NCI Protocol #: N/A

DF/HCC Protocol #: 17-448

TITLE: A Phase 2 Study of pembrolizumab in patients with histiocyte/dendritic cell neoplasms and biologically selected subtypes of relapsed/refractory aggressive lymphomas.

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Study Exempt from IND Requirements per 21 CFR 312.2(b).

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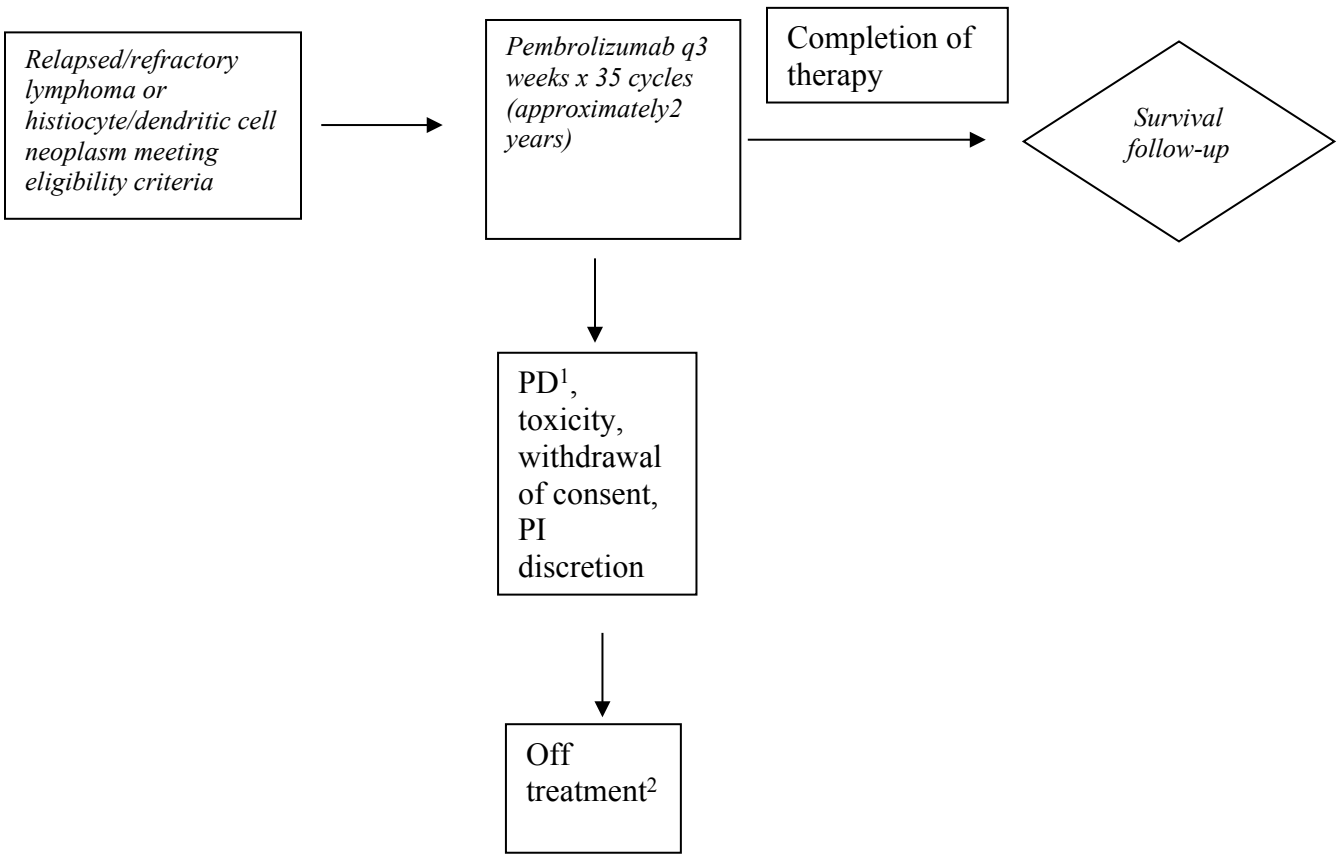
SCHEMA



[1]In certain circumstances, subjects will be allowed to continue treatment past PD (see Section 5.8)
[2]will still have survival follow-up; patients who are removed for reasons other than PD will also be followed for response

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1. OBJECTIVES

1.1 Study Design

This is a phase II, open-label, non-randomized study of pembrolizumab in patients with histiocyte/dendritic cell neoplasms or relapsed or refractory biologically selected subsets lymphoma. Pembrolizumab 200 mg IV will be administered every 3 weeks for 35 cycles (approximately 2 years) or until disease progression, toxicity precluding treatment, sustained CR, withdrawal of consent, and/or investigator discretion.

1.2 Primary Objectives

- To examine the efficacy (overall response rate) of pembrolizumab in patients with biologically selected subsets of relapsed/refractory (R/R) biologically selected subgroups of lymphoma, using 2014 Lugano criteria (31, appendix C).

1.3 Secondary Objectives

- To examine the rates of complete response, partial response, stable disease, and progressive disease with pembrolizumab in the group of patients with biologically selected subsets of R/R biologically selected subgroups of lymphoma and histiocyte/dendritic cell neoplasms, using the 2014 Lugano criteria (31, appendix C)
- To examine the efficacy (overall response rate) of pembrolizumab in patients with histiocytic sarcoma, follicular dendritic cell sarcoma, and interdigitating dendritic cell sarcoma using 2014 Lugano criteria (31, appendix C).
- To examine the duration of response, duration of complete response, and progression-free survival associated with pembrolizumab treatment in this patient population, using the 2014 Lugano criteria (31, appendix C).
- To examine the rates of overall, complete and partial response as well as stable disease, progression-free survival and duration of remission using the LyRIC criteria [32, appendix B]
- To examine the safety and toxicity of pembrolizumab in patients with biologically selected subsets of R/R lymphoma and histiocyte/dendritic cell neoplasms.

1.4 Exploratory Objectives

- To evaluate the expression of PD-L1, genetic integrity of PD-L1/2 locus, and latent viral infection in a selected subset tumors, and preliminarily correlate those with clinical outcome.
- To study the immune microenvironment and circulating lymphocyte subsets in patients before and after pembrolizumab, and preliminarily correlate those with clinical outcome.

2. BACKGROUND

Refer to the Investigator's Brochure (IB)/approved labeling for detailed background information

on pembrolizumab (MK-3475).

2.1 **Study Diseases**

The current standard of care for patients with DLBCL who are refractory to or who relapse after first line therapy consists of salvage chemotherapy and, if a remission is achieved, consolidation by high-dose therapy with autologous stem cell transplantation (ASCT). This is typically considered the last chance at curative therapy. Unfortunately, many patients are not candidates for ASCT. Also, the majority of patients who relapse after modern first-line therapy may not achieve the remission needed to proceed to ASCT. Even among patients who do proceed to ASCT many will relapse. For patients with primary refractory disease or patients who relapse after ASCT, the outcomes are dismal. Thus, relapsed/refractory DLBCL represents an urgent, unmet clinical need.

Immune checkpoint blockade is a promising strategy in DLBCL. Immune checkpoint blockade has already established a favorable track record in the treatment of DLBCL. The anti-PD1 antibody pidilizumab administered to patients with DLBCL after ASCT proved to be safe and associated with promising response rate and progression-free survival especially among the higher risk subgroup of patients on the trial[1]. In a phase 1b study of patients with hematologic malignancies, another anti-PD1 antibody, nivolumab, was associated with a response rate of 36% in DLBCL[2].

It is possible to select a subset of DLBCL tumors which may be particularly vulnerable to PD-1 blockade. In two independent phase 1 studies of PD-1 blockade (one using the monoclonal antibody nivolumab and one using pembrolizumab), patients with heavily pre-treated relapsed/refractory classical Hodgkin lymphoma had remarkably high response rates (87% and 65%, respectively) [3,4]. This validated the pre-clinical work showing that HL tumor cells very frequently over-express the PD-1 ligands PD-L1 and PD-L2 on the cell surface, most often as a result of genetic amplification events at the 9p24.1 locus[5]. These results lend credence to the hypothesis that some hematologic malignancies such as HL may have particularly strong dependence on the PD-1 pathway for survival, and that those tumors are ideal targets for PD-1 blockade. In the case of DLBCL, PD-L1 expression on the tumor cell surface, while encountered occasionally, is not a universal event, and that genetic events such as occur in HL are rare. This difference may explain the variation in response rates between the two histologies seen in clinical studies. It also suggests that selecting DLBCL subtypes with a dependence on PD-1 could result in significantly higher response rates.

Recent work has demonstrated that there are indeed subtypes of DLBCL that seem to have a high frequency of PD-L1 surface over expression, implying a larger reliance on checkpoint blockade for survival and a higher vulnerability to PD-1 blockade. One of those subtypes is primary mediastinal B-cell lymphoma (PMBL), which like HL frequently harbors genetic amplification at 9p24[6,7]. The susceptibility of this entity to pembrolizumab is being tested in an ongoing phase II trial. The other DLBCL subtypes with frequent PD-L1 over expression are EBV-positive DLBCL, post-transplant lymphoproliferative disease (PTLD), plasmablastic lymphoma, and the histological variant of DLBCL T-cell/histiocyte rich DLBCL (TCRLBCL) [8,9]. These DLBCL subtypes represent 30% of unselected DLBCLs.

Histiocyte and dendritic cell neoplasms. Histiocytic sarcoma (HS) is an extremely rare and generally aggressive malignancy for which no standard therapy exists. Patients with unifocal disease amenable to surgical resection and/or radiation with curative intent are thought to have a better prognosis, although in one series of 15 patients there was no difference in survival between those with localized disease and those with disseminated disease (33). Unfortunately, histiocytic sarcoma generally does not respond well to cytotoxic chemotherapy and the outcome for patients with multifocal disease is poor. No standard systemic therapy exists and most clinicians utilize regimens developed for aggressive non-Hodgkin lymphomas. Some of the responses described with these regimens originate from a time when limited diagnostic techniques were available and aggressive lymphomas may have been misdiagnosed as histiocytic sarcoma. Nonetheless, these regimens remain widely used. The two most commonly utilized regimens are cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) or ifosfamide, carboplatin, and etoposide with mesna (ICE) though response rates are poor (33).

BRAF V6000E mutations do occur in a small subset of histiocytic sarcoma and there are case reports describing responses to BRAF inhibitors in histiocytic sarcoma (34). More recently, PD–L1 expression has been demonstrated in 50% of cases of histiocytic sarcoma creating the possibility that immunotherapy with PD–L1 or PD–1 inhibitors may be a potential option (35). At present, however, there is no published clinical experience with these immunotherapies in histiocytic sarcoma.

Follicular dendritic cell sarcoma (FDCS) is a very rare disease of mesenchymal origin (36). The optimal therapy for FDCS remains unknown. In a pooled analysis that included 343 cases of FDCS, 31% of patients presented with isolated nodal disease, 58% had isolated extranodal involvement and only 10% had both nodal and extranodal involvement. With a median follow-up of 20 months, local recurrences or distant metastases occurred in approximate 45% of patients after initial treatment. FDCS is amenable to surgical resection and/or radiation when localized but does not often respond well to chemotherapy as evidenced by 2 year survival rates of 82.4% for early disease, 80% for locally advanced disease, but only 42.8% for metastatic disease (37). Copy number gains in 9p24 and expression of PD-L1 have been reported, making immunotherapy with PD-1 or PD-L1 blockade a therapeutic possibility though there are no clinical reports demonstrating efficacy (38).

Interdigitating dendritic cell sarcoma (IDCS) is an extremely rare disease arising from interdigitating dendritic cells are found in the paracortex of lymph nodes. Pooled data from reported cases demonstrated a significantly lower overall survival in patients with metastatic disease (38.46% at 1 year) compared to local disease (84.8% at 1 year). The median survival for patients with metastatic disease was 9 months. The majority of patients with local disease were still alive at last follow up (82%) and median survival was not reached (39). The SEER registry data revealed a similar pattern with a median survival of 10 months in patients with metastatic disease while the median survival was not reached in those with localised disease (40). Surgery is the mainstay of treatment in patients with localised disease. Patients with metastatic disease are usually treated with chemotherapy. A range of chemotherapy treatments have been reported but responses are often absent/short-lived and outcomes remain poor. Chemotherapy regimens reported include ABVD (doxorubicin, bleomycin, vinblastine, dacarbazine); CHOP (cyclophosphamide, doxorubicin, vincristine and prednisolone); docetaxel + gemcitabine; IE (ifosfamide and eoposide). In the absence of consistent reports of successful treatment with

specific regimens it is not possible to make definitive treatment recommendations and responses to chemotherapy are typically poor (39, 40). Data on PD-L1 expression in IDCS is limited but PD-L1 expression was demonstrated in 40% of cases tested in one small series (35).

T cell lymphomas: Peripheral T-cell lymphomas (PTCL) account for ~10% of all cases of non-Hodgkin's lymphoma (NHL) diagnosed in North America and Western Europe (41). Although initial response rates with anthracycline based chemotherapy with or without autologous stem cell transplantation are high, relapses are extremely common (42). Patients with relapsed/refractory PTCL have a poor prognosis and most patients die within one year (43).With notable exceptions as discussed below, approximately 30% of PTCLs will be characterized by EBV and/or PD-L1 expression (44). However, angioimmunoblastic T cell lymphoma (AITL) is almost always characterized by PD-1 expression and is frequently associated with a clonal EBV+ B cell infiltrate which is of unknown significance in the pathophysiology of the disease (45). Additionally, extranodal NK/T cell lymphoma is universally EBV+ and frequently expresses PD-L1 (46). PD-1 inhibition has been studied in a small, unselected subset of PTCL as well as cutaneous T cell lymphoma and has demonstrated responses (2,47). Selecting histologies with biologic rationale predicting response to pembrolizumab warrants further study.

In summary, the group of tumors included in this protocol represents a very promising target for anti-PD-1 therapy. This hypothesis can be readily tested in a phase 2 study of pembrolizumab in patients with subtypes of relapsed/refractory lymphomas and histiocyte/dendritic cell neoplasms expected to have a high frequency of PD-L1 surface over expression. If the hypothesis is confirmed, it could define a subset of lymphoma and histiocyte/dendritic cell patients in whom pembrolizumab is a therapeutically useful agent leading to further study as a single agent or in combination with other therapies in this subgroup of patients. We therefore propose a multicenter phase 2 trial of pembrolizumab in patients with biologically selected subtypes of lymphoma and histiocyte/dendritic cell neoplasms to establish the efficacy of pembrolizumab in these patient populations.

2.2 **Study Agent**

The importance of intact immune surveillance in controlling outgrowth of neoplastic transformation has been known for decades[10]. Accumulating evidence shows a correlation between tumor-infiltrating lymphocytes (TILs) in cancer tissue and favorable prognosis in various malignancies. In particular, the presence of CD8+ T-cells and the ratio of CD8+ effector T-cells / FoxP3+ regulatory T-cells seems to correlate with improved prognosis and long-term survival in many solid tumors[11-15].

The PD-1 receptor-ligand interaction is a major pathway hijacked by tumors to suppress immune control. The normal function of PD-1, expressed on the cell surface of activated T-cells under healthy conditions, is to down-modulate unwanted or excessive immune responses, including autoimmune reactions. PD-1 (encoded by the gene Pdcd1) is an Ig superfamily member related to CD28 and CTLA-4 which has been shown to negatively regulate antigen receptor signaling upon engagement of its ligands (PD-L1 and/or PD-L2)[16-17]. The structure of murine PD-1 has been resolved[18]. PD-1 and family members are type I transmembrane glycoproteins containing an Ig Variable-type (V-type) domain responsible for ligand binding and a cytoplasmic tail which

is responsible for the binding of signaling molecules. The cytoplasmic tail of PD-1 contains 2 tyrosine-based signaling motifs, an immunoreceptor tyrosine-based inhibition motif (ITIM) and an immunoreceptor tyrosine-based switch motif (ITSM). Following T-cell stimulation, PD-1 recruits the tyrosine phosphatases SHP-1 and SHP-2 to the ITSM motif within its cytoplasmic tail, leading to the dephosphorylation of effector molecules such as CD3ζ, PKCθ and ZAP70 which are involved in the CD3 T-cell signaling cascade[16,19-21]. The mechanism by which PD-1 down modulates T-cell responses is similar to, but distinct from that of CTLA-4 as both molecules regulate an overlapping set of signaling proteins[22,23]. PD-1 was shown to be expressed on activated lymphocytes including peripheral CD4+ and CD8+ T-cells, B-cells, T regs and Natural Killer cells[24,25]. Expression has also been shown during thymic development on CD4-CD8- (double negative) T-cells as well as subsets of macrophages and dendritic cells[26]. The ligands for PD-1 (PD-L1 and PD-L2) are constitutively expressed or can be induced in a variety of cell types, including non-hematopoietic tissues as well as in various tumors[22; 27-29]. Both ligands are type I transmembrane receptors containing both IgV- and IgC-like domains in the extracellular region and contain short cytoplasmic regions with no known signaling motifs. Binding of either PD-1 ligand to PD-1 inhibits T-cell activation triggered through the T-cell receptor. PD-L1 is expressed at low levels on various non-hematopoietic tissues, most notably on vascular endothelium, whereas PD-L2 protein is only detectably expressed on antigen-presenting cells found in lymphoid tissue or chronic inflammatory environments.

PD-L2 is thought to control immune T-cell activation in lymphoid organs, whereas PD-L1 serves to dampen unwarranted T-cell function in peripheral tissues[22]. Although healthy organs express little (if any) PD-L1, a variety of cancers were demonstrated to express abundant levels of this T-cell inhibitor. PD-1 has been suggested to regulate tumor-specific T-cell expansion in subjects with melanoma[30]. This suggests that the PD-1/PD-L1 pathway plays a critical role in tumor immune evasion and should be considered as an attractive target for therapeutic intervention.

Pembrolizumab is a potent and highly selective humanized monoclonal antibody (mAb) of the IgG4/kappa isotype designed to directly block the interaction between PD-1 and its ligands, PD-L1 and PD-L2. Keytruda™ (pembrolizumab) has been approved in the United Stated for the treatment of select patients with unresectable or metastatic melanoma, non-small cell lung cancer, and squamous cell carcinoma of the head and neck.

2.3 **Rationale**

It is possible to select a subset of lymphomas as well as histiocyte/dendritic cell neoplasms that frequently over-expresses PD-L1 or, in the case of AITL, are characterized by near universal PD-1 expression. Such selection could significantly increase the response rate to PD-1 blockade compared to that of an unselected population. If the hypothesis is confirmed, it could define a subset of patients in whom pembrolizumab is a therapeutically useful agent. We therefore propose a multicenter phase 2 trial of pembrolizumab in patients with biologically selected subtypes of lymphoma and histiocyte/dendritic cell neoplasms. The goal of this study is to lay the groundwork for a new treatment paradigm in this lymphoma subgroup.

The choice of the 200 mg Q3W as an appropriate dose for is based on simulations performed using the population PK model of pembrolizumab showing that the fixed dose of 200 mg every 3 weeks will provide exposures that 1) are optimally consistent with those obtained with the 2 mg/kg dose

every 3 weeks, 2) will maintain individual patient exposures in the exposure range established in melanoma as associated with maximal efficacy response and 3) will maintain individual patients exposure in the exposure range established in melanoma that are well tolerated and safe.

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

2.4 Correlative Studies Background

The scientific basis for PD-1 blockade in biologically selected subtypes of lymphoma and histioctye/dendritic cell neoplasms has been discussed above. We propose to conduct correlative studies examining the relationship between PD-1/PD-L1/PD-L2 expression and treatment outcome and on possible mechanisms of immune escape after PD-1 blockade in patients who relapse in whom a post-relapse tumor biopsy can be obtained. The exact studies to be performed are subject to sample and funding availability.

3. PARTICIPANT SELECTION

3.1 Eligibility Criteria

3.1.1 Be willing and able to provide written informed consent for the trial.

3.1.2 Histologically confirmed diagnosis of a histiocyte/dendritic cell neoplasm or relapsed/refractory aggressive lymphoma with at least one of the following features (with review required at a participating study center):

- Diffuse large B-cell lymphoma with EBV positive tumor cells (defined as positive EBV-encoded RNA in tumor cells)
- Diffuse large B-cell lymphoma, leg type (DLBCL-LT)
- Plasmablastic lymphoma
- T cell/histiocyte rich DLBCL
- EBV+ T cell lymphoma of any histology; note, patients with angioimmunoblastic T cell lymphoma will be eligible regardless of EBV status
- Histiocytic sarcoma
- Follicular dendritic cell sarcoma
- Interdigitating dendritic cell sarcoma

3.1.3 For patients with histiocytic sarcoma, interdigitating dendritic cell sarcoma, or follicular dendritic cell sarcoma only: disease that is not amenable to surgical resection and/or radiation therapy with curative intent.

3.1.4 For lymphoma patients only: At least one prior systemic chemotherapy including an alkylating agent and anthracycline (unless contraindicated), and an anti-CD20 monoclonal antibody if the tumor is CD20+. Prior treatment with anthracycline and alkylating agent is not required for patients with NK/T cell lymphoma but prior treatment with platinum-based chemotherapy and/or l-asparaginase is required.

3.1.5 For lymphoma patients only: Participants must have received and relapsed after autologous stem cell transplantation (ASCT), or be ineligible for ASCT (including on the basis of refractory disease), or have declined ASCT

3.1.6 Age 18 years or older at the time of signing consent.

3.1.7 ECOG performance status of 0 or 1 (Karnofsky ≥70%, see Appendix A)

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

- absolute neutrophil count ≥ 500/mcL
- platelets ≥75,000/mcL (≥ 30,000 if there is bone marrow involvement with lymphoma)
- total bilirubin ≤ 1.5 times the institutional upper limit of normal (ULN) OR direct bilirubin ≤ the normal in subjects with total bilirubin >1.5 times the ULN
- AST(SGOT)/ALT(SGPT) ≤2.5 × institutional ULN or ≤ 5 times ULN in patients with known hepatic involvement with lymphoma
- albumin ≥ 2.5 mg/dl
- creatinine ≤ 1.5 times the normal upper institutional limit **OR** creatinine clearance ≥60 mL/min/1.73 m^2 in participants with creatinine levels > 1.5 times the normal upper institutional limit
- INR, aPTT or PT ≤ 1.5 times the ULN unless subject is receiving anticoagulation therapy as long as PT or aPTT are within therapeutic range of intended use of anticoagulant

3.1.9 Be willing to provide tissue from a newly obtained core needle or excisional biopsy. Newly-obtained is defined as a specimen obtained up to and including 90 days prior to treatment day 1. Subjects for whom newly obtained samples cannot be provided may be enrolled only with agreement by the overall PI.

3.1.10 No prior allogeneic transplant unless all of the following apply:

- At least 5 years from time of transplant
- Absence of clinically significant graft-versus-host disease (GVHD)
- Not on immune suppression
- Approval of overall PI

3.1.11 Not a candidate for potentially curative therapy at the time of enrollment

3.1.12 Measurable disease per the Lugano criteria.

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

3.1.14 Female subjects of childbearing potential must be willing to use an adequate method of contraception as outlined in Section 5.4.3 – Contraception for the course of the study through 120 days after the last dose of study medication.

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

3.1.15 Male subjects of childbearing potential must agree to use an adequate method of contraception as outlined in Section 5.4.3- Contraception, starting with the first dose of study therapy through 120 days after the last dose of study therapy.

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

3.1.16 The effects of pembrolizumab on the developing human fetus are unknown. 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.

3.2 **Exclusion Criteria**

3.2.1 Prior treatment with a PD-1, PD-L1 or PD-L2 inhibitor

3.2.2 Has had a prior anti-cancer monoclonal antibody within 4 weeks prior to study day 1 or has not recovered (i.e., ≤ grade 1 or at baseline) from adverse events due to a previously administered agent.

3.2.3 Participants who have had chemotherapy, targeted small molecule therapy, or radiotherapy within 2 weeks prior to study day 1 (6 weeks for nitrosoureas or mitomycin C) or who has not recovered (i.e., ≤ grade 1 or at baseline) from adverse events due to previously administered agents. Note: subjects with ≤ grade 2 peripheral neuropathy are an exception to this criterion and may qualify for the study.

3.2.4 Radiation therapy within 2 weeks of study treatment

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

3.2.6 Has a known history of active tuberculosis.

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

3.2.8 Has an active infection requiring systemic therapy.

3.2.9 Has active autoimmune disease that has required systemic treatment in the past 2 years (i.e., with the use of disease modifying agents, corticosteroids, or immunosuppressive drugs). Replacement therapy (e.g., thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal her pituitary insufficiency, etc.) is not considered a form of systemic treatment.

3.2.10 Has a diagnosis of immunodeficiency or is receiving any form of immunosuppressive therapy within 7 days prior to the first dose of trial treatment or is taking chronic systemic steroids (in doses exceeding 10 mg daily of prednisone equivalent) within 7 days prior to the first dose of trial treatment. Note: Subjects with asthma or chronic obstructive pulmonary disease that require intermittent use of bronchodilators, inhaled steroids, or local steroid injections are not excluded from the study.

3.2.11 Has a history of non-infectious pneumonitis that required systemic corticosteroid treatment or has active pneumonitis.

3.2.12 Known active central nervous system involvement and/or carcinomatous meningitis. Subjects with previously treated brain metastases may participate provided they are stable (without evidence of progression by imaging for at least 4 weeks prior to the first dose of trial treatment and any neurologic symptoms have returned to baseline), have no evidence of new or enlarging brain metastases, and are not using steroids for at least 7 days prior to trial treatment. This exception does not include carcinomatous meningitis which is excluded regardless of clinical stability.

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

3.2.14 Active hepatitis B (e.g., hepatitis B surface antigen reactive) or hepatitis C (e.g., hepatitis C virus RNA detectable).

3.2.15 Human immunodeficiency virus (HIV 1/2).

3.2.16 Is pregnant or breast-feeding or expecting to conceive or father children within the projected duration of the trial, starting with the screening visit until 120 days after the last dose of trial treatment.

3.2.17 Has received a live vaccine within 30 days of planned start of study therapy. (Note: seasonal influenza vaccines for injection are allowed as they are inactivated; however, intranasal influenza vaccines are live attenuated vaccines and are NOT allowed)

3.2.18 History of allergic reactions attributed to compounds of similar chemical or biologic composition to pembrolizumab.

3.2.19 Baseline pulse oximetry <94% or requires oxygen supplementation of any kind

3.2.20 If subject underwent major surgery they must have recovered adequately from the toxicity and/or complications from the procedure prior to starting therapy.

3.2.21 Uncontrolled intercurrent illness including, but not limited to symptomatic congestive heart failure, unstable angina pectoris, or cardiac arrhythmia.

3.3 Inclusion of Women and Minorities

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

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 therapy. Any participant not registered to the protocol before protocol therapy begins 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 therapy. 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 participant's registration on the study must be canceled. Registration cancellations must be made in OnCore as soon as possible.

4.2 Registration Process for DF/HCC Institutions

DF/HCC Standard Operating Procedure for Human Subject Research Titled *Subject Protocol Registration* (SOP #: REGIST-101) must be followed.

4.3 General Guidelines for Other Investigative Sites

Eligible participants will be entered on study centrally at the DF/HCC by the Project Manager. All sites should call the Project Manager at 617-632-2328 to verify study slot availabilities.

Following registration, participants should begin protocol therapy within 5 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 participant's registration on the study must be canceled. The Project Manager 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 DFCI Project Manager:

- Copy of required laboratory tests including: All screening evaluations.
- Signed informed consent document
- HIPAA authorization form (if separate from the informed consent document)
- Other appropriate forms (e.g., Eligibility Screening Worksheet, Registration form)

The research nurse or data manager at the participating site will then call 617-632-2328 or e-mail Megan_Forsyth@DFCI.HARVARD.EDU to verify eligibility. To complete the registration process, the Coordinator will follow DF/HCC Standard Operating Procedure for Human Subject Research Titled Subject Protocol Registration (SOP #: REGIST-101) and register the participant on the protocol. The coordinator will fax or e-mail the participant study number, and if applicable the dose treatment level, to the participating site. The coordinator will also call the research nurse or data manager at the participating site and verbally confirm registration

5. TREATMENT PLAN

5.1 Treatment Regimen

The rationale for selection of doses to be used in this trial is provided in Section 2.3 – Rationale.

Details on preparation and administration of pembrolizumab are provided in the Pharmacy Manual.

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. No dose reductions are allowed. 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 35 cycles (approximately 2 years) or until disease progression, prohibitive toxicity, withdrawal of consent, or investigator discretion.

5.2 **Pre-Treatment Criteria**

5.2.1 Cycle 1, Day 1

In order to receive the first dose of study treatment, the participant must meet all of the eligibility criteria. All study therapy will occur in the outpatient setting.

5.2.2 Subsequent Cycles

Trial treatment should be administered on Day 1 of each cycle after all procedures/assessments have been completed as detailed in the study calendar (Section 10). Trial treatment may be administered up to 3 days before or after the scheduled Day 1 of each cycle due to administrative or logistical reasons.

A bone marrow biopsy at screening will only be required if patients have unexplained cytopenias of grade 2 or greater at baseline or if PET/CT is suggestive of bone marrow involvement.

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. In addition, treatment should be delayed if the subject’s resting oxygen saturation is <94% while breathing ambient air. Criteria to resume treatment are also listed in Section 6.

5.3 **Agent Administration**

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 200 mg for all patients regardless of weight or body surface area.

5.3.2 Drug Administration

Pembrolizumab infusions will be administered as a 30 minute IV infusion, 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. No pre-hydration is necessary. The pharmacy manual contains specific instructions for the preparation of the pembrolizumab infusion fluid and administration of the infusion solution.

5.4 **General Concomitant Medication and Supportive Care Guidelines**

5.4.1 Concomitant Medications/Vaccinations (Allowed & Prohibited)

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

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

- Anti-neoplastic systemic chemotherapy or biological therapy
- Immunotherapy not specified in this protocol
- Investigational agents other than pembrolizumab
- Radiation therapy except in selected cases, radiation to a localized area(s) of symptomatic disease may be allowed, after consultation with the study chair, and if the radiated lesions are not the target lesions for response assessment. In such cases, pembrolizumab treatment will be interrupted during the radiotherapy.
- Live vaccines within 30 days prior to starting treatment and while receiving study treatment.
- Immunosuppressive therapy.
- Systemic glucocorticoids for any purpose. The use of physiologic doses of corticosteroids may be approved after consultation with the overall Principal Investigator. NOTE: Systemic steroids can be given as premedication for blood products, treatment of adverse events, and/or contrast media for imaging procedures.
- Intravenous immune globulin is allowed at the discretion of the treating physician for replacement of immune globulin deficiencies.

Subjects who, in the assessment of the investigator, require the use of any of the aforementioned treatments for clinical management should be removed from the trial.

All treatments that the investigator considers necessary for a subject's welfare may be administered at the discretion of the investigator in keeping with the community standards of medical care. All concomitant medication will be recorded on the case report form (CRF) including all prescription, over-the-counter (OTC), herbal supplements, and IV medications and fluids. If changes occur during the trial period, documentation of drug dosage, frequency, route, and date may also be included on the CRF.

All concomitant medications received within 28 days before the first dose of trial treatment and 30 days after the last dose of trial treatment should be recorded. Concomitant medications administered after 30 days after the last dose of trial treatment should be recorded for SAEs and ECIs as defined in Section 7.2.

The exclusion criteria describe other medications which are prohibited in this trial.

There are no prohibited therapies during the post-treatment follow-up phase.

Nausea/vomiting: Nausea and vomiting should be treated aggressively, and consideration should be given in subsequent cycles to the administration of prophylactic antiemetic therapy per 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.

Cytopenias: growth factors and blood product transfusion support are allowed on this trial.

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

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

Note: if after the evaluation the event is determined not to be related, the investigator does not need to follow the treatment guidance (as outlined below). Refer to Section 6 for dose modification.

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

- **Pneumonitis**:
    - For **Grade 2 events**, treat with systemic corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.
    - For **Grade 3-4 events**, immediately treat with intravenous steroids. Administer additional anti-inflammatory measures, as needed.

      Add prophylactic antibiotics for opportunistic infections in the case of prolonged steroid administration.

- **Diarrhea/Colitis**:

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

    - All subjects who experience diarrhea/colitis should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion. For Grade 2 or higher diarrhea, consider GI consultation and endoscopy to confirm or rule out colitis.
    - For **Grade 2 diarrhea/colitis,** administer oral corticosteroids.
    - For **Grade 3 or 4 diarrhea/colitis,** treat with intravenous steroids followed by high dose oral steroids.
    - When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.

- **Type 1 diabetes mellitus (if new onset, including diabetic ketoacidosis [DKA]) or ≥ Grade 3 Hyperglycemia, if associated with ketosis (ketonuria) or metabolic acidosis (DKA)**
    - For **T1DM** or **Grade 3-4** Hyperglycemia
        - Insulin replacement therapy is recommended for Type I diabetes mellitus and for Grade 3-4 hyperglycemia associated with metabolic acidosis or ketonuria.
        - Evaluate patients with serum glucose and a metabolic panel, urine ketones, glycosylated hemoglobin, and C-peptide.

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

Replacement of appropriate hormones may be required as the steroid dose is tapered.

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

- **Hyperthyroidism or Hypothyroidism**:

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

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

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

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

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

Table 1 below shows treatment guidelines for subjects who experience an infusion reaction associated with administration of pembrolizumab (MK-3475).

Table 1. Infusion Reaction Treatment Guidelines

NCI CTCAE Grade	Treatment	Premedication at subsequentdosing
Grade 1 Mild reaction; infusion interruption not indicated; intervention not indicated	Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator.	None
Grade 2 Requires infusion interruption but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDS, narcotics, IV fluids); prophylactic medications indicated for < =24 hrs	**Stop Infusion and monitor symptoms.** Additional appropriate medical therapy may include but is not limited to: IV fluids Antihistamines NSAIDS Acetaminophen Narcotics Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator. If symptoms resolve within one hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (e.g., from 100 mL/hr to 50 mL/hr). Otherwise dosing will be held until symptoms resolve and the subject should be premedicated for the next scheduled dose. **Subjects who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further trial treatment administration.**	Subject may be premedicated 1.5h (± 30 minutes) prior to infusion of pembrolizumab (MK-3475) with: Diphenhydramine 50 mg po (or equivalent dose of antihistamine). Acetaminophen 500-1000 mg po (or equivalent dose of antipyretic).
Grades 3 or 4 Grade 3: Prolonged (i.e., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (e.g., 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.		

Detailed guidelines for management of irAEs are provided in Table 3.

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.

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

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

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

OR

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

OR

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

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

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

OR

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

Acceptable methods of contraception are[‡]:

(1) Single method (one of the following is acceptable):
  (a) Intrauterine device (IUD)
    (i) Vasectomy of a female subject's male partner
    (ii) Contraceptive rod implanted into the skin

(2) Combination method (requires use of two of the following):
  (a) diaphragm with spermicide (cannot be used in conjunction with cervical cap/spermicide)
  (b) cervical cap with spermicide (nulliparous women only)
  (c) contraceptive sponge (nulliparous women only)

(d) male condom or female condom (cannot be used together)
(e) hormonal contraceptive: oral contraceptive pill (estrogen/progestin pill or progestin-only pill), contraceptive skin patch, vaginal contraceptive ring, or subcutaneous contraceptive injection

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

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

Subjects should be informed that taking the study medication may involve unknown risks to the fetus (unborn baby) if pregnancy were to occur during the study. To participate in the study subjects of childbearing potential must adhere to the contraception requirement (described above) from the day of study medication initiation (or 14 days prior to the initiation of study medication for oral contraception) throughout the study period up to 120 days after the last dose of trial therapy. If there is any question that a subject of childbearing potential will not reliably comply with the requirements for contraception, that subject should not be enrolled on 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 outcome of the pregnancy will be reported to the principal investigator and to Merck without delay and within 24 hours to the principal investigator and within 2 working days to Merck if the outcome is a serious adverse experience (e.g., death, abortion, congenital anomaly, or other disabling or life-threatening complication to the mother or newborn).

The study investigator will make every effort to obtain permission to follow the outcome of the pregnancy and report the condition of the fetus or newborn to 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 principal investigator and to Merck and followed as described above and in Section 7.3.4.

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. In the absence of treatment delays due to adverse event(s), treatment may continue for

35 cycles until one of the following criteria applies:

- Disease progression
- 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, Eric Jacobsen at 617-632-6633 (pager 41475).

5.6 **Duration of Follow Up**

Participants will be followed for survival every 12 weeks (± 14 days) for 24 months after completion of protocol therapy, discontinuation of protocol therapy or until death, whichever occurs first. Survival follow-up may be conducted by telephone or email contact with the participant or his/her primary physician. Participants removed from protocol therapy for unacceptable adverse event(s) will be followed until resolution or stabilization of the adverse event regardless of the duration of follow-up required.

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-related activities
- Lost to follow-up
- Withdrawal of consent
- 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).

For Centralized Subject Registrations, the research team submits a completed Off Treatment/Off Study form to ODQ when a participant comes off study. This form can be found on the ODQ website or obtained from the ODQ registration staff.

For Decentralized Subject Registrations, the research team updates the relevant Off Treatment/Off Study information in OnCore.

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 (the LyRIC criteria) for patients with lymphoma treated with immunotherapy (32). The management of patients with apparent progressive disease on this trial should generally follow the recommendations of the LyRIC criteria. Patients with confirmed PD using LyRIC criteria who are still felt to derive clinical benefit and have no alternative option for care may still continue on therapy past PD, after consultation with the study chair.

Criteria for treatment beyond PD (in addition to discussion with study chair):

- Absence of signs or symptoms of progressive disease, including laboratory abnormalities
- No decrease in ECOG performance status
- Absence of rapid PD
- Absence of PD at an anatomically critical site

6. DOSING DELAYS/DOSE MODIFICATIONS

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 2) **from the time treatment has resumed until all 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 its corresponding assessments should take place on week 15, cycle 6 on week 18, etc.

Pembrolizumab will be withheld for drug-related Grade 4 hematologic toxicities, non-hematological toxicity ≥ Grade 2 or 3 (depending on nature of toxicity) including laboratory abnormalities, and severe or life-threatening AEs as per Tables 2 and 3 below. 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 2. Dose Modification Guidelines for Hematological Drug-Related Adverse Events.

Toxicity	Grade	Hold treatment	Timing for restarting treatment	Treatment discontinuation
Hematological	1,2,3	No	N/a	N/a
	4	Yes	Toxicity resolves to grade ≤ 1	Toxicity does not resolve within 12 weeks of last infusion Permanent discontinuation should be considered for any life-threatening event

Adverse events (both non-serious and serious) associated with pembrolizumab exposure may represent an immunologic etiology. These adverse events may occur shortly after the first dose or several months after the last dose of treatment. Pembrolizumab must be withheld for drug-related toxicities and severe or life-threatening AEs as per Table 3 below.

Table 3. Dose modification guidelines for non-hematological drug related adverse events including immune related adverse events (irAEs)

General instructions:

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

Immune-related AEs	Toxicity grade or conditions (CTCAEv4.0)	Action taken to pembrolizumab	irAE management with corticosteroid and/or other therapies	Monitor and follow-up
Pneumonitis	Grade 2	Withhold	• Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper	• Monitor participants for signs and symptoms of pneumonitis • Evaluate participants with suspected pneumonitis with radiographic imaging and initiate corticosteroid treatment • Add prophylactic antibiotics for opportunistic infections
	Grade 3 or 4, or recurrent Grade 2	Permanently discontinue		
Diarrhea / Colitis	Grade 2 or 3	Withhold	• Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper	• Monitor participants for signs and symptoms of enterocolitis (ie, diarrhea, abdominal pain, blood or mucus in stool with or without fever) and of bowel perforation (ie, peritoneal signs and ileus). • Participants with ≥ Grade 2 diarrhea suspecting colitis should consider GI consultation and performing endoscopy to rule out colitis. • Participants with diarrhea/colitis should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion.
	Grade 4	Permanently discontinue		
AST / ALT elevation or Increased	Grade 2	Withhold	• Administer corticosteroids (initial dose of 0.5- 1 mg/kg prednisone or equivalent) followed by taper	• Monitor with liver function tests (consider weekly or more frequently until liver enzyme value returned to baseline or is

bilirubin	Grade 3 or 4	Permanently discontinue	• Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper	stable
Type 1 diabetes mellitus (T1DM) or Hyperglycemia	Newly onset T1DM or Grade 3 or 4 hyperglycemia associated with evidence of β-cell failure	Withhold	• Initiate insulin replacement therapy for participants with T1DM • Administer anti-hyperglycemic in participants with hyperglycemia	• Monitor participants for hyperglycemia or other signs and symptoms of diabetes.
Hypophysitis	Grade 2	Withhold	• Administer corticosteroids and initiate hormonal replacements as clinically indicated.	• Monitor for signs and symptoms of hypophysitis (including hypopituitarism and adrenal insufficiency)
	Grade 3 or 4	Withhold or permanently discontinue[1]		
Hyperthyroidism	Grade 2	Continue	• Treat with non-selective beta-blockers (eg, propranolol) or thionamides as appropriate	• Monitor for signs and symptoms of thyroid disorders.
	Grade 3 or 4	Withhold or permanently discontinue[1]		
Hypothyroidism	Grade 2-4	Continue	• Initiate thyroid replacement hormones (eg, levothyroxine or liothyroinine) per standard of care	• Monitor for signs and symptoms of thyroid disorders.
Nephritis and Renal dysfunction	Grade 2	Withhold	• Administer corticosteroids (prednisone 1-2 mg/kg or equivalent) followed by taper.	• Monitor changes of renal function
	Grade 3 or 4	Permanently discontinue		
Myocarditis	Grade 1 or 2	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 3 or 4	Permanently discontinue		
All other immune-related AEs	Intolerable/ persistent Grade 2	Withhold	• Based on type and severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 3	Withhold or discontinue based on the type of		

		event. Events that require discontinuation include and not limited to: Gullain-Barre Syndrome, encephalitis		
	Grade 4 or recurrent Grade 3	Permanently discontinue		

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

NOTE:

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

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

Management of suspected immune related AEs should follow the guidelines provided in section 5.4.2.

7. ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS

An adverse event is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product or protocol-specified procedure, whether or not considered related to the medicinal product or protocol-specified procedure. Any worsening (i.e., any clinically significant adverse change in frequency and/or intensity) of a preexisting condition that is temporally associated with the use of the pembrolizumab, is also an adverse event.

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

Adverse events may occur during the use of pembrolizumab in clinical trials, or as prescribed in clinical practice, from overdose (whether accidental or intentional), from abuse and from withdrawal.

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

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

From the time of treatment allocation/randomization through 30 days following cessation of treatment, all adverse events must be reported by the investigator. Such events will be recorded at each examination on the Adverse Event case report forms/worksheets. The reporting timeframe for adverse events meeting any serious criteria is described in Section 7.2. The investigator will make every attempt to follow all subjects with non-serious adverse events for outcome.

Adverse events will not be collected for subjects during the pre-screening period (for determination of archival tissue status) if that subject has not undergone any protocol-specified

procedure or intervention. If the subject requires a blood draw, fresh tumor biopsy etc., the subject is first required to provide consent to the main study and AEs will be captured per guidelines for standard AE reporting. 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
- Occasional: nausea/vomiting, arthralgia, anorexia, fever, pneumonitis, hepatotoxicity, vitiligo, autoimmune endocrinopathies including hypophysitis/hypopituitarism, enterocolitis, edema, weakness, thrombocytopenia, xerophthalmia/xerostomia, peripheral neuropathy
- Rare (<1%): acute kidney injury, encephalopathy, other cytopenias, pericarditis, myositis, myocarditis, Stevens-Johnson Syndrome (SJS)/Toxic Epidermal Necrolysis.

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 website: 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 Expedited Adverse Event Reporting

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.

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.

7.3.1 DF/HCC Expedited Reporting Guidelines

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

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

Attribution	**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	Not required	10 working days	24 hours*
Possible Probable Definite	Not required	10 working days	Not required	10 working 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 AE reports from outside institutions to the DFCI OHRS according to DFCI IRB policies and procedures in reporting adverse events.

7.3.2 Definition of an Overdose for This Protocol and Reporting of Overdose to the principal investigator and to Merck

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

indicated. In the event of overdose, the subject should be observed closely for signs of toxicity. Appropriate supportive treatment should be provided if clinically indicated.

If an adverse event(s) is associated with ("results from") the overdose of pembrolizumab, the adverse event(s) is reported as a serious adverse event, even if no other seriousness criteria are met. If a dose of Merck's product meeting the protocol definition of overdose is taken without any associated clinical symptoms or abnormal laboratory results, the overdose is reported as a non-serious Event of Clinical Interest (ECI), using the terminology "accidental or intentional overdose without adverse effect."

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

Each participating site is responsible for reporting to the Overall PI and the Overall PI is responsible for reporting to Merck Global Safety.

7.3.3 Reporting of Pregnancy and Lactation to the principal investigator and to Merck

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

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

Pregnancies and lactations that occur from the time of treatment allocation/randomization through 120 days following cessation of pembrolizumab, or 30 days following cessation of treatment if the subject initiates new anticancer therapy, whichever is earlier, must be reported by the investigator. All reported pregnancies must be followed to the completion/termination of the pregnancy. Pregnancy outcomes of spontaneous abortion, missed abortion, benign hydatidiform mole, blighted ovum, fetal death, intrauterine death, miscarriage and stillbirth must be reported as serious events (Important Medical Events). If the pregnancy continues to term, the outcome (health of infant) must also be reported. Such events must be reported within 24 hours to the principal investigator and within 2 working days to Merck Global Safety. (Attn: Worldwide Product Safety; FAX 215 993-1220)

Each participating site is responsible for reporting the Overall PI and the Overall PI is responsible for reporting to Merck Global Safety.

7.3.4 Immediate Reporting of Adverse Events to Merck

7.3.4.1 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 another important medical event

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

Refer to section 7.3.4.4 and Table 4 for additional details regarding each of the above criteria.

For the time period beginning when the consent form is signed until treatment allocation, 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 must be reported within 24 hours to the principal investigator and within 2 working days to Merck Global Safety if it causes the subject to be excluded from the trial, or is the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure.

For the time period beginning at treatment allocation/randomization through 90 days following cessation of treatment, or 30 days following cessation of treatment if the subject initiates new anticancer therapy, whichever is earlier, any serious adverse event, or follow up to a serious adverse event, including death due to any cause other than progression of the cancer under study (reference Section 7.2 for additional details), whether or not related to the Merck product, must be reported within 24 hours to the principal investigator and within 2 working days to Merck Global Safety.

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

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

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

7.3.4.2 Events of Clinical Interest

Selected non-serious and serious adverse events are also known as Events of Clinical Interest (ECI) and must be reported within 24 hours to the principal investigator and within 2 working days to Merck Global Safety. (Attn: Worldwide Product Safety; FAX 215 993-1220).

For the time period beginning when the consent form is signed until treatment allocation/randomization, any ECI, or follow up to an ECI, that occurs to any subject must be reported within 24 hours to the principal investigator and within 2 working days to Merck Global Safety if it causes the subject to be excluded from the trial, or is the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure.

For the time period beginning at treatment allocation/randomization through 90 days following cessation of treatment, or 30 days following cessation of treatment if the subject initiates new anticancer therapy, whichever is earlier, any ECI, or follow up to an ECI, whether or not related to Merck product, must be reported within 24 hours to the principal investigator and within 24 hours to Merck Global Safety.

Events of clinical interest for this trial include:

1. An overdose of pembrolizumab, as defined in Section 7.3.2 - Definition of an Overdose for This Protocol and Reporting of Overdose to the principal investigator, that is not associated with clinical symptoms or abnormal laboratory results.
2. An elevated AST or ALT lab value that is greater than or equal to 3X the upper limit of normal and an elevated total bilirubin lab value that is greater than or equal to 2X the upper limit of normal and, at the same time, an alkaline phosphatase lab value that is less than 2X the upper limit of normal, as determined by way of protocol-specified laboratory testing or unscheduled laboratory testing.*

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

7.3.4.3 Protocol-Specific Exceptions to Serious Adverse Event Reporting

Efficacy endpoints as outlined in this section will not be reported to Merck as described in Section 7.3.4- Immediate Reporting of Adverse Events to the Sponsor and to Merck, unless there is evidence suggesting a causal relationship between the drug and the event. Any such event will be submitted to the Sponsor within 24 hours and to Merck Global Safety within 2 working days either by electronic or paper media.

Specifically, the suspected/actual events covered in this exception include any event that is disease progression of the cancer under study.

The principal investigator will monitor unblinded aggregated efficacy endpoint events and safety data to ensure the safety of the subjects in the trial. Any suspected endpoint which upon review is not progression of the cancer under study will be forwarded to Merck Global Safety as a SAE within 2 working days of determination that the event is not progression of the cancer under study.

Hospitalization related to convenience (e.g.transportation issues etc.) will not be considered a SAE.

7.3.4.4 Evaluating adverse events

An investigator who is a qualified physician will evaluate all adverse events according to the NCI Common Terminology for Adverse Events (CTCAE), version 4.0. Any adverse event which changes CTCAE grade over the course of a given episode will have each change of grade recorded on the adverse event case report forms/worksheets.

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

Table 4. Evaluating Adverse Events

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

V4.0 CTCAE Grading	**Grade 1**	**Mild; asymptomatic or mid symptoms; clinical or diagnostic observations only; intervention not indicated.**
	Grade 2	**Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL.**
	Grade 3	**Severe or medically significant but not immediately life-threatening; hospitalization or prolongation or hospitalization indicated; disabling; limiting self-care ADL.**
	Grade 4	**Life threatening consequences; urgent intervention indicated.**
	Grade 5	**Death related to AE**
Seriousness	A serious adverse event is any adverse event occurring at any dose or during any use of Merck product that:	
	†**Results in death**; or	
	†**Is life threatening; or** places the subject, in the view of the investigator, at immediate risk of death from the event as it occurred (Note: This does not include an adverse event that, had it occurred in a more severe form, might have caused death.); or	
	†**Results in a persistent or significant disability/incapacity** (substantial disruption of one's ability to conduct normal life functions); or	
	†**Results in or prolongs an existing inpatient hospitalization** (hospitalization is defined as an inpatient admission, regardless of length of stay, even if the hospitalization is a precautionary measure for continued observation. (Note: Hospitalization for an elective procedure to treat a pre-existing condition that has not worsened is not a serious adverse event. A pre-existing condition is a clinical condition that is diagnosed prior to the use of a Merck product and is documented in the patient's medical history.); or	
	†**Is a congenital anomaly/birth defect** (in offspring of subject taking the product regardless of time to diagnosis);or	
	Is a new **cancer** (that is not a condition of the study) **(**although not serious per ICH definition, is reportable to the principal investigator within 24 hours and to Merck within 2 working days to meet certain local requirements); **or**	
	Is an overdose (whether accidental or intentional). Any adverse event associated with an overdose is considered a serious adverse event for collection purposes. An overdose that is not associated with an adverse event is considered a non-serious event of clinical interest and must be reported within 24 hours to the principal investigator and to Merck within 2 working days..	
	Other important medical events that may not result in death, not be life threatening, or not require hospitalization may be considered a serious adverse event when, based upon appropriate medical judgment, the event may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed previously (designated above by a †).	
Duration	Record the start and stop dates of the adverse event. If less than 1 day, indicate the appropriate length of time and units	
Action taken	Did the adverse event cause Merck product to be discontinued?	

Relationship to pembrolizumab	Did Merck product cause the adverse event? The determination of the likelihood that Merck product caused the adverse event will be provided by an investigator who is a qualified physician. The investigator's signed/dated initials on the source document or worksheet that supports the causality noted on the AE form, ensures that a medically qualified assessment of causality was done. This initialed document must be retained for the required regulatory time frame. The criteria below are intended as reference guidelines to assist the investigator in assessing the likelihood of a relationship between the test drug and the adverse event based upon the available information. **The following components are to be used to assess the relationship between Merck product and the AE**; the greater the correlation with the components and their respective elements (in number and/or intensity), the more likely Merck product caused the adverse event (AE):	
	Exposure	Is there evidence that the subject was actually exposed to Merck product such as: reliable history, acceptable compliance assessment (pill count, diary, etc.), expected pharmacologic effect, or measurement of drug/metabolite in bodily specimen?
	Time Course	Did the AE follow in a reasonable temporal sequence from administration of Merck product? Is the time of onset of the AE compatible with a drug-induced effect (applies to trials with investigational medicinal product)?
	Likely Cause	Is the AE not reasonably explained by another etiology such as underlying disease, other drug(s)/vaccine(s), or other host or environmental factors

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

7.4 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 per institutional policy.

7.5 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 <u>also</u> be reported in routine study data submissions.**

8. LABELING, PACKAGING, STORAGE AND RETURN OF CLINICAL SUPPLIES

8.1 Investigational Product

The investigator shall take responsibility for and shall take all steps to maintain appropriate records and ensure appropriate supply, storage, handling, distribution and usage of investigational product in accordance with the protocol and any applicable laws and regulations. Clinical Supplies will be provided by Merck as summarized in Table 5.

Table 5. Product Descriptions

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

8.2 Packaging and Labeling Information

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

8.3 Clinical Supplies Disclosure

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

8.4 Storage and Handling Requirements

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

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

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

8.5 Returns and Reconciliation

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

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

A list of the adverse events and potential risks associated with pembrolizumab can be found in Section 7.1.

9. BIOMARKER, CORRELATIVE, AND SPECIAL STUDIES

9.1 Correlative Studies

We will analyze tumors from pre-and on-treatment time points, when available. We plan to

analyze EBV expression, PD-L1 and PD-L2 expression, as well as PD-1 expression in the microenvironment. We will also perform FISH to assess the integrity of the PD-L1/2 locus. We will perform multi-parameter analyses of the tumor micro-environment. In addition, peripheral blood samples will be analyzed for absolute and relative amounts of various lymphocyte subsets. Those results will be correlated with responses, in an exploratory fashion. Those studies are subject to sample and funding availability.

10. STUDY CALENDAR

Baseline evaluations are to be conducted within 28 days of the start of protocol therapy with the exception of the bone marrow biopsy and lymph node biopsy which should be performed within 90 days of cycle 1, day 1. Assessments must be performed prior to the administration of any study agent. Study assessments and agents should be administered within $\pm$ 3 days of the protocol-specified date, unless otherwise noted.

Trial period	Screening	Treatment Cycles									EOT	Post-treatment		
							To be repeated beyond 9 cycles until EOT unless otherwise noted							
Treatment cycle/name		1	2	3	4	5	6	7	8	9[l]	30 days after last dose	60 days post-EOT	Follow-up[d]	Survival follow-up[e]
Scheduling window	-28 to -1		±3	±3	±3	±3	±3	±3	±3	±3	(±10 days)	(±10 days)	Q12 weeks (±14 days) from last post-treatment visit	Q12 weeks (±14 days)
Informed consent	X													
Performance status	X	X	X	X	X	X	X	X	X	X	X	X	X	
Demographics	X													
Medical history	X													
Concurrent meds	X	X----------											----------X	
Physical exam	X	X	X	X	X	X	X	X	X	X	X	X	X	
Vital signs including pulse oximetry	X	X	X	X	X	X	X	X	X	X	X	X	X[i]	
Height	X	X	X	X	X	X	X	X	X	X				
Weight	X	X	X	X	X	X	X	X	X	X			X	
Lymph node biopsy (archival or newly obtained biopsy)	X[g]			X[g]								X[g]		
Pembrolizumab		X	X	X	X	X	X	X	X	X				
CBC w/diff (auto or manual)	X	X	X	X	X	X	X	X	X	X	X	X	X	
Serum chemistry[a]	X	X	X	X	X	X	X	X	X	X	X	X	X	
HIV, HCV, HBV[m]	X													
EKG	X													
Adverse event evaluation		X----------												----------X
Blood for correlative studies [n]	X			X		X					X			
PET/CT and EBV viral load [h]	X			X			X			X[f]		X		
B-HCG	X[b]													
T3, Free T4, TSH[o]	X		X		X		X		X	X		X		
Urinalysis	X													
PT/INR and PTT	X													
Pulmonary function tests [c]	X													

Bone marrow biopsy and aspirate	X[j]			X[k]			X[k]			X[k]		X[k]		
Survival status														X

a: Comprehensive metabolic profile, LDH, phosphorus
b: Female subjects of childbearing potential should have a negative urine or serum pregnancy test within 72 hours prior to receiving the first dose of study medication. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required.
c: FVC; FEF25-75; FEV1; DLCO; pulse oximetry; hemoglobin should be obtained within 3 days prior to PFTs; repeat PFTs are at investigator discretion
d: In subjects who discontinue therapy without documented disease progression every effort should be made to continue monitoring disease by radiographic imaging every 12 weeks (± 14 days) until one of the following occurs: star t of new anti-cancer therapy; documented disease progression by investigator assessment; end of study; or death, whichever occurs first
e: After the start of new anti-cancer treatment or documented disease progression by investigator assessment, the subject will transition to the Survival Follow-up and the patient or their primary physician should be contacted by telephone or email every 12 weeks (+/- 14 days) to assess survival status
f: Patients who achieve a metabolic complete remission (defined as Deauville 1-3) may be followed subsequently with CT of the chest, abdomen, and pelvis rather than PET/CT at the discretion of the treating investigator; after cycle 9 radiology restaging will occur every 4 cycles (e.g, on cycles 13, 17, 21, etc) until cycle 33. There is a ± 3-day window for radiology tests but radiographic restaging should occur prior to drug administration for a cycle on which restaging is due though this could include a scan the same day as but prior to dosing of study drug.
g: At screening, fresh biopsy (1 core) or archival tissue within 90 days of C1D1 (5 unstained slides, 5µm) is required, unless an exception is given by the study chair. Fresh biopsy samples at week 6 (± 7 days) and at the time of discontinuation due to disease progression are optional but highly recommended unless the tumors are considered inaccessible by the treating physician or concerns that a biopsy is contraindicated due to safety concerns.
h: In subjects with an unconfirmed PD assessment who continue study therapy a radiology assessment should be performed 12 weeks (± 7 days) from the time of unconfirmed PD assessment or at the time of treatment discontinuation. If a scan was previously obtained within 30 days of the time of treatment discontinuation then a repeat radiology examination is not required. Imaging should occur at any time that disease progression is suspected. Those who have EBV positive lymphoma will have EBV viral load assessed at screening. If positive, it will be subsequently checked at every disease assessment.
i: Pulse oximetry recommended but not required. Study drug should be held for pulse oximetry recording less than 94% when pulse oximetry is obtained during treatment.
j: Must be performed within 90 days of day 1 of therapy. Patients only require a bone marrow biopsy at screening if they have unexplained cytopenias of grade 2 or greater at baseline or if PET/CT is suggestive of bone marrow involvement.
k: Bone marrow biopsy only needs to be repeated to confirm CR
l: Up to 35 cycles
m: HIV 1/2 antibody, hepatitis B surface antigen, hepatitis B surface antibody, hepatitis B core antibody, hepatitis C antibody
n: Please refer to section 9.1 for more details
o: T3, Free T4 and TSH to be drawn every 3 cycles after cycle 9.

11. MEASUREMENT OF EFFECT

11.1 Response Criteria

The primary objective of this study is overall response rate (ORR). Response and progression will be evaluated following the 2014 Lugano criteria for the primary endpoint and LyRIC for secondary endpoint. Patients will undergo tumor restaging, using the appropriate combination of imaging and bone marrow biopsies, after cycles 2 and 5 and 8 and then every 4 cycles thereafter until cycle 32. Radiographic restaging will also be performed at the 60-day post-treatment follow-up visit and at pre-specified intervals thereafter (see Study Calendar, section 10). Imaging will consist of PET/CT scans until the patient has achieved a metabolic CR (defined as Deauville score 1-3) at which juncture transition to CT of the chest, abdomen and pelvis will be acceptable at the discretion of the treating physician. Response assessment will follow standard criteria (Lugano criteria) for lymphoma. Bone marrow biopsy will be required within 30 days of radiology testing to confirm CR for patients with marrow involvement at baseline. A repeat bone marrow biopsy is not necessary to confirm CR if there was no marrow involvement at baseline.

11.2 Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started). The patient's best response assignment will depend on the achievement of both measurement and confirmation criteria.

11.2.1 Duration of Response

Duration of overall response: The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since the treatment started, or death due to any cause. Participants without events reported are censored at the last disease evaluation).

Duration of complete response: The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that progressive disease is objectively documented, or death due to any cause. Participants without events reported are censored at the last disease evaluation.

11.2.2 Progression-Free Survival

Overall Survival: Overall Survival (OS) is defined as the time from randomization (or registration) to death due to any cause, or censored at date last known alive.

Progression-Free Survival: Progression-Free Survival (PFS) is defined as the time from randomization (or registration) to the earlier of progression or death due to any cause. Participants alive without disease progression are censored at date of last disease evaluation.

For patients with progression of disease on imaging, it is strongly recommended that a confirmatory biopsy be obtained whenever possible.

11.2.3 Response Review

The tumor imaging metrics core (TIMC) at Dana-Farber Cancer Institute or an analogous facility at collaborating sites will assess radiographic response

12. DATA REPORTING/REGULATORY REQUIREMENTS

Adverse event lists, guidelines, and instructions for AE reporting can be found in Section 7 (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 in accordance with DF/HCC SOPs.

12.2 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.

12.3 **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 C.

- 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 an open-label phase II clinical trial. The primary endpoint is overall response rate. Secondary end points include examining the overall and complete response rates of pembrolizumab in the subgroup of patients with biologically selected subtypes of relapsed and refractory diffuse large B-cell lymphoma. We will also describe the safety and toxicity of pembrolizumab in patients with biologically selected subsets of relapsed and refractory diffuse large B-cell lymphoma. We will also report the complete response rate, duration of response, duration of complete response, progression free survival, and overall survival.

13.2 **Sample Size, Accrual Rate and Study Duration**

13.2.1 Sample size

The study will be powered based on the number of patients with EBV+ DLBCL enrolled. Patients with other allowed lymphoma histologies will be enrolled until the accrual goal of 20 patients with EBV+ DLBCL/TCHRLCL/plasmablastic lymphoma is met (with a maximum of 10 patients in any given lymphoma histology) at which time accrual to all lymphoma cohorts will close. The exact number of patients enrolled depends on the accrual of non-EBV+ DLBCL patients, but is expected to be 24-30 patients. If by the time 20 patients with EBV+ DLBCL are accrued, the total accrual is <24, accrual will continue to all 3 cohorts (including EBV+ DLBCL) until the total accrual reaches 24.

Six patients with histiocytic sarcoma, follicular dendritic cell sarcoma, and/or interdigitating dendritic cell sarcoma will be included in the trial and accrual to this subgroup can continue independent of closure of the study to accrual of lymphoma patients. Given the extremely rare

nature of these diseases, these patients are being included for exploratory purposes only and the statistics of the trial will not be powered based upon this patient population.

13.2.2 Statistical considerations

The hypothesis of this trial is that the response rate of pembrolizumab in this patient population will be 40% or higher. Assuming at least 20 patients are enrolled, we would consider the treatment promising if at least 6 patients respond. With this design, the study would have approximately 87% power to detect a difference in the response rate between 15% (the null hypothesis) and 40% (the alternative hypothesis), at a significance level of 0.07 (based on the exact binomial distribution). The maximal 90% confidence interval around the estimates for response and toxicity will be approximately +/-20%.

We anticipate accrual of 1 patient per month yielding an accrual period of 24 months. We anticipate following the last patient accrued for 6 months before being able to determine best overall response (the primary endpoint). Patients will be followed for 2 years after accrual for secondary endpoints such as PFS, OS, and duration of response for total study duration of approximately 4 years.

13.3 **Stratification Factors**

Response rates, PFS and DOR will also be reported for each histology (EBV+ DLBCL, PMBL, TCHRLCL).

13.4 **Interim Monitoring Plan**

The trial will be monitored by a DSMC and will be stopped at the judgment of the DSMC should excessive toxicity be observed. There are no stopping rules for futility.

13.5 **Analysis of Primary Endpoints**

Primary and secondary analyses will be performed on all patients who had measurable disease present at baseline, received at least one cycle of study drug, and had their disease re-evaluated for response. Response rates will be tabulated and reported as proportions with 90% exact binomial confidence intervals for each point estimate.

See Section 11 for additional details and definitions.

13.6 **Analysis of Secondary Endpoints**

Complete response rate, duration of response, duration of complete response, progression free survival, and overall survival will be reported for the entire cohort.

Response rates will be tabulated and reported as proportions with 90% exact binomial confidence intervals for each point estimate. Time-to-event endpoints will be assessed using the method of Kaplan and Meier; follow-up time will be estimated using the reverse Kaplan-Meier

method; estimates will be reported along with 90% confidence intervals where estimable using Greenwood's formula to calculate variance.

As secondary analyses, additional response criteria may be used to estimate response rates, and these rates will be assessed and reported as described above.

Sub-populations of patients may also be analyzed for by histology for response and time-to-event endpoints if sample sizes are sufficient. The methods described above will be used to report corresponding endpoints.

Abnormal laboratory test results and attributions to study drug will be summarized.

13.6.1 Safety analyses

Safety evaluations will be performed for the total cohort of patients including all who received at least one dose of study treatment. Incidence, severity, and type of adverse events (AEs) will be tabulated and reported as proportions.

SAEs, deaths, and other safety-related events resulting in discontinuation from study will be reported separately.

Safety analyses may also be performed by sub-populations of patients depending on the size of each.

13.6.2 Correlative analyses

Correlative studies examining the relationship between PD-1/PD-L1/PD-L2 expression, immune microenvironment, and circulating lymphocyte with outcome will be performed where samples are available. The exact studies to be performed are subject to sample and funding availability. In the case of insufficient sample size for meaningful statistical analyses, correlative data will be reported with descriptive statistics.

13.7 **Reporting and Exclusions**

The primary analyses will be on an intent-to-treat basis, considering all patients who are enrolled on study. Secondary analyses and toxicity analyses will be performed on the subset of eligible patients who received at least 1 dose of study drug.

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.

15. REFERENCES

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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 LUGANO AND LYRIC RESPONSE CRITERIA (31, 32)

Criteria	CR	PR	PD
Lugano	PET-CT, score 1, 2, or 3*with or without a residual mass on 5PS† OR on CT, target nodes/nodal masses must regress to ≤1.5 cm in LDi	PET-CT score 4 or 5 with reduced uptake compared with baseline and residual mass(es) of any size. OR On CT ≥50% decrease in SPD of up to 6 target measurable nodes and extranodal sites	PET-CT score 4 or 5 with an increase in intensity of uptake from baseline and/or new FDG-avid foci consistent with lymphoma at interim or end-of-treatment assessment. OR On CT, an individual node/lesion must be abnormal with: LDi >1.5 cm and increase by ≥50% from PPD nadir and an increase in LDi or SDi from nadir 0.5 cm for lesions ≤2 cm 1.0 cm for lesions >2 cm
			In the setting of splenomegaly, the splenic length must increase by >50% of the extent of its prior increase beyond baseline (eg, a 15-cm spleen must increase to >16 cm). If no prior splenomegaly, must increase by ≥2 cm from baseline. New or recurrent splenomegaly
			New or clear progression of preexisiting nonmeasured lesions
			Regrowth of previously resolved lesions
			A new node >1.5 cm in any axis or a new extranodal site >1.0 cm in any axis; if <1.0 cm in any axis, its presence must be unequivocal and must be attributable to lymphoma
			Assessable disease of any size unequivocally attributable to lymphoma
			AND/OR new or recurrent involvement of the bone marrow
			As with Lugano with the following exceptions:
LYRIC	Same as Lugano	Same as Lugano	IR
			IR(1): ≥50% increase in SPD in first 12 weeks
			IR(2): <50% increase in SPD with
			a. New lesion(s), or
			b. ≥50% increase in PPD of a lesion or set of lesions at any time during treatment
			IR(3): Increase in FDG uptake without a concomitant increase in lesion size meeting criteria for PD

- IR, immune response; LDi, longest diameter; PPD, product of the perpendicular diameters; SDi, short diameter; 5PS, 5-point scale.
- ⁎* A score of 3 in many patients indicates a good prognosis with standard treatment, especially if at the time of an interim scan. However, in trials involving PET where de-escalation is investigated, it may be preferable to consider a score of 3 as inadequate response (to avoid undertreatment).
- ⁎† PET 5PS: 1, no uptake above background; 2, uptake ≤ mediastinum; 3, uptake > mediastinum but ≤ liver; 4, uptake greater than liver; 5, uptake markedly higher than liver (2-3 times SUVmax in normal liver) and/or new lesions; X, new areas of uptake unlikely to be related to lymphoma.

APPENDIX C DF/HCC MULTI-CENTER DATA AND SAFETY MONITORING PLAN

1 INTRODUCTION

The Dana-Farber/Harvard Cancer Center Multi-Center Data and Safety Monitoring Plan (DF/HCC DSMP) outlines the pocedures for conducting a DF/HCC Multi-Center research protocol. The DF/HCC DSMP should serve as a reference for any sites external to DF/HCC that will be participating in the research protocol.

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 Standard Operating Procedures.

1.2 Multi-Center Data and Safety Monitoring Plan Definitions

DF/HCC Multi-Center Protocol: A research protocol in which one or more outside institutions are collaborating with Dana-Farber/Harvard Cancer Center where a DF/HCC investigator is the sponsor. DF/HCC includes Dana-Farber/Partners Cancer Care (DF/PCC) Network Clinical Trial Affiliates.

Lead Institution: One of the Dana-Farber/Harvard Cancer Center consortium members (Dana-Farber Cancer Institute (DFCI), Massachusetts General Hospital (MGH), Beth Israel Deaconess Medical Center (BIDMC), Boston Children's Hospital (BCH), Brigham and Women's Hospital (BWH)) responsible for the coordination, development, submission, and approval of a protocol as well as its subsequent amendments per the DFCI IRB and applicable regulatory guidelines (CTEP, Food and Drug Administration (FDA), Office of Biotechnology Activities (OBA) etc.). The Lead Institution is typically the home of the DF/HCC Sponsor. The Lead Institution also typically serves as the Coordinating Center for the DF/HCC Multi-Center Protocol.

DF/HCC Sponsor: The person sponsoring the submitted Multi-Center protocol. Within DF/HCC, this person is the Overall Principal Investigator who takes responsibility for initiation, management and conduct of the protocol at all research locations. In applicable protocols, the DF/HCC Sponsor will serve as the single liaison with any regulatory agencies. The DF/HCC Sponsor has ultimate authority over the protocol and is responsible for the conduct of the study at DF/HCC and all Participating Institutions. In most cases the DF/HCC Sponsor is the same person as the DF/HCC Overall Principal Investigator; however, both roles can be filled by two different people.

Participating Institution: 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 Participating Institution acknowledges the DF/HCC Sponsor as having the ultimate authority and responsibility for the overall conduct of the study.

Coordinating Center: The entity (i.e. Lead Institution, Medical Monitor, Contract Research Organization (CRO), etc) that provides administrative support to the DF/HCC Sponsor in order that he/she may fulfill the responsibilities outlined in the protocol document and DSMP, and as specified in applicable regulatory guidelines (i.e. CTEP Multi-Center Guidelines). In general, the Lead Institution is the Coordinating Center for the DF/HCC Multi-Center Protocol.

DF/HCC Office of Data Quality (ODQ): A group within DF/HCC responsible ensuring high-quality standards are used for data collection and the ongoing management of clinical trials, auditing, and data and safety monitoring. ODQ also coordinates quality assurance efforts related to multi-center clinical research.

DF/HCC Research Informatics for Operations (RIO): A group within DF/HCC responsible for providing a comprehensive data management platform for managing clinical trial data.

2 GENERAL ROLES AND RESPONSIBILITIES

For DF/HCC Multi-Center Protocols, the DF/HCC Sponsor, the Coordinating Center, and the Participating Institutions are expected to adhere to the following general responsibilities:

2.1 DF/HCC Sponsor

The DF/HCC Sponsor, Dr. Eric Jacobsen, will accept responsibility for all aspects of conducting a DF/HCC Multi-Center protocol which includes but is not limited to:

- Oversee the coordination, development, submission, and approval of the protocol as well as subsequent amendments.
- Ensure that the investigators, study team members, and Participating Institutions are qualified and appropriately resourced to conduct the protocol.
- Include the Multi-Center Data and Safety Monitoring Plan as an appendix to the protocol.
- Ensure all Participating Institutions are using the correct version of the protocol.
- Ensure that each participating investigator and study team member receives adequate protocol training and/or a Site Initiation Visit prior to enrolling participants and throughout trial's conduct as needed.
- Ensure the protocol will be provided to each participating site in a language understandable to all applicable site personnel when English is not the primary language.
- Monitor progress and overall conduct of the study at all Participating Institutions.
- Ensure all DFCI Institutional Review Board (IRB), DF/HCC and other applicable reporting requirements are met.
- Review data and maintain timely submission of data for study analysis.
- Act as the single liaison with FDA (investigator-held IND trials), as applicable.
    - Ensure compliance with all requirements as set forth in the Code of Federal Regulations, applicable DF/HCC requirements, HIPAA requirements, and the approved protocol.

- Commit to the provision that the protocol will not be rewritten or modified by anyone other than the DF/HCC Sponsor.
- Identify and qualify Participating Institutions and obtain accrual commitments prior to extending the protocol to that site.
- Monitor accrual and address Participating Institutions that are not meeting their accrual requirements.

2.2 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 Participating Institutions as needed.
- Oversee the data collection process from Participating Institutions.
- Maintain documentation of Serious Adverse Event (SAE) reports and deviations/violation submitted by Participating Institutions and provide to the DF/HCC Sponsor for timely review and submission to the DFCI IRB, as necessary.
- Distribute serious adverse events reported to the DF/HCC Sponsor that fall under the DFCI IRB Adverse Event Reporting Policy to all Participating Institutions.
- Provide Participating Institutions with information regarding DF/HCC requirements that they will be expected to comply with.
- Carry out plan to monitor Participating Institutions either by on-site or remote monitoring.
- Maintain Regulatory documents of all Participating Institutions which includes but is not limited to the following: local IRB approvals/notifications from all Participating Institutions, 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 Participating Institutions (conference calls, emails, etc) and maintain documentation all relevant communications.

2.3 Participating Institution

Each Participating Institution is expected to comply with all applicable federal regulations and DF/HCC requirements, the protocol and HIPAA requirements.

The general responsibilities for each Participating Institution 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 local IRB.

- Maintain regulatory files as per sponsor 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 (i.e. teleconferences).
- Update Coordinating Center with research staff changes on a timely basis.
- Register participants through the Coordinating Center prior to beginning research related activities.
- Submit Serious Adverse Event (SAE) reports to local IRB per institutional requirements and to the Coordinating Center, in accordance with DF/HCC requirements.
- Submit protocol deviations and violations to local IRB per institutional requirements and to the DF/HCC Sponsor in accordance with DF/HCC requirements.
- Order, store and dispense investigational agents and/or other protocol mandated drugs per federal guidelines and protocol requirements.
- Have office space, office equipment, and internet access that meet HIPAA standards.
- 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.

3 DF/HCC REQUIREMENTS FOR MULTI-CENTER PROTOCOLS

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 Distribution

The Coordinating Center will distribute the final DFCI IRB approved protocol and any subsequent amended protocols to all Participating Institutions.

3.2 Protocol Revisions and Closures

The Participating Institutions will receive notification of protocol revisions and closures from the Coordinating Center. It is the individual Participating Institution's responsibility to notify its IRB of these revisions.

- **Non life-threatening revisions:** Participating Institutions will receive written notification of protocol revisions regarding non life-threatening events from the Coordinating Center. Non-life-threatening protocol revisions must be IRB approved and implemented within 90 days from receipt of the notification.

- **Revisions for life-threatening causes:** Participating Institutions will receive immediate notification from the Coordinating Center concerning protocol revisions

required to protect lives with follow-up by fax, mail, e-mail, etc. Life-threatening protocol revisions will be implemented immediately followed by IRB request for approval.

- **Protocol closures and temporary holds:** Participating Institutions 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 Participating Institutions on an ongoing basis about protocol accrual data so that they will be aware of imminent protocol closures.

3.3 Informed Consent Requirements

The DF/HCC approved informed consent document will serve as a template for the informed consent for Participating Institutions. The Participating Institution 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 PI-Initiated Multi-Center Protocols. This document will be provided separately to each Participating Institution.

Participating Institutions are to send their version of the informed consent document and HIPAA authorization, if a separate document, to the Coordinating Center for review and approval prior to submission to their local IRB. 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 Participating Institution will identify the physician members of the study team who will be obtaining consent and signing the consent form for therapeutic protocols. Participating institutions must follow the DF/HCC requirement that only attending physicians obtain informed consent and re-consent for all interventional drug, biologic, or device research.

3.4 IRB Documentation

The following must be on file with the Coordinating Center:

- Initial approval letter of the Participating Institution's IRB.
- Copy of the Informed Consent Form(s) approved by the Participating Institution’s IRB.
- Participating Institution’s IRB approval for all amendments.
- Annual approval letters by the Participating Institution's IRB.

3.5 IRB Re-Approval

Verification of IRB re-approval from the Participating Institutions 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 from the Participating Institution on or before the anniversary of the previous approval date.

3.6 Participant Confidentiality and Authorization Statement

In 1996, congress passed the first federal law covering the privacy of health information known as the Health Insurance Portability and Accountability Act (HIPPA). Any information, related to the physical or mental health of an individual is called Protected Health Information (PHI). HIPAA outlines how and under what circumstances PHI can be used or disclosed.

In order for covered entities to use or disclose protected health information during the course of a study, the study participant must sign an authorization statement. This authorization statement may or may not be separate from the informed consent document. The Coordinating Center, with the approval from the DFCI IRB, will provide a consent template, with information regarding authorization for the disclosure of protected health information.

The DF/HCC Sponsor will use all efforts to limit its use of protected health information in its trials. However, because of the nature of these trials, certain protected health information must be collected. DF/HCC has chosen to use authorizations, signed by the participant in the trial, rather than limited data sets with data use agreements.

3.6.1 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 (as described below) be used for all participant specific documents. Participant initials may be included or retained for cross verification of identification.

3.7 DF/HCC Multi-Center Protocol Registration Policy

3.7.1 Participant Registration and Randomization

To register a participant, the following documents should be completed by the Participating Institution and e-mailed to the Coordinating Center:

Megan Forsyth
Dana-Farber Cancer Institute
450 Brookline Ave
Boston, MA 02215
Megan_Forsyth@DFCI.HARVARD.EDU

Phone: 857-215-1405
Fax: 617-632-6625

- Copy of required laboratory tests including: All screening evaluations.
- Signed informed consent document
- Signed DFCI eligibility checklist

- HIPAA authorization form (if separate from the informed consent document)
- Other appropriate forms (e.g., Eligibility Screening Worksheet, Registration form)

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 Participating Institution and provide the study specific participant case number, and, if applicable, assigned treatment and/or dose level.

Treatment or other protocol-specific interventions may not begin without confirmation from the Coordinating Center that the participant has been registered.

Registration can only occur during normal business hours, Monday through Friday from 8:00 AM to 5:00 PM Eastern Standard Time.

3.7.2 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 Participating Institution receives confirmation of the participant's registration from the Coordinating Center. The DF/HCC Sponsor and DFCI IRB must be notified of any violations to this policy.

3.7.3 Eligibility Exceptions

No exceptions to the eligibility requirements for a protocol without DFCI IRB approval will be permitted. All Participating Institutions are required to fully comply with this requirement.

3.8 DF/HCC Protocol Case Number

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. Participating Institutions should submit all de-identified subsequent communication and documents to the Coordinating Center, using this case number to identify the subject.

3.8.1 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, who in turn is responsible for reporting to the DFCI IRB.

For reporting purposes, DF/HCC uses the terms "violation", "deviation" and "exception" to describe departures from a protocol. All Participating Institutions must adhere to these requirements for reporting to the DF/HCC Sponsor and will follow their institutional policy for reporting to their local IRB.

3.8.2 Definitions

Protocol Deviation: Any departure from the defined procedures set forth in the IRB-approved protocol which is *prospectively approved* prior to its implementation.

Protocol Exception: Any protocol deviation that relates to the eligibility criteria, e.g. enrollment of a participant who does not meet all inclusion/exclusion criteria.

Protocol Violation: Any protocol deviation that was not *prospectively approved* by the IRB prior to its initiation or implementation.

3.8.3 Reporting Procedures

DF/HCC Sponsor: is responsible for ensuring that clear documentation is available in the medical record and/or regulatory documents to describe all protocol exceptions, deviations and violations. The DF/HCC Sponsor will also be responsible for ensuring that all protocol violations/deviations are promptly reported per DFCI IRB guidelines.

Participating Institutions: Protocol deviations require prospective approval from the DFCI IRB. The Participating Institution must submit the deviation request to the Coordinating Center who will then submit the deviation request to the DFCI IRB. Upon DFCI IRB approval the deviation is submitted to the Participating Institution IRB, per institutional policy. A copy of the Participating Institution's IRB report and determination will be forwarded to the Coordinating Center within 10 business days after the original submission. The deviation may not be implemented without all required approvals.

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.

Coordinating Center: Upon receipt of the violation/deviation report from the Participating Institution, the Coordinating Center will submit the report to the DF/HCC Sponsor for review. Subsequently, the Participating Institution's IRB violation/deviation report will be submitted to the DFCI IRB for review per DFCI IRB reporting guidelines. DF/HCC will forward all violation reports to CTEP via an internal DF/HCC process, as applicable.

3.9 Safety Assessments and Toxicity Monitoring

The study teams at all participating institutions are responsible for protecting the safety, rights and well-being of study participants. Recording and reporting of adverse events that occur during the course of a study help ensure the continuing safety of study participants.

All participants receiving investigational agents and/or other protocol mandated treatment will be evaluated for safety. The safety parameters include all laboratory tests and hematological abnormalities, physical examination findings, and spontaneous reports of adverse events reported by participants. All toxicities encountered during the study will be evaluated according to the NCI criteria specified in the protocol. Life-threatening toxicities must be reported immediately to the DF/HCC Sponsor via the Coordinating Center.

Additional safety assessments and toxicity monitoring will be outlined in the protocol.

3.9.1 Guidelines for Reporting Serious Adverse Events

Guidelines for reporting Adverse Events (AEs) and Serious Adverse Events (SAEs) are detailed in protocol section 7.

Participating Institutions must report the SAEs to the DF/HCC Sponsor and the Coordinating Center following the DFCI IRB Adverse Event Reporting Policy.

The Coordinating Center will maintain documentation of all Participating Institution Adverse Event reports and be responsible for communicating to all participating investigators, any observations reportable under the DFCI IRB Reporting Requirements. Participating Institutions will review and submit to their IRB according to their institutional policies and procedures

3.9.2 Guidelines for Processing IND Safety Reports

The DF/HCC Sponsor will review all IND Safety Reports and ensure that all IND Safety Reports are distributed to the Participating Institutions. Participating Institutions will review and submit to their IRB according to their institutional policies and procedures.

3.10 Data Management

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

3.10.1 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.

Responses may be returned on the written query or on an amended paper case report form, or in the case of electronic queries, within the electronic data capture (eDC) system. In the case of a

written query for data submitted on a paper case report form, the query must be attached to the specific data being re-submitted in response.

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

4 REQUISITIONING INVESTIGATIONAL DRUG

The ordering of investigational agent is specified in the protocol section 8.1.

Participating Institutions should order their own agent regardless of the supplier.

If the agent is commercially available, check with the local Director of Pharmacy and/or the Research Pharmacy to ensure that the agent is in stock. If the agent is not stocked, ensure that the agent can be ordered once the protocol is approved by the local IRB.

If the agent is investigational, ensure that the pharmacy will be able to receive and store the agent according to state and federal requirements. The local IRB should be kept informed of who will supply the agent so that any regulatory responsibilities can be met in a timely fashion.

5 MONITORING: QUALITY CONTROL

The quality control process for a clinical trial requires verification of protocol compliance and data accuracy. The Coordinating Center, with the aid of the DF/HCC Office of Data Quality, provides quality control oversight for the protocol.

5.1 Ongoing Monitoring of Protocol Compliance

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

The Coordinating Center will implement ongoing monitoring activities to ensure that Participating Institutions are complying with regulatory and protocol requirements, data quality, and participant safety. Monitoring will occur before the clinical phase of the protocol begins, continue during protocol performance and through study completion. Additional monitoring practices may include but are not limited to; source verification, review and analysis of the following: eligibility requirements of all participants, informed consent procedures, adverse events and all associated documentation, study drug administration/treatment, regulatory files, protocol departures, pharmacy records, response assessments, and data management.

Participating institutions will be required to participate in monthly Coordinating Center initiated teleconferences. E-mails highlighting overall protocol progress and important announcements will be distributed regularly.

On-Site Monitoring: Participating institutions will be required to participate in monitoring one on-site visit. 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: Participating Institutions will be required to forward de-identified copies of participants' eligibility packetsand informed consent documents to the Coordinating Center to aid in source data verification within 30 days of subject enrollment. Source verification of all case report form data will occur remotely once per patient. 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.

5.2 Monitoring Reports

The DF/HCC Sponsor will review all monitoring reports for on-site and remote monitoring of Participating Institutions to ensure protocol compliance. The DF/HCC Sponsor may increase the monitoring activities at Participating Institutions that are unable to comply with the protocol, DF/HCC Sponsor requirements or federal and local regulations. Participating Institutions may also be subject to an audit as determined by the DF/HCC Sponsor.

5.3 Accrual Monitoring

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

It is expected that a minimum accrual of at least 2 patients per site annually will occur.

6 AUDITING: QUALITY ASSURANCE

Auditing is a method of Quality Assurance and involves the systematic and independent examination of all trial related activities and documents. Audits determine if evaluated activities were appropriately conducted and whether data was generated, recorded and analyzed, and accurately reported per the protocol, applicable Standard Operating Procedures (SOPs), and the Code of Federal Regulations (CFR).

6.1 DF/HCC Internal Audits

All Participating Institutions 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.

6.2 Audit Notification

It is the Participating Institution'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.

6.3 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 DFCI IRB as applicable.

6.4 Participating Institution Performance

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

Participating Institutions 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 recommended for a six-month probation period. Such institutions must respond with a corrective action plan and must demonstrate during the probation period that deficiencies have been corrected, as evidenced by the improved performance measures. Participating Institutions that fail to demonstrate significant improvement will be considered by the DF/HCC Sponsor for revocation of participation. A DF/HCC Sponsor and/or the DFCI IRB may terminate a site's participation if it is determined that a site is not fulfilling its responsibilities as described above.