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NCI Protocol #: CITN-12

Local Protocol #: CITN-12

ClinicalTrials.gov Identifier: NCT02595866

TITLE: Phase I Study of MK-3475 (Pembrolizumab) in Patients with Human Immunodeficiency Virus (HIV) and Relapsed/Refractory or Disseminated Malignant Neoplasm

Coordinating Center: Cancer Immunotherapy Trials Network (CITN),
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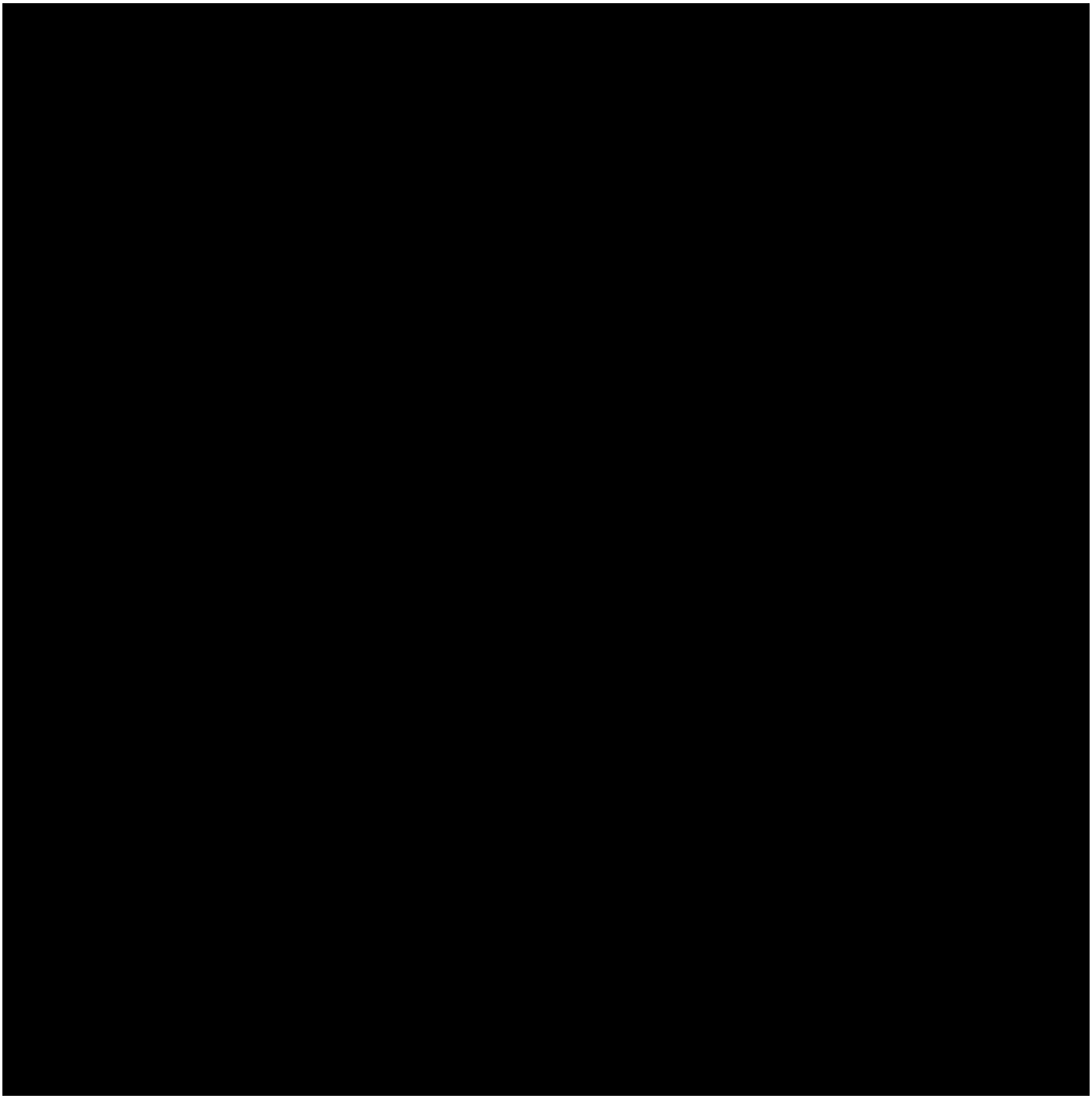
NCI-Supplied Agent(s): MK-3475 (Pembrolizumab, SCH 900475) (NSC # 776864)

Other Agent(s): N/A

Protocol Type / Version # 2 / Version Date: Amendment 6 /May 22, 2018

IND #: 123618

IND Sponsor: DCTD, NCI

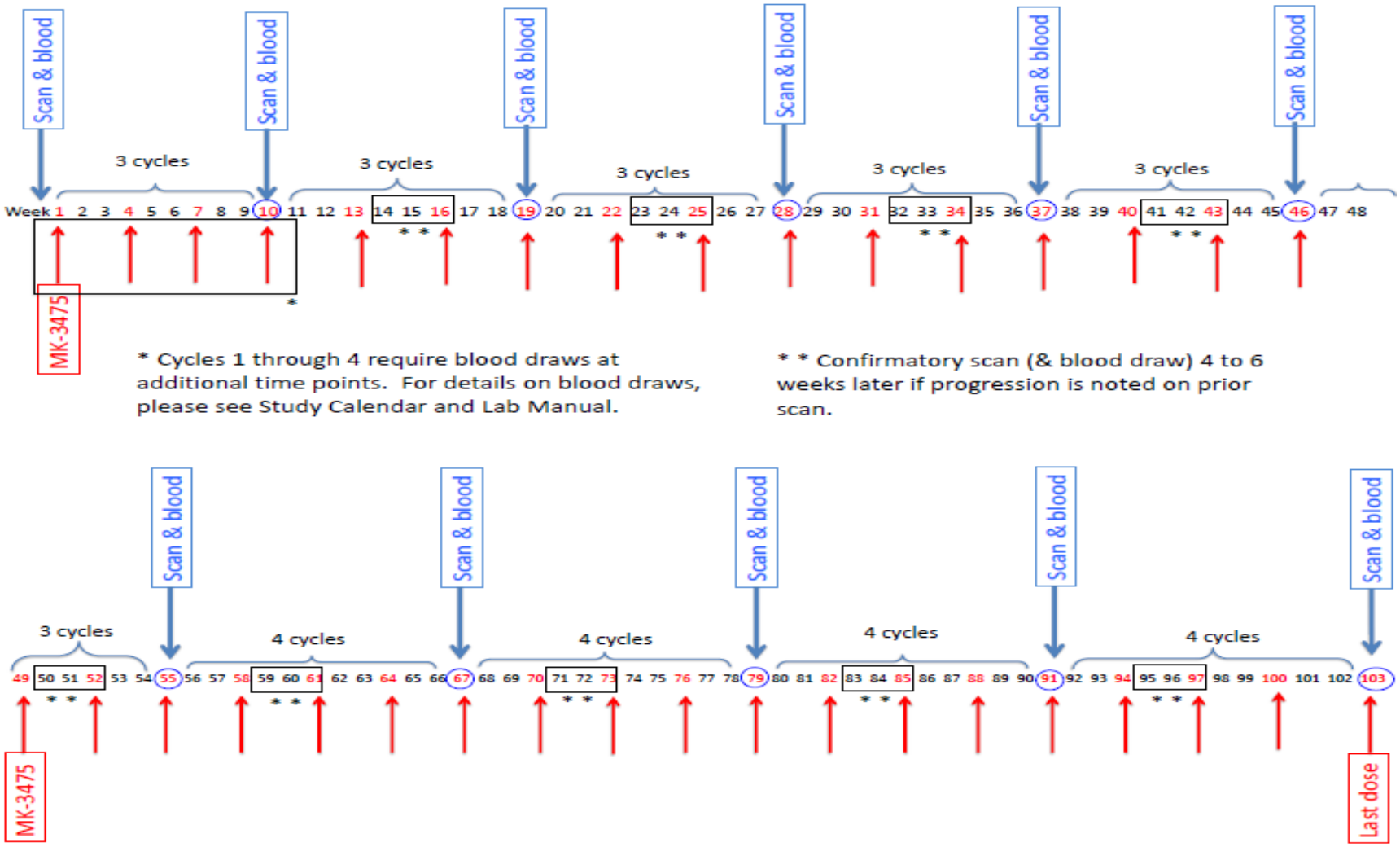


SUMMARY

Title	Phase I Study of MK-3475 (pembrolizumab) in Patients with Human Immunodeficiency Virus (HIV) and Relapsed/Refractory or Disseminated Malignant Neoplasm
Trial Phase	Phase I
Clinical Indication	HIV+ patients on highly effective anti-retroviral therapy (cART) who also have cancer
Trial Type	Single Arm, Therapeutic
Type of control	Nonrandomized trial with primary aim of assessing safety and tolerability of MK-3475 (pembrolizumab) in this population. Efficacy endpoints of ORR, PFS, DOR and OS may be chronicled and reported for each type of cancer.
Route of administration	Intravenous (IV)
Trial Blinding	None
Treatment Group	MK-3475 (pembrolizumab), 200 mg every 3 weeks (q3wks)
Number of trial patients	Three or six patients will initially be enrolled into each of the first 3 cohorts (based on CD4+ T-cell counts), pending safety analysis. If a safe dose is established, each cohort may be expanded to 12 patients for a total of 36 patients. Additionally, a fourth cohort will be enrolled. [redacted]
Estimated duration of trial	3 years
Duration of Participation	Each patient will participate in the trial from the time the Informed Consent Form (ICF) is signed through final protocol-specified contact. After a screening phase for eligibility, patients will receive MK-3475 (pembrolizumab) every 3 weeks in addition to ongoing established cART regimen. Treatment for patients that achieve a stable disease (SD) or a partial response (PR) may continue for a maximum of 2 years. Patients will be stratified into 3 cohorts based on CD4+T-cell counts standard in many HIV therapy trials (cohorts 1-3) [redacted] Cohort 1: 100-199 CD4+ T cells/mcL Cohort 2: 200-350 CD4+ T cells/mcL Cohort 3: >350 CD4+ T cells/mcL [redacted] Accrual to each cohort (cohorts 1-3) will be based on unacceptable AEs experienced during first treatment cycle of 21 days. If 2 or more unacceptable AEs occur in the first 6 patients, the cohort will not be expanded to 12 patients until the AEs are assessed by the Toxicity Evaluation Committee and the Committee approves the expansion.

	[redacted] MK-3475 (pembrolizumab) will be continued in each patient until confirmed progression or the development of an unacceptable AE. Safety will be assessed after the initial 3 participants in each cohort have completed one cycle of therapy (21 days), and again if 2 unacceptable AEs are observed during the first cycle for the first 6 participants subsequently treated in the same cohort. If 2 or more of the first 6 patients in any individual cohort, and/or ≥1/3 participants in any individual cohort at any time experience unacceptable AEs, the entry into that cohort will be suspended and toxicities assessed by the Toxicity Evaluation Committee. The Toxicity Evaluation Committee will decide whether accrual should be stopped in that cohort or for the entire trial. If greater than 1/3 total patients, across all cohorts, develop an unacceptable AE in the first cycle of therapy (21 days), the Toxicity Evaluation Committee will evaluate the totality of the data to determine whether accrual will be suspended in the trial. Objective responses and disease progression will be monitored by computed tomography (CT) scans and physical examination, scheduled at 9-week intervals during the first year of treatment and at 12-week intervals during the second year of treatment. Responses and progression will be assessed by RECIST 1.1, 2014 "Lugano Classification" Response Criteria for Malignant Lymphoma, or other relevant tumor-specific criteria. Administration of MK-3475 (pembrolizumab) will be stopped with: documented disease progression warranting alternative systemic therapy, unacceptable adverse event(s), intercurrent illness that prevents further administration of treatment, investigator's decision to withdraw the patient, patient withdraws consent, pregnancy of the patient, noncompliance with trial treatment or procedure requirements, completion of 2 years of treatment, or other administrative reasons. After the end of treatment, each patient will be followed for 30 days for adverse event monitoring and attend a Post-Treatment follow up visit. Serious adverse events will be collected for 90 days after the end of treatment with investigator attribution as to whether the SAE is associated with MK-3475 (pembrolizumab) or subsequent therapies. After the Post-Treatment Safety Follow-Up Visit, patients will be seen in follow up visits every 3 months for 1 year.

Patient Visit Timeline (dosing, disease assessments, and correlative blood draws) (v 1.0)



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1. OBJECTIVES

1.1 Primary Objectives

1.1.1 To assess the safety and tolerability of MK-3475 (pembrolizumab) in HIV-infected patients on effective antiretroviral therapy and with relapsed/refractory or disseminated AIDS-defining or non-AIDS defining malignancy.

Hypothesis: MK-3475 (pembrolizumab) is safe and tolerable in patients with HIV and cancer who are on effective antiretroviral therapy.

1.1.2 To assess the safety and feasibility of MK-3475 (pembrolizumab) administration as first systemic therapy for HIV associated Kaposi sarcoma in patients on effective antiretroviral therapy.

Hypothesis: MK-3475 (pembrolizumab) administration will be safe and feasible in this patient population with appropriate supportive care.

1.2 Secondary Objectives To obtain preliminary insights into clinical benefit (e.g., tumor shrinkage or stabilization ≥24 weeks) across a variety of tumors in patients infected with HIV and on effective antiretroviral therapy.

Hypothesis: MK-3475 (pembrolizumab) will have antitumor activity in some patients with HIV and cancer, measurable by clinical response or disease stabilization of ≥24 weeks.

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1.3 [redacted]

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2. BACKGROUND

2.1 Cancer in People with HIV

2.1.1 Rationale and Background:

Human immunodeficiency virus (HIV)–infected individuals with cancer are often excluded from clinical trials that test novel agents. Improving access to clinical trials for this population is an ongoing focus of the Division of Cancer Treatment and Diagnosis/National Cancer Institute (DCTD/NCI), and these efforts have been funded in part by funds to Cancer Therapy Evaluation Program (CTEP) from the Office of Acquired

Immunodeficiency Syndrome (AIDS) Research. This joint proposal from the Cancer Immunotherapy Trials Network (CITN) and the NIH Center for Cancer Research HIV and AIDS Malignancy Branch is primarily aimed at showing the feasibility of administering MK-3475 (pembrolizumab) to individuals with both HIV infection and cancer. If this trial shows that the agent can be safely given in this setting, exclusion from other trials using this agent then will have no medical basis for exclusion based solely on HIV infection in patients otherwise meeting protocol eligibility criteria. Thus, a major public health intent of this trial is to further the public health mission of the NCI in providing access to clinical trials for the American population regardless of HIV serostatus. To accomplish this goal, we propose to evaluate the safety and tolerability and to establish the tolerated dose of MK-3475 (pembrolizumab) in a phase I study adequately sized to provide confidence of the safety of administering MK-3475 (pembrolizumab) in patients with HIV and cancer.

This study may also inform future studies of MK-3475 (pembrolizumab) in specific cancers, such as HIV-associated lung cancer or HIV-associated classic Hodgkin lymphoma (cHL), where there is strong rationale for disease-specific clinical studies. Indeed, the NCI Board of Scientific Advisors (BSA) Ad Hoc Subcommittee on HIV and AIDS Malignancy recently identified the study of agents that target the programmed cell death-1 (PD-1) checkpoint in lung cancer as a research priority. It will also provide prospective safety data for its use in patients with HIV who have malignancies for which the drug has approval from the US Food and Drug Administration (FDA). Lastly, the proposed trial is expected to provide important virologic and immunologic correlative science related to the effect of checkpoint blockade in patients with HIV and cancer.

2.1.2 The Growing Burden of Cancer in People with HIV

HIV and associated immune suppression has been strongly associated with several mature B-cell lymphomas and Kaposi sarcoma (KS) since the beginning of the AIDS epidemic. Although the incidence of these cancers have decreased in relative terms since the introduction of effective combination antiretroviral therapy (cART), the relative incidence for these tumors remains dramatically elevated compared to the general population. It is increasingly recognized that several additional cancers occur with increased frequency in people with HIV, most importantly lung cancer, cancers associated with human papillomavirus (HPV; anal cancer, cervical cancer, oropharyngeal cancer), cHL, and hepatocellular carcinoma (HCC) (Table 1). In addition to occurring with increased frequency, some epidemiologic data suggests that the natural history of many of these tumors may be somewhat different in patients with HIV.[Shiels 2010]

With the introduction of effective antiretroviral therapy, infectious mortality has decreased dramatically in this patient population, and malignancies have become a leading cause of morbidity and mortality. In the United States, an estimated 1.2 million people have HIV infection. As this population ages, the burden of certain cancers such as lung cancer, anal cancer, and cHL continues to increase.[Shiels 2011] Cancer is estimated to be responsible for over one-third of all deaths in this patient population.[Bonnet 2009] A recent report from the French Mortalite 2010 survey of deaths in 82,000 HIV-infected patients looked at the underlying causes of over 700 deaths from 2000 to 2010. AIDS-defining malignancies

were the cause of death in 10% of patients. Non-AIDS defining malignancies (NADM) were the cause of death in 26% of the patients in the most recent period, doubling from 2000. Of the 193 NADM deaths, the commonest were bronchopulmonary malignancies (32%), HCC (17%), head and neck cancers (8%), and anal cancer (8%).[Morlat 2014] Lymphoma, lung cancer, and liver cancer are currently the leading causes of death from cancer in patients with HIV.[Bonnet 2009; Simard 2010; Achenbach 2011] In addition, more than 35 million people are infected with HIV globally, and with rapidly expanding HIV treatment programs, cancer in people with HIV is becoming a major global health issue.

At the same time as cancers are becoming a leading cause of morbidity and mortality among people with HIV, disparities in the treatment and outcomes of patients with HIV and cancer persisting in the cART era have been reported and are most notable for disparities in lymphoma and lung cancer.[Suneja 2014; Uldrick 2014] For these tumors, HIV-infected patients are less likely to receive chemotherapy or surgery. HIV infection in patients with non–small lung cancer (NSCLC) is associated with a higher cancer-specific mortality. Decreasing these disparities requires the implementation of effective therapies, and the inclusion of patients with HIV in clinical trials for diseases without good treatment options.

Advances in cancer therapeutics are urgently needed for several viral-associated tumors, lung cancer, and refractory lymphomas in people with HIV.[Persad 2008; Suneja 2014] For some of these tumors, immunotherapy might be more active in patients with HIV than in the general population. Recent advances in the treatment of diffuse large B-cell lymphoma, Burkitt lymphoma, and cHL. [Dunleavy 2010; Montoto 2012; Dunleavy 2013] have demonstrated that with appropriate management of HIV, patients with HIV and cancer can tolerate standard regimens. Nonetheless, specific attention to the safety of immunotherapy in patients with HIV and activity of immunotherapy in certain common tumors occurring in this setting is required. In addition, correlative studies that evaluate the dysregulation of checkpoint inhibition in HIV infection are likely to advance our understanding of control of chronic viral infections and perhaps malignancies in people with HIV.

Table 1: Common Malignancies in People with HIV in the cART Era [Engels 2006; Engels 2008; Shiels 2011; Shiels 2011; Robbins 2014]

Malignancies	Standard Incidence Ratio (HIV only/AIDS)	Recent Incidence in HIV (per 100,000 person-yrs.)	Estimated % of all cancers 2004-2007 in HIV/AIDS in US	Viral Associations
AIDS-Defining Malignancies				
Non-Hodgkin lymphoma*				
Systemic	10-15/30-60	>153*	25.9%	EBV, KSHV
Primary CNS lymphoma	250/1,020	27	3%	EBV
Kaposi sarcoma	1,300/3,640	110	18.5%	KSHV
Cervical cancer	2.9/5.3	47	2.4%	HPV
Non-AIDS Defining Malignancies				
Lung cancer	2.6/2.6	78	10%	-
Anal cancer	9.2/20	59	5.7%	HPV
cHL	5.6/14	33	4.4%	EBV
Oropharyngeal carcinoma	1.7/2.1	22	2.5%	HPV
HCC	2.7/3.3	32	2.3%	HBV, HCV

Abbreviations: cHL, classic Hodgkin lymphoma; EBV, Epstein-Barr virus; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HPV, human papillomavirus; KSHV, Kaposi sarcoma–associated herpes virus; US, United Stated.
*Includes diffuse large B-cell lymphoma and Burkitt lymphoma, but not other rarer histologies

2.1.3 PD-1/PD-L1 Checkpoint Blockade

Programmed cell death-1 (PD-1) is a co-inhibitor receptor that negatively regulates antigen receptor signaling of CD8+ effector T cells.[Nishimura 1999; Brahmer 2012] PD-1 is expressed on the surface of T-cells [Ishida 1992; Agata 1996; Vibhakar 1997] as well as on other immune cells such as monocytes and macrophages.[Ma 2011] Program cell death ligand 1 (PD-L1) is a cell-surface glycoprotein and one of the ligands of PD-1. PD-L1 is expressed on the surface of many tumor cells and antigen-presenting cells.[Dong 2002; Iwai 2002; Zou 2008] Binding of PD-L1 to PD-1 leads to the inhibition of T-cell–mediated lymphocyte proliferation and cytokine secretion, resulting in T-cell exhaustion and hampering of immune responses.[Freeman 2000] Targeting and inhibiting the interaction of PD-L1 with PD-1 releases the immune checkpoint blockade and may elicit antitumor activity for some cancers.[Dong 2002; Iwai 2002]

2.1.4 Chronic Viral Infections, Including HIV and the PD-1/PD-L1 Pathway

Chronic viral infections, including HIV, generate "exhausted" CD8+ T cells with a diminished capacity to both produce cytokines and lyse infected cells. In the setting of chronic antigenic stimulation, this diminished immune function is associated with T-cell upregulation of messenger RNA (mRNA) encoding PD-1. In viral infections, PD-1 and PD-L1 are also upregulated by interferons in various cell types, including monocytes and antigen-presenting cells.[Cheng 2007; Ma 2011; Teijaro 2013] Additional viral-specific mechanisms are poorly understood; however one recent mechanistic study demonstrated that the HIV gene *nef* appears necessary for PD-1 upregulation and that PD-1 upregulation can be decreased by the phosphatidylinositol 3-kinase and protein kinase B (PI3K/Akt) pathway or inhibitors of the p38 mitogen-activated protein kinase (MAPK) pathway.[Muthumani 2008; Muthumani 2011] Additional viral- and tissue-specific mechanisms are possible. Dysregulation of PD-1 in the setting of HIV may be relevant to both the natural history of cancer and the maintenance of viral reservoirs in these patients.

In mice, blockade of the PD-1 receptor caused an increase in virus-specific CD8+ T-cell proliferation and enhanced the clearance of the chronic viral infection.[Barber 2006] PD-L1 knockout mice also have increased clearance of viral infection with lymphocytic choriomeningitis virus, further supporting a role for the PD-1/PD-L1 pathway in chronic viral infections. However, in this setting, PD-L1 knockout mice also have increased inflammation in the lung and liver when exposed to viruses than wild-type mice.[Mueller 2010]

In HIV infection, PD-1 expression on HIV-specific CD8+ cells is associated with disease progression, an increase in plasma viral load, and a decrease in CD4+ T-cell counts.[Day 2006] In a prospective study of HIV-infected patients treated with highly active antiretroviral therapy (cART), T-cell activation (CD38+HLADR+) and immune exhaustion parameters (PD-1+) were measured upon the initiation of therapy. T-cell exhaustion (CD4+PD-1+ and CD8+PD-1+ T cells) was significantly associated with suboptimal CD4 reconstitution and persisted despite long-term sustained HIV-RNA viral suppression.[Nakanjako 2011] Interestingly, blockade of PD-1 reversed HIV-induced T-cell exhaustion *in vitro*, enhanced a virus-specific immune response, and decreased viral load *in vivo* in humanized mice and macaques infected with simian immunodeficiency virus (SIV).[Trautmann 2006; Seung 2013],[Velu 2009; Zhou 2013],[Palmer 2013] Recently, Cubas *et al* proposed a model in which HIV infection may drive the expansion of both T follicular cell helper (Tfh) cells and germinal center B cells (GCBs), as corroborated by the findings of an increased frequency of PD-L1 in GCBs. That, in turn, led to excessive triggering of PD-1 on Tfh cells and affected their capacity to provide GCB help and decreased B-cell antibody responses. Thus, blocking PD-1 enhanced HIV-specific immunoglobulin production *in vitro*.[Cubas 2013]

In addition to HIV, increased PD-1 on virus-specific CD8+ T cells is associated with T-cell exhaustion in hepatitis C virus (HCV) and is also associated with tolerance in virus-specific T-cells against Epstein Barr virus (EBV) and cytomegalovirus (CMV).[Day 2006; Duraiswamy 2007; Radziewicz 2007]

Therapy with the antibody to PD-1 (anti-PD-1) has been evaluated in the setting of chronic HCV. BMS-936558 (nivolumab), a humanized anti-PD-1 monoclonal antibody, was evaluated in a phase I study of 42 patients with chronic HCV who were previously treated with interferon. A total of 35 patients received BMS-936558 doses from 0.03–10 mg/kg, and 7 patients received placebo. The most frequent adverse events (AEs; mostly grade 1 to 2) were fatigue, headache, diarrhea, and pharyngeal pain. Transient decreases in CD4+, CD8+, and CD19+ cells were noted. Six patients had probable reversible grade 1–2 immune-related AEs (irAEs), including hypothyroidism, diarrhea, and rash, and 2 had possible irAEs (thyroid and worsening glycemic control) [Gardiner 2013]. Interestingly, 1 patient had grade 4 aspartate aminotransferase/alanine aminotransferase (AST/ALT) abnormalities associated with anti-HCV response. A total of 5 patients who received the study drug and 1 patient receiving placebo had a reduction in HCV RNA ≥0.5 log10 IU/mL on at least 2 consecutive visits; 3 patients had a >4 log10 reduction. Preliminary results from an ongoing study of nivolumab in 19 hepatitis virus-infected patients with HCC suggests that anti PD1 therapy is safe and tolerable, with no dose limiting toxicity AE reported, and with few and reversible Grade 3 and 4 elevation of liver enzymes (5-12%) [El-Khoueiry 2015].

In addition to having a chronic viral infection that may benefit from anti-PD-1 therapy, patients with HIV and AIDS are at risk of developing several virally associated tumors that may be particularly suitable for treatment with immunotherapy. However, specific safety data are needed for this approach, as some HIV-infected patients develop immune reconstitution inflammatory syndrome (IRIS) against infectious agents upon T-cell expansion after initiating cART.[DeSimone 2000; French 2000] IRIS consists of an exacerbation of inflammatory disorders with paradoxical worsening of preexisting infectious processes in the setting of improving immunologic function. Patients who develop IRIS are typically successfully managed with glucocorticoid therapy. For patients with HIV, IRIS itself is associated with increased PD-1 expression on CD4+ and CD8+ T cells. [Antonelli 2010] The effect of PD-1–PD-L1 checkpoint blockade in this setting is unknown.

2.1.5 PD-L1 Expression in Lung cancer, Classical Hodgkin lymphoma, and other Virally-Associated NADMs

Upregulation of PD-L1 has been noted in many virus-associated tumors, and associated immune evasion may play a role in tumorigenesis. PD-L1 expression in tumors is associated with the treatment effect of anti-PD-1 therapy. PD-1 is a particularly interesting target in patients with HIV and cancer, as many tumors are virally related. Furthermore, patients with HIV are also at an increased risk for lung cancer independent of smoking, which may be in part also related to chronic immune activation and inflammation associated with HIV,[Giorgi 1993; Fulop 2010] although PD-L1 has not been formally evaluated in this setting. As chronic HIV itself is associated with T-cell exhaustion through the upregulation of PD-1, [Day 2006] we hypothesize that PD-1 blockade may lead to improved antitumor responses in the setting of HIV in malignancies amenable to immunotherapy.

Based on recent NSCLC tumor responses to both anti-PD-L1 and anti-PD-1 antibodies, [Brahmer 2010; Brahmer 2012; Topalian 2012; Sznol 2013] there is increasing interest in identifying possible predictors of response and prognostic markers to these therapies. *In situ* mRNA hybridization techniques and quantitative fluorescence approaches were used to measure PD-L1 in 2 cohorts of patients with NSCLC. PD-L1 protein expression was identified in 25% and 36% in the 2 cohorts. The authors also showed that the expression of PD-L1 protein or mRNA was associated with better outcome.[Velcheti 2014] However, the literature is controversial on this topic, as other series showed that higher expression of PD-L1 may portend a worse prognosis.[Mu 2011] Overall the expression of PD-L1 in NSCLC tumors is present in around 25–50% of the cases depending on the series and method of PD-L1 measurement.[Chen 2012; Velcheti 2014] Validated predictive biomarkers are required.

PD-L1 expression has also been evaluated in other tumor types. A series of 654 tumor samples from 19 types of solid tumors was analyzed using a commercially available PD-L1 immunohistochemistry (IHC) assay (Dako). PD-L1 was positive (≥5% frequency) in 14% of the tumors. Highest PD-L1 frequencies were seen in several tumors with increased in incidence in patients with HIV, including head and neck cancers (17/54 [31%]), cervical cancer (10/34 [29%]), and HCC (6/41 [15%]), among others.[Joseph Grosso 2013]

In malignancies associated with the gamma herpesvirus, which are common in patients with HIV/AIDS, PD-L1 expression is often detected in the virally infected malignant cells. In particular, PD-L1 can be expressed by Reed-Sternberg (RS) cells in cHL and by malignant B cells of EBV-positive post-transplant lymphoproliferative disorders (PTLD),[Chen 2013] and in HIV-associated diffuse large B cell lymphoma (DLBCL) cells.[Kutok 2006; Taylor 2011] A recent series used a rabbit anti-PD-L1 monoclonal antibody (Sino Biological) to measure IHC-stained sections of selected hematologic and virus-associated malignancies. PD-L1 was highly expressed (defined as ≥5% malignant cells positive) in 33/87 cHL cases, 16/16 EBV-associated DLBCL, 7/7 EBV- and immunodeficiency-associated DLBCL, 6/10 EBV+ PTLD cases, and 4/9 plasmablastic lymphomas. However, PD-L1 was not expressed on any of the 7 EBV+ Burkitt lymphoma cases.[Chen 2013]

Of clinical interest, patients without HIV with relapsed/refractory cHL treated with a different PD-1 inhibitor, nivolumab, [Ansell 2014] had a response rate of 87%, with a complete response occurring in 4 patients. A subgroup analysis of 10 patients with available tumor samples was also evaluated. In all tumors analyzed by fluorescence in situ (FISH), tumor cells had 3 to 15 copies of PD-L1 characterized by amplification, relative copy gain, or polysomy of chromosome 9p24. In all the samples, RS cells expressed PD-L1. In patients with HIV-associated cHL, the RS cells are generally EBV infected. One analysis of cHL tumor samples suggests that PD-L1 upregulation in EBV-infected RS cells may occur through virally mediated upregulation of PD-L1 rather than through 9p24 amplification.[Green 2012] Evaluating MK-3475 (pembrolizumab) in this patient population is of particular interest.

HPV-associated tumors include cervical carcinoma, squamous cell carcinomas of the head and neck and anal canal carcinomas. HPV-associated squamous cell carcinomas of the head and neck have improved clinical outcomes compared to tobacco-associated counterparts.[Gillison 2008; Mueller 2010] PD-L1 expression in HPV-associated head and neck cancers was found in 14/20 tumor samples and was noted on both tumor cells and tumor-associated macrophages, while tumor-infiltrating CD8+ T lymphocytes from the same specimens expressed high levels of PD-1.[Lyford-Pike 2013] In addition, PD-L1 was expressed in 22/115 tumor samples of unselected patients with cervical adenocarcinomas although PD-1 was highly expressed in infiltrating lymphocytes [Karim 2009]. PD-L1 may also play an important role in the pathogenesis of HPV-associated premalignant lesions, such as cervical intraepithelial neoplasia (CIN) [Insinga 2011] or anal intraepithelial neoplasia (AIN). Increased expression of PD-1 and PD-L1 have been associated with CIN in women with high-risk HPV, and PD-L1 expression correlated positively with CIN grade.[Yang 2013] This suggests that PD-1 blockade modulation may have a beneficial effect on *in situ* premalignant HPV-associated lesions.

Lastly, Merkel cell carcinoma (MCC) is a rare and aggressive cutaneous tumor, and in most patients is associated with Merkel cell polyomavirus (MCPV). In 49 patients with MCC, PD-L1 expression in tumor cells was present in 49% [Lipson 2013], with expression limited to tumors where MCPV was detectable. A smaller series of 18 patients with MCC also showed tumor PD-L1 expression in 9/13 samples.[Afanasiev 2013] These findings add to the mounting evidence that viral antigens create a local inflammatory response leading to PD-L1 expression.

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2.1.7 Correlation of PD-L1 Expression and Response to Treatment

Attempts have been made to identify biomarkers to predict response to immunotherapies. The relationship between PD-L1 expression and response to PD-1/PD-L1 antibodies remains unclear at this time. However, in a phase 1 trial of MK-3475 (pembrolizumab), a humanized monoclonal immunoglobulin G4 (IgG4) antibody against PD-1, tumor responses and progression-free-survival correlated with expression levels of PD-L1.[Daud 2014] In another study in patients with NSCLC using the same monoclonal antibody, antitumor activity correlated with PD-L1 expression.[Gandhi 2014] PD-L1 expression also has been shown to correlate with response in a small series of patients treated with the PD-1 antibody.[Topalian 2012; Sznol 2013] The threshold of staining and whether to stain tumor cells, tumor-infiltrating cells, or stromal cells are still unresolved, however, positive staining—even at 1–5% level for staining of malignant or infiltrating tumor or stromal cells—seems to correlate with response.[Dong 2002; Taube 2012; Topalian 2012; Chen 2013]

2.1.8 Evaluation of HIV in Patients on cART with Undetectable Viral Load Using Commercial Assays

During effective antiretroviral therapy, HIV persists in a reservoir of cells, and the additional effects of various immunomodulatory agents are currently under investigation. In such patients, the majority of HIV exists as integrated proviral DNA with CD4+ T-cells and other cells. Although persistent plasma viremia remains detectable using sensitive assays during cART, it is not known whether the virus is the product of complete cycles of replication or is the product of long-lived cells with integrated proviruses. The distinction

between these possibilities is critical for understanding HIV pathogenesis and for designing strategies for HIV eradication. For instance, if persistent viremia is the result of complete ongoing cycles of replication, then current antiretroviral therapy, which targets active infection, requires improvement.[Chun 2008; Buzon 2010] In contrast, if persistent viremia is derived from long-lived cells with integrated proviruses, then current antiretroviral therapy is maximally suppressive, and alternative strategies are necessary to eliminate virus infection.[Dinoso 2009; McMahon 2010] Several approaches have been useful in determining the nature of HIV viremia on therapy. The NCI HIV Drug Resistance Program has developed a sensitive real-time reverse transcription polymerase chain reaction (RT-PCR) assay for HIV with a limit of sensitivity of approximately 0.3 copies/mL plasma,[Palmer 2003] as well as assays for evaluating cell associated integrated provirus. Analysis of viremia during standard and intensive antiretroviral therapy has yielded useful insights on the source of persistent viremia. In addition, techniques to amplify genetic sequences from low-level viremia have enabled detailed phylogenetic analysis of HIV genetic diversity and molecular evolution.[Kearny 2010] Additional methods have also been recently employed to evaluate HIV latency reversal, and include kinetic evaluation of plasma HIV RNA and CD4+ T-cell unspliced HIV RNA[Elliott 2014] as well as estimate the size of the HIV reservoir through quantitation of inducible HIV producing cells using a "Tat/Rev Induced Limiting Dilution Assay" (TILDA) developed by Nicholas Chomont from the VTGI, Florida.

We will gain new insights in the proposed studies by analyzing HIV viremia before, during, and after treatment with MK-3475 (pembrolizumab). In addition, genetic analysis of persistent viremia should identify molecular evolution and provide novel insights into the clonality of long-lived HIV infected cells. If we find no effect of immune checkpoint blockade on the levels of HIV viremia, estimates of the cellular reservoir, or on population genetic characteristics, then persistent viremia may be the result of either long-lived cells that do not undergo frequent cell division that are not modifiable by PD-1 blockade. Modest increases in viremia during therapy may be the result of induced replication. Analysis of both the kinetics of viremia using single copy assay and population genetics will help distinguish these possibilities, as new active cycles of replication may result in ongoing accumulation of new mutations or shifts in the population structure. In addition, assays evaluating HIV-specific CD8+ T-cell cytotoxic activity against autologous targets have been developed in the Intramural Program in the laboratory of Mark Connors, MD, at the National Institute of Allergy and Infectious Diseases (NIAID) and will be employed to evaluate the effect of PD-1 blockade on anti-HIV CD8+ T-cell activity.[Migueles 2009]

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2.2 CTEP IND Agent: MK-3475 (pembrolizumab)

MK-3475 (pembrolizumab) (previously known as SCH 900475) is a potent and highly selective humanized mAb of the IgG4/kappa isotype designed to directly block the interaction between PD-1 and its ligands, PD-L1 and PD-L2.

PD-1 is an immune-checkpoint receptor expressed on T cells that can suppress antitumor immunity when bound to either of its ligands, PD-L1 or PD-L2. PD-L1 and PD-2 are transmembrane proteins that play a major role in suppressing the immune system. In chronic T cell driven immune responses, PD-L1 expression is upregulated on T cells, NK cells, macrophages, myeloid DCs, B cells, epithelial cells, and vascular endothelial cell upon IFN-γ stimulation. In addition, some tumor cells upregulate the PD-L1 to evade active T-cell immune surveillance. MK-3475 (pembrolizumab) is a potent and highly selective humanized mAb designed to directly block the interaction between PD-1 and its ligands, thereby enhancing tumor regression and ultimately immune rejection.

Thus, the PD-1 receptor-ligand interaction is a major normal pathway designed to limit or dampen down T-cell responses and also is a 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 downmodulate unwanted or excessive immune responses, including autoimmune reactions. PD-1 (encoded by the gene Pdcd1) is an Ig superfamily member related to CD28 and cytotoxic T-lymphocyte–associated antigen-4 (CTLA-4), which has been shown to negatively regulate antigen receptor signaling upon engagement of its ligands (PD-L1 and/or PD-L2) [Usubutun 1998] [Talmadge 2007].

The structure of murine PD-1 has been resolved [Al-Shibli 2008]. 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). After 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 [Diez 1998; Galon 2006; Talmadge 2007; Deschoolmeester 2010].

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 [Nobili 2008; Hiraoka 2010]. PD-1 was shown to be expressed on activated lymphocytes including peripheral CD4+ and CD8+ T cells, B cells, T regulatory cells (T regs), and natural killer (NK) cells [Kloor 2009; Hodi 2010]. Expression has also been shown during thymic development on CD4-CD8- (double negative) T cells as well as subsets of macrophages and dendritic cells [Hillen 2008]. The ligands for PD-1 (PD-L1 and PD-L2) are constitutively expressed or can be induced in a variety of cell types, including nonhematopoietic tissues as well as in various tumor [Nishimura 2000; Lee 2008; Leffers 2009; Hiraoka 2010]. 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 nonhematopoietic 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 [Hiraoka 2010]. 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 patients with melanoma. 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.

In mouse models, blockade of the PD-1 pathway effectively promoted CD8+ T-cell infiltration into the tumor and the presence of IFN-γ, granzyme B, and perforin, indicating that the mechanism of action involved local infiltration and activation of effector T-cell function in vivo [Korman 2007]. In addition, the combination of gemcitabine and anti-PD-L1 mAb demonstrated synergy in the rejection of pancreatic mouse tumors [Nomi 2007]. Merck in-house experiments have confirmed the in vivo efficacy of PD-1 blockade as a monotherapy. Therapeutic studies in mouse models show that administration of antibodies blocking PD-1/PD-L1 interaction enhances infiltration of tumor-specific CD8+ T cells and leads ultimately to tumor rejection, either as a monotherapy or in combination with other treatment modalities. Anti-mouse PD-1 or anti-mouse PD-L1 have demonstrated antitumor responses as a monotherapy in models of squamous cell carcinoma, pancreatic carcinoma, melanoma, and colorectal carcinoma. Blockade of the PD-1 pathway effectively unleashes a T-cell response when used alone as well as in combination with chemotherapy in syngeneic mouse tumor models.

MK-3475 (pembrolizumab) is a humanized IgG4 anti-PD-1 mAb with similar preclinical characteristics as BMS-936558. Both MK-3475 (pembrolizumab) and BMS-936558 contain the

S228P stabilizing mutation. MK-3475 (pembrolizumab) is a pure PD-1 antagonist. MK-3475 (pembrolizumab) potency in PD-1 binding, inhibition of ligand binding, and inhibition of PD-1 function has been similar or up to several-fold higher than that of an analogue of BMS-936558. Modeling of MK-3475 (pembrolizumab) pharmacokinetics (PK) in monkeys vs BMS-936558 PK reported in humans suggested comparable concentration-time curves at various dose levels. A 1 month, repeat-dose, Good Laboratory Practice toxicity study with 4-month observation after dosing of MK-3475 (pembrolizumab) revealed no major safety findings. The "No observed adverse effect level" (NOAEL) was ≥200 mg/kg.

Recent data of MK-3475 (pembrolizumab) have validated PD-1 as an attractive target for clinical intervention and have provided proof of concept for anti-PD-1 mAbs in melanoma [Hamid 2013]. Patients with advanced melanoma were treated with MK-3575 with 10 mg/kg every 2 or 3 weeks. The response rate by RECIST was 38%. Responses were durable in the majority of patients (median follow-up, 11 months among patients who had a response); 81% of the patients who had a response (42 of 52) were still receiving treatment at the time of last published analysis in March 2013. The overall median PFS among the 135 patients was longer than 7 months. Common adverse events (AEs) attributed to treatment were fatigue, rash, pruritus, and diarrhea; most of the AEs were low grade (Trial detailed below in Section 2.2.2). On September 14, 2014, the US Food and Drug Administration (FDA) granted accelerated approval of pembrolizumab for the treatment of patients with unresectable or metastatic melanoma and disease progression following ipilimumab and, if BRAF V600 mutation positive, a BRAF inhibitor.

These data are similar to data in melanoma and renal carcinoma published for a similar agent, BMS-936558 [Sznol 2010]. BMS-936558 has shown an overall response rate of approximately 30% in patients with advanced melanoma and RCC who had failed prior therapy. Responses were of long duration, and the agent was generally well tolerated.

2.2.1 MK-3475 (pembrolizumab)

MK-3475 (pembrolizumab) (SCH 900475) is a humanized immunoglobulin (Ig) G4 monoclonal antibody (mAb) which binds the programmed death 1 (PD-1) receptor, thus inhibiting the interaction with its ligands, PD-L1 or PD-L2 [Merck & Co. 2014]. PD-1 is an immune-checkpoint receptor expressed by T cells. When bound to either PD-L1 or PD-L2, the PD-1 pathway negatively regulates T-cell effector functions. The PD-1 pathway functions to limit unwanted or excessive immune responses, including autoimmune reactions. PD-L1 is typically expressed at low levels on various non-hematopoietic tissues, and PD-L2 is only detectably expressed on antigen-presenting cells in the lymphoid tissue or chronic inflammatory environments.

PD-L1 is also expressed in the tumor microenvironment of various cancers [Zou 2008]. Activation of the PD-1 pathway may be a critical mechanism to evade T-cell mediated tumor rejection [Dong 2002; Pardoll 2012]. High levels of PD-L1 expression are correlated with poor prognosis and survival in renal cell carcinoma (RCC) [Thompson 2007], pancreatic carcinoma [Nomi 2007], hepatocellular carcinoma (HCC) [Gao 2009], and ovarian carcinoma [Hamanishi 2007].

Immune-checkpoint inhibition of another inhibitory T-cell receptor, cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4), with the mAb ipilimumab, demonstrated significant prolongation of overall survival (OS) in patients with melanoma in two phase 3 trials [Hodi 2010; Robert 2011; Ribas 2012]. As an immunotherapy target, PD-1 is distinct from CTLA-4 because it can be activated directly by the cancer and it regulates the effector phase of T-cell response, whereas CTLA-4 regulates the initial stage of T-cell activation [Pardoll 2012; Ribas 2012]. Antibodies targeting the PD-1 pathway have demonstrated durable objective responses in phase 1 and 2 trials. Nivolumab showed an overall response rate (ORR) of approximately 28% in subjects with advanced melanoma, 27% in subjects with RCC, and 18% in subjects with non-small cell lung cancer (NSCLC) who had failed prior therapy [Topalian 2012]. MK-3475 (pembrolizumab) has shown an ORR of approximately 38% in patients with melanoma [Hamid 2013] and ~20% in patients with NSCLC [Merck & Co. 2014].

2.2.1.1 *Clinical Development of MK-3475 (pembrolizumab)*

Clinical data are derived from an ongoing, first-in human phase 1 study (PN001, NCT01295827) to evaluate the safety and clinical activity of MK-3475 (pembrolizumab) as a monotherapy, sponsored by Merck Sharp & Dohme. There are five parts to this study (Parts A-D and F) [Merck & Co. 2014].

Part A was a 3+3 dose-escalation study in subjects with solid tumors to evaluate safety, tolerability, pharmacokinetics (PK), and pharmacodynamics, and to determine a maximum tolerated dose (MTD) or preliminary recommended phase 2 doses (RP2Ds). Doses were 1, 3, and 10 mg/kg every 2 weeks (Q2W); doses of either 2 mg/kg or 10 mg/kg were also administered every 3 weeks (Q3W). All 3 dose levels were well tolerated and no dose-limiting toxicities (DLTs) were observed; therefore, the MTD was not determined. The RP2D was determined by the sponsor based on safety, PK, and pharmacodynamic measurements, along with the strength of antitumor activity signals observed.

The remaining four parts aim to characterize the safety profile and tolerability of MK-3475 (pembrolizumab) and to evaluate the clinical activity of MK-3475 (pembrolizumab) in the following patient populations:

Part B: Advanced melanoma patients who have either received prior ipilimumab (IPI-treated) or were naïve to prior ipilimumab (IPI-naïve). Patients in Part B receive MK-3475 (pembrolizumab) three dose levels: 2 mg/kg Q3W, 10 mg/kg Q3W, and 10 mg/kg Q2W.

Part C: NSCLC patients. Patients in Part C receive MK-3475 (pembrolizumab) at 10 mg/kg Q3W.

Part D: Advanced melanoma patients that are IPI-naïve. Patients in Part D receive MK-3475 (pembrolizumab) at 2 mg/kg Q3W and 10 mg/kg Q3W.

Part F: NSCLC patients with and without prior systemic therapy whose tumors express PD-L1 when exposed to MK-3475 (pembrolizumab). Patients in Part F receive MK-3475 (pembrolizumab) at 2 mg/kg or 10 mg/kg Q3W, or 10 mg/kg Q2W.

Pharmacokinetics
The half-life ($t_{1/2}$) of MK-3475 (pembrolizumab) is approximately 4 weeks and there is no indication of dose dependency of half-life in the three dose groups (1, 3, and 10 mg/kg) (Investigator's Brochure, 2014). The long $t_{1/2}$ supports a dosing interval of every 2 or 3 weeks.

There was a dose-related increase in exposure from 1 to 10 mg/kg (Investigator's Brochure, 2014). Serum concentrations of MK-3475 (pembrolizumab) were lower by a factor of approximately 5 in patients receiving 2 mg/kg Q3W than in those receiving 10 mg/kg Q3W [Hamid 2013], [Merck & Co. 2014]. Steady-state trough concentrations were 20% greater in the patients receiving 10 mg/kg Q2W than in those receiving the same dose Q3W.

Anti-Drug Antibodies (ADA) Data
The occurrence of ADA has been observed in less than 1% of the patients screened, indicating a low potential of MK-3475 (pembrolizumab) to elicit the formation of ADA [Merck & Co. 2014]. No impact of ADA on MK-3475 (pembrolizumab) exposure has been observed.

Efficacy
When treated with MK-3475 (pembrolizumab) monotherapy, the ORR for IPI-treated patients with melanoma (Part B) was 25%/27% according to the Response Evaluation Criteria in Solid Tumors (RECIST)/investigator-assessed immune-related response criteria (irRC), respectively [Merck & Co. 2014]. The ORR for IPI-naïve patients with melanoma (Parts B and D) was 39%/43% by RECIST/investigator-assessed irRC, respectively. The majority of responses were seen in patients with melanoma by 16 weeks of therapy with MK-3475 (pembrolizumab); however, some responses have been reported after 24 weeks or more of therapy with MK-3475 (pembrolizumab). Responses can be delayed, and in some patients, a RECIST-defined progression followed by a response has been observed.

The preliminary objective response rate for 38 patients with NSCLC (Part C) was 21%/24% by RECIST/investigator-assessed irRC, respectively [Merck & Co. 2014].

Pharmacodynamics/Biomarkers
PD-L1 is being investigated as a predictive biomarker for MK-3475 (pembrolizumab) treatment. At the 15th World Conference on Lung Cancer, Garon, et al. presented preliminary data on a subset of patients suggesting that higher levels of tumor PD-L1 expression are associated with increased clinical activity [Garon 2013]. Objective responses by RECIST 1.1 occurred in 4 out of 7 patients with higher levels of PD-L1 expression (57%, 95% confidence interval [CI] 18-90%) vs. 2 out of 22 patients with

lower levels of PD-L1 expression (9%, 95% CI 1-29%). These data are extremely preliminary, and PD-L1 is not being used for patient selection.

Biomarkers to evaluate immune modulation and markers in the tumor microenvironment, such as T-cell infiltration, the baseline expression of markers of T-cell suppression FoxP3 or the immunoregulatory enzyme indoleamine 2,3-dioxygenase (IDO) in tumor biopsies, were associated with a high response rate [Berman 2009; Hamid 2009].

2.2.1.2 *Safety data*

The most frequent treatment-related adverse events (AEs) were fatigue, nausea, cough, pruritus, diarrhea, and rash [Merck & Co. 2014]. Most AEs were not considered serious. The most commonly reported immune-related AEs were rash, pruritus, vitiligo, hypothyroidism, arthralgia, diarrhea, and pneumonitis.

The most frequent treatment-related adverse events (AEs) were fatigue, nausea, cough, pruritus, diarrhea, and rash (Investigator's Brochure, 2014). Most AEs were not considered serious. The most commonly reported immune-related AEs were rash, pruritus, vitiligo, hypothyroidism, arthralgia, diarrhea, and pneumonitis.

Important identified risks include: pneumonitis, thyroid disorders (hypothyroidism and hyperthyroidism), colitis, diarrhea, hepatitis, nephritis, uveitis, rash/pruritus and neuropathy.

Important identified risks include: pneumonitis, thyroid disorders (hypothyroidism and hyperthyroidism), colitis, diarrhea, hepatitis, nephritis, uveitis, rash/pruritus and neuropathy.

2.3 Other Agent(s): Combination Antiretroviral therapy (cART)

Patients must be on an effective cART regimen, generally a 3-drug regimen based on Department of Health and Human Services (DHHS) treatment guidelines: http://aidsinfo.nih.gov/contentfiles/lvguidelines/adultandadolescentgl.pdf. For most current product information on antiretroviral agents, refer to manufacturers' Prescribing Information. Appendix D provides a table of common side effects observed with agents prescribed as part of DHHS- recommended and alternate cART regimens.

Effective antiretroviral therapy in people with HIV leads to substantially decreased infectious mortality and mortality, CD4+ T-cell immune reconstitution, and substantially increased longevity. Contemporary antiretroviral therapies are very well tolerated, and when taken regularly, lead to effective control of HIV viremia. Concurrent cART in this protocol is required for optimal patient outcomes. There are no predicted drug-drug interactions and minimal expected overlapping toxicities with addition of MK-3475 (pembrolizumab) to a cART regimen with established efficacy and tolerability.

2.4 Rationale

In addition to optimal care for patients with HIV, optimal management of HIV using cART is required to maximize T-cell immunity and for evaluation of the effect of MK-3475 (pembrolizumab) on the HIV reservoir. We hypothesize that patients with HIV and cancer will tolerate and benefit clinically from anti-PD-1 therapy through antitumor responses and improved control of HIV and other concurrent viral infections when present. We propose to implement a multicenter phase 1 trial investigating the safety of the monoclonal anti-PD-1, MK-3475 (pembrolizumab), in patients with HIV/AIDS and malignancy. Correlative studies will evaluate the effect of MK-3475 (pembrolizumab) on immune cell subsets in patients with HIV (virally suppressed on cART) and cancer, and evaluate the effect of MK-3475 (pembrolizumab) on the HIV reservoir. Anti-PD-1 therapy may be particularly useful in this patient population; however, specific safety data are required. Furthermore, patients with HIV/AIDS are often excluded from early phase clinical trials of cancer therapy, so the current proposal addresses an extremely important unmet clinical need.

2.5 Correlative Studies Background

2.5.1 Evaluation of Peripheral Blood CD4+ and CD8+ T-cell counts— Integral Correlative Study #1

CD4+ and CD8+ T-cells are important biomarkers for the effect of HIV on T-cell immunity. In the setting of HIV in patients with cancer, the CD4+ and CD8+ T-cell counts may also be affected by the underlying malignancy (i.e. classical Hodgkin lymphoma) or else chemotherapy of radiation therapies used to treat malignancy. Commonly used thresholds that have been used historically for initiation of HIV therapy include CD4+ T-cell <200 cells/uL and CD4+ T-cell < 350 cells/uL. The highest risk for infectious complications and poor outcomes occur in patients with a CD4+ T-cell count <100. Historically, CD4+ T-cell count less than 100 has been associated with poor outcomes in therapeutic studies for AIDS –related lymphomas and KS. In addition to absolute CD4+ T-cell count, the ratio of CD4+/CD8+ T-cells may provide additional prognostic information, and a ratio < 0.4 has been shown to be associated with poor outcomes in the cART era.[Serrano-Villar 2014]

Importantly, in patients with HIV but not cancer, the degree of PD-1 upregulation on T-cells is inversely proportional to the CD4+ T-cell count [Cockerham 2014], and this provides additional justification for the stratification employed in this study.

CD4+ and CD8+ T-cell counts are routinely evaluated in Clinical Laboratory Improvement Amendments (CLIA) certified laboratories at US institutions that care for patients with HIV, and this study will employ results from the CLIA certified laboratories at the treating institution for evaluation of protocol eligibility, stratification to cohort, and monitoring for potential decreases that would require changes in supportive care or alterations in therapy may all be affected by this Integral Correlative Study. CD4+ and CD8+ T-cell counts will be evaluated at baseline, Cycle 1 Day 8, prior to Cycles 2, 3, and 4, then prior to every third cycle, at end of therapy, and at the 30-Day Safety Follow-up Visit.

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3. PATIENT SELECTION

3.1 Eligibility Criteria

3.1.1 Histologically or cytologically proven metastatic or locally advanced tumors for which no standard therapy exists, or where standard therapy has failed, or in patients otherwise ineligible for standard therapy, or for an indication that anti-PD-1 therapy has been shown to be effective in studies in HIV-uninfected participants. Disease-specific criteria will be applied for certain common cancers and cancers strongly associated with HIV. However, enrollment will not be confined to these tumors.

3.1.1.1 NSCLC

i. Metastatic or locally advanced disease that progressed after at least one prior therapy

Note: Patients that have actionable molecular targets (e.g., epidermal growth factor receptor [EGFR], anaplastic lymphoma kinase [ALK], c-ros oncogene 1[ROS1] mutations) must have received (when indicated) prior appropriate targeted therapy using FDA-approved agents

3.1.1.2 AIDS-related non-Hodgkin lymphoma and other non-Hodgkin lymphoma

i. Failed standard first-line therapy; and
ii. Failed autologous stem cell transplant if indicated for histology (i.e diffuse large B-cell lymphoma) or autologous stem cell transplant is not feasible

3.1.1.3 Classical Hodgkin lymphoma

i. Relapsed or refractory de novo classical Hodgkin lymphoma having failedstandard first-line therapy; and

ii. May have failed to achieve a response or progressed after treatment with brentuximab vedotin or may be brentuximab vedotin naïve but is ineligible or unable to receive brentuximab vedotin; and
iii. May have failed to achieve a response to, progressed after, or is ineligible for autologous stem cell transplant (auto-SCT)

3.1.1.4 HCC
i. Not eligible for curative attempt resection or liver transplant

3.1.1.5 Kaposi sarcoma (following prior KS-specific therapy (Cohorts 1-3)
KS impacting physical and/or psychological wellbeing and not amenable to local therapy and one or more of the following:
i. Stable KS despite 6 or more cycles of liposomal doxorubicin or paclitaxel or other active cytotoxic agents (i.e. etoposide, bleomycin, anthracyclines, vincristine, vinblastine); or
ii. Progressive disease despite 3 or more cycles of liposomal doxorubicin or paclitaxel or other active cytotoxic agents (i.e. etoposide, bleomycin, antracyclines, vincristine, vinblastine); or
iii. Patient who received a cumulative lifetime dose of anthracyline of ≥550 mg/m^2; or
iv. Recurrent or progressive KS after completion of prior first line chemotherapy
v. Intolerant of or refuses further cytotoxic chemotherapy
vi. No KSHV-associated multicentric Castleman disease in past 5 years
vii. For KS patients, the following laboratory values supersede values in section 3.1.6:

- platelets > lower limit of normal
- hemoglobin >10 g/dL

[redacted]

3.1.1.7 Melanoma

i. Unresectable or metastatic disease progression following a BRAF inhibitor if BRAF V600 positive

Note: Prior therapy with ipilimumab not required

3.1.2 Available pretreatment biopsy, either fresh (optimal) or archival (acceptable)

3.1.3 Resolution of any AEs from prior treatments must be resolved to baseline or grade ≤1 at enrollment (with the exception of alopecia), neuropathy, and ototoxicity (i.e., AEs that are not expected to improve within the washout period).

3.1.4 On an effective combination cART regimen, generally a 3-drug regimen based on Department of Health and Human Services (DHHS) treatment guidelines.

i. Patients must be on cART ≥4 weeks; and
ii. Evidence of viral suppression defined as HIV viral load <200 copies/mL; and
iii. No symptomatic AEs > Grade 1 by CTCAE criteria probably or definitely attributed to cART; and
iv. No laboratory AEs noted on protocol defined screening laboratories

> Grade 1 by CTCAE criteria probably or definitely attributed to cART, with exceptions noted below in section 3.1.6.

Note: If cART is modified during the screening period, patients must be on an effective new regimen for ≥ 2 weeks and otherwise meet eligibility criteria.

Most patients have viral loads that are suppressible to <50 copies/mL, but about 25% of patients will occasionally have blips up to 400–500 copies/mL, which do not appear to correlate with lack of viral suppression in most studies. Thus, an HIV viral load of ≤400 copies/mL for an occasional "blip" will be allowed, if there is documentation of an HIV viral load <200 on the same regimen and no significant treatment interruption.

3.1.5 CD4+ T-cell count ≥100 cells/μL

3.1.6 Patients must have marrow function and organ function as defined below.

Note: To remain on treatment, any abnormal lab values allowed by the PI must remain stable or improve during treatment. Similar off treatment rules will be applied to all patients, except the following: the grade of any abnormal lab value allowed by the Protocol P.I. at enrollment will be considered the patient's baseline for potentially resuming therapy after modification/holding of therapy when off treatment criteria are applied.

System	Laboratory value
- leukocytes	no lower limit
- absolute neutrophil count	>500/mcL
- platelets	>50,000/mcL
- hemoglobin	>9 g/dL
- total bilirubin	<1.5 X upper limit of normal (ULN); or <3 x institutional ULN for Gilbert's syndrome or HIV protease inhibitors; or <5 x ULN and direct bilirubin < 0.7 mg/dL for patients on atazanvir containing HIV regimen
- AST(SGOT)/ALT(SGPT)	<2.5 × institutional ULN
- Creatine kinase	<5 X institutional ULN
- serum creatinine	<2.5 X institutional ULN OR
- Measured or calculated[a] creatinine clearance (CrCl) (Glomerular filtration rate [GFR] can also be used in place of creatinine or CrCl)	≥30 mL/min for subject with creatinine levels >2.5 X institutional ULN
- Thyroid Stimulating Hormone (TSH)	Within Institutional Limits (ie: Normal). If TSH is greater or less than institutional limits patients may participate if their T4 is WNL. Patients may be on a stable dose of replacement thyroid medication. Dose adjustments are allowed if needed.

[a]Creatinine clearance should be calculated per institutional standard.

3.1.7 Eastern Cooperative Oncology Group (ECOG) performance score of 0 to 1 (Appendix A)

3.1.8 At least 2 weeks from end of chemotherapy with resolution of neutropenia to above level

3.1.9 At least 2 weeks from end of radiation therapy

3.1.10 At least 4 weeks from end of monoclonal antibody therapy

3.1.11 At least 2 weeks from end of targeted therapy

3.1.12 Female patients of childbearing potential must have a negative urine or serum pregnancy within 72 hours before 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.

Note: The effects of MK-3475 on the developing human fetus are unknown. For this reason and because anti-PD-1 agents may be teratogenic, women of child-bearing potential must agree to use 2 methods of birth control, or be surgically sterile, or abstain from heterosexual activity beginning with the screening visit and for the duration of study

participation, through 120 days beyond last dose of MK-3475 administration. Patients of childbearing potential are those who have not been surgically sterilized or have not been free from menses for >1 year.

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.

3.1.13 Men treated or enrolled on this protocol must agree to use 2 adequate methods of contraception starting with the screening visit, for the duration of study participation and through 120 days after the last dose of MK-3475 administration.

3.1.14 No prior treatment with anti-PD-1 or anti-PD-L1

3.1.15 Measurable disease by Response Evaluation Criteria In Solid Tumors (RECIST) v1.1 or other tumor-specific criteria or disease assessable by physical exam or other methods if not measurable by RECIST

3.1.16 Baseline tumor tissue, either fresh (preferred) or from paraffin block/unstained slides if contemporary biopsy is unsafe or not otherwise obtainable from the primary tumor site or metastatic site to be available for use on correlative studies

3.1.17 Age ≥18 years.

Because no dosing or adverse event data are currently available on the use of MK-3475 (pembrolizumab) in combination with cART in patients <18 years of age, children are excluded from this study, but will be eligible for future pediatric trials.

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

3.2 Exclusion Criteria

3.2.1 Active systemic immunosuppressive therapy

3.2.2 Systemic steroid therapy or steroid therapy that cannot be discontinued with more than 7 consecutive days of steroids within the prior 2 weeks

Note: The use of prednisone or equivalent <0.125 mg/kg/day (absolute maximum of 15 mg/day) as replacement therapy is permitted. Inhaled or topical corticosteroids are permitted.

3.2.3 Current or history of systemic autoimmune disease requiring systemic therapy.

Note: the following will NOT be exclusionary:

i. The presence of laboratory evidence of autoimmune disease (e.g., positive antinuclear antibody (ANA) titer or lupus anticoagulant) without associated symptoms
ii. Clinical evidence of vitiligo or other forms of depigmenting illness
iii. Mild autoimmunity not impacting the function of major organs (e.g., limited psoriasis)

3.2.4 Grade 3 or 4 immune related toxicity associated with prior ipilimumab therapy that has not resolved to grade 0 or 1.

3.2.5 Cardiovascular disease that meets one of the following: congestive heart failure (New York Heart Association Class III or IV), active angina pectoris, or recent myocardial infarction (within the last 6 months)

3.2.6 Active tuberculosis (TB):

i. Patients who are undergoing first month of therapy (RIPE or equivalent) for active TB
ii. Patients with TB immune reconstitution syndrome (IRIS) requiring corticosteroids

Note: Patients who are receiving therapy beyond month one of initial therapy with no evidence of TB IRIS requiring corticosteroid therapy, or those receiving treatment for latent tuberculosis (INH or alternative) may be eligible after discussion with the Protocol P.I.

3.2.7 Cirrhosis with Child-Pugh score of B or C

3.2.8 Uncontrolled HBV infection, defined as plasma HBV DNA detectable by PCR

Note: the following will NOT be exclusionary:
i. A positive hepatitis B serology indicative of previous immunization (i.e., HBsAb positive and HBcAb negative), or a fully resolved acute HBV infection
ii. Patients with chronic HBV suppressed by appropriate antiretroviral therapy with activity against HBV, as outlined in DHHS guidelines

3.2.9 Uncontrolled HCV infection, defined as plasma HCV RNA detectable by PCR.

Note: the following will NOT be exclusionary:
i. Positive HCV serology but no detectable HCV RNA, indicative of spontaneously cleared HCV infection
ii. Patients who have been successfully treated for HCV as long as therapy for HCV has been completed

3.2.10 Patients who are receiving any other investigational agents for cancer

3.2.11 Extensive active brain disease including symptomatic brain metastases or the presence of leptomeningeal disease, and all patients with infratentorial tumors

Note*:* Patients with brain metastasis after definitive therapy with surgery or stereotactic radiation and stable off steroids for >4 weeks are eligible as are patients with asymptomatic brain metastasis as long as less than 1 cm and thus deemed as not requiring therapy by the primary physician and the lesions(s) are not infratentorial.

3.2.12 Pregnancy or nursing or unwilling to take adequate birth control during therapy

3.2.13 Prior organ allograft or allogeneic transplantation, if the transplanted tissue is still in place.

3.2.14 Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia

3.2.15 Medical or psychiatric illness or social situations that would, in the opinion of the investigator, preclude participation in the study or the ability of patients to provide informed consent for themselves

3.2.16 Clinically significant lung disease including known history or evidence of interstitial lung disease or chronic obstructive pulmonary disease (COPD) that requires oxygen therapy.

3.2.17 Active non-infectious pneumonitis ≥ Grade 2 or history of Grade 3 non-infectious pneumonitis requiring steroids within the past 12 months; or any history of Grade 4 non-infectious pneumonitis.

3.2.18 Grade 3-4 ascites or pleural effusion.

Note: The following will NOT be exclusionary: A participant who is clinically stable following treatment for ascites or pleural effusion (including therapeutic thoracentesis or paracentesis).

3.2.19 Receipt of live vaccines within 30 days before the first dose of trial treatment and while participating in the trial. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, chicken pox, yellow fever, seasonal flu, H1N1 flu, rabies, BCG, and typhoid vaccine.

3.2.20 History of allergic reactions attributed to compounds of similar chemical or biologic composition to MK-3475 (pembrolizumab).

3.3 Inclusion of Women and Minorities

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

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4.4 General Guidelines

Following registration, patients should begin protocol treatment as soon as possible. Issues that would cause treatment delays should be discussed with the Principal Investigator. If a patient does not receive protocol therapy following registration, the patient's registration on the study may be canceled. The Study Coordinator should be notified of cancellations as soon as possible.

5. TREATMENT PLAN

This is a phase I multi-institutional trial of MK-3475 (pembrolizumab) in patients with stable, treated HIV on cART with metastatic or refractory/advanced malignant neoplasm including AIDS-defining or NADM. The primary aim is to assess safety and tolerability of MK-3475 (pembrolizumab) in this patient category. The trial is open-labeled and nonrandomized.

Patients will be stratified based on CD4+ T-cell counts at entry as some issues of safety and tolerability may vary according to CD4+ T-cell levels. Patients with HIV and malignancy that have been treated with multiple lympholytic therapies will present with a wide spectrum of CD4+ T-cell counts, even when on optimal HIV therapy and otherwise eligible to participate in a research protocol. For results of a safety study to be generalizable in this population, an adequate sample size is required to evaluate safety across a range of CD4+ T-cell counts, especially for a drug that modulates the immune system. For example, the safety of MK-3475 (pembrolizumab) may vary based on CD4+ T-cell count. As in some non-cancer settings, PD1 upregulation on CD4+ and CD8+ T cells in patients with HIV correlates with CD4+ T-cell count. In order to better address the primary objective, the accrual will be stratified by CD4+ T-cell levels. The CD4+ T-cell levels indicated below for definition of the cohorts are standard for many HIV therapy trials.

Cohort 1: 100-199 CD4+ T cells/mcL

Cohort 2: 200-350 CD4+ T cells/mcL

Cohort 3: >350 CD4+ T cells/mcL

[redacted]

Accrual to each cohort (1-3) will be based on unacceptable AE during first treatment cycle of 21 days. If 2 or more unacceptable AE occur in the first 6 patients, the cohort will not be expanded to 12 patients until the AE are assessed by the Toxicity Evaluation Committee and the Committee approves the expansion.

The treatment plan and study procedures are detailed in the Study Calendars and footnotes (Section 10). Study procedures described in the Study Calendars will be performed prior to drug administration for a given cycle, with the exception of certain blood draws. Disease assessments are performed prior to starting study drug regimen, then every 9 weeks thereafter during the first year of treatment, and every 12 weeks during the second year of treatment.

5.1 Agent Administration

5.1.1 MK-3475 (pembrolizumab)

After a screening phase for eligibility, patients will receive the standard pembrolizumab regimen with a fixed dose of 200 mg every 3 weeks by IV infusion over 30 minutes in conjunction with effective cART therapy administered orally daily (Section 5.1.2).

Trial treatment should be administered on Day 1 of each cycle after all procedures/assessments have been completed. Trial treatment may be administered up to 7 days before or after the scheduled Day 1 of each cycle due to administrative reasons. See also Sections 6.1 and 6.2 for guidelines related to modification of therapy and delayed visits for reasons other than toxicity. Treatment will generally be administered on an outpatient basis. MK-3475 (pembrolizumab) will be administered as a 30 minute IV infusion (treatment cycle intervals may be increased due to toxicity as described in Section 6.1). Infusion timing should be as close to 30 minutes as possible; however, a window of -5 minutes and +10 minutes is permitted (i.e., infusion time is 30 minutes: -5 min/+10 min).

Reported adverse events and potential risks are described in Section 7. Appropriate dose modifications are described in Section 6. No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the patient's malignancy.

Agent	Dose	Route	Schedule	Cycle Length
MK-3475 (pembrolizumab)	200 mg	IV infusion over 30 minutes	Day 1 of each cycle	21days (3 weeks)

5.1.2 Other Agent(s)

Patients must be on an effective cART regimen, generally a 3-drug regimen based on Department of Health and Human Services (DHHS) treatment guidelines http://aidsinfo.nih.gov/contentfiles/lvguidelines/adultandadolescentgl.pdf. Administration of cART will follow instructions and dosing in the manufacturers' Prescribing Information for any given individual regimen.

Patients with concurrent HBV require cART regimens based on DHHS Guidelines that are effective against concurrent HBV. Active agents include 3TC, TDF, and FTC. A cART regimen containing TDF and FTC is preferred for HBV co-infected patients if feasible.

Antiretroviral therapy will generally be managed in conjunction with a primary care physician or infectious disease specialist. The following regimens are current DHHS recommended and alternative regimen for treatment naive patients with no caveats regarding HIV viral load or CD4 count at baseline, and are all acceptable regimens. This list will be updated periodically at the time of protocol amendments.

Table 2: DHHS Recommended and Alternative cART regimens

Recommended	Brand Names
Integrase Strand Transfer Inhibitor (INSTI) Based Regimens	
Dolutegravir/abacavir/lamivudine (DTG/ABC/3TC)	*Triumeq®*
Dolutegravir plus tenofovir disoproxil fumarate (TDF) /emtricitabine (FTC)	*Tivicay® + Truvada®*
Elvitegravir/cobicistat/TDF/FTC (EVG/c/TDF/FTC)	*Stribild®*
Raltegravir (RAL) plus TDF/FTC	*Isentress® + Truvada®*
Protease Inhibitor Based Regimens	
Darunavir/ritonavir (DRV/r) plus TDF/FTC	*Prezista® + Truvada®*
Alternative Regimens	
Protease Inhibitor Based Regimen	
Atazanavir/ritonavir plus TDF/FTC	*Reyataz® + Norvir® + Truvada®*
Non-nucleoside reverse transcriptase-based regimen	

Efavirenz/TDF/FTC	*Atripla®*

All patients on abacavir (ABC) based regimens must have documentation of being HLA B57*01 negative. Combination tablets are noted above, but in some instances, individual agents may be preferable for some cART regimens. cART regimens that are not on this list that are proven effective and tolerable in a given patient need not be modified.

All regimens not on this list should be discussed with the Principal Investigator (PI).

All patients with AEs attributed to cART noted during the screening process should be discussed with the PI.

Modification of cART is allowed during the screening process, although patients must be on a modified regimen for at least 2 weeks, and otherwise meet eligibility criteria before enrolling.

Modification of cART is allowed for patients while on study after completing the first cycle.

There are no predicted drug-drug interactions between cART and MK-3475 (pembrolizumab).

5.1.3 Other Modality(ies) or Procedures: N/A

5.2 Safety Monitoring and Definition of Unacceptable Adverse Events (AEs)

5.2.1 Safety will be evaluated on all cycles. AEs will be evaluated using the Common Terminology Criteria for Adverse Events (CTCAE) v4 or current CTCAE version.

Unacceptable AEs are used to determine whether to stop or hold therapy in individual patients. AEs requiring stopping or holding therapy in a particular patient, are defined in Section 5.2.3. Management of specific AEs, including criteria for holding and resuming MK-3475 (pembrolizumab), are outlined in Section 6.1.

Unacceptable AEs are also used to determine whether to expand individual cohorts from 6 to 12 patients (Section 5.2.2). Rules for expanding or not expanding the individual cohorts are based upon unacceptable AEs observed during the first 21 days of therapy and deemed at least possibly attributable to MK-3475 (pembrolizumab). (See Statistical Section 13.1). For the purpose of cohort expansion, unacceptable AEs are defined as any grade 4 AE or any grade 3 AE that requires holding therapy in an individual patient (see below). Any grade 3 or grade 4 AE that does not require holding therapy in an individual patient will not be considered an unacceptable AE for purposes of cohort expansion.

5.2.2 Safety will be monitored by the ad hoc Toxicity Evaluation Committee will be composed of the trial principal investigator (PI), two site PIs (one with HIV expertise and one with cancer expertise), the CITN Director, a representative from CTEP and ad hoc members as warranted for specific toxicity issues.

If the unacceptable AEs (defined below) observed are typical of known MK-3475 (pembrolizumab) toxicities, the Toxicity Evaluation Committee will consider (1) revising the protocol eligibility requirements to decrease the likelihood of toxicities, (2) modifying the dose, or (3) allowing the trial to proceed as designed given that patients in this trial will have fatal diseases and few other treatment options. The Toxicity Evaluation Committee will need to evaluate the risk/benefit ratio in this situation.

If unexpected, unacceptable AEs observed are considered to be related to concurrent administration of cART and MK-3475 (pembrolizumab), the Toxicity Evaluation Committee will consider revising the protocol eligibility requirements to decrease the likelihood of toxicities or may consider allowing the trial to proceed as designed given the risk/benefit ratio for this population.

During prolonged dosing of MK-3475 (pembrolizumab) in patients who are benefiting from therapy, modification of the cART regimen will be allowed.

5.2.3 Unacceptable AEs

MK-3475 (pembrolizumab) will be withheld in individual patients for unacceptable AEs until or unless the toxicity resolves to an acceptable level. If an unexpected event occurs in a patient who was previously tolerating cART that is not probably or definitely attributable to another cause, then that event will be at least possibly attributable to MK-3475 (pembrolizumab), and stopping rules will be applied as outlined for MK-3475 (pembrolizumab)–related events. In that circumstance, cART will not be stopped, especially during the period in which unacceptable AEsare being evaluated. MK-3475 (pembrolizumab) dose will not be modified or delayed for potential cART-related events.

Unacceptable AEs requiring holding therapy and acceptable toxicity level for restarting therapy are listed below and in Sections 5.7 and 6.1. The list is not comprehensive for all potential happenstances. Any nondefined AE or exceptions will be presented to the Toxicity Evaluation Committee for assessment and decision.

Grade 4 AEs

- Grade 4 AE will require stopping trial therapy in the affected patient. The patient will not be rechallenged, except in exceptional circumstances, after review by the Toxicity Evaluation Committee. There are several exceptions to stopping therapy for Grade 4 AE:
    - Given the possibility of transient effects of MK-3475 (pembrolizumab) on CD4 counts, patients with Grade 4 lymphocytopenia or CD4 lymphocytopenia in the absence of infectious complication or other indications to come off therapy may be monitored on therapy and given appropriate prophylactic antibiotics for one

cycle. If follow-up evaluation of CD4 count also reveals Grade 4 lymphocytopenia or CD4 lymphocytopenia, MK-3475 (pembrolizumab) will be held for up to 12 weeks until CD4 lymphpocytopenia resolves to Grade 2 or less, but resumed in patients otherwise tolerating therapy with stable disease or better.

- MK-3475 (pembrolizumab) will be held in patients with Grade 4 neutropenia or thrombocytopenia, and can be restarted if resolves to ≤ Grade 1.

Grade 3 AEs

- Grade 3 AE will require holding trial therapy in the affected patient until or unless the AE resolves to a grade 2 AE within 12 weeks, and the trial PI and the CITN Director agree with reinstitution of therapy (exceptions noted below and in Section 5.7).
- Grade 3 colitis and pneumonitis need to resolve to grade 1 before considering reinstituting therapy.
- Any grade 3 AE lasting >12 weeks will require permanently stopping trial therapy in the affected patient, except in exceptional circumstances after review by the Toxicity Evaluation Committee. A most important exceptional circumstance potentially allowing continued therapy would be a patient responding to MK-3475 (pembrolizumab) in the face of a nonemergent life-threatening AE.
- A drug-related autoimmune or inflammatory event including uveitis, pneumonitis, diarrhea, colitis, neurologic AEs, hypersensitivity reaction, infusion reaction, or immune reconstitution inflammatory syndrome (IRIS) or incident KSHV-associated multicentric Castleman disease of any duration requires discontinuation if the AE/symptoms do not resolve to baseline within 12 weeks with appropriate medical management.
- An irAE requiring continued systemic steroid or other immunosuppressive treatment and patient cannot be tapered to a steroid dose ≤15 mg prednisone equivalent within 12 weeks.
- Grade 3 AE that <u>do not</u> require holding therapy in the affected patient include:
  - Infusion-related reaction resolving within 6 hours and controlled with medical management
  - Transient (≤12 hours) flu-like symptoms or fever, which is controlled with medical management
  - Transient (≤24 hours) fatigue, local reactions, headache, nausea, or emesis that resolves to ≤grade 1
  - Single laboratory values out of normal range that are unlikely related to trial treatment according to the investigator, do not have any clinical correlate, and resolve to ≤grade 1 within 21 days with adequate medical management
  - Transient creatine phosphokinase (CPK) elevation due to exercise or trauma

  - Tumor-flare phenomenon defined as local pain, irritation, or rash localized at sites of known or suspected tumor that resolves to ≤grade 2 within 21 days with appropriate therapy
  - Lymphopenia, CD4+ T-cell lymphopenia, neutropenia
  - Anemia, unless hemoglobin less than 7 gm/dL
  - For patients on protease inhibitor–based cART regimens, a total bilirubin < 5x ULN will not be an unacceptable AE in patients with a grade 2-3 elevation in bilirubin at baseline due to Gilbert's disease or protease inhibitors.
  - Asymptomatic hypophosphatemia
  - Dry skin, not limiting self-care activities of daily living (ADL)

- Grade 2 AEs that require holding therapy in affected patients include:
  - - Drug-related uveitis or eye pain or blurred vision that does not respond to topical therapy and does not improve to grade 1 severity within 12 weeks
- Any dosing interruption lasting >12 weeks requires stopping and not reinstituting therapy with the following exceptions:
  - - Dosing interruptions >12 weeks that occur for non–drug-related reasons may be allowed if approved by the PI. Before reinitiating treatment in a participant with a dosing interruption lasting >12 weeks, the PI must be consulted.
- The following conditions will not be considered unacceptable AEs:
  - - Preexisting manifestations of HIV infection or therapy for HIV infection

5.3 General Concomitant Medication and Supportive Care Guidelines

5.3.1 Concomitant Medication

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 Protocol PI and CITN Director. The final decision on any supportive therapy or vaccination rests with the investigator and/or the subject's primary physician; however, the decision to continue the subject on trial therapy or vaccination schedule requires the mutual agreement of the Investigator, Protocol PI and CITN Director, and the patient. Non-urgent medications will not be introduced during the first cycle of MK-3475 (pembrolizumab), as they may interfere with evaluation of AEs and DLTs during this time period.

Acceptable Concomitant Medications
All treatments that the investigator considers necessary for a patient'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.

Opportunistic Infection Prophylaxis:
Patients with CD4+ T-cell counts less than 200 cells/uL should receive prophylaxis against *Pneumocystis* pneumonia with one of the following:

- Trimethoprim/sulfamethoxazole 160/800 mg (Bactrim DS® tab) orally every Monday, Wednesday, Friday (Preferred)
- Atovaquone 1500 mg orally daily
- Pentamidine 300 mg via nebulizer every 4 weeks

Prohibited Concomitant Medications
Patients are prohibited from receiving the following therapies during the Screening and Treatment Phase of this trial:

- Anti-cancer systemic chemotherapy or biological therapy

  Note: Exception for patients with concurrent prostate cancer s successfully controlled on hormonal therapy or history of breast cancer on adjuvant hormonal therapy.

- Immunotherapy not specified in this protocol.
- Investigational agents other than MK-3475 (pembrolizumab).
- Radiation therapy

  Note: Generally, patients who have symptomatic progression requiring radiation therapy while on protocol should be taken off protocol-directed therapy and judged to have progressed. Exceptional cases should be discussed with the Protocol P.I, CITN, and CTEP on an individual basis, after consultation with a local radiation oncologist. Any lesion treated with radiation cannot serve as a predefined target lesion for evaluating MK-3475 (pembrolizumab) efficacy.

- Live vaccines within 30 days prior to the first dose of trial treatment and while participating in the trial. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, chicken pox, yellow fever, rabies, BCG, and typhoid (oral) vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed; however, intranasal influenza vaccines (*e.g.* Flu-Mist®) are live attenuated vaccines, and are not allowed.
- Glucocorticoids for any purpose other than to modulate symptoms from an event of suspected immunologic etiology. The use of physiologic doses of corticosteroids no

greater than prednisone 15 mg (or equivalent) may be approved after consultation with CITN.

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

The Exclusion Criteria describes other medications which are prohibited in this trial. There are no prohibited therapies during the Post-Treatment Follow-up Phase.

5.4 Duration of Therapy

MK-3475 (pembrolizumab) will be continued in each patient until confirmed progression or the development of an unacceptable AE that meets criteria defined in Section 5.2.3. Treatment for patients that achieve a stable disease (SD) or a partial response (PR) can continue for a maximum of 2 years.

In the absence of treatment delays due to adverse event(s), treatment may continue for up to 2 years or until one of the following **criteria for discontinuation of therapy** applies:

- Disease progression warranting alternative therapy. Progression will be confirmed by RECIST, Lugano criteria for malignant lymphoma or other methods for participants with non-measurable disease, or other tumor specific criteria such as the modified ACTG criteria for participants with Kaposi sarcoma; or
- Intercurrent illness that prevents further administration of treatment; or
- Patient decides to withdraw from the study; or
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator.
- An individual participant will not receive any further investigational product if any of the following occur in the participant in question:
  - Withdrawal of consent from further participation in study-related assessments and follow-up
  - Withdrawal of consent from further treatment with investigational product
  - Lost to follow-up
  - An AE that, in the opinion of the investigator or the sponsor, contraindicates further dosing
  - Any AE that meets criteria for discontinuation as defined above
  - Study participant is determined to have met one or more of the exclusion criteria for study participation following study entry and continuing investigational therapy might constitute a safety risk
  - Pregnancy or intent to become pregnant

- Participant noncompliance that, in the opinion of the investigator or sponsor, warrants withdrawal (e.g., refusal to adhere to scheduled visits)
- Initiation of alternative anticancer therapy, including another investigational agent
- Confirmed progressive disease (solid tumors) and continued treatment criteria (below) in setting of progressive disease are not fulfilled

5.5 Duration of Follow Up

Patients will be followed for 1 year after discontinuation of MK-3475 (pembrolizumab) or until death, whichever occurs first. Patients removed from study for unacceptable adverse event(s) will be followed until resolution or stabilization of the adverse event.

After the end of treatment, (time of decision to discontinuation of therapy, based on above criteria), patients will undergo and end of therapy evaluation.

Subsequently, each patient will be followed for 30 days for AE monitoring and be scheduled for an evaluation at 30 days +/- 3 days. All AEs occurring within 30 days after the last dose of study treatment will be recorded. Serious AEs (SAEs) related and unrelated to study treatment will be collected for 90 days after the last dose of study treatment or the start of new anticancer treatment, whichever comes first. After 90 days only SAEs related to study treatment are to be reported.

Subsequent follow up visits will be scheduled every 12 weeks (+/- 2 weeks) for review of medication, review of AEs, physical exam, and laboratory evaluations.

Patients who discontinue study therapy without documented disease progression should continue to be monitored for disease status by radiologic imaging according to the guidelines to be described in the Study Calendars for post-treatment follow-up.

5.6 Criteria for Removal from Study

Patients will be removed from study when any of the applicable criteria, including progressive disease warranting alternative therapy, withdrawal of consent, completion of follow up (Section 5.5), or inability to follow study protocol as listed in Section 5.4. The reason for study removal and the date the patient was removed must be documented in the Case Report Form.

5.7 Criteria to Resume Treatment

For non-autoimmune or inflammatory events, patients may resume treatment with study drug when the drug-related AE(s) resolve to Grade ≤1 or baseline value, with the following exceptions:

- Patients may resume treatment in the presence of Grade 2 fatigue.
- Patients with baseline Grade 1 AST/ALT or total bilirubin, or elevated total bilirubin due to Gilbert disease or HIV protease inhibitor therapy who require dose delays for reasons other than a 2-grade shift in AST/ALT or total bilirubin may resume treatment in the presence of Grade 2 AST/ALT OR total bilirubin, or <5X ULN in patients with Gilbert disease or on HIV Protease Inhibitor therapy (Section 5.1.2, Table 2).
- Patients with combined Grade 2 AST/ALT AND total bilirubin values meeting study parameters outlined in Section 5.2.3 should have treatment permanently discontinued.

- Non-drug-related toxicity including hepatic, pulmonary toxicity, diarrhea, or colitis, must have resolved to baseline or grade 1 AE before treatment is resumed.
- Drug-related endocrinopathies (not including drug-related adrenal insufficiency or hypophysitis) adequately controlled with only physiologic hormone replacement may resume treatment after replacement correction and clinically stable regimen.

If the criteria to resume treatment are met, the patient should restart treatment no sooner than the next scheduled time point per protocol. However, if the treatment is delayed past the next scheduled time point per protocol, the treatment should resume at the earliest convenient point that is within the 12-week delay period.

If treatment is delayed >12 weeks, the patient must be permanently discontinued from study therapy, except as specified in [Section 5.4 (Duration of Therapy)].

5.8 Treatment Beyond Progression

Immunotherapeutic agents such as MK-3475 (pembrolizumab) may produce antitumor effects by potentiating endogenous cancer-specific immune responses. The response patterns seen with such an approach may extend beyond the typical time course of responses seen with cytotoxic agents, and can manifest as a clinical response after an initial increase in tumor burden or even the appearance of new lesions.

Patients with documented progressive disease will have the option of continuing MK-3475 until confirmation approximately 4-6 weeks later, because of the possibility that the first follow up scan indicating PD may document pseudoprogression. A small subset of patients treated with MK-3475 for melanoma experienced late responses with continued therapy. In the KEYNOTE-001 melanoma trial using MK-3475 there was an additional 3.6% response rate with continued therapy. This category of response was defined as an “unconventional response” with “delayed pseudoprogression: ≥25% increase in tumor burden at any assessment after week 12 that was not confirmed as progressive disease per irRC at the next assessment”[Hodi 2014]

If radiologic imaging shows progressive disease (PD), tumor assessment may be repeated by the site approximately 4 - 6 weeks later in order to confirm PD with the option of continuing treatment per below while awaiting radiologic confirmation of progression. If repeat imaging shows a reduction in the tumor burden compared to the initial scan demonstrating PD, treatment may be continued as per treatment calendar. If repeat imaging confirms PD, patients will be generally discontinued from study therapy if alternative therapy is warranted. In determining whether or not the tumor burden has increased or decreased, investigators should consider all target lesions as well as non-target lesions. The decision to continue study treatment after the 1st evidence of disease progression determined by radiologic imaging is at the Investigator’s discretion based on the clinical status of the patient as described in the table below.

Patients may receive study treatment while waiting for confirmation of PD if they are clinically stable as defined by the following criteria:

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

- Absence of progressive tumor at critical anatomical sites (e.g., cord compression) requiring urgent alternative medical intervention

	Clinically Stable		Clinically Unstable	
	Imaging	**Treatment**	**Imaging**	**Treatment**
1st radiologic evidence of PD	Repeat imaging at approximately 4 to 6 weeks to confirm PD	May continue study treatment at the Investigator's discretion while awaiting confirmatory scan	Repeat imaging at approximately 4 to 6 weeks to confirm PD if possible	Discontinue treatment if alternative therapy is warranted
Repeat scan confirms PD	No additional imaging required	Discontinue treatment (exception is possible upon consultation with CTEP)	No additional imaging required	N/A
Repeat scan shows SD, PR, or CR	Continue regularly scheduled imaging assessments every 9 weeks	Continue study treatment at the Investigator's discretion	Continue regularly scheduled imaging assessments every 9 weeks*	May restart study treatment if condition has improved and/or clinically stable per Investigator's discretion

*Tumor imaging/assessment will be performed at baseline and every 9 weeks (63±7 days) during the first year of treatment. Subsequently, tumor imaging will be performed every 12 weeks (84 ±7 days).

5.9 Criteria for Discontinuing MK-3475 (pembrolizumab) in Patients Achieving a CR

Patients that achieve a complete response (CR) can discontinue treatment after 6 months of therapy provided that the patient has had at least 2 cycles of treatment after validation of CR. Patients will continue to be followed as outlined in Section 5.5.

5.10 Retreating with MK-3475 (pembrolizumab) in Patients with Recurrence

Patients that have a CR for whom the disease subsequently recurs off of therapy may be retreated off protocol at patient and investigator discretion. Patients that discontinue due to progression will not be eligible for re-treatment.

6. DOSING DELAYS/DOSE MODIFICATIONS

6.1 MK-3475 (pembrolizumab) Dose Modifications

6.1.1 General MK-3475 (pembrolizumab) Dose Modifications

Immune-related adverse events (irAEs), defined as AEs of unknown etiology, associated with drug exposure and consistent with an immune phenomenon, may be predicted based

on the nature of the pembrolizumab compound, its mechanism of action, and reported experience with immunotherapies that have a similar mechanism of action. Special attention should be paid to AEs that may be suggestive of potential irAEs. An irAE can occur shortly after the first dose or several months after the last dose of treatment. All AEs of unknown etiology associated with drug exposure should be evaluated to determine if they are possibly immune-related. If an irAE is suspected, efforts should be made to rule out neoplastic, infectious, metabolic, toxin or other etiologic causes prior to labeling an adverse event as an irAE.

The table below includes general guidelines for toxicities that are not listed in the AE-specific table (see section 6.1.2).

General Dose Modification Guidelines for Ongoing Drug-Related Immune-Related Adverse Events, Including Immune Reconstitution Inflammatory Syndromes or KSHV-associated multicentric Castleman disease (MCD)*

irAE	Withhold/Discontinue MK-3475 (pembrolizumab)?	Supportive Care
Grade 1	No action If KSHV-associated multicentric Castleman disease, discontinue	Provide symptomatic treatment If symptom complex ≥probably due to immune reconstitution syndrome or KSHV-MCD
Grade 2	May withhold MK-3475 (pembrolizumab) Recommend holding while performing diagnostic evaluations If KSHV-MCD, discontinue and administer therapy for KSHV-MCD	Consider systemic or topical corticosteroids in addition to appropriate symptomatic treatment If symptom complex ≥ possibly due to immune reconstitution syndrome or KSHV-MCD
Grade 3	Withhold MK-3475 (pembrolizumab) Discontinue if unable to reduce corticosteroid dose to ≤ 15 mg per day prednisone equivalent within 12 weeks of toxicity If KSHV-associated MCD, discontinue and administer therapy for KSHV-MCD	Systemic corticosteroids are indicated in addition to appropriate symptomatic treatment. May utilize 1 to 2 mg/kg prednisone or equivalent per day. Steroid taper should be considered once symptoms improve to Grade 1 or less and tapered over at least 4 weeks. If symptom complex ≥ possibly due to immune reconstitution syndrome or KSHV-MCD, perform diagnostic studies
Grade 4	Discontinue If KSHV-MCD, discontinue and administer therapy for KSHV-associated MCD	Systemic corticosteroids as for Grade 3 above. If symptom complex ≥ possibly due to immune reconstitution syndrome or KSHV-MCD, perform diagnostic studies

* KSHV-MCD is a B-cell lymphoproliferative disorder that is associated with an interleukin-6 related symptom complex. Patients may have concurrent Kaposi sarcoma. KSHV-associated laboratory abnormalities and symptoms include anemia,

thrombocytopenia, hypoalbuminemia, elevated C-reactive protein. Patients generally have B-symptoms, adenopathy and splenomegaly, and may also have edema, effusion and nonspecific respiratory and gastrointestinal symptoms. Blood should be evaluated for an elevated KSHV viral load, which supports the diagnosis.

Additionally, MK-3475 (pembrolizumab) will be withheld for other drug-related Grade 4 hematologic toxicities, non-hematological toxicity ≥Grade 3 including laboratory abnormalities, and severe or life-threatening AEs.

The table below includes dose modification guidelines for other toxicities that do not appear to be irAEs and are not listed in the AE-specific table (see section 6.1.2).

Dose Modification Guidelines for Other Drug-Related Adverse Events

Toxicity	Grade	Hold Treatment (Y/N)	Timing for restarting treatment	Dose/Schedule for restarting treatment	Discontinue Subject
Hematological Toxicity	1, 2, 3	No	N/A	N/A	N/A
	4	Yes, with the exception of lymphocyto-penia or CD4 lympho-cytopenia or exceptional circumstances, after review by the Toxicity Evaluation Committee (see 5.2.3)	Toxicity resolves to Grade 0-1 or baseline	May increase the dosing interval by 1 week	Toxicity does not resolve within 12 weeks of last infusion *Permanent discontinuation should be considered for any severe or life-threatening event*
Non-hematological toxicity Note: Exception to be treated similar to grade 1 toxicity Grade 2 alopecia Grade 2 fatigue For additional information regarding Adverse Events with a potential Immune-Etiology reference Section 6.1.2.	1	No	N/A	N/A	N/A
	2	Consider withholding for persistent symptoms	Toxicity resolves to Grade 0-1 or baseline	*Clinical AE resolves within 4 weeks*: Same dose and schedule *Clinical AE does not resolve within 4 weeks:* May increase the dosing interval by 1 week for each occurrence	Toxicity does not resolve within 12 weeks of last infusion
	3	Yes	Toxicity resolves to Grade 2 or baseline	May increase the dosing interval by 1 week for each occurrence	Toxicity does not resolve within 12 weeks of last infusion
	4	Yes	N/A	N/A	Subject must be discontinued

In case toxicity does not resolve to Grade 2 within 12 weeks after last infusion, trial treatment should be discontinued. With Principal Investigator agreement, subjects with a laboratory adverse event still at Grade 2 after 12 weeks may continue treatment in the trial only if asymptomatic and controlled. Patients who experience a recurrence of the same severe or life-threatening event at the same grade or greater with re-challenge of MK-3475 (pembrolizumab) should be discontinued from trial treatment.

6.1.2 AE-specific MK-3475 (pembrolizumab) Dose Modifications and Supportive Care Guidelines

The table below includes recommendations on the management of specific AEs and when to hold and/or discontinue MK-3475 (pembrolizumab). These guidelines are intended to be applied when the investigator determines the events to be treatment-related. Note: if after the evaluation the event is determined not to be related, the investigator does not need to follow the treatment guidance. Therefore, these recommendations should be seen as guidelines and the treating physician should exercise individual clinical judgment based on the patient.

Dose Modification and Toxicity Management Guidelines for Immune-related AEs Associated with Pembrolizumab

General instructions:

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

Immune-related AEs	**Toxicity grade or conditions (CTCAE v 5.0)**	**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 (i.e., peritoneal signs and ileus). Participants with ≥ Grade 2 diarrhea suspecting colitis should consider GI
	Grade 4	Permanently discontinue		

Immune-related AEs	Toxicity grade or conditions (CTCAE v 5.0)	Action taken to pembrolizumab	irAE management with corticosteroid and/or other therapies	Monitor and follow-up
				consultation and performing endoscopy to rule out colitis. Participants with diarrhea/colitis should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion.
AST / ALT elevation or Increased bilirubin	Grade 2	Withhold	Administer corticosteroids (initial dose of 0.5- 1 mg/kg prednisone or equivalent) followed by taper	Monitor with liver function tests (consider weekly or more frequently until liver enzyme value returned to baseline or is stable
	Grade 3 or 4	Permanently discontinue	Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper	
Type 1 diabetes mellitus (T1DM) or Hyperglycemia	Newly onset T1DM or Grade 3 or 4 hyperglycemia associated with evidence of β-cell failure	Withhold	Initiate insulin replacement therapy for participants with T1DM Administer anti-hyperglycemic in participants with hyperglycemia	Monitor participants for hyperglycemia or other signs and symptoms of diabetes.
Hypophysitis	Grade 2	Withhold	Administer corticosteroids and initiate hormonal replacements as clinically indicated.	Monitor for signs and symptoms of hypophysitis (including hypopituitarism and adrenal insufficiency)
	Grade 3 or 4	Withhold or permanently discontinue[1]		
Hyperthyroidism	Grade 2	Continue		Monitor for signs and symptoms of thyroid disorders.

Immune-related AEs	**Toxicity grade or conditions (CTCAE v 5.0)**	**Action taken to pembrolizumab**	**irAE management with corticosteroid and/or other therapies**	**Monitor and follow-up**
	Grade 3 or 4	Withhold or permanently discontinue[1]	Treat with non-selective beta-blockers (e.g., propranolol) or thionamides as appropriate	
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		

Immune-related AEs	Toxicity grade or conditions (CTCAE v 5.0)	Action taken to pembrolizumab	irAE management with corticosteroid and/or other therapies	Monitor and follow-up
[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).				

6.1.3 Immediate Evaluation for Potential Skin Events

6.1.3.1 *Photographs*

Every attempt should be made to get a photograph of the actual skin lesion or rash as soon as possible. **Obtain appropriate consent for subject photographs if a consent form addendum is required by your IRB/ERC**.

- Take digital photographs of:
  - the head (to assess mucosal or eye involvement),
  - the trunk and extremities, and
  - a close-up of the skin lesion/rash.
- If possible, a ruler should be placed alongside the site of a skin occurrence as a fixed marker of distance.
- The time/date stamp should be set in the 'ON' position for documentation purposes.
- Photographs should be stored with the patient's study records.

6.1.3.2 *Dermatology Consult*

Refer the subject to a dermatologist as soon as possible.

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

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

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

6.1.4 Treatment Guidelines for Infusion Reactions

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

Treatment Guidelines for Infusion Reactions

NCI CTCAE Grade	Treatment	Premedication at subsequent dosing
Grade 1 Mild reaction; infusion interruption not indicated; intervention not indicated	Increase monitoring of vital signs as medically indicated until the patient is deemed medically stable in the opinion of the investigator.	None

NCI CTCAE Grade	Treatment	Premedication at subsequent dosing
Grade 2 Requires infusion interruption but responds promptly to symptomatic treatment (*e.g.*, antihistamines, NSAIDS, narcotics, IV fluids); prophylactic medications indicated for ≤24 hours	**Stop Infusion.** Additional appropriate medical therapy may include but is not limited to: IV fluids Antihistamines NSAIDS Acetaminophen Narcotics Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator. If symptoms resolve within one hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (*e.g.* from 100 mL/hr to 50 mL/hr). **Please note:** prior to restarting the infusion, confirm that the 4 hour room temperature stability from the time of the IV bag preparation will not be exceeded. Otherwise dosing will be held until symptoms resolve and the subject should be pre-medicated for the next scheduled dose. **Subjects who develop Grade 2 toxicity upon rechallenge despite adequate premedication should be permanently discontinued from further trial treatment administration.**	Subject may be premedicated 1.5h (± 30 minutes) prior to infusion of MK-3475 (pembrolizumab) with: Diphenhydramine 50 mg PO (or equivalent dose of antihistamine). Acetaminophen 500-1000 mg PO (or equivalent dose of antipyretic).

NCI CTCAE Grade	Treatment	Premedication at subsequent dosing
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.	Subsequent treatment may be allowed following Grade 3 infusion reaction if reaction resolved within 6 hours and was controlled with medical management.
Appropriate resuscitation equipment should be available in the room and a physician readily available during the period of drug administration. For Further information, please refer to the Common Terminology Criteria for Adverse Events v5.0 (CTCAE) at http://ctep.cancer.gov		

6.2 Delayed Visits for Reasons Other Than Toxicity

A schedule for return visits should be established at the first visit. If a participant misses a treatment, the missed treatment will be administered as soon as possible, so that the subsequent treatments are given in the appropriate intervals. Treatment may be continued for an additional time period, if needed. Participants who are treated outside of the established schedule should return to the original schedule as soon as possible.

7. ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS

Adverse event (AE) monitoring and reporting is a routine part of every clinical trial. The following list of AEs (Section 7.1) and the characteristics of an observed AE (Section 7.2) will determine whether the event requires expedited reporting via the CTEP Adverse Event Reporting System (CTEP-AERS) **in addition** to routine reporting.

7.1 Comprehensive Adverse Events and Potential Risks List(s) (CAEPRs)

The Comprehensive Adverse Event and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. In addition to the comprehensive list, a subset of AEs, the

Specific Protocol Exceptions to Expedited Reporting (SPEER), appears in a separate column and is identified with ***bold*** and ***italicized*** text. The SPEER is a list of events that are protocol-specific exceptions to expedited reporting to NCI (except as noted below). Refer to the 'CTEP, NCI Guidelines: Adverse Event Reporting Requirements' http://ctep.cancer.gov/protocolDevelopment/adverse_effects.htm for further clarification.

Note: The highest grade currently reported is noted in parentheses next to the AE in the SPEER. Report **ONLY** AEs higher than this grade expeditiously. If this CAEPR is part of a combination protocol using multiple investigational agents and has an AE listed on different SPEERs, use the lower of the grades to determine if expedited reporting is required.

7.1.1 CAEPRs for CTEP IND Agent(s): MK-3475 (pembrolizumab)

Comprehensive Adverse Events and Potential Risks list (CAEPR)

for

MK-3475 (pembrolizumab, NSC 776864)

The Comprehensive Adverse Events and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. In addition to the comprehensive list, a subset, the Specific Protocol Exceptions to Expedited Reporting (SPEER), appears in a separate column and is identified with bold and italicized text. This subset of AEs (SPEER) is a list of events that are protocol specific exceptions to expedited reporting to NCI (except as noted below). Refer to the 'CTEP, NCI Guidelines: Adverse Event Reporting Requirements' http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf for further clarification. *Frequency is provided based on 3793 patients.* Below is the CAEPR for MK-3475 (pembrolizumab, NSC 776864).

Note: Report AEs on the SPEER **ONLY IF** they exceed the grade noted in parentheses next to the AE in the SPEER. If this CAEPR is part of a combination protocol using multiple investigational agents and has an AE listed on different SPEERs, use the lower of the grades to determine if expedited reporting is required.

Version 2.4, March 16, 2018[1]

Adverse Events with Possible Relationship to MK-3475 (pembrolizumab) (CTCAE 5.0 Term) [n= 3793]			**Specific Protocol Exceptions to Expedited Reporting (SPEER)**
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
BLOOD AND LYMPHATIC SYSTEM DISORDERS			
	Anemia[2]		
	Lymph node pain[2]		
	Thrombotic thrombocytopenic purpura[2]		
CARDIAC DISORDERS			
		Myocarditis[2]	
		Pericarditis[2]	
ENDOCRINE DISORDERS			
	Adrenal insufficiency[2]		
	Endocrine disorders - Other (thyroiditis)[2]		
	Hyperthyroidism[2]		
	Hypophysitis[2]		
	Hypopituitarism[2]		
	Hypothyroidism[2]		
EYE DISORDERS			
		Uveitis[2]	
GASTROINTESTINAL DISORDERS			
	Abdominal pain		
	Colitis[2]		
	Diarrhea[2]		***Diarrhea[2] (Gr 2)***
	Mucositis oral[2]		
	Nausea		***Nausea (Gr 2)***
	Pancreatitis[2]		
	Small intestinal mucositis[2]		
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
	Chills[2]		
Fatigue			***Fatigue (Gr 2)***
	Fever[2]		
HEPATOBILIARY DISORDERS			
	Hepatobiliary disorders - Other (autoimmune hepatitis)[2]		
IMMUNE SYSTEM DISORDERS			
		Anaphylaxis[2]	
		Cytokine release syndrome[2]	

Adverse Events with Possible Relationship to MK-3475 (pembrolizumab) (CTCAE 5.0 Term) [n= 3793]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
		Immune system disorders – Other (acute graft-versus-host disease)[2,3]	
		Immune system disorders - Other (hemophagocytic lymphohistiocytosis)[2]	
	Immune system disorders - Other (pseudoprogression/tumor inflammation)[2]		
	Immune system disorders – Other (sarcoidosis)[2]		
		Serum sickness[2]	
INFECTIONS AND INFESTATIONS			
	Infection[4]		
INJURY, POISONING AND PROCEDURAL COMPLICATIONS			
		Infusion-related reaction	
INVESTIGATIONS			
	Alanine aminotransferase increased[2]		
	Alkaline phosphatase increased		
	Aspartate aminotransferase increased[2]		
	Blood bilirubin increased		
	CPK increased		
		GGT increased	
		Serum amylase increased	
METABOLISM AND NUTRITION DISORDERS			
	Anorexia		
	Hyponatremia		
		Metabolic and nutrition disorders – Other (diabetic ketoacidosis)[2]	
		Metabolism and nutrition disorders – Other (type 1 diabetes mellitus) [2]	
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS			
	Arthralgia[2]		***Arthralgia***[2] ***(Gr 2)***
	Arthritis[2]		
	Avascular necrosis[2]		
	Back pain		
	Joint effusion[2]		

Adverse Events with Possible Relationship to MK-3475 (pembrolizumab) (CTCAE 5.0 Term) [n= 3793]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
	Joint range of motion decreased		
	Musculoskeletal and connective tissue disorder - Other (tenosynovitis)[2]		
	Myalgia[2]		
	Myositis[2]		
NERVOUS SYSTEM DISORDERS			
		Guillain-Barre syndrome[2]	
		Nervous system disorders - Other (myasthenic syndrome)[2]	
		Nervous system disorders - Other (neuromyopathy)[2]	
		Nervous system disorders – Other (non-infectious encephalitis)[2]	
		Nervous system disorders – Other (non-infectious meningitis)[2]	
		Nervous system disorders - Other (polyneuropathy)[2]	
		Paresthesia	
		Peripheral motor neuropathy[2]	
RENAL AND URINARY DISORDERS			
		Renal and urinary disorders - Other (autoimmune nephritis)[2]	
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
	Cough		
	Pleuritic pain[2]		
	Pneumonitis[2]		
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
	Bullous dermatitis[2]		
		Erythema multiforme[2]	
	Erythroderma		
		Palmar-plantar erythrodysesthesia syndrome	
	Pruritus[2]		***Pruritus[2] (Gr 2)***
	Rash acneiform[2]		
	Rash maculo-papular[2]		***Rash maculo-papular[2] (Gr 2)***
	Skin and subcutaneous tissue disorders - Other (dermatitis)[2]		
	Skin hypopigmentation[2]		

Adverse Events with Possible Relationship to MK-3475 (pembrolizumab) (CTCAE 5.0 Term) [n= 3793]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
		Stevens-Johnson syndrome[2]	
		Toxic epidermal necrolysis	
	Urticaria[2]		
VASCULAR DISORDERS			
		Vasculitis[2]	

[1]This table will be updated as the toxicity profile of the agent is revised. Updates will be distributed to all Principal Investigators at the time of revision. [redacted]

[2] Immune-mediate adverse reactions have been reported in patients receiving MK-3475 (pembrolizumab). Adverse events potentially related to MK-3475 (pembrolizumab) may be manifestations of immune-mediated adverse events. In clinical trials, most immune-mediated adverse reactions were reversible and managed with interruptions of MK-3475 (pembrolizumab), administration of corticosteroids and supportive care.

[3] Acute graft-versus-host disease has been observed in patients treated with MK-3475 (pembrolizumab) who received hematopoietic stem cell transplants.

[4] Infection includes all 75 sites of infection under the INFECTIONS AND INFESTATIONS SOC.

Adverse events reported on MK-3475 (pembrolizumab) trials, but for which there is insufficient evidence to suggest that there was a reasonable possibility that MK-3475 (pembrolizumab) caused the adverse event:

BLOOD AND LYMPHATIC SYSTEM DISORDERS - Blood and lymphatic system disorders - Other (pancytopenia); Disseminated intravascular coagulation; Hemolysis
CARDIAC DISORDERS - Atrial fibrillation; Cardiac arrest; Chest pain - cardiac; Heart failure; Myocardial infarction; Pericardial effusion; Pericardial tamponade; Ventricular arrhythmia
EYE DISORDERS - Eye pain
GASTROINTESTINAL DISORDERS - Abdominal distension; Ascites; Constipation; Duodenal hemorrhage; Dysphagia; Gastritis; Gastrointestinal disorders - Other (diverticulitis); Gastrointestinal disorders - Other (intestinal obstruction); Gastrointestinal disorders - Other (intussusception); Oral pain; Rectal hemorrhage; Small intestinal perforation; Upper gastrointestinal hemorrhage; Vomiting
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Edema face; Edema limbs; Facial pain; Gait disturbance; General disorders and administration

site conditions - Other (general physical health deterioration); Generalized edema; Malaise; Non-cardiac chest pain; Pain
INVESTIGATIONS - Cholesterol high; Creatinine increased; Fibrinogen decreased; Lymphocyte count decreased; Neutrophil count decreased; Platelet count decreased; Weight loss; White blood cell decreased
METABOLISM AND NUTRITION DISORDERS - Dehydration; Hypercalcemia; Hyperglycemia; Hyperkalemia; Hypertriglyceridemia; Hyperuricemia; Hypoalbuminemia; Hypokalemia; Hypophosphatemia; Metabolism and nutrition disorders - Other (failure to thrive); Tumor lysis syndrome
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Bone pain; Generalized muscle weakness; Musculoskeletal and connective tissue disorder - Other (groin pain); Pain in extremity
NERVOUS SYSTEM DISORDERS - Aphonia; Depressed level of consciousness; Dysarthria; Edema cerebral; Encephalopathy; Headache; Hydrocephalus; Lethargy; Meningismus; Nervous system disorders - Other (brainstem herniation); Seizure; Syncope; Tremor
PSYCHIATRIC DISORDERS - Agitation; Confusion
RENAL AND URINARY DISORDERS - Acute kidney injury; Proteinuria; Renal and urinary disorders - Other (hydronephrosis); Nephrotic syndrome; Urinary incontinence; Urinary tract pain
REPRODUCTIVE SYSTEM AND BREAST DISORDERS - Pelvic pain
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Dyspnea; Hypoxia; Laryngeal inflammation; Pleural effusion; Pneumothorax; Respiratory failure
SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Alopecia; Dry skin; Skin and subcutaneous tissue disorders - Other (drug eruption)
VASCULAR DISORDERS - Hypertension; Peripheral ischemia; Thromboembolic event

Note: MK-3475 (pembrolizumab) in combination with other agents could cause an exacerbation of any adverse event currently known to be caused by the other agent, or the combination may result in events never previously associated with either agent.

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 until March 31, 2018 for AE reporting. CTCAE version 5.0 will be utilized for AE reporting beginning April 1, 2018. All appropriate treatment areas should have access to a copy of the CTCAE version 5.0. A copy of the CTCAE version 5.0 can be downloaded from the CTEP web site http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.
- **For expedited reporting purposes only:**
  - AEs for the agent that are ***bold and italicized*** in the CAEPR (*i.e.*, those listed in the SPEER column, Section 7.1.1) should be reported through CTEP-AERS only if the grade is above the grade provided in the SPEER.

- Other AEs for the protocol that do not require expedited reporting are outlined in section 7.3.4.

- **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

Expedited AE reporting for this study must use CTEP-AERS (CTEP Adverse Event Reporting System), [redacted] These requirements are briefly outlined in the tables below (Section 7.3.3).

[redacted].

7.3.1 Distribution of Adverse Event Reports

CTEP-AERS is programmed for automatic electronic distribution of reports to the following individuals: Principal Investigator and Adverse Event Coordinator(s) (if applicable) of the Corresponding Organization or Lead Organization, the local treating physician, and the Reporter and Submitter. CTEP-AERS provides a copy feature for other e-mail recipients.

The Coordinating Center of the Corresponding Organization is responsible for submitting to the CTSU documentation of AEs that they deem reportable for posting on the CTSU protocol web page and inclusion on the CTSU bi-monthly broadcast.

7.3.2 Expedited Reporting Guidelines

Use the NCI protocol number and the protocol-specific patient ID assigned during trial registration on all reports.

Note: **A death on study requires <u>both</u> routine and expedited reporting, regardless of causality. Attribution to treatment or other cause must be provided.**

Death due to progressive disease should be reported as **Grade 5 "Disease Progression"** in the system organ class (SOC)"General disorders and administration site conditions". Evidence that the death was a manifestation of underlying disease (*e.g.*, radiological changes suggesting tumor growth or progression: clinical deterioration associated with a disease process) should be submitted.

Pregnancy loss

Pregnancy loss is defined in CTCAE as "Death in Utero".

Any pregnancy loss should be reported expeditiously, as Grade 4 "pregnancy loss" under the Pregnancy, puerperium and perinatal conditions SOC.

A pregnancy loss should NOT be reported as a Grade 5 event under the Pregnancy, puerperium and perinatal conditions SOC, as currently CTEP AERS recognizes this event as a patient death.

Phase 1 and Early Phase 2 Studies: Expedited Reporting Requirements for Adverse Events that Occur on Studies under an IND/IDE within 30 Days of the Last Administration of the Investigational Agent/Intervention [1, 2]

FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312)
NOTE: Investigators **MUST** immediately report to the sponsor (NCI) ANY Serious Adverse Events, whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64)
An adverse event is considered serious if it results in **ANY** of the following outcomes:

1) Death
2) A life-threatening adverse event
3) An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization for ≥ 24 hours
4) A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
5) A congenital anomaly/birth defect.
6) Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. (FDA, 21 CFR 312.32; ICH E2A and ICH E6).

ALL SERIOUS adverse events that meet the above criteria MUST be immediately reported to the NCI via electronic submission within the timeframes detailed in the table below.

Hospitalization	Grade 1 and Grade 2 Timeframes	Grade 3-5 Timeframes
Resulting in Hospitalization ≥ 24 hrs	10 Calendar Days	24-Hour 5 Calendar Days
Not resulting in Hospitalization ≥ 24 hrs	Not required	

NOTE: Protocol specific exceptions to expedited reporting of serious adverse events are found in the Specific Protocol Exceptions to Expedited Reporting (SPEER) portion of the CAEPR.
Expedited AE reporting timelines are defined as:

- "24-Hour; 5 Calendar Days" - The AE must initially be submitted electronically within 24 hours of learning of the AE, followed by a complete expedited report within 5 calendar days of the initial 24-hour report.
- "10 Calendar Days" - A complete expedited report on the AE must be submitted electronically within 10 calendar days of learning of the AE.

[1]Serious adverse events that occur more than 30 days after the last administration of investigational

agent/intervention and have an attribution of possible, probable, or definite require reporting as follows:
Expedited 24-hour notification followed by complete report within 5 calendar days for:
- All Grade 3, 4, and Grade 5 AEs

Expedited 10 calendar day reports for:
- Grade 2 AEs resulting in hospitalization or prolongation of hospitalization

[2]For studies using PET or SPECT IND agents, the AE reporting period is limited to 10 radioactive half-lives, rounded UP to the nearest whole day, after the agent/intervention was last administered. Footnote "1" above applies after this reporting period.

Effective Date: May 5, 2011

7.3.3 N/A

7.4 Routine Adverse Event Reporting

All Adverse Events **must** be reported in routine study data submissions. **AEs reported expeditiously through CTEP-AERS must <u>also</u> be reported in routine study data submissions**.

*<u>The following paragraph **only** applies to trials using **Medidata Rave**; other trials may delete**:**</u>*
Adverse event data collection and reporting, which are required as part of every clinical trial, are done to ensure the safety of patients enrolled in the studies as well as those who will enroll in future studies using similar agents. AEs are reported in a routine manner at scheduled times during the trial using Medidata Rave. For this trial the Adverse Event CRF is used for routine AE reporting in Rave.

7.5 Secondary Malignancy

A *secondary malignancy* is a cancer caused by treatment for a previous malignancy (*e.g.*, treatment with investigational agent/intervention, radiation or chemotherapy). A secondary malignancy is not considered a metastasis of the initial neoplasm.

CTEP requires all secondary malignancies that occur following treatment with an agent under an NCI IND/IDE be reported expeditiously via CTEP-AERS. Three options are available to describe the event:

- Leukemia secondary to oncology chemotherapy (*e.g.*, acute myelocytic leukemia [AML])
- Myelodysplastic syndrome (MDS)
- Treatment-related secondary malignancy

Any malignancy possibly related to cancer treatment (including AML/MDS) should also be reported via the routine reporting mechanisms outlined in each protocol.

7.6 Second Malignancy

A second malignancy is one unrelated to the treatment of a prior malignancy (and is **NOT** a metastasis from the initial malignancy). Second malignancies require **ONLY** routine AE reporting unless otherwise specified.

7.7 Reporting of Pregnancy and Lactation to the Sponsor

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

8. PHARMACEUTICAL INFORMATION

A list of the adverse events and potential risks associated with the investigational or commercial agents administered in this study can be found in Section 7.1.

8.1 CTEP IND Agent

8.1.1 MK-3475 (pembrolizumab) (SCH 900475) (NSC 776864)

Other Names: pembrolizumab, SCH 900475

Classification: Anti-PD-1 MAb

Molecular Weight: 148.9-149.5 KDa

CAS Number: 1374853-91-4

Mode of Action: The programmed cell death 1 (PD-1) receptor is an inhibitory receptor expressed by T cells. When bound to either of its ligands, PD-L1 or PD-L2, activated PD-1 negatively regulates T-cell activation and effector function. The pathway may be engaged by tumor cells to suppress immune control. MK-3475 (pembrolizumab) blocks the negative immune regulatory signaling by binding to the PD-1 receptor, inhibiting the interaction between PD-1 and its ligands.

Description: MK-3475 (pembrolizumab) is a humanized MAb of the IgG4/kappa isotype.

How Supplied: MK-3475 (pembrolizumab) is supplied by Merck & Co., Inc. and distributed by the Pharmaceutical Management Branch, CTEP/DCTD/NCI as single-use 100 mg vials containing a sterile, non-pyrogenic, clear to opalescent aqueous solution (25 mg/mL). Proteinaceous particles may be present. MK-3475 (pembrolizumab) solution for infusion is formulated in 10mM histidine buffer, pH 5.2-5.8, containing 7% sucrose and 0.02% polysorbate 80, supplied in Type I glass vials with a cap color of red, salmon, or blue.

Preparation: MK-3475 (pembrolizumab) solution for infusion must be diluted prior to administration. Allow the required number of vials to equilibrate to room temperature. Do not shake the vials. Do not use if opaque or extraneous particulate matter other than translucent to white proteinaceous particles is observed. Do not use if discolored. To prepare the infusion solution add the dose volume of MK-3475 (pembrolizumab) to an infusion bag containing 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP. Gently invert the bag 10-15 times to mix the solution. The final concentration must be between **1 mg/mL to 10 mg/mL**.

Compatible IV bag materials: PVC plasticized with DEHP, non-PVC (polyolefin), EVA, or PE lined polyolefin

Storage: Store intact vials between 2°C - 8°C (36°F - 46°F). Do not freeze. Protect from light by storing in the original box. If a storage temperature excursion is identified, promptly return MK-3475 vials to 2-8°C and quarantine the supplies. [redacted]

Stability: Stability testing of the intact vials is on-going**.**

Administer prepared solutions immediately after preparation. If not administered immediately, prepared solutions may be stored refrigerated for up to 20 hours. MK-3475 (pembrolizumab) solutions may be stored at room temperature for a cumulative time of up to 4 hours. This includes room temperature storage of liquid drug product in vials, room temperature storage of admixture solutions in the IV bag, and the duration of infusion.

Route of Administration: IV infusion only. Do not administer as an IV push or bolus injection.

Method of Administration: Infuse over approximately 30 minutes (range: 25 - 40 minutes) using an infusion set containing a low-protein binding 0.2 to 5 µm in-line filter made of polyethersulfone or polysulfone. Infusion rate should not exceed 6.7 mL/min. A central line is not required; however if a subject has a central venous catheter in place, it is recommended that it be used for the infusion. Do not co-administer other drugs through the same infusion line. Following the infusion, flush the IV line with normal saline.

Compatible infusion set materials: PVC plasticized with DEHP or DEHT, PVC and tri-(2-ethylhexyl) trimellitate, polyethylene lined PVC, polyurethane, or polybutadiene

Patient Care Implications: Refer to the protocol for information on evaluation and management of potential immune-related adverse events.

Availability: MK-3475 (pembrolizumab) is an investigational agent supplied to investigators by the Division of Cancer Treatment and Diagnosis (DCTD), NCI.

MK-3475 (pembrolizumab) is provided to the NCI under a Collaborative Agreement between the Pharmaceutical Collaborator and the DCTD, NCI (see Section 12.3).

In general, sites may order initial agent supplies when a subject is being screened for enrollment onto the study.

8.1.2 Agent Ordering and Agent Accountability

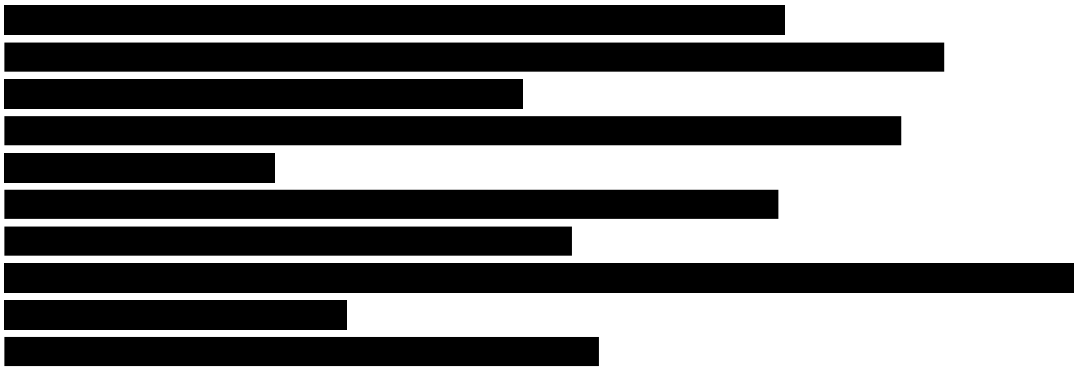
8.1.2.1 NCI-supplied agents may be requested by eligible participating Investigators (or their authorized designee) at each participating institution. The CTEP-assigned protocol number must be used for ordering all CTEP-supplied investigational agents. The eligible participating investigators at each participating institution must be registered with CTEP, DCTD through an annual submission of FDA Form 1572 (Statement of Investigator), NCI Biosketch, Agent Shipment Form, and Financial Disclosure Form (FDF). If there are several participating investigators at one institution, CTEP-supplied investigational agents for the study should be ordered under the name of one lead participating investigator at that institution.

Active CTEP-registered investigators and investigator-designated shipping designees and ordering designees can submit agent requests through the PMB Online Agent Order Processing (OAOP) application. Access to OAOP requires the establishment of a CTEP Identity and Access Management (IAM) account and the maintenance of an "active" account status and a "current" password. [redacted]

8.1.2.2 Agent Inventory Records – The investigator, or a responsible party designated by the investigator, must maintain a careful record of the receipt, dispensing and final disposition of all agents received from the PMB using the NCI Investigational Agent (Drug) Accountability Record (DARF) available on the CTEP forms page. Store and maintain separate NCI Investigational Agent Accountability Records for each agent, strength, formulation and ordering investigator on this protocol.

8.1.2.3 Investigator Brochure Availability – The current version of the IB will be accessible to site investigators and research staff through the PMB Online Agent Order Processing (OAOP) application. Access to OAOP requires the establishment of a CTEP Indentity and Access Management (IAM) account and the maintenance of an "active" account status, a current password, and active person registration status. Questions about IB access may be directed to the PMB IB coordinator via email.

8.1.2.4 MK-3475 Useful links and Contacts:
CTEP Forms, Templates, Documents: http://ctep.cancer.gov/forms/
[redacted]
PMB policies and guidelines:



8.2 Other Investigational Agent(s): N/A

8.3 Commercial Agent(s): N/A

9. BIOMARKER, CORRELATIVE, AND SPECIAL STUDIES

The study calendars and lab manual describe blood draws for safety labs, research labs, and storage of leftover samples in the Biorepository. In the interest of patient safety, we are including a provision to draw less blood if patients are anemic. A CBC will be performed as part of the safety labs each time research labs and biorepository blood needs to be drawn (safety labs drawn for screening will used for this purpose prior to the first blood draws for research). The results of the CBC will be reviewed and the following blood volumes will be drawn based upon the patient's hemoglobin level (Please refer to the CITN-12 Laboratory Manual for a detailed description on types and numbers blood tubes for correlative studies):

- For a hemoglobin over 10.0 g/dL, draw the full volume of blood for safety labs and research labs.
- For a hemoglobin between 9.0 and 10.0 g/dL, draw the full volume of blood for safety labs and CD4+ /CD8+ T-cell counts. Limit research blood draws to 30 mL for plasma HIV studies, and 62 mL for cell associated studies.
- For a hemoglobin less than 9.0 g/dL, draw the full volume of blood for safety labs, and CD4+ /CD8+ T-cell counts. Limit research blood draws to 20 mL for plasma HIV studies, and 36 mL for cell associated studies.

9.1 Integral Laboratory Studies

9.1.1 Evaluation of CD4+ and CD8+ T-cell counts – Integral Laboratory Correlative Study #1

CD4+ and CD8+ T-cell total number and percent total lymphocytes will be performed at the treatment site in a CLIA compliant laboratory. Results will be used for determining eligibility, stratifying patients, and monitoring for possible toxicity in the form of falling CD4+ and/or CD8+ T-cells.

9.1.1.1 Collection of Specimen(s): Per local institutional procedures

9.1.1.2 Handling of Specimens(s): Per local institutional procedures

9.1.1.3 Shipping of Specimen(s): NA

9.1.1.4 Site(s) Performing Correlative Study: To be performed at local site

9.2 Exploratory/Ancillary Correlative Studies

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

9.3 Special Studies

9.3.1 HLA Class I and Class II typing

DNA will be prepared at the CITN Central Lab by extraction of DNA from residual cells off the PBMC preparations described in section 9.2.2. DNA will be stored at -80°C at the CITN Central Lab. Specimens will be assayed at the laboratory of Dr. Dan Geraghty (FHCRC). The CITN Central Laboratory will coordinate batch sample shipping to Geraghty Lab.

10. STUDY CALENDARS

Baseline evaluations are to be conducted within 2 weeks prior to start of protocol therapy. Scans and other baseline disease assessments must be done ≤4 weeks prior to the start of therapy. In the event that the patient's condition is deteriorating, laboratory evaluations should be repeated within 48 hours prior to initiation of the next cycle of therapy.

Calendar 1: Screening and Cycles 1 through 4

Trial Period	Screening Phase	Treatment Cycles [a]								
			To be repeated up to 2 years							
Therapy Cycle/Title	Pre-Therapy	Cycle 1 Day 1	Cycle 1 Day 1, 2 hrs post tx	Cycle 1 Day 2	Cycle 1 Day 8	Cycle 2 Day 1	Cycle 2 Day 1, 2 hrs post tx	Cycle 2 Day 2	Cycle 3 Day 1	Cycle 4 Day 1
Scheduling Window (Days)	Day -28 to Day 0					Day1±7			Day1±7	Day1±7
MK-3475 (pembrolizumab) administration [b]		X				X			X	X
cART therapy [x]	X									
Administrative procedures										
Informed Consent	X									
Concomitant Meds [n]	X	X				X			X	X
Medical History, demographics, etc.	X									
[redacted]	[redacted]									
Clinical Procedures/Assessments [a]										
Review of AEs [d, e]		X		X	X	X		X	X	X
Physical Exam [t]	X	X				X			X	X
Vital Signs	X	X			X	X			X	X
Height and Weight [f]	X	X				X			X	X
12-Lead EKG [g]	X									
Pulmonary function [u]	X									
ECOG PS	X	X			X	X			X	X

Trial Period	Screening Phase	Treatment Cycles [a]								
			To be repeated up to 2 years							
Therapy Cycle/Title	Pre-Therapy	Cycle 1 Day 1	Cycle 1 Day 1, 2 hrs post tx	Cycle 1 Day 2	Cycle 1 Day 8	Cycle 2 Day 1	Cycle 2 Day 1, 2 hrs post tx	Cycle 2 Day 2	Cycle 3 Day 1	Cycle 4 Day 1
Scheduling Window (Days)	Day -28 to Day 0					Day1±7			Day1±7	Day1±7
Laboratory Assessments (Safety Labs)[a,h,k]										
Pregnancy Test (Urine or Serum HCG) [h, i]	X					X			X	X
CBC with Diff/Reticulocytes	X	X			X	X			X	X
Comprehensive serum chemistry panel [k]	X	X			X	X			X	X
Creatine kinase	X	X			X	X			X	X
HBV/HCV serology	X									
HBV DNA viral load	X									X
HCV RNA viral load	X									X
HIV viral load	X					X			X	X
Urinalysis[k, l]	X									
FT4, and TSH [k, l]	X									
Correlative Studies Blood Draws [c]										
CD4+, CD8+ T cells	X				X	X			X	X
HIV SC plasma RNA		X	X	X	X	X	X	X	X	X
PBMC HIV DNA and unspliced RNA		X		X	X	X				X
HIV RNA sequencing/ molecular evolution		X				X				X
Plasma cytokines		X			X	X		X	X	X
HIV-specific T-cell immunity		X								X
Flow Cytometry		X				X				X
PBMC TILDA		X								
HIV transcriptome		X		X						
[redacted]										
[redacted]		[redacted]		[redacted]	[redacted]	[redacted]				[redacted]
[redacted]		[redacted]								[redacted]

Trial Period	Screening Phase	Treatment Cycles [a]								
			To be repeated up to 2 years							
Therapy Cycle/Title	Pre-Therapy	Cycle 1 Day 1	Cycle 1 Day 1, 2 hrs post tx	Cycle 1 Day 2	Cycle 1 Day 8	Cycle 2 Day 1	Cycle 2 Day 1, 2 hrs post tx	Cycle 2 Day 2	Cycle 3 Day 1	Cycle 4 Day 1
Scheduling Window (Days)	Day -28 to Day 0					Day1±7			Day1±7	Day1±7
[redacted]		[redacted]								[redacted]
[redacted]		[redacted]		[redacted]	[redacted]	[redacted]				[redacted]
[redacted]		[redacted]								
Efficacy Measurements										
Tumor Imaging [o,p,q]	X									X
KS Measurements		X[w]							X[w]	
KS Photography[v]		X[w]	X (at time of documentation of CR, PR or PD)							
Tumor Biopsies and Archival Tissue Collection										
Tumor Biopsies [r]	X									

Calendar 2: Cycles 5 and Beyond, End of Treatment and Post-Treatment Follow Up

Trial Period	Treatment Cycles, Cycle 5 and beyond		Time of PR and/or CR	End of Tx	Post-treatment follow-up		
Tx Cycle/Title	Cycles without scans, q 3 weeks beginning with Cycle 5	Cycles with scans, q 9 weeks (Cycles 7, 10, 13, etc., during year 1), q 12 weeks year 2	PR and/or CR	D/C therapy	Post-Tx Safety FU	Follow-up Visits[p]	Survival Follow-up[s]
Scheduling Window (Days)	Day 1±7	Day 1 ±7		At time of D/C	30 days ±3 days post D/C	Every 12 weeks ± 2 weeks post-D/C	Every 12 weeks ± 2 weeks phone contact
MK-3475 (pembrolizumab) administration [b]	X	X					
cART therapy[x]	X						
Administrative Procedures							
Concomitant Meds [n]	X	X	X	X	X	X	X
Clinical Procedures/Assessments							
Review of AEs [d, e]	X	X	X	X	X	X	
Physical Exam [t]	X	X	X	X	X	X	
Vital Signs, Height and Weight [f]	X	X		X	X	X	
ECOG PS	X	X		X	X	X	
Pregnancy Test (Urine or Serum HCG) [h, i]	X	X		X			
CBC with Diff/Reticulocytes	X	X		X	X[m]	X	
Comprehensive Serum chemistry panel [k]	X	X		X	X[m]	X	
Creatine kinase	X	X		X	X		
HBV/HCV serology							
HBV DNA viral load		X (if seropositive)		X	X (if seropositive)		
HCV RNA viral load		X (if seropositive)		X	X (if seropositive)		
HIV viral load		X		X	X		
Urinalysis [k, l]		X (Cycle 7 and every 6th cycle)		X[m]			

Trial Period	Treatment Cycles, Cycle 5 and beyond		Time of PR and/or CR	End of Tx	Post-treatment follow-up		
Tx Cycle/Title	Cycles without scans, q 3 weeks beginning with Cycle 5	Cycles with scans, q 9 weeks (Cycles 7, 10, 13, etc., during year 1), q 12 weeks year 2	PR and/or CR	D/C therapy	Post-Tx Safety FU	Follow-up Visits[p]	Survival Follow-up[s]
Scheduling Window (Days)	Day 1±7	Day 1 ±7		At time of D/C	30 days ±3 days post D/C	Every 12 weeks ± 2 weeks post-D/C	Every 12 weeks ± 2 weeks phone contact
FT4, and TSH [k, l]		X (Cycle 7 and every 6th cycle)		X[m]			
Correlative Studies Blood Draws							
CD4+, CD8+ T cells		X		X	X	X	
HIV SC plasma RNA			X	X	X (optional)		
HIV RNA sequencing/ molecular evolution			X	X	X (optional)		
Plasma cytokines			X	X	X (optional)		
HIV-specific T-cell immunity				X (or at 1 year)			
PBMC HIV DNA and US-RNA			X	X	X (optional)		
Flow Cytometry		X (Cycles 7 and 13)	X	X (or at time of PD)			
PBMC TILDA		X (Cycle 7 and 13)	X	X			
HIV Transcriptome		X (Cycle 7)		X			
[redacted]							
[redacted]				[redacted]			
[redacted]				[redacted]			
Efficacy Measurements							
Tumor Imaging [o, p, q]		X	X	X		X	
KS Photography[x]	X (at time of documentation of CR, PR or PD)		X	X			
KS Measurements	Prior to odd numbered cycles and on days photography is performed						

Trial Period	Treatment Cycles, Cycle 5 and beyond		Time of PR and/or CR	End of Tx	Post-treatment follow-up		
Tx Cycle/Title	Cycles without scans, q 3 weeks beginning with Cycle 5	Cycles with scans, q 9 weeks (Cycles 7, 10, 13, etc., during year 1), q 12 weeks year 2	PR and/or CR	D/C therapy	Post-Tx Safety FU	Follow-up Visits[p]	Survival Follow-up[s]
Scheduling Window (Days)	Day 1±7	Day 1 ±7		At time of D/C	30 days ±3 days post D/C	Every 12 weeks ± 2 weeks post-D/C	Every 12 weeks ± 2 weeks phone contact
Tumor Biopsies/Archival /Tissue Collection							
Tumor Biopsies [r]				X (or at time of PD)			

Abbreviations: AE, adverse event(s);; CBC, complete blood count; D/C, discontinuation/discontinue; ECG, electrocardiogram; ECOG, Eastern Cooperative Oncology Group; EOC, end of cycle; FU, follow-up; HCG, human chorionic gonadotropin; HIV, human immunodeficiency virus; Kyn/Trp, kynurenine/tryptophan; KS, Kaposi sarcoma; PBMC, peripheral blood mononuclear cell; PS, performance status; RNA, ribonucleic acid; TILDA, TAT/REV induced limiting dilution assay; TSH, thyroid-stimulating hormone; tx, treatment; US, unspliced.

a. In general, safety labs and assessments/procedures are to be performed on Day 1 and before the first dose of treatment for each cycle unless otherwise specified. Safety labs may be drawn on Day -1 or Day 1 prior to Cycle 1 and up to 72 hours before drug administration for subsequent cycles. In general, the window for each drug administration visit after Cycle 1 is ± 7 days unless otherwise noted. Treatment cycles are 3 weeks (21 days); however, the treatment cycle interval may be increased due to toxicity according to the dose-modification guidelines provided in Section 6. If the interval is increased, all procedures except imaging should be performed based on the new dosing schedule.
b. MK-3475 (pembrolizumab) will be administered as an IV infusion over 30 minutes. The dose is 200 mg every 3 weeks (21 days). The infusion is given in an out-patient setting. Patients who restart treatment after relapse from CR should resume at the same dose and cycle interval which they were receiving before discontinuation.
c. Blood for correlative studies will be drawn as indicated on Study Calendars. Study Calendar 1 includes the Screening Phase and Cycles 1 through 4. Study Calendar 2 includes Cycles 5 and beyond, End of Treatment, 30 Day Safety Visit and Follow Up visits. After Cycle 4, most correlative labs will be drawn every 3rd cycle during year 1 of treatment and every 4th cycle during year 2, If the correlative blood draw is not obtained at time of determination of CR, PR or disease progression, then this collection will be done at the End-of-Therapy visit.
d. AEs and laboratory safety measurements will be graded per NCI CTCAE version 5.0. All AEs, whether gradable by CTCAE or not, will also be evaluated for seriousness.
e. Record all AEs occurring within 30 days after the last dose of trial treatment. Report all SAEs (related and unrelated to trial treatment) and occurring up until 90 days after the last dose of trial treatment or the start of new anticancer treatment, whichever comes first. Afterwards, report only SAEs and ECIs that are related to trial treatment.
f. Vital signs to include temperature, pulse, respiratory rate, weight, and blood pressure. Height will be measured at baseline only.
g. EKG will be performed at baseline.
h. Laboratory tests for screening are to be performed within 14 days before the first dose of trial treatment. See Section 5.1.1 for details regarding laboratory tests. HBV DNA and HCV RNA may be performed within 28 days of enrolling the patient on protocol.

i. For women of reproductive potential, pregnancy testing will be performed prior to each cycle. A urine pregnancy test should be performed within 72 hours before first dose of trial treatment. If urine pregnancy results cannot be confirmed as negative, a serum pregnancy test performed by the local study site laboratory will be required. Pregnancy tests (serum and/or urine tests) should be repeated if required by local guidelines.
k. Serum chemistry to include albumin, alkaline phosphatase, total bilirubin, bicarbonate, BUN, calcium, chloride, creatinine, glucose, LDH, phosphorus, potassium, total protein, SGOT [AST], SGPT [ALT], and sodium. After Cycle 1, lab samples can be collected up to 72 hours before the scheduled time point.
l. Urinalysis and thyroid function testing to be repeated every 6 cycles after baseline beginning with Cycle 7 (cycles 7, 13, 19, etc) and at the Post-Treatment Follow Up visit.
m. Unresolved abnormal labs that are drug related AEs should be followed until resolution. Labs do not need to be repeated after the end of treatment if labs are within normal range.
n. Concomitant medications – Enter new medications started during the trial through the safety follow-up visit. Record all medications taken for SAE reporting as defined in Section 5.3.1.
o. The initial tumor imaging/disease assessment will be performed within 28 days before the first dose of trial treatment. Scans performed as part of routine clinical management are acceptable for use as the screening scan if they are of diagnostic quality and performed within 28 days before the first dose of trial treatment. On-study imaging will be performed prior to Cycle 4 and reviewed before drug administration. Patients who show progression at Cycle 4 will continue on therapy and have a conformational scan 4 to 6 weeks later. Patients with no evidence of disease progression will have scans every 3 cycles (every 9 weeks) during the first year of treatment. Scan frequency will be decreased to every 4 cycles (every 12 weeks) during second year of treatment. For cycles with scans scheduled, scans should occur within 7 days before scheduled drug administration so that the investigator may evaluate the patient for possible progression before administering the next dose of study medication. The same imaging technique should be used in a patient throughout the trial. Local reading (investigator assessment with site radiology reading) will be used to determine eligibility and for patient management; Sponsor may collect radiological assessments for retrospective analysis by a central vendor. (See Patient Visit Timeline). Imaging is not required in patients with Kaposi sarcoma. If performed to evaluate lymph node or non-cutaneous disease, imaging should be performed every 4 cycles and timed with KS cutaneous disease assessments.
p. In patients who discontinue study therapy without confirmed disease progression, a radiological evaluation should be performed at the time of treatment discontinuation (i.e., date of discontinuation ± 4 week window). If a previous scan was obtained within 4 weeks before the date of discontinuation, then a scan at treatment discontinuation is not mandatory. Patients will attend follow up visits every 12 weeks for 1 year. Patients will continue to have tumor assessments during post-treatment follow-up performed based on the standard of care for a given malignancy. For patients with measurable disease, this will include, at minimum, imaging at the final 12 month follow up visit. Patients who discontinue study therapy due to progression will be followed for survival via phone contacts every 12 weeks.
q. A scan/disease assessment must be performed within 28 days before restarting treatment with MK-3475 (pembrolizumab) after relapse from CR. Imaging should continue to be performed at frequencies described in footnote “o” above from the first dose of trial treatment or more frequently if clinically indicated. The Sponsor may collect radiological assessments for retrospective analysis by a central vendor.
r. Tumor biopsy tissue is required per screening requirements. When feasible, when therapy is discontinued, optional post-treatment biopsy samples will be obtained when tumors do not fully respond.
s. After the start of new anticancer treatment or documented disease progression, the patient should be contacted by telephone every 12 weeks to assess for survival status.
t. After cycle 1, limited physical exam performed on visits not correlated with scans.
u. PFTs required for patients with clinically significant lung disease, including chronic obstructive pulmonary disease (COPD), which requires oxygen therapy.
v. For KS patients, photography is to be performed at baseline, at PD or CR, and at the End of Treatment visit.

w. May be performed any time after enrollment, but before the first dose of study drug. KS measurements may be performed up to 3 days prior to drug administration in subsequent cycles.
x. cART is required, and will generally include agents recommended by the DHHS guidelines: http://aidsinfo.nih.gov/contentfiles/lvguidelines/adultandadolescentgl.pdf.

[redacted]

* No additional blood volumes are required for this laboratory test. Testing will be performed on blood drawn for research labs.

11. MEASUREMENT OF EFFECT

Although the clinical benefit of MK-3475 (pembrolizumab) in patients with HIV and cancer has not yet been established, the intent of offering this treatment is to provide a possible therapeutic benefit, and thus the patient will be carefully monitored for tumor response and symptom relief in addition to safety and tolerability. Patients with measurable disease will be assessed by standard criteria.

11.1 Antitumor Effect – Solid Tumors

For the purposes of this study, patients should be evaluated for response by spiral CT scan in accordance with standard practice at 9-week intervals during the first year of treatment, with the initial scan at week 9 of the trial, before drug administration. During the second year of treatment, scans will be performed every 12 weeks. Throughout the trial, for cycles with scans scheduled, scans shall occur before scheduled drug administration so that the investigator may evaluate the patient for possible progression before administering the next dose of study medication. Response and progression will be evaluated in this study using the new international criteria proposed by the revised RECIST guideline (Version 1.1) [Eisenhauer 2009].

Immunotherapeutic agents such as MK-3475 (pembrolizumab) may produce antitumor effects by potentiating endogenous cancer-specific immune responses that may be functionally anergic. The response patterns seen with such an approach may extend beyond the typical time course of responses seen with cytotoxic agents and can manifest a clinical response after an initial increase in tumor burden or even the appearance of new lesions. Standard RECIST guidelines may not provide a CR assessment of immunotherapeutic agents such as MK-3475 (pembrolizumab), especially at early therapeutic time points. Because of the possibility that the initial scan at 9 weeks may misclassify MK-3475 (pembrolizumab) responders as progressing on therapy, those MK-3475 (pembrolizumab)–treated patients who appear to be progressing at week 9 can continue therapy until progression is confirmed 4 to 6 weeks later, providing they meet the guidelines stated above (Section 5.8). If progression is confirmed, then MK-3475 (pembrolizumab) therapy will be discontinued and the patient will attend the end-of-treatment and 30-day follow-up visits. The time of progression will be reported as the first time that progression was noted. If patients regress or have SD as determined by the confirmatory imaging study, the time of eventual progression will be separately reported.

If progression is noted on subsequent routine disease monitoring scans, which will continue throughout the trial at 9-week to 12-week intervals, a confirmatory scan will be obtained 4 to 6 weeks later. If this confirmatory scan identifies a MK-3475 (pembrolizumab)-treated patient as progressing on therapy, the patient will discontinue treatment and be followed as indicated above. (See Patient Visit Timeline).

Response and progression will be evaluated in this study using the new international criteria proposed by the revised Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1) [Eisenhauer 2009].

11.1.1 Definitions

Evaluable for toxicity. All patients will be evaluable for toxicity from the time of their first treatment with MK-3475 (pembrolizumab).

Evaluable for objective response. Only those patients who have measurable disease present at baseline, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for response. Patients who received at least one cycle of treatment but did not have a response assessment will be counted as not evaluable and included in the estimates of response. Patients will have their response classified according to the definitions stated below. (Note: Patients who exhibit objective disease progression prior to the end of cycle 1 will also be considered evaluable.)

Evaluable Non-Target Disease Response. Patients who have lesions present at baseline that are evaluable but do not meet the definitions of measurable disease, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for non-target disease. The response assessment is based on the presence, absence, or unequivocal progression of the lesions.

11.1.2 Disease Parameters

Measurable disease. Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥20 mm (≥2 cm) by chest x-ray or as ≥10 mm (≥1 cm) with CT scan, MRI, or calipers by clinical exam. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

Note: Tumor lesions that are situated in a previously irradiated area might or might not be considered measurable.

Malignant lymph nodes. To be considered pathologically enlarged and measurable, a lymph node must be ≥15 mm (≥1.5 cm) in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm [0.5 cm]). At baseline and in follow-up, only the short axis will be measured and followed.

Non-measurable disease. All other lesions (or sites of disease), including small lesions (longest diameter <10 mm [<1 cm] or pathological lymph nodes with ≥10 to <15 mm [≥1 to <1.5 cm] short axis), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonitis, inflammatory breast disease, and abdominal masses (not followed by CT or MRI), are considered as non-measurable.

Note: Cystic lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.

'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions.

Target lesions. All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, should be identified as **target lesions** and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected. A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

Non-target lesions. All other lesins (or sites of disease) including any measurable lesions over and above the 5 target lesions should be identified as **non-target lesions** and should also be recorded at baseline. Measurements of these lesions are not required, but the presence, absence, or in rare cases unequivocal progression of each should be noted throughout follow-up.

11.1.3 Methods for Evaluation of Measurable Disease

All measurements should be taken and recorded in metric notation using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

Clinical lesions: Clinical lesions will only be considered measurable when they are superficial (*e.g.*, skin nodules and palpable lymph nodes) and ≥10 mm (≥1 cm) diameter as assessed using calipers (*e.g.*, skin nodules). In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

Chest x-ray: Lesions on chest x-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT is preferable.

Conventional CT and MRI: This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm (0.5 cm) or less. If CT

scans have slice thickness greater than 5 mm (0.5 cm), the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (*e.g.* for body scans).

Use of MRI remains a complex issue. MRI has excellent contrast, spatial, and temporal resolution; however, there are many image acquisition variables involved in MRI, which greatly impact image quality, lesion conspicuity, and measurement. Furthermore, the availability of MRI is variable globally. As with CT, if an MRI is performed, the technical specifications of the scanning sequences used should be optimized for the evaluation of the type and site of disease. Furthermore, as with CT, the modality used at follow-up should be the same as was used at baseline and the lesions should be measured/assessed on the same pulse sequence. It is beyond the scope of the RECIST guidelines to prescribe specific MRI pulse sequence parameters for all scanners, body parts, and diseases. Ideally, the same type of scanner should be used and the image acquisition protocol should be followed as closely as possible to prior scans. Body scans should be performed with breath-hold scanning techniques, if possible.

PET-CT: At present, the low dose or attenuation correction CT portion of a combined PET-CT is not always of optimal diagnostic CT quality for use with RECIST measurements. However, if the site can document that the CT performed as part of a PET-CT is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast), then the CT portion of the PET-CT can be used for RECIST measurements and can be used interchangeably with conventional CT in accurately measuring cancer lesions over time. Note, however, that the PET portion of the CT introduces additional data which may bias an investigator if it is not routinely or serially performed.

Ultrasound: Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. Ultrasound examinations cannot be reproduced in their entirety for independent review at a later date and, because they are operator dependent, it cannot be guaranteed that the same technique and measurements will be taken from one assessment to the next. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised. If there is concern about radiation exposure at CT, MRI may be used instead of CT in selected instances.

Endoscopy, Laparoscopy: The utilization of these techniques for objective tumor evaluation is not advised. However, such techniques may be useful to confirm complete pathological response when biopsies are obtained or to determine relapse in trials where recurrence following complete response (CR) or surgical resection is an endpoint.

Tumor markers: Tumor markers alone cannot be used to assess response. If markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response. Specific guidelines for both CA-125 response (in recurrent ovarian cancer) and PSA response (in recurrent prostate cancer) have been published [Bubley 1999; Rustin 2004]; *J Clin Oncol* 26:1148-1159, 2008]. In addition, the Gynecologic Cancer Intergroup has developed CA-125 progression criteria which are to

be integrated with objective tumor assessment for use in first-line trials in ovarian cancer [Vergote 2000].

Cytology, Histology: These techniques can be used to differentiate between partial responses (PR) and complete responses (CR) in rare cases (*e.g.*, residual lesions in tumor types, such as germ cell tumors, where known residual benign tumors can remain).

The cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment when the measurable tumor has met criteria for response or stable disease is mandatory to differentiate between response or stable disease (an effusion may be a side effect of the treatment) and progressive disease.

FDG-PET: While FDG-PET response assessments need additional study, it is sometimes reasonable to incorporate the use of FDG-PET scanning to complement CT scanning in assessment of progression (particularly possible 'new' disease). New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:

a. Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.
b. No FDG-PET at baseline and a positive FDG-PET at follow-up: If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD. If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan). If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.
c. FDG-PET may be used to upgrade a response to a CR in a manner similar to a biopsy in cases where a residual radiographic abnormality is thought to represent fibrosis or scarring. The use of FDG-PET in this circumstance should be prospectively described in the protocol and supported by disease-specific medical literature for the indication. However, it must be acknowledged that both approaches may lead to false positive CR due to limitations of FDG-PET and biopsy resolution/sensitivity.

Note: A ‘positive’ FDG-PET scan lesion means one which is FDG avid with an uptake greater than twice that of the surrounding tissue on the attenuation corrected image.

11.1.4 Response Criteria

11.1.4.1 *Evaluation of Target Lesions*

Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm (<1 cm).

Partial Response (PR): At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum diameters.

Progressive Disease (PD): At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm (0.5 cm). (Note: the appearance of one or more new lesions is also considered progressions).

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

11.1.4.2 *Evaluation of Non-Target Lesions*

Complete Response (CR): Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10 mm [<1 cm] short axis).

Note: If tumor markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response.

Non-CR/Non-PD: Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.

Progressive Disease (PD): Appearance of one or more new lesions and/or *unequivocal progression* of existing non-target lesions. *Unequivocal progression* should not normally trump target lesion status. It must be representative of overall disease status change, not a single lesion increase.

Although a clear progression of "non-target" lesions only is exceptional, the opinion of the treating physician should prevail in such circumstances, and the progression status should be confirmed at a later time by the review panel (or Principal Investigator).

11.1.4.3 *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.

For Patients with Measurable Disease (*i.e.*, Target Disease)

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Best Overall Response when Confirmation is Required*
CR	CR	No	CR	≥4 wks. Confirmation**
CR	Non-CR/Non-PD	No	PR	≥4 wks. Confirmation**
CR	Not evaluated	No	PR	

PR	Non-CR/Non-PD/not evaluated	No	PR	
SD	Non-CR/Non-PD/not evaluated	No	SD	Documented at least once ≥4 wks. from baseline**
PD	Any	Yes or No	PD	no prior SD, PR or CR
Any	PD***	Yes or No	PD	
Any	Any	Yes	PD	

See RECIST 1.1 manuscript for further details on what is evidence of a new lesion.

** Only for non-randomized trials with response as primary endpoint.

*** In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.

Note: Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "*symptomatic deterioration."* Every effort should be made to document the objective progression even after discontinuation of treatment.

For Patients with Non-Measurable Disease (*i.e.*, Non-Target Disease)

Non-Target Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD*
Not all evaluated	No	not evaluated
Unequivocal PD	Yes or No	PD
Any	Yes	PD

'Non-CR/non-PD' is preferred over 'stable disease' for non-target disease since SD is increasingly used as an endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised

11.1.5 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).

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.

Duration of stable disease: Stable disease is measured from the start of the treatment until the criteria for progression are met, taking as reference the smallest measurements recorded since the treatment started, including the baseline measurements.

11.1.6 Progression-Free Survival

Progression-free survival is defined as the time from the first dose of study drug to progressive disease or death, whichever occurs earlier, based upon investigator assessment using RECIST 1.1, "Lugano Criteria" for Malignant Lymphoma or other tumor-specific criteria. Patients without documented progressive disease or death will be censored at the last disease assessment date.

11.1.7 Response Review

Imaging studies will be collected for a possible expert review of responses. Investigator determined responses will be chronicled and reported unless or until a central expert review takes place.

11.2 Antitumor Effect – Hodgkin Lymphoma and non-Hodgkin Lymphoma

The response categories being used to assess efficacy are based on the Response Assessment of Hodgkin and Non-Hodgkin Lymphoma: The Lugano Classification [Cheson 2014].

These criteria strongly recommend PET-CT for staging of routinely FDG-avid, nodal-lymphomas (essentially all histologies except chronic lymphocytic leukemia/small lymphocytic lymphoma, lymphoplasmacytic lymphoma/Waldenström's macroglobulinemia, mycosis fungoides, and marginal zone NHLs, unless there is a suspicion of aggressive transformation) especially in clinical trials. A contrast enhanced CT scan should be included for a more accurate measurement of nodal size if required for trials; if necessary, to more accurately distinguish bowel from lymphadenopathy; and in the setting of compression/thrombosis of central/mediastinal vessels. Contrast enhanced CT is also preferred for radiation planning. Variably FDG avid and low FDG avid histologies should be staged with a CT scan.

11.2.1 Disease Parameters

11.2.1.1 *For patients assessed with PET-CT:*
Focal uptake in nodal and extranodal sites that is in keeping with lymphoma, according to the distribution and/or CT characteristics, is considered involvement with lymphoma, including spleen, liver, bone, thyroid, and so on.

11.2.1.2 *For patients staged with CT:*
Measured dominant lesions: up to six of the largest target nodes, nodal masses, or other lymphomatous lesions that are measurable in two diameters (longest diameter [LDi] and shortest diameter) should be identified from different body regions representative of the patient's overall disease burden and include mediastinal and retroperitoneal disease, if involved. A measurable node must have an LDi greater than 1.5 cm. Measurable extranodal disease (e.g., hepatic nodules) may be included in the six representative, measured lesions. A measurable extranodal lesion should have an LDi greater than 1.0 cm.

Non-measured lesions: Any disease not selected as measured, dominant disease and truly assessable disease should be considered not measured. These sites include any

nodes, nodal masses, and extranodal sites not selected as dominant or measurable or that do not meet the requirements for measurability but are still considered abnormal, as well as truly assessable disease, which is any site of suspected disease that would be difficult to follow quantitatively with measurement, including pleural effusions, ascites, bone lesions, leptomeningeal disease, abdominal masses, and other lesions that cannot be confirmed and followed by imaging.

11.2.1.3 Cytology confirmation of DLBCL is required when there is an appearance on CT of a new lesion ≥1.5 cm in its long axis and is PET-negative.

11.2.1.4 For fluid collection (ascites, pleural, or pericardial effusions), cytology confirmation for presence of lymphoma is required.

11.2.2 Response Criteria

	PET-CT Based Response	CT-Based Response
Complete Response	**Complete Metabolic Response**	**Complete Radiologic Response (all of the following)**
Lymph nodes and extralymphatic sites	Score 1, 2, or 3* with or without a residual mass on 5PS† *It is recognized that in Waldeyer's ring or extra-nodal sites with high physiologic uptake or with activation within spleen or marrow (e.g., with chemotherapy or myeloid colony-stimulating factors), uptake may be greater than normal mediastinum and/or liver. In this circumstance, complete metabolic response may be inferred if uptake at sites of initial involvement is no greater than surrounding normal tissue even if the tissue has high physiologic uptake*	Target nodes/nodal masses must regress to ≤ 1.5 cm in longest transverse diameter of a lesion No extralymphatic sites of disease
Non-measured lesion	Not applicable	Absent
Organ enlargement	Not applicable	Regress to normal
New lesions	None	None
Bone marrow	No evidence of FDG-avid disease in marrow	Normal by morphology; if indeterminate, IHC negative

Abbreviations: CT, computed tomography; FDG, fluorodeoxyglucose; IHC, immunohistochemistry; PET, positron emission tomography

† PET 5point scale: 1, no uptake above background; 2, uptake _ mediastinum; 3, uptake _ mediastinum but _ liver; 4, uptake moderately _ liver; 5, uptake markedly higher than liver and/or new lesions; X, new areas of uptake unlikely to be related to lymphoma.

*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-CT Based Response	CT-Based Response
Partial Response	**Partial Metabolic Response**	**Partial Remission (all of the following)**
Lymph nodes and extralymphatic sites	Score 4 or 5† with reduced uptake compared with baseline and residual mass(es) of any size *At interim, these findings suggest responding disease. At end of treatment, these findings indicate residual disease.*	≥ 50% decrease in SPD of up to 6 target measurable nodes and extranodal sites *When a lesion is too small to measure on CT, assign 5 mm x 5 mm as the default value; when no longer visible, 0 x 0 mm* *For a node > 5 mm x 5 mm, but smaller than normal, use actual measurement for calculation*
Non-measured lesion	Not applicable	Absent/normal, regressed, but no increase
Organ enlargement	Not applicable	Spleen must have regressed by > 50% in length beyond normal
New lesions	None	None
Bone marrow	Residual uptake higher than uptake in normal marrow but reduced compared with baseline (diffuse uptake compatible with reactive changes from chemotherapy allowed). If there are persistent focal changes in the marrow in the context of a nodal response, consideration should be given to further evaluation with MRI or biopsy or an interval scan	Not applicable

Abbreviations: CT, computed tomography; MRI, magnetic resonance imaging; PET, positron emission tomography; SPD, sum of the product of the perpendicular diameters for multiple lesions.

† PET 5point scale: 1, no uptake above background; 2, uptake _ mediastinum; 3, uptake _ mediastinum but _ liver; 4, uptake moderately _ liver; 5, uptake markedly higher than liver and/or new lesions; X, new areas of uptake unlikely to be related to lymphoma.

	PET-CT Based Response	CT-Based Response
No Response or Stable Disease	**No metabolic response**	**Stable disease**
Lymph nodes and extralymphatic sites	Score 4 or 5† with no significant change in FDG uptake from baseline at interim or end of treatment	< 50% decrease from baseline in SPD of up to 6 dominant, measurable nodes and extranodal sites; no criteria for progressive disease are met
Non-measured lesion	Not applicable	No increase consistent with progression
Organ enlargement	Not applicable	No increase consistent with progression
New lesions	None	None
Bone marrow	No changes from baseline	Not applicable
Progressive Disease	Progressive Metabolic Disease	Progressive Disease (at least 1 of the following)
Individual target nodes/nodal masses Extranodal lesions	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	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 (e.g., a 15-cm spleen must increase to > 16 cm). If no prior splenomegaly, must increase by at least 2 cm from baseline New or recurrent splenomegaly
Non-measured lesion	None	New or clear progression of preexisting nonmeasured lesions
New lesions	New FDG-avid foci consistent with lymphoma rather than another etiology (eg, infection, inflammation). If uncertain regarding etiology of new lesions, biopsy or interval scan may be considered	Regrowth of previously resolved lesions A new node > 1.5 cm in any axis 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
Bone marrow	New or recurrent FDG-avid foci	New or recurrent involvement

Abbreviations: CT, computed tomography; FDG, fluorodeoxyglucose; LDi, longest transverse diameter of a lesion; PET, positron emission tomography; PPD, cross product of the LDi and perpendicular diameter; SDi, shortest axis perpendicular to the LDi; SPD, sum of the product of the perpendicular diameters for multiple lesions.

† PET 5point scale: 1, no uptake above background; 2, uptake _ mediastinum; 3, uptake _ mediastinum but _ liver; 4, uptake moderately _ liver; 5, uptake markedly higher than liver and/or new lesions; X, new areas of uptake unlikely to be related to lymphoma.

11.3 Antitumor Effect - Kaposi Sarcoma

Subjects will be assessed according to the response schedule established in the study calendar (Section 10). Kaposi sarcoma will be evaluated using a modified version (consistent with other HAM Branch studies) of the AIDS Clinical Trial Group Oncology Committee staging and response definitions for Kaposi sarcoma [Krown 1989]. (Assessment guidelines are provided in Appendix E). It should be noted that there is some observer variability in the evaluation of the number, size, nodularity, and color of lesions, and this must be taken into account when measurements are interpreted.

- For evaluation of less than complete responses in subjects with more than 50 lesions at entry, only the previously selected 1 - 3 representative areas that contain at least 20 lesions will be considered. However, complete responses still require the absence of any detectable disease over the entire body (i.e. not confined to the representative areas).

11.3.1 Methods of Evaluation for Measurable Disease

11.3.1.1 *KS Tumor Photography*

Scheduled as per study calendar (Section 10)

Whole body photographs will be obtained upon entry into the study and at time of change in response (i.e. determination of partial or complete response or time of progressive disease) as well as at the end of the study. At these time points, 5 lesions (hereafter called marker lesions), representative of the patient's disease and, if possible, located on separate areas of the body will be selected. These marker lesions should be lesions that have never been treated with local therapies such as radiation therapy or intralesional injections. An attempt will be made to distribute the "marker" lesions between the representative areas (described below in Section 11.3.1.3.1) and the rest of the body. Detailed photographs of these lesions will be obtained with a metric rule beside them.

11.3.1.2 *Documentation of Marker Lesions*

Scheduled as per study calendar (Section 10)

The size, color and nodularity of the marker lesions will be recorded. Documentation will depend on the number of lesions.

11.3.1.3 *Documentation of Extent of Disease*

Scheduled as per study calendar (Section 10)

11.3.1.3.1. *Subjects with 50 or more KS lesions:* for subjects with 50 or more lesions at entry, between 1 and 3 representative areas will be selected at baseline and these will be used for each subsequent evaluation. Representative areas are sections of the body (e.g. the back, a leg, an arm, etc.), which contain at least 20 KS lesions. The total number of lesions in these representative areas will be counted and a record made of whether they are flat or raised. If, in the course of treatment, a single lesion breaks up into 2 or more smaller lesions whose area does not extend beyond the boundary of the initial lesion, these lesions will still be counted as single lesions for the purpose of assessing total numbers in defining a response to therapy.

11.3.1.3.2. *Subjects with fewer than 50 KS lesions:* for subjects with less than 50 lesions at entry, the total number of lesions will be counted and a record made of whether they are flat or raised.

11.3.1.3.3. Additional studies for visceral KS involvement: additional studies, including but not limited to, gastrointestinal endoscopy and bronchoscopy will be performed at baseline where clinically indicated, based on clinical evaluation of the patient. Abnormal studies will be repeated at the end of EPOCH-RP

11.3.2 KS Response Criteria

11.3.2.1 *Complete Response*

- The absence of any detectable residual disease, including tumor associated edema, persisting for at least 4 weeks.
- For subjects with pigmented macular skin lesions persisting after apparent complete response, a biopsy of at least one representative lesion is required to document the absence of malignant cells. If a lesion has not been biopsied, the patient may be classified as having a clinical CR.
- For subjects with visceral disease, the diagnostic radiologic or endoscopic study should be repeated if not medically contraindicated and found to be negative for evidence of disease. If such procedures are medically contraindicated but the patient has no clinical evidence of visceral disease, the patient may be classified as having a clinical CR.

11.3.2.2 *Clinical Complete Response*

The absence of any detectable residual disease, including tumor associated edema, persisting for at least 4 weeks.

- For subjects with pigmented macular skin lesions persisting after apparent complete response, if a representative lesion has not been biopsied.
- For subjects with visceral disease, the diagnostic radiologic or endoscopic study should be repeated if not medically contraindicated and found to be negative for evidence of disease. If such procedures are medically contraindicated but the patient has no clinical evidence of visceral disease, the patient may be classified as having a clinical CR.

11.3.2.3 *Partial Response*

No progressive disease (see below and noting, that single lesions which split up into 2 or more smaller lesions during the course of treatment will still be counted as one); no new lesions occurring in previously uninvolved areas of the body; no new visceral sites of involvement or the appearance or worsening of tumor-associated edema or

effusions *and*:

- A 50% or greater decrease in the number and/or size of previously existing lesions lasting for at least 4 weeks *or*
- Complete flattening of at least 50% of all previously raised lesions (i.e., 50% of all previously nodular or plaque-like lesions become macular) lasting for at least 4 weeks *or*
- A 50% decrease in radiologically measurable visceral lesions sustained without evidence of re-growth for at least 4 weeks *or*
- A 50% decrease in radiologically measurable visceral lesions sustained without evidence of re-growth for at least 4 weeks *or*
- Subjects who otherwise meet the criteria for a CR but still have residual tumor-associated edema or effusions will be classified as having a PR.

11.3.2.4 *Progressive Disease*

For those criteria that involve measurement of lesions in the clinic, the designation of progression should be made, when feasible, only when the criteria below have been met in two measurements spaced at least 1 week apart. For the assignment of progressive disease for the primary outcome analysis, progression will be defined in comparison to baseline measurements.

- An increase of 25% or more over baseline in the number of lesions and/or the size (sum of the products of the largest perpendicular diameters) of the marker lesions *or*
- A change in character from macular to plaque-like or nodular of at least 25% of the lesions *or*
- New visceral sites of involvement or progression of visceral disease *or*
- The development of new or increasing tumor-associated edema or effusion that lasts at least 1 week and interferes with the patient's normal activities.

11.3.2.5 *Stable Disease*

Any tumor measurement not meeting the criteria for Complete Response, Partial Response, or Progressive Disease.

12. DATA REPORTING / REGULATORY REQUIREMENTS

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

12.1 Data Reporting

Data collection for this study will be done exclusively through Medidata Rave. Access to the trial in Rave is granted through the iMedidata application to all persons with the appropriate roles assigned in the Regulatory Support System (RSS). To access Rave via iMedidata, the site user must have an active CTEP IAM account (check at < https://ctepcore.nci.nih.gov/iam >) and the appropriate Rave role (Rave CRA, Read-Only, or Site Investigator) on either the Corresponding Organization or Participating Organization roster at the enrolling site. To the hold Rave CRA role or CRA Lab Admin role, the user must hold a minimum of an AP registration type. To hold

the Rave Site Investigator role, the individual must be registered as an NPIVR or IVR. Associates can hold read-only roles in Rave.

Upon initial site registration approval for the study in RSS, all persons with Rave roles assigned on the appropriate roster will be sent a study invitation e-mail from iMedidata. To accept the invitation, site users must log into the Select Login (https://login.imedidata.com/selectlogin) using their CTEP-IAM user name and password, and click on the "accept" link in the upper right-corner of the iMedidata page. Please note, site users will not be able to access the study in Rave until all required Medidata and study specific trainings are completed. Trainings will be in the form of electronic learnings (eLearnings), and can be accessed by clicking on the link in the upper right pane of the iMedidata screen.

Users that have not previously activated their iMedidata/Rave account at the time of initial site registration approval for the study in RSS will also receive a separate invitation from iMedidata to activate their account. Account activation instructions are located on the CTSU website, Rave tab under the Rave resource materials (Medidata Account Activation and Study Invitation Acceptance). Additional information on iMedidata/Rave is available on the CTSU members' website under the Rave tab or by contacting the [redacted]

12.1.1 Method

This study will be monitored by the Clinical Trials Monitoring Service (CTMS). Data will be submitted to CTMS at least once every two weeks via Medidata Rave (or other modality if approved by CTEP). Information on CTMS reporting is available at: http://www.theradex.com/CTMS. On-site audits will be conducted on an 18-36 month basis as part of routine cancer center site visits. More frequent audits may be conducted if warranted by accrual or due to concerns regarding data quality or timely submission. For CTMS monitored studies, after users have activated their accounts, please contact the [redacted] for additional support with Rave and completion of CRFs.

12.1.2 Responsibility for Data Submission

It is the responsibility of the PI(s) at the site to ensure that all investigators at the site understand the procedures for data submission that protocol specified data are submitted accurately and in a timely manner to the CTMS via the electronic data capture system, Medidata Rave.

Data are to be submitted via Medidata Rave to CTMS on a real-time basis, but no less than once every 2 weeks. The timeliness of data submissions and timeliness in resolving data queries will be tracked by CTMS. Metrics for timeliness will be followed and assessed on a quarterly basis. For the purpose of Institutional Performance Monitoring, data will be considered delinquent if it is greater than 4 weeks past due.

Data from Medidata Rave and CTEP-AERS is reviewed by the CTMS on an ongoing basis as data is received. Queries will be issued by CTMS directly within Rave. The queries will appear on the Task Summary Tab within Rave for the CRA to resolve. Monthly web-based reports are posted for review by the Drug Monitors in the IDB,

CTEP. Onsite audits will be conducted by the CTMS to ensure compliance with regulatory requirements, GCP, and NCI policies and procedures with the overarching goal of ensuring the integrity of data generated from NCI-sponsored clinical trials

An End of Study CRF is to be completed by the PI, and is to include the recommended phase 2 dose (RP2D), and a description of any dose-limiting toxicities (DLTs). CTMS will utilize a core set of eCRFs that are Cancer Data Standards Registry and Repository (caDSR) compliant (http://cbiit.nci.nih.gov/ncip/biomedical-informatics-resources/interoperability-and-semantics/metadata-and-models). Customized eCRFs will be included when appropriate to meet unique study requirements. The PI is encouraged to review the eCRFs, working closely with CTMS to ensure prospectively that all required items are appropriately captured in the eCRFs prior to study activation. CTMS will prepare the eCRFs with built-in edit checks to the extent possible to promote data integrity.

CDUS data submissions for will be carried out by the CTMS contractor, Theradex. CDUS submissions are performed by Theradex on a monthly basis. The trial's lead institution is responsible for timely submission to CTMS via Rave, as above.

12.2 CTEP Multicenter Guidelines

This protocol will adhere to the policies and requirements of the CTEP Multicenter Guidelines. The specific responsibilities of the Principal Investigator and the Coordinating Center (Study Coordinator) and the procedures for auditing are presented in Appendix B.

- The Principal Investigator/Coordinating Center is responsible for distributing all IND Action Letters or Safety Reports received from CTEP to all participating institutions for submission to their individual IRBs for action as required. Submit documentation of reportable adverse events to [redacted] and state in the subject line "Safety Report for NCI protocol #" or "Action Letter for NCI protocol #", as appropriate. A brief summary cover page on Coordinating Center letterhead is encouraged. These documents will be posted to the CTSU protocol web page and included in the next CTSU bi-monthly broadcast.
- Except in very unusual circumstances, each participating institution will order DCTD-supplied agents directly from CTEP. Agents may be ordered by a participating site only after the initial IRB approval for the site has been forwarded by the Coordinating Center to the [redacted]) except for Group studies.

12.3 Collaborative Agreements Language

The agent(s) supplied by CTEP, DCTD, NCI used in this protocol is/are provided to the NCI under a Collaborative Agreement (CRADA, CTA, CSA) between the Pharmaceutical Company(ies) (hereinafter referred to as "Collaborator(s)") and the NCI Division of Cancer Treatment and Diagnosis. Therefore, the following obligations/guidelines, in addition to the provisions in the "Intellectual Property Option to Collaborator" (http://ctep.cancer.gov/industryCollaborations2/intellectual_property.htm) contained within the terms of award, apply to the use of the Agent(s) in this study:

1. Agent(s) may not be used for any purpose outside the scope of this protocol, nor can

Agent(s) be transferred or licensed to any party not participating in the clinical study. Collaborator(s) data for Agent(s) are confidential and proprietary to Collaborator(s) and shall be maintained as such by the investigators. The protocol documents for studies utilizing Agents contain confidential information and should not be shared or distributed without the permission of the NCI. If a copy of this protocol is requested by a patient or patient's family member participating on the study, the individual should sign a confidentiality agreement. A suitable model agreement can be downloaded from: http://ctep.cancer.gov.

2. For a clinical protocol where there is an investigational Agent used in combination with (an)other Agent(s), each the subject of different Collaborative Agreements, the access to and use of data by each Collaborator shall be as follows (data pertaining to such combination use shall hereinafter be referred to as "Multi-Party Data"):

    a. NCI will provide all Collaborators with prior written notice regarding the existence and nature of any agreements governing their collaboration with NCI, the design of the proposed combination protocol, and the existence of any obligations that would tend to restrict NCI's participation in the proposed combination protocol.

    b. Each Collaborator shall agree to permit use of the Multi-Party Data from the clinical trial by any other Collaborator solely to the extent necessary to allow said other Collaborator to develop, obtain regulatory approval or commercialize its own Agent.

    c. Any Collaborator having the right to use the Multi-Party Data from these trials must agree in writing prior to the commencement of the trials that it will use the Multi-Party Data solely for development, regulatory approval, and commercialization of its own Agent.

3. Clinical Trial Data and Results and Raw Data developed under a Collaborative Agreement will be made available to Collaborator(s), the NCI, and the FDA, as appropriate and unless additional disclosure is required by law or court order as described in the IP Option to Collaborator (http://ctep.cancer.gov/industryCollaborations2/intellectual_property.htm). Additionally, all Clinical Data and Results and Raw Data will be collected, used and disclosed consistent with all applicable federal statutes and regulations for the protection of human subjects, including, if applicable, the *Standards for Privacy of Individually Identifiable Health Information* set forth in 45 C.F.R. Part 164.

4. When a Collaborator wishes to initiate a data request, the request should first be sent to the NCI, who will then notify the appropriate investigators (Group Chair for Cooperative Group studies, or PI for other studies) of Collaborator's wish to contact them.

5. Any data provided to Collaborator(s) for Phase 3 studies must be in accordance with the guidelines and policies of the responsible Data Monitoring Committee (DMC), if there is a DMC for this clinical trial.

6. Any manuscripts reporting the results of this clinical trial must be provided to CTEP by the Group office for Cooperative Group studies or by the principal investigator for non-Cooperative Group studies for immediate delivery to Collaborator(s) for advisory review and

comment prior to submission for publication. Collaborator(s) will have 30 days from the date of receipt for review. Collaborator shall have the right to request that publication be delayed for up to an additional 30 days in order to ensure that Collaborator's confidential and proprietary data, in addition to Collaborator(s)'s intellectual property rights, are protected. Copies of abstracts must be provided to CTEP for forwarding to Collaborator(s) for courtesy review as soon as possible and preferably at least three (3) days prior to submission, but in any case, prior to presentation at the meeting or publication in the proceedings. Press releases and other media presentations must also be forwarded to CTEP prior to release. Copies of any manuscript, abstract and/or press release/ media presentation should be sent to:

Email: [redacted]

The Regulatory Affairs Branch will then distribute them to Collaborator(s). No publication, manuscript or other form of public disclosure shall contain any of Collaborator's confidential/ proprietary information.

13. STATISTICAL CONSIDERATIONS

13.1 Study Design/Endpoints

13.1.1 Phase 1

The primary objective is to assess the safety and tolerability of MK-3475 (pembrolizumab) in HIV-infected patients on effective antiretroviral therapy and with metastatic or locally advanced AIDS-defining malignancies or NADMs for which no standard therapy exists or where standard therapy has failed.

This is a phase I multi-institution trial of MK-3475 (pembrolizumab) to assess the safety and tolerability of MK-3475 (pembrolizumab) in HIV-infected patients on effective antiretroviral therapy with metastatic or locally advanced AIDS-defining or non-AIDS defining malignancies. The trial is open-labeled and nonrandomized. As the primary aim is to assess the safety and tolerability of MK-3475 (pembrolizumab) in this patient category, formal statistical sample size calculations do not apply.

Safety and tolerability of MK-3475 (pembrolizumab) is well defined for patients without concurrent HIV, but might be different in patients with HIV and confounded in unexpected ways by prior and concurrent administration of cART. Furthermore, safety and tolerability might be associated with initial CD4+ T-cell level. Patients will be stratified based on CD4+ T-cell counts at entry as some issues of safety and tolerability may vary according to CD4+ T-cell levels. Patients with HIV and malignancy that have been treated with multiple lympholytic therapies will present with a wide spectrum of CD4+ counts, even when on optimal HIV therapy and otherwise eligible to participate in a research protocol. For results of a safety study to be generalizable in this population, an adequate sample size is required to evaluate safety across a range of CD4+ counts, especially for a drug that modulates the immune system. For example, the safety of MK-3475 (pembrolizumab) may vary based on CD4+ count. As in some non-cancer settings, PD1 upregulation on CD4+ and CD8+ T cells in patients with HIV correlates with CD4+

count. In order to better address the primary objective, the accrual will be stratified by CD4+ T-cell levels. The CD4+ T-cell levels indicated below for definition of the cohorts are standard for many HIV therapy trials.

Cohort 1: 100-199 CD4+ T cells/mcL

Cohort 2: 200-350 CD4+ T cells/mcL

Cohort 3: >350 CD4+ T cells/mcL

[redacted]

Accrual to each cohort will be based on unacceptable AEs reported during first treatment cycle of 21 days. If 2 or more unacceptable AEs occur in the first 6 patients, the cohort will not be expanded to 12 patients until the AEs are assessed by the Toxicity Evaluation Committee and the Committee approves the expansion.

The definition of an unacceptable AE for l expansion of a cohort from 6 to 12 patients for the trial is detailed above in Section 5.2.1.

- If 2 or more of the first 6 patients in any individual cohort, and/or ≥1/3 of participants in any individual cohort in at any time experience unacceptable drug-related AE during the first 21 days of therapy, the entry into that cohort will be suspended and toxicities assessed by the Toxicity Evaluation Committee. The Toxicity Evaluation Committee will decide whether accrual should be stopped in that cohort or for the entire trial. The Toxicity Assessment Committee will need to assess the risk/benefit ratio given that all participants will have an otherwise fatal disease where conventional therapy has failed.
- If greater than 1/3 of total patients, across all cohorts, develop an unacceptable AE in the first 21 days of therapy, the Toxicity Evaluation Committee will evaluate the totality of the data to determine whether accrual will be suspended in the trial.

With an initial sample size of 6 participants in a specific cohort and a true unacceptable AE rate of 30%, there is a 58% chance of observing at least 2 unacceptable AEs. In the enrollment expansion, in a given cohort of 12 patients there is a 75% chance of observing at least 3 unacceptable AEs.

13.1.2 Safety Endpoints

The primary safety endpoint is based on frequency of observed AEs graded using CTCAE (Version 5.0) criteria. Safety will be assessed based on the toxicities and grades experienced by treated participants, including SAEs and events of clinical interest (ECIs). Safety will be monitored by cumulative data reviews throughout the trial.

Immune-related ECIs (irECIs), which include the occurrence of grade 2 or higher AEs with an immune etiology will be monitored.

cART-related ECIs of grade 2 or higher AEs will be collected and summarized. Any AE of unknown etiology associated with study therapy will be evaluated to determine if it is possibly an ECI of a potentially immunologic etiology (i.e., irECI) or related to cART.

Other safety endpoints include laboratory safety assessments, ECOG performance status, vital signs, and physical examinations.

13.1.2.1 *Safety Analysis Population*

The safety population will include all patients who receive at least 1 dose of the study drug. The safety population will be used for the analysis of safety data in this study.

13.1.2.2 *Statistical Methods for Safety Analyses*

Safety and tolerability will be assessed by summarizing all relevant parameters including AEs, SAEs, laboratory tests, vital signs, and electrocardiogram measurements. All summaries will be presented for each cohort and overall. Additional summaries of AEs will be presented by CTCAE grade. If the numbers are sufficient, the results may additionally be stratified by tumor type. No statistical hypothesis tests will be performed on safety parameters.

13.1.3 Efficacy Endpoints

The primary and secondary efficacy endpoints are described below. Given that there will be many different histologic types of tumors in enrolled participants, no overall analysis will be performed. The efficacy endpoints may be summarized for each relevant cancer type if the numbers are sufficient (at least five in a given type) by the use of tables or graphs. No statistical hypothesis tests will be performed.

Objective response rate (ORR) is defined as the proportion of patients who have achieved CR or PR according to RECIST 1.1, “Lugano Criteria” for Malignant Lymphoma or other tumor-specific criteria. Patients with missing outcomes will be considered non-responders.

Progression-Free Survival (PFS) is defined as the time from the first dose of study drug to progressive disease or death, whichever occurs earlier, based upon investigator assessment using RECIST 1.1, “Lugano Criteria” for Malignant Lymphoma or other tumor-specific criteria. Patients without documented progressive disease or death will be censored at the last disease assessment date.

Duration of response (DOR) is defined in participants experiencing CR or PR as the interval between the date of first response (CR/PR) and the date of progression, based upon investigator assessment using RECIST 1.1, “Lugano Criteria” for Malignant Lymphoma or other tumor-specific criteria. Patients without documented progression will be censored at the last disease assessment date.

Overall survival (OS) is defined as the time from the first dose of study drug to death due to any cause. Patients without documented death at the time of analysis will be censored at the date last known to be alive.

13.1.3.1 *Populations Chronicled*

The safety population will be used for the analysis of efficacy data in this study. The safety population consists of all patients who received at least 1 dose of study drug.

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13.2 Summaries of Baseline Characteristics, Demographics, and Other Analyses

Demographic variables (e.g., age) and baseline characteristics will be summarized either by descriptive statistics (mean, standard deviation, median, range) or frequency tables.

13.2.1 Extent of Exposure

The extent of exposure will be summarized as duration of treatment in cycles. Dose intensity will also be summarized as appropriate.

13.2.2 Reporting and Exclusions

13.2.2.1 *Evaluation of Toxicity*

All patients will be evaluable for toxicity from the time of their first treatment. AEs will be collected for 30 days after the last dose of study drug.

13.2.2.2 *Evaluation of Response*

All patients enrolled in the study will be assessed for response to treatment, even if major deviations from protocol treatment occur or if they are ineligible. Response for each patient will be assigned one of the following categories as each response assessment: (1) CR, (2) PR, (3) SD (duration of SD will be noted, SD lasting ≥24 weeks will be categorized separately), (4) progressive disease, (5) early death from malignant disease, (6) early death from toxicity, (7) early death because of other cause, or (9) unknown (not assessable, insufficient data). The best response observed during the study will be used in analysis.

All of the patients who met the eligibility criteria (with the possible exception of those who received no study medication) will be included in the main analysis of the response rate. Response in categories 4–9 will be considered to be a treatment failure (i.e., disease progression).

13.3 Sample Size/Accrual Rate - Cohorts 1-3

This study will initially evaluate up to 6 patients in each of three cohorts. If a safe dose (no more than 1 unacceptable AE out of 6 patients) is established in a specific cohort, an additional 6 participants will be evaluated for safety and toxicities in that cohort. Thus, a minimum of 6 (2 per cohort) and a maximum of 36 (12 per cohort) participants may be treated. Allowing for up to 1 patient, one per cohort, to be replaced for patients consented and assigned but not receiving MK-3475 (pembrolizumab), a maximum of 39 participants will be enrolled.

This protocol is designed to meet clinical needs of women and members of minority groups. The planned enrollment report (below) is based on US HIV demographics, and previous studies conducted in the HIV and AIDS Malignancy Branch.

PLANNED ENROLLMENT REPORT (Cohorts 1-3)

Racial Categories	Ethnic Categories				Total
	Not Hispanic or Latino		Hispanic or Latino		
	Female	Male	Female	Male	
American Indian/ Alaska Native					
Asian		1			1
Native Hawaiian or Other Pacific Islander					
Black or African American	3	9	1	2	**15**
White	2	9	1	2	**14**
More Than One Race	1	2	1	2	**6**
Total	**6**	**21**	**3**	**6**	**36**

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13.5 Stratification Factors

Patients will be stratified based on CD4+ T-cell counts at entry as some issues of safety and tolerability may vary according to CD4+ T-cell levels. Patients with HIV and malignancy that have been treated with multiple lympholytic therapies will present with a wide spectrum of CD4+ T-cell counts, even when on optimal HIV therapy and otherwise eligible to participate in a research protocol. For results of a safety study to be generalizable in this population, an adequate sample size is required to evaluate safety across a range of CD4+ T-cell counts, especially for a drug that modulates the immune system. For example, the safety of MK-3475 (pembrolizumab) may vary based on CD4+ T-cell count. As in some non-cancer settings, PD1 upregulation on CD4+ and CD8+ T cells in patients with HIV correlates with CD4+ T-cell count. In order to better address the primary objective, the accrual will be stratified by CD4+ T-cell levels. The CD4+ T-cell levels indicated below for definition of the cohorts are standard for many HIV therapy trials.

Cohort 1: 100-199 CD4+ T cells/mcL

Cohort 2: 200-350 CD4+ T cells/mcL

Cohort 3: >350 CD4+ T cells/mcL

Accrual to each cohort will be based on unacceptable AE during first treatment cycle of 21 days. If 2 or more unacceptable AEs occur in the first 6 patients, the cohort will not be expanded to 12 patients until the AEs are assessed by the Toxicity Evaluation Committee and the Committee approves the expansion.

13.6 Analysis of Secondary Endpoints

Analysis of secondary endpoints is discussed in Section 13.1.3.

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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. CTEP MULTICENTER GUIDELINES

If an institution wishes to collaborate with other participating institutions in performing a CTEP-sponsored research protocol, then the guidelines below must be followed.

Responsibility of the Protocol Chair

- The Protocol Chair will be the single liaison with the CTEP Protocol and Information Office (PIO). The Protocol Chair is responsible for the coordination, development, submission, and approval of the protocol as well as its subsequent amendments. The protocol must not be rewritten or modified by anyone other than the Protocol Chair. There will be only one version of the protocol, and each participating institution will use that document. The Protocol Chair is responsible for assuring that all participating institutions are using the correct version of the protocol.
- The Protocol Chair is responsible for the overall conduct of the study at all participating institutions and for monitoring its progress. All reporting requirements to CTEP are the responsibility of the Protocol Chair.
- The Protocol Chair is responsible for the timely review of Adverse Events (AE) to assure safety of the patients.
- The Protocol Chair will be responsible for the review of and timely submission of data for study analysis.

Responsibilities of the Coordinating Center

- Each participating institution will have an appropriate assurance on file with the Office for Human Research Protection (OHRP), NIH. The Coordinating Center is responsible for assuring that each participating institution has an OHRP assurance and must maintain copies of IRB approvals from each participating site.
- Prior to the activation of the protocol at each participating institution, an OHRP form 310 (documentation of IRB approval) must be submitted to the CTEP PIO.
- The Coordinating Center is responsible for central patient registration. The Coordinating Center is responsible for assuring that IRB approval has been obtained at each participating site prior to the first patient registration from that site.
- The Coordinating Center is responsible for the preparation of all submitted data for review by the Protocol Chair.
- The Coordinating Center will maintain documentation of AE reports. There are two options for AE reporting: (1) participating institutions may report directly to CTEP with a copy to the Coordinating Center, or (2) participating institutions report to the Coordinating Center who in turn report to CTEP. The Coordinating Center will submit AE reports to the Protocol Chair for timely review.
- Audits may be accomplished in one of two ways: (1) source documents and research records for selected patients are brought from participating sites to the Coordinating Center for audit, or (2) selected patient records may be audited on-site at participating sites. If the NCI chooses to have

an audit at the Coordinating Center, then the Coordinating Center is responsible for having all source documents, research records, all IRB approval documents, NCI Drug Accountability Record forms, patient registration lists, response assessments scans, x-rays, etc. available for the audit.

Inclusion of Multicenter Guidelines in the Protocol

- The protocol must include the following minimum information:
  - The title page must include the name and address of each participating institution and the name, telephone number and e-mail address of the responsible investigator at each participating institution.
  - The Coordinating Center must be designated on the title page.
  - Central registration of patients is required. The procedures for registration must be stated in the protocol.
  - Data collection forms should be of a common format. Sample forms should be submitted with the protocol. The frequency and timing of data submission forms to the Coordinating Center should be stated.
  - Describe how AEs will be reported from the participating institutions, either directly to CTEP or through the Coordinating Center.
  - Describe how Safety Reports and Action Letters from CTEP will be distributed to participating institutions.

Agent Ordering

- Except in very unusual circumstances, each participating institution will order DCTD-supplied investigational agents directly from CTEP. Investigational agents may be ordered by a participating site only after the initial IRB approval for the site has been forwarded by the Coordinating Center to the CTEP PIO.

APPENDIX C. BIOASSAY TEMPLATES

Biomarker Name[a] **AND Lead PI and Site**	**Assay** **(CLIA: Y/N)**	**Use (Integral, Integrated, or Exploratory) AND Purpose** [b]	**Tissue/Body Fluid Tested** **and Timing of Assay**	**M/O**	**Funding Source(s)** [c]
CD4+ T and CD8+ T-cell counts	To performed at each site by at a CLIA compliant laboratory. The technique is not specified by the protocol. CLIA: Yes	Integral To be used as eligibility criterion for clinical monitoring for possible toxicity in the form of falling T-cell levels.	Peripheral Blood Prior to first 3 doses of MK-3475 (pembrolizumab) then before every third dose	M	CITN
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Biomarker Name[a] **AND Lead PI and Site**	**Assay** **(CLIA: Y/N)**	**Use (Integral, Integrated, or Exploratory) AND Purpose [b]**	**Tissue/Body Fluid Tested** **and Timing of Assay**	**M/O**	**Funding Source(s) [c]**
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Biomarker Name[a] AND Lead PI and Site	Assay (CLIA: Y/N)	Use (Integral, Integrated, or Exploratory) AND Purpose [b]	Tissue/Body Fluid Tested and Timing of Assay	M/O	Funding Source(s) [c]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Biomarker Name[a] **AND Lead PI and Site**	**Assay** **(CLIA: Y/N)**	**Use (Integral, Integrated, or Exploratory) AND Purpose [b]**	**Tissue/Body Fluid Tested** **and Timing of Assay**	**M/O**	**Funding Source(s) [c]**
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

APPENDIX D. COMMON SIDE EFFECTS OBSERVED WITH AGENTS PRESCRIBED AS PART OF DHHS- RECOMMENDED AND ALTERNATE CART REGIMENS

cART	Common Side Effects (Observed in >5% of subjects on clinical studies)
Atripla®	Diarrhea, nausea, vomiting, **fatigue**, upper respiratory infections, headache, **drowsiness, dizziness, anxiety, depression, insomnia**, **abnormal dreams, rash, elevated cholesterol**, elevated CK, elevated amylase, **increased creatinine**
Isentress®	Insomnia, headache, dizziness, nausea, fatigue, neutropenia, elevated AST/ALT**,** elevated bilirubin, **elevated CK**, elevated fasting glucose, elevated amylase, elevated lipase,
Norvir®	**Abdominal pain**, **dyspepsia, nausea, vomiting,** fatigue blurred vision, cough, dizziness, dysguesia, flushing, pruritis, , rash, back pain, myalgia, neuropathy, edema, elevated AST/ALT, **elevated** triglycerides, elevated cholesterol, elevated CK,
Prezista®	**Abdominal pain, nausea, diarrhea**, headache, rash, elevated AST/ALT, **elevated total cholesterol, elevated triglycerides,** elevated glucose, elevated amylase
Reyataz®	**Jaundice, elevated direct bilirubin, nausea**, elevated CK, **elevated total cholesterol, elevated triglycerides**
Stribild®	**Diarrhea, nausea,** headache, abnormal dreams, **elevated CK, increased creatinine**
Tivicay®	Elevated AST/ALT, **elevated CK,** elevated glucose, elevated lipase
Triumeq®	Elevated AST/ALT, **elevated CK,** elevated glucose, elevated lipase
Truvada®	Diarrhea, nausea, fatigue, sinusitis, elevated CK, elevated cholesterol, elevated amylase, **hypophosphatemia, decreased bone mineral density,** neutropenia, **increased creatinine**

See Section 5.1.2, Table 2, for Generic names and DHHS recommendations.

Most AEs listed above are grade 1-2. For full list of adverse events, please see manufacturers' Prescribing Information for individual agents. More common side effects attributed to medications are bold. Many symptomatic side effects decrease with continued use. Renal function should be monitored in patients on tenofovir containing regimens.

Norvir® and Stibild® have significant CYP3A4 inhibitory effects, drug-drug interactions should be considered.

APPENDIX E. KS CUTANEOUS AND ORAL EXAM AND EVALUATION KS RESPONSE

1.0 Kaposi's Sarcoma Examination

1.1 Kaposi's Sarcoma Entry Examination

Timing - The KS entry examination should be performed prior to receiving study medication but no earlier than 2 weeks before initiating treatment. Tumor measurements should include the following:

A. **Identify and Measure** Cutaneous Marker Lesions

Select Marker Lesions

Select bi-dimensionally measurable marker lesions for assessing changes in lesion dimensions. Select the largest lesions with clearly defined margins. When available, a minimum of five bi-dimensionally measureable KS cutaneous marker lesions should be selected. If fewer than five bi-dimensionally measureable marker lesions are available, the total surface area of the marker lesion(s) should be $\geq 700 mm^2$. To facilitate repeated lesion measurements, the location of each marker lesion should be described in the Marker Lesion Table, recorded on the standard body diagram (Page 2 of Response Flow Sheet) in relation to body landmarks and other nearby lesions and photographed as described in Section 3.

> ***Note:*** Lesions used as marker lesions for measuring response to treatment should NOT be the lesions chosen for biopsies for Tumor Marker Assessments.

Measure Marker Lesions

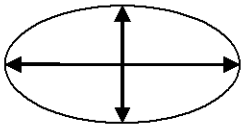
Each marker lesion should be measured in millimeters, indicating the longest linear dimension and the longest dimension perpendicular to it. For this protocol, the product of the largest perpendicular diameters of the marker lesion will be considered the AREA of the marker lesion. Please refer to the diagrams below:

Next, calculate the sum of the products of the areas of the indicator lesion(s).

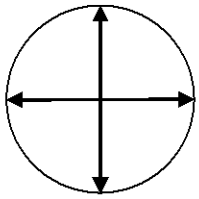
The sum calculated at entry or at the best response will be used to determine the response status at follow-up visits.

Calculate and Record Thresholds from Baseline for Partial Response and Progressive Disease

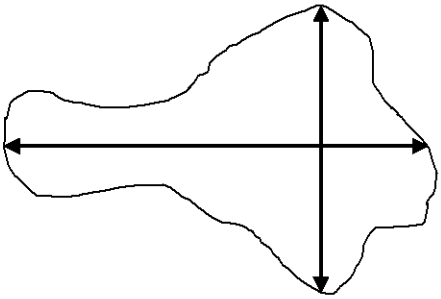
Examples of calculating the **area** of the indicator lesions



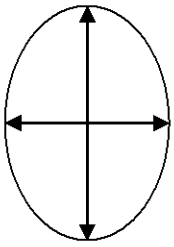
Oval Lesion: 35mm X 16mm = 560 mm²



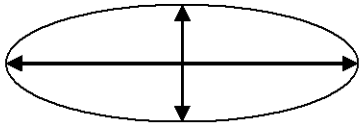
Round Lesion: 25mm X 25mm = 625 mm²



Irregular Lesion: 57mm X 39mm = 2223 mm²



Oval Lesion: 32mm X 22mm = 704 mm²



Oval Lesion: 47mm X 16mm = 752 mm²

Next, calculate the sum of the products of the areas of the indicator lesion(s).

To calculate the **sum of the areas** of the 5 example indicator lesions above, simply add the areas of each lesion:

560 mm^2 + 625 mm^2 + 2223 mm^2 + 704 mm^2 + 752 mm^2 = 4864 mm^2

Using the five marker lesions above, the sum of the areas is 4864 mm^2.

The sum calculated at entry or at the best response will be used to determine the response status at follow-up visits.

Calculate and Record Thresholds from Baseline for Partial Response and Progressive Disease

Partial Response threshold = Total product x 0.5
Progressive Disease threshold = Total Product x 1.25

Record Product thresholds on Page 1 of the Worksheet.

B. Evaluate Lesion Number (Total and Nodular/Raised)

Select Representative Areas
For participants with ≤50 total skin lesions, all lesions should be evaluated for changes in number and characteristics. For participants with >50 total skin lesions, choose three representative areas, if possible, for evaluating change in lesion numbers and characteristics (preferably each selected representative area should have at least 5 lesions, and the total number of lesions counted should be at least 20). **If it is not practical to choose three representative areas, the number of areas selected is left to the investigator's clinical judgment.** On Measurement worksheet, note if greater than 50 lesions.

> ***Note:*** A representative area is a single extremity, the back, chest, or face that has lesions similar in characteristics, i.e., nodularity, size, color, and number, to those found on other parts of the body. A representative area does not need to be the area with the largest number of lesions but should contain lesions that are truly representative of those throughout the remainder of the body. **Confluent lesions should be avoided when possible.**

Lesion Count (Nodular/raised and Flat)
The total number of nodular/raised and flat lesions (either total body or in the representative area(s)) must be counted. Use the Lesion Count tally sheet on the Page 2 of the measurement worksheet. Label body area counted, and use separate columns for Nodular and Flat lesions. Consider using a pen to mark lesions on skin as they are counted to aid. Mark the area counts and totals on Page 1 on the Worksheet.

C. Evaluate Edema

On page 2 of the Worksheet, record the presence or absence of tumor-associated the severity of edema, and the location of tumor-associated edema, if present.

In addition, lower extremity edema should be measured. Measure the circumference, in centimeters, of the ankle at the level of the malleoli and of the calf at a point 10 cm below the lower border of the patella. This must be done at entry in all participants whether there is edema or not. For patients with lower extremity edema, consider alos documenting edema at the level of the thigh and pelvis. For each measurement, note the distance from an anatomical landmark.

D. Perform Oral Examination

An oral mucosal tissue examination will be conducted on all study participants to detect the presence of oral cavity KS lesions.

The recommended standardized oral mucosal tissue examination should be conducted wearing gloves and 2x2 inch gauze and light. The oral examination should be conducted in the following sequence:

Lips
Begin examination by observing the lips, with the mouth both closed and opened. Note the color, texture, and any surface abnormalities of the upper and lower lip.

Labial Mucosa
With the mouth partially open, visually examine the lower labial mucosa by pulling the lower lip and stretching it over the chin, holding it between your thumb and index finger and using both hands. Repeat the same steps for the examination of the upper labial mucosa by pulling the upper lip and stretching it over the nose.

Buccal Mucosa and Vestibules
With the mouth open wide, examine first the right buccal mucosa (inside of cheek) extending from the labial commissures (corner of the lips) and back to the anterior tonsilar pillar. Examine both the upper and lower vestibule using the mirror to stretch the buccal mucosa and to help visualize the posterior vestibules. Examine the left buccal mucosa, following the same guidelines.

Hard and Soft Palate
With the mouth wide open and the participant's head tilted backwards, inspect the hard palate (note the ridges or rugae) located in the anterior part, and then the soft palate and uvula (ask the participant to say "ahhh" to better visualize the soft palate).

Tongue
With the participant's tongue at rest and mouth partially open, inspect the dorsum of the tongue for any swelling, ulceration, coating or variation in size, color, or texture. Also note any change in the pattern of the papillae covering the surface of the tongue and examine the top and the tip of the tongue. The participant should then protrude the

tongue, and the examiner should gasp the tip of the tongue with a piece of gauze to assist with full protrusion and allow examination of the margins or lateral borders. Note the small "lumps" located on each side of the posterior lateral tongue in the base of tongue area; these are the foliate papillae (considered to be an extension of the lingual tonsils). Then observe the ventral surface.

Floor of Mouth
With the tongue still elevated, inspect the floor of the mouth for swellings or other abnormalities.

Gingiva
First, examine the buccal and labial aspects of the gingiva and alveolar ridge. Start with the right maxillary posterior gingiva and alveolar ridge and move around the arch to the left posterior gingiva. Continue with the left mandibular posterior gingiva and alveolar ridge and move around the arch to the right posterior gingiva.

Second, examine the palatal and lingual aspects as has been done on the facial side, from right to left on the palatal (maxilla) and left to right on the lingual (mandible). Use the mouth mirror to retract the posterior part of the tongue and focus the light to better visualize the lingual gingiva.

Record the presence or absence of oral cavity KS lesions and their location on Page 1 of the Worksheet. Note whether lesions are raised or flat.

E. Evaluating Disease that cannot be Measured by Physical Exam (Evaluable Disease, Visceral KS)

Screening and Follow up for Visceral Disease
A chest X-ray (CXR) will be performed at screening. If the CXR findings are abnormal, additional evaluations are required in consultation with a pulmonologist. Bronchoscopy with visualization of lesions consistent with Kaposi sarcoma or lung biopsy are required for documentation of pulmonary KS. Appropriate microbiologic evaluation to exclude infectious etiologies is required. If pulmonary KS is noted, a CT scan should be performed to document disease.

At screening, potential study participants must be asked about the presence of gastrointestinal (GI) symptoms (odynophagia, nausea, vomiting, rectal bleeding, and/or abdominal pain). **If GI symptoms are present or microcytic anemia are noted at baseline, further evaluations should include stool tests for occult blood and infectious etiologies if infection is suspected.** Consultation with a gastroenterologist for upper and/or lower GI endoscopy is recommended in cases of occult blood loss or unexplained gastrointestinal symptoms. Documentation of gastroentestinal KS requires direct visualization of pigmented lesion(s) consistent with KS on endoscopy (with or without biopsy confirmation).

Other Sites of Disease
CT scanning is not required at baseline in patients without other indications for a CT scan. If performed, KS involving other visceral organs or lymph nodes may be detected by advanced imaging techniques (e.g., CT or MRI scan, ultrasound) and confirmed by biopsy. If KS is confirmed by biopsy in visceral organs, this information should be recorded. If there is an unconfirmed abnormality on a scan or ultrasound, and KS cannot be confirmed by biopsy, that information should be recorded and the abnormality followed during study treatment to determine if it changes.

Note presence of visceral lesions on page 1 of the Worksheet.

Evaluable Disease
Evaluable disease (also known as non-measurable disease) is disease that cannot be measured directly by the size of the tumor but can be evaluated by other methods. For purposes of this study, lesions considered truly non-measurable include: ascites, pleural or pericardial effusions, lymphangitic lung disease, abdominal masses/abdominal organomegaly identified by physical examination that is not measurable by reproducible imaging techniques, bone lesions without an identifiable soft tissue component that can be evaluated by cross-sectional imaging techniques, and lesions that can be identified only by endoscopic, bronchoscopic, or laparoscopic techniques. Changes in the size of other types of disease may not be accurately quantifiable, for example discrete lung lesions on chest x-ray.

Effusions, when noted, should be evaluated to exclude primary effusion lymphoma whenever feasible before starting therapy.

For purposes of response assessment, the evaluation of non-measurable disease is used primarily to determine whether an individual has shown tumor progression when evaluation of measurable disease (i.e., cutaneous marker lesions, lesion counts, numbers of raised and flat lesions, edema, visceral disease that is measurable in two dimensions on CT scan) indicates response or stable disease. We will use the standard of "unequivocal progression", i.e., an overall level of substantial worsening of disease that is of a magnitude that, even in the presence of stable disease or partial response in measurable disease, the treating physician would feel it important to change therapy. This requires clinical judgment on the part of the investigator. For further guidance on the evaluation of non-measurable disease, please refer to the following:
Therasse P, Arbuck SG, Eisenhauer EA, et al. New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. J Natl Cancer Inst 2000; 92(3):205-216.

The KS follow-up examination will be performed according to the schedule of events. Tumor evaluation should follow the guidelines noted in Section 1.1 above, and include:

- Record measurements of the longest linear dimension in millimeters and the longest dimension perpendicular to it of the same marker lesion(s) selected at entry;

- Record the total number of raised and flat lesions (in the same areas that were evaluated at entry, either total body or the representative area(s) selected at entry);
- Record the location, size, or characteristics of oral cavity lesions, after the oral mucosal tissue examination is conducted in the same sequence as the oral examination at entry;
- Record the severity of edema and the location of tumor-associated edema. If no edema was present at entry and no edema is present on the follow-up visit, repeat measurements are not required. If there was no edema at entry and edema develops at a follow-up visit, a re-measure at each KS follow-up evaluation is required. If edema was noted at entry, a re-measure at each KS follow-up evaluation is required.
- Record changes of visceral KS at the intervals required by the protocol if visceral disease was present at entry, or if symptoms suggesting visceral disease develop.

2.0 Calculating Response Status

Response status will be classified as complete response **(CR),** partial response **(PR),** stable disease, or progressive disease **(PD).** For a detailed definition of the KS response status, please refer Section 11.3 of the protocol, as well as reference article provided.

Response should be calculated from Baseline. For patients with decreasing tumor area or lesion counts, new thresholds should also be calculated for values at best response and used as a reference for comparison to subsequent values. **Document Response for Baseline and Response from addition time points (by Date or cycle number) on Page 1 of the Worksheet.**

2.1 Calculate Response Status Based on Area of Marker Lesion(s)

To calculate the KS response status **based on area of marker lesions** you will need the area of the indicator lesions from entry. Next, calculate the area of the same indicator lesion(s) for the current visit. Subtract the area at the current visit from the area at entry, then divide this difference by the area at entry. **Multiplying by 100%** will give you the percentage change from entry. After a participant has had a **confirmed CR** or **PR**, subsequent measurements for PD should also be compared with the "best response" seen at a previous visit.

An initial confirmed PR is a ≥50% decrease in the area of the indicator lesion(s) compared to entry lasting for at least 4 weeks. For example, if a participant had an area of the indicator lesions of 4000mm² at entry and an area of the indicator lesions of 2000mm² at week 3, and this decrease was maintained for at least 4 weeks, the participant would have a **confirmed PR.**

PD is considered a ≥ 25% increase in the area of the indicator lesion(s) compared to entry or best response. For example, if the same participant as in the example above had an area of the indicator lesions of 5000mm² at week 3, the participant would have PD. Similarly, if a participant had an area of the indicator lesions of 4000mm² at entry and an area of the indicator lesions of 2000mm² at week 9 **that lasted for four weeks** (a

confirmed PR) but at a subsequent visit was found have an area of 3000mm2 (a greater than 25% increase over the best response), the participant would have PD. **PD after a confirmed CR is defined by the presence of any KS following that confirmed CR.**

> ***Note:*** **If a confirmed CR has been achieved and subsequent evaluations do not meet criteria for CR, this would be reported as PD.**

Please note that "best response" may improve after the initial **confirmed PR** is documented. For example, if the **entry** area of the indicator lesions was 5000mm² and the area decreased to 2400mm² at weeks **9 and 15**, this would be the initial **confirmed PR**. If, at week 18, the area of the indicator lesions decreased further to 2000mm², **then 2000mm2 is the new "best response". In this example, subsequent assessments of PD for the area of indicator lesions would be with respect to the number 2000mm², not to 2400mm². Thus, if the area of the indicator lesions at week 24 increased from 2000 to 2500mm2, this increase would constitute PD, despite the fact that 2500mm2 is 50% smaller than the entry lesion area.**

> *Note*: **If a confirmed PR has been achieved and subsequent evaluations do not meet criteria for PD or CR, this would continue to be reported as PR. In the example above, if the entry area of the indicator lesions was 5000mm² and the area decreased to 2400mm² at weeks 9 and 15, and remained at 2400mm² at week 18, 2400mm² is the "best response" to date. If, at week 24, the area of the indicator lesions increased to 2800mm² this would continue to be reported as a PR because 2800 is less than a 25% increase from 2400. Similarly, if at week 24, the area of the indicator lesions decreased by an additional 10% to 2160mm², this would also continue to be reported as a PR.**

2.2 Calculate Response Status Based on the Total Number of Lesions

To calculate the response status based on the total number of lesions, you will need the total number of lesions (either whole body or, in the case of participants with over 50 lesions at entry, in the combined representative areas) from the entry KS exam. After an initial **confirmed CR** or **PR**, the percentage change for PD should be calculated from the "best response" seen at a previous visit.

An initial confirmed PR is a 50% or greater decrease in the number of lesions present at entry (either whole body or, in the case of participants with over 50 lesions at entry, in the combined representative areas) lasting for at least 4 weeks. For example, if a participant had 40 lesions at entry and had only 20 lesions at follow-up and this decrease was maintained for at least 4 weeks, that participant would have a **confirmed PR**.

For participants with ≤50 cutaneous lesions **at entry,** PD is defined as ≥25% increase in the total lesion count or a minimum of five new lesions, **whichever is greater**, compared to entry or best response. For example, if a participant had 35 lesions at entry and has 44 at follow-up, that would be classified as PD. **PD after a confirmed CR is defined by the presence of any KS following that confirmed CR.**

Note: **If a confirmed CR has been achieved and subsequent evaluations do not meet criteria for CR, this would be reported as PD.**

For participants with >50 cutaneous lesions **at entry**, PD is defined as ≥25% increase in the total number of lesions **or a minimum of five new lesions, whichever is greater,** in the combined prospectively-defined anatomic sites containing representative lesions **compared to entry or best response,** or a total of five new lesions in anatomic sites which were previously documented as having no evidence of cutaneous disease. For example, if a participant had a total of 40 lesions at entry on the back and the right leg and had a total of 50 lesions at follow-up on the back and the right leg that would be classified as PD. Also, if a participant had no lesions at entry on the right arm and had five lesions on the right arm at follow-up that would be classified as PD. Similarly, if a participant had 40 lesions at entry and 20 lesions at weeks **9 and 15 (a confirmed PR)** but at a subsequent visit was found to have 30 lesions (a greater than 25% increase over the best response), the participant would have PD. **PD after a confirmed CR is defined by the presence of any KS following that confirmed CR.**

Please note that "best response" may improve after the initial **confirmed PR** is documented. For example, if the **entry** number of lesions was 30 and the number of lesions decreased to 15 at weeks **9 and 15**, this would be the initial **confirmed PR**. If, at the week 18 evaluation the number of lesions decreased further, e.g., to 10**, then 10 is the new "best response"** and subsequent assessments of PD for lesion counts would be with respect to the number 10, not to 15. **Furthermore, if the number of lesions at week 24 increased from 10 to 15, this increase would constitute PD, despite the fact that 15 is 50% smaller than the entry lesion count.**

Note: **If a confirmed PR has been achieved and subsequent evaluations do not meet criteria for PD or CR, this would continue to be evaluated as PR. In the example above, if the entry lesion count was 30 and the number of lesions decreased to 15 at weeks 9 and 15, then 15 is the "best response" to date. If, at week 24, the number of lesions increased to 18, this would continue to be reported as a PR because 18 is less than a 25% increase from 15. Similarly, if at week 24, the number of lesions decreased by an additional 20% to 12, this would also continue to be reported as a PR.**

2.3 Calculate Response Status Based on the Number of Raised Lesions

To calculate the response status based on the number of raised lesions, you will need the total number of raised **lesions** (either whole body or, in the case of participants with >50 lesions at entry, in the combined representative areas) from the entry KS exam. If, after an initial **confirmed** response, the disease appears to be getting worse, the percentage change **for PD** should be calculated from the "best response" seen at a previous visit.

An initial confirmed PR is a complete flattening of at least 50% of all previously raised lesions (i.e., 50% of all nodular or plaque-like lesion become macules) present at entry (either whole body or, in the case of participants with >50 lesions at entry, in the combined representative areas) lasting for at least 4 weeks. For example, if a participant

had 30 raised lesions at entry and had only 15 raised lesions at follow-up and this decrease was maintained for at least 4 weeks that would be classified as a **confirmed PR.**

For participants with ≤50 cutaneous lesions **at entry**, PD is defined as ≥25% increase in the number of raised lesions (minimum of 5 new raised lesions if there are very few raised lesions, for example <8), compared to entry or best response. For example, if a participant had 20 raised lesions at entry and had 25 raised lesions at follow-up that would be classified as PD. Also, if a participant had 7 raised lesions at entry and had 12 at follow-up that would be classified as PD. **PD after a confirmed CR is defined by the presence of any KS following that confirmed CR.**

> ***Note:*** If a confirmed CR has been achieved and subsequent evaluations do not meet criteria for CR, this would be reported as PD.

For participants with >50 cutaneous lesions **at entry**, PD is defined as ≥25% increase in the total number of raised lesions **or a minimum of five new raised lesions, whichever is greater,** in the combined prospectively-defined anatomic sites containing representative lesions (minimum of 5 raised lesions if there are very few raised lesions, for example <8). For example, if a participant had a total of 28 raised lesions on the back and right arm at entry and had a total of 35 raised lesions on the back and right arm at follow-up that would be classified as PD. Also, if a participant had a total of 7 raised lesions on the back and right arm at entry and had 12 raised lesions on the back and right arm at follow-up that would be classified as PD. Similarly, if a participant had 40 raised lesions at entry and 20 raised lesions at weeks **9 and 15 (a confirmed PR)** but at a subsequent visit was found have 30 raised lesions (a greater than 25% increase over the best response), the participant would have PD. **PD after a confirmed CR is defined by the presence of any KS following that confirmed CR.**

Please note that "best response" may improve after the initial **confirmed PR** is documented. For example, if the **entry** number of raised lesions was 30 and the number of raised lesions decreased to 15 at weeks **9 and 15,** this would be the initial **confirmed PR.** If, at the week 18 evaluation, the number of raised lesions decreased further, e.g., to 10, **then 10 is the new "best response" and** subsequent assessments of PD for raised lesions would be with respect to the number 10, not to 15. **Furthermore, if the number of raised lesions at week 24 increased from 10 to 15, this increase would constitute PD, despite the fact that 15 is 50% smaller than the entry raised lesion count.**

> ***Note:*** **If a confirmed PR has been achieved and subsequent evaluations do not meet criteria for PD or CR, this would continue to be evaluated as PR. In the example above, it the entry raised lesion count was 30 and the number of raised lesions decreased to 15 at weeks 9 and 15, then 15 is the "best response" to date. If, at week 24, the number of raised lesions increased to 18, this would continue to be reported as a PR because 18 is less than a 25% increase from 15. Similarly, if at week 24, the number of raised lesions decreased by an additional 20% to 12, this would also continue to be reported as a PR.**

2.4 Determining Response Status Combining Measurements of Lesion Size, Character, and Number and Visceral Disease and Edema

Participants who show the absence of any detectable residual disease, including tumor-associated edema, persisting for at least 4 weeks, will be classified as having CR. In some individuals, residual skin color changes may remain visible at one or more sites of lesions that were previously raised and/or red or violaceous. Suspected CR in those lesions refers only to residual macules (flat, non-palpable lesions) that are slightly darker than the surrounding normal skin. In the event such lesions are present in a participant otherwise believed to have a CR, biopsy of at least one such lesion is required to document the absence of malignant cells and to confirm CR. In the event that such a confirmatory biopsy is not performed and residual pigment persists, the response will be considered **PR.** In participants in whom all detectable cutaneous disease has resolved and in whom there are no visible pigmented macules as described above, a confirmatory skin biopsy is not required. In participants known to have had visceral disease, an attempt at restaging with appropriate endoscopic or radiographic procedures should be made.

Participants who do not meet the criteria for **CR, PR,** or **PD** will be classified as Stable.

The criteria for classifying participants as showing either **PR** or **PD** are shown in the tables below.

Partial Response

PR requires at least one of the highlighted criteria in the table below AND all of the categories shown on the same row, when compared to entry.

Note: If any of the criteria for PD have been met, even in the presence of a criterion for **PR,** it is considered PD.

Note: **PR** is always a comparison to entry even if there has been a prior **PR**.

Criteria for Classifying **PR**					
Total body or representative areas					
PR Category	**Marker lesion area**	**Number of lesions**	**Number of raised lesions**	**Visceral or Oral KS***	**Edema**
1	**Decrease ≥50%**	<25% Increase	<25% Increase	<25% Increase of measurable lesions without unequivocal worsening of non-measurable disease	No significant increase or new sites
2	<25% Increase	**Decrease ≥50%**	<25% Increase	<25% Increase of measurable lesions without unequivocal worsening of non-measurable disease	No significant increase or new sites

Criteria for Classifying **PR**					
Total body or representative areas					
PR Category	**Marker lesion area**	**Number of lesions**	**Number of raised lesions**	**Visceral or Oral KS***	**Edema**
3	<25% Increase	<25% Increase	**Decrease ≥50%**	<25% Increase of measurable lesions without unequivocal worsening of non-measurable disease	No significant increase or new sites
4	<25% Increase	<25% Increase	<25% Increase	**Decrease ≥50% of measurable lesions without unequivocal worsening of non-measurable disease or complete disappearance of non-measureable disease**	No significant increase or new sites

*Please note that there is no need to physically measure the visceral or oral KS.

Progressive Disease

Any of the following (increase refers to a change over entry visit or when compared to the best response). If there has been a previous confirmed CR or PR, subsequent assessments of PD should be made with comparison to the best response for the category (or categories) that previously led to the assessment of CR or PR; for the other categories, the comparison should be made to entry.

Note: PD is a comparison to entry unless there has been a **confirmed** PR or CR in which case it is then a comparison to best response. Only PD is compared to best response (see Section 3.4 below).

Total body or representative areas				
Marker lesion area	Number of lesions	Number of raised lesions	Visceral or Oral KS	Edema
≥25% Increase	≥25% Increase	≥25% Increase	≥25% Increase or new sites or unequivocal worsening of non-measurable disease	Significant increase or new sites*

*Significant increase in edema or new sites compared to entry or best response** are defined as:

- an increase in non-pitting/woody edema in an upper or lower extremity associated with an increase in limb circumference of at least 3 cm from entry **or best response**, sustained for at least two consecutive evaluations, and measured at a fixed point on the extremity with respect to a bony landmark (e.g., 10 cm below the lower border of the patella); AND/OR,

- new appearance of non-pitting/woody edema in an extremity when none was previously present, sustained for at least two consecutive evaluations;

AND/OR,

- new or worsening edema in a non-extremity site (e.g., periorbital, genital) that interferes with function and is sustained for at least two consecutive evaluations.

**** If edema is present at entry and resolves completely (and this lasts for at least 4 weeks), this is considered a "best response" of edema. Otherwise, all evaluations of edema in a given step are with respect to the status at entry to that step.**

2.5 Assessment of Response Status During Steps 2, 3 and 4

At the time of Step 2, 3, or 4 entry, a different representative area, if preferable, may be chosen for determination of response status during Step 2, 3, or 4. Response status during Step 2, 3 or 4 will be determined by comparing Step 2, 3 or 4 visits to Step 2, 3, or 4 entry, respectively. If possible, the same marker lesion(s) should be followed and measured throughout Steps 1, 2, 3, and 4.

3.0 Photographic Record

Photographs will be taken to assist in documentation of the diagnosis of KS and for clinical monitoring purposes. The difficulty in standardizing these photographs is acknowledged.

In all participants, photographs will be needed of the marker lesion(s), defined at study enrollment and used for clinical assessment of response. The marker lesion**(s)** must be labeled in the photographs #1–#5, **as applicable**. The same lesion**(s)** must be consistently labeled throughout the trial. For each lesion, two photos will be taken. The first photo will be a close-up of the lesion. A millimeter ruler should be included in the photograph to demonstrate the size of the lesion. The second photo will be a larger view photo that will show the lesion's location on the body.

In all participants, photos will also be needed of larger views of the back, chest, arms (front and back), legs (front and back), feet (including soles), whether involved with KS or not. In addition, photos should be taken of any other area with significant involvement at entry (e.g., the face).

In participants with >50 cutaneous lesions, photographs will be taken of the representative areas (each **should have at least 5** lesions), defined at study enrollment and used for clinical assessment of response.

Photographic documentation will be completed at entry and then at each visit when the KS response status changes. For example, if a participant's KS response status changes from no

response to **PR**, the site will take photos of this to document the category change. If there was no change in the KS response status, no photos are required.

> ***Note:*** The same markers lesions should be used throughout the study. In the event that the marker lesions coalescence or become immeasurable during follow-up, a new marker lesion may be selected at the entry of a new step for follow-up evaluations during that step.

Photographs will be stored electronically under the participant ID number and back-up electronic storage will be kept. Only dedicated study staff and the sponsor should have access to the photographs.

Appropriate measures must be taken to protect participant confidentiality. Photographs of participants' faces should be avoided unless the area is being monitored for KS response. In cases where a participant's face is photographed, no participant photos should be used in publication prior to removal of identifying characteristics, for example, the blacking out of a participant's eyes. **Site should take necessary measures to black out eyes and/or tattoos prior to uploading photos.**

Absolutely no identifying information should be included with the digital picture file.

Photography Tips

1. We recommend a 5 megapixel camera minimum.
2. Include the participants PID in all of the photos.
3. Always try to take the photos in the same setting with respect to participant positioning, lighting, background, and camera setting.
4. Use auto-focus. The team does not recommend the use of manual controls.
5. Use the "macro" mode for close-ups. The universal symbol for "macro" mode is a flower.
6. Use the flash mode as often as possible when the lighting is poor, but avoid getting too close to the lesions as overexposure may wipe out the details.
7. For very close shots, oblique views may be preferred
8. Eliminate all distractions from the background. Try to take all photographs with a plain blue or green background.

Framing Tips

1. For different body areas certain standard framing patterns are followed
2. For all lesions, make it a point to take at least 2 shots from each point of focus. Minimal blurring may not be obvious on the LCD screen and may be noticeable only after the image is viewed on the monitor. It is always better to have an extra copy from every focus point so that the best image can be selected.
3. Always try to capture distinctive elements like typical representative lesions, particular configurations, or distribution patterns.

For generalized lesions take shots from at least three ranges:

- A complete vertical view of the participant showing the extent and distribution of the rash;
- A medium distance shot showing the arrangement and configuration of the rash;
- A close-up view highlighting a representative lesion.

For localized lesions take shots from at least two points:

- A medium view showing the rash /lesion with respect to location and configuration

Always include a recognizable body landmark so that the location is obvious. For example, lesions on the abdomen include the umbilicus in the medium distance shot)

- A close-up view of the representative lesion

For isolated lesions it is also advisable to include a discernible landmark in one of the shots. For the close-up shots use a measuring tape/ruler in the frame to demonstrate the size of the lesion. It would be advisable to take the close-up shots from more than one angle and include oblique shots. Shots with and without flash may be taken and the best shot selected for storage.

Recommended Saving, Storing, and Uploading Files

1. SAVE as a JPG file. The major advantage of the JPG format is that the image size can be compressed considerably without significant visible loss of resolution. The back-up copies can also be saved in the compressed JPG format so that the space taken up can be minimized. It always makes sense to delete images that are blurred as they are unlikely to be used by you and will unnecessarily clutter up the hard disk space.
2. Make it a point to catalog all saved images (or containing folders) tagging them with the participant's identification number, date and even the provisional diagnosis, if possible. Meticulous cataloging may seem cumbersome at the beginning but make future retrieval of images very convenient.

APPENDIX F. KAPOSI SARCOMA RESPONSE SHEET

CITN-12 KAPOSI SARCOMA MEASUREMENT AND RESPONSE SUMMARY

Initials		Date		Study		Cycle		Photos	
Baseline TIS		T: I: S:			REASON T1:				

MARKER LESIONS

LESION	COLOR, LOCATION	FLAT OR NODULAR	DIMENSIONS	PRODUCT
ONE				
TWO				
THREE				
FOUR				
FIVE				

LESION COUNT

TOTAL LESIONS	OVER 50 _____ UNDER 50* _____
*FOR PATIENTS WITH UNDER 50 LESIONS, WRITE 'TOTAL BODY' FOR AREA AND USE LEFT COLUMN	

BODY AREA	1	2	3	TOTAL
NUMBER FLAT				
NUMBER NODULAR				
TOTALS				

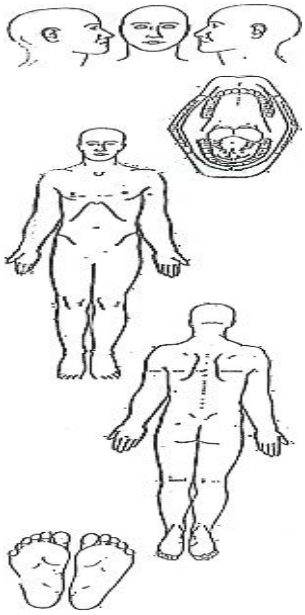
ORAL LESIONS	PRESENT		NONE		NO EVAL	
DESCRIPTION IF PRESENT						
VISCERAL LESIONS	PRESENT		NONE		NO EVAL	
DESCRIPTION IF PRESENT						

RESPONSE THRESHOLDS FROM:_____			RESPONSE FROM BASELINE		
PARTIAL RESPONSE		PROGRESSIVE DISEASE		RESPONSE BASED ON	
TOTAL		TOTAL		RESPONSE FROM_____	
NODULAR		NODULAR		RESPONSE BASED ON	
PRODUCT		PRODUCT		RESPONSE CONFIRMED BY	
RECORDER			SIGNATURE		

HAMHAMB KAPOSI SARCOMA MEASUREMENT AND RESPONSE SUMMARYKAPOSI SARCOMA MEASUREMENT AND RESPONSE SUMMARY	
REGIONS: NOTE MARKER LESIONS	LESION COUNT

TUMOR EDEMA
NO [ ] YES [ ] LOCATION

LEFT			RIGHT		
LEVEL	DIST.	DIAM.	LEVEL	DIST.	DIAM.
ANKLE	0cm		ANKLE	0cm	
CALF			CALF		
THIGH			THIGH		
PELVIS			PELVIS		



SUMMARY OF CHANGES
Informed Consent Document

For Protocol Amendment 6, Version 2.0

NCI Procotol #: CITN-12
Local Protocol #: CITN-12
NCI Version Date: May 22, 2018
Protocol Date: May 22, 2018

I. Consent form changes requested by CTEP

#	Section	Pages(s)	Change

1.	Possible Risks	7 - 11	Replaced Risks table with updated Risks table per Request for Rapid Amendment dated April 26, 2018. Changes are as follows:
			• *Added New Risks:*
			  • Occasional:
			  • Blood clot which may cause bleeding, confusion, paralysis, seizures and blindness
			  • Rare:
			  • Feeling of "pins and needles" in arms and legs;
			  • Redness, pain or peeling of palms and soles;
			  • Damage to organs in the body when donor cells attack host organs which may cause yellowing of eyes and skin, itchy dry skin;
			  • Damage to organs in the body when the body produces too many white cells;
			  • A condition with high blood sugar which leads to tiredness, frequent urination, excessive thirst, headache, nausea and vomiting, and can result in a coma;
			  • Inflammation of the brain (encephalitis/meningitis) which may cause headache, confusion, sleepiness, seizures, and stiff neck
			• *Increase in Risk Attribution:*
			  • Changed to Occasional from Also Reported on MK-3475 Trials But With Insufficient Evidence for Attribution (i.e., added to the Risk Profile): Pain in back; Cough

			• *Decrease in Risk Attribution:*
			  • Changed to Rare from Occasional: Reaction during or following a drug infusion which may cause fever, chills, rash
			
			• *Provided Further Clarification:*
			  • "Lung problems (pneumonitis and pleural effusion). Symptoms may include: new or worsening cough, chest pain, shortness of breath." (under Occasional) is now reported as "Lung problems (pneumonitis and other conditions). Symptoms may include: new or worsening cough, chest pain, shortness of breath." (under Occasional).

II. Changes Initiated by P.I.

#	Section	Page(s)	Change
2.	All	All	Updated version and date.
3.	Why is this study being done?	2	Corrected number of study participants.
4.	Possible Risks	11-13	Deleted list of New Risks Identified by Manufacturer.

NOTES FOR LOCAL INVESTIGATORS*:

- The goal of the informed consent process is to provide people with sufficient information for making informed choices about participating in research. The consent form provides a summary of the study, of the individual's rights as a study participant, and documents their willingness to participate. The consent form is, however, only one piece of an ongoing exchange of information between the investigator and study participant. For more information about informed consent, review the "Recommendations for the Development of Informed Consent Documents for Cancer Clinical Trials" prepared by the Comprehensive Working Group on Informed Consent in Cancer Clinical Trials for the National Cancer Institute. The Web site address for this document is http://cancer.gov/clinicaltrials/understanding/simplification-of-informed-consent-docs/

- A blank line, "_____", indicates that the local investigator should provide the appropriate information before submitting to the IRB.

*These notes for investigators are instructional and should not be included in the consent form sent to IRBs.

Consent Form

Study Title for Study Participants: Testing the addition of an experimental medication MK-3475 (pembrolizumab) to usual anti-retroviral medications in patients with HIV and cancer

Official Study Title for Internet Search on http://www.ClinicalTrials.gov: Phase I Study of MK-3475 (Pembrolizumab) in Patients with Human Immunodeficiency Virus (HIV) and Relapsed/Refractory or Disseminated Malignant Neoplasm

NCI Protocol #: CITN-12

PRINCIPAL INVESTIGATOR(S)

[Note to Local Investigator: Contact information for principal investigator(s) should be listed here.]

INTRODUCTION

We are asking you if you would like to join this research study. Research is not the same as treatment or medical care. A research study answers scientific questions.

This consent form will help you decide whether joining the study is right for you. Please read this form carefully. We can read it with you if you want. Ask questions about anything that is not clear. Also, you can talk to people whom you respect to help you decide about joining the study. If you agree to join, you will sign this consent form. We will offer you a copy to keep.

What is the usual approach to treating cancer in patients with HIV?

You are being asked to take part in this study because you have cancer and HIV. You have already been treated with chemotherapy for your cancer and your disease is now growing. People who are not in a study are usually treated with more chemotherapy or other treatments listed above.

Depending upon the type of cancer you have, the usual approach to treat your cancer may involve treatment with chemotherapy, radiation therapy, surgery, hormonal agents, or biologics such as vaccines or antibodies. Patients with HIV are usually treated with a combination of anti-viral drugs. Throughout this consent form we will refer to this treatment as cART, which means combination antiretroviral therapy. There is not a single approach to treating all types of cancer

in patients with HIV, and decisions about continuing cART vary. For this study, participants must be on effective and tolerable cART
MK-3475 (pembrolizumab) is in a class of drugs called monoclonal antibodies, which include some relatively new types of cancer therapies. This drug works through its effect on the immune system, and is therefore considered an "Immunotherapy". If you decide to participate in this study, you will not be able to receive additional cancer therapiesat the same time, but you will continue on your cART medications. If another cancer therapytreatment is needed for your disease, it must be delayed until you are off the study treatement.

This study is being conducted by the Cancer Immunotherapy Trials Network (CITN), sponsored by the National Cancer Institute. The CITN administrative coordinating center is located at the Fred Hutchinson Cancer Research Center (FHCRC) and works with researchers from several cancer centers and universities across the country.

What are my other choices if I do not take part in this study?

If you decide not to take part in this study, you have other choices. For example:

- You may choose to have the usual approach appropriate for your type of cancer
- You may choose to take part in a different study, if one is available
- You may decide not to be treated.
- You may choose to get comfort care. This type of care helps reduce pain, tiredness, appetite problems, and other problems caused by cancer. It does not treat the cancer directly, but instead tries to improve how you feel. Comfort care tries to keep you as active and comfortable as possible.

Why is this study being done?

The purpose of this study is to test the safety of MK-3475 (pembrolizumab) in combination with cART to find out what effects, if any, it has on people with HIV and cancer. There will be about 54 people taking part in this study.

What are the study groups?

This study has four study groups. You will be assigned to one of four study groups based on your $CD4^+$ T-cell counts. The fourth study group is for patients with Kaposi sarcoma who have not received previous treatment for it. All four groups will receive MK-3475 (pembrolizumab) (study medication) and stay on cART therapy. Everyone will receive the same dose of study medication. If the drug does not cause serious side effects in the first 6 patients treated in each group, it will be given to more study participants. The fourth group of patients will be included in the study after at least 6 patients are enrolled in the first three groups of patients.

How long will I be in this study?

You may receive the MK-3475 (pembrolizumab) for up to 2 years if your cancer responds or does not worsen. You will continue your usual cART medications while you are getting MK-3475 (pembrolizumab). After you finish treatment with MK-3475 (pembrolizumab) your doctor

will continue to watch you for side effects and follow your condition for 1 year. During this year, we will ask you to come in for a visit every three months.

What extra tests and procedures will I have if I take part in this study?

Most of the exams, tests, and procedures you will have are part of the usual approach for your cancer. However, there are some extra exams, tests, and procedures that you will need to have if you take part in this study.

Before you begin the study:

You will need to have the following exams, tests, and procedures to find out if you can be in the study:

- Give you a physical examination.
- Give you a test called an EKG to learn about your heart.
- Ask you questions about your health and the medications that you take.
- Draw blood as described in the blood collection table.
- Collect a urine sample.
- Give you CT scans or PET CT scans for tumor measurements.
- Ask your permission to obtain a sample of your tumor tissue.
    - If you have already had surgery to remove your tumor, it is likely that your doctor has sent that tissue to a pathologist to establish the diagnosis. The pathologist may release some leftover tissue to us for this research study.
    - If there is not tissue available from an earlier biopsy, we would take a biopsy of one of your tumors for testing. The doctor will remove a small piece of your tumor using a needle, a circular blade called a punch, or a small scalpel (knife).

Neither you nor your health care plan/insurance carrier will be billed for the exams or the sample collections that will be used for this study if they are not part of your usual care.

If the exams, tests, and procedures show that you are eligible to be in this study, and you choose to particiapte, then you will need the following exams, tests, treatments or procedures. These may not be part of the usual approach for your type of cancer. Please ask your study doctor what exams, tests, and procedures are the usual approach for your cancer.

During the study**:**

- We will give you a dose of the study medication every 3 weeks. (A treatment cycle starts every 3 weeks). The study medication will be given to you by intravenous infusion (through a needle into a vein over about 30 minutes).
- Cycle 1 and Cycle 2 of treatment require additional visits:
    - Cycle 1: Study drug is given on Day 1, and then you will attend visits on Day 2 and Day 8.
    - Cycle 2: Study drug is given on Day 1, and you will also attend a visit on Day 2.

- For the rest of the cycles, you will only come to the clinic for the Day 1 visit, when study drug is given.
- We will take blood samples as described in the collection table below.
- Take a CT scan or PET CT scan for tumor measurements around the time of the third dose of study medication, and then around every third dose (every 9 weeks). After one year, you would have a CT or PET CT only every fourth dose (every12 weeks).
- If you have Kaposi sarcoma,
    - We will measure and take medical pictures of your tumors at the beginning of the study, before you receive MK-3475 (pembrolizumab), and when your tumors worsen or improve, and at the end of treatment. This will help us to assess the extent of your disease and whether it responds to the study medication.
    - If your disease is visceral (present in tissues other than your skin), we may do other tests to record location and size of tumors at the beginning of the study, and later on to document response to treatment. Depending on the location of visceral disease, these tests could include bronchoscopy or endoscopy.
    - If it appears that all tumors on your skin have responded to treatment, but there are still remaining areas that are darker than the surrounding skin, we may ask to take an optional biopsy to see if any cancer cells remain.
- Ask you questions at each visit about your health and any symptoms you may be having. We will also ask about your medications.
- Give you a physical examination every 3 weeks.
- Collect a urine sample every 6th cycle (every 18 weeks).

If you agree, we will collect extra biopsies and store leftover blood samples:

If your physical exams CT, PET-CT scans or other tests show that your tumor is increasing in size or worsening, the study doctor will discuss with you whether to stop or continue the study medication. If this happens, your doctor will ask you if you agree to a biopsy of your tumor. If you agree to the optional biopsy, the doctor will remove a small piece of your tumor or lymph node using a needle, a circular blade called a punch, or a small scalpel. The tests done on this optional biopsy would only be used for research and not to guide your medical care.

As discussed in the study procedure section above, if you have Kaposi sarcoma your doctor will ask you if you agree to a biopsy of your tumor. If you agree to this optional biopsy, the doctor will remove a small piece of your tumor or lymph node using a needle, a circular blade called a punch, or a small scalpel. The tests done on this optional biopsy would only be used for research and not to guide your medical care.
We would like your permission to store any leftover biopsy samples or blood samples that we do not use during the study in the biobank. Storing samples for future studies is called "biobanking."

At the end of this consent form, we will ask you if you will allow us to collect the optional biopsies and store leftover tissue and blood samples in the biobank. You can decide not to give the extra biopsy samples and still be in the study. You can also decide to not allow us to store

your leftover blood samples and still be in the study. If you agree to provide these samples, you can change your mind at any time during the study.
Neither you nor your health care plan/insurance carrier will be billed for the collection of the optional biopsies that will be used for this study.

Blood Collection:

During the pre-study phase of the trial and throughout the treatment phase of the trial, we will draw differing amounts of blood at each visit. The blood will be collected by inserting a needle in your vein or when possible using an existing port in your vein or at the same time as other blood collection procedures. Neither you nor your health care plan/insurance carrier will be billed for the collection of the blood that will be used for research purposes.

The blood will be used for three distinct purposes including:

1) Safety labs: These are tests that help us monitor any good or bad effects on your body that the study medication might have. These safety labs are similar to the labs we would monitor for patients receiving other types of cancer therapy.
2) Research labs: These samples are required in order for you to take part in this study because the research on your blood is an important part of the study. This blood will help us understand how your body, especially your immune system, is responding to the study medication. The tests done for research purposes are different from the tests done for safety monitoring.
3) Biobanking: Leftover blood will be stored for studies that may be conducted in the future.

The blood collection visits in the table below are listed by Cycle. A Cycle is 3 weeks. The volumes of blood that we will draw at each visit for the purposes mentioned above are outlined in the following table:

Cycle	**Safety Labs**	**Research Labs**
Pre-study	47 ml (about 9½ teaspoons)	
Cycle 1, Day 1, before study drug administration	7 ml (about 1½ teaspoons)	152 ml (about 2/3 cup)
Cycle 1, Day 1, 2 hours after drug administration		20 ml (about 4 teaspoons)
Cycle 1, Day 2		56 ml (about 11 teaspoons)
Cycle 1, Day 8	10 ml (about 2 teaspoons)	54 ml (about 11 teaspoons)
Cycle 2	22 ml (about 4½ teaspoons)	90 ml (about 6 tablespoons)
Cycle 2, Day 1, 2 hours after drug administration		20 ml (about 4 teaspoons)
Cycle 2, Day 2		20 ml (about 4 teaspoons)
Cycle 3	18 ml (about 3 ½ teaspoons)	30 mL (about 2 tablespoons)
Cycle 4	Up to 38 ml (about 7½ teaspoons)	124 mL (about ½ cup plus 1 teaspoon)

Cycle	Safety Labs	Research Labs
Cycle 5, 6	7 ml (about 1½ teaspoons)	
Cycle 7	Up to 38 ml (about 7½ teaspoons)	62 ml (about 12½ teaspoons)
Cycle 8, 9	7 ml (about 1½ teaspoons)	
Cycle 10	Up to 38 ml (about 7½ teaspoons)	
Cycle 11, 12	7 ml (about 1½ teaspoons)	
Cycle 13	Up to 38 ml (about 7½ teaspoons)	62 ml (about 12½ teaspoons)
Cycle 14, 15	7 ml (about 1½ teaspoons)	
Cycle 16	Up to 38 ml (about 7½ teaspoons)	
Cycle 17, 18, 19	7 ml (about 1½ teaspoons)	
Cycle 20	Up to 38 ml (about 7½ teaspoons)	
Cycle 21, 22, 23	7 ml (about 1½ teaspoons)	
Cycle 24	Up to 38 ml (about 7½ teaspoons)	
Cycle 25, 26, 27	7 ml (about 1½ teaspoons)	
Cycle 28	Up to 38 ml (about 7½ teaspoons)	
Cycle 29, 30, 31	7 ml (about 1½ teaspoons)	
Cycle 32	Up to 38 ml (about 1½ teaspoons)	
Cycle 33, 34, 35	7 ml (about 1½ teaspoons)	
At time of Partial Response and/or Complete Response		124 ml (about 1/2 cup plus 1 teaspoon)
End of Treatment	Up to 38 ml (about 7½ teaspoons)	152 ml (about 2/3 cup)
Post-Treatment Follow-Up, at 30 days	Up to 38 ml (about 7½ teaspoons)	60 ml (about 4 tablespoons)

The results of the tests done on your research and biobank samples are for research purposes only. The lab will not give the results to you or this clinic. If you have low red blood counts (anemia), we will draw less blood than is stated in the table.

What possible risks can I expect from taking part in this study?

If you choose to take part in this study, there is a risk that:

- You may lose time at work or home and spend more time in the hospital or doctor's office than usual
- You may be asked sensitive or private questions which you normally do not discuss
- There is a risk someone could get access to the personal information in your medical records or other information researchers have kept about you. Someone might be able to

trace this information back to you. The researchers believe the chance that someone will identify you is very small, but the risk may change in the future as people come up with new ways of tracing information. In some cases, this information could be used to make it harder for you to get or keep a job. There are laws against misuse of genetic information, but they may not give full protection. The researchers believe the chance these things will happen is very small, but cannot promise that they will not occur.

- There can also be a risk in finding out new genetic information about you. New health information about inherited traits that might affect you or your blood relatives could be found during a study.

The study medication may affect how different parts of your body work such as your liver, kidneys, heart, and blood. The study doctor will be testing your blood and will let you know if changes occur that may affect your health. If the study medication causes changes in how your organs work, it is possible that it would be unsafe to administer chemotherapy to you in the future.

There is also a risk that you could have side effects from the study drug(s)/study approach.

Here are important points about side effects:

- The study doctors do not know who will or will not have side effects.
- Some side effects may go away soon, some may last a long time, or some may never go away.
- Some side effects may interfere with your ability to have children.
- Some side effects may be serious and may even result in death.

Here are important points about how you and the study doctor can make side effects less of a problem:

- Tell the study doctor if you notice or feel anything different so they can see if you are having a side effect.
- The study doctor may be able to treat some side effects.
- The study doctor may adjust the study drugs to try to reduce side effects.

The tables below show the most common and the most serious side effects that researchers know about. There might be other side effects that researchers do not yet know about. If important new side effects are found, the study doctor will discuss these with you.

COMMON, SOME MAY BE SERIOUS In 100 people receiving MK-3475 (pembrolizumab), more than 20 and up to 100 may have:
• Tiredness

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving MK-3475 (pembrolizumab), from 4 to 20 may have:
• Nausea • Infection • Loss of appetite • Pain in back • Joint stiffness • Cough • Swelling and redness of the skin MK-3475 (pembrolizumab) may cause your immune system to attack normal organs and cause side effects in many parts of the body. These problems may include but are not limited to: • Anemia which may require blood transfusion • Pain in lymph nodes • Blood clot which may cause bleeding, confusion, paralysis, seizures and blindness • Hormone gland problems (especially the thyroid, pituitary and adrenal glands, and pancreas). Signs and symptoms may include: headaches that will not go away or unusual headaches, extreme tiredness or changes in mood or behavior; decreased sex drive; weight loss or weight gain; excessive thirst or urine; dizziness or fainting • Intestinal problems (colitis) that can rarely lead to tears or holes in your intestine. Signs and symptoms of colitis may include: diarrhea or increase in bowel movements, blood in your stools or dark, tarry, sticky stools, severe belly pain or tenderness • Diarrhea • Sores in the mouth which may cause difficulty swallowing • Pain in belly • Sores in the bowels • Chills, fever • Liver problems (hepatitis) which can cause liver failure. Signs and symptoms of hepatitis may include: yellowing of your skin or the whites of your eyes, severe nausea or vomiting; drowsiness; pain in the right upper belly • Pain or swelling of the joints • Problem of the muscle, including swelling, which can cause muscle pain and severe muscle weakness sometimes with dark urine • Fluid in the joints • Pain in chest • Lung problems (pneumonitis and other conditions). Symptoms may include: new or worsening cough, chest pain, shortness of breath. • Skin: itching; acne; rash (can be severe); blisters and peeling on the skin, mouth; skin changes; hives

RARE, AND SERIOUS In 100 people receiving MK-3475 (pembrolizumab), 3 or fewer may have:
• Feeling of "pins and needles" in arms and legs • Redness, pain or peeling of palms and soles MK-3475 (pembrolizumab) may cause your immune system to attack normal organs and cause side effects in many parts of the body. These problems may include but are not limited to: • Heart problems including swelling and heart failure. Symptoms and signs of heart problems may include: Shortness of breath, swelling of the ankles and body. • Swelling and redness of the eye • Allergic reaction which may cause rash, low blood pressure, wheezing, shortness of breath, swelling of the face or throat • Reaction during or following a drug infusion which may cause fever, chills, rash • Damage to organs in the body when donor cells attack host organs which may cause yellowing of eyes and skin, itchy dry skin • Damage to organs in the body when the body produces too many white cells • A condition with high blood sugar which leads to tiredness, frequent urination, excessive thirst, headache, nausea and vomiting, and can result in a coma • Problem of the nerves that can cause paralysis. Signs and symptoms may include: numbness, tingling of hands and feet; weakness of the arms, legs. • Swelling of the brain (encephalitis/meningitis) which may cause headache, confusion, sleepiness, seizures, and stiff neck • Kidney problems, including nephritis and kidney failure requiring dialysis. Signs of kidney problems may include: decrease in the amount of urine, blood in your urine, ankle swelling. • Swelling or tenderness of blood vessels

Risks of CT and PET scans:

Any scans done while you are on the study will be ordered by your physician as routine or standard-of-care scans. The CT scans that you will receive in this study will expose you to low amounts of radiation. Every day, people are naturally exposed to low levels of radiation that come from the sun and the environment. No one knows for sure whether exposure to low amounts of radiation is harmful for your body. However, scientists believe that being exposed to too much radiation can cause harmful side effects, including causing a new cancer.

Risks of bronchoscopy:

In some patients, bronchoscopy may be needed during tumor evaluations. Bronchoscopy is not typically painful but it may cause throat numbness, cough, a sore throat and fever. The numbing spray may make your mouth feel funny and has an unpleasant taste. Common side effects of the drug administered to sedate you for the procedure include feeling dizzy, faint, lightheaded, tired or out of breath. You will be watched closely throughout the procedure and we will treat any side effects that occur.

Risks of endoscopy:

In some patients, endoscopy may be needed during tumor evaluations. Risks associated with endoscopy include aspiration (choking and/or gagging), sore throat, bleeding, and infection. Major complications occur in a small number of people who have endoscopy. The endoscope could puncture or pierce the intestines. This could require additional treatment or surgery.

Reproductive risks:

You should not become pregnant, breastfeed, or father a baby while in this study because the study medication may affect a developing baby. In addition, you should not become pregnant, breastfeed, or father a baby for 120 days after the last dose of study medication.

It is important that you use 2 methods of birth control from the time you sign this consent form and through 120 days after you stop receiving the study medication. This includes both men and women who participate in the trial. We will talk with you about your birth control choices. Some methods might not be approved for use in this study.

If you are a female and become pregnant, we will stop giving you the study medication. We will follow the outcome of your pregnancy. If you are a man and your female partner becomes pregnant, please tell us. We will ask permission to follow the outcome of the pregnancy.

Risks of blood draws:

The most common risks related to drawing blood from your arm are brief pain and possibly a bruise. There is a very small chance that you could get an infection where we take the blood. You might also feel lightheaded or even faint. You could develop anemia or need a blood transfusion. Please tell the study staff if you are in another study or have a medical procedure where blood is drawn.

Risks of EKG:

When the electrodes are removed from your chest after having the EKG, it may cause discomfort. The feeling is similar to removing a bandage.

Risks of biopsies:

Common side effects of a biopsy are a small amount of bleeding at the time of the procedure, pain at the biopsy site, bruising, swelling, and scarring. Rarely, an infection can occur.

Let your study doctor know of any questions you have about possible side effects. You can ask the study doctor questions about side effects at any time.

What possible benefits can I expect from taking part in this study?

It is unknown whether this study will help you. This study may help us learn things that may help people in the future.
If any of the research leads to new tests, drugs, or other commercial products, you will not share in any profits.

Can I stop taking part in this study?

Yes. You can decide to stop at any time. If you decide to stop for any reason, it is important to let the study doctor know as soon as possible so you can stop safely. If you stop, you can decide whether or not to let the study doctor continue to provide your medical information to the organization running the study.

The study doctor will tell you about new information or changes in the study that may affect your health or your willingness to continue in the study.
The study doctor may take you out of the study:

- If your health changes and the study is no longer in your best interest
- If new information becomes available
- If you do not follow the study rules
- If the study is stopped by the sponsor, IRB or FDA.

What are my rights in this study?

Taking part in this study is your choice. No matter what decision you make, and even if your decision changes, there will be no penalty to you. You will not lose medical care or any legal rights.

For questions about your rights while in this study, call the _____ *(insert name of center)* Institutional Review Board at _____ *(insert telephone number).*

What are the costs of taking part in this study?

The study medication will be supplied at no charge while you take part in this study. The cost of getting the study medication ready and giving it to you is not paid by the study sponsor so you or your insurance company may have to pay for this. It is possible that the study medication may not continue to be supplied while you are on the study. Although not likely, if this occurs, your study doctor will talk to you about your options.

The study will not pay for your cART, so you or your insurance company will have to pay for this.

You and/or your health plan/insurance company will need to pay for all of the other costs of treating your cancer while in this study, including the cost of tests, procedures, or medicines to manage any side effects, unless you are told that certain tests are supplied at no charge. Before you decide to be in the study, you should check with your health plan or insurance company to find out exactly what they will pay for.

You will not be paid for taking part in this study.

What happens if I am injured or hurt because I took part in this study?

If you feel you have been injured or hurt as a result of taking part in the study, it is important that you tell the study doctor. You will get medical treatment if you are injured or hurt as a result of taking part in this study.

The study sponsors will not offer to pay for medical treatment for injury. Your insurance company may not be willing to pay for study-related injury. If you have no insurance coverage, you would be responsible for any costs. Even though you are in a study, you keep all of your legal rights to receive payment for injury caused by medical errors.

Who will see my medical information?

Your privacy is very important to us and the researchers will make every effort to protect it. Your information may be given out if required by law. For example, certain states require doctors to report to health boards if they find a disease like tuberculosis. However, the researchers will do their best to make sure that any information that is released will not identify you. Some of your health information, and/or information about your specimen, from this study will be kept in a central database for research. Your name or contact information will not be put in the database.

There are organizations that may inspect your records. These organizations are required to make sure your information is kept private, unless required by law to provide information. Some of these organizations are:

- The Cancer Immunotherapy Trials Network (CITN) and the people who work for it;
- The Fred Hutchinson Cancer Research Center (FHCRC) and the people who work for it;
- The study sponsor, the National Cancer Institute (NCI), and the people who work for it;
- The drug company supporting the study;
- The Institutional Review Board (IRB), which is a group of people who review the research with the goal of protecting the people who take part in the study;
- Safety monitoring committees;
- The U.S. Food and Drug Administration (FDA), the U.S. National Cancer Institute (NCI), the U.S. Office for Human Research Protections (OHRP), and other government agencies that oversee research.

To help us protect your privacy, we have obtained a Certificate of Confidentiality from the National Institutes of Health. The researchers can use this Certificate to legally refuse to disclose information that may identify you in any federal, state, or local civil, criminal, administrative, legislative, or other proceedings, for example, if there is a court subpoena. The researchers will use the Certificate to resist any demands for information that would identify you, except as explained below.

The Certificate cannot be used to resist a demand for information from personnel of the U.S. government that is used for auditing or evaluation of federally funded projects or for information that must be disclosed in order to meet the requirements of the Food and Drug Administration (FDA).

How is My Genetic Information Protected?

A federal law called the Genetic Information Nondiscrimination Act (GINA) helps protect your genetic information. GINA restricts access to your genetic information so that it cannot be used for health insurance coverage decisions. GINA won't allow health insurance companies or group health plans to:

- Ask for your genetic information you have provided in research studies; or
- Use your genetic information when making decisions regarding your eligibility or premiums.

GINA does not help or protect you against genetic discrimination by companies that sell life, disability, or long-term care insurance.

Where can I get more information?

You may visit the NCI Web site at http://cancer.gov/ for more information about studies or [redacted]

A description of this clinical trial will be available on http://www.ClinicalTrials.gov , as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

Who can answer my questions about this study?

You can talk to the study doctor about any questions or concerns you have about this study or to report side effects or injuries. Contact the study doctor _____ *(insert name of study doctor[s])* at _____ *(insert telephone number).*

ADDITIONAL STUDIES SECTION:

This section is about optional studies you can choose to take part in.

PERMISSION FOR OPTIONAL TISSUE SAMPLE COLLECTION AND USE

Earlier in this consent form, we told you about the optional collection of a additional biopsies of your tumor. Please circle your answer to show whether you do or do not agree.

I agree to the optional biospsy of my tumor if my disease progresses.

YES NO

For patients with Kaposi sarcoma: I agree to the optional biospsy of my tumor if the tumors on my skin appear to have responded to treatment, but there are still remaining areas that are darker than the surrounding skin.

YES NO

PERMISSION FOR OPTIONAL SAMPLE STORAGE

What is involved?

We are asking for your permission to store and use your samples and related health information (for example, your response to cancer treatment, results of study tests, and medicines you are given) in a biobank for medical research. The research that may be done is unknown at this time. The biobank is run by the Cancer Immunotherapy Trials Network (CITN) and supported by the National Cancer Institute (NCI).

Your samples and some related information may be stored in the biobank. The samples will be kept until they are used up. Qualified researchers can submit a request to use the materials stored in the biobank. A science committee at the clinical trials organization, and/or the National Cancer Institute, will review each request. There will also be an ethics committee review to ensure that the request is necessary and proper. Researchers will not be given your name or any other information that could directly identify you. Neither you nor your study doctor will be notified when research will be conducted or given reports or other information about any research that is done using your samples.

Some of your genetic and health information may be placed in central databases that may be public, along with information from many other people. Information that could directly identify you will not be included.

What are the possible risks?

There is a risk that someone could get access to the personal information in your medical records or other information researchers have stored about you.

There is a risk that someone could trace the information in a central database back to you. Even without your name or other identifiers, your genetic information is unique to you. The researchers believe the chance that someone will identify you is very small, but the risk may change in the future as people come up with new ways of tracing information.

In some cases, this information could be used to make it harder for you to get or keep a job or insurance. There are laws against the misuse of genetic information, but they may not give full protection. There can also be a risk in knowing genetic information. New health information about inherited traits that might affect you or your blood relatives could be found during a study.

The researchers believe the chance these things will happen is very small, but cannot promise that they will not occur.

How will information about me be kept private?

Your privacy is very important to the researchers and they will make every effort to protect it. Here are just a few of the steps they will take:

- When your samples are sent to the researchers, no information identifying you (such as your name) will be sent. Samples will be identified by a unique code only.
- The list that links the unique code to your name will be kept separate from your sample and health information. Any Bio-bank staff with access to the list must sign an agreement to keep your identity confidential.
- Researchers to whom CITN sends your sample and information will not know who you are. They must also sign an agreement that they will not try to find out who you are.
- Information that identifies you will not be given to anyone, unless required by law.
- If research results are published, your name and other personal information will not be used.

What are the possible benefits?

You will not benefit from taking part. The researchers, using the samples from you and others, might make discoveries that could help people in the future.

Are there any costs or payments?

There are no costs to you or your insurance. You will not be paid for taking part. If any of the research leads to new tests, drugs, or other commercial products, you will not share in any profits.

What if I have more questions?

If you have questions about the use of your samples for research, contact the study doctor, _____, *(insert name of study doctor for main trial)*, at _____ *(insert telephone number of study doctor for main trial)*.

Earlier in this consent form, we told you about the optional storage of leftover blood and leftover tissue samples for storage in a biobank. Please circle your answer to show whether you do or do not agree to each option.

I agree that my leftover blood samples and related information may be kept in a Biobank for use in future research.

YES NO

I agree that my leftover tissue samples and related information may be kept in a Biobank for use in future health research.

YES NO

MY SIGNATURE AGREEING TO TAKE PART IN THE MAIN STUDY

I have read this consent form or had it read to me. I have discussed it with the study doctor and my questions have been answered. I will be given a signed copy of this form. I agree to take part in the study.

Participant's name (print)	**Participant's signature**	**Date** (dd-MMM-yyyy)

[If the protocol permits the inclusion of participants who require a witness to facilitate consent, include the following signature block]

Witness's name (print)	**Witness's signature**	**Date** (dd-MMM-yyyy)

STUDY STAFF SIGNATURE

Study staff conducting consent discussion (print)	**Study staff signature**	**Date** (dd-MMM-yyyy)