; the greater the correlation with the components and their respective elements (in number and/or intensity), the more likely pembrolizumab caused the adverse event (AE):	
	Exposure	Is there evidence that the subject was actually exposed to pembrolizumab such as: reliable history, acceptable compliance assessment (pill count, diary, etc.), expected pharmacologic effect, or measurement of drug/metabolite in bodily specimen?
	Time Course	Did the AE follow in a reasonable temporal sequence from administration of pembrolizumab? Is the time of onset of the AE compatible with a drug-induced effect (applies to trials with investigational medicinal product)?
	Likely Cause	Is the AE not reasonably explained by another etiology such as underlying disease, other drug(s)/vaccine(s), or other host or environmental factors
Relationship pembrolizumab (continued)	The following components are to be used to assess the relationship between the test drug and the AE: (continued)	
	Dechallenge	Was pembrolizumab discontinued or dose/exposure/frequency reduced? If yes, did the AE resolve or improve?

		If yes, this is a positive dechallenge. If no, this is a negative dechallenge. (Note: This criterion is not applicable if: (1) the AE resulted in death or permanent disability; (2) the AE resolved/improved despite continuation of the Sponsor's product; or (3) the trial is a single-dose drug trial); or (4) Sponsor's product(s) is/are only used one time.)
	Rechallenge	Was the subject re-exposed to pembrolizumab in this study? If yes, did the AE recur or worsen? If yes, this is a positive rechallenge. If no, this is a negative rechallenge. (Note: This criterion is not applicable if: (1) the initial AE resulted in death or permanent disability, or (2) the trial is a single-dose drug trial); or (3) Sponsor's product(s) is/are used only one time). NOTE: IF A RECHALLENGE IS PLANNED FOR AN ADVERSE EVENT WHICH WAS SERIOUS AND WHICH MAY HAVE BEEN CAUSED BY THE SPONSOR'S PRODUCT, OR IF REEXPOSURE TO PEMBROLIZUMAB POSES ADDITIONAL POTENTIAL SIGNIFICANT RISK TO THE SUBJECT, THEN THE RECHALLENGE MUST BE APPROVED IN ADVANCE BY THE PRINCIPAL INVESTIGATOR AS PER DOSE MODIFICATION GUIDELINES IN THE PROTOCOL.
	Consistency with Trial Treatment Profile	Is the clinical/pathological presentation of the AE consistent with previous knowledge regarding pembrolizumab or drug class pharmacology or toxicology?
The assessment of relationship will be reported on the case report forms /worksheets by an investigator 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 pembrolizumab relationship).
Yes, there is a reasonable possibility of pembrolizumab relationship.		There is evidence of exposure to pembrolizumab. The temporal sequence of the AE onset relative to the administration of pembrolizumab is reasonable. The AE is more likely explained by pembrolizumab than by another cause.
No, there is not a reasonable possibility of pembrolizumab relationship		Subject did not receive pembrolizumab OR temporal sequence of the AE onset relative to administration of the pembrolizumab is not reasonable OR there is another obvious cause of the AE. (Also entered for a subject with overdose without an associated AE.)

8.3 ADVERSE EVENT REPORTING REQUIREMENTS

8.3.1 ROUTINE ADVERSE EVENT REPORTING

All Adverse Events **must** be reported in routine study data submissions. **AEs reported using the Serious Event Reporting Form and/or MedWatch Form discussed below must also be reported in routine study data submissions.**

8.3.2 SERIOUS ADVERSE EVENT REPORTING TO THE COORDINATING CENTER

All serious adverse events (as defined in section 8.2.3.1) and all adverse events that have been specified to require expedited reporting in the section 8.2.3.2 occurring on this study require expedited reporting to the University of Chicago Comprehensive Cancer Center (UC CCC). The responsible Research Nurse or other designated individual at the treating site should report the SAE to the Principal Investigator and the CCTO by the end of the business day when s/he becomes aware of the event. Events occurring after business hours should be reported to the CCTO by 12pm (noon) the next business day. Reports should be made using the 'Serious Event Report' Form.

All unexpected adverse reactions must be reported to the IND holder so that the University of Chicago CCTO can inform the FDA. The responsible Research Nurse or other designated individual at the treating site should provide a complete written report using the FDA MedWatch 3500A form. The completed form should be sent to the CCTO at qaccto@bsd.uchicago.edu within the specified timelines below regardless of whether all information regarding the event is available. If applicable, a follow-up report should be provided to the CCTO if additional information on the event becomes available.

Study staff should not forward any adverse event reports directly to the FDA. The CCTO will report all events to the FDA as per the current FDA guidelines.

Fatal or Life-threatening Events: within 4 calendar days from treating investigator knowledge of the event

All Other Reportable Events: within 10 calendar days of treating investigator knowledge of the event

All serious adverse events should also be reported to the local IRB of record according to their policies and procedures.

8.4 TRIAL GOVERNANCE AND OVERSIGHT

8.4.1 DATA MONITORING COMMITTEE

The principal investigator will ensure that trial is conducted and data are generated,

documented, and reported in compliance with the protocol, accepted standards of Good Clinical Practice, and all applicable federal, state, and local laws, rules and regulations relating to the conduct of the clinical trial. The trial will specifically be evaluated by the principal investigator after the first 12 patients are enrolled to assess if the trial should be continued.

A quality assurance audit/inspection of this study may be conducted by regulatory authorities. The quality assurance auditor will have access to all medical records, the investigator's study-related files and correspondence, and the informed consent documentation of this clinical study.

9.0 STATISTICAL ANALYSIS PLAN

9.1 STATISTICAL ANALYSIS PLAN SUMMARY

This section contains a brief summary of the statistical analysis for this trial. Full details can be found in the statistical analysis plan (SAP) in Section 8.2.

9.1.1 SAFETY ANALYSES

The study will initially enroll 12 patients in the first stage of the two-stage trial design. The accrual rate will be 1 patient/month in relapsed/refractory myeloid and B cell malignancies following allogeneic stem cell transplant to assess the safety and feasibility of pembrolizumab. If at least 5 of the first 12 patients complete pembrolizumab treatment without developing a DLT, we will open an expansion cohort to enroll with plans to enroll 14 additional patients should DLT-associated stopping rule not be met in the first 12 patients. Specifically, if 5 or more of the first 12 enrolled patients develop a DLT, including grade 3-4 GHVD, then the study will be halted. If at least 14 of the 26 patients remain DLT-free, we would have sufficient evidence to warrant further study of pembrolizumab in a future trial. Furthermore, if severe GVHD (grade 3-4) develops within the first 90 days of pembrolizumab treatment in each of the first 5 patients treated on the study (i.e. develop a DLT), it will be permanently closed to accrual as a measure to ensure safety.

Toxicity will be graded per the CTCAE guidelines and the maximally tolerated dose will be defined a less or equal than 1 in 6 patients with DLTs. All patients who receive any amount of the study drug will be evaluable for toxicity.

9.1.2 EFFICACY ANALYSES

The intention-to-treat population, defined as subjects who received at least one dose of pembrolizumab, will serve as the primary analysis population in this study. The primary efficacy endpoint is the overall response rate (ORR), defined as those patients who achieve a PR or CR (lymphoma), PR or CR (MDS), or a CR, CRp, CRi or PR (AML). Secondary efficacy endpoints include duration of response (DOR) and overall survival (OS).

An outline of the efficacy analysis strategy is shown in Table 12 below.

Table 12. Primary analysis strategy for efficacy endpoints

Endpoint/Variable (Description, Time Point)	Statistical Method	Analysis Population	Missing Data Approach
Primary:			
Overall response rate (ORR) using defined criteria	Exact test of binomial parameter	ITT	Subjects with missing data are considered non-responders
Secondary:			
Duration of response (DOR)	Summary statistics using Kaplan-Meier method	All responders	Non-responders are excluded in analysis
Overall survival (OS)	Summary statistics using Kaplan-Meier method	ITT	Censored at last assessment

9.1.3 INTERIM ANALYSIS

After the first 12 patients have been enrolled and have received at least 1 dose of pembrolizumab, an interim safety analysis will be performed. If < 5 of the first 12 patients develop a DLT (including grade 3-4 acute GVHD) following pembrolizumab treatment, an expansion cohort of 14 additional patients will be enrolled in order to obtain a more robust safety signal, as well as to enhance numbers of treated patients for efficacy analyses, given that patients with a wide variety of hematological malignancies will be enrolled. However, if ≥ 5 of the first 12 enrolled patients develop a DLT, then the study will be permanently closed to accrual. Furthermore, if severe GVHD (grade 3-4) develops in each of the first 5 patients treated on the study, it will be permanently closed to accrual as a measure to ensure safety.

9.2 STATISTICAL ANALYSIS PLAN

9.2.1 HYPOTHESES

The objectives and hypotheses of the study are stated in Section 3.

9.2.2 ANALYSIS ENDPOINTS

9.2.2.1 SAFETY ENDPOINTS

Safety measurements are described in Section 8.

9.2.2.2 EFFICACY ENDPOINTS

Efficacy endpoints that will be evaluated for are listed below.

The primary efficacy endpoint is the overall response rate (ORR), defined as the proportion of subjects in the analysis population who achieve at least a partial response to pembrolizumab. Specifically, for B cell lymphoma patients, partial and complete responses will be defined according to the International Working Group criteria [39] (Appendix). For MDS patients, partial and complete responses (including cytogenetic responses) will be defined according to the International Working Group criteria [40]. Lastly, for AML patients, complete (including CR, CRp, CRi), and partial responses will be defined according to the European Leukemia Net response criteria (Appendix) [41].

9.2.3 ANALYSIS POPULATION

9.2.3.1 SAFETY ANALYSIS POPULATION

The All Patients as Treated (APaT) population will be used for the analysis of safety data in this study. The APaT population consists of all enrolled subjects who received at least 1 dose of study treatment. At least one laboratory or vital sign measurement obtained subsequent to at least one dose of trial treatment is required for inclusion in the analysis of each specific parameter. To assess change from baseline, a baseline measurement is also required.

9.2.3.2 EFFICACY ANALYSIS POPULATION

The analysis of primary efficacy endpoints are based on the intention-to-treat (ITT) population, i.e., subjects will be included if they receive at least one dose of study medication.

9.2.4 STATISTICAL METHODS

9.2.4.1 STATISTICAL METHODS FOR TOLERABILITY ANALYSES

The trial will feature a two-stage minimax trial design (Simon 1989, A'hern, 2001) which tests for futility in a smaller sample of patients before proceeding with treatment of the full cohort. The accrual rate will be 1 patient/month in relapsed/refractory myeloid and B cell malignancies following allogeneic stem cell transplant to assess the safety and feasibility of pembrolizumab. The primary outcome is whether the patient remains DLT-free at the end of treatment. *A priori*, we expect 40% or fewer patients on an unsafe treatment would finish without experiencing a DLT, and at least 65% of patients would be DLT-free on a safe treatment. For $\alpha = 0.05$ and 80% power, we would need to observe

at least 5 DLT-free treatments out of a small sub-sample of 12 patients before we would consider evaluating pembrolizumab in the full sample of 26 patients. If at least 14 of the 26 patients respond remain DLT-free, we would have sufficient evidence to warrant further study of pembrolizumab in a future trial.

9.2.4.2 STATISTICAL METHODS FOR EFFICACY ANALYSES

9.2.4.2.1 OVERALL RESPONSE RATE (ORR)

ORR will be summarized as a proportion. ORR will depend on the tumor type, and we will analyze for HL NHL, MDS, and AML individually, acknowledging that the numbers will be small. Descriptive statistics will be used to test the hypothesis that the ORR exceeds 10%.

9.2.4.2.2 DURATION OF RESPONSE (DOR)

DOR will be summarized using a Kaplan-Meier survival curve.

9.2.4.2.3 OVERALL SURVIVAL (OS)

OS will be summarized using a Kaplan-Meier survival curve.

10.0 LABELING, PACKAGING, STORAGE AND RETURN OF CLINICAL SUPPLIES

10.1 INVESTIGATIONAL PRODUCT

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

Clinical Supplies will be provided by Merck as summarized in **Table 13**.

Table 13. Product description

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

10.2 PACKAGING AND LABELING INFORMATION

Clinical supplies will be affixed with a clinical label in accordance with regulatory requirements. Subjects will receive open label pembrolizumab (MK-3475) vials.

10.3 CLINICAL SUPPLIES DISCLOSURE

This trial is open-label.

10.4 STORAGE AND HANDLING REQUIREMENTS

Clinical supplies must be stored in a secure, limited-access location under the storage conditions specified on the label. Receipt and dispensing of trial medication must be recorded by an authorized person at the trial site. Clinical supplies may not be used for any purpose other than that stated in the protocol.

10.5 DISCARD/DESTRUCTION/RETURNS AND RECONCILIATION

The investigator is responsible for keeping accurate records of the clinical supplies received from the sponsor, the amount dispensed to and returned by the subjects and the amount remaining at the conclusion of the trial. Where local discard and destruction is appropriate, the investigator is responsible for ensuring that a local discard/destruction procedure is documented.

11.0 ADMINISTRATIVE AND REGULATORY DETAILS

11.1 CONFIDENTIALITY

11.1.1 CONFIDENTIALITY OF DATA

All study records will be maintained in confidence, and such information will be divulged to the institutional review board, ethics review committee (IRB/ERC) or similar or expert committee; affiliated institution and employees, only under an appropriate understanding of confidentiality with such board or committee, affiliated institution and employees. Data generated by this trial will be considered confidential by the investigator, except to the extent that it is included in a publication as provided in the Publications section of this protocol.

11.1.2 CONFIDENTIALITY OF SUBJECT RECORDS

The study team, Merck, IRB/ERC, or regulatory authority representatives may consult and/or copy trial documents in order to verify worksheet/case report form data. By signing the consent form, the subject agrees to this process. If trial documents will be photocopied during the process of verifying worksheet/case report form information, the subject will be identified by unique code only; full names/initials will be masked prior to transmission to any party outside of the coordinating site. All subject data will be used and disclosed in connection with this trial in accordance with all applicable privacy laws, rules and regulations.

11.2 OBLIGATIONS OF SITE INVESTIGATOR

The Principal Investigator is responsible for the conduct of the clinical trial at the site in accordance with Title 21 of the Code of Federal Regulations and/or the Declaration of

Helsinki. The Study Site Principal Investigator is responsible for personally overseeing the treatment of all study patients. He/she must assure that all study site personnel, including sub-investigators and other study staff members, adhere to the study protocol and all FDA/GCP/NCI regulations and guidelines regarding clinical trials both during and after study completion.

The Principal Investigator will be responsible for assuring that all the required data will be collected and entered into the CRFs. Periodically, monitoring visits or audits will be conducted and he/she must provide access to original records to permit verification of proper entry of data.

11.3 AUDITING

The University of Chicago Comprehensive Cancer Center will perform routine Quality Assurance Audits of investigator-initiated clinical trials as described in the NCI-approved UC CCC DSM Plan. Audits provide assurance that trials are conducted and study data are collected, documented and reported in compliance with the protocol. Further, quality assurance audits ensure that study data are collected, documented and reported in compliance with Good Clinical Practices (GCP) Guidelines and regulatory requirements. The audit will review subjects enrolled at the University of Chicago in accordance with audit procedures specified in the UC CCC Data and Safety Monitoring plan.

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

11.4 DATA MANAGEMENT

The investigator or qualified designee is responsible for recording and verifying the accuracy of subject data.

11.5 PUBLICATION

This trial is intended for publication, even if terminated prematurely. Publication may include any or all of the following: posting of a synopsis online, abstract and/or presentation at a scientific conference, or publication of a full manuscript.

12.0 APPENDICES

12.1 ECOG PERFORMANCE STATUS

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

12.2 COMMON TERMINOLOGY CRITERIA FOR ADVERSE EVENTS V4.0 (CTCAE)

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

12.3 RESPONSE EVALUATION OF HODGKIN AND NON-HODGKIN LYMPHOMA.

Response Evaluation of Hodgkin and non-Hodgkin lymphoma will occur via the 2007 International Working Group criteria (Cheson et al.); MDS response evaluation by International Working Group (IWG) criteria (Cheson et al.); AML evaluation via an international expert panel, on behalf of the European LeukemiaNet (Dohner et al.) (43-45).

12.3.1 CRITERIA FOR LYMPHOMA DISEASE ASSESSMENT

Table 2. Response Definitions for Clinical Trials

Response	Definition	Nodal Masses	Spleen, Liver	Bone Marrow
CR	Disappearance of all evidence of disease	(a) FDG-avid or PET positive prior to therapy; mass of any size permitted if PET negative (b) Variably FDG-avid or PET negative; regression to normal size on CT	Not palpable, nodules disappeared	Infiltrate cleared on repeat biopsy; if indeterminate by morphology, immunohistochemistry should be negative
PR	Regression of measuable disease and no new sites	≥ 50% decrease in SPD of up to 6 largest dominant masses; no increase in size of other nodes (a) FDG-avid or PET positive prior to therapy; one or more PET positive at previously involved site (b) Variably FDG-avid or PET negative; regression on CT	≥ 50% decrease in SPD of nodules (for single nodule in greatest transverse diameter); no increase in size of liver or spleen	Irrelevant if positive prior to therapy; cell type should be specified
SD	Failure to attain CR/PR or PD	(a) FDG-avid or PET positive prior to therapy; PET positive at prior sites of disease and no new sites on CT or PET (b) Variably FDG-avid or PET negative; no change in size of previous lesions on CT		
Relapsed disease or PD	Any new lesion or increase by ≥ 50% of previously involved sites from nadir	Appearance of a new lesion(s) > 1.5 cm in any axis, ≥ 50% increase in SPD of more than one node, or ≥ 50% increase in longest diameter of a previously identifed node > 1 cm in short axis Lesions PET positive if FDG-avid lymphoma or PET positive prior to therapy	> 50% increase from nadir in the SPD of any previous lesions	New or recurrent involvement

Abbreviations: CR, complete remission; FDG, [^{18}F]fluorodeoxyglucose; PET, positron emission tomography; CT, computed tomography; PR, partial remission; SPD, sum of the product of the diameters; SD, stable disease; PD, progressive disease.

12.4 INTERNATIONAL PROGNOSTIC SCORING SYSTEM (IPSS) FOR MDS PROGNOSTIC VARIABLE

Survival and MDS Evolution Score Value

0	0.5	1	1.5	2
Marrow Blasts (%)	<5	5 to 10	N/a	11 to 20	21 to 30
Karyotype	Good Normal or any 1 of: -Y (del(5q) del(20q)	Intermed. Any other abnormality	Poor chromosome 7 anomalies; Complex: ≥ 3 abnormalities	n/a	n/a
Cytopenias Neutrophil Count < 1800/mcL Platelets < 100,000 mcL Hemoglobin < 10 g/dL	0 or 1	2 or 3	n/a	n/a	n/a

Low: total score = 0
Int-1: total score 0.5-1.0
Int-2: total score 1.5-2.0
High: total score ≥ 2.5

12.5 MDS RESPONSE CRITERIA:

Modified International MDS Working Group (IWG) Criteria for Measurement of Response/Treatment Effect in MDS will be used to assess response.

12.5.1 COMPLETE REMISSION (CR)

Bone marrow evaluation: Bone marrow showing < 5% myeloblasts with normal maturation of all cell lines, with no evidence for dysplasia (see dysplasia qualifier under peripheral blood evaluation). When erythroid precursors constitute < 50% of bone marrow nucleated cells, the percent of blasts is based on all nucleated cells; when there are ≥ 50% erythroid cells, the percent blasts should be based on the non-erythroid cells.

- Peripheral Blood Counts (Absolute values must last ≥ 8 weeks).
- Hemoglobin greater than 11 g/dL.
- Neutrophils 1500/mm3 or more (not on a myeloid growth factor).
- Platelets 100 000/mm3 or more (not on a thrombopoetic agent).
- Blasts ≤ 5%.
- No dysplasia. The presence of mild megaloblastoid changes may be permitted if they are thought to be consistent with treatment effect. However, persistence of pretreatment abnormalities (e.g., pseudo-Pelger Huet cells, ringed sideroblasts, dysplastic megakaryocytes) is not consistent with CR.

12.5.2 PARTIAL REMISSION (PR)

- All of the CR criteria (if abnormal prior to treatment), except:
- Bone marrow evaluation: Blasts decreased by 50% over pretreatment, or a less advanced MDS WHO classification than pretreatment. Cellularity and morphology are not relevant.

12.5.3 STABLE DISEASE

Failure to achieve at least a PR, but with no evidence of progression for ≥ 2 months.

12.5.4 FAILURE

Death during treatment or disease progression characterized by worsening of cytopenias, with increase in the percent of bone marrow blasts (as defined in Section 6 below), and/or progression to an MDS FAB subtype more advanced than pretreatment.

12.5.5 RELAPSE (FOLLOWING A CR OR PR)

One or more of the following:

- Return to pretreatment bone marrow blast percentage.
- Decrement of > 50% from maximum remission response levels in neutrophils or platelets
- RBC transfusion dependence (≥ 2 units RBC transfusions over an 8 week period) or a reduction in hemoglobin concentration by ≥ 2 g/dL in the absence of acute infection, gastrointestinal bleeding, hemolysis, treatment hiatus etc.

12.5.6 DISEASE PROGRESSION

- A 50 % increase in blasts, depending on baseline blast percent.
- For patients with < 5% blasts: increase to ≥ 10% blasts.
- For patients with 5% to 10% blasts: ≥ 50% increase to > 10% blasts.
- For patients with 10% to 20% blasts: ≥ 50% increase to ≥ 20% blasts.

12.5.7 DISEASE TRANSFORMATION

- Transformation to AML (≥ 20% blasts).

12.5.8 CYTOGENETIC RESPONSE

Requires 20 analyzable metaphases when using conventional techniques. Analysis of data will require 20 metaphases before and after treatment, which must be done on bone marrow only (peripheral blood is not a substitute). Fluorescent *in situ* hybridization (FISH) may be used as a supplement to follow a specifically defined cytogenetic abnormality, but it is not a substitute for conventional cytogenetic studies. Cytogenetic response is defined as follows:

12.5.8.1 COMPLETE CYTOGENETIC RESPONSE:

Restoration of a normal karyotype in patients with a documented pre-existing clonal (>2 metaphases abnormal) chromosome abnormalities.

12.5.8.2 PARTIAL RESPONSE:

- 50% reduction in the percentage of Hematologic Improvement.
- Improvements must last ≥ **8 consecutive weeks.**

12.5.8.3 ERYTHROID RESPONSE

Major Erythroid Response: Transfusion-independence for ≥ 8 consecutive weeks for patients

who were RBC transfusion-dependent at baseline AND a ≥ 1 g/dL hemoglobin rise compared to mean pre-transfusion baseline value; or a > 2 g/dL rise in hemoglobin without transfusion for non-transfusion dependent patients.

Minor Erythroid Response: The mean hemoglobin is sustained 1.0 to 2.0 g/dL above the baseline value for a minimum of 8 weeks; or a 50% or greater decrease in 8-week RBC transfusion requirements compared to baseline.

12.5.8.4 PLATELET RESPONSE

Major Platelet Response: For patients with a pretreatment count < 100,000/mm3, an absolute increase of ≥ 30,000/mm3; for platelet transfusion-dependent patients, stabilization of platelet counts and platelet transfusion independence.

Minor Platelet Response: For patients with a pretreatment platelet count < 100,000/mm3, a > 50% increase in platelet count with a net increase > 10,000/mm3 but < 30,000/mm3.

12.5.8.5 NEUTROPHIL RESPONSE

Major Neutrophil Response: For pretreatment ANC < 1500/mm3, ≥ 100% increase, or an absolute increase of ≥ 500/mm3, whichever is greater.

Minor Neutrophil Response: For ANC > 1500/mm3 before therapy, ANC increase of at least 100%, but absolute increase less than 500/mm3, lasting greater than 8 weeks (56 days).

12.5.8.6 PROGRESSION/RELAPSE FOLLOWING ERYTHROID HEMATOLOGIC IMPROVEMENT

For patients who achieve RBC transfusion independence: requirement for ≥ 2 units RBC transfusion in an 8 week period or a reduction in hemoglobin concentration by ≥ to 2 g/dL in the absence of acute infection, gastrointestinal bleeding, hemolysis, etc., reaching a hemoglobin < 9.5 g/dL.

For patients who achieve ≥ 50% decrease in RBC transfusions: return to pre-treatment RBC transfusion requirement over an 8 week period.

12.5.8.7 DURATION OF RESPONSE

Time to disease progression (as per Bone Marrow Responses above) or progression/relapse following hematologic improvement (as per Hematologic Improvement above).

12.6 IDENTIFICATION AND FOLLOW-UP OF LESIONS IN AML

12.6.1 COMPLETE REMISSION (CR)

For subjects to be classified as being in CR, they must have bone marrow regenerating normal hematopoietic cells and achieve a morphologic leukemia-free state (<5% bone marrow blasts in bone marrow, no blasts with Auer rods and no persistence of extramedullary disease) and must have an ANC ≥1 × 109/L and platelet count >100 × 10^9/L

and they will be RBC and platelet transfusion independent (defined as 4 weeks without RBC transfusions and 1 week without platelet transfusion).

12.6.2 COMPLETE REMISSION WITH INCOMPLETE PLATELET RECOVERY (CRP)

For subjects to be classified as being in CRp, they must achieve CR except for incomplete platelet recovery ($<100 \times 10^9$/L).

12.6.3 COMPLETE REMISSION WITH INCOMPLETE HEMATOLOGICAL RECOVERY (CRI)

For subjects to be classified as being in CRi, they must fulfill all the criteria for CR except for incomplete hematological recovery with residual neutropenia $<1 \times 10^9$/L and/or platelet count $>100 \times 10^9$/L. RBC and platelet transfusion independence is not required.

12.6.4 PARTIAL REMISSION (PR)

For subjects to be classified as being in PR, they must meet the criteria for CRi but only require a decrease of at least 50% in the percentage of blasts in the bone marrow with the total marrow blasts between 5% and 25% inclusive.

12.6.5 RELAPSE

Relapse after CR, CRp, or CRi is defined as a reappearance of leukemic blasts in the peripheral blood or ≥5% blasts in the bone marrow aspirate or biopsy not attributable to any other cause or reappearance or new appearance of extramedullary leukemia. Relapse after PR is similarly defined with reappearance of significant numbers of peripheral blasts and an increase in the percentage of blasts in the bone marrow aspirate to >25% not attributable to any other cause or reappearance or new appearance of extramedullary leukemia.

12.6.6 DEFINITIVE PROGRESSION

NHL, HL, MDS, and AML response and progression data will be subjected to IRC review. The subject should continue on study pending confirmation of progression by the IRC.

12.6.7 ACUTE GVHD GRADING [42]

The Gluckenberg scale will be used to grade and stage acute GVHD.

Organ	Stage	Description
Skin	1	Maculopapular rash over <25 percent of body area
	2	Maculopapular rash over 25 to 50 percent of body area
	3	Generalized erythroderma
	4	Generalized erythroderma with bullous formation and often with desquamation
Liver	1	Bilirubin 2.0 to 3.0 mg/dL; SGOT 150 to 750 international units
	2	Bilirubin 3.1 to 6.0 mg/dL
	3	Bilirubin 6.1 to 15.0 mg/dL
	4	Bilirubin >15.0 mg/dL
Gut	1	Diarrhea >30 mL/kg or >500 mL/day
	2	Diarrhea >60 mL/kg or >1000 mL/day
	3	Diarrhea >90 mL/kg or >1500 mL/day
	4	Diarrhea >90 mL/kg or >2000 mL/day; or severe abdominal pain with or without ileus

Glucksberg grade
I – Stage 1 or 2 skin involvement; no liver or gut involvement; ECOG PS 0
II – Stage 1 to 3 skin involvement; Grade 1 liver or gut involvement; ECOG PS 1
III – Stage 2 or 3 skin, liver, or gut involvement; ECOG PS 2
IV – Stage 1 to 4 skin involvement; Stage 2 to 4 liver or gut involvement; ECOG PS 3
International Bone Marrow Transplant Registry Severity Index
A – Stage 1 skin involvement; no liver or gut involvement
B – Stage 2 skin involvement; Stage 1 to 2 gut or liver involvement
C – Stage 3 skin, liver, or gut involvement
D – Stage 4 skin, liver, or gut involvement

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