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TITLE: A Phase 2 Study of pembrolizumab (MK-3475) after Autologous Stem Cell Transplantation in Patients with Relapsed/Refractory Classical Hodgkin Lymphoma, Diffuse Large B Cell Lymphoma and T- Cell non-Hodgkin Lymphoma

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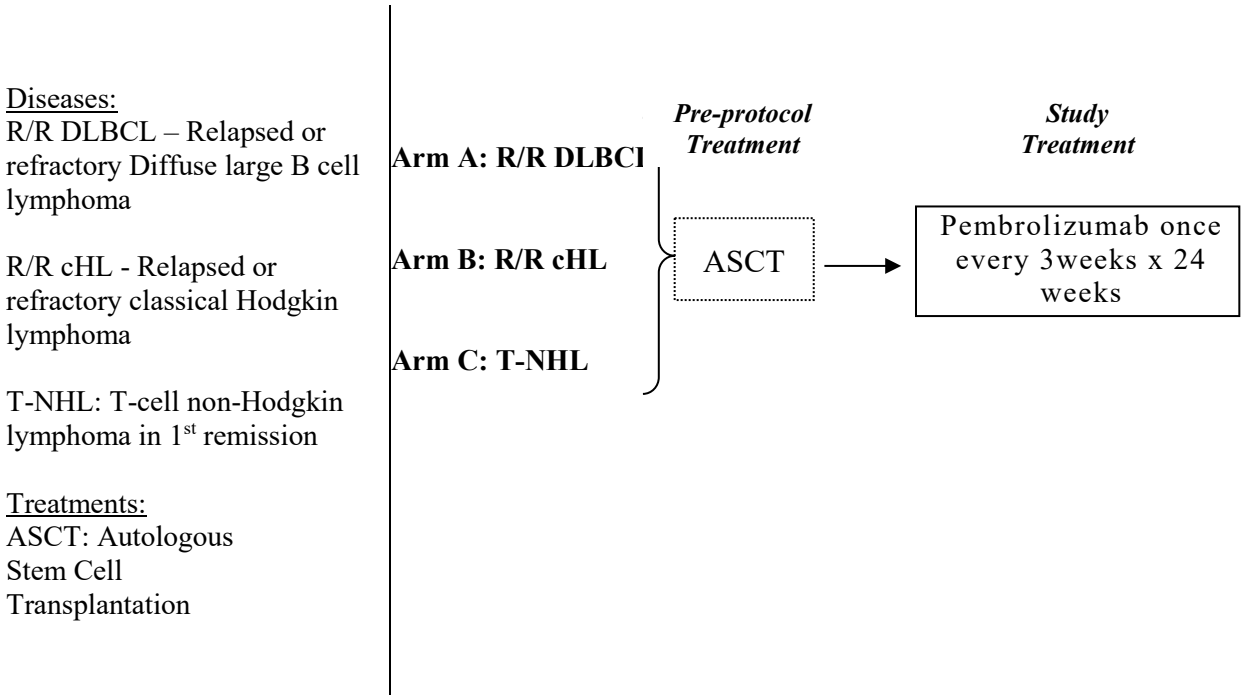
SCHEMA


Diseases:
R/R DLBCL – Relapsed or refractory Diffuse large B cell lymphoma
R/R cHL - Relapsed or refractory classical Hodgkin lymphoma
T-NHL: T-cell non-Hodgkin lymphoma in 1st remission
Treatments:
ASCT: Autologous Stem Cell Transplantation
Pre-protocol Treatment
Study Treatment
Arm A: R/R DLBCl
Arm B: R/R cHL
Arm C: T-NHL
ASCT
Pembrolizumab once every 3weeks x 24 weeks

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1. OBJECTIVES

This phase II study is designed to determine the clinical efficacy of PD-1 blockade, using the anti-PD-1 monoclonal antibody pembrolizumab (MK-3475), administered as consolidation therapy after autologous stem cell transplant (ASCT), in patients with relapsed or refractory (R/R) Diffuse Large B Cell Lymphoma (DLBCL), R/R classical Hodgkin Lymphoma (cHL), or peripheral T-cell lymphoma (PTCL) in 1st remission.

1.1 Study Design

This is a non-randomized, open-label, two-arm phase II clinical trial in patients with R/R DLBCL (Arm A), R/R cHL (Arm B), or PTCL in 1st remission (Arm C). Patients can enroll before or after ASCT. They will receive the study drug (the anti-PD-1 monoclonal antibody pembrolizumab (MK-3475); Merck, Whitehouse Station, NJ) starting within 2-**3** weeks of post-ASCT recovery **and no more than 60 days from stem cell reinfusion** (see Section 3.1.9), and will continue treatment for up to 8 doses (24 weeks).

1.2 Primary Objective

The primary objective is to estimate the 18-month progression-free survival (PFS) rate after ASCT in patients treated with pembrolizumab as early consolidation post-ASCT. This will be assessed separately for all 3 arms.

1.3 Secondary Objectives

1. **Efficacy objectives:**
    a. To determine the 18-month overall survival (OS) and cumulative incidence of relapse (CIR);
    b. To determine the 18-month PFS and OS in the high-risk subset of patients not in PET-CR prior to ASCT for the entire cohort and within each arm.
    c. To determine the rates of complete response, partial response, and stable disease in patients with measurable disease after ASCT treated with pembrolizumab.

2. **Safety objectives:**
    a. To establish the safety and tolerability of pembrolizumab in the early post-ASCT setting, defined as the rate of grade 3 and above toxicities with this treatment.
    b. To determine the rate of grade 2 and above attributable toxicities.
    c. To determine the proportion of patients who can complete the planned study treatment.

3. **Correlative and exploratory objectives:**
    a. To study immune reconstitution in patients receiving post-ASCT pembrolizumab.
    b. To examine the association between 9p24 amplification in cHL and relapse.
    c. To examine the association between EBV positivity, PD1/PD-L1/PD-L2 surface expression on tumor cells and relapse.
    d. To compare when possible, in patients who relapse on or after treatment, the

tumor expression of PD-1/PD-L1/PD-L2 to that in a pre-ASCT tumor sample.

2. BACKGROUND

2.1 Study Diseases

2.1.1 Diffuse Large B Cell Lymphoma (DLBCL)

DLBCL is an aggressive B-cell non-Hodgkin lymphoma (NHL) and the most common lymphoid malignancy in the United States, with approximately 22,000 estimated new cases and 10,000 deaths in 2013. First-line chemo-immunotherapy with rituximab + multi-agent chemotherapy can cure up to 2/3 of patients with DLBCL, leaving a third of patients with relapsed or refractory disease. For those patients, the standard treatment is salvage chemo-immunotherapy, followed by ASCT if the disease is chemosensitive. Unfortunately, concomitantly with the improvement in first-line therapy outcomes obtained from the addition of anti-CD20 therapy, there has been a worsening of the outcome for R/R patients[1]. In particular, it is now harder to get patients to a metabolic complete remission (CR), as assessed by PET scans, with salvage therapy. There is strong evidence that the inability to achieve a CR by PET is associated with a worse ASCT outcome, with a risk of relapse around 70% in most studies, including in a study of DLBCL patients transplanted at our institutions[2]. In general, for the nearly 50% of patients who relapse after ASCT, the outcomes are dismal, with few patients able to re-enter remission and proceed to allogeneic transplantation, and few of those remaining in long-term remission subsequently. There is therefore an urgent need to improve the treatment of patients with R/R DLBCL.

2.1.2 Classical Hodgkin lymphoma (cHL)

Classical HL is another type of lymphoma of B-cell origin, with approximately 9,000 new cases in the United States in 2013 and 1,200 deaths. While those numbers speak to the efficacy of first-line multi-agent chemotherapy, cHL has the demographic particularity of affecting young patients, with a median age at diagnosis of 38. As with DLBCL, for patients who are refractory to or relapse after first-line therapy, the standard of care is salvage chemotherapy followed by ASCT when the disease is chemosensitive. As with DLBCL, roughly one half of patients who undergo ASCT will subsequently relapse, and the long-term outcomes for those patients are equally dismal to those of patients with DLBCL[3,4]. Based on this, and the often young age of affected patients, improving the outcomes of R/R cHL also represents an urgent clinical need.

2.1.3 Peripheral T Cell Lymphoma (PTCL)

The PTCLs are a heterogeneous group of diseases that account for approximately 10% of non-Hodgkin lymphoma diagnosed in North America and Western Europe. The three most common variants in the United States are PTCL, not otherwise specified (PTCL, NOS); angioimmunoblastic T cell lymphoma (AITL); and anaplastic large cell lymphoma which is subdivided based upon expression of the ALK protein (ALK+ ALCL and ALK- ALCL). With the exception of ALK+ ALCL, the prognosis for PTCL is poor compared to aggressive B cell non-Hodgkin lymphoma. The optimal treatment for most types of T cell lymphoma remains to

be defined. Aggressive lymphoma regimens such as CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) have overall response rates of 50% to 70% with a median progression free survival (PFS) of 12-14 months[5]. Given the poor prognosis of patients with PTCL even with optimal chemotherapy, ASCT in first remission is considered standard of care at most institutions, unlike for cHL and DLBCL where ASCT is reserved for patients with R/R disease. Despite the ability of ASCT to improve patients' outcome when used to consolidate first remission, at least 50% of patients will recur after transplant even when performed in first complete remission. Patients who recur after autologous stem cell transplantation are generally considered incurable with the exception of a small proportion who may be cured with allogeneic transplant. The development of effective therapy for PTCL is considered one of the greatest unmet medical needs in lymphoma.

2.1.4 PD-1 blockade in cHL, DLBCL and PTCL

Over the last few years, immune checkpoint blockade, via monoclonal antibodies targeted against the CTLA-4 or PD-1 pathways, have yielded incredibly promising results in the treatment of cancer, by disabling what appears to be a primary mechanism for immune escape by tumors. While the early work has focused on solid tumors[6,7], it has long been recognized that hematologic malignancies in general, and lymphoid malignancies in particular, are especially susceptible to immunologic attack, as evidenced by the curative potential of allogeneic stem cell transplantation in those diseases. Although cHLs have an extensive polymorphous inflammatory infiltrate, there is little evidence of an effective host anti-tumor immune response. In fact, recent studies indicate that Hodgkin RS cells produce certain molecules that limit the efficacy of T-cell mediated anti-tumor immune responses[8,9]. By integrating high-resolution copy number data with transcriptional profiles, we identified the immune-regulatory genes, *PD-L1* and *PD-L2*, as key targets of the 9p24.1 amplification in cHL and mediastinal large B cell lymphoma (MLBCL) cell lines[10]. We also extended these findings to primary tumors and found amplification of the PD-L ligand genes, *PD-L1* and *PD-L2* at 9p24.1, in ~40% of primary cHLs and ~70% of primary MLBCLs[10]. Using quantitative immunohistochemical methods, we demonstrated that PD-1 ligand gene amplification is associated with increased protein expression in primary tumors [6]. The 9p24.1 amplification region also includes the *JAK2* locus; *JAK2* amplification increases JAK2 protein expression and activity, and specifically induces PD-1 ligand transcription. Other studies have also identified chromosomal translocations resulting in deregulated increased expression of PD-L1 or PD-L2 in a small number of cHLs and MLBCLs [11-12]. In additional studies, we found that EBV infection is another mechanism of up-regulating PD-L1[8,9]. EBV-associated B-cell malignancies including cHL, post-transplant lymphoproliferative disorder (PTLD) and EBV+ DLBCL and plasmablastic lymphoma all frequently express PD-L1[13-14]. An additional DLBCL subtype that shares certain features with Hodgkin lymphoma, T-cell/histiocyte-rich large B-cell lymphoma, is also near-uniformly positive for PD-L1[10]. Together, these results strongly suggest that the PD-1 pathway provides a critical immune escape pathway for cHL/MLBCL and for at least a subset of DLBCLs, and therefore that PD-1 blockade is very likely to be an effective anti-tumor strategy in this setting.

Preliminary clinical results support this hypothesis. A phase II study of the anti-PD1 antibody pidilizumab administered as post-ASCT consolidation for patients with DLBCL suggested an improvement in outcome over historical controls, especially in the high-risk subset of patients

who were not in metabolic CR after salvage therapy, and also demonstrated the safety and feasibility of PD-1 blockade after ASCT. Two ongoing phase I studies of newer-generation anti-PD1 antibodies (nivolumab and pembrolizumab) have tested PD-1 blockade in hematologic malignancies including in cHL and DLBCL. Preliminary results from the pembrolizumab study suggest a response rate over 50% in patients with cHL[15].

PD-1 inhibition has not been studied extensively in T cell lymphomas. However, there is now promising preclinical and clinical data supporting the activity of PD-1 blockade in these diseases. Preclinical data demonstrated that PD-L1 was expressed by tumor cells, monocytes, and monocyte-derived cells within the tumor microenvironment in T-cell NHL and promoted the induction of FoxP3(+) regulatory T cells[16]. However, over 90% of cases of AITL will express PD-1 as will a significant percentage of PTCL, NOS[17]. In a phase I study, single agent nivolumab resulted in a 40% ORR in PTCL, NOS[18].

2.2 Pembrolizumab (MK-3475)

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

2.2.1 Introduction and ongoing studies

Pembrolizumab is a potent humanized IgG4 mAb with high specificity of binding to the PD-1 receptor, thus inhibiting its interaction with PD-L1 and PD-L2. Based on preclinical in vitro data, pembrolizumab has higher affinity and receptor blocking activity compared to other anti-PD-1 products in development. Several ongoing studies are testing the anti-tumor activity of pembrolizumab. Protocol 001 (PN001), an open-label Phase I study is being conducted to evaluate the safety and clinical activity of pembrolizumab when administered as monotherapy. The dose escalation portion of this study evaluated three dose levels of single agent pembrolizumab (1 mg/kg, 3 mg/kg, and 10 mg/kg), in subjects with advanced solid tumors. All three dose levels were well tolerated and no dose-limiting toxicities (DLTs) were observed, therefore the maximum tolerated dose (MTD) has not been determined. The ongoing expansion part of this study is evaluating pembrolizumab in subjects with melanoma and non-small cell lung cancer (NSCLC). Protocol 002 (PN002), a Phase II study, is also being conducted to evaluate the safety and clinical activity of pembrolizumab in melanoma. This study is examining two dose levels of pembrolizumab (2 mg/kg and 10 mg/kg) in subjects with metastatic melanoma. Due to the limited amount of safety data for this compound a well-defined safety profile has not been established, however immune-related adverse events (irAEs) are expected based on the nature of the compound, its mechanism of action and reported experience with immunotherapies that have a similar mechanism of action. Protocol 013 is a Phase 1b study testing pembrolizumab at a fixed dose of 10 mg/kg every 2 weeks in patients with myelodysplastic syndromes, cHL, PD-L1-positive non-Hodgkin lymphoma, and multiple myeloma. This study is ongoing.

2.2.2 Nonclinical Pharmacology

Pembrolizumab strongly enhances T lymphocyte immune responses in cultured blood cells from healthy human donors, cancer subjects, and primates. In T-cell activation assays using human donor blood cells, the EC50 has been 0.1 to 0.3 nM. In addition to interleukin-2 (IL-2), tumor necrosis factor alpha (TNFα), interferon gamma (IFNγ), and levels of other cytokines were found to be modulated by pembrolizumab. The antibody potentiates existing immune responses only in the presence of antigen and does not non-specifically activate T cells. Using an anti-murine PD-1 analog antibody, PD-1 blockade has been shown to significantly inhibit tumor growth in a variety of syngeneic murine tumor models.

2.2.3 Nonclinical Pharmacokinetics

After intravenous (IV) administration of pembrolizumab to cynomolgus monkeys, systemic exposure to
pembrolizumab independent of sex, increased with increasing dose. Systemic exposure for the 7-day dosing interval increased after repeated dosing from 40 to 200 mg/kg. Area under the concentration-time curve (AUC) for the 7-day dosing interval (AUC[0-7 days]) after one dose appeared to be dose-proportional from 0.3 to 200 mg/kg, suggesting dose-independent pharmacokinetics (PK). Terminal half-life (t½) values from individual animals after repeated IV dosing ranged from 11.8 to 23.7 days (mean values ranged from 15.7 to 22.3 days) across the doses tested.

2.2.4 Safety

The potential for systemic toxicity of pembrolizumab was assessed in a 1-month repeat-dose toxicity study with a 4-month recovery in cynomolgus monkeys and in a 6-month repeat- dose toxicity study with a 4-month recovery period in cynomolgus monkeys. In the 1- month toxicity study, cynomolgus monkeys were administered an IV dose of 6, 40, or 200 mg/kg once weekly for a total of five doses. Four monkeys per sex per group were euthanized during Week 5. The remaining two monkeys/sex/group were euthanized during Week 23, after a four-month post-dose period. In this study, pembrolizumab was well- tolerated in monkeys with the systemic exposure (AUC) up to approximately 170,000 µg/day/mL over the course of the study. There was no test article-related mortality, and test article-related changes were limited to an increased incidence of inguinal swelling, and increased splenic weights in males receiving
200 mg/kg. Both of these findings were not considered adverse and there was no histopathologic correlation. Splenic weights were normal at the post-dose necropsy. Anti-pembrolizumab antibodies were detected in seven (out of eight) animals in the 6 mg/kg dose group and one (out of eight) animal in the 40 mg/kg dose group, and were associated with an apparent increase in clearance of pembrolizumab. The presence of anti-drug antibodies (ADA) in monkeys in the low-dose group and in one monkey in the mid-dose group did not impact the pharmacodynamic response as sufficient target engagement was demonstrated for the duration of the study (with the exception of one low-dose monkey). Additionally, anti-pembrolizumab antibodies were not detected in any monkeys in the high-dose group, suggesting that potential toxicity has been evaluated at the highest exposure levels in the study. Based on the lack of adverse test article-related findings in this study, the No Observable Adverse Effect Level

(NOAEL) was ≥200 mg/kg. In the 6-month toxicity study, the potential for systemic toxicity was assessed in cynomolgus monkeys administered an IV dose of 6, 40, or 200 mg/kg once every other week for approximately 6 months (a total of 12 doses) followed by a 4-month treatment-free period. Three animals/sex/group were designated for interim necropsy at the end of the 6-month dosing phase (3 days after receiving the last dose in Study Week 23); and the remaining monkeys were designated for final necropsy following the 4-month treatment-free period. Pembrolizumab was well tolerated at all dose levels. There were no test article-related antemortem findings. There were no test article-related electrocardiographic or ophthalmic findings. There were no test article-related changes at injection sites. There were no test article-related gross observations or organ weight changes at the interim or final necropsy. Since there were no test article-related histomorphologic findings at interim necropsy, histomorphologic evaluation of tissues collected at final necropsy was not conducted. The presence of ADA was observed in five out of ten animals at 6 mg/kg/dose during the dosing phase, which correlated with an apparent increased rate of elimination of pembrolizumab in these animals. No anti-pembrolizumab antibodies were detected at 40 or 200 mg/kg/dose during the dosing phase, and no pembrolizumab serum concentration profiles in these two groups suggested an effect of ADA on pembrolizumab elimination rate. During the treatment-free period, anti-pembrolizumab antibodies were detected in two animals at 6 mg/kg/dose, which already had ADA present during the dosing phase, and in two additional animals (one at 6 mg/kg/dose and one at 200 mg/kg/dose), which were ADA negative during the dosing phase. The detection of anti-pembrolizumab antibodies had a minimal effect on the mean group systemic exposure to pembrolizumab during the study and did not impact the evaluation of potential toxicity of pembrolizumab for the duration of the 6-month study as there were no test article-related effects on any of the parameters examined and as no monkey in the mid- and high-dose groups developed ADA during the dosing phase. In conclusion, pembrolizumab administered once every other week over a 6-month duration to cynomolgus monkeys was well tolerated and the no observed effect level (NOEL) was ≥200 mg/kg/dose (the highest dose tested).

In addition, tissue cross-reactivity studies using monkey and human specimens were conducted to evaluate the potential cross reactivity of pembrolizumab with cryosections of cynomolgus monkey tissues and normal human tissues. Results demonstrated the expected on-target staining of the membranes of mononuclear leukocytes in both species. The off-target staining (cytoplasmic and stromal) that occurred in many tissues of both species was considered spurious binding inherent to the experimental conditions of the in vitro tissue cross reactivity studies with no in vivo toxicological significance.

2.2.5 Clinical Pharmacology and Safety

In PN001, there have been 350 subjects treated with pembrolizumab as a 30-minute IV infusion. Based upon this safety database consisting of subjects treated up to 10 mg/kg once every two to three weeks, pembrolizumab has been generally well-tolerated at doses up to 10 mg/kg every other week without DLTs. Three (0.86%) subjects assayed to date had samples confirmed positive for ADA and among these, no impact on safety has been observed. Pembrolizumab PK results have been obtained from PN001 following the first dose at 1, 3 and 10 mg/kg IV of pembrolizumab administered to 17 subjects with solid tumors. The observed pharmacokinetic profile of pembrolizumab was typical of other IgG mAbs with a half-life (t½) of approximately 2

to 3 weeks. There was no indication of dose dependency of half-life in the 3 dose groups and a dose related increase in exposure was observed from 1 to 10 mg/kg. The long half-life supports a dosing interval of every 2 or 3 weeks. Exposure obtained with sparse sampling after dosing melanoma and non-small cell lung cancer (NSCLC) subjects at 2 and 10 mg/kg, every 2 or 3 weeks, is consistent with this profile.

Currently, safety data are available from 2799 subjects from the Sponsor's Reference Safety Dataset (Investigator's brochure 12th edition). 97% of the patients experienced a drug-related AE (DRAE), and 14% a grade 3 or high DRAE; 37% a serious AE (SAE). 12% discontinued treatment for AE, and 10% experienced a drug-related SAE. The overall AE summary suggests that MK-3475 is generally tolerable and AEs are generally manageable in advanced cancer subjects. In the ongoing MK3475-013 study in patients with hematologic malignancies, the safety profile has so far been consistent with that in solid tumors. Durable objective responses have been reported in subjects with melanoma, NSCLC, and other tumor types. Adverse events have generally been manageable and infrequently require discontinuation of pembrolizumab treatment. For additional information on the study agent, please refer to the Investigator's Brochure.

2.3 Rationale

2.3.1 Overview

Immune checkpoint blockade is emerging as an effective anti-tumor strategy in a variety of cancer types. PD-1 blockade appears to provide the best balance of efficacy and toxicity of all the checkpoint blockade strategies tested to date. Pembrolizumab is an anti-PD1 monoclonal antibody with extensive pre-clinical and clinical experience, documented safety and efficacy in solid tumors, and preliminary safety and efficacy in cHL and DLBCL. A closely related agent, nivolumab, has shown also preliminary activity om PTCL. There is an urgent clinical need for more effective salvage strategies for patients with R/R cHL and DLBCL, and for patients with PTCL undergoing 1st line treatment. In all 3 diseases, a large fraction of patients who undergo ASCT will still relapse, and their prognosis with current therapies is poor. Therefore, the ability to potentially increase the cure rate of ASCT for R/R cHL, R/R DLBCL, and PTCL in 1st remission would provide a major improvement in the management of those diseases. The biological study of cHL and DLBCL suggests most cHL tumors and a subset of DLBCL and PTCL tumors use the PD-1 pathway as a mechanism of tumor escape. This provides a strong scientific and clinical rationale for the use of pembrolizumab in cHL, DLBCL and PTCL.

2.3.2 Rationale for using pembrolizumab after ASCT

The post-ASCT setting is an ideal setting to test PD-1 blockade for cHL and DLBCL. This setting is characterized by a minimal disease state. Moreover, it is a state of immune remodeling with gradual reconstitution of a full immune system, and an early preponderance of lymphocytes that are the target for PD-1 blockade. It represents the last effective intervention point for cure of relapsed/refractory patients, since patients who fail ASCT have a dismal prognosis. Because of the minimal residual disease state, this is also a setting in which there would be time for pembrolizumab to reverse immune exhaustion without the expectation of early rapid tumor

progression. Moreover, there is already experience with PD-1 blockade in the post-ASCT setting for DLBCL with encouraging clinical results[15]. Finally, it is now possible to easily define a high-risk subset of patients (those with residual FDG avid disease after salvage therapy), in whom the stakes and possible therapeutic benefit may be even greater.

2.3.3 Rationale for dosing schedule

The dose regimen of 200 mg Q3W of pembrolizumab is being used for current trials. Available PK results in subjects with melanoma, NSCLC, and other solid tumor types support a lack of meaningful difference in PK exposures obtained at a given dose among tumor types. An open-label Phase 1 trial (PN001) in melanoma subjects is being conducted to evaluate the safety and clinical activity of single agent pembrolizumab. The dose escalation portion of this trial evaluated three dose levels, 1 mg/kg, 3 mg/kg, and 10 mg/kg, administered every 2 weeks (Q2W) in subjects with advanced solid tumors. All three dose levels were well tolerated and no dose-limiting toxicities were observed. This first in human study of pembrolizumab 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) was identified.

In KEYNOTE-001, two randomized cohort evaluations of melanoma subjects receiving pembrolizumab at a dose of 2 mg/kg versus 10 mg/kg Q3W have been completed. The clinical efficacy and safety data demonstrate a lack of clinically important differences in efficacy response or safety profile at these doses. For example, in Cohort B2, advanced melanoma subjects who had received prior ipilimumab therapy were randomized to receive pembrolizumab at 2 mg/kg versus 10 mg/kg Q3W. The overall response rate (ORR) was 26% (21/81) in the 2mg/kg group and 26% (25/79) in the 10 mg/kg group. The proportion of subjects with drug-related adverse events (AEs), grade 3-5 drug-related AEs, serious drug-related AEs, death or discontinuation due to an AE was comparable between groups or lower in the 10 mg/kg group.

Available pharmacokinetic results in subjects with melanoma, NSCLC, and other solid tumor types support a lack of meaningful difference in pharmacokinetic exposures obtained at a given dose among tumor types. Population PK analysis has been performed and has confirmed the expectation that intrinsic factors do not affect exposure to pembrolizumab to a clinically meaningful extent. Taken together, these data support the use of lower doses (with similar exposure to 2 mg/kg Q3W) in all solid tumor indications. 2 mg/kg Q3W is being evaluated in NSCLC in PN001, Cohort F30 and PN010, and 200 mg Q3W is being evaluated in head and neck cancer in PN012, which are expected to provide additional data supporting the dose selection.

Selection of 200 mg as the appropriate dose for a switch to fixed dosing is based on simulation results indicating that 200 mg will provide exposures that are reasonably consistent with those obtained with 2 mg/kg dose and importantly will maintain individual patient exposures within the exposure range established in melanoma as associated with maximal clinical response. A population PK model, which characterized the influence of body weight and other patient covariates on exposure, has been developed using available data from 476 subjects from PN001. The distribution of exposures from the 200 mg fixed dose are predicted to considerably overlap those obtained with the 2 mg/kg dose, with some tendency for individual values to range slightly

higher with the 200 mg fixed dose. The slight increase in PK variability predicted for the fixed dose relative to weight-based dosing is not expected to be clinically important given that the range of individual exposures is well contained within the range of exposures shown in the melanoma studies of 2 and 10 mg/kg to provide similar efficacy and safety. 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 tumor types and indication settings.

Extensive pharmacokinetic and pharmacodynamic modeling performed by the sponsor based on the results obtained with pembrolizumab studies to date (Merck, unpublished data) support the use of a flat dose for pembrolizumab. The dose used in other advanced phase studies of this antibody is 200mg (flat dose) given every 3 weeks, and will be the dose used in this trial. In the PN013 trial of pembrolizumab in hematologic malignancies, the dose was 10 mg/kg every 2 weeks, with acceptable safety to date. Therefore, we expect that the lower dose of 200mg every 3 weeks would be equally safe.

2.3.4 Rationale for dose duration

Most relapses after ASCT for cHL and ASCT happen in the first year after transplantation. The relative predominance of immune cells that are the likely targets of PD-1 blockade after ASCT extends to roughly 6 months post-transplantation. Also, prior clinical trials of PD-1 blockade have suggested that responses remain durable even after discontinuation of drug treatment, possibly given the long tissue half-life of anti-PD1 antibodies. Therefore, the period of treatment on the present study will extend to ~6 months post-ASCT.

2.3.5 Summary of study

We therefore propose a phase 2 study of pembrolizumab as early consolidation therapy for patients with cHL or DLBCL undergoing ASCT for R/R disease and for patients with PTCL undergoing ASCT as first consolidation therapy. The study will have 3 arms, one for patients with cHL, one for patients with DLBCL (including mediastinal large B cell lymphoma, which resembles cHL biologically and in PD-1 ligand amplification), and one for patients with PTCL. The null hypothesis is well defined on all 3 arms since there is extensive data on the outcomes of ASCT in this setting, allowing us to convincingly detect potentially promising result with this experimental strategy that would then justify phase 3 trials in those patient populations.

2.4 Correlative Studies Background

The scientific basis for PD-1 blockade in cHL, DLBCL and PTCL has been discussed above. Based on this, we propose to conduct correlative studies on the effect of PD-1 blockade on post-ASCT immune reconstitution, on the relationship between PD-1/PD-L1/PD-L2 expression and treatment outcome, on the relationship between EBV tumorigenesis in DLBCL and treatment outcome, and on possible mechanisms of immune escape after PD-1 blockade in patients who relapse after ASCT and in whom a post-relapse tumor biopsy can be obtained. We will also explore the outcome of high risk patients, defined based on post-salvage and post-ASCT PET status and possibly MRD status.

3. PARTICIPANT SELECTION

In order to be eligible for participation in this study, subjects must meet all of the following inclusion and exclusion criteria.

3.1 Eligibility Criteria

3.1.1 Histologically confirmed diagnosis with review of the diagnostic pathology specimen at one of the participating institutions. Eligible histologies are:

- **For Arm A**: Diffuse large B cell lymphoma; patients with a prior history of indolent B-cell NHL are eligible, as long as they have histologically confirmed DLBCL prior to their pre-transplant salvage treatment. Patients with mediastinal large B cell lymphoma are also eligible.

- **For Arm B**: Classical Hodgkin lymphoma (patients with nodular lymphocyte predominant Hodgkin lymphoma [NLPHL] are **NOT** eligible)

- For Arm C: Peripheral T cell lymphoma – eligible subtypes will include PTCL, NOS; AITL; ALK-negative ALCL; enteropathy-associated T-cell lymphoma (EATL) and monomorphic epitheliotropic intestinal T-cell lymphoma (MEITL); and extranodal NK/T-cell lymphoma (ENKTL). Patients with other PTCL histologies, including ALK-positive PTCL, and cutaneous T-cell lymphoma will not be eligible.

3.1.2 Age ≥ 18 at the time of enrollment. Pembrolizumab has not been studied in pediatric populations, and children are therefore not eligible for this study.

3.1.3 For arms A and B, participants must have relapsed after or been refractory to first-line chemotherapy, i.e., they must have failed to achieve CR after first-line therapy or must have relapsed subsequently if they achieved CR. For arm C, participants will be eligible if transplant is performed as consolidation of first remission (partial or complete).

3.1.4 Participants must be planning to receive or have received autologous stem cell transplantation. Participants may enroll prior to ASCT, but will not be eligible to begin treatment until after ASCT, and must fulfill all inclusion and exclusion criteria at that time. ASCT will be performed according to institutional standards and is not a part of this study.

3.1.5 Participants must have chemosensitive disease prior to ASCT, defined as achieving at least a partial remission (as determined with PET imaging) to salvage treatment using International Harmonization Project (IHP) criteria[16]. Participants with cHL or DLBCL (arms A and B) transplanted in 1st remission after only one line of treatment are not eligible. Participants with PTCL (arm C) transplanted beyond 1st remission are also not eligible.

3.1.6 No more than 1 line of anthracycline-containing chemotherapy prior to ASCT, and no more than 3 lines of therapy total prior to ASCT for arms A and B; no more than 1 line of therapy prior to ASCT for arm C.

3.1.7 Participants cannot have received any anti-neoplastic therapy (including radiotherapy, chemotherapy or immunotherapy) after ASCT

3.1.8 Participants must have had PET-CT for restaging after salvage therapy and before ASCT.

3.1.9 Participants must begin study treatment **no later than 21 days from the post-ASCT discharge.** Additionally, they must have recovered from **ASCT toxicities at the time of first study treatment**. Recovery from ASCT toxicity is defined using the eligibility criteria in this section, as well as outpatient status, ability to drink and eat normally, without the need for intravenous hydration. Participants must be no later than 60 days from stem cell reinfusion. Exceptions to these time frames may be made in discussion with the Overall PI and will not constitute study violations.

3.1.10 ECOG performance status ≤1 (see Appendix A)

3.1.11 Participants must have normal organ and marrow function as defined below:

- absolute neutrophil count ≥ 1,000/mcL
- platelets ≥ 50,000/mcL
- Hemoglobin ≥ 8 g/dl
- total bilirubin ≤ 1.5 × institutional upper limit of normal (ULN), or direct bilirubin ≤ ULN in patients with Gilbert's syndrome
- AST(SGOT)/ALT(SGPT) ≤ 2.5 × ULN
- Creatinine ≤ 1.5 × ULN or creatinine clearance ≥ 60 mL/min/1.73 m^2
- Resting and ambulatory oxygen saturation ≥ 94% on room air
- FEV1 and DLCO (adjusted for Hemoglobin) ≥ 50% predicted

3.1.12 The effects of pembrolizumab on the developing human fetus are unknown. For this reason women of child-bearing potential and men must agree to use adequate contraception as defined in Section 3.4 for the duration of study participation and for 120 days after the last treatment with pembrolizumab. Should a woman become pregnant or suspect she is pregnant while she or her partner is participating in this study, she should inform her treating physician immediately. Men treated or enrolled on this protocol must also agree to use adequate contraception prior to the study (see Section 3.4), for the duration of study participation, and for 120 days after the last treatment with pembrolizumab.

3.1.13 Ability to understand and the willingness to sign a written informed consent document.

3.2 Exclusion Criteria

3.2.1 Participants who are receiving any other investigational agents after ASCT.

3.2.2 Participants with active CNS involvement are excluded. Patients with suspected CNS disease should be worked up appropriately prior to enrollment.

3.2.3 History of or active autoimmune disease, or other syndrome that requires systemic steroids or autoimmune agents. Participants with vitiligo, resolved childhood asthma or atopy, hypothyroidism, or Sjogren's syndrome, as well as participants requiring only intranasal steroids, intermittent use of bronchodilators, local steroid injections, or physiologic replacement doses of prednisone (≤ 10 mg/d) are not excluded from this study.

3.2.4 History of allergic reactions attributed to compounds of similar chemical or biologic composition to pembrolizumab. Prior hypersensitivity reactions to anti-CD20 therapy or anti-CD30 therapy is not an exclusion criterion.

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

3.2.6 Receipt of > 600 mg/m2 total dose of BCNU with prior treatments including transplant conditioning regimen.

3.2.7 Uncontrolled illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements or pose excess risk to the participant in the opinion of the treating clinician..

3.2.8 Pregnant or lactating women are excluded from this study because the effects of pembrolizumab on the developing fetus are unknown, and because there is an unknown but potential risk for adverse events in nursing infants secondary to treatment of the mother with pembrolizumab.

3.2.9 HIV-positive participants on combination antiretroviral therapy are ineligible because the effect of pembrolizumab on the course of HIV infection is unknown. Appropriate studies will be undertaken in participants receiving combination antiretroviral therapy when indicated.

3.2.10 Participants with active viral hepatitis (positive HepB sAg, positive HepB core Ab with positive HepB viral load, or positive HepC antibody with positive HepC viral load).

3.2.11 Receipt of a live vaccine within 30 days of the start of treatment. Examples are measles, mumps, rubella, varicella, yellow fever, rabies, BCG, oral polio vaccine, and oral typhoid vaccine.

3.2.12 Prior treatment with an anti PD-1, anti PD-L1, or anti CTLA-4 agent. Participants who entered clinical remission with one of those agents and proceeded to ASCT without intervening relapse may be eligible after discussion with the Study Chair. Note that for patients who enter remission with checkpoint blockade therapy, this will not count towards the 3 lines of prior therapy.

3.3 Inclusion of Women and Minorities

Both men and women of all races and ethnic groups are eligible for this trial.

3.4 Contraception Requirements

Women of childbearing potential (WOCBP), defined as women who have not been surgically sterilized and have had a menses in the last 24 months, must remain abstinent or use at least 2 methods of birth control during the course of this study and for 120 days after the last dose of pembrolizumab. At least one of these methods must be a highly effective method (hormonal contraception, intrauterine device). Men who have sexual intercourse with WOCBP must agree to remain abstinent or use 2 methods of contraception, including a highly effective method (hormonal contraception, intrauterine device for their female partner(s)) during this study and for 120 days after the last dose of pembrolizumab. All WOCBP must be tested for pregnancy before receiving the first study treatment.

4. REGISTRATION PROCEDURES

4.1 General Guidelines for DF/HCC Institutions

Institutions will register eligible participants in the Clinical Trials Management System (CTMS) OnCore. Registrations must occur prior to the initiation of protocol-specific therapy or intervention. Any participant not registered to the protocol before protocol-specific therapy or intervention will be considered ineligible and registration will be denied.

An investigator will confirm eligibility criteria and a member of the study team will complete the protocol-specific eligibility checklist.

Following registration, participants may begin protocol-specific therapy and/or intervention. Issues that would cause treatment delays should be discussed with the Overall Principal Investigator (PI). If a participant does not receive protocol therapy following registration, the subject must be taken off study in the CTMS (OnCore) with an appropriate date and reason entered.

4.2 Registration Process for DF/HCC Institutions

Applicable DF/HCC policy (REGIST-101) must be followed.

4.3 General Guidelines for Other Investigative Sites

Eligible participants will be entered on study centrally at the Dana-Farber Cancer Institute by the Project Manager. All sites should call the Project Manager at 617-632-2328 to verify dose level availabilities. Following registration, participants should begin protocol therapy within 7 days. Issues that would cause treatment delays should be discussed with the Overall PI. If a participant does not receive protocol therapy following registration, the subject must be taken off study in the CTMS (OnCore) with an appropriate date and reason entered.. The Study Coordinator should be notified of cancellations as soon as possible.

4.4 Registration Process for Other Investigative Sites

To register a participant, the following documents should be completed by the research nurse or data manager and e-mailed to the Project Manager (contact information on study contact list):

- Copy of all relevant medical records
- Signed participant consent form
- HIPAA authorization form
  Completed DFCI Eligibility Checklist

The participating site will then e-mail the Project Manager at Samantha_Pazienza@dfci.harvard.edu to verify eligibility. The Project Manager will follow DF/HCC policy (REGIST-101) and register the participant on the protocol. The Project Manager will e-mail the participant study number, and if applicable the dose treatment level, to the participating site. The Project Manager may also contact the participating site and verbally confirm registration

5. TREATMENT PLAN

5.1 Treatment Regimen

Pembrolizumab will be administered once every 3 weeks, with 21 consecutive days defined as a treatment cycle (unless the treatment cycle length is increased for adverse effect, as detailed in Section 6). Treatment will be administered on an outpatient basis. Reported adverse events and potential risks are described in Section 7. Appropriate dose modifications are described in Section 6. No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the participant's malignancy.

All participants will receive pembrolizumab at a fixed dose of 200 mg intravenously every 3 weeks for up to 8 cycles.

5.2 Pre-Treatment Criteria

Participants who were enrolled prior to ASCT must have completed ASCT and have recovered from ASCT toxicities. Participants must begin study treatment no later than 21 (preferably 14) days from the post-ASCT discharge and recovery from ASCT toxicities. Recovery from ASCT

toxicity is defined using the eligibility criteria in Section 3.1 and 3.2, as well as outpatient status, able to drink and eat normally, without the need for intravenous hydration. Participants must be no later than 60 days from stem cell reinfusion. Exceptions to these time frames may be made in discussion with the Overall PI and will not constitute study violations.

In order to receive the first dose of study treatment, the participant must meet all of the eligibility criteria.

5.2.1 Subsequent Cycles

As detailed in Section 6, pembrolizumab administration should be held for grade 4 hematologic events or grade 3 non-hematologic events, if the event is judged to be at least possibly related to study drug. In all cases, dose delay, treatment discontinuation, and toxicity management for immune-related adverse events should follow the guidelines in Section 6 and Appendix E.

In addition, treatment should be delayed if the subject's resting oxygen saturation is <94% while breathing ambient air.

5.3 Agent Administration

Pembrolizumab will be administered as a 30 minute IV infusion on the first day of every 3-week cycle, unless treatment is delayed for toxicity (Section 6). The treatment day may be advanced or postponed up to 3 days for scheduling convenience if necessary. The infusion length should be as close to 30 minutes as possible. However, given the variability of infusion pumps from site to site, a window of -5 minutes and +10 minutes is permitted (i.e., infusion time is 30 minutes: -5 min/+10 min). The dose will be the same for every patient.

No pre-hydration or hydration is necessary.

Pembrolizumab may be prepared per institutional standards.

The general instructions for study drug preparations can be found in the MK-3475 Pharmacy Manual. The drug will be provided as a solution for infusion, 100mg/vial. MK-3475 Solution for Infusion vials should be stored at refrigerated conditions (2 – 8 °C) and protected from light. Note: vials should be stored in the original box to ensure the drug product is protected from light. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration. Discard the drug product vial if opaque or extraneous particulate matter other than proteinaceous particles is observed. In addition, the following precautions should be observed:

- **Do not shake or freeze the vial(s).**
- **Do not administer the product as an intravenous (iv) push or bolus.**
- **Do not combine, dilute or administer it as an infusion with other medicinal products.**

5.3.1 Dose calculation

The dose on this trial is a flat dose of 200mg for all patients regardless of weight or body surface area.

5.3.2 Drug administration

Pembrolizumab infusions should be administered in 30 minutes, with a window of -5 and +10 minutes, using an infusion pump. A central catheter is not required for infusion; however if a subject has a central venous catheter in place, it is recommended that it be used for the infusion.

It is recommended that the infusion solution in the IV bag is used within 4 hours after preparation in order to maintain microbiological control and quality. The time for which the solution remains in the vial prior to preparation of the infusion solution should be counted in those 4 hours.

Use 30 mL normal saline to flush the infusion line at the end of infusion. If institutional guidelines do not allow the flushing of the infusion line at the completion of the infusion please prepare the specific volume of drug/diluent solution that is required to make up for the volume of the dosing solution lost in the infusion line.

For example if a 100 mL IV infusion bag will be prepared and it is known that 18mL will be left in the infusion line, the pharmacist should prepare 118 mL of drug solution in a 200 mL bag to make sure that 100 mL will be delivered to the patient.

- **Do not co-administer other drugs through the same infusion line.**
- **Unused infusion solution for injection should not be used for another infusion of the same subject or different subject.**

5.3.3 Infusion Reaction

The management of infusion reactions is given in Appendix E, Section 3.11.

5.4 General Concomitant Medication and Supportive Care Guidelines

5.4.1 Concomitant Medications/Vaccinations (Allowed & Prohibited)

The following concomitant treatments are prohibited during the treatment phase of this study:

- Antineoplastic chemotherapy or immunotherapy
- Radiotherapy
- Live vaccines within 30 days prior to starting treatment and while receiving study treatment.
- Immunosuppressive therapy, except for glucocorticoids intended to treat immune adverse events.

Nausea/vomiting: Nausea and vomiting should be treated aggressively, and consideration should be given in subsequent cycles to the administration of prophylactic antiemetic therapy according to standard institutional practice. Subjects should be strongly encouraged to maintain liberal oral fluid intake.

Infection: Subjects with a documented infectious complication should receive oral or IV antibiotics or other anti-infective agents as considered appropriate by the treating investigator for a given infectious condition, according to standard institutional practice.

5.4.2 Supportive Care Guidelines for Immune-Related Adverse Events (irAEs)

Immune-related adverse events (irAEs) may be defined as adverse events associated with drug exposure and consistent with an immune phenomenon without alternative explanation. irAEs may be predicted based on the nature of the pembrolizumab compound, its mechanism of action, and reported experience with immunotherapies that have a similar mechanism of action. Special attention should be paid to AEs that may be suggestive of potential irAEs. An irAE can occur shortly after the first dose or several months after the last dose of treatment.

If an irAE is suspected, efforts should be made to rule out neoplastic, infectious, metabolic, toxin or other etiologic causes prior to labeling an adverse event as an irAE. Subjects who develop a Grade 2 or higher irAEs should be discussed as soon as possible with the Overall PI.

Detailed guidelines for management of irAEs are provided in the irAE guidance document in Appendix E.

5.4.3 Contraception

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

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

Subjects should be informed that taking the study medication may involve unknown risks to the fetus (unborn baby) if pregnancy were to occur during the study. In order to participate in the study they must adhere to the contraception requirement described above. If there is any question

that a subject will not reliably comply with the requirements for contraception, that subject should not be entered into the study.

5.4.4 Use in Pregnancy

If a subject inadvertently becomes pregnant while on treatment with pembrolizumab, the subject will immediately be removed from the study. The site will contact the subject at least monthly and document the subject's status until the pregnancy has been completed or terminated. The 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 IRB and to Merck.

If a male subject impregnates his female partner the study personnel at the site must be informed immediately and the pregnancy reported to the IRB and to Merck and followed as described above.

5.4.5 Use in Nursing Women

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

5.5 Criteria for Taking a Participant Off Protocol Therapy

Duration of therapy will depend on individual response, evidence of disease progression and tolerance. Treatment may continue for 8 cycles or until one of the following criteria applies:

- Disease progression (in certain situations, treatment past disease progression may be acceptable, as per Section 5.8)
- Intercurrent illness that prevents further administration of treatment
- Unacceptable adverse event(s)
- Participant demonstrates an inability or unwillingness to comply with the oral medication regimen and/or documentation requirements
- Participant decides to withdraw from the protocol therapy
- General or specific changes in the participant's condition render the participant unacceptable for further treatment in the judgment of the treating investigator

Participants will be removed from the protocol therapy when any of these criteria apply. The reason for removal from protocol therapy, and the date the participant was removed, must be documented in the case report form (CRF). Alternative care options will be discussed with the participant.

In the event of unusual or life-threatening complications, treating investigators must immediately notify the Overall PI, Philippe Armand, MD, at 617 632 3352 (pager).

If a participant is taken off study treatment prior to the end of planned treatment (8 cycles) for reason other than death or disease progression, the participant should still have the week 10,

week 22, month 9, month 12 and month 18 assessments as described in Section 10 (Table 10.1) including tumor assessments, unless the participant has withdrawn consent for study.

5.6 Duration of Follow Up

Participants will be followed until 18 months after the day of stem cell reinfusion or until death, whichever occurs first. Participants removed from protocol therapy for unacceptable adverse event(s) will be followed until resolution or stabilization of the adverse event. All participants will be thereafter followed approximately every 6 months for survival and relapse only until 36 months from stem cell reinfusion, using telephone or email contact with the participant or his/her oncologist or transplant physician.

5.7 Criteria for Taking a Participant Off Study

Participants will be removed from study when any of the following criteria apply:

- Completion of all study activities
- Lost to follow-up
- Withdrawal of consent for data submission
- Death

The reason for taking a participant off study, and the date the participant was removed, must be documented in the case report form (CRF).

In addition, if a participant relapses or progresses during the course of the study, this participant will only be followed for survival thereafter, until 36 months from the date of stem cell reinfusion, as described in Section 5.6.

5.8 Treatment Past Disease Progression

It is now increasingly recognized that patterns of response may differ with immunotherapeutic anti-cancer agents, compared with patterns seen with conventional cytotoxic agents. In particular, in patients receiving checkpoint blockade therapy for solid tumors, the phenomenon of immune flare or pseudo-progression has been described; patients who experience pseudo-progression can still derive significant benefit from treatment. This has led to a modification of response criteria for patients with solid tumors treated with immunotherapy[19]. This has not yet been adapted to patients with hematologic malignancies. Nonetheless, the accumulating experience with PD-1 blockade in lymphoma suggests that this phenomenon can occur as well in this setting. Therefore, patients formally meeting criteria for disease progression at the week 10 restaging who otherwise appear to derive clinical benefit may continue treatment, as detailed below. This is consistent with ongoing trials of checkpoint blockade in lymphoma.

Specifically, subjects meeting progression defined by relapsed disease (after CR) or progressive disease (after PR, SD) per 2007 IWG criteria may continue receiving study medication beyond investigator-assessed progression as long as they meet the following criteria:

- Continue to meet all other study protocol eligibility criteria.

- Investigator-assessed clinical benefit and do not have rapid disease progression.
- Stable performance status.
- Treatment beyond progression will not delay an imminent intervention to prevent serious complications of disease progression.
- Tolerance of study drug.
- The decision to continue treatment beyond investigator-assessed progression should be discussed with the study chair and documented in the study records. The assessment of clinical benefit should take into account whether the subject is clinically deteriorating and unlikely to receive further benefit from continued treatment.

6. DOSING DELAYS/DOSE MODIFICATIONS (ESCALATION/TITRATION/OTHER)

There will be no dose modifications on this study. Dose delays will be made as indicated in the following table(s). The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for dose delays and dose modifications. A copy of the CTCAE version 4.0 can be downloaded from the CTEP website http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

If a participant is delayed but is subsequently able to resume treatment, then subsequent visits, assessments and treatments will continue every 3 weeks (unless the dosing interval is modified per Table 6.1) **from the time treatment has resumed until 8 cycles of therapy are completed.** For example, if cycle 4 is delayed 2 weeks and administered on week 12 instead of 10, cycle 5 and cycle 5 assessments should take place on week 15, cycle 6 on week 18, etc. The 9, 12, 15 and 18 month visits should still occur at the original time points (eg, 9 months from ASCT).

Pembrolizumab will be withheld for drug-related Grade 4 hematologic toxicities, non-hematological toxicity ≥ Grade 3 including laboratory abnormalities, and severe or life-threatening AEs as per Tables 6.1 and 6.2 below. Please note that any **immune-related AE should be managed as per the guidelines in Appendix E.** The tables below only apply to non-immune related AEs. If there is a question as to whether an AE is or is not immune-related, this should be discussed with the study chair.

Table 6.1. Dose Delay Guidelines for Hematological Drug-Related Adverse Events.

Toxicity	Grade	Hold Treatment (Y/N)	Timing for restarting treatment	Dose/Schedule for restarting	Discontinue Subject (after consultation with
Hematological Toxicity	1, 2, 3	No	N/A	N/A	N/A
	4	Yes	Toxicity resolves to Grade 0-1 or baseline	May increase the dosing interval by 1 week	Toxicity does not resolve within 12 weeks of last infusion *Permanent discontinuation should be considered for any*

Table 6.2. Dose Modification Guidelines for Non-Hematological Drug-Related Adverse Events.

Toxicity	Grade	Hold Treatment (Y/N)	Timing for restarting treatment	Dose/Schedule for restarting	Discontinue Subject (after
Non-hematological toxicity Note: Exceptions to be treated similar to Grade 1 toxicity Grade 2 alopecia Grade 2 fatigue For additional information regarding Adverse Events with a potential Immune-Etiology reference Section 5.	1	No	N/A	N/A	N/A
	2	Consider withholding for persistent symptoms	Toxicity resolves to Grade 0-1 or baseline	***Clinical AE resolves within 4 weeks*:** Same dose and schedule (See Section 5.4.3 for recommendations regarding pneumonitis)	Toxicity does not resolve within 12 weeks of last infusion
	3	Yes	Toxicity resolves to Grade 0-1 or baseline	May increase the dosing interval by 1 week for	Toxicity does not resolve within 12
	4	Yes	N/A	N/A	Subject is discontinue

For immune-related adverse events requiring treatment with corticosteroids, the subject may resume when toxicity resolves to Grade 0-1 or baseline AND the dose of steroids is less than or equal to 10 mg per day of prednisone or equivalent.

In case the toxicity does not resolve to Grade 0-1 within 12 weeks after last infusion, trial treatment should be discontinued after consultation with the Overall PI. For information on the management of specific adverse events, see Section 5.

If the dosing interval is increased according to the guidelines above, future treatments should continue on the increased dosing interval. The maximum dosing interval is 6 weeks. Participants should still receive 8 cycles regardless of treatment interval if they meet treatment criteria.

7. ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS

Adverse event (AE) monitoring and reporting is a routine part of every clinical trial. The following list of reported and/or potential AEs (Section 7.1) and the characteristics of an observed AE (Section 7.2) will determine whether the event requires expedited reporting **in addition** to routine reporting.

7.1 Expected Toxicities

Based on the experience with pembrolizumab to date, expected toxicities are listed below.

- Frequent (>10%): fatigue, rash/pruritus, diarrhea or constipation, nausea/vomiting, anorexia, cough, dyspnea, arthralgia, rash, headache, fever, back pain, anemia, and edema, thrombocytopenia, neutropenia.
- Occasional (1-10%): pneumonia, pleural effusion, pneumonitis, pulmonary embolism, colitis.
- Rare (<1%): , abdominal pain, kidney injury, hyponatremia, basal or squamous cell carcinoma, COPD, pericardial effusion, cellulitis, confusion, urinary tract infection, respiratory failure, sepsis, myocarditis, Stevens-Johnson's syndrome/Toxic Epidermal Necrolysis (TEN).

7.2 Adverse Event Characteristics

- **CTCAE term (AE description) and grade:** The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 4.0. A copy of the CTCAE version 4.0 can be downloaded from the CTEP web site http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

- **For expedited reporting purposes only:**
  - AEs for the agent(s) that are listed above should be reported only if the adverse event varies in nature, intensity or frequency from the expected toxicity information which is provided.
  - Other AEs for the protocol that do not require expedited reporting are outlined in the next section (Expedited Adverse Event Reporting) under the sub-heading of Protocol-Specific Expedited Adverse Event Reporting Exclusions.

- **Attribution** of the AE:
  - Definite – The AE *is clearly related* to the study treatment.
  - Probable – The AE *is likely related* to the study treatment.
  - Possible – The AE *may be related* to the study treatment.
  - Unlikely – The AE *is doubtfully related* to the study treatment.
  - Unrelated – The AE *is clearly NOT related* to the study treatment.

7.3 Adverse Event Reporting

7.3.1 In the event of an unanticipated problem or life-threatening complications treating investigators must immediately notify the Overall PI.

7.3.2 Investigators **must** report to the Overall PI any serious adverse event (SAE) that occurs after the initial dose of study treatment, during treatment, or within 30 days of the last dose of treatment on the local institutional SAE form.

7.3.3 For multi-institution studies where a DF/HCC investigator is serving as the Overall Principal Investigator, each participating institution **must** abide by the reporting requirements set by the DF/HCC. This applies to any medical event equivalent to an unexpected grade 2 or 3 with a possible, probable or definite attribution, unexpected grade 4 toxicities, and grade 5 (death) regardless of study phase or attribution.

7.3.4 DF/HCC Expedited Reporting Guidelines

Investigative sites within DF/HCC will report SAEs directly to the DFCI Office for Human Research Studies (OHRS) per the DFCI IRB reporting policy.

Other investigative sites will report SAEs to their respective IRB according to the local IRB's policies and procedures in reporting adverse events. A copy of the submitted institutional SAE form should be forwarded to the Overall PI and project manager at DFCI within the timeframes detailed in the table below.

Attribution	Table 7.1 DF/HCC Reportable AEs				
	Gr. 2 & 3 AE Expected	**Gr. 2 & 3 AE Unexpected**	**Gr. 4 AE Expected**	**Gr. 4 AE Unexpected**	**Gr. 5 AE Expected or Unexpected**
Unrelated Unlikely	Not required	Not required	5 calendar days[#]	5 calendar days	24 hours*
Possible Probable Definite	Not required	5 calendar days	5 calendar days[#]	5 calendar days	24 hours*
# If listed in protocol as expected and not requiring expedited reporting, event does not need to be reported.					
* For participants enrolled and actively participating in the study ***or*** for AEs occurring within 30 days of the last intervention, the AE should be reported within 1 business day of learning of the event.					

The Overall PI will submit SAE reports from outside institutions to the DFCI OHRS according to DFCI IRB policies and procedures in reporting adverse events.

7.4 Expedited Reporting to the Food and Drug Administration (FDA)

The Overall PI, as study sponsor, will be responsible for all communications with the FDA. The Overall PI will report to the FDA, regardless of the site of occurrence, any serious adverse event that meets the FDA's criteria for expedited reporting following the reporting requirements and timelines set by the FDA.

7.5 Expedited Reporting to Hospital Risk Management

Participating investigators will report to their local Risk Management office any participant safety reports or sentinel events that require reporting according to institutional policy.

7.6 Routine Adverse Event Reporting

All Adverse Events **must** be reported in routine study data submissions to the Overall PI on the toxicity case report forms. **AEs reported through expedited processes (e.g., reported to the IRB, FDA, etc.) must also be reported in routine study data submissions.**

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

For purposes of this trial, an overdose will be defined as any dose exceeding the prescribed dose for pembrolizumab by 20% over the prescribed dose. 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 a Merck product, the adverse event(s) is reported as a serious adverse event, even if no other seriousness criteria are met.

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

All reports of overdose with and without an adverse event must be reported within 1 business day to the Sponsor and within 2 business days to Merck Global Safety (Attn: Worldwide Product Safety; FAX 215 993-1220). Each participating site is responsible for reporting to Merck Global Safety.

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

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

Such events must be reported within 1 business day to the Sponsor and within 2 business days to Merck Global Safety (Attn: Worldwide Product Safety; FAX 215 993-1220). Each participating site is responsible for reporting to Merck Global Safety.

7.9 Immediate Reporting of Adverse Events to Merck

7.9.1 Serious Adverse Events

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

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

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 that occurs to any subject from the time the consent is signed through 90 days following cessation of treatment, or the initiation of new anti-cancer therapy, whichever is earlier, whether or not related to Merck product, must be reported within 1 business day to the Sponsor and within 2 business days to Merck Global Safety. Each participating site is responsible for reporting to Merck Global Safety.

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

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

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

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

7.9.2 Events of Clinical Interest

Selected non-serious and serious adverse events are also known as Events of Clinical Interest (ECI) and must be reported to the Sponsor.

For the time period beginning when the consent form is signed until treatment allocation/randomization, any ECI, or follow up to an ECI, that occurs to any subject must be reported within 24 hours to the Sponsor if it causes the subject to be excluded from the trial, or is the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure.

For the time period beginning at treatment allocation/randomization through 30 days following cessation of treatment, any ECI, or follow up to an ECI, whether or not related to the Sponsor's product, must be reported within 24 hours to the Sponsor, either by electronic media or paper. Electronic reporting procedures can be found in the EDC data entry guidelines. Paper reporting procedures can be found in the Investigator Trial File Binder (or equivalent).

Events of clinical interest for this trial include:

- An overdose of Sponsor's product, as defined in Section 7.2.2, that is not associated with

clinical symptoms or abnormal laboratory results.

- 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 that 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).

A separate guidance document has been provided entitled "Immune-Related Adverse Event Guidance Document." This document provides guidance regarding identification, evaluation and management of irAEs. Additional irAEs are identified in this guidance document and also need to be reported to the Sponsor within 24 hours and to Merck Global Safety within 2 working days of the event.

Subjects should be assessed for possible ECIs and irAEs 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 AE 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 AE, 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.

Serious irAEs that occur in any subject from the date of first dose through 90 days following cessation of treatment, or the initiation of a new anticancer therapy, whichever is earlier, whether or not related to the Merck's product, must be reported within 24 hours to the Sponsor and to Merck Global Safety within 2 working days.

8. PHARMACEUTICAL INFORMATION

A list of the adverse events and potential risks associated with the investigational agent administered in this study can be found in Section 7.1. For details please refer to the Investigator's Brochure.

8.1 Pembrolizumab

8.1.1 Chemical Properties

Pembrolizumab is a humanized anti-PD-1 mAb of the IgG4/kappa isotype with a stabilizing S228P sequence alteration in the fragment crystallizable (Fc) region. Pembrolizumab binds to human PD-1 and blocks the interaction between PD-1 and its ligands. For additional information, please consult the Investigator's Brochure.

8.1.2 Physico-Chemical Properties

Pembrolizumab drug substance is an aqueous solution stored under refrigerated conditions at a concentration of ≥35 mg/mL in 10 mM Histidine buffer, pH 5.0-6.0. The drug substance is a clear to opalescent solution and may contain particulates.

8.1.3 Pharmaceutical Formulation, Storage and Stability

Pembrolizumab is provided as a white to off-white lyophilized powder in Type I glass vials intended for single use only. Pembrolizumab is formulated with L-histidine as buffering agent, polysorbate 80 as surfactant, sucrose as stabilizer/tonicity modifier, and hydrochloric acid (HCl) and/or sodium hydroxide (NaOH) for pH adjustment (if necessary). Storage including allowed temperature excursions should follow standard procedures.

8.1.4 Handling

Qualified personnel, familiar with procedures that minimize undue exposure to themselves and the environment, should undertake the preparation, handling, and safe disposal of the chemotherapeutic agent in a self-contained and protective environment.

8.1.5 Availability

Pembrolizumab will be provided by Merck directly to the participating centers. Clinical Supplies will be provided by Merck as summarized in Table 8.1. Study drug request form with instructions for ordering will be provided to each participating site. For any commercially available product that is provided by the trial site, subsidiary or designee every attempt will be made to source these supplies from a single lot/batch number. The trial site will be responsible for recording the lot number, manufacturer and expiry date of any locally purchased product.

Table 8.1 Product Descriptions

Product Name & Potency	Dosage Form
MK-3475 100 mg/ 4mL	Solution for Injection

8.1.6 Packaging and Labeling information

Clinical supplies will be affixed with a clinical label in accordance with regulatory requirements. Vials will be provided in an open label fashion for subject dosing.

8.1.7 Clinical Supplies Disclosure

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

8.1.8 Preparation and administration

Please refer to Section 5 for details.

8.1.9 Accountability

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. The investigator, or a responsible party designated by the investigator, should maintain a careful record of the inventory and disposition of the agent using the NCI Drug Accountability Record Form (DARF) or another comparable drug accountability form. See the NCI Investigator's Handbook for Procedures for Drug Accountability and Storage.

8.1.10 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.

8.1.11 Returns and Reconciliation

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

For all trial sites, the local country Sponsor personnel or designee will provide appropriate documentation that must be completed for drug accountability and return.

9. BIOMARKER, CORRELATIVE, AND SPECIAL STUDIES

The correlative studies described below are meant to be exploratory, in order to better understand the biology and clinical relevance of the PD-1 pathway in cHL and DLBCL. Various assessments will be performed on tumor and peripheral blood (PB) samples, as discussed below. Some of the results will be correlated with outcome (progression-free survival). These studies are not powered for statistical significance, and are only meant for exploratory purposes to generate hypotheses that may be tested in future studies. Furthermore, it is anticipated that the exact nature of the studies may change during the course of the study as new techniques currently in development come on-line. The following therefore do not necessarily represent an exhaustive list.

Whenever possible, the archival tissue from pre-ASCT tumor biopsies will be retrieved. For patients who relapsed after first line therapy, the preferred source of archival tissue would be a post-relapse biopsy, but if this is not available the diagnostic biopsy will be used instead. If the tumor block is not available, unstained slides will be used, preferably at least 8 slides. The tumor

specimens will be stained for PD-L1, PD-L2, PD-1, with evaluation of those markers on both tumor cells and on the microenvironment. The tumors will also be tested for:

- EBV RNA expression, given the data showing that latent EBV infection is one of the mechanisms of PD-L1 overexpression;
- Phospho-STAT3, as a surrogate marker of JAK-2 pathway activation, given the data showing that in cHL JAK-2 is one of the drivers for PD-L1 expression;
- Amplification of PD-L1 and PD-L2 by FISH, which may provide information on 9p24 amplification or on translocations involving one or the other ligand.
- Multiparameter evaluation of the inflammatory immune infiltrate, especially in HL, as the phenotype of the immune micro-environment could be a better representation of pembrolizumab target than the tumor itself.

In addition, serial PB samples obtained pre-ASCT, post-ASCT/pre-treatment, on-treatment, and post-treatment will be used to monitor immune reconstitution and pembrolizumab target cell population using multiparameter flow cytometry, for various lymphocyte subsets including PD-L1 and PD-L2 bearing lymphocytes. If this becomes feasible in our laboratory, we will also measure soluble PD-L1 in those samples, given recent data suggesting an association with outcome in DLBCL[20]. Samples may be tested for the presence of minimal residual disease (MRD) either through a commercial platform (ClonoSeq®, Adaptive, Seattle WA) or through a collaboration with Stanford University (Dr. Ash Alizadeh). In all cases, samples will be deidentified prior to sending out for testing.

10. STUDY CALENDAR

In the event that the participant's condition is deteriorating, laboratory evaluations should be repeated within 48 hours prior to initiation of the next cycle of therapy.

Assessments must be performed prior to administration of any study agent. Study assessments and agents should be administered within $\pm$ 3 days of the protocol-specified date, unless otherwise noted.

Table 10.1 Study Calendar

		Study Treatment period								**Follow-up period**			
		Treatment Cycle								Months from ASCT[c]			
		1	2	3	4	5	6	7	8				
		Week[b]											
	Screening[a]	1	4	7	10	13	16	19	22	9	12	15	18
Pembrolizumab		**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**				
Informed consent	X												
Demographics	X												
Medical history	X												
Concurrent meds	X	X----------X											
Adverse event Evaluation		X----------X											
Physical exam	X	X	X	X	X	X	X	X	X	X	X	X	X
Vital signs	X[i]	X	X	X	X	X	X	X	X	X	X	X	X
Height	X												
Weight	X	X	X	X	X	X	X	X	X				X
Performance status	X	X	X	X	X	X	X	X	X				X
CBC w/diff, plts	X	X	X	X	X	X	X	X	X	X	X	X	X
Serum chemistry[d]	X	X	X	X	X	X	X	X	X	X	X	X	X
TSH	X		X		X		X		X		X		X
Infectious Disease Markers	X[h]												
B-HCG (serum or urine)	X												
EKG	X												
Pulmonary function tests[e]	X												
PET-CT[f]	X				X				X		X		X
Whole blood collection 2 tubes (Research sample)[g]			X	X			X						
Whole blood collection 4 tubes (Research sample)[g]		X			X				X		X		X

a: Participants enrolled prior to ASCT must be re-screened and meet all eligibility criteria after transplantation. Participants must receive their first treatment (Week 1 visit) within 21 days of post-ASCT hospital discharge (See Section 3.1), unless discussed and approved by the Overall PI. Screening studies should be obtained within 14 days of cycle 1, except for imaging which should be obtained within 21 days of cycle 1.

b: Week 1 is defined as the first week of study treatment. All dates are +/- 3 days to accommodate scheduling needs.

c: Months are counted from the day of stem cell reinfusion ("day 0"), regardless of the timing of study treatment. All dates are +/- 4 weeks to accommodate scheduling needs.

d: Albumin, alkaline phosphatase, total bilirubin, bicarbonate, BUN, calcium, chloride, creatinine, glucose, LDH, potassium, total protein, SGOT [AST], SGPT [ALT], sodium.

e: To include spirometry, lung volume measurements and diffusion capacity measurement.

f: See Section 11 for details

g: See Section 10.4

h: Hepatitis B sAg, cAb; Hepatitis C antibody; HepB or HepC viral loads only if serologies positive. Prior results can be used if available within 120 days of starting study treatment.

i: Including ambulatory oxygen saturation

10.1 Screening Visit

Participants enrolled prior to ASCT must be re-screened and meet all eligibility criteria after transplantation. They will also be re-consented at that time. Participants must receive their first treatment (Week 1 visit) within 21 days of post-ASCT hospital discharge, and must have recovered from ASCT toxicities (See Section 3.1), unless discussed and approved by the Overall PI. Screening studies may be obtained on the 1st day of planned treatment, provided that eligibility is confirmed prior to treatment. At the time of screening, participants will have laboratory evaluation (See Table 10.1), EKG, and pulmonary function testing.

10.2 On-Treatment Evaluations

Note that treatment weeks are counted from the 1st day of drug treatment, which is Week 1. This should be within 21 days (preferably within 14 days) of post-ASCT discharge (See Section 3.1). At each treatment visit (week 1, 4, 7, 10, 13, 16, 19 and 22), participants will have an assessment for adverse events, review of concomitant medications, and a physical exam. Laboratory evaluations will be conducted as per Table 10.1. Labs should be drawn within 24 hours prior to study drug administration on the days of treatment.

10.3 Follow-up Evaluations

Following the last study treatment, participants will be followed at 9, 12, 15, and 18 months, counted from the day of stem cell reinfusion. At each follow-up visit, participants will have an assessment for adverse events, review of concomitant medications, and a physical exam. Laboratory evaluations will be conducted as per Table 10.1.

10.4 Research sample collection

At the week 1, 4, 7, 10, 16 and 22 on-treatment visits, as well as at the 12 and 18 month follow-up visits, participants will have a peripheral blood sample drawn for research. This should be collected in 2 large lavender-top (K2 EDTA) tubes of approximately 10 ml blood each. At the week 1, 10, 22 on-treatment visit as well as at the 12 and 18 months follow-up visits, two more tubes (4 total) (large lavender top K2 EDTA, approximately 10cc) should be collected. These research tubes will be sent fresh to the laboratory of Jerome Ritz, MD, at the address below, to be used for correlative analyses.

For outside sites, the samples will be sent overnight at around +4C with a refrigerated cool pack in an appropriate contained to the address below. Please note that the samples can only be received Mon-Fri, so should only be sent Mon-Thu. For any shipment, the sending site should have the FED EX # e-mailed upon shipment to DFCIPasquarelloLab@DFCI.harvard.edu. In addition, the samples should be accompanied by a form listing the study ID, the protocol number, the date of collection, the study time point, **as well as a copy of the latest CBC results (with differential) and the date of the test.**

Samples will be stored for up to 10 years following the end of the study. Philippe Armand, MD, PhD will be the administrator. Forms for investigator and non-investigator sample use request

are attached as Appendices C and D, respectively. Requests for samples from non-study investigators will be granted only if they fall within the scope of this study. If they do not, the samples will not be released without IRB approval.

Shipping address:
Doreen Hearsey/Pasquarello Tissue Lab
Dana-Farber Cancer Institute
Smith Receiving
1 Jimmy Fund Way, DA-L181A
Boston, MA 02115

Please note that samples should only be sent from outside sites on Monday-Thursday for receipt Tuesday-Friday.

10.5 Tumor sample collection

There are no mandatory biopsies on this trial. However, whenever possible archival tumor tissue will be used for correlative studies. In addition, for patients who progress or relapse after ASCT, a confirmatory biopsy is strongly encouraged. Unstained slides (preferably 15, and at least 8) from the latest available pre-transplant archival tissue should be sent to the overall PI at the address below. In addition, unstained slides (preferably 15, and at least 8) from any biopsy obtained after transplantation for relapse/progression should also be sent when available.

Shipping address:

Rohini Loke
Dana-Farber Cancer Institute
450 Brookline Avenue
Boston, MA 02215
Phone: 617-632-2328

11. MEASUREMENT OF EFFECT

Participants on this study will have a tumor measurement by PET-CT scan at baseline, weeks 10 and 22 on treatment, and at 12 and 18 months in the follow-up period. PET and CT may be co-acquired or acquired separately. Additional necessary restaging studies including dedicated CT scans, MRI, or bone marrow biopsies, are permitted at the investigator's discretion. Response and progression will be evaluated following the International Harmonization Project criteria (IHP)[16].

The baseline assessment should be obtained within the 21 days preceding first treatment, and may be obtained on the day of treatment prior to study drug administration. If a PET-CT cannot be obtained at this time point, a diagnostic quality CT scan of the neck, chest, abdomen and pelvis is acceptable per protocol. At all other time points, if PET-CT cannot be obtained, obtaining instead diagnostic quality CT scans of neck, chest, abdomen and pelvis is acceptable per protocol, as long as the last PET-CT showed complete remission; if that is not the case,

obtaining a CT scan instead of a PET scan will constitute a minor violation. Regardless, PET-CT should be obtained at all time points if at all possible.

All scans should be sent to Dana-Farber (at the address below), so that a centralized response assessment can be made. CDs and shipping supplies will be provided by DFCI.

For patients with progression of disease on imaging, it is strongly recommended that a confirmatory biopsy be obtained whenever possible. Note that an FDG-negative PET scan will only be considered complete remission in patients whose tumor was FDG-avid at baseline.

For all study-required tumor imaging, and for the post-salvage, pre-ASCT PET scan, a disc copy of the images should be sent to the Overall PI.

Shipping address:

Samantha Pazienza
Dana Farber Cancer Institute
450 Brookline Avenue
Boston, MA 02215
Phone: 617-632-232

12. DATA REPORTING / REGULATORY REQUIREMENTS

Adverse event lists, guidelines, and instructions for AE reporting can be found in Section 7.0 (Adverse Events: List and Reporting Requirements).

12.1 Data Reporting

12.1.1 Method

The Office of Data Quality (ODQ) will collect, manage, and perform quality checks on the data for this study.

12.1.2 Responsibility for Data Submission

Investigative sites within DF/HCC or DF/PCC are responsible for submitting data and/or data forms to the Office of Data Quality (ODQ) in accordance with DF/HCC policies.

12.1.3 Data Safety Monitoring

The DF/HCC Data and Safety Monitoring Committee (DSMC) will review and monitor toxicity and accrual data from this study. The committee is composed of clinical specialists with experience in oncology and who have no direct relationship with the study. Information that raises any questions about participant safety will be addressed with the Overall PI and study team.

The DSMC will review each protocol up to four times a year or more often if required to review toxicity and accrual data. Information to be provided to the committee may include: up-to-date participant accrual; current dose level information; DLT information; all grade 2 or higher unexpected adverse events that have been reported; summary of all deaths occurring with 30 days of intervention for Phase I or II protocols; for gene therapy protocols, summary of all deaths while being treated and during active follow-up; any response information; audit results, and a summary provided by the study team. Other information (e.g. scans, laboratory values) will be provided upon request.

12.2 Multicenter Guidelines

This protocol will adhere to the policies and requirements of the DF/HCC Multi-Center Data and Safety Monitoring Plan. The specific responsibilities of the Overall PI, Coordinating Center, and Participating Institutions and the procedures for auditing are presented in Appendix B.

- The Overall PI/Coordinating Center is responsible for distributing all IND Action Letters or Safety Reports to all participating institutions for submission to their individual IRBs for action as required.

- Mechanisms will be in place to ensure quality assurance, protocol compliance, and adverse event reporting at each site.

- Except in very unusual circumstances, each participating institution will order the study agent(s) directly from supplier. A participating site may order the agent(s) only after the initial IRB approval for the site has been forwarded to the Coordinating Center.

13. STATISTICAL CONSIDERATIONS

13.1 Study Design/Endpoints

This study is a 3-arm, open-label, phase II clinical trial. The primary endpoint is the 18-month progression-free survival (PFS) rate after ASCT in each cohort. PFS is defined as time from ASCT to disease progression (relapse from CR or progressive disease [PD] from PR, all defined according to IHP criteria) or death whichever occurs first. Secondary endpoints include18-month overall survival (OS), cumulative incidence of relapse, response, toxicity for all patients as well as in the high-risk subset of patients not in PET-CR prior to ASCT, and response rate to pembrolizumab in patients with measurable disease after ASCT (based on tumor imaging obtained at screening).

13.2 Sample Size for cHL and DLBCL (Arms A and B)

Based on published studies and our own published and unpublished analyses, the expected 18-month PFS rate after ASCT in patients with chemosensitive R/R cHL or DLBCL is around 50-60%. This figure is similar for cHL and DLBCL patients. We thus hypothesize that consolidation treatment with pembrolizumab will result in improvement of the 18-month PFS rate to 80%. The desired sample size is 30 patients in the cHL arm and 30 in the DLBCL arm.

We would consider the treatment promising on either arm if at least 22 patients remain alive and progression-free at 18 month post-ASCT. For this analysis, patients lost to follow-up before the 18 month time point will be considered treatment failures. With this design, the probability of considering the treatment promising on a given arm is 0.09 if the true but unknown progression-free rate is 60% (null hypothesis), and 0.87 if the true but unknown progression-free rate is 80% (alternative hypothesis). This decision rule is calculated using the exact binomial method. Table 13.1 below presents the operating characteristics of this design.

Table 13.1 Operating Characteristics

	True but unknown PFS rate at 18 months post ASCT				
	0.6	0.65	0.7	0.75	0.8
Prob. treatment is promising (≥22 out of 30 patients)	0.094	0.225	0.432	0.674	0.871

13.3 Sample Size for T-NHL (Arm C)

The study is amended to include an arm for patients with T-NHL receiving ASCT in 1st remission. Based on the current practice, the expected 18-month PFS rate after ASCT in patients with chemosensitive T-NHL is around 40-50% and we hypothesize that consolidation treatment with pembrolizumab will result in improvement of the 18-month PFS rate to 70%. The sample size is 21 patients. We would consider the treatment promising if at least 13 patients remain alive and progression-free at 18 month post-ASCT. With this design, the probability of considering the treatment promising in treating R/R T-NHL is 0.09 if the true but unknown progression-free rate is 45%, and 0.85 if the true but unknown progression-free rate is 70%. This decision rule is calculated using the exact binomial method. Table 13.2 below presents the operating characteristics of this design.

Table 13.2 Operating Characteristics

	True but unknown PFS rate at 18 months post ASCT					
	0.45	0.5	0.55	0.6	0.65	0.7
Prob. treatment is promising (≥13 out of 21 patients)	0.091	0.192	0.341	0.524	0.706	0.852

13.4 Toxicity monitoring

Close and continuous monitoring for toxicity will occur throughout the study duration per institutional standards. Of the first 10 patients in each arm who receive at least one cycle of the treatment, if 3 or more experience grade 3 or higher toxicity that is at least possibly attributed to study drug, enrollment will be suspended and the data will be reviewed by the DSMC. With this design, if the true but unknown rate of grade 3 or higher toxicity that is related to the study drug is 10%, the probability of early stopping is 0.07 and 0.74 if the rate is 35%. If the study completes with a total of 30 patients in cHL or DLBCL arm, the 90% confidence interval of

grade 3 or higher related toxicity rate will be within ±16%. If the T-NHL arm completes with 21 patients, the 90% confidence interval of grade 3 or higher related toxicity rate will be (33%, 71%). The stopping guidelines serve as a trigger for consultation with the sponsor and the DSMC for additional review, and are not formal stopping rules that would mandate automatic closure of study enrollment.

13.5 Accrual

With an anticipated accrual of 4 patients per month for DLBCL, 2 per month for HL, and 2 per month for T-NHL based on historical rates, accrual should complete in <18 months. With a follow-up of 18 months from ASCT for the last patient enrolled (for the primary endpoint), the total anticipated study time will be approximately 36 months to primary endpoint.

13.6 Stratification Factors

N/A

13.7 Analysis of Primary Endpoints

See Section 13.2. To estimate the PFS, the Kaplan Meier estimate will be used. Patients who are lost to follow-up before the 18 month endpoint without documentation of relapse, progression or death will be censored at the time of last follow-up for the primary analysis. However, we will also perform a sensitivity analysis in which those patients will be counted as failure events for PFS.

13.8 Analysis of Secondary Endpoints

PFS and OS will be estimated for the entire cohort in each arm, as well as in the subgroups of 1) participants who were PET-positive versus PET-negative after salvage therapy, and 2) participants whose tumor demonstrated over-expression of PD-L1 or PD-L2 by immunohistochemistry. The subgroup analyses are exploratory and mainly descriptive. PFS and OS will be estimated using the Kaplan-Meier method. Cumulative incidence of relapse will be estimated using a competing risks method, considering non-relapse mortality as a competing risk. All reported serious adverse events potentially associated with study drug will be carefully examined with respect to the severity and relationship to study drug. The incidence of SAEs will be calculated for the entire cohort and within each arm. Toxicity and response rates will be analyzed and reported using descriptive statistics and 90% confidence intervals.
Laboratory tests will be performed during the study. Descriptive statistics will be calculated for each of the major laboratory tests. Abnormal laboratory test results will be summarized in the report.

13.9 Reporting and Exclusions

The primary analyses will be on a modified intent-to-treat basis, considering all patients who are enrolled on study and receive at least 1 dose of study drug. Patients who enroll on study but are discontinued from study before receiving the first dose of study drug will be unevaluable for the

primary endpoint and will be replaced to achieve a sample size of 30 or 21 *treated* patients in cHL/DLBCL or T-NHL arm, respectively.

14. PUBLICATION PLAN

The results should be made public within 24 months of reaching the end of the study. The end of the study is the time point at which the last data items are to be reported, or after the outcome data are sufficiently mature for analysis, as defined in the section on Sample Size, Accrual Rate and Study Duration. If a report is planned to be published in a peer-reviewed journal, then that initial release may be an abstract that meets the requirements of the International Committee of Medical Journal Editors. A full report of the outcomes should be made public no later than three (3) years after the end of the study.

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APPENDIX A PERFORMANCE STATUS CRITERIA

ECOG Performance Status Scale		**Karnofsky Performance Scale**	
Grade	Descriptions	Percent	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.	100	Normal, no complaints, no evidence of disease.
		90	Able to carry on normal activity; minor signs or symptoms of disease.
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).	80	Normal activity with effort; some signs or symptoms of disease.
		70	Cares for self, unable to carry on normal activity or to do active 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.	60	Requires occasional assistance, but is able to care for most of his/her needs.
		50	Requires considerable assistance and frequent medical care.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.	40	Disabled, requires special care and assistance.
		30	Severely disabled, hospitalization indicated. Death not imminent.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.	20	Very sick, hospitalization indicated. Death not imminent.
		10	Moribund, fatal processes progressing rapidly.
5	Dead.	0	Dead.

APPENDIX B DANA-FARBER HARVARD CANCER CENTER, MULTI-CENTER DATA AND SAFETY MONITORING

1 INTRODUCTION

The Dana-Farber/Harvard Cancer Center Multi-Center Data and Safety Monitoring Plan (DF/HCC DSMP) outlines the procedures for conducting a DF/HCC Multi-Center research protocol. The DF/HCC DSMP serves as a reference for any sites external to DF/HCC that are participating in a DF/HCC clinical trial.

1.1 Purpose

To establish standards that will ensure that a Dana-Farber/Harvard Cancer Center Multi-Center protocol will comply with Federal Regulations, Health Insurance Portability and Accountability Act (HIPAA) requirements and applicable DF/HCC Policies and Operations.

2 GENERAL ROLES AND RESPONSIBILITIES

For DF/HCC Multi-Center Protocols, the following general responsibilities apply, in addition to those outlined in DF/HCC Policies for Sponsor-Investigators:

2.1 Coordinating Center

The general responsibilities of the Coordinating Center may include but are not limited to:

- Assist in protocol development.
- Maintain FDA correspondence, as applicable.
- Review registration materials for eligibility and register participants from Participating Institutions in the DF/HCC clinical trial management system (CTMS).
- Distribute protocol and informed consent document updates to External Sites as needed.
- Oversee the data collection process from External Sites.
- Maintain documentation of Serious Adverse Event (SAE) reports and deviations/violation submitted by External Sites and provide to the DF/HCC Sponsor for timely review and submission to the IRB of record, as necessary.
- Distribute serious adverse events reported to the DF/HCC Sponsor that fall under the reporting requirements for the IRB of record to all External Sites.
- Provide External Sites with information regarding DF/HCC requirements that they will be expected to comply with.
- Carry out plan to monitor External Sites either by on-site or remote monitoring.
- Maintain Regulatory documents of all External Sites which includes but is not limited to the following: local IRB approvals/notifications from all External Sites, confirmation of Federalwide Assurances (FWAs) for all sites, all SAE submissions, Screening Logs for all sites, IRB approved consents for all sites
- Conduct regular communications with all External Sites (conference calls, emails, etc) and maintain documentation all relevant communications.

2.2 External Site

An External Site is an institution that is outside the DF/HCC and DF/PCC consortium that is collaborating with DF/HCC on a protocol where the sponsor is a DF/HCC investigator. The External Site acknowledges the DF/HCC Sponsor as having the ultimate authority and responsibility for the overall conduct of the study.

Each External Site is expected to comply with all applicable DF/HCC requirements stated within this Data and Safety Monitoring Plan and/or the protocol document.

The general responsibilities for each External Site may include but are not limited to:

- Document the delegation of research specific activities to study personnel.
- Commit to the accrual of participants to the protocol.
- Submit protocol and/or amendments to their IRB of record. For studies under a single IRB, the Coordinating Center will facilitate any study-wide submissions..
- Maintain regulatory files as per ICH GCP and federal requirements.
- Provide the Coordinating Center with regulatory documents or source documents as requested.
- Participate in protocol training prior to enrolling participants and throughout the trial as required.
- Update Coordinating Center with research staff changes on a timely basis.
- Register participants through the Coordinating Center prior to beginning research related activities when required by the sponsor.
- Submit Serious Adverse Event (SAE) reports to sponsor, Coordinating Center, and IRB of record as applicable, in accordance with DF/HCC requirements.
- Submit protocol deviations and violations to the Sponsor, Coordinating Center, and IRB of record as applicable..
- Order, store and dispense investigational agents and/or other protocol mandated drugs per federal guidelines and protocol requirements.
- Participate in any quality assurance activities and meet with monitors or auditors at the conclusion of a visit to review findings.
- Promptly provide follow-up and/or corrective action plans for any monitoring queries or audit findings.
- Notify the sponsor immediately of any regulatory authority inspection of this protocol at the External Site.

3 DF/HCC REQUIREMENTS FOR MULTI-CENTER PROTOCOLS

Certain DF/HCC Policy requirements apply to External Sites participating in DF/HCC research. The following section will clarify DF/HCC requirements and further detail the expectations for participating in a DF/HCC Multi-Center protocol.

3.1 Protocol Revisions and Closures

The External Sites will receive notification of protocol revisions and closures from the Coordinating Center. When under a separate IRB, it is the individual External Site's responsibility to notify its IRB of these revisions.

- **Protocol revisions:** External Sites will receive written notification of protocol revisions from the Coordinating Center. All protocol revisions should be IRB approved and implemented within a timely manner from receipt of the notification.

- **Protocol closures and temporary holds:** External Sites will receive notification of protocol closures and temporary holds from the Coordinating Center. Closures and holds will be effective immediately. In addition, the Coordinating Center, will update the External Sites on an ongoing basis about protocol accrual data so that they will be aware of imminent protocol closures.

3.2 Informed Consent Requirements

The DF/HCC approved informed consent document will serve as a template for the informed consent for External Sites. The External Site consent form must follow the consent template as closely as possible and should adhere to specifications outlined in the DF/HCC Guidance Document on Model Consent Language for Investigator-Sponsored Multi-Center Trials. This document will be provided separately to each External Site upon request.

External Sites must send their version of the informed consent document to the Coordinating Center for sponsor review and approval. If the HIPAA authorization is a separate document, please submit to the sponsor for the study record. Once sponsor approval is obtained, the External site may submit to their IRB of record, as applicable. In these cases, the approved consent form must also be submitted to the Coordinating Center after approval by the local IRB for all consent versions.

The Principal Investigator (PI) at each External Site will identify the appropriate members of the study team who will be obtaining consent and signing the consent form for protocols. External Sites must follow the DF/HCC requirement that for all interventional drug, biologic, or device research, only attending physicians may obtain initial informed consent and any re-consent that requires a full revised consent form.

3.3 IRB Re-Approval

Verification of IRB re-approval for the External Sites is required in order to continue research activities. There is no grace period for continuing approvals.

The Coordinating Center will not register participants if a re-approval letter is not received for the External Site on or before the anniversary of the previous approval date.

3.4 DF/HCC Multi-Center Protocol Confidentiality

All documents, investigative reports, or information relating to the participant are strictly confidential. Whenever reasonably feasible, any participant specific reports (i.e. Pathology Reports, MRI Reports, Operative Reports, etc.) submitted to the Coordinating Center should be de-identified. It is recommended that the assigned protocol case number be used for all participant specific documents. Participant initials may be included or retained for cross verification of identification.

3.5 Participation Registration

To register a participant, the following documents should be completed by the External Site and emailed to the Coordinating Center:

Samantha Pazienza
Dana-Farber Cancer Institute
450 Brookline Ave, BP1150
Boston, MA 02215
Samantha_Pazienza@DFCI.HARVARD.EDU
Phone: 617-632-2328

- Copy of all relevant medical records
- Signed informed consent document
- HIPAA authorization form (if separate from the informed consent document)
- Completed DFCI Eligibility Checklist

The Coordinating Center will review the submitted documents in order to verify eligibility and consent. To complete the registration process, the Coordinating Center will:

- Register the participant on the study with the DF/HCC Clinical Trial Management System (CTMS).
- Upon receiving confirmation of registration, the Coordinating Center will inform the External Site and provide the study specific participant case number, and if applicable, assigned treatment and/or dose level.

At the time of registration, the following identifiers are required for all subjects: initials, date of birth, gender, race and ethnicity. Once eligibility has been established and the participant successfully registered, the participant is assigned a unique protocol case number. External Sites should submit all de-identified subsequent communication and documents to the Coordinating Center, using this case number to identify the subject.

3.5.1 Initiation of Therapy

Participants must be registered with the DF/HCC CTMS before the initiation of treatment or other protocol-specific interventions. Treatment and other protocol-specific interventions may not be initiated until the External Site receives confirmation of the participant's registration from

the Coordinating Center. The DF/HCC Sponsor and IRB of record must be notified of any violations to this policy.

3.5.2 Eligibility Exceptions

No exceptions to the eligibility requirements for a protocol without IRB approval will be permitted. All External Sites are required to fully comply with this requirement. The process for requesting an eligibility exception is defined below.

3.6 Data Management

DF/HCC develops case report forms (CRF/eCRFs), for use with the protocol. These forms are designed to collect data for each study. DF/HCC provides a web based training for all eCRF users.

3.6.1 Data Forms Review

Data submissions are monitored for timeliness and completeness of submission. If study forms are received with missing or questionable data, the submitting institution will receive a written or electronic query from the DF/HCC Office of Data Quality, Coordinating Center, or designee.

Responses to all queries should be completed and submitted within 14 calendar days.

If study forms are not submitted on schedule, the External Sites will periodically receive a Missing Form Report from the Coordinating Center noting the missing forms.

3.7 Protocol Reporting Requirements

3.7.1 Protocol Deviations, Exceptions and Violations

Federal Regulations require an IRB to review proposed changes in a research activity to ensure that researchers do not initiate changes in approved research without IRB review and approval, except when necessary to eliminate apparent immediate hazards to the participant. DF/HCC requires all departures from the defined procedures set forth in the IRB approved protocol to be reported to the DF/HCC Sponsor and to the IRB of record.

3.7.2 Reporting Procedures

Requests to deviate from the protocol require approval from the IRB of record and the sponsor.

All protocol violations must be sent to the Coordinating Center in a timely manner. The Coordinating Center will provide training for the requirements for the reporting of violations.

3.7.3 Guidelines for Processing IND Safety Reports

The DF/HCC Sponsor will review all IND Safety Reports per DF/HCC requirements, and ensure that all IND Safety Reports are distributed to the External Sites as required by DF/HCC Policy. External Sites will review/submit to the IRB according to their institutional policies and procedures.

4 MONITORING: QUALITY CONTROL

The Coordinating Center, with the aid of the DF/HCC Office of Data Quality, provides quality control oversight for the protocol.

4.1 Ongoing Monitoring of Protocol Compliance

The External Sites may be required to submit participant source documents to the Coordinating Center for monitoring. External Sites may also be subject to on-site monitoring conducted by the Coordinating Center.

The Coordinating Center will implement ongoing monitoring activities to ensure that External Sites are complying with regulatory and protocol requirements, data quality, and participant safety. Monitoring practices may include but are not limited to source data verification, and review and analysis of eligibility requirements, informed consent procedures, adverse events and all associated documentation, review of study drug administration/treatment, regulatory files, protocol departures reporting, pharmacy records, response assessments, and data management.

Participating institutions will be required to participate in regular Coordinating Center initiated teleconferences.

On-Site Monitoring: External Sites will be required to participate in annual on-site monitoring visits. At this time, source documentation verification (SDV) will be conducted by having access to participants' complete medical record and source documents. Access to the site regulatory binder and site's pharmacy records will also be required.

Remote Monitoring: External Sites will be required to forward de-identified copies of participants' eligibility packets and informed consent documents to the Coordinating Center to aid in source data verification within 30 days of subject enrollment. Source verification of case report form data will occur remotely approximately every 6 months. At the time of visit, participating institutions will be required to forward de-identified copies of the participant's medical record to the Coordinating Center for review.

4.2 Monitoring Reports

The DF/HCC Sponsor will review all monitoring reports to ensure protocol compliance. The DF/HCC Sponsor may increase the monitoring activities at External Sites that are unable to comply with the protocol, DF/HCC Sponsor requirements or federal and local regulations.

4.3 Accrual Monitoring

Prior to extending a protocol to an external site, the DF/HCC Sponsor will establish accrual requirements for each External Site. Accrual will be monitored for each External Site by the DF/HCC Sponsor or designee. Sites that are not meeting their accrual expectations may be subject to termination.

5 AUDITING: QUALITY ASSURANCE

5.1 DF/HCC Internal Audits

All External Sites are subject to audit by the DF/HCC Office of Data Quality (ODQ). Typically, approximately 3-4 participants would be audited at the site over a 2-day period. If violations which impact participant safety or the integrity of the study are found, more participant records may be audited.

5.2 Audit Notifications

It is the External Site's responsibility to notify the Coordinating Center of all external audits or inspections (e.g., FDA, EMA, NCI) that involve this protocol. All institutions will forward a copy of final audit and/or re-audit reports and corrective action plans (if applicable) to the Coordinating Center, within 12 weeks after the audit date.

5.3 Audit Reports

The DF/HCC Sponsor will review all final audit reports and corrective action plans, if applicable. The Coordinating Center, must forward any reports to the DF/HCC ODQ per DF/HCC policy for review by the DF/HCC Audit Committee. For unacceptable audits, the DF/HCC Audit Committee would forward the final audit report and corrective action plan to the IRB as applicable.

5.4 External Site Performance

The DF/HCC Sponsor and the IRB of record are charged with considering the totality of an institution's performance in considering institutional participation in the protocol.

External Sites that fail to meet the performance goals of accrual, submission of timely and accurate data, adherence to protocol requirements, and compliance with state and federal regulations, may be put on hold or closed.

APPENDIX C INVESTIGATOR SAMPLE REQUEST FORM

Once the request has been received, the Pasquarello Tissue Bank staff will verify the list. Once checked, the Pasquarello Tissue Bank staff member will arrange for pick-up of the vials. This form is NOT to accompany the samples.

1. Name of Investigator using vials:_____
2. Name of person requesting vials (printed):_____
    2.1. Address:_____
    2.2. Telephone:_____
3. Purpose:_____

Sample Usage Agreement

The recipient acknowledges that the conditions for use of this research material are governed by the Dana-Farber Cancer Institute Institutional Review Board (IRB) on behalf of the DF/HCC in accordance with Department of Health and Human Services regulations at 45 CFR Part 46. The recipient agrees to comply fully with all such conditions and to report promptly to the Principal Investigator (Philippe Armand, MD, PhD), Tissue Bank Administrator (Jerome Ritz, MD) or the Tissue Bank Sample Trafficking Supervisor (Doreen Hearsey) any proposed changes in the recipient's research project and any unanticipated problems involving risks to subjects or others. The recipient remains subject to applicable State or local laws or regulations and DF/HCC policies that provide additional protections for human subjects. The research material provided to the recipient may be utilized only in accordance with the conditions stipulated in this Usage Agreement, as approved by the DFCI IRB, as follows:

• Specimens requested via this form must be in compliance with the research outlined in the 09-073 protocol. (Reference the Potential Studies in Experimental Design section of Protocol for approved studies.)
• Collaborating scientists who are not named investigators on this protocol who require patient identifiers must submit specific protocols for IRB review.
• Samples provided under this agreement are only for the use of the Principal Investigator requesting these samples. Release of these samples or products derived from these samples for use by other investigators will require the written permission of the Tissue Bank Principal Investigator or Tissue Bank Administrator.

Any use of this material beyond the terms of this agreement requires prior review and approval by the DFCI IRB and, where appropriate, by an IRB at the recipient site, which must be convened under an Office of Human Research Protections approved Federal Wide Assurance. If the recipient's use of this material is within the above guidelines and conditions, DFCI IRB review of the recipient's research project is not required.

I agree to conform to the guidelines above.

Signature of investigator requesting vials:_____Date:_____

Vial Identification

Patient Name	MRN	CM#	Date	Sample type	# vials	Verified by Pasquarello Tissue Bank tech/comments

Reviewed by Pasquarello Tissue Bank Administrator:_____Date:_____

APPENDIX D NON-INVESTIGATOR SAMPLE REQUEST FORM

Once the request has been received, the Pasquarello Tissue Bank staff will verify the list. Once checked, the Pasquarello Tissue Bank staff member will arrange for pick-up of the vials. This form is NOT to accompany the samples.

1. Name of Investigator using vials:_____
2. Name of person requesting vials (printed):_____
    2.1. Address:_____
    2.2. Telephone:_____
3. Purpose:_____

Sample Usage Agreement

The recipient acknowledges that the conditions for use of this research material are governed by the Dana-Farber Cancer Institute Institutional Review Board (IRB) on behalf of the DF/HCC in accordance with Department of Health and Human Services regulations at 45 CFR Part 46. The recipient agrees to comply fully with all such conditions and to report promptly to the Principal Investigator (Philippe Armand, MD), Tissue Bank Administrator (Jerome Ritz, MD) or the Tissue Bank Sample Trafficking Supervisor (Doreen Hearsey) any proposed changes in the recipient's research project and any unanticipated problems involving risks to subjects or others. The recipient remains subject to applicable State or local laws or regulations and DF/HCC policies that provide additional protections for human subjects.

The research material provided to the recipient may be utilized only in accordance with the conditions stipulated in this Usage Agreement, as approved by the DFCI IRB, as follows:

- The recipient will receive no information that could identify the subject.
- If the recipient requests identifying information, the personnel of the Pasquarello Tissue Bank will not provide it.
- The recipient may not contact individuals who are collecting the material to obtain any identifying information.
- All material is identified by a code number that is assigned by the Tissue Bank for tracking purposes.
- Subject information will be kept confidential in the password-protected, electronic STIP database, accessible only via authorized computer terminals in secure, non-public areas by Pasquarello Tissue Bank personnel.
- In addition to the research material itself, at the recipient's request, the Tissue Bank may provide the recipient with the following information about the subject/material:
    - o Type of sample (bone marrow, peripheral blood cells, plasma, serum, or other)
    - o Dates of sample collection and receipt at the Tissue Bank
    - o Patient diagnosis at time of collection
- Specimens requested via this form must be in compliance with the research outlined in the protocol.
- Collaborating scientists who are not named investigators on this protocol who require patient identifiers must submit specific protocols for IRB review.

• Samples provided under this agreement are only for the use of the Principal Investigator requesting these samples. Release of these samples or products derived from these samples for use by other investigators will require the written permission of the Tissue Bank Principal Investigator or Tissue Bank Administrator.

Any use of this material beyond the terms of this agreement requires prior review and approval by the DFCI IRB and, where appropriate, by an IRB at the recipient site, which must be convened under an Office of Human Research Protections approved Federal Wide Assurance.

If the recipient's use of this material is within the above guidelines and conditions, DFCI IRB review of the recipient's research project is not required.

I agree to conform to the guidelines above.

Signature of investigator requesting vials:_____Date:_____

APPENDIX E MANAGEMENTS OF IMMUNE-RELATED ADVERSE EVENTS (IRAES)/IRAE GUIDANCE DOCUMENT

1. OVERVIEW

The purpose of this document is to provide study sites with guidance on the identification and management of Immune-Related Adverse Events (irAEs) for the MK-3475 (also known as pembrolizumab) program.

Immune-related AEs are adverse events associated with the treatment of patients with immunotherapy treatments that appear to be associated with the immune therapy's mechanism of action. Based on these potential irAEs, the sponsor has defined a list of specific adverse event terms (irAEs) that are selected adverse experiences that **when serious must be reported to Merck within 24 hours** from the time the Investigator/physician is aware of such an occurrence, regardless of whether or not the investigator/physician considers the event to be related to study drug(s). In addition, these irAEs require additional detailed information to be collected and entered in the study database. irAEs may be identified through spontaneous patient report and / or upon review of subject data. **Table 1** provides the list of terms and reporting requirements for AEs that must be reported as irAEs for MK-3475 protocols.

Given that our current list of irAEs interest is not comprehensive for all potential immune-related events, it is possible that AEs other than those listed in this document may be observed in patients receiving pembrolizumab. Therefore any **serious** event that the investigator/physician considers to be immune-related should be reported as an irAE regardless of whether the specific event term is in Table 1 **and reported to Merck within 24 hours** from the time the Investigator/physician is aware of such an occurrence. Adverse events that are both an SAE and an irAE should be reported one time as an SAE only, however the event must be appropriately identified as an irAE as well in the database.

Table 1: Events of Clinical Interest

Pneumonitis		
Acute interstitial pneumonitis	Interstitial lung disease	Pneumonitis
Colitis		
Intestinal Obstruction	Colitis	Colitis microscopic
Enterocolitis	Enterocolitis hemorrhagic	Gastrointestinal perforation
Necrotizing colitis	Diarrhea	
Endocrine		
Adrenal Insufficiency	Hyperthyroidism	Hypophysitis
Hypopituitarism	Hypothyroidism	Thyroid disorder
Thyroiditis		
Hematologic		
Autoimmune hemolytic anemia	Aplastic anemia	Thrombotic Thrombocytopenic Purpura (TTP)
Idiopathic (or immune) Thrombocytopenia Purpura (ITP)	Disseminated Intravascular Coagulation (DIC)	Haemolytic Uraemic Syndrome (HUS)
Any Grade 4 anemia regardless of underlying mechanism		
Hepatic		
Hepatitis	Autoimmune hepatitis	Transaminase elevations
Infusion Reactions		
Allergic reaction	Anaphylaxis	Cytokine release syndrome
Serum sickness	Infusion reactions	Infusion-like reactions
Neurologic (reported as irAE for any grade)		
Autoimmune neuropathy	Guillain-Barre syndrome	Demyelinating polyneuropathy
Myasthenic syndrome		
Ocular		
Uveitis	Iritis	
Renal		
Nephritis	Nephritis autoimmune	Renal Failure
Renal failure acute	Creatinine elevations (report as irAE if ≥Grade 3 or any grade resulting in dose modification or use of systemic steroids to treat the AE)	
Skin		
Dermatitis exfoliative	Erythema multiforme	Stevens-Johnson syndrome
Toxic epidermal necrolysis		
Skin		
Pruritus	Rash	Rash generalized
Rash maculo-papular		
Any rash considered clinically significant in the physician's judgment		
Other		
Myocarditis	Pancreatitis	Pericarditis
Any other Grade 3 event which is considered immune-related by the physician		

Each of the events above is described within this guidance document, along with site requirements for reporting these events to the Sponsor. The information collected should be entered into the narrative field(s) of the Adverse Event module in the database (please note, if narrative entry into the database is not available, please use the narrative text box on the 1727/AER Form). If additional Medical History or Concomitant Medications are reported, the Medical History and Concomitant Medication modules in the database must be updated.

In addition, the guidelines include recommendations on the management of these irAEs. These guidelines are intended to be applied when the physician determines the events to be related to pembrolizumab.

Note: if after the evaluation the event is determined not to be related, the physician is instructed to follow the irAE reporting guidance but does not need to follow the treatment guidance (below). Therefore, these recommendations should be seen as guidelines and the treating physician should exercise individual clinical judgment based on the patient. For any question of dose modification or other treatment options, the specific language in the protocol should be followed. Any questions pertaining to the collection of this information or management of irAEs should be directed to your local Sponsor contact.

1.1 Dose Modification/Discontinuation

The treatment guidance provides specific direction when to hold and/or discontinue pembrolizumab for each immune related adverse event. Of note, when the guidance states to "discontinue" pembrolizumab this is the permanent discontinuation of treatment with pembrolizumab. "Hold" means to stop treating with pembrolizumab but resumption of treatment may be considered assuming the patient meets the criteria for resumption of treatment.

2. irAE REPORTING GUIDELINES

irAEs are selected events that **when serious** must be reported to Merck **within 24 hours** regardless of attribution to study treatment. The AEs listed in this document and any event that meets the irAE criteria (as noted) in Table 1 or in the respective protocol (event term and Grade) and that is serious must be reported regardless of physician-determined causality with study medication and whether or not considered immune-related by the physician (unless otherwise specified). Physicians/study coordinators/designated site personnel are required to record these experiences as irAEs on the Adverse Experience electronic Case Report Forms (eCRFs) (or on paper) and to provide supplemental information (such as medical history, concomitant medications, investigations, etc.) about the event.

- Please refer to the Data Entry Guidelines (DEGs) for your protocol.
- Please refer to protocol for details on reporting timelines and reporting of Overdose and Drug Induced Liver Injury (DILI).

3. irAE CATEGORIES AND TERMS

This section describes the irAE categories and outlines subject management guidelines when an irAE is reported.

3.1 Pneumonitis

The following AE terms, if considered ≥ Grade 2, are considered irAEs and should be reported to the Sponsor within 24 hours of the event if serious:

- Pneumonitis
- Interstitial lung disease
- Acute interstitial pneumonitis

If symptoms indicate possible new or worsening cardiac abnormalities additional testing and/or a cardiology consultation should be considered.

All attempts should be made to rule out other causes such as metastatic disease, bacterial or viral infection**. It is important that patients with a suspected diagnosis of pneumonitis be managed as per the guidance below until treatment-related pneumonitis is excluded. Treatment of both a potential infectious etiology and pneumonitis in parallel may be warranted. Management of the treatment of suspected pneumonitis with steroid treatment should not be delayed for a therapeutic trial of antibiotics.** If an alternative diagnosis is established, the patient does not require management as below; however the AE should be reported regardless of etiology.

Course of Action

Grade 2 events:
- Hold pembrolizumab.
- Consider pulmonary consultation with bronchoscopy and biopsy/BAL.
- Consider ID consult
- Conduct an in person evaluation approximately twice per week
- Consider frequent Chest X-ray as part of monitoring
- Treat with systemic corticosteroids at a dose of 1 to 2 mg/kg/day prednisone or equivalent. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.
- Permanently discontinue for inability to reduce corticosteroid dose to 10 mg or less of prednisone or equivalent per day within 12 weeks.
- Second episode of pneumonitis – discontinue pembrolizumab if upon re-challenge the patient develops a second episode of Grade 2 or higher pneumonitis.

Grade 3 and 4 events:
- Discontinue pembrolizumab.
- Hospitalize patient
- Bronchoscopy with biopsy and/or BAL is recommended.
- Immediately treat with intravenous steroids (methylprednisolone 125 mg IV). When symptoms improve to Grade 1 or less, a high dose oral steroid (prednisone 1 to 2 mg/kg

once per day or dexamethasone 4 mg every 4 hours) taper should be started and continued over no less than 4 weeks.

- If IV steroids followed by high dose oral steroids does not reduce initial symptoms within 48 to 72 hours, treat with additional anti-inflammatory measures. Discontinue additional anti-inflammatory measures upon symptom relief and initiate a prolonged steroid taper over 45 to 60 days. If symptoms worsen during steroid reduction, initiate a retapering of steroids starting at a higher dose of 80 or 100 mg followed by a more prolonged taper and administer additional anti-inflammatory measures, as needed
- Add prophylactic antibiotics for opportunistic infections.

3.2 Colitis

The following AE terms are considered irAEs and should be reported to the Sponsor within 24 hours of the event if serious:

- Colitis
- Colitis microscopic
- Enterocolitis
- Enterocolitis hemorrhagic
- Gastrointestinal perforation
- Intestinal obstruction
- Necrotizing colitis
- Diarrhea

All attempts should be made to rule out other causes such as metastatic disease, bacterial or parasitic infection, viral gastroenteritis, or the first manifestation of an inflammatory bowel disease by examination for stool leukocytes, stool cultures, a Clostridium difficile titer and endoscopy. However the AE should be reported regardless of etiology.

Course of Action

Grade 2 Diarrhea/Colitis (4-6 stools/day over baseline, dehydration requiring IV fluids < 24 hours, abdominal pain, mucus or blood in stool):

- Hold pembrolizumab.
- Symptomatic Treatment
- For Grade 2 diarrhea that persists >1 week, and for diarrhea with blood and/or mucus,
    - Consider GI consultation and endoscopy to confirm or rule out colitis
    - Administer oral corticosteroids (prednisone 1-2 mg/kg QD or equivalent)
- When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.
- Permanently discontinue for inability to reduce corticosteroid dose to 10 mg or less of prednisone or equivalent per day within 12 weeks.
- If symptoms worsen or persist > 3 days treat as Grade 3

Grade 3 Diarrhea/Colitis (or Grade 2 diarrhea that persist for greater than 3 days):

- Hold pembrolizumab.
- Rule out bowel perforation. Imaging with plain films or CT can be useful.
- Recommend consultation with Gastroenterologist and confirmation biopsy with endoscopy.
- Treat with intravenous steroids (methylprednisolone 125 mg) followed by high dose oral steroids (prednisone 1 to 2 mg/kg once per day or dexamethasone 4 mg every 4 hours) When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. Taper over 6 to 8 weeks in patients with diffuse and severe ulceration and/or bleeding.

- Permanently discontinue for inability to reduce corticosteroid dose to 10 mg or less of prednisone or equivalent per day within 12 weeks.
- If IV steroids followed by high dose oral steroids does not reduce initial symptoms within 48 to 72 hours, consider treatment with additional anti-inflammatory measures as described in the literature [5]. Discontinue additional anti-inflammatory measures upon symptom relief and initiate a prolonged steroid taper over 45 to 60 days. If symptoms worsen during steroid reduction, initiate a retapering of steroids starting at a higher dose of 80 or 100 mg followed by a more prolonged taper and administer additional anti-inflammatory measures as needed.

Grade 4 events:

- Permanently discontinue pembrolizumab.
- Manage as per Grade 3.

3.3 Endocrine

The following AE terms are considered irAEs and should be reported to the Sponsor within 24 hours of the event if serious:

- Adrenal insufficiency
- Hyperthyroidism
- Hypophysitis
- Hypopituitarism
- Hypothyroidism
- Thyroid disorder
- Thyroiditis

All attempts should be made to rule out other causes such as brain metastases, sepsis and/or infection. However the AE should be reported regardless of etiology.

Hypophysitis or other symptomatic endocrinopathy other than hypo- or hyperthyroidism

Grade 2 events:

- Hold pembrolizumab
- Monitor thyroid function or other hormonal level tests and serum chemistries more frequently until returned to baseline values.
- Pituitary gland imaging should be considered (MRIs with gadolinium and selective cuts of the pituitary can show enlargement or heterogeneity and confirm the diagnosis).
- Treat with prednisone 40 mg p.o. or equivalent per day. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. Replacement of appropriate hormones may be required as the steroid dose is tapered.
- Permanently discontinue for inability to reduce corticosteroid dose to 10 mg or less of prednisone or equivalent per day within 12 weeks.
- Consultation with an endocrinologist may be considered.

Grade 3 events:

- Hold pembrolizumab.
- Endocrine consultation is recommended.
- Rule out infection and sepsis with appropriate cultures and imaging.
- Treat with an initial dose of methylprednisolone 1 to 2 mg/kg intravenously followed by oral prednisone 1 to 2 mg/kg per day. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. Replacement of appropriate hormones may be required as the steroid dose is tapered.
- Permanently discontinue for inability to reduce corticosteroid dose to 10 mg or less of prednisone or equivalent per day within 12 weeks.
- Hypophysitis with clinically significant adrenal insufficiency and hypotension, dehydration, and electrolyte abnormalities (such as hyponatremia and hyperkalemia) constitutes adrenal crisis.

– Hospitalization and endocrine consultation should be considered.

Grade 4 events:
– Discontinue pembrolizumab.
– Manage as per Grade 3

Hyperthyroidism and Hypothyroidism

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

Grade 2 events (and Grade 3-4 hypothyroidism):
– Monitor thyroid function or other hormonal level tests and serum chemistries more frequently until returned to baseline values.
– Thyroid hormone and/or steroid replacement therapy to manage adrenal insufficiency.
– Therapy with pembrolizumab can be continued while treatment for the thyroid disorder is instituted.
– In hyperthyroidism, non-selective beta-blockers (e.g. propranolol) are suggested as initial therapy.
– In hypothyroidism, thyroid hormone replacement therapy, with levothyroxine or liothyroinine, is indicated per standard of care.
– Consultation with an endocrinologist may be considered.

Grade 3 hyperthyroidism events:
– Hold pembrolizumab.
– Rule out infection and sepsis with appropriate cultures and imaging.
– Treat with an initial dose of methylprednisolone 1 to 2 mg/kg intravenously followed by oral prednisone 1 to 2 mg/kg per day. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. Replacement of appropriate hormones may be required as the steroid dose is tapered.
– Permanently discontinue for inability to reduce corticosteroid dose to 10 mg or less of prednisone or equivalent per day within 12 weeks.

Grade 4 events:
– Discontinue pembrolizumab.
– Manage as per Grade 3

3.4 Hematologic

The following AE term, are considered an irAE and should be reported to the Sponsor within 24 hours of the event if serious:

- Autoimmune hemolytic anemia
- Aplastic anemia
- Disseminated Intravascular Coagulation (DIC)
- Haemolytic Uraemic Syndrome (HUS)
- Idiopathic (or immune) Thrombocytopenia Purpura (ITP)
- Thrombotic Thrombocytopenic Purpura (TTP)
- Any Grade 4 anemia regardless of underlying mechanism

All attempts should be made to rule out other causes such as metastases, sepsis and/or infection. Relevant diagnostic studies such as peripheral blood smear, reticulocyte count, LDH, haptoglobin, bone marrow biopsy or Coomb's test, etc., should be considered to confirm the diagnosis. However the AE should be reported regardless of etiology.

Course of Action

Grade 2 events:
- Hold pembrolizumab
- Prednisone 1-2 mg/kg daily may be indicated
- Consider Hematology consultation.
  Permanently discontinue for inability to reduce corticosteroid dose to 10 mg or less of prednisone or equivalent per day within 12 weeks.

Grade 3 events:
- Hematology consultation.
- Hold pembrolizumab Discontinuation should be considered as per specific protocol guidance.
- Treat with methylprednisolone 125 mg iv or prednisone 1-2 mg/kg p.o. (or equivalent) as appropriate
- Permanently discontinue for inability to reduce corticosteroid dose to 10 mg or less of prednisone or equivalent per day within 12 weeks.

Grade 4 events:
- Hematology consultation
- Discontinue pembrolizumab for all solid tumor indications; refer to protocol for hematologic malignancies.
- Treat with methylprednisolone 125 mg iv or prednisone 1-2 mg/kg p.o. (or equivalent) as appropriate

3.5 Hepatic

The following AE terms are considered irAEs and should be reported to the Sponsor within 24 hours of the event if serious:

- Autoimmune hepatitis
- Hepatitis
- Transaminase elevations

All attempts should be made to rule out other causes such as metastatic disease, infection or other hepatic diseases. However the AE should be reported regardless of etiology.

Drug Induced Liver Injury (DILI)

In addition, the event must be reported as a Drug Induced Liver Injury (DILI) irAE, if the patient meets the laboratory criteria for potential DILI defined as:

- An elevated alanine transaminase (ALT) or aspartate transaminase (AST) lab value that is greater than or equal to three times (3X) the upper limit of normal (ULN) and
- An elevated total bilirubin lab value that is greater than or equal to two times (2X) ULN and
- At the same time, an alkaline phosphatase (ALP) lab value that is less than 2X ULN,
- As a result of within-protocol-specific testing or unscheduled testing.

Note that any hepatic immune irAE meeting DILI criteria should only be reported once as a DILI event.

Course of Action

Grade 2 events:

- Hold pembrolizumab when AST or ALT >3.0 to 5.0 times ULN and/or total bilirubin >1.5 to 3.0 times ULN.
- Monitor liver function tests more frequently until returned to baseline values (consider weekly).
    - Treat with 0.5-1 mg/kg/day methylprednisolone or oral equivalent and when LFT returns to grade 1 or baseline, taper steroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections, and resume pembrolizumab per protocol
- Permanently discontinue for inability to reduce corticosteroid dose to 10 mg or less of prednisone or equivalent per day within 12 weeks.
- Permanently discontinue pembrolizumab for patients with liver metastasis who begin treatment with Grade 2 elevation of AST or ALT, and AST or ALT increases ≥50% relative to baseline and lasts ≥1 week.

Grade 3 events:

- Discontinue pembrolizumab when AST or ALT >5.0 times ULN and/or total bilirubin >3.0 times ULN.
- Consider appropriate consultation and liver biopsy to establish etiology of hepatic injury, if necessary
- Treat with high-dose intravenous glucocorticosteroids for 24 to 48 hours. When symptoms improve to Grade 1 or less, a steroid taper with dexamethasone 4 mg every 4 hours or prednisone at 1 to 2 mg/kg should be started and continued over no less than 4 weeks.
- If serum transaminase levels do not decrease 48 hours after initiation of systemic steroids, oral mycophenolate mofetil 500 mg every 12 hours may be given. Infliximab is not recommended due to its potential for hepatotoxicity.
- Several courses of steroid tapering may be necessary as symptoms may worsen when the steroid dose is decreased.
- Permanently discontinue for inability to reduce corticosteroid dose to 10 mg or less of prednisone or equivalent per day within 12 weeks.

Grade 4 events:

- Permanently discontinue pembrolizumab
- Manage patient as per Grade 3 above

3.6 Neurologic

The following AE terms, regardless of grade, are considered irAEs and should be reported to the Sponsor within 24 hours of the event if serious:

- Autoimmune neuropathy
- Demyelinating polyneuropathy
- Guillain-Barre syndrome
- Myasthenic syndrome

All attempts should be made to rule out other causes such as metastatic disease, other medications or infectious causes. However the AE should be reported regardless of etiology.

Course of Action

Grade 2 events:

- Moderate (Grade 2) – consider withholding pembrolizumab.
- Consider treatment with prednisone 1-2 mg/kg p.o. daily as appropriate
- Consider Neurology consultation. Consider biopsy for confirmation of diagnosis.
- Permanently discontinue for inability to reduce corticosteroid dose to 10 mg or less of prednisone or equivalent per day within 12 weeks.

Grade 3 and 4 events:

- Discontinue pembrolizumab
- Obtain neurology consultation. Consider biopsy for confirmation of diagnosis
- Treat with systemic corticosteroids at a dose of 1 to 2 mg/kg prednisone or equivalent once per day. If condition worsens consider IVIG or other immunosuppressive therapies as per local guidelines

When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.

3.7 Ocular

The following AE terms, is considered an irAE and if serious should be reported to the Sponsor within 24 hours of the event:

- Uveitis
- Iritis

All attempts should be made to rule out other causes such as metastatic disease, infection or other ocular disease (e.g. glaucoma or cataracts). However the AE should be reported regardless of etiology.

Course of Action

Grade 2 events:
- Evaluation by an ophthalmologist is strongly recommended.
- Treat with topical steroids such as 1% prednisolone acetate suspension and iridocyclitics.
- Discontinue pembrolizumab as per protocol if symptoms persist despite treatment with topical immunosuppressive therapy.

Grade 3 events:
- Evaluation by an ophthalmologist is strongly recommended
- Hold pembrolizumab and consider permanent discontinuation as per specific protocol guidance.
- Treat with systemic corticosteroids such as prednisone at a dose of 1 to 2 mg/kg per day. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.
- Permanently discontinue for inability to reduce corticosteroid dose to 10 mg or less of prednisone or equivalent per day within 12 weeks.

Grade 4 events:
- Evaluation by an ophthalmologist is strongly recommended
- Permanently discontinue pembrolizumab.
- Treat with corticosteroids as per Grade 3 above

3.8 Renal

The following AEs if ≥ Grade 2 are considered irAEs and if serious should be reported to the Sponsor within 24 hours of the event:

- Nephritis
- Nephritis autoimmune
- Renal failure
- Renal failure acute

Creatinine elevations ≥ Grade 3 or any grade with dose modification or use of systemic steroids to treat the AE.

All attempts should be made to rule out other causes such as obstructive uropathy, progression of disease, or injury due to other chemotherapy agents. A renal consultation is recommended. However the AE should be reported regardless of etiology.

Course of Action

Grade 2 events:
- Hold pembrolizumab
- Treatment with prednisone 1-2 mg/kg p.o. daily.
- Permanently discontinue for inability to reduce corticosteroid dose to 10 mg or less of prednisone or equivalent per day within 12 weeks.

Grade 3-4 events:
- Discontinue pembrolizumab
- Renal consultation with consideration of ultrasound and/or biopsy as appropriate
- Treat with systemic corticosteroids at a dose of 1 to 2 mg/kg prednisone IV or equivalent once per day.

When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.

3.9 Skin

Rash and Pruritus

The following AEs should be considered as irAEs if ≥ Grade 3 and if serious should be reported to the Sponsor within 24 hours of the event:

- Pruritus
- Rash
- Rash generalized
- Rash maculo-papular
- In addition to CTCAE Grade 3 rash, any rash that is considered clinically significant, in the physician's judgment, should be treated as an irAE. Clinical significance is left to the physician to determine, and could possibly include rashes such as the following:
  - rash with a duration >2 weeks; OR
  - rash that is >10% body surface area; OR
  - rash that causes significant discomfort not relieved by topical medication or temporary cessation of study drug.

Other Skin irAEs

The following AEs should **always** be considered as irAEs, regardless of grade, and should be reported to the Sponsor within 24 hours of the event if serious:

- Dermatitis exfoliative
- Erythema multiforme
- Steven's Johnson syndrome
- Toxic epidermal necrolysis

Please note, the AE should be reported regardless of etiology.

Course of Action

Grade 2 events:
- Symptomatic treatment should be given such as topical glucocorticosteroids (e.g., betamethasone 0.1% cream or hydrocortisone 1%) or urea-containing creams in combination with oral anti-pruritics (e.g., diphenhydramine HCl or hydroxyzine HCl).
- Treatment with oral steroids is at physician's discretion for Grade 2 events.

Grade 3 events:
- Hold pembrolizumab.
- Consider Dermatology Consultation and biopsy for confirmation of diagnosis.
- Treatment with oral steroids is recommended, starting with 1 mg/kg prednisone or equivalent once per day or dexamethasone 4 mg four times orally daily. When symptoms

improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.
- Permanently discontinue for inability to reduce corticosteroid dose to 10 mg or less of prednisone or equivalent per day within 12 weeks.

Grade 4 events:
- Permanently discontinue pembrolizumab.
- Dermatology consultation and consideration of biopsy and clinical dermatology photograph.
- Initiate steroids at 1 to 2 mg/kg prednisone or equivalent. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.

3.9.1. Immediate Evaluation for Potential Skin irAEs

A. Photographs:
Every attempt should be made to get a photograph of the actual irAE skin lesion or rash as soon as possible**. Obtain appropriate consent for subject photographs if a consent form addendum is required by your IRB/ERC.**
- Take digital photographs of:
  - the head (to assess mucosal or eye involvement),
  - the trunk and extremities, and
  - a close-up of the skin lesion/rash.
- If possible, a ruler should be placed alongside the site of a skin occurrence as a fixed marker of distance.
- The time/date stamp should be set in the 'ON' position for documentation purposes.
- Photographs should be stored with the subject's study records.
- The Sponsor may request copies of photographs. The local study contact (e.g., CRA) will provide guidance to the site, if needed.

B. Past Medical History:
Collect past medical history relevant to the event, using the questions in Appendix 2 (Past Medical History Related to Dermatologic Event) as a guide. Any preexisting conditions not previously reported (e.g., drug allergy) should be entered into the Medical History eCRF.

C. Presentation of the Event:
Collect information on clinical presentation and potential contributing factors using the questions in Appendix 3 (Presentation of the Dermatologic Event) as a guide. This information should be summarized and entered in narrative format in the AE eCRF. Please use the available free-text fields, such as Signs and Symptoms. Note pertinent negatives where applicable to reflect that the information was collected. Any treatments administered should be entered on the Concomitant Medication eCRF.

D. Vitals Signs and Standard Laboratory Tests:
Measure vital signs (pulse, sitting BP, oral temperature, and respiratory rate) and record on the Vital Signs eCRF. Perform standard laboratory tests (CBC with manual differential and serum chemistry panel, including LFTs).

E. Focused Skin Examination:
Perform a focused skin examination using the questions in Appendix 4 (Focused Skin Examination) as a guide. Information should be summarized and entered on the Adverse Experience eCRF as part of the narrative.

F. Dermatology Consult
Refer the subject to a dermatologist as soon as possible.

- For a **"severe rash"**, the subject must be seen within **1-2 days** of reporting the event.
- For **clinically significant rash**, the subject should be seen within **3-5 days**.

The dermatologist should submit a biopsy sample to a certified dermatopathology laboratory or to a pathologist experienced in reviewing skin specimens.

The site should provide the dermatologist with all relevant case history, including copies of clinical photographs and laboratory test results.

3.10 Other

The following AEs, regardless of grade, are considered irAEs and should be reported to the Sponsor within 24 hours of the event if serious:

- Myocarditis: for grade 1 or 2, treatment should be held; for grade 3 or above, treatment should be permanently discontinued. Steroids may be used depending on severity (recommended for grade 2 or above), in consultation with cardiology and after exclusion of other potential causes.
- Pericarditis
- Pancreatitis
- Any additional Grade 3 or higher event which the physician considers to be immune related

All attempts should be made to rule out other causes. Therapeutic specialists should be consulted as appropriate. However the AE should be reported regardless of etiology.

Course of Action

Grade 2 events or Grade 1 events that do not improve with symptomatic treatment:
- Withhold pembrolizumab.
- Systemic corticosteroids may be indicated.
- Consider biopsy for confirmation of diagnosis.
- If pembrolizumab held and corticosteroid required, manage as per grade 3 below.

Grade 3 events:
- Hold pembrolizumab
- Treat with systemic corticosteroids at a dose of 1 to 2 mg/kg prednisone or equivalent once per day.
- When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.
- Permanently discontinue for inability to reduce corticosteroid dose to 10 mg or less of prednisone or equivalent per day within 12 weeks. Otherwise, pembrolizumab treatment may be restarted and the dose modified as specified in the protocol

Grade 4 events:
- Treat with systemic corticosteroids at a dose of 1 to 2 mg/kg prednisone or equivalent once per day.
- Discontinue pembrolizumab

3.11 Infusion Reactions

The following AE terms, regardless of grade, are considered irAEs and should be reported to the Sponsor within 24 hours of the event if serious:

- Allergic reaction
- Anaphylaxis
- Cytokine release syndrome
- Serum sickness
- Infusion reactions
- Infusion-like reactions

Please note, the AE should be reported regardless of etiology.

Course of Action

Refer to infusion reaction table in the protocol and below.

Table 2: Infusion Reactions

NCI CTCAE Grade	Treatment	Premedication at subsequent dosing
Grade 1 Mild reaction; infusion interruption not indicated; intervention not indicated	Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator.	None
Grade 2 Requires infusion interruption but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDS, narcotics, IV fluids); prophylactic medications indicated for < =24 hrs	**Stop Infusion.** Additional appropriate medical therapy may include but is not limited to: IV fluids Antihistamines NSAIDS Acetaminophen Narcotics Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator. If symptoms resolve within one hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (e.g. from 100 mL/hr to 50 mL/hr). Otherwise dosing will be held until symptoms resolve and the subject should be premedicated for the next scheduled dose. **Subjects who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further trial treatment administration.**	Subject may be premedicated 1.5h (± 30 minutes) prior to infusion of pembrolizumab with: Diphenhydramine 50 mg p.o. (or equivalent dose of antihistamine). Acetaminophen 500-1000 mg p.o. (or equivalent dose of antipyretic).
Grades 3 or 4 Grade 3: Prolonged (i.e., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (e.g., renal impairment, pulmonary infiltrates) Grade 4: Life-threatening; pressor or ventilatory support indicated	**Stop Infusion.** Additional appropriate medical therapy may include but is not limited to: IV fluids Antihistamines NSAIDS Acetaminophen Narcotics Oxygen Pressors Corticosteroids Epinephrine Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator. Hospitalization may be indicated. **Subject is permanently discontinued from further trial treatment administration.**	No subsequent dosing
Appropriate resuscitation equipment should be available 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		

3.12 Follow-up to Resolution

Subjects should be followed to resolution. The Adverse Experience eCRF should be updated with information regarding duration and clinical course of the event. Information obtained from the consulting specialist, including diagnosis, should be recorded in the appropriate AE fields. Free-text fields should be used to record narrative information:

- Clinical course of the event
- Course of treatment
- Evidence supporting recovery
- Follow-up to the clinical course

Any treatments administered for the event should also be entered in the Concomitant Medication eCRF.

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APPENDIX 1 – Events of Clinical Interest (irAE) – Reference Table

Pneumonitis (reported as irAE if ≥ Grade 2)		
Acute interstitial pneumonitis	Interstitial lung disease	Pneumonitis
Colitis (reported as irAE if ≥ Grade 2 or any grade resulting in dose modification or use of systemic steroids to treat the AE)		
Intestinal Obstruction	Colitis	Colitis microscopic
Enterocolitis	Enterocolitis hemorrhagic	Gastrointestinal perforation
Necrotizing colitis	Diarrhea	
Endocrine (reported as irAE if ≥ Grade 3 or ≥ Grade 2 and resulting in dose modification or use of systemic steroids to treat the AE)		
Adrenal Insufficiency	Hyperthyroidism	Hypophysitis
Hypopituitarism	Hypothyroidism	Thyroid disorder
Thyroiditis		
Hematologic (reported as irAE if ≥ Grade 3 or any grade resulting in dose modification or use of systemic steroids to treat the AE)		
Autoimmune hemolytic anemia	Aplastic anemia	Thrombotic Thrombocytopenic Purpura (TTP)
Idiopathic (or immune) Thrombocytopenia Purpura (ITP)	Disseminated Intravascular Coagulation (DIC)	Haemolytic Uraemic Syndrome (HUS)
Any Grade 4 anemia regardless of underlying mechanism		
Hepatic (reported as irAE if ≥ Grade 2, or any grade resulting in dose modification or use of systemic steroids to treat the AE**)**		
Hepatitis	Autoimmune hepatitis	Transaminase elevations
Infusion Reactions (reported as irAE for any grade)		
Allergic reaction	Anaphylaxis	Cytokine release syndrome
Serum sickness	Infusion reactions	Infusion-like reactions
Neurologic (reported as irAE for any grade)		
Autoimmune neuropathy	Guillain-Barre syndrome	Demyelinating polyneuropathy
Myasthenic syndrome		
Ocular (report as irAE if ≥ Grade 2 or any grade resulting in dose modification or use of systemic steroids to treat the AE)		
Uveitis	Iritis	
Renal (reported as irAE if ≥ Grade 2)		
Nephritis	Nephritis autoimmune	Renal Failure
Renal failure acute	Creatinine elevations (report as irAE if ≥Grade 3 or any grade resulting in dose modification or use of systemic steroids to treat the AE)	
Skin (reported as irAE for any grade)		
Dermatitis exfoliative	Erythema multiforme	Stevens-Johnson syndrome
Toxic epidermal necrolysis		
Skin (reported as irAE if ≥ Grade 3)		
Pruritus	Rash	Rash generalized
Rash maculo-papular		
Any rash considered clinically significant in the physician's judgment		

Other (reported as irAE for any grade)		
Myocarditis	Pancreatitis	Pericarditis
Any other Grade 3 event which is considered immune-related by the physician		

APPENDIX 2 – Past Medical History Related to Dermatologic Event

Past Medical History:
Any preexisting conditions not previously reported (e.g., drug allergy) should be entered into the Medical History eCRF.

1. Does the subject have any allergies? □ Yes □ No

If yes, please obtain the following information:

a. Any allergy to drugs (including topical or ophthalmic drugs)? □ Yes □ No

List the drug name(s) and describe the type of allergic response (e.g. rash, anaphylaxis, etc): _____

_____

b. Any allergy to external agents, such as laundry detergents, soaps, poison ivy, nickel, etc.? □ Yes □ No

Describe the agent and type of allergic response: _____

_____

_____

c. Any allergy to food? □ Yes □ No

Describe the food and type of allergic response: _____

_____

d. Any allergy to animals, insects? □ Yes □ No

Describe the allergen and type of allergic response:

_____

_____

e. Any other allergy? □ Yes □ No

Describe the allergen and type of allergic response: _____

_____

2. Does the subject have any other history of skin reactions, skin eruptions, or rashes? □ Yes □ No

If so what kind? _____

3. Has the subject ever been treated for a skin condition? □ Yes □ No

If so what kind? _____

4. Is the current finding similar to a past experience? □ Yes □ No

APPENDIX 3 – Presentation of the Dermatologic Event

Presentation of the event:
Collect information on clinical presentation and potential contributing factors. Key information should be summarized and entered on the Adverse Experience eCRF. Any treatments administered should be entered on the Concomitant Medication eCRF.

1. What is the onset time of the skin reaction, skin eruption, or rash relative to dose of study drug?

_____

2. Has the subject contacted any known allergens? □ Yes □ No

If so what kind? _____

3. Has the subject contacted new, special, or unusual substances (e.g., new laundry detergents, soap, personal care product, poison ivy, etc.)? □ Yes □ No

If so what kind? _____

4. Has the subject taken any other medication (over the counter, prescription, vitamins, and supplement)? □ Yes □ No

If so what kind? _____

5. Has the subject consumed unaccustomed, special or unusual foods? □ Yes □ No

If so what kind? _____

6. Does the subject have or had in the last few days any illness? □ Yes □ No

If so what kind? _____

7. Has the subject come into contact with any family or house members who are ill? □ Yes □ No

If so who and what? _____

8. Has the subject recently been near children who have a skin reaction, skin eruption, or rash (e.g. *Molluscum Contagiosum*)? □ Yes □ No

9. Has the subject had recent sun exposure? □ Yes □ No

10. For the current rash, have there been any systemic clinical signs? □ Yes □ No

If so what kind? _____

i. Anaphylaxis? □ Yes □ No
ii. Signs of hypotension? □ Yes □ No
iii. Signs of dyspnea? □ Yes □ No
iv. Fever, night sweats, chills? □ Yes □ No

11. For the current rash, has the subject needed subcutaneous epinephrine or other systemic catecholamine therapy? □ Yes □ No

If so what kind? _____

12. For the current rash, has the subject used any other medication, such as inhaled bronchodilators, antihistaminic medication, topical corticosteroid, and/or systemic corticosteroid? □ Yes □ No

List medication(s) and dose(s): _____
_____

13. Is the rash pruritic (itchy)? □ Yes □ No

APPENDIX 4 – Focused Skin Examination

Focused Skin Examination:
Key information should be summarized and entered on the Adverse Experience eCRF.

Primary Skin Lesions Description
Color: _____

General description:
_____
_____

Describe the distribution of skin reaction, skin eruption, or rash on the body:
_____
_____

Is skin reaction, skin eruption, or rash resolving or continuing to spread?
_____
_____

Any associated signs on physical examination?
_____
_____