SUMMARY OF CHANGES

For Protocol Amendment #6, v1.0

NCI Protocol #: CITN-13, A6_v1.0
Local Protocol #: CITN-13, A6_v1.0

Protocol Date: March 3, 2020

I. CTEP Request for Rapid Amendment:

#	Section	Pages	Comments
1.	7.1.1	73-81	Insertion of Revised CAEPR (Version 2.5, December 27, 2019) per CTEP Request for Rapid Amendment dated February 14, 2020. The following changes are incorporated: • Added New Risk: Rare but Serious: Eye disorders - Other (Vogt-Koyanagi-Harada syndrome); Nervous system disorders - Other (non-infectious myelitis)
2.	8.1.1	91	Removed "Allow the required number of vials to equilibrate to room temperature" since it is no longer required by the pharmaceutical collaborator.
3.	8.1.1	92	Revised stability information to read: "Administer prepared solutions immediately after preparation. If not administered immediately, prepared solutions may be stored refrigerated for up to 24 hours. MK-3475 solutions may be stored at room temperature for a cumulative time of up to 6 hours."

II. Administrative Changes

#	Section	Pages	Comments
4.	All sections	All pages	Revised protocol version and date throughout the protocol

NCI Protocol #: CITN-13

Local Protocol #: CITN-13

ClinicalTrials.gov Identifier: NCT03063632

TITLE: A Phase II Trial of MK-3475 (pembrolizumab) and Interferon Gamma 1-b Combination Immunotherapy in Patients with Previously Treated Mycosis Fungoides and Sézary Syndrome (Treatment Group 1) and in Patients with Advanced Synovial Sarcoma (Treatment Group 2)

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NCI-Supplied Agent: MK-3475 (pembrolizumab) (NSC 776864)

NCI-Supplied Agent: Interferon Gamma-1b, Horizon Pharmaceuticals (NSC 600662)

Protocol Type/Version #/Version Date: Amendment 6/Version 1.0/ March 3, 2020

IND #:

IND Sponsor: DCTD, NCI

<table>
<tr><th colspan="3">CONTACT INFORMATION</th></tr>
<tr><th>For regulatory requirements:</th><th>For patient enrollments:</th><th>For study data submission:</th></tr>
<tr><td>Regulatory documentation must be submitted to the CTSU via the Regulatory Submission Portal.

(Sign in at www.ctsu.org, and select the Regulatory > Regulatory Submission..)

Institutions with patients waiting that are unable to use the Portal should alert the CTSU Regulatory Office immediately at 1-866-651-2878 to receive further instruction and support.

Contact the CTSU Regulatory Help Desk at 1-866-651-2878 for regulatory assistance.</td><td>Refer to the patient enrollment section of the protocol for instructions on using the Oncology Patient Enrollment Network (OPEN). OPEN can be accessed at https://www.ctsu.org/OPEN_SYSTEM/ or https://OPEN.ctsu.org.

Contact the CTSU Help Desk with any OPEN-related questions at ctsucontact@westat.com.</td><td>Data collection for this study will be done exclusively through Medidata Rave. Refer to the data submission section of the protocol for further instructions.</td></tr>
<tr><td colspan="3">The most current version of the study protocol and all supporting documents must be downloaded from the protocol-specific page located on the CTSU members' website (https://www.ctsu.org). Access to the CTSU members' website is managed through the Cancer Therapy and Evaluation Program - Identity and Access Management (CTEP-IAM) registration system and requires log on with CTEP-IAM username and password. Permission to view and download this protocol and its supporting documents is restricted and is based on person and site roster assignment housed in the CTSU Regulatory Support System (RSS).</td></tr>
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Contact the CITN Central Operations and Statistical Center at citn@fhcrc.org or 206-667-7607</td></tr>
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SCHEMA

Title	A Phase II Trial of MK-3475 (pembrolizumab) and Interferon Gamma 1-b Combination Immunotherapy in Patients with Previously Treated Mycosis Fungoides and Sézary Syndrome (Treatment Group 1) and in patients with Advanced Synovial Sarcoma (Treatment Group 2)
Trial Phase	Phase II
Clinical Indication	**Treatment Group 1:** Stage IB-IVB Mycosis Fungoides/Sézary Syndrome, and who have relapsed, are refractory, or progressed after at least one standard systemic therapy **Treatment Group 2:** Translocation associated sarcoma that generally expresses NY-ESO-1 (e.g. Synovial Sarcoma or Myxoid/Round Cell Liposarcoma). Patient must have metastatic or unresectable disease.
Trial Type	Nonrandomized, open-label, phase II, interventional study
Type of control	None
Route of administration	Intravenous (IV) for MK-3475 (pembrolizumab), Subcutaneous for Interferon-Gamma
Trial Blinding	None
Treatment Groups	**Treatment Group 1:** **Patients with Mycosis Fungoides and Sézary Syndrome:** MK-3475 (pembrolizumab), 200 mg every 3 weeks in combination with Interferon Gamma-1b (ACTIMMUNE®), 50 mcg/m^2 three times per week. **Treatment Group 2:** **Patients with advanced synovial sarcoma:** MK-3475 (pembrolizumab), 200 mg every 3 weeks [2 mg/kg (max= 200 mg) in patients under 18 years of age] in combination with Interferon Gamma-1b (ACTIMMUNE®), 100 mcg/m^2 once per week.
Number of trial subjects	**Treatment Group 1**: Mycosis Fungoides and Sézary Syndrome (n=30) **Treatment Group 2**: Synovial Sarcoma (n=16)
Estimated duration of trial	3 years
Duration of Participation	Patients may receive study directed therapy for up to 2 years if they continue to respond.

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1. OBJECTIVES

1.1 Primary Objectives

Treatment Group 1

1.1.1 To assess the overall response rate (ORR) of MK-3475 (pembrolizumab) and IFN-gamma (Actimmune®) combination immunotherapy in subjects with previously treated Mycosis Fungoides or Sézary Syndrome.

In this single stage phase II open label trial, we will have an interim futility analysis. When 12 patients have been followed for 6 months, we will perform the interim futility analysis. If ORR is less than 33% (4 or less CR+PR), the trial will stop and we will accept the null that combination therapy is no better than monotherapy. Otherwise, trial will continue until 30 patients accrue. If ORR is at least 57% (17 or more CR+PR) at the final analysis, we will accept the alternative that combination therapy is significantly better than monotherapy.

Hypothesis: Administration of MK-3475 (pembrolizumab) and IFN-gamma (Actimmune®) as a combination immunotherapy regimen to subjects with previously treated Mycosis Fungoides or Sézary Syndrome will result in a clinically meaningful ORR that is an improvement over the ORR of MK-3475 (pembrolizumab) or IFN-gamma as monotherapy.

Treatment Group 2

1.1.2 To determine whether the combination of interferon gamma-1b (ACTIMMUNE®) and MK-3475 (pembrolizumab) improves the ORR of pembrolizumab in patients with unresectable or metastatic synovial sarcoma.

The ORR of single agent pembrolizumab is ≤ 5%. Accordingly, a Simon 2-stage design will be used: Twelve patients will be enrolled initially. If 0 respond the study will be stopped for futility. Otherwise, an additional four patients will be enrolled. If three or more out of 16 patients respond, the treatment will be considered promising and would likely lead to widespread use of this regimen in the clinic.

Hypothesis: The combination of interferon gamma-1b and MK-3475 (pembrolizumab) will lead to an ORR of ≥25% in patients with metastatic or unresectable synovial sarcoma. The ORR is defined by the complete response rate (CR) plus the partial response rate (PR) by RECIST 1.1.

1.2 Secondary Objectives

Treatment Group 1

1.2.1 To explore the safety/tolerability and clinical activity of MK-3475 (pembrolizumab) and IFN-G (Actimmune®) in subjects with previously treated Mycosis Fungoides or Sézary Syndrome with respect to the following secondary endpoints:

1.2.1.1 Safety and tolerability (interim safety review based on distinct patient SAE's following the first 3 doses of pembrolizumab (10 weeks of therapy) that are attributable to study drugs; We will allow 10% or less of patients to develop study drug related SAEs. If 4 or more patients amongst the first 12 evaluable patients for toxicity at pre-C4 (week 10) have experienced study drug related serious adverse events (SAEs), we will conclude that the combination immunotherapy regimen is too toxic and accrual will stop. If accrual is not stopped for either interim futility or safety reasons, a final safety evaluation will be conducted based on the percentage of the 30 patients who have experienced SAEs. We will consider the safety profile being acceptable if less than 6 patients have experienced study drug related SAEs. Otherwise, we will evaluate the tradeoff between safety and efficacy benefits based on the magnitude of ORR improvements.

1.2.1.2 Time to response (TTR)

1.2.1.3 Duration of response (DOR): Defined as the time interval between the date of first response (CR/PR) and the date of progression

1.2.1.4 Progression-free survival (PFS): Defined as the time from enrollment to PD or death, whichever occurs earlier, based upon investigator assessment. Patients without documented PD/death will be censored at the last disease assessment date.

1.2.1.5 Event-free survival (EFS events defined as termination due to toxicity, initiation of next significant treatment, progressive disease, or death of any cause).

1.2.1.6 Percentage of all patients who have a response duration of at least 12 months (ORR12)

Hypothesis: Combination immunotherapy of MK-3475 (pembrolizumab) and IFN-gamma (Actimmune®) will have acceptable safety/tolerability profile in previously treated Mycosis Fungoides/Sézary Syndrome population and meaningful clinical activity will be reflected in other clinical outcome parameters including DOR, PFS, EFS and ORR12.

Treatment Group 2

1.2.2 To determine the progression-free survival (PFS) and overall survival (OS) for patients with advanced synovial sarcoma receiving interferon gamma-1b and MK-3475 (pembrolizumab).

1.2.3 To determine the tolerability of the combination of interferon gamma-1b and MK-3475 (pembrolizumab) based on CTCAE version 5.0

Hypotheses: The combination of interferon gamma-1b and pembrolizumab will lead to superior PFS and OS. Both RECIST v. 1.1 and the immune related response criterion will be used for this endpoint.

The combination of interferon gamma-1b and MK-3475 (pembrolizumab) will be well tolerated in patients with advanced synovial sarcoma.

1.3 Exploratory Objectives

Treatment Group 1

1.3.1 To investigate the relationship between the following putative biomarkers for combination immunotherapy of MK-3475 (pembrolizumab) and IFN-gamma (Actimmune®) and clinical outcomes (as measured by safety/tolerability and ORR, DOR, PFS, EFS) in subjects with previously treated Mycosis Fungoides/Sézary Syndrome, including tumor/microenvironment (PD-1/PD-L1/PD-L2 expression, CTLs, Tregs, macrophages, DCs; nanostring gene expression profile), systemic immune response (flow cytometry, CyTOF, Luminex multiplexed cytokine profile), and molecular/genomic immune correlates (exome sequencing, high throughput sequencing (HTS) for TCR)

Hypothesis: The putative biomarkers and immune regulators tested will be related to clinical response induced by combination immunotherapy of MK-3475 (pembrolizumab) and IFN-gamma (Actimmune®) and will help define actionable causes of not achieving CR.

Treatment Group 2

1.3.2 To investigate paired, serial biopsy specimens from pre-treatment and 8-12 weeks after starting treatment for the following:

- MHC class I expression (scored by pathologist)
- Number of infiltrating T cells per mm^2
- Tumor associated macrophage number and phenotype using multiplex immunohistochemistry
- T cell clonality
- Gene expression profiling

To investigate peripheral blood samples from patients to determine:

- The number and phenotype of T cells specific for CT antigens and potential neo-antigens
- The phenotype and activation state of circulating monocytes and PBMC
- Cytokines associated with response

Hypotheses:

The combination of interferon gamma-1b and MK-3475 (pembrolizumab) will lead to increased MHC expression and T cell infiltration on paired, serial tumor biopsies.

The combination of interferon gamma-1b and MK-3475 (pembrolizumab) will lead to increased antigen-specific T cells and T cell responses targeting NY-ESO-1, PRAME and MAGE-A4 and a potential neo-antigen, the SSX-SYT fusion protein, in the peripheral blood of synovial sarcoma patients.

The combination of interferon gamma-1b and MK-3475 (pembrolizumab) will lead to increased MHC expression on peripheral monocytes and increased activation of effector T cells.

2. BACKGROUND

2.1 Relapsed/Refractory Mycosis Fungoides/Sézary Syndrome (Treatment Group 1)

Mycosis fungoides/Sézary syndrome is the most common type of cutaneous T-cell lymphoma (CTCL), a subset of mature non-Hodgkin lymphoma. Mycosis Fungoides exhibits an epidermotropic clonal expansion of CD4+ T helper cells that induces pleomorphic skin lesions. Mycosis Fungoides may present gradually over many years as an indolent, chronic skin disease or present with more rapidly advancing skin disease, especially in those with worse prognostic factors such as folliculotropism or large cell transformation. Sézary syndrome is a leukemic variant of CTCL in which subjects have generalized erythroderma and are at risk for lymph node and visceral disease. Mycosis Fungoides /Sézary Syndrome comprise the most common cutaneous T-cell lymphomas, with continued increase in overall annual incidence (currently approximately 0.9 per 100,000 persons in the United States). There is a 2:1 male to female prevalence and peak age of presentation is 55 to 60 years. It is rarely seen in the pediatric age group (*i.e.,* diagnosis at age < 18 years of age) [Horwitz 2008].

Therapeutic options for Mycosis Fungoides and Sézary Syndrome are primarily determined by the patient's clinical stage. The National Comprehensive Cancer Network [NCCN 2016] has recently published consensus guidelines for stage-based treatment of Mycosis Fungoides /Sézary Syndrome. The first line treatment of early stage Mycosis Fungoides (IA, IB, and IIA) are skin-directed therapies including phototherapy, topical medications (corticosteroids, chemotherapeutic agents, and retinoids), and radiation therapy.

At more advanced stages (*i.e.,* IIB and higher), systemic therapies are often utilized. These include bexarotene, low-dose methotrexate, interferons (alpha and gamma), extracorporeal

photopheresis, total skin electron beam therapy, HDAC inhibitors (vorinostat, romidepsin), brentuximab vedotin, cytotoxic chemotherapeutic agents (pralatrexate, liposomal doxorubicin, gemcitabine), and investigational agents. Only 4 systemic agents (bexarotene, denileukin diftitox, vorinostat, romidepsin) are FDA approved, thus most are used off-label without prospective trial data. Despite a wide array of available therapeutic options, subjects with Mycosis Fungoides and Sézary Syndrome remain incurable other than a subset of patients who receive allogeneic HSC transplantation. Response rates for FDA-approved systemic agents are 30-35% with infrequent complete responses; these clinical responses are often short-lived with most approved agents yielding median duration of responses in the range of 6 months [Duvic 2001];[Olsen 2001];[Olsen 2007] with the exception of romidepsin with a median near 12 months [Whittaker 2010].

It has been understood that immune impairment or dysregulation is a key contributor towards the clinical and pathologic characteristics in patients with Mycosis Fungoides or Sézary Syndrome [Kim 2005]; [Spaccarelli 2015]. The malignant T cells in Mycosis Fungoides/Sézary Syndromeare typically mature homing or resident memory CD4+ T cells which mostly exhibit a Th2 phenotype with secretion of IL-4, IL-5, and IL-10 cytokines. This increased Th2 activity is thought to provide/induce suppression of Th1-mediated immune activity. There is evidence of decreased production of IFN-G, IL-12, and IFN-Alpha in patients with Mycosis Fungoides/Sézary Syndrome and attempts to correct this suppressed state with cytokine or other immune therapies have resulted in meaningful clinical responses. The decreased Th1 activity may also partly account for the underlying impaired function and decreased numbers of dendritic cells observed in Mycosis Fungoides/Sézary Syndrome. There are also reports of decreased number and/or function of NK cells and possible immune suppressive roles of regulatory T cells in the tissue microenvironment.

Furthermore, there has been mounting evidence that T cell immunity may be pertinent for clinical anti-tumor activity in Mycosis Fungoides/Sézary Syndrome:

2.1.1 Tumor-infiltrating T cells are prognostic of survival.

CD8+ Cytotoxic T Lymphocytes (CTLs) are present in Mycosis Fungoides lesions and high proportion of these cells correlated with an improved prognosis [Hoppe 1995]; [Vermeer 2001].

2.1.2 Therapies which augment T cell function are effective in Mycosis Fungoides/Sézary Syndrome.

Interferon alpha has been shown in a number of studies to be a highly active agent in CTCL with overall response rate (ORR) ranging from 40% to 50% with concurrent improvement in T cell cytotoxicity.

Interferon gamma has been used as a monotherapy in 16 patients with refractory disease, with an ORR of 30% and duration of response (DOR) of 10 months and concurrent augmented T cell activity [Kaplan 1990].

IL-12 has also demonstrated activity in relapsed CTCL. In phase I and II studies, nearly half of the 32 evaluable patients achieved a response [Rook 1999]; [Duvic 2006].

In a phase 1 study of 28 patients with recurrent or advanced CTCL who received CPG7909 (TLR9 agonist), in weekly subcutaneous doses for 24 weeks, the ORR was 25% [Kim 2004]. Five patients (18%) achieved PRs and 2 (7%) achieved CRs. Moreover, Kim utilized an in-situ vaccination method in which this CPG7909 was combined with local radiation therapy, which demonstrated meaningful clinical responses in distant lesions [Kim 2012] validating the potential of anti-tumor T cell responses.

Allogeneic HSC transplantation is superior to autologous transplantation with superior progression-free survival [Wu 2009]. Long-term, if not curative, clinical responses are demonstrated in patients with advanced, high-risk Mycosis Fungoides/Sézary Syndrome, in support of effective graft versus lymphoma T cell response.

2.1.3 PD-1 and PD-L1 expression in lesional tissue and peripheral blood tumor cells in Mycosis Fungoides/Sézary Syndrome, which may serve to create an immune-suppressive microenvironment, evade immune surveillance, and inhibit anti-tumor T cell activity [Samimi 2010]; [Kantekure 2012].

2.1.4 Genomic evidence of immune escape in Mycosis Fungoides/Sézary Syndrome. Reports of 9p24.1/PD-L2 translocation, breakpoints in PD-L1 (CD274), recurrent Single Nucleotide Variant (SNV) in CD28, or CTLA4-CD28 fusion in Mycosis Fungoides/Sézary Syndrome support a potential genomic basis for immune evasion [Lesokhin 2014]; [Ungewickell 2015]; [Choi 2015].

2.2 Synovial Sarcoma (Treatment Group 2)

Synovial sarcoma is a rare, translocation-driven, soft-tissue sarcoma (STS) subtype affecting approximately 800 Americans annually, most commonly young adults (typically about 20-30 years of age), but also children and adolescents. These cancers often initially present with localized, curable disease but for about 50% of patients, the median survival is approximately 16 months [Constantinidou 2013]; [Ladanyi 2002]; [Sultan 2009]; [Kampe 1993]. Synovial sarcoma should be an ideal target disease for immunotherapy as these tumors typically have high expression level of a number of highly-immunogenic, cancer-testis (CT) antigens including NY-ESO-1, MAGE-A4 and PRAME (**Fig. 1**) [Sultan 2009]. Unlike other cancers that most often have sporadic heterogeneous expression of CT antigens, in synovial sarcoma tumors NY-ESO-1 is expressed in >80% of patients and generally with very strong, homogenous expression throughout the tumor (**Fig. 2**). Despite strong expression of these highly immunogenic proteins, synovial sarcoma has not responded well to anti-programmed death-1 (anti-PD-1)/ anti-programmed death-ligand 1 (anti-PD-L1) targeted therapies. In the SARC28 study, only one of 10 synovial sarcoma patients had a partial response, and no PRs were seen on the Alliance trial using nivolumab [Tawbi 2016]; [D'Angelo 2015]. A randomized vaccine trial recently presented at the 2017 ESMO treated 43 patients with single agent atezolizumab and none had a PR [Chawla 2017].

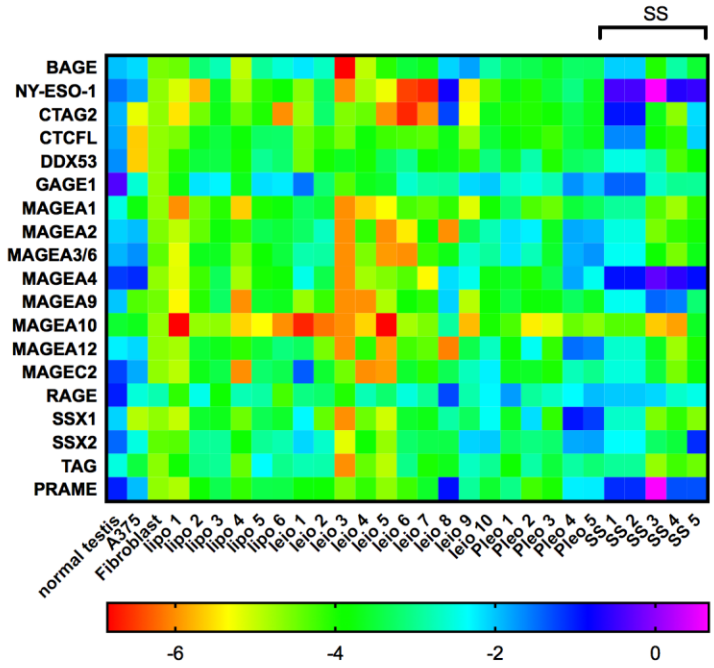


Fig. 1: Heat map illustrating results from a custom made qPCR array testing for levels of gene expression of 19 Cancer-Testis Antigens. RNA was extracted from frozen, banked well/de-differentiated liposarcomas (MRCL not shown), leiomyosarcomas, undifferentiated pleomorphic sarcomas and synovial sarcoma tumors. Synovial sarcoma tumors had strong expression of NY-ESO-1, MAGE-A4 and PRAME.

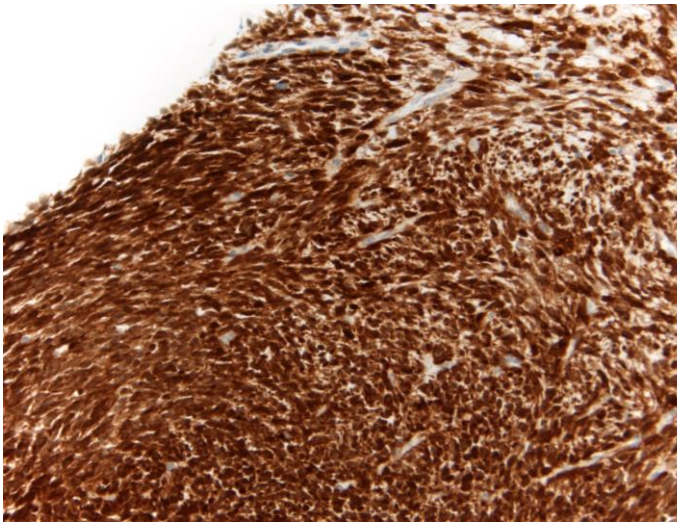


Fig. 2: Immunohistochemistry testing for NY-ESO-1 expression in a synovial sarcoma patient treated at the Seattle Cancer Care Alliance. This staining illustrates the classic homogenous staining pattern

2.3 CTEP IND Agent(s)

2.3.1 *MK-3475 (pembrolizumab)*

MK-3475 (pembrolizumab) has high affinity and potent receptor-blocking activity for the programmed cell death 1 (PD-1) receptor, based on preclinical in vitro data (Investigator's Brochure, 2016). MK-3475 (pembrolizumab) has an acceptable preclinical safety profile and is being advanced for clinical development as an intravenous (IV) immunotherapy for advanced malignancies.

The importance of intact immune surveillance function in controlling outgrowth of neoplastic transformations has been known for decades [Disis 2010]. Accumulating evidence shows a correlation between tumor-infiltrating lymphocytes in cancer tissue and favorable prognosis in various malignancies. In particular, the presence of CD8+ T-cells and the ratio of CD8+ effector T-cells/FoxP3+ regulatory T-cells (T-regs) correlates with improved prognosis and long-term survival in solid malignancies, such as ovarian, colorectal, and pancreatic cancer; hepatocellular carcinoma; malignant melanoma; and renal cell carcinoma. Tumor-infiltrating lymphocytes can be expanded ex vivo and re-infused, inducing durable objective tumor responses in cancers such as melanoma [Dudley 2005]; [Hunder 2008].

The PD-1 receptor-ligand interaction is a major pathway hijacked by tumors to suppress immune control. The normal function of PD-1, expressed on the cell surface of activated T-cells under healthy conditions, is to down-modulate unwanted or excessive immune responses, including autoimmune reactions. PD-1 (encoded by the gene Pdcd1) is an Ig superfamily member related to cluster of differentiation 28 (CD28) and cytotoxic T lymphocyte-associated protein 4 (CTLA-4) that has been shown to negatively regulate antigen receptor signaling upon engagement of its ligands (programmed cell death ligand 1 [PD-L1] and/or programmed cell death ligand 2 [PD-L2]) [Greenwald 2005]; [Okazaki 2001].

The structure of murine PD-1 has been resolved [Zhang 2004]. PD-1 and family members are type I transmembrane glycoproteins containing an Ig Variable–type (IgV type) domain responsible for ligand binding and a cytoplasmic tail 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, and an immunoreceptor tyrosine-based switch motif. Following T-cell stimulation, PD-1 recruits the tyrosine phosphatases, SHP 1 and SHP-2, to the immunoreceptor tyrosine-based switch motif within its cytoplasmic tail, leading to the dephosphorylation of effector molecules such as CD3 zeta (CD3ζ), protein kinase C-theta (PKCθ), and zeta-chain-associated protein kinase (ZAP70), which are involved in the CD3 T-cell signaling cascade [Chemnitz 2004]; [Sheppard 2004]; [Riley 2009]. The mechanism by which PD-1 down modulates T-cell responses is similar to, but distinct from, that of CTLA-4, because both molecules regulate an overlapping set of signaling proteins [Parry 2005]; [Francisco 2010]. As a consequence, the PD-1/PD-L1 pathway is an attractive target for therapeutic intervention in Mycosis Fungoides/Sézary Syndrome.

2.3.2 *MK-3475 (pembrolizumab) Background and Clinical Trials*

MK-3475 (pembrolizumab, Keytruda®), a humanized monoclonal antibody against the PD-1 protein, has been developed by Merck & Co. for the treatment of cancer. MK-3475 (pembrolizumab) is approved for treatment of melanoma in several countries; in the United States (US) and European Union it is approved for the treatment of advanced (unresectable or metastatic) melanoma in adults. MK-3475 (pembrolizumab) has also been approved for treatment of NSCLC in several countries; in the US it is indicated for the treatment of patients with metastatic NSCLC whose tumors express PD-L1 as determined by a Food and Drug Administration (FDA)-approved test and who have disease progression on or after platinum-containing chemotherapy. Patients with NSCLC and epidermal growth factor receptor (EGFR) or anaplastic lymphoma kinase (ALK) genomic tumor aberrations should also have disease progression on FDA-approved therapy for these aberrations before receiving MK-3475 (pembrolizumab). MK-3475 (pembrolizumab) is approved in the US for the treatment of patients with recurrent or metastatic head and neck squamous cell carcinoma (HNSCC) with disease progression on or after platinum-containing chemotherapy.

MK-3475 (pembrolizumab) has demonstrated initial clinical efficacy in single-arm monotherapy trials in patients with NSCLC, HNSCC, urothelial cancer, gastric cancer, triple negative breast cancer, and Hodgkin's Lymphoma as determined by response rate. Ongoing clinical trials are being conducted in these tumor types as well as a number of other advanced solid tumor indications and hematologic malignancies. For study details please refer to the [Investigator's Brochure 2016].

2.3.3 *Interferon-Gamma-1b (Actimmune)*

In order to address the putative Th1 vs Th2 imbalance in Mycosis Fungoides/Sézary Syndrome, various cytokines have been used to reverse the host's immune profile including the interferons and interleukins. Treatment with interferons has long been part of standard of care in patients with Mycosis Fungoides or Sézary Syndrome and is listed as an off-label treatment option in the NCCN Practice Guidelines [NCCN 2016]. Subcutaneously administered IFN-alpha or IFN-gamma can be used alone or in combination with skin-directed or systemic therapies to augment anti-tumor clinical response and to improve overall clinical outcome [Bunn 1986] [Kaplan 1990]; [Raphael 2011]; [Spaccarelli 2015].

However, interferon type cytokine therapy has been limited by short-lived responses or undesirable toxicities when doses are increased to improve clinical responses. Thus the key role for interferons in the treatment landscape in Mycosis Fungoides/Sézary Syndrome (CTCL) has been to find rational partnering agents for potential synergistic activity to yield a more meaningful clinical outcome and address the unmet need of therapies with more reliable and durable responses in Mycosis Fungoides/Sézary Syndrome.

Of the two interferons used in treatment of patients with Mycosis Fungoides/Sézary Syndrome, IFN-gamma has been less commonly used than IFN-alpha. The initial greater

availability of IFN-alpha led to greater use followed by more experience and publications with IFN-alpha. Although there were no rigorously planned/conducted prospective trials with IFN-alpha monotherapy, given reports of efficacy in patient series, IFN-alpha has been widely accepted as useful in all clinical stages of Mycosis Fungiodes and Sézary Syndrome. IFN-alpha has been shown to activate CD8+ T cells and NK cells and to reduce the production of suppressive cytokines, IL-4 and IL-5. However, its common toxicities including fatigue, asthenia, flu-like symptoms, and mood changes/depression can be a deterrent for chronic use.

The only commercially available source of IFN-gamma is IFN-gamma-1b (Actimmune®), a recombinant form of IFN-gamma approved by the FDA for the treatment of chronic granulomatous disease and osteopetrosis. Although there has been less clinical use of IFN-gamma, it has a potential for much broader and potent immune activation than IFN-alpha, with influence in both the innate and adaptive immunity. Endogenous IFN-gamma secreted during immune responses is central to effective T cell responses and is used as a surrogate or pharmacodynamic marker of successful immune activation in pre-clinical and clinical studies of cancer immune therapies. More specifically, IFN-gamma can stimulate dendritic cells (DCs) and macrophages to upregulate their MHC molecules leading to enhanced antigen presentation, activation of cytotoxic T cells (CTLs)/NK cells, and increasing expression of costimulatory molecules [McGinnis 2005]; [Spaccarelli 2015]. These features highlight advantages of using IFN-gamma over IFN-alpha. IFN-gamma is considered essential for the Th1 immune response, and IFN-gamma treatment in patients with Mycosis Fungoides/Sézary Syndrome has shown normalization of the Th2 skewing and activation of CTLs [Seo 1998]; [Hino 2005]. The adverse effects of IFN-gamma are similar to those of IFN-alpha, including the flu-like symptoms, fatigue, dose-dependent cytopenias, and potential for aggravating autoimmune phenomena. However, the severity of these adverse effects appear to be less with IFN-gamma and with less concern for impairment of the cognitive function or mood changes than with IFN-alpha.

In summary, IFN-gamma is likely better tolerated at the active dose ranges than IFN-alpha, and capable of broader range of immune activity spanning from priming of DCs, augment APC function, enhancement of cytotoxicity mediated by CD8+ T cells and NK cells, reduced Th2 immune activity, increased Th1 immune activity, inhibition of regulatory T cells, and inhibition of tumor cell proliferation, which collectively constitute a great profile as cancer immunotherapy. Central to the current proposed protocol, the efficacy of IFN-gamma in driving T cell responses is limited by downstream IFN-gamma induction of PD-L1.

2.4 Rationale

2.4.1 *Rationale for MK-3475 (pembrolizumab) Dose Selection*

The dose of MK-3475 (pembrolizumab) planned to be studied in this trial is 200 mg administered every 3 weeks (Q3W). The dose recently approved in the US and several other countries for treatment of melanoma patients is 2 mg/kg Q3W. Information on the rationale for selecting 200 mg Q3W is summarized below.

The initial phase 1 study of MK-3475 (pembrolizumab) (KN001) evaluated 5 dose levels (1 mg/kg every 2 weeks [Q2W], 3 mg/kg Q2W, 10 mg/kg Q2W, 2 mg/kg Q3W, and 10 mg/kg Q3W) in patients with advanced solid tumors. All 5 dose levels were well tolerated and no dose-limiting toxicities (DLTs) were observed. MK-3475 (pembrolizumab) showed evidence of target engagement and objective evidence of tumor size reduction at all dose levels (1 mg/kg, 3 mg/kg, and 10 mg/kg Q2W). No maximum tolerated dose (MTD) has been identified to date. In addition, 2 randomized cohort evaluations of melanoma patients receiving MK-3475 (pembrolizumab) 2 mg/kg or 10 mg/kg Q3W have been completed, and 1 randomized cohort evaluating 10 mg/kg Q3W or 10 mg/kg Q2W has also been completed. The clinical efficacy and safety data demonstrate a lack of any important differences in efficacy or safety profile across doses.

An integrated body of evidence suggests that 200 mg Q3W is expected to provide similar response to 2 mg/kg Q3W, 10 mg/kg Q3W, and 10 mg/kg Q2W. Previously, a flat MK-3475 (pembrolizumab) exposure-response relationship for efficacy and safety has been found in patients with melanoma in the range of doses between 2 mg/kg and 10 mg/kg. Exposures for 200 mg Q3W are expected to lie within this range and will be close to those obtained with 2 mg/kg Q3W dose.

The PK profile of MK-3475 (pembrolizumab) is consistent with that of other humanized monoclonal antibodies, which typically have a low clearance and a limited volume of distribution. A population PK model, which characterized the influence of body weight and other patient covariates on exposure, has been developed. The distribution of exposures from the 200 mg fixed dose are predicted to considerably overlap those obtained with the 2 mg/kg dose and importantly will maintain individual patient exposures within the exposure range established in melanoma as associated with maximal clinical response. The PK properties of MK-3475 (pembrolizumab), specifically the weight-dependency in clearance and volume of distribution, are consistent with no meaningful advantage to weight-based dosing relative to fixed dosing.

In translating to other tumor indications, similarly flat exposure-response relationships for efficacy and safety as observed in patients with melanoma can be expected. As the antitumor effect of MK-3475 (pembrolizumab) is driven through immune system activation rather than through a direct interaction with tumor cells, it is rendered independent of the specific tumor type. In addition, available PK results in patients with melanoma, NSCLC, and other tumor types support a lack of meaningful difference in PK exposures obtained at tested doses across tumor types. Thus, the 200 mg Q3W fixed-dose regimen is considered an appropriate fixed dose for other tumor indications as well.

A fixed-dose regimen will simplify the dosing regimen to be more convenient for physicians and to reduce potential for dosing errors. A fixed-dosing scheme will also reduce complexity in the logistical chain at treatment facilities and reduce wastage. The existing data suggest 200 mg Q3W as the appropriate dose for MK-3475 (pembrolizumab).

2.4.2 *Immune checkpoint blockade in Mycosis Fungoides/Sézary Syndrome to augment anti-tumor T cell response*

With the goal of unleashing the desired anti-tumor T cell response in Mycosis Fungoides and Sézary Syndrome, we conducted a clinical trial with anti-PD-1 monoclonal antibody, MK-3475 (pembrolizumab), initiated and coordinated by CITN and jointly funded by Merck. MK-3475 (pembrolizumab) is a potent and highly selective humanized mAb of the immunoglobulin G4 (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. Some tumor cells up-regulate the PD-1 or PD-1 ligands to evade active T-cell immune surveillance. MK-3475 (pembrolizumab) or nivolumab has been shown to effectively block the interaction between PD-1 and its ligands, thereby enhancing tumor regression in melanoma, other solid tumors, or Hodgkin lymphoma [Topalian 2012]; [Robert 2015] [Ansell 2015].

2.4.3 *Anti-PD-1 monoclonal antibody MK-3475 (pembrolizumab) monotherapy in Mycosis Fungoides/Sézary Syndrome: CITN-10 clinical trial*

We explored the clinical activity of MK-3475 (pembrolizumab) as an immune checkpoint blockade targeting PD-1 to restore and augment the effector T cell activity. Approximately one third of patients responded and many of the responses appear to be durable and increasing over time with continued therapy.

Patients (pts) with Mycosis Fungoides/Sézary Syndrome stages IB-IV with at least 1 prior systemic therapy were enrolled in this phase 2, single-arm study. A Simon two-stage design was applied where stage 2 was initiated with 1 of 9 pts achieving an objective response. MK-3475 (pembrolizumab) was administered at 2 mg/kg every 3 weeks with treatment allowed up to 2 years. Primary endpoint was overall response rate as determined by the consensus global response criteria (GRS). Secondary endpoints include safety/tolerability, TTR, and DOR/PFS. Expansive correlative science was planned and is ongoing to evaluate biomarkers of clinical response and to elucidate the mechanisms of immune escape in those who fail to respond or develop new tumors on therapy.

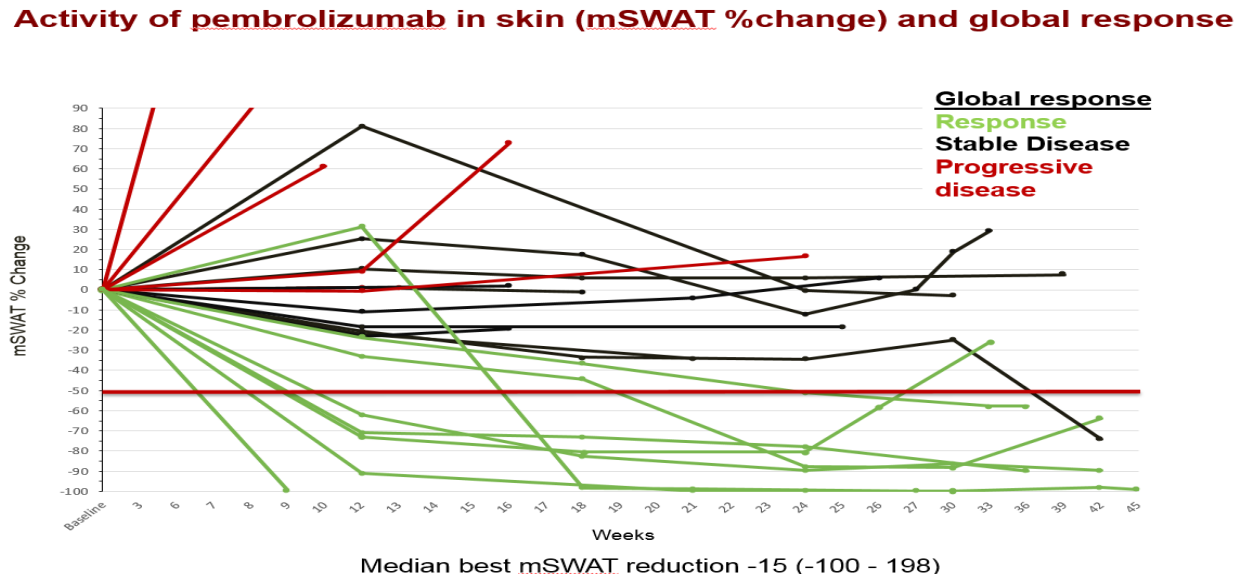
Enrollment of the planned 24 pts is completed and all received at least one dose of MK-3475 (pembrolizumab). Median age is 67 (44-85); 18 are male. All but 1 patient (stage IB) had advanced disease (stages IIB-IV); 2 IIB, 3 IIIA, 3 IIIB, 15 with IVA. 15 of 24 were SS. Most pts were heavily treated with median of 4 prior systemic therapies (range 1-10). Nine pts have confirmed clinical response (38% ORR; 8 PR, 1 CR) and 5 of these responders are continuing on therapy with median follow-up of 49 weeks. Of the 9 current responders, 5 are Mycosis Fungoides (2 IIB, 2 IIIA, 1 IIIB; 4, 6, 3 and 7 prior systemic therapies) and 4 SS (4 IVA; 1, 3, 4, and 6 prior systemic therapies). Two of the PRs are in near global CR; both are SS with complete clearing of circulating Sézary cells. Four pts had deep skin response with >90% mSWAT reduction (3 SS, all IVA; 1 Mycosis Fungoides, IIIA). Median time to response is 11 weeks (range 8-22 weeks). Median PFS is 44 weeks and 75% were progression-free at 6 months by KM estimate. To

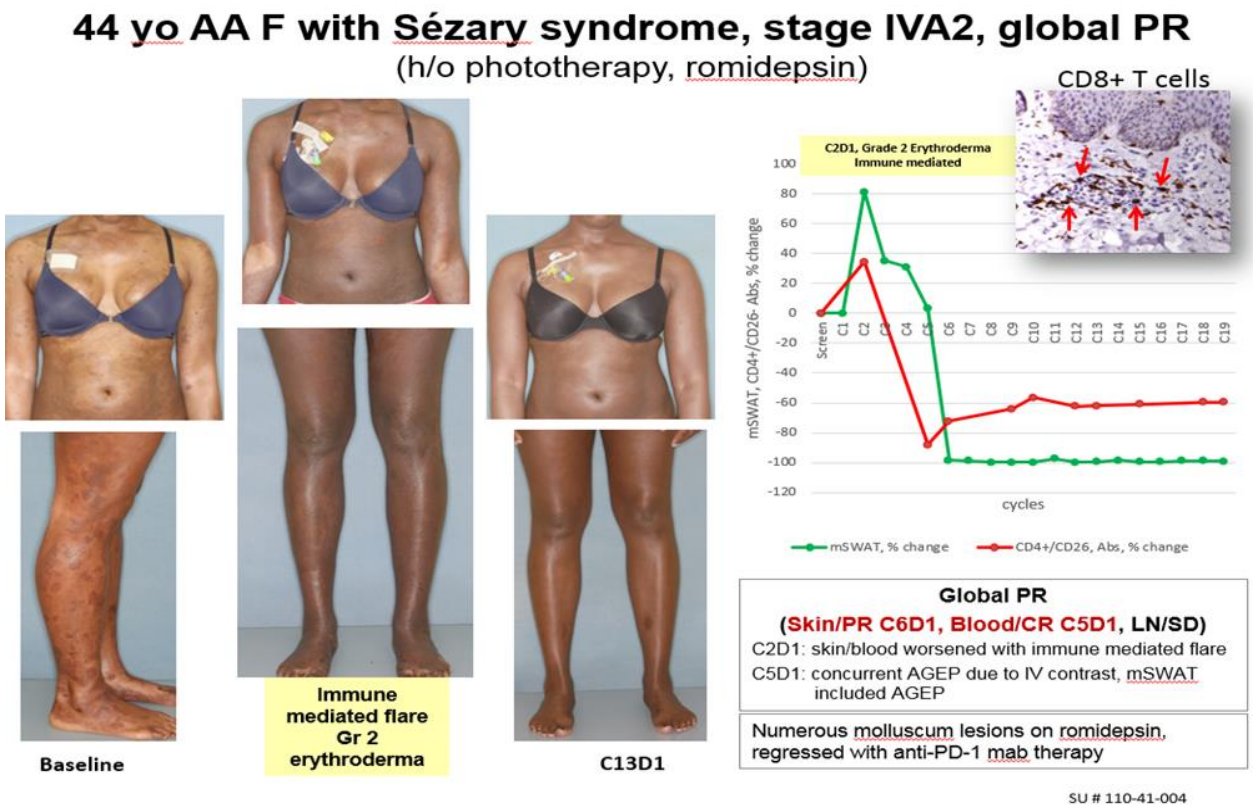
date, related AEs reported in greater than 5% of patients are dermatitis (n=6), anemia (n=3), leukopenia (n=3), elevated liver enzymes (n=2), diarrhea (n=2), and pneumonitis (n=2). Most AEs were grade 1-2 and limited to AEs previously reported with MK-3475 (pembrolizumab) in other malignancies. Grade 3/4 AEs were immune mediated exfoliative dermatitis (n=2), anemia (n=2), elevated liver enzymes (n=1), pneumonitis (n=1), and hyperuricemia (n=1). Only two MK-3475 (pembrolizumab) related SAE's were reported including one grade 3 pneumonitis and one grade 3 diarrhea secondary to steroid refractory duodenitis. In one patient with moderate immune-mediated skin disease flare, we observed significant tumor-infiltrating CD8+ T cells, followed by clinical response.

Planned and ongoing correlative studies include those to characterize the tumor microenvironment (IHC/multiparametric, nanostring gene expression profiling, multiplexed ion beam imaging), systemic immune response (flow cytometry, CyTOF, Luminex cytokine profiling), and the molecular/genomic immune profile (exome sequencing, neoantigen discovery, high throughput sequencing of TCR).

In summary, we observed meaningful clinical responses in previously treated Mycosis Fungoides /Sézary Syndrome with MK-3475 (pembrolizumab) including deep PRs and a global CR with 38% ORR. In the blood compartment of SS pts, MK-3475 (pembrolizumab) is capable of clearing the malignant T cells. The PFS data is continuing to mature and the ongoing responses in several responders is very encouraging and may be reflective of a potential sustained antitumor immune response. Overall toxicity profile is acceptable in this population and limited to those expected with checkpoint blockade. Very comprehensive correlative studies are planned, that will help design immune strategies to improve the clinical outcome beyond that observed with MK-3475 (pembrolizumab) monotherapy and the planned trial of MK-3475 (pembrolizumab) plus IFN-gamma.

The CITN-10 trial was designed and implemented when the commonly accepted dose of MK-3475 (pembrolizumab) was 2mg/kg administered every 3 weeks. Since then the flat dose of 200mg IV every 3 weeks has become well accepted based upon the extensive rationale outlined in section 2.3.1. In this trial we will utilize the flat dose of 200mg IV every 3 weeks with the understanding that it will be comparable to the 2mg/kg IV every 3 weeks utilized in the CITN-10 trial.





2.4.4 *Clinical activity and tolerability of interferon gamma (IFN-gamma) therapy in Mycosis Fungoides/Sézary Syndrome*

Although IFN-gamma has not been widely used in Mycosis Fungoides/Sézary Syndrome (CTCL), earlier reports and sizable cohort experience at U Penn (personal

communications by A Rook) have shown promising activity either as monotherapy or as part of combination strategy [Kaplan 1990]; [Sugaya 2014]; [Raphael 2011].

As early as 1990, Kaplan et al reported in their phase 2 study of IFN-gamma in Mycosis Fungoides/Sézary Syndrome, 31% ORR (all PRs) among 16 patients with clinical stage ranging from IB to IVB [Kaplan 1990]. One of 5 responders previously progressed on IFN-alpha. IFN-gamma was administered IM x 8 weeks, initial dose of 0.25 mg/m^2 per day, and escalated to 0.5 mg/m^2 per day after 1 week if tolerated.

Later, Dummer et al reported 5 Mycosis Fungoides/Sézary Syndrome patients treated with intralesional administration of IFN-g expressing plasmid constructed with an adenoviral vector [Dummer 2004]. The intralesional injections were followed by not only impressive improvement of treated lesions but regression of distant/untreated lesions associated with increased serum levels of IFN-gamma.

More recently, Sugaya and colleagues conducted a phase 2 study of IFN-gamma monotherapy in 15 pts with stage IA – IIIA Mycosis Fungoides/CTCL [Sugaya 2014]. Eleven of 15 pts had PRs including 9 of 10 with early stage (IA-IIA) and 2 of 5 with more advanced stage (IIB/IIIA) Mycosis Fungoides. IFN-gamma was administered IV at 2 MU daily x 5 days for 4 weeks, followed by intermittent SC injections. It is important to note that this trial excluded any patient with clinically significant blood disease or anyone with LN or visceral involvement.

Shimauchi et al treated 12 pts with Mycosis Fungoides with a 4-week course of combination therapy of IFN-g daily x 5 days and nbUVB phototherapy given 3 times per week [Shimauchi 2008]. Of 12pts, 6 had PR and 4 CR. Th1 cytokine levels were increased and Th2 cytokines decreased in the combination group whereas control pts with nbUVB treatment alone did not show he favorable cytokine profile changes.

In a retrospective cohort study of 98 Sezary syndrome pts managed with multimodality immunomodulatory therapy by U Penn investigators, 75% ORR was reported with 30% CR rate [Raphael 2011]. All 73 pts with objective response were treated with photopheresis. Of these, IFN-gamma was added in 23 patients who were either intolerant or refractory to IFN-alpha and/or bexarotene to achieve PR or CR. The authors recommend a starting dose of 25-50 mcg/m^2 (0.5-1 MU/m^2), given SC thrice-weekly to daily, as tolerated. The high ORR observed in this multimodality immunotherapy study supports potential utility of IFN-g as part of a combination strategy to target synergistic immune activity.

In all of these studies in Mycosis Fungoides/Sézary Syndrome, IFN-gamma was observed as well-tolerated with mostly grade 1-2 AEs including local injection site reaction, flu-like symptoms, asthenia, neutropenia, mood affect, and elevated liver function tests.

2.4.5 *Rationale for a combination approach of anti-PD-1 antibody and IFN-gamma*

The clinical ORR with MK-3475 (pembrolizumab) monotherapy is ~33% and that for the comparable clinical stage patients treated with IFN-gamma as monotherapy is also ~33%.

IFN-gamma activated immune CD8+ T cells but is limited by induction of PD-L1. Anti-PD1 unleashes activated CD8+ T cells. Both are effective as single agents. In all likelihood, or at least theoretically, the combination will be synergistic. The combination of agents could provide substantial and sustained responses.

IFN-gamma is thought to be a critical antitumor cytokine and serves as a key biomarker of antitumor immune response in cancer immunotherapy. And as described, IFN-gamma has objective clinical activity in patients with Mycosis Fungoides/Sézary Syndrome and correlative studies in the clinical responders have shown evidence towards normalization of disease related immune dysregulation. However, there is also a concern that IFN-gamma, secreted by CTLs, can act as an inducer of immune escape activity through mechanisms such as increasing PD-1 or PD-L1 expression when tumor cells encounter CTLs in the local environment [Mandai 2016]. This potential dual opposing role of IFN-gamma may be a key mechanism for immune escape in various immunotherapies. Thus, combining an anti-PD-1 agent, such as MK-3475 (pembrolizumab) will address this potential escape path created by IFN-gamma in the local tissue while harnessing the broad and potent immune activating role of IFN-gamma. Furthermore, we have scheduled a week of a lead-in block where IFN-gamma is given as monotherapy with an intent to optimize priming of DCs and activated immune milieu, and up-regulate PD-1 and/or PD-L1 expression immediately before targeting PD-1 followed by countering any blockade in immune activation with MK-3475 (pembrolizumab). Moreover, we will have an opportunity to generate immune correlative studies with IFN-gamma alone before evaluating biologic effects of the combination immune strategy.

We hypothesize that combining an anti-PD-1 agent, MK-3475 (pembrolizumab), with IFN-gamma, an immune-augmenting agent with a wide range of immune activity, would result in a synergistic or complementary immune activity and yield superior clinical outcome with improved ORR and PFS in similar cohort of Mycosis Fungoides/Sézary Syndrome patients studied with MK-3475 (pembrolizumab) monotherapy. We would deem the combination successful if the ORR is 58% or greater, our primary efficacy endpoint. We also hope to improve the PFS with favorable DOR, our secondary endpoints.

With combination immune strategies, we are always mindful of possible additive toxicities, thus safety/tolerability is an important endpoint especially in our CTCL population where the disease course is often chronic and a curative outcome is not anticipated other than with an allogeneic HSC transplantation. Immune checkpoint blockade has been known to induce immune-mediated adverse events, although, anti-PD-1 agents have demonstrated a better safety profile than PD-L1 or CTLA-4 blockade [Weber 2015]; [Larkin 2015]. Our monotherapy with MK-3475 (pembrolizumab) has demonstrated an acceptable toxicity profile; however, we have observed a subset of patients experiencing grade 3 skin reactions and one patient with possible MK-3475 (pembrolizumab) related grade 3 pneumonitis which was reported as a serious adverse event (SAE). Interferons have been associated with anticipated immune activating cytokine related adverse events. Patients who receive continuous dosing of interferons suffer from constant symptoms that can lead to decreased quality of life and early termination of treatment. Thus, we plan to use an interrupted dosing strategy of IFN-

gamma where after the first 12 weeks of the combination course, patients will have interval courses off and on IFN-gamma, which we hope will result in acceptable tolerability while improving the efficacy profile beyond what we observed with anti-PD-1 monotherapy. We plan to keep the MK-3475 (pembrolizumab) dose schedule the same as the monotherapy trial, administered uninterrupted throughout the combination trial, thus keeping IFN-gamma as the only agent that will be given as immune boost blocks. We plan to allow dose increase of IFN-gamma to optimize best responses if patients demonstrate acceptable tolerability profile. To ensure overall safety of our patients, we have scheduled an interim planned safety based evaluation at week 10, C4D1 of MK-3475 (pembrolizumab) dosing in the first 12 patients enrolled in the study. If 4 or more out of 12 patients experience a study drug related SAE within the first 10 weeks of therapy, the trial will not be allowed to continue further enrollment and treatment unless or until reviewed and approved by the CITN and NCI CTEP.

Essential to this trial is to incorporate correlative studies that are critical for maximal learning of the mechanism of improved efficacy and/or immune escape in those who do not benefit or experience disease progression on therapy. The planned correlatives will be exploratory in nature and not considered endpoints. We aim to be robust and comprehensive with our correlative science and plan to evaluate the local and systemic immune activity/mechanisms and characterize gene expression profiles and mutational landscape to further understand the mechanism(s) and biomarkers of successful or failed anti-tumor immune response. We will apply state-of-the-art and/or novel tools to achieve this goal.

2.4.6 *Previous Clinical Experience in Synovial Sarcoma (Treatment Group 2) and Rationale*

To better understand the reasons why these tumors do not respond to anti-PD-1/PD-L1 targeted therapies, the tumor microenvironment (TME) and potential mechanisms of immune evasion in these tumors were analyzed. A retrospective analysis of immune-related gene expression in synovial sarcoma and several other STS subtypes was performed, using the NanoString platform (**Fig. 3**). It was observed that synovial sarcoma tumors had significantly lower expression of genes associated with inflammation, T cell activity, and antigen presentation ($p<0.05$, t-test, for HLA-A, B and C), compared with certain other common sarcoma subtypes including undifferentiated pleomorphic sarcoma (UPS) and leiomyosarcoma (LMS) (**Fig. 4**). Genes associated with T cell infiltration (e.g. IL-7R) were also less expressed in synovial sarcoma tumors (**Fig. 5**). Low MHC class I and class II expression in 18 synovial sarcoma cases by immunohistochemistry (IHC) was confirmed (**Fig. 6**). Almost all cases had either absent (0+) or low (1+) levels of class I MHC staining and no cases had high or very high (3-5+) staining. Low levels of T cell infiltration using deep sequencing of the TCR Vβ region was confirmed, in collaboration with Adaptive Biotechnologies. It was found that synovial sarcoma tumors had few tumor-infiltrating T cells based on the T cell fraction (not shown) and lower clonality (**Fig. 7**), suggesting a less "focused" oligoclonal response. Low levels of PD-L1 and PD-1 in these tumors by IHC were also observed, as would be expected in a "cold" tumor where immune evasion is achieved through avoidance rather than inhibition of infiltrating T cells (**Fig. 8**) [Pollack 2017]. In summary, these synovial sarcoma TME lacked all of the features that would be expected in a tumor type responsive to checkpoint blockade.

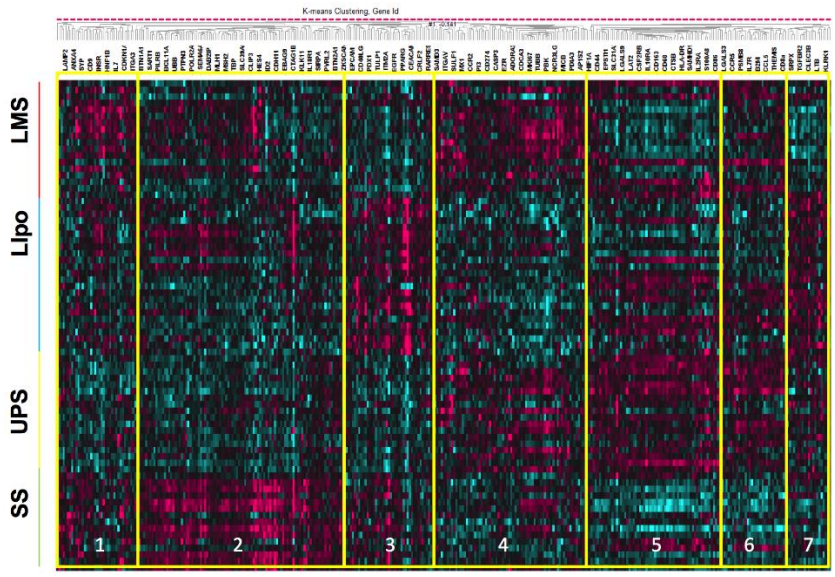


Fig. 3: Heat map illustrating gene expression data from the nanostring platform including 780 genes, a majority of which were related to immunity. A cluster analysis of genes significantly different between sarcoma subtype found 7 gene groups. Synovial sarcoma had lower levels of genes related to antigen presentation and T cell infiltration.

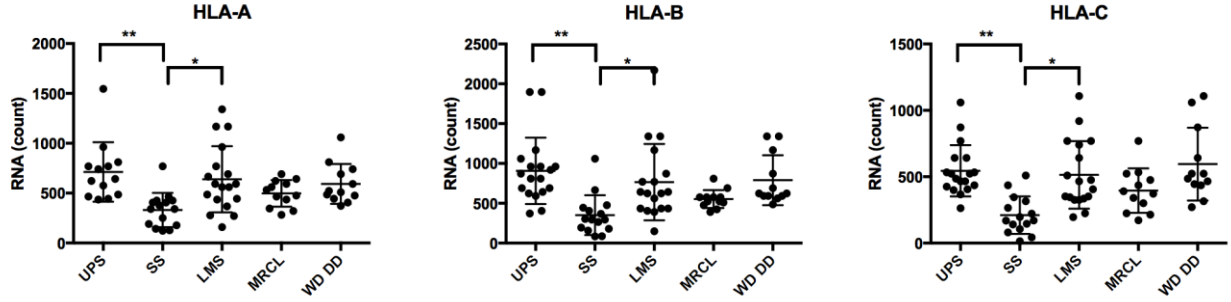


Fig. 4: Nanostring data illustrating expression of class I MHC genes in soft tissue sarcoma subtypes.* $p< 0.05$, ** $p<0.005$

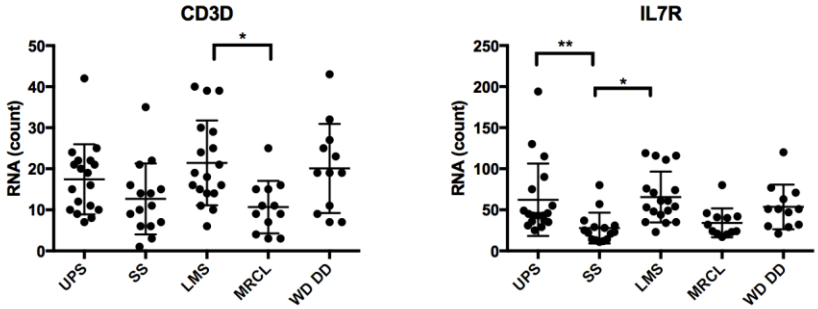


Fig. 5: Nanostring gene expression of CD3D and IL7R, two genes associated with T cell infiltration. * p< 0.05, ** p<0.005

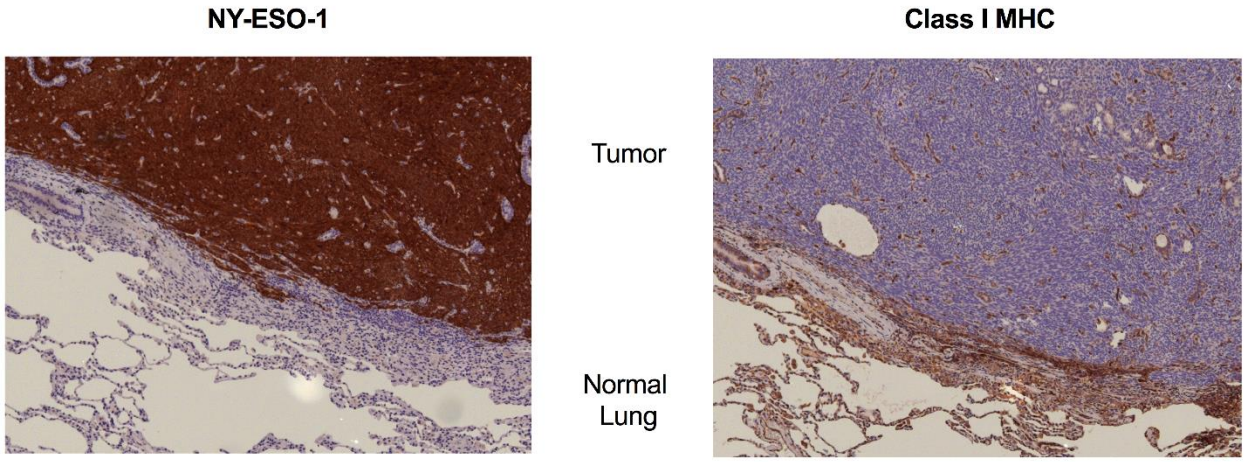


Fig. 6: Immunohistochemistry of a synovial sarcoma lung metastasis. This tumor stains strongly with NY-ESO-1 (left) but class I MHC staining is absent on the tumor cells (right).

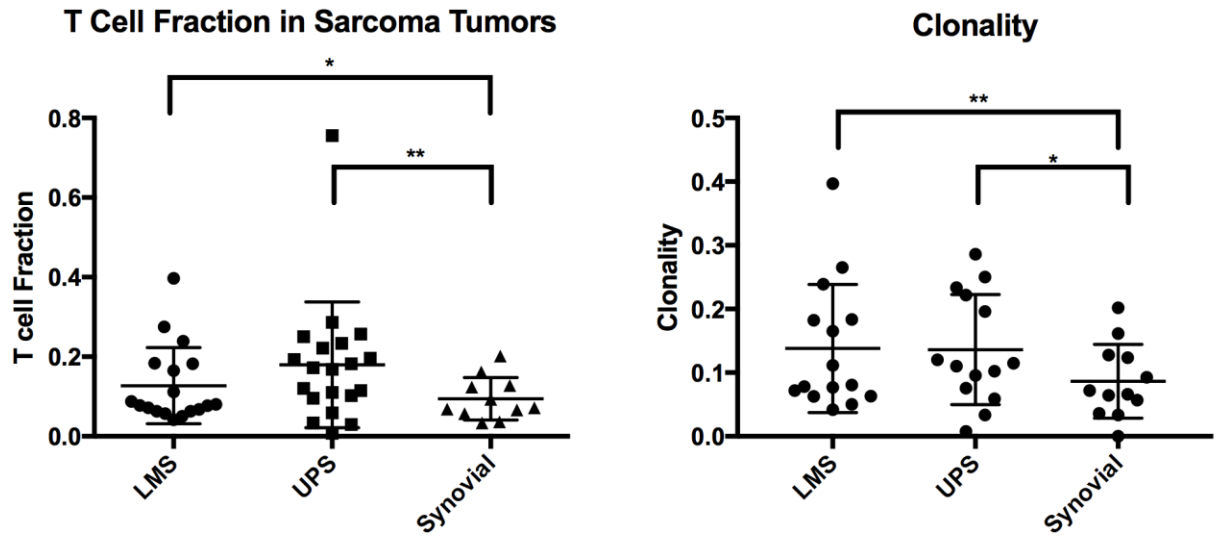


Fig. 7: Results of deep sequencing of the TCR Vβ region on FFPE preserved tumor samples. Leiomyosarcoma (LMS), undifferentiated pleomorphic sarcoma (UPS) and synovial sarcoma results are shown. T cell fraction (left) and clonality (right) are shown. Liposarcoma tumors also had low T cell fraction and clonality (not shown). * $p < 0.05$, ** $p<0.005$

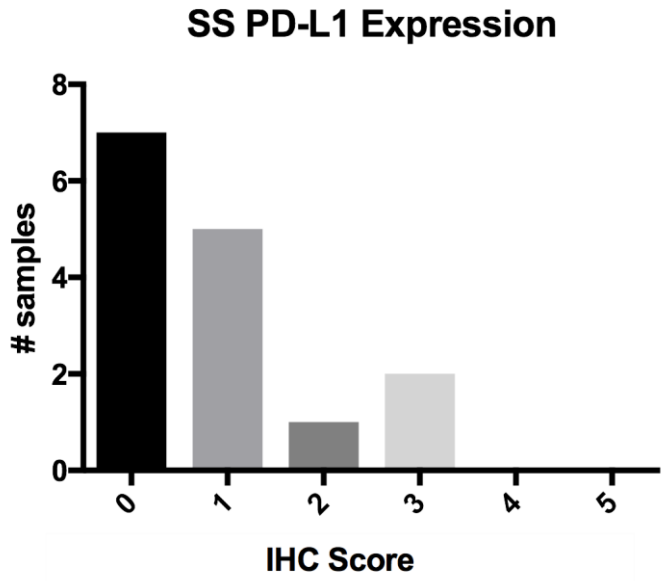


Fig. 8: Immunohistochemistry for PD-L1 on SS tumors. Staining was scored on a scale from 0 (absent staining) to 5 (homogenous staining) by a pathologist blinded to the tumor type.

2.4.7 *A Trial of Interferon-gamma (IFN-γ) to inflame the synovial sarcoma and myeloid/round cell liposarcoma (MRCL) Microenvironment*

Interferon-gamma (IFN-γ) is one of the most highly inflammatory cytokines and is capable of activating diverse immune cell repertoires and increases antigen presentation in a wide variety of tissues and tumor types [Propper 2003]. As had been seen in other tumor models, it was shown *in vitro* that class I MHC could be increased on synovial sarcoma tumor cells resulting in improved T cell mediated tumor killing. However, IFN-γ had never been studied in the context of an immunologically "cold" tumor in humans. Based on this data, an IRB-approved protocol to determine the impact of weekly IFN-γ (100 mcg/m^2 subcutaneously) on the sarcoma immune microenvironment was started (NCT01957709; PI: Pollack). On this protocol five patients who had undergone pre- and post-treatment biopsies were treated. IFN-γ was well tolerated on the weekly schedule; although patients had flu-like symptoms on the day of the injection, most felt better by the following day. No patients had any grade 3 or higher toxicity related to the IFN-γ. MHC expression was significantly increased post-treatment ($p<0.05$; **Fig. 9**). By flow cytometry, HLA-ABC expression on tumor cells rose from a mean of 3.3% to 17.0%. A substantial infiltration with class II expression on infiltrating cells was also noted. Markedly increased CD3+ T cell infiltration was also observed in each patient (**Fig. 10**). In order to interrogate the specificity of these T cells, TIL were expanded from each 1-2 mm core sample. Using an ELISPOT assay consisting of overlapping 15 amino acid peptides from the most immunogenic regions of cancer testis antigens (including NY-ESO-1) it was found that post-treatment T cells had improved recognition of these antigens (**Fig. 11**). Importantly however, increased PD-L1 both on tumor cells and tumor-infiltrating macrophages in patients on the trial was observed suggesting that this checkpoint may be an important blockade preventing T cell mediated tumor elimination.

In conclusion it has been shown that IFN-γ can consistently transform this cold TME into a hot TME. Accordingly, it is likely that synovial sarcoma patients treated with IFN-γ will respond to checkpoint inhibition. The proposed study will test the concept that concurrent IFN-γ and anti-PD-1 will induce remissions and benefit patients.

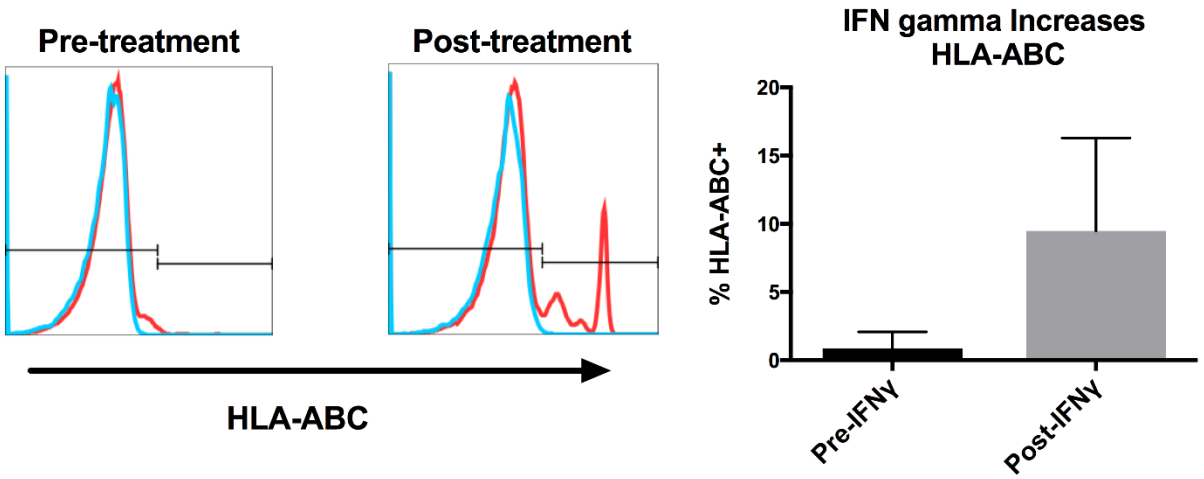


Fig. 9: Flow cytometry for class I MHC molecules on freshly procured tumor samples from synovial sarcoma and MRCL patients treated with weekly IFNγ. In order to focus on tumor cells and not immune cells, data was gated on CD45- cells. Histogram from a synovial sarcoma patient is shown (left). Percentage class I MHC+ cells before and after IFNγ treatment in the first 4 patients on the trial is shown (right).

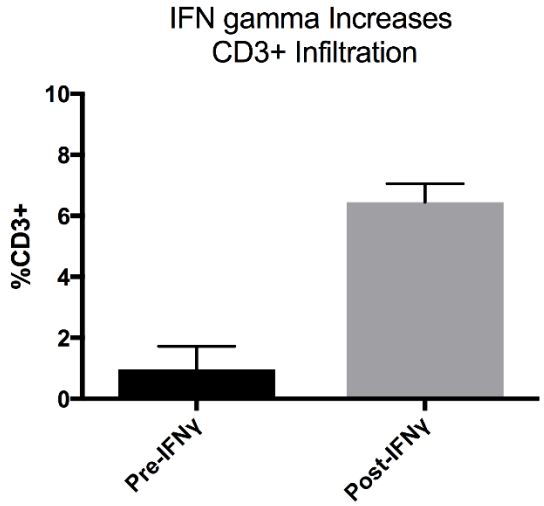


Fig. 10: Flow cytometry staining for CD3+ cells on freshly procured tumor samples from synovial sarcoma and MRCL patients treated with weekly IFNγ.

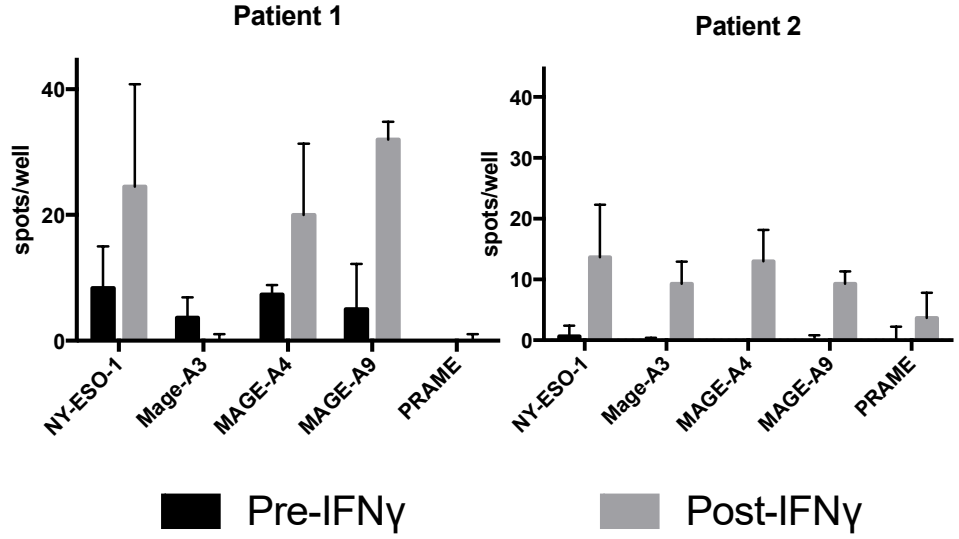


Fig. 11: Tumor infiltrating lymphocytes were expanded and tested for antigen recognition by ELIspot using a panel of overlapping 15mer peptides from the most immunogenic regions NY-ESO-1, MAGE-A3, MAGE-A4, MAGE-A9 and PRAME.

2.5 Correlative Studies Background (Treatment Group 1)

The proposed trial provides a rich context for the investigation of biomarkers for anti-PD1 therapy. Treatment of cutaneous T cell lymphomas with MK-3475 (pembrolizumab) monotherapy produced a response rate of ~33%, and we expect that the addition of interferon gamma will result in an even higher rate of clinical response. This high rate of response will improve our statistical power in discovering novel biomarkers. Additionally, as a cutaneous malignancy with frequent leukemia, CTCL affords the opportunity for serial collection of high quality biopsies of skin and blood. Thus, from an exploratory biomarker perspective, this disease offers an opportunity to investigate the determinants of response and resistance to anti-PD-1 and immune therapies, as well as to discover additional molecular targets governing immune dysregulation in cancer.

Correlates will focus on potential predictive biomarkers for PD-1 therapy (*e.g.,* as expression of PD-L1 and mutational/neoantigen burden) and assessment of the effects of IFN-gamma (*e.g.,*Th1 vs Th2 skewing). The addition of interferon gamma is hypothesized to affect the tumor microenvironment in two ways: 1) IFN-gamma will upregulate PD-L1 expression on suppressive cell populations. 2) IFN-gamma will skew CD4 T cells towards a Th1 phenotype. Sampling time points have been selected to explore these effects.

The majority of proposed biomarkers are designed to be hypothesis-generating by applying novel technologies such as multiple ion beam imaging and CyTOF to provide means to analyze the effects of checkpoint blockade both systemically and in the tumor microenvironment in an unprecedented manner. We anticipate that these studies will yield candidate biomarkers that correlate with prognosis, have predictive value in the selection of which subjects benefit from anti-PD1/IFN-gamma immunotherapy, and will investigate the hypothesis that Th1 skewing of the T cell repertoire can potentiate immune checkpoint blockade therapy.

Assays may include but are not be limited to:

2.5.1 *Chromagenic (Single-Color) immunohistochemistry for PD-L1*

PD-L1 expression has emerged as the leading biomarker for response to anti-PD1 therapy, but studies thus far have found this to be far from a perfect biomarker. This may be due at least in part to the dynamic nature of PD-L1 expression. Interferon gamma is known to upregulate PD-L1 expression in some tumor cells and frequently on tumor infiltrating leukocytes. With this biomarker we will explore the predictive value of PD-L1 expression before treatment as well as the inducible expression after interferon gamma treatment. FFPE skin biopsies will be stained with the FDA approved 22C3 assay. Staining will be assess both pre-treatment and after interferon gamma treatment. We will test whether PD-L1 expression (baseline and/or inducible) correlates with MK-3475 (pembrolizumab) response in the Mycosis Fungoides/Sézary Syndrome population.

2.5.2 *Multiparametric immunohistochemistry*

The skin microenvironment plays a critical role in the development and progression of cutaneous T cell lymphomas (CTCL). There are a number of potentially suppressive immune populations, such as regulatory T cells and M^2 macrophages, present within

CTCL involved skin that may blunt response to immunotherapy. Conversely, the presence of a tumor infiltrating lymphocyte population has been correlated with response to immune checkpoint blockade in other malignancies. To better define the spatial relationship between CTCL cells and the other key microenvironment residents, we will employ multiparametric immunohistochemistry for CD3, CD4, CD8, Foxp3, and CD163. In addition, we will co-stain for PD1, PD-L1, PD-L2, to define expression of these key markers on the relevant immune subsets.

2.5.3 *Multiplexed Ion Beam Imaging*

The skin microenvironment of CTCL includes CD8+ tumor infiltrating T cells, dendritic cells, macrophages, mast cells, and non-malignant CD4+ T cells including regulatory T cells. While the above studies will provide essential data with standard methodologies, they are unable to discriminate many critical cell populations due to the limitation of simultaneously detectable parameters. As a relevant example, in CTCL, the malignant T cells themselves can only be reliably identified by the expression pattern of a minimum of two parameters, typically CD4 and either CD7 or CD26. Until recently, there has been no imaging technology available capable of providing sufficient dimensionality to both discriminate relevant immune populations and simultaneously detect expression of other key markers.

A mass spectrometry-based approach dubbed multiplexed ion beam imaging (MIBI) is a novel approach to antibody-mediated labeling and imaging of tissue. The use of heavy metal isotope labels enables high dimensional multiplexing with minimal overlap between metals from formalin-fixed paraffin embedded tissue samples resulting in a theoretical limit of over 100 parameters collected per image. Currently, access to MIBI technology is very limited, with only two systems available worldwide. In collaboration with researchers at Stanford University, we have the opportunity to apply MIBI technology to study the CTCL skin microenvironment in unprecedented detail from primary patient samples collected before and during therapy. Through high dimensional analysis, we will decipher the complex interactions between tumor cells and the diverse immune residents within their local microenvironment. MIBI is uniquely capable of simultaneously discerning both the spatial relationship between CTCL cells and interacting immune cells and their relative expression of relevant immunomodulatory molecules such as PD-1 and PD-L1. Applying MIBI to paired samples will provide an unparalleled glimpse into the perturbation of the immune microenvironment induced by immune checkpoint blockade.

2.5.4 *Transcriptional Analyses*

The Nanostring platform will be used to profile mRNA expression of approximately 730 genes in an attempt to define a gene set predictive for clinical response to MK-3475 (pembrolizumab). The utility of this assay is two-fold. First, it will test the hypothesis that there is an immune related gene expression signature that predicts response to MK-3475 (pembrolizumab) and interferon gamma. Second, it will assess for Th1 polarization by interferon gamma of helper T cells in the tumor site. Profiling will be performed on

RNA extracted from FFPE skin biopsies and may also be performed on peripheral blood mononuclear cells.

2.5.5 *Whole exome sequencing and Neoantigen prediction*

Genomic studies of CTCL have revealed frequent alterations in T cell receptor signaling and CD28 co-stimulatory pathways as well as a translocation event involving PD-L1. We propose to perform whole exome sequencing of paired germline/tumor DNA to determine whether these or other genomic alterations are associated with response to PD-1 blockade. Mutational burden and neoantigen burden have been found to correlate with response to immune checkpoint blockade in other malignancies. Somatic mutations identified by whole exome sequencing will be analyzed for predicted formation of neoantigens. Neoantigen specific T cells will be detected by a combination of peptide-MHC tetramer staining and functional assays such as upregulation of CD137, OX-40, and interferon-gamma production after stimulation with candidate neoantigen peptides.

2.5.6 *Immunophenotyping*

CyTOF is a mass spectrometry-based method of single cell analysis analogous to flow cytometry that is capable of collecting >30 parameters for each cell. CyTOF and multiparametric flow cytometry will be employed to extensively immunophenotype circulating peripheral lymphocytes before treatment, after 1 week of interferon gamma treatment and after the treatment with a combination of MK-3475 (pembrolizumab) and interferon gamma. In addition to standard immunophenotyping, cells will be analyzed with and without TCR stimulation (either by PMA/ionomycin or anti-CD3) to assess for function defects in T cells. In addition, other cell types (*e.g.,*Tregs and myeloid-derived cells with T cell suppressor function) and immunomodulatory molecules (*e.g.,*IL-10) may be identified as additional components of the immunosuppressive milieu in Mycosis Fungoides/Sézary Syndrome. Flow cytometry will also be used to evaluate peripheral blood mononuclear cells.

2.5.7 *Cytokine/Chemokine Analysis (serum ELISA)*

Perturbations in cytokines, chemokines, and growth factors have been associated with cancers and changes in plasma cytokine concentrations of proinflammatory and immunosuppressive cytokines may correlate with clinical responses to therapy. Using a highly multiplexed ELISA-based platform, we will perform a longitudinal analysis of cytokines, chemokines and other serum tumor/oncogene-associated proteins at baseline (before treatment) and on treatment. Exploratory analysis will be performed to determine whether any cytokines/chemokines correlate with response to therapy. These assays will also provide a glimpse into the systemic immune perturbations caused by systemic interferon gamma therapy.

2.5.8 *T cell receptor high throughput sequencing*

High throughput sequencing of TCR genes is emerging as a valuable disease marker and measure of minimal residual disease in cutaneous T cell lymphomas. In addition to providing a measurement of the burden of the malignant clone, high throughput

sequencing allows interrogation of the entire T cell repertoire. This correlate will enable an exploratory analysis of the TCR repertoire as a potential biomarker for response to therapy. Characteristics such as repertoire diversity and clonal dynamics will be correlated to clinical responses. We will also compare TCR to flow cytometry in the identification and quantification of Circulating Sézary Cells.

2.5.9 *Kyn/Trp Ratio*

IDO catabolizes the conversion of Tryptophan to Kynurenine, which has potent immunosuppressant properties. An increase in Kynurenine levels over time, relative to Tryptophan levels, is known to be inhibitory to T cell function. For patients who are failing anti-PD-1 therapy increased Kyn/Trp ratios could indicate that IDO expression may be leading to treatment failure. Kyn/Trp ratios will be assayed in patients receiving a regimen of MK-3475 (pembrolizumab) as measured in peripheral blood at baseline and at specified intervals throughout the trial. We have defined the Kyn/Trp Ratio as a special study because the results may help to elucidate a likely mechanism for anti-PD-1 failure. This mechanism of resistance could potentially be overcome with an IDO inhibitor.

2.5.10 *Microbiome Analyses*

Recent evidence suggests that the microbiome has an effect on response to checkpoint blockade immunotherapy, and there is growing evidence that the intestinal microbiome in particular may have major influences on anti-tumor immune responses. The microbiota has long been known to have profound effects on innate and adaptive immunity. However, the impact and importance of the gut microbiome in human cancer patients' responses to immunotherapy has not yet been well-characterized and will be important to determine. To begin to understand the role of the microbiome in responses to immunotherapy in this protocol, we will collect microbiome samples from patients and perform taxonomic profiling via 16S rRNA gene sequencing and metagenomic whole genome shotgun (WGS) sequencing. Fecal samples will be collected and stored using standard, at home stool-collection procedures and we will assess the landscape of the gut microbiome. Sequencing data will be analyzed and compared to clinical responses to determine whether response or non-response to treatment can be correlated with specific microbiota.

2.6 Correlative Studies Background (Treatment Group 2)

2.6.1 *Flow Cytometry for Selected Class I HLA Alleles and Tetramer Analyses for Antigen-Specific T Cell Phenotyping on PBMC (Flow Cytometry)*

Antibodies for HLA-A02 and A-24 will be used to select patients for further analysis using MHC tetramers. Cryopreserved PBMC from those subjects expressing these alleles will be analyzed using flow panels that include MHC tetramers for known epitopes to NY-ESO-1, PRAME, MAGE-4, MAGE-A3, and MAGE-A9 along with other markers to look for changes in the number and phenotype of antigen specific T cells. Markers may include, but are not limited to: CD45, CD3, CD4, CD8, CD45RA, CD197 (CCR7), CD28, CD127, CD25, HLA-DR, CD279 (PD-1), CD278, CD45RO, CD62L, CD28 and

FoxP3. Additional MHC tetramers directed to MHC/peptide combinations may be used depending on availability and identifying potential appropriate MHC alleles from HLA-typing.

2.6.2 *Immune Phenotype Panel (Multispectral Immunohistochemistry)*

Paired baseline and post-baseline tumor biopsies will be evaluated using quantitative multicolor immunohistochemistry (IHC) with Perkin-Elmer's Vectra IHC platform. This platform employs spectral deconvolution imaging to separate optical signals from each antibody together with state-of–the-art image analysis capabilities to facilitate robust quantitative slide-based immunophenotyping. Multicolor tyramide-based IHC was previously employed to analyze PD-L1, PD-1 and their close spatial proximity, which was associated with response to anti-PD1 blockade. Using the Vectra multi-spectral imaging platform (PerkinElmer), adjacent tumor sections will be stained and imaged with a series of 5-6 antibodies per section simultaneously to investigate the spatial relationship between key immunomodulatory cell types and molecules. The antibodies will include, but are not limited to, the following: CD8, CD4, PD-1, PD-L1, CD68, CD163, FOXP3, arginase, pan-MHC class I and class II. Data will be generated in the form of total positive cells, positive cells/mm2, percentage positive cells in a population, ratios of cells and molecules of interest (e.g. PD-L1:CD8 or FOXP3+CD4+:CD8). Furthermore, quantitative analysis of tumor-infiltrating lymphocyte (TIL) distribution (i.e., stromal, and interface/invasive margin) will be performed. These analyses will be performed using qualified analytes and analytic tools at the immunopathology lab of the FHCRC in a non-CLIA approved environment. Chromogenic anti-PD-L1 immunohistochemical staining with the 22C3 antibody (Dako) kit (which has been approved as a companion diagnostic assay for the selection of NSCLC patients) will be performed in addition to the multispectral IHC (msIHC) to serve as both an independent test and control for the reproducibility of the msIHC assay.

2.6.3 *Immune Gene Expression Signature (NanoString®Gene Expression using the nCounter® Human Immunology V2 Panel and the nCounter®PanCancer Immune Profiling Panel)*

NanoString®-based gene expression analysis, specifically for the "IFN γ Signature", will be used to test the hypothesis that the investigational study treatment regimen, IFNγ and pembrolizumab, will promote a pro-inflammatory anti-tumor immune response. We hypothesize that induction of such a response will correlate with clinical outcomes. RNA will be extracted from all paraffin-embedded tumor samples and analyzed using the NanoString® nCounter Immunology V2 Profiling Pane, which includes over 700 other genes associated with inflammation. The samples used for the planned gene expression analyses will be taken from tissue sections adjacent to those stained for multi-spectral IHC to facilitate comparison between these analysis sets. Samples will consist of matched pre- and post-treatment FFPE biopsies.

2.6.4 *T Cell Receptor (TCR) Clonality (TCR ImmunoSeq)*

High throughput sequencing of TCR genes is emerging as a potentially valuable disease marker and allows interrogation of the entire T cell repertoire. This correlate enables an exploratory analysis of the TCR repertoire as a potential biomarker for response to therapy. Characteristics such as repertoire diversity and clonal dynamics, as surrogates of expanded responses against tumor antigens will be correlated to clinical responses. TCR sequencing will be performed when pretreatment and post-treatment biopsies are available. TCR repertoire analysis will be performed on RNA extracted from FFPE biopsies. TCR repertoire analysis has been standardized and commercialized by Adaptive Biosciences. The TCR sequences will also specifically be queried for sequences already known to encode for TCRs reactive to shared antigens often expressed in synovial sarcoma (e.g., MAGE-A3, NY-ESO-1, LAGE-1, and PRAME).

2.6.5 *PD-L1 Baseline and Post-Treatment (Immunohistochemistry)*

PD-L1 has been identified as an important correlative biomarker for clinical response to anti-PD-L1 and anti-PD-1 therapies. In particular, given that the function of MK-3475 (pembrolizumab) is to block binding of PD-1 to PD-L1, expression of PD-L1 will be quantitated by IHC in baseline formalin-fixed paraffin-embedded tumor specimens, and from biopsies obtained after treatment. This is an important part of the correlative studies to explore whether this marker which correlates with response in other circumstances also correlates with response in this protocol population. For baseline samples, formalin-fixed, paraffin-embedded tissue block(s) from tumor obtained before treatment will be obtained by the clinical site either from archival samples obtained from the relevant pathology laboratories where they were processed and stored, or from baseline biopsy as part of this protocol (core, punch, or excisional). Post-treatment, formalin-fixed paraffin-embedded tumor specimens will be obtained from biopsy at week 8-12 as part of this protocol.

2.6.6 *Whole Blood Lymphocyte and Monocyte Immunophenotyping (Whole Blood Multiparametric Flow Cytometry)*

Multiparametric flow cytometry will be used to assess the effect of interferon gamma-1b and MK-3475 (pembrolizumab) on circulating lymphocyte and monocyte numbers and phenotype.

We will assess the effects of treatment on the frequency and phenotypic character of PBMC subsets including dendritic cells (DCs), monocyte populations, T cells, NK cells, and B cells. The effect on these immune cell subtypes of checkpoint inhibitors, and other immune modulators is being investigated in other CITN trials and may provide important correlative information on the success or failure of combination immunotherapy.

A 14-color whole blood immunophenotyping assay will quantify in one panel the absolute number and proportion of T cells (both CD8+ and CD4+), NK cells (CD56+CD3-), NKT cells (CD56+CD3+), B cells (CD19+/CD20+), monocytes (CD16+), neutrophils (CD15+), as well as both myeloid DCs (CD45+HLA-DR+CD11c+CD123-) and plasmacytoid DCs (CD45+HLA-DR+CD11c-CD123+). In addition, myeloid-derived suppressor cells (MDSC) will be measured using antibodies to HLA-DR, CD11b, and CD33 in this same multiparameter flow cytometric assay. Multiparameter flow cytometry on whole blood with a 12-color panel may also be used in parallel to further define the phenotype of T cells and to identify activated T cells, T-cell subsets (including regulatory T cells). This validated panel includes the markers CD45, CD3, CD4, CD8, CD45RA, CD197 (CCR7), CD28, CD127, CD25, HLA-DR, CD279 (PD-1), CD278. Assays will be performed under the direction of Dr. Steven Fling in the CIML at the Fred Hutch.

2.6.7 *Anti-Tumor Immune T cell Responses (ELISPOT)*

The ability of the investigational treatment to induce a tumor antigen-specific immune response will be assessed using ex vivo incubation of PBMC-derived T cells with autologous PBMC-derived antigen presenting cells (APCs), pulsed with peptide antigens from proteins that these tumors are known to express. Quantitation of the strength of the antigen-specific T cell responses using ELISPOT assays will be done and compared to each patient's baseline and post-baseline T cell (IFN-γ secretion) for each of these known immunogenic antigens. The hypothesis predicts that treatment will lead to an increase in the strength and number of antigen-specific IFN-γ secreting T cells in responding patients.

2.6.8 *Multiplex Cytokines (Affymatrix or Luminex)*

We will perform a longitudinal analysis of cytokines, chemokines and other serum tumor/oncogene-associated proteins at baseline (before treatment) and on treatment. Exploratory analysis will be performed to determine whether any cytokines/chemokines correlate with response to therapy. Serum cytokine analysis will be used to explore whether reactive changes in cytokine levels correlates with toxicity and efficacy of interferon gamma-1b and MK-3475 (pembrolizumab).

2.6.9 *Microbiome Analyses*

Recent evidence suggests that the microbiome has an effect on response to checkpoint blockade immunotherapy, and there is growing evidence that the intestinal microbiome in particular may have major influences on anti-tumor immune responses. The microbiota has long been known to have profound effects on innate and adaptive immunity.

However, the impact and importance of the gut microbiome in human cancer patients' responses to immunotherapy has not yet been fully characterized. To begin to understand the role of the microbiome in responses to immunotherapy in this protocol, we will collect microbiome samples from patients and perform taxonomic profiling via 16S rRNA gene sequencing and metagenomic whole genome shotgun (WGS) sequencing. Fecal samples will be collected and stored using standard, at home stool-collection procedures and we will assess the landscape of the gut microbiome. Sequencing data will be analyzed and compared to clinical responses to determine whether response or non-response to treatment can be correlated with specific microbiota.

2.6.10 *HLA Class I and Class II Typing*

To further select samples for analysis using additional, potential MHC/peptide tetramers, MHC typing will be performed. DNA will be extracted from residual blood collected at baseline and processed and sequenced in the laboratory of Dr. Dan Geraghty (FHCRC).

3. PATIENT SELECTION

3.1 Eligibility Criteria

3.1.1 Mycosis Fungoides/Sézary Syndrome (Treatment Group 1)

3.1.1.1 Stage IB-IVB Mycosis Fungoides/Sézary Syndrome, and who have relapsed, are refractory, or progressed after at least one standard systemic therapy. Maximal stage since diagnosis will determine eligibility. Current disease stage at time of entry will also be documented but will not be used for eligibility.

3.1.1.2 Subjects must have the following minimum wash-out from previous treatments and without treatment between documentation of relapse/progression and enrollment:

- ≥2 weeks for local radiation therapy.
- ≥8 weeks for low dose (12 Gy or less) Total Skin Electron Beam Therapy (TSEBT)
- ≥4 weeks for systemic cytotoxic anticancer agents, anticancer investigational agents that are not defined as immunotherapy, or for tumor-targeting monoclonal antibodies (mAbs) with the exception of alemtuzumab for which the washout is at least 16 weeks.
- ≥15 weeks for anti-CD137 or anti-CTLA-4 (including ipilimumab or any other antibody or drug specifically targeting T-cell co-stimulation or checkpoint pathways).
- ≥2 weeks from resolution (*i.e.,* < Grade 1 or at baseline) from AEs due to procedures performed or therapeutic agents administered.
- ≥2 weeks for retinoids, interferons, vorinostat, romidepsin and denileukin diftitox.

- ≥4 weeks for doses of systemic corticosteroids greater than 10mg/day of Prednisone or equivalent. Patients who are on physiologic doses of corticosteroids (prednisone equivalent 10mg/day or less) may participate, however, they must be on a stable dose for at least 4 weeks before enrollment. Patients who are on low or moderate potency topical corticosteroids may participate if they are on a stable dose for at least 4 weeks before enrollment. Inhaled corticosteroids are acceptable. Local injections of corticosteroids are acceptable. All corticosteroids will be reported as concomitant medications.
- ≥2 weeks for phototherapy.
- ≥1 week for topical therapy (including retinoid, nitrogen mustard, or imiquimod).

3.1.1.3 Patients with prior treatment with IFN-gamma will be eligible, if they previously tolerated IFN-gamma, however patients must be off of IFN-gamma for at least three weeks before initiation of therapy on this trial.

3.1.1.4 Age ≥18 years.

3.1.1.5 Have measurable disease based on mSWAT (definition provided in Appendix). Tumor lesions situated in a previously irradiated area are considered measurable if progression has been demonstrated in such lesions.

3.1.1.6 Have a performance status of 0 or 1 on the ECOG Performance Scale.

3.1.1.7 Patients must have normal organ and marrow function (all screening labs should be performed within 10 days of treatment initiation) as defined below:

System	**Laboratory Value**
Hematological	
Absolute neutrophil count (ANC)	≥1500/mcL
Platelets	≥100 000/mcL
Hemoglobin	≥9 g/dL or ≥5.6 mmol/L
Renal	
Creatinine **OR** measured or calculated creatinine clearance (CrCl) [a,b]	≤1.5 × ULN **OR** ≥60 mL/min for patient with creatinine levels >1.5 × institutional ULN
Hepatic	
Total bilirubin	≤1.5 × ULN **OR** Direct bilirubin ≤ULN for patients with total bilirubin levels >1.5 × ULN
AST (SGOT) and ALT (SGPT)	≤2.5 × ULN **OR** ≤5 × ULN for patients with liver metastases
[a] Creatinine clearance (CrCl) should be calculated per institutional standard. [b] Glomerular filtration rate (GFR) can also be used in place of creatinine or CrCl.	

3.1.1.8 The effects of MK-3475 (pembrolizumab) and Interferon-gamma on the developing human fetus are unknown. For this reason and because anti-PD-1agents and Interferons may be teratogenic, women of child-bearing potential and men must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) before study entry and for the duration of study participation.

3.1.1.9 Female patients of childbearing potential must have a negative urine or serum pregnancy test 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.

3.1.1.10 Female patients of childbearing potential (Section 5.7) must be willing to use an adequate method of contraception as outlined in Section 5.7 Contraception and Pregnancy, for the course of the study through 120 days after the last dose of study medication.

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

3.1.1.11 Male patients of reproductive potential must agree to use an adequate method of contraception as outlined in Section 5.7 Contraception and Pregnancy, starting with the first dose of study therapy through 120 days after the last dose of study therapy.

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

3.1.1.12 Should a woman become pregnant or suspect she is pregnant while she or her partner is participating in this study, she should inform her treating physician immediately. Men treated or enrolled on this protocol must also agree to use adequate contraception before the study, for the duration of study participation, and 4 months after completion of MK-3475 (pembrolizumab) and Interferon-gamma administration.

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

3.1.2 **Synovial Sarcoma (Treatment Group 2)**

3.1.2.1 Diagnosis of translocation associated sarcoma that generally expresses NY-ESO-1 (e.g., Synovial Sarcoma or Myxoid/Round Cell Liposarcoma). Tumor must have been reviewed by a bone and soft tissue pathologist. Patient must have metastatic or unresectable disease.

3.1.2.2 At least one prior line of chemotherapy

3.1.2.3 Age ≥12 years. Patients ≥18 years of age must be able and willing to provide informed consent. Patients under 18 years of age must have a parent or guardian willing and able to provide consent.

3.1.2.4 Eastern Cooperative Oncology Group (ECOG) performance status of 0, 1 or 2

3.1.2.5 Life expectancy greater than or equal to (>/=) 12 weeks

3.1.2.6 Measurable disease, as defined by RECIST v1.1

3.1.2.7 Tumor safely accessible for biopsy

3.1.2.8 Adequate hematologic and end organ function

3.1.2.9 For female participants of childbearing potential and male participants with partners of childbearing potential, agreement (by participant and/or partner) to use highly effective form(s) of contraception as outlined in Section 5.7

3.2 Exclusion Criteria

3.2.1 Mycosis Fungoides/Sézary Syndrome (Treatment Group 1)

3.2.1.1 Has disease that is suitable for local therapy administered with curative intent.

3.2.1.2 Patients who have had chemotherapy or targeted small molecule therapy within 4 weeks (6 weeks for nitrosoureas or mitomycin C) before entering the study.

3.2.1.3 Patients who have had an allogeneic stem cell transplant are excluded because such transplants disrupt the normal immune response to a very substantial degree. In addition, emerging data suggests exacerbation of lethal GVHD may occur in such patients when treated post allotransplant with PD-1 blockade.

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

3.2.1.5 Patients who have received an investigational agent or have used an investigational device within 4 weeks of the first dose of study drug.

3.2.1.6 Has a history of a well-characterized and defined immune deficiency before the diagnosis of Mycosis Fungoides/Sézary Syndrome or is receiving systemic steroid therapy greater than 10mg/day of Prednisone or equivalent within 4 weeks or any other form of immunosuppressive therapy within 7 days before the first dose of trial treatment. The use of physiologic replacement doses of corticosteroids, along with topical, inhaled and local injection is discussed in section 3.1.2.

3.2.1.7 Has had a prior monoclonal antibody within 4 weeks before study Day 1 or who has not recovered (i.e., ≤ Grade 1 or at baseline) from AEs due to agents administered more than 4 weeks earlier.

***Note**:* The following will not be exclusionary:

- Patients may have any grade alopecia or lymphopenia and still participate if other inclusion/exclusion criteria are met. Patients may have grade 1 or 2 neuropathy at baseline and still participate if other inclusion/exclusion criteria are met.

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

3.2.1.9 Patients with known brain metastases should be excluded from this clinical trial because of their poor prognosis and because they often develop progressive neurologic dysfunction that would confound the evaluation of neurologic and other adverse events.

Patients with carcinomatous meningitis should also be excluded.

Patients with previously treated brain metastases may participate provided they are stable (without evidence of progression by imaging using the identical imaging modality for each assessment, either magnetic resonance imaging (MRI) or computed tomography (CT) scan, for at least 4 weeks before the first dose of trial treatment and any neurologic symptoms have returned to baseline), have no evidence of new or

enlarging brain metastases, and are not using steroids for at least 7 days before trial treatment.

3.2.1.10 History of allergic reactions attributed to compounds of similar chemical or biologic composition to MK-3475 (pembrolizumab) and Interferon-gamma. Patients who are hypersensitive to E. Coli are also excluded.

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

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

3.2.1.13 Has a history or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the trial, interfere with the patient's participation for the full duration of the trial, or is not in the best interest of the patient to participate, in the opinion of the treating investigator.

3.2.1.14 Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, interstitial lung disease or active, non-infectious pneumonitis, congestive heart failure NYHA grade ≥3, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements.

3.2.1.15 Pregnant women are excluded from this study because MK-3475 (pembrolizumab) is an agent with the potential for teratogenic or abortifacient effects. Because there is an unknown but potential risk for adverse events in nursing infants secondary to treatment of the mother with MK-3475 (pembrolizumab), breastfeeding should be discontinued if the mother is treated with MK-3475 (pembrolizumab). These potential risks may also apply to Interferon-gamma.
MK-3475 (pembrolizumab) and Interferon-gamma may have adverse effects on a fetus *in utero*. Furthermore, it is not known if MK-3475 (pembrolizumab) or Interferon-gamma have transient adverse effects on the composition of sperm. Patients are excluded from this study if pregnant or breastfeeding, or expecting to conceive or father children within the projected duration of the trial, starting with the screening visit through 120 days after the last dose of trial treatment.

See Section 5.7 for information on contraception and pregnancy.

3.2.1.16 *Patients who are Human Immunodeficiency Virus (HIV) positive may participate IF they meet the following eligibility requirements:*

1. They must be stable on their anti-retroviral regimen, and they must be healthy from an HIV perspective.
2. They must have a CD4 count of greater than 250 cells/mcL.
3. They must not be receiving prophylactic therapy for an opportunistic infection.
4. Must be on antiretroviral therapy and there must be minimal interactions or

overlapping toxicity of the antiretroviral therapy with the experimental cancer treatment.

5. HIV viral load must be <200 copies/ mm^3 by standard clinical assays.

3.2.1.17 Has known active hepatitis B (e.g., HBsAg reactive) or hepatitis C (e.g., HCV RNA [qualitative] is detected).

***Note**:* The following will not be exclusionary:

1. A positive hepatitis B serology indicative of previous immunization (*i.e.,* HBsAb positive and HBcAb negative), or a fully resolved acute HBV infection
2. Patients with chronic HBV suppressed by appropriate antiretroviral therapy with activity against HBV, as outlined in DHHS guidelines
3. Positive HCV serology but no detectable HCV RNA, indicative of spontaneously cleared HCV infection
4. Patients who have been successfully treated for HCV as long as therapy for HCV has been completed

3.2.1.18 Has received a live vaccine within 30 days before the first dose of trial treatment. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, chicken pox, yellow fever, seasonal flu (some), H1N1 flu, rabies, BCG, and typhoid vaccine. Seasonal flu vaccines that do not contain live virus are permitted.

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

3.2.2 **Synovial Sarcoma (Treatment Group 2)**

3.2.2.1 Any approved or investigational anti-cancer therapy within 14 days prior to initiation of study treatment.

Note: Prior treatment with anti-programmed death-1 (anti-PD-1) or anti-programmed death-ligand 1 (anti-PD-L1) therapeutic antibodies is allowed as is prior therapy with other immunotherapies.

3.2.2.2 Active or untreated central nervous system (CNS) metastases as determined by computed tomography (CT) or magnetic resonance imaging (MRI) evaluation during screening and prior radiographic assessments. Patients with prior brain metastases or CNS disease are permitted, but must have completed treatment and either (1) have no evidence of active CNS disease for at least 4 weeks prior to the first dose OR (2) have stable CNS lesions, or be at least 2 weeks past radiation or gamma-knife therapy. Patients with past CNS disease must also have a Screening head CT or MRI demonstrating stable disease compared to their most recent CNS evaluation.

3.2.2.3 Active therapy for malignancies other than sarcoma.

3.2.2.4 Pregnant and lactating women

3.2.2.5 New York Heart Association (NYHA) class 3 or 4 or clinically symptomatic cardiovascular disease

3.2.2.6 Severe infections requiring intravenous antibiotic treatment within 2 weeks prior to initiation of treatment

3.2.2.7 Major surgical procedure other than for diagnosis within 4 weeks prior to initiation of treatment

3.2.2.8 Active autoimmune disease requiring systemic treatment with steroids greater than 10 mg/day of prednisone or who have required steroids with a dose of 40 mg/day for the treatment of their autoimmune disease more than twice over the past year. Patients with an autoimmune disease who are on active therapy with a drug targeting TNF alpha.

3.2.2.9 Prior allogeneic stem cell or solid organ transplant

3.2.2.10 History of idiopathic pulmonary fibrosis, organizing pneumonia, drug-induced pneumonitis, idiopathic pneumonitis, or evidence of active pneumonitis on screening chest CT scan

3.2.2.11 Active tuberculosis

3.2.2.12 HIV on effective antiretroviral therapy will not be excluded.

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

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

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

- Note: the following will NOT be exclusionary:

- Positive HCV serology but no detectable HCV RNA, indicative of spontaneously cleared HCV infection
- Patients who have been successfully treated for HCV as long as therapy for HCV has been completed

3.3 Inclusion of Women and Minorities

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

4. REGISTRATION PROCEDURES (TREATMENT GROUP 1 AND 2)

4.1 Investigator and Research Associate Registration with CTEP

4.1.1 *CTEP Registration Procedures*

Food and Drug Administration (FDA) regulations and National Cancer Institute (NCI) policy require all individuals contributing to NCI-sponsored trials to register and to renew their registration annually. To register, all individuals must obtain a Cancer Therapy Evaluation Program (CTEP) Identity and Access Management (IAM) account at https://ctepcore.nci.nih.gov/iam. In addition, persons with a registration type of Investigator (IVR), Non-Physician Investigator (NPIVR), or Associate Plus (AP) (*i.e.,* clinical site staff requiring write access to OPEN, Rave, or acting as a primary site contact) must complete their annual registration using CTEP's web-based Registration and Credential Repository (RCR) at https://ctepcore.nci.nih.gov/rcr.

RCR utilizes five person registration types.

- IVR – MD, DO, or international equivalent;
- NPIVR – advanced practice providers (e.g., NP or PA) or graduate level researchers (e.g., PhD);
- AP – clinical site staff (e.g., RN or CRA) with data entry access to CTSU applications (e.g., Roster Update Management System (RUMS), OPEN, Rave);
- Associate (A) – other clinical site staff involved in the conduct of NCI-sponsored trials; and
- Associate basic (AB) – individuals (e.g., pharmaceutical company employees) with limited access to NCI-supported systems.

RCR requires the following registration documents:

Documentation Required	IVR	NPIVR	AP	A	AB
FDA Form 1572	✓	✓			
Financial Disclosure Form	✓	✓	✓		
NCI Biosketch (education, training, employment, license, and certification)	✓	✓	✓		
GCP training	✓	✓	✓		
Agent Shipment Form (if applicable)	✓				
CV (optional)	✓	✓	✓		

An active CTEP-IAM user account and appropriate RCR registration is required to access all CTEP and Cancer Trials Support Unit (CTSU) websites and applications. In addition, IVRs and NPIVRs must list all clinical practice sites and Institutional Review Boards (IRBs) covering their practice sites on the FDA Form 1572 in RCR to allow the following:

- Addition to a site roster;
- Assign the treating, credit, consenting, or drug shipment (IVR only) tasks in OPEN;
- Act as the site-protocol Principal Investigator (PI) on the IRB approval; and
- Assign the Clinical Investigator (CI) role on the Delegation of Tasks Log (DLT).

In addition, all investigators act as the Site-Protocol PI, consenting/treating/drug shipment, or as the CI on the DTL must be rostered at the enrolling site with a participating organization (i.e., Alliance).

Additional information is located on the CTEP website at https://ctep.cancer.gov/investigatorResources/default.htm. For questions, please contact the **RCR Help Desk** by email at RCRHelpDesk@nih.gov.

4.2 CTSU Registration Procedures

This study is supported by the NCI CTSU.

4.2.1 *IRB Approval*

For CTEP and Division of Cancer Prevention (DCP) studies open to the National Clinical Trials Network (NCTN) and NCI Community Oncology Research Program (NCORP) Research Bases after March 1, 2019, all U.S.-based sites must be members of the NCI Central Institutional Review Board (NCI CIRB). In addition, U.S.-based sites must accept the NCI CIRB review to activate new studies at the site after March 1, 2019. Local IRB review will continue to be accepted for studies that are not reviewed by the CIRB, or if the study was previously open at the site under the local IRB. International sites should continue to submit Research Ethics Board (REB) approval to the CTSU Regulatory Office following country-specific regulations.

Sites participating with the NCI CIRB must submit the Study Specific Worksheet for Local Context (SSW) to the CIRB using IRB Manager to indicate their intent to open the study locally.

The NCI CIRB's approval of the SSW is automatically communicated to the CTSU Regulatory Office, but sites are required to contact the CTSU Regulatory Office at CTSURegPref@ctsu.coccg.org to establish site preferences for applying NCI CIRB approvals across their Signatory Network. Site preferences can be set at the network or protocol level. Questions about establishing site preferences can be addressed to the CTSU Regulatory Office by emailing the email address above or calling 1-888-651-CTSU (2878).

Sites using their local IRB or REB, must submit their approval to the CTSU Regulatory Office using the Regulatory Submission Portal located in the Regulatory section of the CTSU website. Acceptable documentation of local IRB/REB approval includes:

- Local IRB documentation;
- IRB-signed CTSU IRB Certification Form; and/or
- Protocol of Human Subjects Assurance Identification/IRB Certification/Declaration of Exemption Form.

In addition, the Site-Protocol Principal Investigator (PI) (i.e. the investigator on the IRB/REB approval) must meet the following criteria to complete processing of the IRB/REB approval record:

- Holds an Active CTEP status;
- Rostered at the site on the IRB/REB approval and on at least one participating roster;
- If using NCI CIRB, rostered on the NCI CIRB Signatory record;
- Includes the IRB number of the IRB providing approval in the Form FDA 1572 in the RCR profile; and
- Holds the appropriate CTEP registration type for the protocol.

4.2.2 *Additional Requirements*

Additional requirements to obtain an approved site registration status include:

- An active Federal Wide Assurance (FWA) number;
- An active roster affiliation with the Lead Protocol Organization (LPO) or a Participating Organization (PO); and
- Compliance with all protocol-specific requirements (PSRs).

4.2.3 *Downloading Site Registration Documents*

Download the site registration forms from the protocol-specific page located on the CTSU members' website. Permission to view and download this protocol and its supporting documents is restricted based on person and site roster assignment. To participate, the institution and its associated investigators and staff must be associated with the LPO or a PO on the protocol.

- Log on to the CTSU members' website (https://www.ctsu.org) using your CTEP-IAM username and password;
- Click on *Protocols* in the upper left of your screen
  - Enter the protocol number in the search field at the top of the protocol tree, or
  - Click on the By Lead Organization folder to expand, then select CITN, and protocol number CITN-13;
- Click on *Documents*, select *Site Registration*, and download and complete the forms provided.
  (Note: For sites under the CIRB initiative, IRB data will load automatically to the CTSU as described above.)

4.2.4 *Submitting Regulatory Documents*

Submit required forms and documents to the CTSU Regulatory Office via the Regulatory Submission Portal on the CTSU website.

To access the Regulatory Submission Portal log on to the CTSU members' website → Regulatory → Regulatory Submission.

Institutions with patients waiting that are unable to use the Regulatory Submission Portal should alert the CTSU Regulatory Office immediately at 1-866-651-2878 in order to receive further instruction and support.

4.2.5 *Checking Your **Site's** Registration Status*

You can verify your site's registration status on the members' side of the CTSU website.

- Log on to the CTSU members' website;
- Click on *Regulatory* at the top of your screen;
- Click on *Site Registration*;
- Enter your 5-character CTEP Institution Code and click on Go

***Note**:* The status shown only reflects institutional compliance with site registration requirements as outlined above.. It does not reflect compliance with protocol requirements for individuals participating on the protocol or the enrolling investigator's status with the NCI or their affiliated networks.

4.3 Patient Enrollment

4.3.1 *OPEN*

The Oncology Patient Enrollment Network (OPEN)is a web-based registration system available on a 24/7 basis. OPEN is integrated with CTSU regulatory and roster data and with the Lead Protocol Organization (LPO) registration/randomization systems or Theradex Interactive Web Response System (IWRS) for retrieval of patient registration/randomization assignment. OPEN

will populate the patient enrollment data in NCI's clinical data management system, Medidata Rave.

Requirements for OPEN access:

- A valid CTEP-IAM account;
- To perform enrollments or request slot reservations: Be on a LPO roster, ETCTN Corresponding roster, or PO roster with the role of Registrar. Registrars must hold a minimum of an AP registration type;
- If a Delegation of Tasks Log (DTL) is required for the study, the registrar(s) must hold the OPEN Registrar task on the DTL for the site; and
- Have an approved site registration for a protocol prior to patient enrollment.

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To assign an Investigator (IVR) or Non-Physician Investigator (NPIVR) as the treating, crediting, consenting, drug shipment (IVR only), or receiving investigator for a patient transfer in OPEN, the IVR or NPIVR must list the IRB number used on the site's IRB approval on their Form FDA 1572 in RCR. If a DTL is required for the study, the IVR or NPIVR must be assigned the appropriate OPEN-related tasks on the DTL.

Prior to accessing OPEN, site staff should verify the following:

- Patient has met all eligibility criteria within the protocol stated timeframes; and
- All patients have signed an appropriate consent form and HIPAA authorization form (if applicable).

***Note**:* The OPEN system will provide the site with a printable confirmation of registration and treatment information. Please print this confirmation for your records.

Access OPEN at https://open.ctsu.org or from the OPEN link on the CTSU members' website. Further instructional information is in the OPEN section of the CTSU website at https://www.ctsu.org or https://open.ctsu.org. For any additional questions contact the CTSU Help Desk at 1-888-823-5923 or ctsucontact@westat.com.

Patient enrollment for this study will be facilitated using the Slot Reservation System in conjunction with the registration system in OPEN. Prior to discussing protocol entry with the patient, all site staff must use the CTSU OPEN Slot Reservation System to ensure that a slot on the protocol is available to the patient. Once a slot reservation confirmation is obtained, site staff may then proceed to enroll the patient to this study.

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 Clinical Research Site (CRS) must notify the CITN Coordinating Center of cancellations as soon as possible.

5. TREATMENT PLAN

5.1 Agent Administration

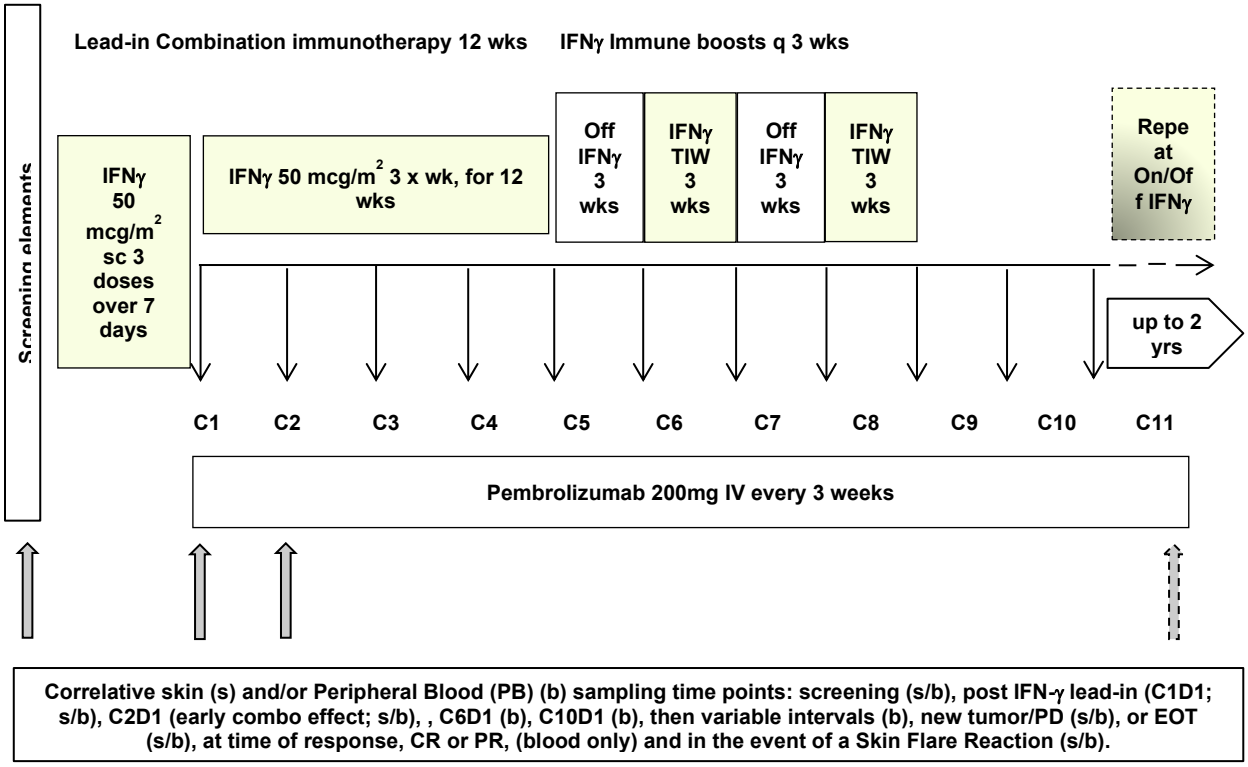
Treatment will be administered on an outpatient basis. Reported AEs and potential risks are described in Section 7. Appropriate dose modifications are described in Section 6. No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat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

5.1.1 Mycosis Fungoides/Sézary Syndrome (Treatment Group 1)

Treatment Plan

- MK-3475 (pembrolizumab) will be administered at a dose of 200 mg every 3 weeks by IV infusion. No dose modification will be allowed.
- IFN-gamma will be initiated at 50 mcg/m^2 administered subcutaneously 3 times a week (*e.g.*, M/W/F or T/Th/Sat).

Regimen Description (Treatment Group 1)					
Agent	**Premedications; Precautions**	**Dose**	**Route**	**Schedule**	**Cycle Length**
MK-3475 (pembrolizumab)	None	200 mg	Intravenous Refer to section 8.1.1 for compatible infusion set materials including in-line filter.	Every 3 weeks (Day 1 of each cycle)	3 weeks
Interferon-gamma-1b	Antihistamines, analgesics, nonsteroidal anti-inflammatory drugs (NSAIDs), anti-depressants. Refer to Section 6.1.5	50 mcg/m^2 (Dose Varies, see below)	Subcutaneous	Three times weekly (*e.g.,* M/W/F or T/Th/Sat)	Variable



The combination will be administered following the schema above:

- IFN-gamma lead-in treatment x 1 week = > opportunity to obtain correlative biomarkers after IFN-gamma monotherapy for correlative studies
- Combination of MK-3475 (pembrolizumab) 200mg every 3 weeks and IFN-gamma 50 mcg/m^2 3 doses per week for 12 weeks
- Followed by MK-3475 (pembrolizumab) continued every 3 weeks up to 2 years. IFN-gamma boost (3 weeks) blocks every 2 cycles (6 weeks) of MK-3475 (pembrolizumab). IFN-gamma will be given 3 weeks on followed by 3 weeks off. If patients are experiencing intolerable toxicities and need additional time off, the investigator may increase time off in 1 week increments up to 3 weeks. A re-assessment of symptoms is made during this time period. The decision to increase time off is at the discretion of the investigator in consultation with the patient. If a patient is tolerating IFN-gamma well, IFN-gamma can be given continuously without break at the discretion of the investigator and in consultation with the patient starting at cycle 7. This option is intended for patients who experienced worsening of disease or associated symptoms during the cycles off of IFN-gamma, or in cases where the investigator believes the patient would otherwise benefit from continuous IFN-gamma therapy.
- Intra-patient dose increase for IFN-gamma: dose increases by 25 mcg/m^2 can be considered at each boost event if a CR cannot be confirmed at a global clinical assessment, to a max IFN-gamma dose of 100 mcg/m^2. If toxicity seen at higher IFN-gamma dose is deemed intolerable by the treating physician, the IFN-gamma dose can be reduced to the previously tolerable dose.

- The dose of IFN-gamma will be reduced to 25 mcg/m^2 for certain Gr 3 toxicities as outlined in Section 6.1.4, and may be reduced at the investigator discretion to 25mcg/m^2 for constitutional symptoms as in Section 5.1.1.2. If patients are experiencing intolerable toxicities, IFN-gamma may be held for up to a period of 3 weeks at the discretion of the investigator and in consultation with the patient. A re-assessment of symptoms is made during this time period, and treatment may be restarted at any point during the cycle. If such a hold occurs after cycle 5, treatment would recommence at the next planned cycle on IFN-gamma. For example, if IFN-gamma were held throughout cycle 8, the next IFN-gamma treatment would be at the start of cycle 10.

Disease Assessments

- All patients: mSWAT at screening, pre-IFN-gamma lead-in, C1D1, C2D1, then every other cycle thereafter, and for CR/PR, PD or EOT, and in the event of a Skin Flare Reaction.
- Presence of extracutaneous disease at enrollment: Sezary flow at pre-IFN-gamma lead-in, C2, C6, C10, then every 4 cycles and in the event of a Skin Flare Reaction; Imaging at screening, C5-6, C9-10, (before MK-3475 (pembrolizumab) is administered at cycle 6, and 10) then every 4 cycles, both Sezary flow and imaging are performed to confirm PR and/or CR, when suspect PD and at EOT.
- Absent extracutaneous disease at enrollment: Imaging at screening, Sezary flow at pre-IFN-gamma lead-in, then both are performed to confirm PR and/or CR, when suspect PD, at EOT and in the event of a Skin Flare Reaction.

5.1.1.1 *MK-3475 (pembrolizumab)*

Trial treatment of MK-3475 (pembrolizumab) will be administered on Day 1 of each 3-week treatment 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, beginning with Cycle 2. A 3-day window is allowed for Cycle 1.

***Note**:* Dosing interruptions are permitted in the case of medical / surgical events or logistical reasons (*i.e.,* elective surgery, unrelated medical events, patient vacation, holidays) not related to study therapy. Patients should be placed back on study therapy within 3 weeks of the scheduled interruption. The reason for interruption should be documented in the patient's study record.

MK-3475 (pembrolizumab) will be administered as a dose of 200 mg using a 30-minute IV infusion. 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 25 – 40 minutes).

5.1.1.2 *Interferon-gamma (Actimmune)*

IFN-gamma will be administered subcutaneously per the approved package insert instructions, self-administered by the patient whenever possible. The optimum sites of subcutaneous injection are the abdomen, right and left deltoid and anterior thigh. Appropriate counseling in the administration of subcutaneous injections must occur

before patients are allowed to self-administer IFN-gamma. If the patient is unable to self-administer, a family member or caregiver may administer IFN-gamma to the patient after proper counseling in the administration of subcutaneous injections. Dosages will be increased for inadequate response as described above and will be decreased for toxicities as described above. Since toxicities may be constitutional in nature, investigator discretion will be necessary to determine the appropriate dose, the goal being to find a tolerable dose to keep patients on study.

5.1.2 Synovial Sarcoma

Regimen Description (Treatment Group 2)				
Agent	**Premedications; Precautions**	**Dose**	**Route**	**Schedule**
MK-3475 (pembrolizumab)	None	Patients ≥18 years of age: 200 mg Patients <18 years of age: 2 mg/kg (max= 200 mg)	Intravenous	Every three weeks starting on Day 1 of Cycle 1, followed by Day 1 of each 3-week cycle.
Interferon-gamma-1b	Antihistamines, analgesics, nonsteroidal anti-inflammatory drugs (NSAIDs), anti-depressants.	100 mcg/m^2	Subcutaneous	Once per week starting one week prior to the first dose of MK-3475 (pembrolizumab).

5.1.2.1 *MK-3475 (pembrolizumab)*

MK-3475 (pembrolizumab) will be administered on Day 1 of each 3-week cycle after all procedures/assessments have been completed. MK-3475 (pembrolizumab) may be administered up to 7 days before or after the scheduled Day 1 of each cycle, if needed due to logistical reasons, beginning with Cycle 2. A 3 day window is allowed for Cycle 1.

Note: Dosing interruptions are permitted in the case of medical/surgical events or logistical reasons (e.g., elective surgery, unrelated medical event, patient vacations or holidays) not related to study therapy. Patients should be placed back on study therapy within 3 weeks of the scheduled interruption. The reason for interruption should be documented in the patient's study record.

In patients ≥18 years of age, MK-3475 (pembrolizumab) will be administered at a fixed dose of 200 mg using a 30-minute IV infusion.

In patients <18 years of age, MK-3475 (pembrolizumab) will be administered at a dose of 2 mg/kg (max=200 mg) using a 30-minute IV infusion.

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 25-40 minutes).

5.1.2.2 *Interferon Gamma-1b (ACTIMMUNE®)*

Interferon gamma-1b will be administered at a dose of 100 mcg/m^2 once per week, starting one week prior to initiating pembrolizumab. Interferon gamma-1b will be administered subcutaneously per the approved package insert instructions, self-administered by the patient whenever possible. If the patient is unable to self-administer, a family member or caregiver may administer interferon gamma-1b to the patient. Appropriate counseling in the administration of subcutaneous injections must occur prior to the start of treatment. Patients will be given an injection log to record drug self-administration and to make note of toxicities. If substantial toxicity occurs, interferon gamma-1b, but not pembrolizumab, will be dose de-escalated. The dose of interferon gamma-1b will be reduced to for certain Gr 3 toxicities as outlined in Section 6.1.4.

NOTE: For synovial sarcoma patients the dose of interferon gamma-1b will be reduced by 50 mcg/m^2 (50%). Grade 3 flu-like symptoms including fevers, fatigue, myalgias, or other patient reported symptoms that resolve to grade 1 within 48 hours should not trigger an interferon gamma-1b dose change.

5.2 Study Design, Interim Futility, and Safety Evaluation

5.2.1 Mycosis Fungoides/Sézary Syndrome (Treatment group 1)

This is a single arm, open label, interventional study to evaluate the efficacy and safety of the combination immunotherapy with MK-3475 (pembrolizumab) and IFN-gamma in Mycosis Fungoidesor Sézary Syndrome, stages IB-IV, who have relapsed, progressed or otherwise failed after at least one standard systemic therapy. There is no planned stratification. 30 patients will be enrolled on a continuous basis.

MK-3475 (pembrolizumab) will be a 200-mg flat dose administered intravenously every 3 weeks, remaining unchanged throughout the study.

In this single stage phase II open label trial, we will have an interim futility analysis. When 12 patients have been followed for 6 months, we will perform the interim futility analysis. If ORR is less than 33% (4 or less CR+PR), the trial will stop and we will accept the null that combination therapy is no better than monotherapy. Otherwise, trial will continue until 30 patients accrue. If ORR is at least 57% (17 or more CR+PR) at the final analysis, we will accept the alternative that combination therapy is significantly better than monotherapy.

There is a planned interim safety review after the first 12 patients are enrolled. If 4 or more out of 12 patients experience a study drug related SAE within the first 10 weeks of therapy, the trial will not be allowed to continue further enrollment and treatment unless or until reviewed and approved by the CITN and NCI CTEP.

5.2.2 Synovial Sarcoma (Treatment Group 2)

The study is a single arm, open label trial of interferon gamma-1b and MK-3475 (pembrolizumab) for patients with advanced (unresectable or metastatic) synovial sarcoma. Both adult and pediatric patients are eligible to participate in this trial. Patients will receive interferon gamma-1b at a dose of 100 mcg/m^2 weekly, as this dose has been found to be relatively well tolerated and successful at inducing MHC expression and T cell infiltration into synovial sarcoma tumors. Interferon gamma-1b will begin one week prior to initiating MK-3475 (pembrolizumab). MK-3475 (pembrolizumab) will be given at a standard fixed dose of 200 mg administered every 3 weeks. Thus patients will receive one dose of interferon gamma-1b priming their tumors for checkpoint blockade using MK-3475 (pembrolizumab). If substantial toxicity occurs, interferon gamma-1b, but not MK-3475 (pembrolizumab), will be dose de-escalated.

The primary endpoint of the study will be the overall response rate (ORR) based on RECIST v. 1.1. The ORR is defined as the complete response rate (CR) combined with the partial response rate (PR). Based on historical controls, we estimate the ORR of single agent pembrolizumab is less than 5%. Twelve patients will be enrolled initially. If one or more of these patients respond, an additional four patients will be enrolled. If three or more patients respond the treatment will be considered promising.

Toxicity will be assessed by CTCAE v. 5.0. Although interferon gamma-1b in combination with MK-3475 (pembrolizumab) has previously been seen to be safe, its side effect profile has not been confirmed in a synovial sarcoma patient population or in a population of patients with cold tumors. There is no reason to suspect there would be additional toxicity in these patients however, we will adopt CTEP's data safety monitoring plan of every two week teleconferences attended by all participating site principal investigators, CTEP staff and CITN Coordinating Center staff to oversee the safety of the trial. During each activated protocol teleconference all patient toxicities, including all serious adverse events (SAE) and all other clinical data will be reviewed. Any SAE suspected to be attributed to the study regimen will be distributed to all participating site principal investigators and their staff on an urgent basis. If necessary, an ad hoc teleconference may be convened to discuss any adverse event determined to be a patient safety issue or if the adverse event is suspected of being related to study treatment.

Radiographic assessment by CT scan will occur every 12 weeks. Response and progression will be determined using RECIST v1.1. All patients with either a CR, PR or stable disease (SD) will continue therapy for up to two years. Patients will be followed for up to two years after study discontinuation for disease status and survival. Patients with radiographic progression but who are otherwise stable without symptomatic progression may continue treatment up until confirmation at the next radiographic imaging time point in order to assess for possible pseudo progression. ORR based on immune related response criteria (IRRC) will also be noted as an exploratory endpoint.

5.3 General Concomitant Medication and Supportive Care Guidelines (Treatment Group 1 and 2)

5.3.1 *MK-3475 (pembrolizumab) 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 any medication or vaccination specifically prohibited during the trial, discontinuation from trial therapy or vaccination may be required. The investigator should discuss any questions regarding this with CTEP. The final decision on any supportive therapy or vaccination rests with the investigator and/or the patient's primary physician; however, the decision to continue the patient on trial therapy or vaccination schedule requires the mutual agreement of the Investigator, CTEP, and the patient.

5.3.1.1 *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 30 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 serious adverse events (SAEs).

5.3.1.2 *Prohibited Concomitant Medications*

Patients are prohibited from receiving the following therapies during the Screening and Treatment Phase (including retreatment for post-complete response relapse) of this trial:

- Antineoplastic systemic chemotherapy or biological therapy.
- Immunotherapy not specified in this protocol.
- Chemotherapy not specified in this protocol.
- Investigational agents other than MK-3475 (pembrolizumab) and Interferon-gamma (Actimmune).
- Radiation therapy

***Note**:* Radiation therapy to a symptomatic solitary lesion or to the brain may be considered on an exceptional case by case basis after consultation with CTEP. The patient must have clear measurable disease outside the radiated field. Administration of palliative radiation therapy will be considered clinical progression for the purposes of determining PFS.

- 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, rabies, Bacillus Calmette–Guérin (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.

- Systemic glucocorticoids for any purpose other than to modulate symptoms from an event of suspected immunologic etiology or for physiologic replacement using 10mg/day or less of Prednisone or equivalent. The use of physiologic doses of corticosteroids may be approved after consultation with the study PI and CTEP.
- ***NOTE:*** For the synovial sarcoma patients in this trial, systemic glucocorticoids used for ≤ 10 days for acute inflammatory symptoms (e.g., allergic reaction), or used at a low dose (prednisone ≤ 10 mg/day or equivalent) for physiologic replacement may be administered at the discretion of the treating physician.

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 (Treatment Group 1 and 2)

In the absence of treatment delays due to AE(s), treatment may continue for up to two years or until 1 of the following criteria applies:

- Disease progression warranting alternative systemic therapy and without evidence of clinical benefit from continued MK-3475 (pembrolizumab) + Interferon-gamma. Patients who continue MK-3475 (pembrolizumab) + Interferon-gamma after initial disease progression will be discontinued from study for any additional disease progression of 25% or more.
- Intercurrent illness that prevents further administration of treatment
- Adverse event(s) which require(s) treatment discontinuation (see also Section 6):
  - Any dosing interruption lasting >12 weeks with the following exceptions: Dosing interruptions >12 weeks that occur for non-drug-related reasons may be allowed if approved by the Principal Investigator. Before re-initiating treatment in a patient with a dosing interruption lasting >12 weeks, the Principal Investigator must be consulted.
  - Tumor assessments should continue as per protocol even if dosing is interrupted.
- Any patient requiring systemic steroid or other immunosuppressive treatment. (Steroids may be allowed if they can be tapered, see section 6.1.3.

- Patient decides to withdraw from the study
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator
- Patient noncompliance
- Pregnancy
    - All women of child bearing potential should be instructed to contact the investigator immediately if they suspect they might be pregnant (*e.g.,* missed or late menstrual period) at any time during study participation.
    - The investigator must immediately notify CTEP in the event of a confirmed pregnancy in a patient participating in the study.
- Termination of the study by sponsor
- The drug manufacturer can no longer provide the study agent

The reason(s) for protocol therapy discontinuation, the reason(s) for study removal, and the corresponding dates must be documented in the Case Report Form (CRF).

5.5 Duration of Follow-Up (Treatment Group 1 and 2)

All patients, regardless of reason for discontinuation from study, will be followed for AE/SAE resolution for 30 days after removal from study. All patients will be followed for survival either by in-person visit or by telephone assessment every 12 weeks until 1 year after EOT.

Disease status and overall survival data will be collected and reported every 12 weeks, either by in-person visit or by telephone assessment.

After disease progression or start of new anticancer treatment, patient will be followed for overall survival only. Survival follow-up will continue until death or 1 year after the end of treatment, whichever occurs first.

In subjects who discontinue study therapy without documented disease progression, every effort should be made to continue monitoring their disease status by Olsen assessment (for patients with Mycosis Fungoides) or by CT scan (for patients with synovial sarcoma) every 12 weeks (± 7 days) until (1) the start of new anticancer treatment, (2) documented disease progression, (3) death, or (4) the end of the study, whichever occurs first. If a previous assessment was obtained within 4 weeks before the date of discontinuation, then an additional assessment at treatment discontinuation isn't mandatory.

Patients removed from study for unacceptable AE(s) will be followed until resolution or stabilization of AE; in addition the patients will be followed for disease status and overall survival, as described above.

5.6 Criteria to Resume Treatment (Treatment Group 1 and 2)

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.
- Non-drug-related toxicity including hepatic, pulmonary toxicity, diarrhea, or colitis, must have resolved to baseline 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).

5.7 Contraception and Pregnancy (Treatment Group 1 and 2)

5.7.1 Contraception

MK-3475 (pembrolizumab) may have adverse effects on a fetus in utero. Furthermore, it is not known if MK-3475 (pembrolizumab) has transient adverse effects on the composition of sperm.

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

Female patients will be considered of nonreproductive potential if they are either:

1. Postmenopausal (defined as at least 12 months with no menses without an alternative medical cause; in women <45 years of age, a high follicle-stimulating hormone [FSH] level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy. In the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.);
   OR
2. Have had a hysterectomy and/or bilateral oophorectomy, bilateral salpingectomy or bilateral tubal ligation/occlusion, at least 6 weeks before screening;
   OR
3. Has a congenital or acquired condition that prevents childbearing.

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

1. Practice abstinence† from heterosexual activity;
   OR
2. Use (or have their partner use) acceptable contraception during heterosexual activity.

Acceptable methods of contraception are‡:

Single method (1 of the following is acceptable):

- intrauterine device (IUD)
- vasectomy of a female patient's male partner
- contraceptive rod implanted into the skin

Combination method (requires use of 2 of the following):

- diaphragm with spermicide (cannot be used in conjunction with cervical cap/spermicide)
- cervical cap with spermicide (nulliparous women only)
- contraceptive sponge (nulliparous women only)
- male condom or female condom (cannot be used together)
- hormonal contraceptive: oral contraceptive pill (estrogen/progestin pill or progestin-only pill), contraceptive skin patch, vaginal contraceptive ring, or subcutaneous contraceptive injection

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

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

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

5.7.2 *Use in Pregnancy*

If a patient inadvertently becomes pregnant while on treatment with MK-3475 (pembrolizumab), the patient will immediately be removed from the study. The site will contact the patient at least monthly and document the patient's status until the pregnancy

has been completed or terminated. The outcome of the pregnancy will be reported without delay and within 24 hours if the outcome is a serious adverse experience (*e.g.,* death, abortion, congenital anomaly, or other disabling or life-threatening complication to the mother or newborn). The study investigator will make every effort to obtain permission to follow the outcome of the pregnancy and report the condition of the fetus or newborn. If a male patient impregnates his female partner, the study personnel at the site must be informed immediately and the pregnancy reported and followed.

5.7.3 *Use in Nursing Women*

It is unknown whether MK-3475 (pembrolizumab) is excreted in human milk. Since many drugs are excreted in human milk, and because of the potential for serious adverse reactions in the nursing infant, patients who are breast-feeding are not eligible for enrollment.

5.8 Treatment Beyond Progression

5.8.1 Mycosis Fungoides/Sézary Syndrome (Treatment Group 1)

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.

If Olsen Global Disease Assessment (including CT scans if applicable, mSWAT and Circulating Sézary Cells) shows progressive disease (PD), tumor assessment may be repeated by the site ≥4 weeks later in order to confirm PD with the option of continuing treatment per the instructions below while waiting for confirmation of progression. If repeat disease assessment shows a reduction in the tumor burden compared to the initial assessment demonstrating PD, treatment may be continued as per treatment calendar. In determining whether or not the tumor burden has increased or decreased, investigators should follow Olsen Disease Assessment Criteria (Protocol, Section 11). The decision to continue study treatment after the 1st evidence of disease progression determined by disease assessment is at the Investigator's discretion based on the clinical status of the patient as described in the table below.

A subject with unconfirmed progression of disease may continue trial treatment if clinically stable other than disease progression. A biopsy is recommended in cases of suspected pseudoprogression to determine if the patient has true progression of disease or pseudoprogression. Patients in whom the biopsy confirms pseudoprogression based on a predominance of immune infiltrate are recommended to remain on study. Biopsy findings consistent with pseudoprogression, evidence of a lymphoid infiltrate, necrotic tumor, without significant increase in viable tumor at site of suspected pseudoprogression, may justify continued treatment at the discretion of the PI.

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

Continuation after confirmation of progression:
Patients who are determined to have confirmed progression may continue to receive study treatment 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

The following assessment and stopping criteria apply to patients who continue study treatment beyond progression:

- Patients who continue therapy after progression will have mSWAT performed with every cycle (every 3 weeks) and a full Olsen Criteria assessment including mSWAT, CT scans, for those with measurable disease, and CSC, if positive for Sézary cells, every 4 cycles (every 12 weeks). At the discretion of the investigator these assessments may be repeated more frequently.
- Study drug will be discontinued if any compartment increases in value by 25% or more over the new baseline including mSWAT score, measurable disease by CT scan, or Circulating Sezary Cell Counts. The new baseline being defined as the assessments obtained at the confirmation of progression.

	Clinically Stable		**Clinically Unstable**	
	Imaging	**Treatment**	**Imaging**	**Treatment**
1st evidence of PD** (Based upon Olsen Criteria including scans (if applicable), mSWAT and Circulating Sézary Cells)	Repeat assessment at approximately 4 weeks to confirm PD	May continue study treatment at the Investigator's discretion while awaiting confirmatory assessment	Repeat assessment at approximately 4 weeks to confirm PD if possible	Discontinue treatment
Repeat assessment confirms PD**	If patient continues with study therapy, repeat mSWAT every cycle. mSWAT, CT scans, for measurable disease, and CSC, for patients who are positive, will be repeated every 4 cycles	Patient may continue therapy with MK-3475.	No additional assessments required	N/A

	(every 12 weeks) Must stop if any compartment increases by 25% or more.			
Repeat assessment shows SD, PR, or CR**	Continue regularly scheduled assessments per the study calendar	Continue study treatment at the Investigator's discretion	Continue regularly scheduled assessments per the study calendar	May restart study treatment if condition has improved and/or clinically stable per Investigator's discretion

** ***Note****:* Mycosis Fungoides and Sézary Syndrome may not be measurable by CT or PET/CT scan. Disease assessments will include CT or PET/CT Scans (only for those patients with measurable disease), mSWAT and Circulating Sézary Cell (CSC) measurement by flow cytometry. All of these will be taken into account to assess disease progression or regression through the use of the Olsen global assessment criteria for Mycosis Fungoides/Sézary Syndrome. In the table above PD, SD, PR and CR will be determined by Global Response Assessment as described in section 11.

5.8.2 Synovial Sarcoma (Treatment Group 2)

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 radiographic progression but who are otherwise stable without symptomatic progression may continue treatment up until confirmation. Confirmation imaging may be done as early as 6 weeks and up to 12 weeks later in order to assess for possible pseudo progression.

Confirmation of progression means that tumor growth has continued. If a progressing patient has a repeat scan that shows tumor regression from the previous scan this does not count as confirmation even if it is still progressive disease compared to baseline.

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

5.9 Guidelines for Management of Skin Flare Reaction in Patients with Mycosis Fungoides/Sézary Syndrome (Treatment Group 1)

In this trial the term "Skin Flare Reaction" will be used to describe skin changes that are felt by the investigator to be due to a MK-3475 (pembrolizumab)/Interferon-gamma immune related process. Patients may have dermatologic adverse events that are **not** immune related. We will **not** use the term "Skin Flare Reaction" to describe these reactions. Instead, other terms such as erythroderma or maculo-papular rash may be used, as applicable, to describe these non-immune-related dermatologic adverse events. The immune mediated, study drug related AE's will be termed "Skin Flare Reactions" for consistency.

If a patient has a Skin Flare Reaction they may be seen at a regular protocol visit or, if timing does not permit, they will be seen for an unscheduled visit. All patients with Skin Flare Reactions will have medical photography (mSWAT) performed for documentation purposes. Skin biopsies will be performed in accordance with section 9.1 with tissue being sent for local pathology review and tissue sent for research purposes to the CITN Central Lab. The tissue sent for local pathology will be used to help differentiate between an immune mediated flare reaction and progressive disease. In addition, all correlative studies except whole exome sequencing and neoantigen prediction, and microbiome analyses will be repeated. (See Study Calendars Section 10).

If it is not clear whether the event is a Skin Flare Reaction or Progressive disease the investigator is encouraged to consider TCR High Throughput Sequencing to determine whether the increase in T-cell density is from a rise in the original dominant tumor TCR sequence versus something new or reactive.

Patients with Skin Flare Reaction grade 1-2 should be managed with supportive care including the use of mild or moderate potency topical steroids for up to two weeks and diphenhydramine. Patients with grade 3-4 Skin Flare Reaction may receive at investigator's discretion a two week course of prednisone (30mg for 3 days, 20mg for 3 days, 10mg for 3 days, 5mg for 3 days).

5.10 Discontinuation of Treatment Following Complete Response (Treatment Group 1 and 2)

Discontinuation of treatment may be considered for patients who have attained a confirmed complete response (CR) that have been treated for at least 24 weeks with MK-3475 (pembrolizumab) in combination with interferon gamma-1b and had at least two treatment cycles beyond the date when the initial CR was declared.

5.11 Treatment Up to 2 Years (Treatment Group 1 and 2)

Treatment with MK-3475 (pembrolizumab) in combination with interferon gamma-1b will continue for up to 2 years, or until documented disease progression, 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, or administrative reasons.

6. DOSING DELAYS/DOSE MODIFICATIONS

6.1 Dose Modifications and Supportive Care Guidelines for Drug-Related Adverse Events (Treatment Group 1 and 2)

6.1.1 *MK-3475 (pembrolizumab) Dose Modifications*

Adverse events (both nonserious and serious) associated with MK-3475 exposure may represent an immunologic etiology. These AEs may occur shortly after the first dose or several months after the last dose of treatment. MK-3475 must be withheld for drug-related toxicities and severe or life-threatening AEs as the table in Section 6.1.3.

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

6.1.2 *MK-3475 (pembrolizumab) Supportive Care Guidelines*

Patients should receive appropriate supportive care measures as deemed necessary by the treating investigator. Suggested supportive care measures for the management of AEs with potential immunologic etiology are also outlined in the table in Section 6.1.3. Where appropriate, these guidelines include the use of oral or IV treatment with corticosteroids as well as additional anti-inflammatory agents if symptoms do not improve with administration of corticosteroids. Note that several courses of steroid tapering may be necessary as symptoms may worsen when the steroid dose is decreased. For each disorder, attempts should be made to rule out other causes such as metastatic disease or bacterial or viral infection, which might require additional supportive care. The treatment guidelines are intended to be applied when the investigator determines the events to be related to MK-3475.

***Note**:* If after the evaluation the event is determined not to be related, the investigator does not need to follow the treatment guidance (as outlined below).

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

6.1.3 *Dose Modification and Toxicity Management Guidelines for Immune-related AEs Associated with MK-3475 (pembrolizumab)*

General instructions:

1. Severe and life-threatening irAEs should be treated with IV corticosteroids followed by oral steroids. Other immunosuppressive treatment should begin if the irAEs are not controlled by corticosteroids.
2. Pembrolizumab must be permanently discontinued if the irAE does not resolve or the corticosteroid dose is not ≤10 mg/day within 12 weeks of the last pembrolizumab treatment.
3. The corticosteroid taper should begin when the irAE is ≤ Grade 1 and continue at least 4 weeks.
4. If pembrolizumab has been withheld, pembrolizumab may resume after the irAE decreased to ≤ Grade 1 after corticosteroid taper.

irAEs	Toxicity grade (CTCAE V5.0)	Action with pembrolizumab	Corticosteroid and/or other therapies	Monitoring and follow-up
Pneumonitis	Grade 2	Withhold	• Administer corticosteroids (initial dose of 1 - 2 mg/kg prednisone or equivalent) followed by taper • Add prophylactic antibiotics for opportunistic infections	• Monitor participants for signs and symptoms of pneumonitis • Evaluate participants with suspected pneumonitis with radiographic imaging and initiate corticosteroid treatment
	Recurrent Grade 2, Grade 3 or 4	Permanently discontinue		
Diarrhea / Colitis	Grade 2 or 3	Withhold	• Administer corticosteroids (initial dose of 1 - 2 mg/kg prednisone or equivalent) followed by taper	• Monitor participants for signs and symptoms of enterocolitis (ie, diarrhea, abdominal pain, blood or mucus in stool with or without fever) and of bowel perforation (ie, peritoneal signs and ileus) • Participants with ≥Grade 2 diarrhea suspecting colitis should consider GI consultation and performing endoscopy to rule out colitis • Participants with diarrhea/colitis should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion
	Recurrent Grade 3 or Grade 4	Permanently discontinue		

AST or ALT elevation or Increased Bilirubin	Grade 2 [a]	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 [b] or 4 [c]	Permanently discontinue	• Administer corticosteroids (initial dose of 1 - 2 mg/kg prednisone or equivalent) followed by taper	
Type 1 diabetes mellitus (T1DM) or Hyperglycemia	New onset T1DM or Grade 3 or 4 hyperglycemia associated with evidence of β-cell failure	Withhold [d]	• 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 [d]		
Hyperthyroidism	Grade 2	Continue	• Treat with non-selective beta-blockers (eg, propranolol) or thionamides as appropriate	• Monitor for signs and symptoms of thyroid disorders
	Grade 3 or 4	Withhold or permanently discontinue [d]		
Hypothyroidism	Grade 2, 3, 4	Continue	• Initiate thyroid replacement hormones (eg, levothyroxine or liothyronine) per standard of care	• Monitor for signs and symptoms of thyroid disorders
Nephritis: grading according to increased creatinine or acute kidney injury	Grade 2	Withhold	• Administer corticosteroids (prednisone 1 – 2 mg/kg or equivalent) followed by taper	• Monitor changes of renal function
	Grade 3 or 4	Permanently discontinue		
Myocarditis	Grade 1 or 2	Withhold		• Ensure adequate evaluation to confirm

	Grade 3 or 4	Permanently discontinue	• Based on severity of AE administer corticosteroids	etiology and/or exclude other causes
All Other immune-related AEs	Persistent Grade 2	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology or exclude other causes
	Grade 3	Withhold or discontinue based on the event [e]		
	Recurrent Grade 3 or Grade 4	Permanently discontinue		

[a] AST/ALT: >3.0 - 5.0 x ULN if baseline normal; >3.0 - 5.0 x baseline, if baseline abnormal; bilirubin:>1.5 - 3.0 x ULN if baseline normal; >1.5 - 3.0 x baseline if baseline abnormal

[b] AST/ALT: >5.0 to 20.0 x ULN, if baseline normal; >5.0 - 20.0 x baseline, if baseline abnormal; bilirubin:>3.0 - 10.0 x ULN if baseline normal; >3.0 - 10.0 x baseline if baseline abnormal

[c] AST/ALT: >20.0 x ULN, if baseline normal; >20.0 x baseline, if baseline abnormal; bilirubin: >10.0 x ULN if baseline normal; >10.0 x baseline if baseline abnormal

[d] The decision to withhold or permanently discontinue pembrolizumab is at the discretion of the investigator or treating physician. If control achieved or ≤ Grade 2, pembrolizumab may be resumed.

[e] Events that require discontinuation include but are not limited to: Guillain-Barre Syndrome, encephalitis, Stevens-Johnson Syndrome and toxic epidermal necrolysis.

6.1.4 MK-3475 (pembrolizumab) and Interferon Gamma-1b[a, b] Dose Modification and Toxicity Management for Other Drug-Related Adverse Events

	Dose Modification Guidelines			**Supportive Care Guidelines**	
Toxicity	**Hold treatment for Grade**	**Timing for Restarting Treatment**	**Treatment Discontinuation**	**CTCAE v5.0 Grade**	**Action / Supportive Care Guidelines**
Infusion Reaction (MK-3475)	General Considerations across all Grades: Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion. Appropriate resuscitation equipment should be available in the room and a physician readily available during the period of drug administration.				
				1[c]	Increase monitoring of vital signs as medically indicated until the patient is deemed medically stable in the opinion of the investigator. No premedication at subsequent dosing:
	2[d]	Toxicity resolves to Grade 0-1	Permanently discontinue if toxicity develops despite adequate premedication	2[e]	**Stop infusion and monitor symptoms.** Additional appropriate medical therapy may include, but is not limited to: • IV fluids • Antihistamines • NSAIDS • Acetaminophen • Narcotics Increase monitoring of vital signs as medically indicated until the patient is deemed medically stable in the opinion of the investigator. If symptoms resolve within 1 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: Before 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 patient should be premedicated for the next scheduled dose. **Patients who develop Grade 2 toxicity upon rechallenge despite adequate premedication should be permanently discontinued from further trial treatment administration.** Patient may be premedicated 1.5h (± 30 minutes) before infusion of pembrolizumab with:

	Dose Modification Guidelines			Supportive Care Guidelines	
Toxicity	**Hold treatment for Grade**	**Timing for Restarting Treatment**	**Treatment Discontinuation**	**CTCAE v5.0 Grade**	**Action / Supportive Care Guidelines**
					• Diphenhydramine 50 mg PO (or equivalent dose of antihistamine). • Acetaminophen 500-1000 mg PO (or equivalent dose of antipyretic).
	3-4	Permanently discontinue	Permanently discontinue	3[f] or 4[g]	**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 patient is deemed medically stable in the opinion of the investigator. Hospitalization may be indicated. **Patient is permanently discontinued from further trial treatment administration.**
Neutropenia, Thrombocytopenia	3	Hold MK-3475 and Interferon gamma until toxicity resolves to grade 0-1 and reduce Interferon gamma by 50% when restarting treatment	Toxicity >7 days or associated with bleeding requires discontinuation		
	4	Permanently discontinue	Permanently discontinue		
Hematologic AE other than neutropenia, thrombocytopenia or lymphopenia	3	Hold MK-3475 and Interferon gamma until toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks		

	Dose Modification Guidelines			Supportive Care Guidelines	
Toxicity	**Hold treatment for Grade**	**Timing for Restarting Treatment**	**Treatment Discontinuation**	**CTCAE v5.0 Grade**	**Action / Supportive Care Guidelines**
	4	Permanently discontinue	Permanently discontinue		
Skin-only Toxicity				2-4	Treat with topical corticosteroids (including high potency corticosteroids) and/or systemic corticosteroids. If systemic steroids are given, a steroid taper should start once symptoms improve to Grade 1 or less. For treatment group 1, if symptoms are consistent with a skin flare reaction, then management should follow the guidelines in section 5.9.
Drug-related neurologic sequelae including seizure, altered mental status or gait disturbance.	3-4	Permanently discontinue	Permanently discontinue		
All Other Drug-Related Toxicity[h]	3 or Severe	Hold both MK-3475 and Interferon gamma until toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks		
	4	Permanently discontinue	Permanently discontinue		

a. As described in section 5.1, the dose of Interferon-gamma will be increased at specified time points if patients have had less than a CR and are tolerating their current dose. The dose of Interferon-gamma may also need to be reduced, most likely for constitutional symptoms for patient tolerability. Interferon-gamma may also need to be held for up to a period of 3 weeks at the discretion of the investigator and in consultation with the patient (as described in section 5.1) if necessary for patient tolerance. Close communications between the patient and treating investigator will be needed to determine a tolerable and hopefully effective dose of Interferon-gamma.
b. In the event of an irAE (Table 6.1.3) Interferon-Gamma-1b will be withheld when MK-3475 is withheld, resumed when MK3475 is resumed and discontinued when MK-3475 (pembrolizumab) is discontinued.
c. Mild reaction; infusion interruption not indicated; intervention not indicated
d. If symptoms resolve within 1 hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (*e.g.,* from 100 mL/hr to 50 mL/hr). Otherwise dosing will be held until symptoms resolve and the patient should be premedicated for the next scheduled dose.
e. Requires infusion interruption but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDS, narcotics, IV fluids); prophylactic medications indicated for < =24 hrs
f. 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)
g. Life-threatening; pressor or ventilatory support indicated
h. Patients with intolerable or persistent Grade 2 drug-related AE may hold study medication at physician discretion. Permanently discontinue study drug for persistent Grade 2 adverse reactions for which treatment with study drug has been held, that do not recover to Grade 0-1 within 12 weeks of the last dose.

	Dose Modification Guidelines			Supportive Care Guidelines	
Toxicity	**Hold treatment for Grade**	**Timing for Restarting Treatment**	**Treatment Discontinuation**	**CTCAE v5.0 Grade**	**Action / Supportive Care Guidelines**

NOTE: For synovial sarcoma patients (Treatment group 2) the dose of interferon gamma-1b will be reduced by 50 mcg/m^2 (50%). For Treatment Group 2 (synovial sarcoma) grade 3 flu-like symptoms including fevers, fatigue, myalgias, or other patient reported symptoms that resolve to grade 1 within 48 hours should not trigger an interferon gamma-1b dose change.

6.1.5 *Interferon-gamma Supportive Care Guidelines*

- Acetaminophen 325 mg orally PRN per patient preference can be taken 30-60 minutes before injection for fevers and myalgias and may be used supportively at a dose of 325-650 mg orally Q6H PRN (≤ 3 gm/day).
- Anti-depressant medication in the form of a selective serotonin re-uptake inhibitor (SSRI) or next generation anti-depressant medication may be taken orally by patient to start up to two weeks prior or at any point during therapy to treat or protect against the development of depression. This should be decided between the patient and treating clinician.
- Ibuprofen 200 mg orally to 400 mg orally Q4-6H PRN (≤ 1200 mg/day) may be taken prophylactically or for supportive purposes for fevers and myalgias assuming adequate renal function as viewed by the treating clinician
- Diphenhydramine 25 to 50 mg orally Q4-6H (</= 300mg/day)

7. ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS (TREATMENT GROUP 1 AND 2)

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 and 7.3) 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: 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.

7.1.1 *CAEPRs for CTEP IND Agent(s)*

7.1.1.1 *CAEPR for CTEP IND Agent(s) MK-3475*

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).

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 2.5, December 27, 2019[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]		

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%)**	
CARDIAC DISORDERS			
		Myocarditis[2]	
		Pericarditis[2]	
ENDOCRINE DISORDERS			
	Adrenal insufficiency[2]		
	Endocrine disorders - Other (thyroiditis)[2]		
	Hyperthyroidism[2]		
	Hypohysitis[2]		
	Hypopituitarism[2]		
	Hypothyroidism[2]		
EYE DISORDERS			
		Uveitis[2]	
		Eye disorders - Other (Vogt-Koyanagi-Harada syndrome)	
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]		

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%)**	
Fatigue			***Fatigue (Gr 2)***
	Fever[2]		
HEPATOBILIARY DISORDERS			
	Hepatobiliary disorders - Other (autoimmune hepatitis)[2]		
IMMUNE SYSTEM DISORDERS			
		Anaphylaxis[2]	
		Cytokine release syndrome[2]	
		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		

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%)**	
	Aspartate aminotransferase increased[2]		
	Blood bilirubin increased		
	CPK increased		
		GGT increased	
		Serum amylase increased	
METABOLISM AND NUTRITION DISORDERS			
	Anorexia		
	Hyponatremia		
		Metabolism 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]		
	Joint range of motion decreased		
	Musculoskeletal and connective tissue disorder - Other (tenosynovitis)[2]		
	Myalgia[2]		
	Myositis[2]		
NERVOUS SYSTEM DISORDERS			

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%)**	
		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 (non-infectious myelitis)	
		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		

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%)**	
		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]		
		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. The current version can be obtained by contacting PIO@CTEP.NCI.NIH.GOV. Your name, the name of the investigator, the protocol and the agent should be included in the e-mail.

[2]Immune-mediated 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 hematopoeitic 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; Nephrotic syndrome; Proteinuria; Renal and urinary disorders - Other (hydronephrosis); 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.

7.1.1.2 *Common Adverse Events for Interferon-gamma (Actimmune Package Insert)*

The following data on adverse reactions are based on the subcutaneous administration of ACTIMMUNE at a dose of 50 mcg/m^2, three times weekly, in patients with CGD during a clinical trial in the United States and Europe.

The most common adverse reactions observed in patients with CGD are shown in the following table:

Adverse Reactions Occurring in 2 % or Greater of Chronic Granulomatous Disease (CGD) Patients Receiving ACTIMMUNE in Clinical Trials

	Percent of Patients	
Adverse Reactions	**ACTIMMUNE CGD (n=63)**	**Placebo CGD (n=65)**
Fever	52	28
Headache	33	9
Rash	17	6
Chills	14	0
Injection site erythema or tenderness	14	2
Fatigue	14	11
Diarrhea	14	12
Vomiting	13	5
Nausea	10	2
Myalgia	6	0
Arthralgia	2	0

The most common adverse reactions include constitutional symptoms such as fever, headache, chills, myalgia or fatigue which may decrease in severity as treatment continues.

7.1.1.3 *Less Common Adverse Reactions*

The following adverse reactions are assessed as potentially related to ACTIMMUNE (interferon gamma-1b) therapy:

Blood and Lymphatic System—neutropenia (reversible), febrile neutropenia, leukopenia, and thrombocytopenia.

Cardiovascular— angina pectoris, arrhythmia, atrial fibrillation, atrioventricular block, cardiac failure (including congestive cardiac failure), tachyarrhythmia, heart block, (acute) myocardial infarction, myocardial ischemia, syncope, and tachycardia.

Gastrointestinal—abdominal pain, dyspepsia, gastrointestinal bleeding, granulomatous colitis, hepatic insufficiency, and pancreatitis, including pancreatitis with fatal outcome.

General Disorders and Administration Site Conditions—asthenia, chest pain/discomfort, influenza-like illness/flu-like symptoms, injection site hemorrhage, injection site pain, malaise, rigors, and weakness.

Hepatobiliary Disorders—hepatic insufficiency and hepatomegaly.

Immunological—hypersensitivity, increased autoantibodies, lupus-like syndrome (including systemic lupus erythematosus-flares and drug-induced lupus erythematosus), and Stevens-Johnson syndrome.

Infections and Infestations—upper respiratory tract infection.

Investigations—blood alkaline phosphatase increased, liver function tests abnormal/ elevation of hepatic enzymes, increased triglycerides, and weight decreased.

Metabolic—hyponatremia, hypokalemia, hyperglycemia, and hypertriglyceridemia.

Musculoskeletal—back pain, clubbing, and muscle spasms.

Nervous System—dizziness (excluding vertigo), gait disturbance, headache, Parkinsonian symptoms, convulsion/seizure (including grand mal convulsions), and transient ischemic attacks.

Psychiatric—confusion, depression, disorientation, hallucinations, mental status changes, and mental status decreased.

Pulmonary—tachypnea, bronchospasm, pulmonary edema, and interstitial pneumonitis.
Renal—acute renal failure (which may be reversible) and proteinuria.

Skin and Subcutaneous Tissue Disorders—atopic dermatitis, (exacerbation of) dermatomyositis, transient cutaneous rash, and urticaria.

Vascular Disorder—deep venous thrombosis, hypotension, pulmonary embolism.

Abnormal Laboratory Test Values: Elevations of ALT and AST have been observed

7.1.2 *Adverse Event List(s) for [Other Investigational Agent(s)]:* N/A

7.1.3 *Adverse Event List(s) for Commercial Agent(s):* N/A

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 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

7.3.1 Expedited AE reporting for this study must use CTEP-AERS (CTEP Adverse Event Reporting System), accessed via the CTEP Web site (https://eapps-ctep.nci.nih.gov/ctepaers). The reporting procedures to be followed are presented in the "NCI Guidelines for Investigators: Adverse Event Reporting Requirements for DCTD (CTEP and CIP) and DCP INDs and IDEs" which can be downloaded from the CTEP Web site (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/adverse_events.htm). These requirements are briefly outlined in the tables below (Section 7.3.3).

In the rare occurrence when Internet connectivity is lost, a 24-hour notification is to be made to CTEP by telephone at 301-897-7497. Once Internet connectivity is restored, the 24-hour notification phoned in must be entered electronically into CTEP-AERS by the original submitter at the site.

7.3.2 *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.

7.3.3 *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 both 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.

A neonatal death should be reported expeditiously as Grade 4, "Death neonatal" under the general disorders and administration SOC.

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

7.3.4 *Additional Protocol-Specific Expedited Adverse Event Reporting Exclusions* 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 also be reported in routine study data submissions.**

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.

8. PHARMACEUTICAL INFORMATION (TREATMENT GROUP 1 AND 2)

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(s)

8.1.1 *MK-3475 (pembrolizumab) (NSC 776864)*

Other Names: SCH 900475, pembrolizumab

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 before administration. . 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 (pembrolizumab) vials to 2-8°C and quarantine the supplies. Provide a detailed report of the excursion (including documentation of temperature monitoring and duration of the excursion) to PMBAfterHours@mail.nih.gov for determination of suitability.

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 24 hours. MK-3475 (pembrolizumab) solutions may be stored at room temperature for a cumulative time of up to 6 hours. This includes room temperature storage of liquid drug product solution in vials, room temperature storage of infusion solution 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 patient 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).

Investigator Brochure Availability:
The current version of the Pembrolizumab 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 Identity 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 *Interferon-gamma-1b injection (NSC# 600662)*

Other Names: Actimmune

Classification: An Interferon-gamma

Mode of Action:
Interferons bind to specific cell surface receptors and initiate a sequence of intracellular events that lead to the transcription of interferon-stimulated genes. The three major groups of interferons (alpha, beta, gamma) have partially overlapping biological activities that include immunoregulation such as increased resistance to microbial pathogens and inhibition of cell proliferation. Type 1 interferons (alpha and beta) bind to the alpha/ beta receptor. Interferon gamma binds to a different cell surface receptor and is classified as Type 2 interferon. Specific effects of interferon gamma include the enhancement of the oxidative metabolism of macrophages, antibody dependent cellular cytotoxicity (ADCC), activation of natural killer (NK) cells, and the expression of Fc receptors and major histocompatibility antigens.

Description:
ACTIMMUNE (Interferon gamma-1b), an interferon gamma, is a single-chain polypeptide containing 140 amino acids. Production of ACTIMMUNE is achieved by fermentation of a genetically engineered Escherichia coli bacterium containing the DNA which encodes for the recombinant protein. Purification of the product is achieved by conventional column chromatography. ACTIMMUNE is a highly purified sterile solution consisting of non-covalent dimers of two identical 16,465 Dalton monomers; with a

specific activity of 20 million International Units/mg (2x106 International Units/0.5 mL) which is equivalent to 30 million units/mg.

How Supplied:
ACTIMMUNE (interferon gamma-1b) is supplied by Horizon Pharma and distributed by the Pharmaceutical Management Branch, CTEP/DCTD/NCI as a sterile, clear, colorless solution filled in a single-use vial for subcutaneous injection. Each vial permits the extraction of up to 0.5 mL of ACTIMMUNE with additional volume to facilitate solution withdrawal. Each 0.5 mL of ACTIMMUNE contains: 100 mcg (2 million International Units) of interferon gamma-1b.

Preparation:
Actimmune solution is withdrawn from the vial and is administered by the patient or a caregiver as a subcutaneous injection.

Storage:
Store vials in the refrigerator at 2°C to 8°C (36 °F-46 °F). Do Not Freeze.

Avoid excessive or vigorous agitation. Do Not Shake.

Stability:
Refer to the package label for product expiration. An unused vial of ACTIMMUNE can be stored at room temperature up to 12 hours before use. Discard vials if not used within the 12-hour period. Do not return to the refrigerator.

Route of Administration: Subcutaneous

Patient Care Implications: See section 6.1.5 (Supportive Care Guidelines)

Availability:
Commercial supplies of Interferon Gamma-1b (ACTIMMUNE) are supplied to investigators by the Division of Cancer Treatment and Diagnosis (DCTD), NCI.

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

8.1.3 *Agent Ordering and Agent Accountability*

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 investigator at that institution.

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

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. For questions about drug orders, transfers, returns, or accountability, call or email PMB any time. Refer to the PMB's website for specific policies and guidelines related to agent management.

8.1.3.1 *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 appropriate 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.

8.1.4 *Useful Links and Contacts*

- CTEP Forms, Templates, Documents: http://ctep.cancer.gov/forms/
- NCI CTEP Investigator Registration: RCRHelpDesk@nih.gov
- PMB policies and guidelines: http://ctep.cancer.gov/branches/pmb/agent_management.htm
- PMB Online Agent Order Processing (OAOP) application: https://ctepcore.nci.nih.gov/OAOP/
- CTEP Identity and Access Management (IAM) account: https://ctepcore.nci.nih.gov/iam/
- CTEP IAM account help: ctepreghelp@ctep.nci.nih.gov
- PMB email: PMBAfterHours@mail.nih.gov
- PMB phone and hours of service: (240) 276-6575 Monday through Friday between 8:30 am and 4:30 pm (ET)
- IB Coordinator: IBCoordinator@mail.nih.gov
- PMB phone and hours of service: (240) 276-6575 Monday through Friday between 8:30 am and 4:30 pm (ET)

9. BIOMARKER, CORRELATIVE, AND SPECIAL STUDIES

9.1 Mycosis Fungoides/Sézary Syndrome (Treatment Group 1)

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 before 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:

- For a hemoglobin over 10.0 g/dL, draw the full volume of blood for safety labs, flow cytometry for Circulating Sézary Cells, research labs and the biorepository.
- For a hemoglobin between 9.0 and 10.0, draw the full volume of blood for safety labs, flow cytometry for Circulating Sézary Cells, and research labs. Do not draw for the biorepository.
- For a hemoglobin less than 9.0 g/dL, draw only the safety labs and flow cytometry for Circulating Sézary Cells.

9.1.1 Biomarker Studies

To assess the immune response and pre-determined correlative studies a skin biopsy will be collected and peripheral blood collected at baseline (screening). Skin and blood will then be required post IFN lead-in (C1D1). Skin and blood will then be required at C2D1 to detect an early combination effect. Blood samples will then be drawn at intervals specified in the study calendars. Skin and blood are required for new tumors or progressive disease, at EOT and for skin flare reactions.

Table 9.1 Tumor Tissue and Blood Collection

		Response (PR/CR)/PD	**EOT and Skin Flare Rxn**
5 mm punch biopsies*	**Required at baseline**– (Sent to CITN Central Lab in formalin) and at C1D1 and C2D1	**Required at progression or appearance of a new lesion** –(Sent to CITN Central Lab in formalin) **Optional at response (PR/CR)**	**Required** – (Sent to CITN Central Lab in formalin)
Image guided Core Biopsy (subjects with known LN disease only)	***Optional*** – (Core biopsy to CITN Central Laboratory in Formalin)	***Optional*** – (Core biopsy to CITN Central Laboratory in Formalin)	***Optional*** – (Core biopsy to CITN Central Laboratory in Formalin)
Biomarkers (blood)	**Required** (Sent to CITN Central Lab) timing of specific biomarkers are variable, see study calendar	**Required for both response and PD (**Sent to CITN Central Lab)	**Required** (Sent to CITN Central Lab)
Biorepository: 30 mL total volume. (20 mL for PBMCs and 10 mL for Serum)	***Optional*** (Sent to CITN Central Lab) at screening, then every 3rd cycle	***Optional*** (Sent to CITN Central Lab)	***Optional*** (Sent to CITN Central Lab)

*Any tissue remaining after testing has been completed will be stored in the CITN Central Laboratory Biorepository for storage and future testing if the patient has given permission in the consent form.

**All blood that is drawn for storage in the Biorepository will be shipped to the CITN Central Laboratory Biorepository for storage and future testing.

9.1.1.1 *Biopsy Instructions*

Two side-by-side 5 mm (minimal) punch biopsies per lesion should be obtained if at all possible. If the skin lesion is too small for side-by-side biopsies, one 6-8 mm punch can be obtained and bisected for handling. Samples from more than one lesion type (patch, plaque, tumor) or anatomic site (if all same type of lesion) are strongly encouraged. If diagnostic tissue is needed (to send to clinical/surgical pathology), bisected half of a punch biopsy can be sent; the remaining skin samples should be handled per lab manual.

9.1.1.2 *Archival Tissue*

Archival tissue is not mandatory, however if it is available and if the patient has given permission in the consent form an FFPE block may be sent to the CITN Central Laboratory where slides will be made and tested for Chromogenic (Single-Color) IHC for PD-L1 and for Multiparametric (Two-Color) IHC. The CITN Central Lab will also test archival tissue for Transcriptional Analyses using the Nanostring platform. If archival tissue is not available it is important to review the pathology report and confirm the diagnosis.

9.1.1.3 *Image Guided Core Biopsy*

If a patient has known lymph node disease an optional image-guided core biopsy of the lymph node may be obtained at the other biopsy time points. Patients may refuse the lymph node biopsies and still participate in the trial. Lymph node core biopsies will be obtained at the respective Cancer Center according to their clinical SOP's.

9.1.1.4 *Circulating Tumor Cells*

Circulating Tumor Cells will be referred to as circulating Sézary cells or CSCs in this protocol). Sézary cells are typically CD4+CD26- and/or CD4+CD7- however in rare cases the phenotype is CD8+ or loss of CD3 expression. For an individual patient only one of the phenotypes will be used. We will follow the defined Sézary cell phenotype over time using the Olsen Criteria for response assessment. [Olsen 2011]

One of the Global Measurements for response will be Response in Blood which will involve a quantitative measurement of blood tumor burden using flow cytometry (testing for the percentage and absolute number of Circulating Sézary Cells). The flow cytometry testing for Sézary Cell Quantification will be performed locally at the individual research sites.

9.1.2 Exploratory/Ancillary Correlative Studies

9.1.2.1 *Chromagenic (Single-Color) immunohistochemistry for PD-1*

PD-L1 expression has emerged as the leading biomarker for response to anti-PD1 therapy, but studies thus far have found this to be far from a perfect biomarker. This may be due at least in part to the dynamic nature of PD-L1 expression. Interferon

gamma is known to upregulate PD-L1 expression in some tumor cells and frequently on tumor infiltrating leukocytes. With this biomarker we will explore the predictive value of PD-L1 expression before treatment as well as the inducible expression after interferon gamma treatment. FFPE skin biopsies will be stained with the FDA approved 22C3 assay. Staining will be assess both pre-treatment and after interferon gamma treatment. We will test whether PD-L1 expression (baseline and/or inducible) correlates with MK-3475 (pembrolizumab) response in the Mycosis Fungoides/Sézary Syndrome population.

Collection of Specimen(s):
Specimens will include archived and prospectively obtained tumor biopsies including skin and/or lymph nodes including possible punch and/or core biopsies.

Handling of Specimens(s)
Biopsy samples will be placed in formalin and shipped to the CITN Central Laboratory.

Shipping of Specimen(s)
Participating sites will send biopsy tissue in formalin for overnight delivery to the CITN Central Laboratory. The CITN Central Laboratory will prepare FFPE blocks then prepare slides.

Site(s) Performing Correlative Study
The CITN Central Laboratory will coordinate the Chromagenic IHC testing using shared resources of the Fred Hutchinson Cancer Research Center (FHCRC) under the direction of Dr. Rob Pierce.

9.1.2.2 *Multiparametric Immunohistochemistry*
The skin microenvironment plays a critical role in the development and progression of cutaneous T cell lymphomas (CTCL). There are a number of potentially suppressive immune populations, such as regulatory T cells and M^2 macrophages, present within CTCL involved skin that may blunt response to immunotherapy. Conversely, the presence of a tumor infiltrating lymphocyte population has been correlated with response to immune checkpoint blockade in other malignancies. To better define the spatial relationship between CTCL cells and the other key microenvironment residents, we will employ multiparametric immunohistochemistry for CD3, CD4, CD8, Foxp3, and CD163. In addition, we will co-stain for PD1, PD-L1, PD-L2, to define expression of these key markers on the relevant immune subsets.

Collection of Specimen(s)
Specimens will include archived and prospectively obtained tumor biopsies from skin and/or lymph nodes including possible punch and/or core biopsies

Handling of Specimens(s)
Biopsy samples will be placed in formalin and shipped to the CITN Central Laboratory.

Shipping of Specimen(s)
Participating sites will send biopsy tissue in formalin to the CITN Central Laboratory. The CITN Central Laboratory will prepare FFPE blocks then prepare the slides.

Site(s) Performing Correlative Study
The CITN Central laboratory will coordinate the multiparametric immunohistochemical assays using shared resources of the FHCRC under the direction of Dr. Rob Pierce to identify and enumerate key cellular components and immunoregulatory molecules to include PD-1, PD-L1, among other analytes.

9.1.2.3 *Multiplexed Ion Beam Imaging*
The skin microenvironment of CTCL includes CD8+ tumor infiltrating T cells, dendritic cells, macrophages, mast cells, and non-malignant CD4+ T cells including regulatory T cells. While the above studies will provide essential data with standard methodologies, they are unable to discriminate many critical cell populations due to the limitation of simultaneously detectable parameters. As a relevant example, in CTCL, the malignant T cells themselves can only be reliably identified by the expression pattern of a minimum of two parameters, typically CD4 and either CD7 or CD26. Until recently, there has been no imaging technology available capable of providing sufficient dimensionality to both discriminate relevant immune populations and simultaneously detect expression of other key markers.

A mass spectrometry based approach dubbed multiplexed ion beam imaging (MIBI) is a novel approach to antibody-mediated labeling and imaging of tissue. The use of heavy metal isotope labels enables high dimensional multiplexing with minimal overlap between metals from formalin-fixed paraffin embedded tissue samples resulting in a theoretical limit of over 100 parameters collected per image. Currently, access to MIBI technology is very limited, with only two systems available worldwide. In collaboration with researchers at Stanford University, we have the opportunity to apply MIBI technology to study the CTCL skin microenvironment in unprecedented detail from primary patient samples collected before and during therapy. Through high dimensional analysis, we will decipher the complex interactions between tumor cells and the diverse immune residents within their local microenvironment. MIBI is uniquely capable of simultaneously discerning both the spatial relationship between CTCL cells and interacting immune cells and their relative expression of relevant immunomodulatory molecules such as PD-1 and PD-L1. Applying MIBI to paired will provide an unparalleled glimpse into the perturbation of the immune microenvironment induced by immune checkpoint blockade.

Collection of Specimen(s)
Specimens will include archived and prospectively obtained tumor biopsies including skin and/or lymph nodes including possible punch and/or core biopsies

Handling of Specimens(s)
Biopsy samples will be placed in formalin and shipped to the CITN Central Laboratory.

Shipping of Specimen(s)
Participating sites will send biopsy tissue in formalin to the CITN Central Laboratory. The CITN Central Laboratory or designate will prepare FFPE blocks then prepare slides. Slides will be sent to Stanford for testing.

Site(s) Performing Correlative Study
Stanford University, under the direction of Dr. Jinah Kim.

9.1.2.4 *Transcriptional Analyses*
The Nanostring platform will be used to profile mRNA expression of approximately 730 genes in an attempt to define a gene set predictive for clinical response to MK-3475 (pembrolizumab). The utility of this assay is two-fold. First, it will test the hypothesis that there is an immune related gene expression signature that predicts response to MK-3475 (pembrolizumab) and interferon gamma. Second, it will assess for Th1 polarization by interferon gamma of helper T cells in the tumor site. Profiling will be performed on RNA extracted from FFPE skin biopsies and may also be performed on peripheral blood mononuclear cells.

Collection of Specimen(s)
Specimens will include archived and prospectively obtained tumor biopsies including skin and/or lymph nodes including possible punch and/or core biopsies

Handling of Specimens(s)
Biopsy samples will be placed in formalin and shipped to the CITN Central Laboratory.

Shipping of Specimen(s)
Participating sites will send biopsy tissue in formalin to the CITN Central Laboratory. The CITN Central Laboratory or designate will prepare FFPE blocks then prepare slides. Slides will be sent to Nanostring Technologies in Seattle for Nanostring gene panel

Site(s) Performing Correlative Study
The CITN Central lab will perform the analyses of testing results from Nanostring.

9.1.2.5 *Whole Exome Sequencing and Neoantigen Prediction*
Genomic studies of CTCL have revealed frequent alterations in T cell receptor signaling and CD28 co-stimulatory pathways as well as a translocation event involving PD-L1. We propose to perform whole exome sequencing of paired germline/tumor DNA to determine whether these or other genomic alterations are associated with response to PD-1 blockade. Mutational burden and neoantigen burden have been found to correlate with response to immune checkpoint blockade in other

malignancies. Somatic mutations identified by whole exome sequencing will be analyzed for predicted formation of neoantigens. Neoantigen specific T cells will be detected by a combination of peptide-MHC tetramer staining and functional assays such as upregulation of CD137, OX-40, and interferon-gamma production after stimulation with candidate neoantigen peptides.

Collection of Specimen(s)
Germline DNA will be collected from FACS sorting of cryopreserved PBMCs for all patients. Tumor DNA will either be collected from sorting PBMCs (in patients with sufficient numbers of circulating tumor cells) or else from skin and/or lymph node biopsy specimens.

Handling of Specimens(s)
Biopsy samples will be placed in formalin and shipped to the CITN Central Laboratory. In situations where PBMC's will be tested, the sites will ship tubes to the Central Lab for processing. PBMCs will then be processed and cryopreserved at the Central Lab.

Shipping of Specimen(s)
The CITN Central Lab will send frozen PBMC's for all patients to provide germline DNA and/or tumor DNA when circulating tumor cells are present. For patients with insufficient numbers of circulating tumor cells, the CITN Central Lab will section and ship material from FFPE preserved tissue blocks.

Site(s) Performing Correlative Study
The Stanford Laboratory of Dr. Paul Khavari, or an equivalent laboratory, will perform the Exome Sequencing and neoantigen identification.

9.1.2.6 *Immunophenotyping*
CyTOF is a mass spectrometry-based method of single cell analysis analogous to flow cytometry that is capable of collecting >30 parameters for each cell. CyTOF and multiparametric flow cytometry will be employed to extensively immunophenotype circulating peripheral lymphocytes before treatment, after 1 week of interferon gamma treatment and after the treatment with a combination of MK-3475 (pembrolizumab) and interferon gamma. In addition to standard immunophenotyping, cells will be analyzed with and without TCR stimulation (either by PMA/ionomycin or anti-CD3) to assess for function defects in T cells. In addition, other cell types (*e.g.,*Tregs and myeloid-derived cells with T cell suppressor function) and immunomodulatory molecules (*e.g.,*IL-10) may be identified as additional components of the immunosuppressive milieu in Mycosis Fungoides/Sézary Syndrome. Flow cytometry will also be used to evaluate peripheral blood mononuclear cells.

Collection of Specimen(s)
Whole blood will be collected into heparinized tubes.

Handling of Specimens(s)
Blood samples will be shipped to the CITN Central Laboratory for processing. The CITN Central Laboratory will subsequently ship frozen PBMC samples to Stanford for testing.

Shipping of Specimen(s)
Frozen PBMCs will be shipped to Stanford University.

Site(s) Performing Correlative Study
Analysis to be performed at Stanford University in the laboratory of Dr. Michael Khodadoust.

9.1.2.7 *Cytokine/Chemokine Analysis (serum ELISA)*
Using a highly multiplexed ELISA-based platform, we will perform a longitudinal analysis of cytokines, chemokines and other serum tumor/oncogene-associated proteins at baseline (before treatment) and on treatment. Exploratory analysis will be performed to determine whether any cytokines/chemokines correlate with response to therapy. These assays will also provide a glimpse into the systemic immune perturbations caused by systemic interferon gamma therapy.

Collection of Specimen(s)
Whole blood will be collected into red-top tubes.

Handling of Specimens(s)
Blood samples will be processed to frozen serum at the local labs. Frozen serum vials will be shipped from clinical sites to the CITN Central Laboratory. The Central Laboratory will subsequently ship aliquots of serum to Stanford University, Khodadoust Laboratory. Aliquots will be thawed and analyzed by Luminex.

Shipping of Specimen(s)
Frozen serum will be shipped by the CITN Central Laboratory to Stanford University.

Site(s) Performing Correlative Study
All sites will provide samples for analysis to be performed at Stanford University in the laboratory of Dr. Michael Khodadoust.

9.1.2.8 *T cell Receptor High Throughput Sequencing*
High throughput sequencing of TCR genes is emerging as a valuable disease marker and measure of minimal residual disease in cutaneous T cell lymphomas. In addition to providing a measurement of the burden of the malignant clone, high throughput sequencing allows interrogation of the entire T cell repertoire. This correlate will enable an exploratory analysis of the TCR repertoire as a potential biomarker for response to therapy. Characteristics such as repertoire diversity and clonal dynamics will be correlated to clinical responses. We will also utilize TCR-HTS to identify and quantify Sézary Cells and we will compare the utility of this testing methodology to Flow Cytometry.

Collection of Specimen(s)
Specimens will include archived and prospectively obtained tumor skin biopsies and blood samples.

Handling of Specimen(s)
Biopsy samples will be placed in formalin and shipped to the CITN Central Laboratory. Whole blood will be shipped directly to the CITN Central Laboratory for processing and testing.

Shipping of Specimen(s)
All samples will be shipped to the CITN Central Laboratory for testing.

Site(s) Performing Correlative Study
The CITN Central Lab will coordinate the TCR-HTS testing using shared resources of the FHCRC or Adaptive Biosciences.

9.1.3 Special Studies

9.1.3.1 *Special Correlative Study #1: Whole Blood Kyn/Trp Ratios*
It is postulated that enhanced IDO expression may occur in patients who fail anti-PD-1 therapy. Thus, Kyn/Trp ratios will be assayed as measured in peripheral blood at baseline and at specified intervals throughout the trial. Evidence of this mechanism of resistance would suggest that some anti-PD-1 failures could potentially be overcome with an IDO inhibitor.

Collection of Specimens
Whole blood will be collected into heparinized tubes and processed to frozen plasma at the local lab.

Handling of Specimen(s)
Frozen vials of plasma will be batch shipped to the CITN Central Laboratory.

Shipping of Specimens
Frozen vials of plasma will be shipped from the CITN Central Laboratory to the Incyte Corporation for testing.

Site(s) Performing Correlative Study
The Kyn/Trp analysis will be conducted at Incyte Corporation

9.1.3.2 *Special Correlative Study #2: Microbiome Analyses*
The impact and importance of the gut microbiome in human cancer patients' responses to immunotherapy has not yet been well-characterized and will be important to determine. We will collect microbiome samples from patients at baseline and perform taxonomic profiling via 16S rRNA gene sequencing and metagenomic whole genome shotgun (WGS) sequencing. Sequencing data will be analyzed and compared to clinical responses to determine whether response or non-response to treatment can be correlated with specific microbiota.

Assays will be performed in collaboration with Dr. David Fredricks at FHCRC or other agreed upon collaborator.

Collection of Specimen(s)
Enrolled study subjects will be provided with fecal swab/storage devices and SOPs. Fecal samples will be collected by patients before initiating therapy using standard, at home stool-collection procedures using standardized fecal swab/storage devices.

Handling of Specimens(s)
Samples will be initially stored frozen or at 4°C at home by patients and returned to the clinical research site at the first study visit and stored at the local site at -80°C.

Shipping of Specimen(s)
Frozen samples will be batch shipped overnight on dry ice to the CITN Central Laboratory (CIML). Sites will utilize a web-based specimen system (BSI) to communicate with the CIML. The CIML will coordinate the shipment of samples to Dr. David Fredricks at FHCRC.

Site(s) Performing Correlative Study
Assays will be performed in collaboration with Dr. David Fredricks at FHCRC, or a CIMAC or other collaborator.

9.2 Synovial Sarcoma (Treatment Group 2)

9.2.1 Blood Draws in Anemic and Pediatric Patients

The study calendar and lab manual describe blood draws for safety- and research labs. In the interest of patient safety, we are including a provision to draw less blood if patients are anemic or <18 years of age.

9.2.1.1 *Blood Draw Instructions based on Hemoglobin Level*

A complete blood count (CBC) will be performed as part of the safety labs at each study visit. The results of the CBC will be reviewed and the following blood volumes will be drawn based upon the patient's hemoglobin level:

- For a hemoglobin value over 10.0 g/dL, draw the full volume of blood for safety labs and research labs.
- For a hemoglobin value between 9.0 and 10.0 g/dL, draw blood for safety labs and research labs for Flow Cytometry and Cytokines only (Do not draw blood for ELISPOT).
- For a hemoglobin less than 9.0 g/dL, draw only the safety labs.

9.2.1.2 *Blood Draw instructions based on patient weight if <18 years of age*

For patients <18 years of age, blood draws will be prioritized as follows:

- For patients weighing ≥30 kg (66 lbs) draw the full volume of safety labs and research labs (up to 165 mL total volume).
- For patients weighing <30 kg (<64 lbs) only draw blood for safety labs and cytokines (up to 25 mL total volume).

9.2.2 Research Biopsies for Correlative Studies

A mandatory research biopsy will occur prior to the initiation of study therapy. There is no time limit on the pretreatment biopsy. However, the patient cannot have undergone a different therapy since its collection. Archival tissue can be used in lieu of a pretreatment biopsy if the patient has not undergone any treatment since that tissue was collected. Archival tissue may also be used in lieu of a fresh biopsy for patients <18. The second biopsy is mandatory for participant ≥18 years of age, but will be performed only if deemed safe by the principal investigator. For participants <18 years of age a second biopsy is optional and will only be performed if deemed safe by the principal investigator. The second biopsy will be performed after Week 8 but before the patient's first scan which will occur 12 weeks after starting treatment. Multiplex immunohistochemistry of tumor biopsy samples will test whether clinical outcomes correlate with the level of increased MHC expression, T cell infiltration and the presence of other immune infiltrates on paired biopsy specimens. Gene expression using the NanoString platform will be used to determine whether increased expression of inflammatory markers at 8-12 weeks correlates with clinical outcomes.

9.2.3 Biopsy Instructions

A biopsy will be performed on a safely accessible lesion to be chosen by the patient's treating physician. This lesion should not have received prior radiation or any other locally directed therapy (e.g., hepatic artery ablation, clinical trial of intra-tumor therapy). When possible, four cores will be pulled so long as the treating physician thinks this can be done safely and with high quality. In general, all cores should be fixed in formalin immediately after they are pulled and sent to the CITN Immune Monitoring Lab (CIML). However, the PI may select samples where there is particular scientific interest for cores to be processed differently, such as placed in RPMI for digestion and flow cytometric analysis or cell culture. In those special cases the PI will give specific instructions for handling those samples.

9.2.4 Archival Tissue

Archival tissue is not mandatory, however if it is available and if the patient has given permission in the consent form a formalin-fixed paraffin-embedded (FFPE) block will be sent to the CITN Central Laboratory for storage and analysis.

9.2.5 Blood Sampling for Correlative studies

Blood samples for correlative studies, including peripheral blood mononuclear cells (PBMC) and serum, will be drawn prior to starting treatment and then as indicated in the Study Calendar. Patients will be tested for HLA-A*0201 and HLA-A*2402 and in patients expressing the alleles, MHC tetramers will be used to test for increased antigen specific populations. We hypothesize that large, central memory T cell populations with specificity for NY-ESO-1, PRAME and MAGE family antigens will result in improved clinical outcomes. Furthermore, robust expansion of highly activated T central memory cell derived populations after starting treatment will correlate with better clinical outcomes.

9.2.6 Integrated/Exploratory Correlative Studies

9.2.6.1 *Flow Cytometry for Selected Class I HLA Alleles and Tetramer Analyses for Antigen-Specific T Cell Phenotyping on PBMC (Flow Cytometry)*

Collection of Specimens
Whole blood will be collected into heparinized tubes. Blood draws will be performed by venipuncture on study subjects just before, during and at end of treatment.

Handling and Shipping of Specimens
Blood Samples will be collected at room temperature and shipped ambient to the CIML the same day as the blood draw. The sample must be received at the CIML within 24 hours of blood draw. Blood samples will be shipped to the CIML for processing to PBMC and stored in liquid nitrogen. Clinical sites will utilize a web-based specimen system (BSI) to communicate with the CIML.

Site(s) Performing Correlative Study
Analysis will be performed at the Fred Hutchinson Cancer Research Center (FHCRC) in the laboratory of Dr. Seth Pollack and/or at the CIML under the direction of Dr. Steven Fling.

9.2.6.2 *Immune Phenotype Panel (Multispectral Immunohistochemistry)*

Collection of Specimens
Tumor biopsy tissue will be collected prior to and during therapy as described in sections 9.2.2, 9.2.3 and 9.2.4.

Handling and Shipping of Specimens
Tissue will be placed in formalin for overnight shipping to the CIML where they will be embedded in paraffin. For archival samples, clinical sites will arrange for the formalin-fixed, paraffin-embedded tumor blocks or FFPE slide to be shipped at ambient temperature to the CIML. Clinical sites will utilize a web-based specimen system (BSI) to communicate with the CIML. Paraffin blocks (or FFPE slides) will be stored at 4ºC under desiccant. The CIML will coordinate shipment to the FHCRC immunopathology lab or other vendor.

Site(s) Performing Correlative Study
Analysis will be performed in the laboratory of Dr. Rob Pierce at the FHCRC Core Laboratory, and FHCRC shared services.

9.2.6.3 *Immune Gene Expression Signature (NanoString®Gene Expression using the nCounter® Human Immunology V2 Panel and the nCounter®PanCancer Immune Profiling Panel)*

Collection of Specimens
Tumor biopsy tissue will be collected prior to and during therapy as described in sections 9.2.2, 9.2.3 and 9.2.4.

Handling and Shipping of Specimens
Tissue will be placed in formalin for overnight shipping to the CIML where they will be embedded in paraffin. Clinical sites will utilize a web-based specimen system (BSI) to communicate with the CIML. For archival samples, clinical sites will arrange for the formalin-fixed, paraffin-embedded tumor blocks or FFPE slide to be shipped at ambient temperature to the CIML. Paraffin blocks (or FFPE slides) will be stored at 4ºC under desiccant. The CIML will coordinate shipment to Nanostring or designated Cancer Immune Monitoring and Analysis Center (CIMAC).

Site(s) Performing Correlative Study
Analysis to be performed at NanoString Corp.and at the CIML/FHCRC or at a designated vendor or CIMAC.

9.2.6.4 *T Cell Receptor (TCR) Clonality (TCR ImmunoSeq)*

Collection of Specimens
Tumor biopsy tissue will be collected prior to and during therapy as described in sections 9.2.2, 9.2.3 and 9.2.4.

Handling and Shipping of Specimens
Biopsy samples will be placed in formalin and shipped to the CIML. For biopsies done as part of this protocol, tissue in formalin will be shipped overnight at ambient temperature to the CIML where they will be embedded in paraffin. For archival samples, clinical sites will arrange for the formalin-fixed, paraffin-embedded tumor blocks or FFPE slide to be shipped at ambient temperature to the CIML. Clinical sites will utilize a web-based specimen system (BSI) to communicate with the CIML. Paraffin blocks (or FFPE slides) will be stored at 4ºC under desiccant. The CIML will coordinate shipment to Adaptive Biotechnologies or designated CIMAC.

Site(s) Performing Correlative Study
Analysis to be performed at Adaptive Biotechnologies or designated CIMAC.

9.2.7 Exploratory/Ancillary Correlative Studies

9.2.7.1 *PD-L1 Baseline and Post-Treatment (Immunohistochemistry)*

Collection of Specimens
Tumor biopsy tissue will be collected prior to and during therapy as described in sections 9.2.2, 9.2.3 and 9.2.4.

Handling and Shipping of Specimens
Biopsy samples will be placed in formalin and shipped to the CIML. For biopsies done as part of this protocol, tissue in formalin will be shipped overnight at ambient temperature to the CIML where they will be embedded in paraffin. For archival samples, clinical sites will arrange for the formalin-fixed, paraffin-embedded tumor blocks or FFPE slide to be shipped at ambient temperature to the CIML. Clinical sites will utilize a web-based specimen system (BSI) to communicate with the CIML. Paraffin blocks (or FFPE slides) will be stored at 4ºC under desiccant. The CIML will coordinate shipment to the FHCRC immunopathology lab or other vendor.

Site(s) Performing Correlative Study
These analyses will be performed using qualified analytes and analytic tools at the immunopathology lab and shared resources of the FHCRC under the direction of Dr. Rob Pierce, or at a vendor to be determined or at Merck.

9.2.7.2 *Whole Blood Lymphocyte and Monocyte Immunophenotyping (Whole Blood Multiparametric Flow Cytometry)*

Collection of Specimens
Whole blood will be collected into heparinized tubes. Blood draws will be performed by venipuncture on study subjects just before, during, and at end of treatment.

Handling and Shipping of Specimens
Blood Samples will be collected at room temperature and shipped ambient to the CIML the same day as the blood draw. The sample must be received at the CIML within 24 hours of blood draw. Clinical sites will utilize a web-based specimen system (BSI) to communicate with the CIML. Blood samples will be shipped to the CIML for processing and the Whole Blood Assay.

Site(s) Performing Correlative Study
Analysis will be done at FHCRC/CIML under the direction of Dr. Steven Fling.

9.2.7.3 *Anti-Tumor Immune T cell Responses (ELISPOT)*

Collection of Specimens
Whole blood will be collected into heparinized tubes. Blood draws will be performed by venipuncture on study subjects just before, during, and at end of treatment.

Handling and Shipping of Specimens
Blood Samples will be collected at room temperature and shipped ambient to the CIML the same day as the blood draw. The sample must be received at the CIML within 24 hours of blood draw. Clinical sites

will utilize a web-based specimen system (BSI) to communicate with the CIML. Blood samples will be shipped to the CIML for processing to PBMC and stored in Liquid Nitrogen.

Site(s) Performing Correlative Study
Analysis will be done at the FHCRC at the CIML under the direction of Dr. Steven Fling.

9.2.7.4 *Multiplex Cytokines (Affymatrix or Luminex)*

Collection of Specimens
Whole blood will be collected into red-top tubes by venipuncture. Blood draws will be performed by venipuncture on study subjects just before, during, and at end of treatment.

Handling and Shipping of Specimens
Blood samples will be processed to frozen serum at the local labs and stored frozen at -80°C. Frozen serum vials will be shipped in Batch from clinical sites to the CIML. Clinical sites will utilize a web-based specimen system (BSI) to communicate with the CIML. The CIML will coordinate shipments of serum to the FHCRC Shared Resource facility, to CIMAC collaborator, as needed.

Site(s) Performing Correlative Study
Analysis will be done at FHCRC shared services, or at a CIMAC collaborator.

9.2.7.5 *Microbiome Analyses*

Collection of Specimens
Enrolled study subjects will be provided with fecal swab/storage devices and SOPs. Fecal samples will be collected by patients prior to initiating therapy using standard, at home stool-collection procedures using standardized fecal swab/storage devices.

Handling and Shipping of Specimens
Samples will be initially stored frozen or at 4°C at home by patients and returned to the clinical research site at the first study visit and stored at the local site at -80°C. Frozen samples will be batch shipped overnight on dry ice to the CITN Central Laboratory (CIML). Sites will utilize a web-based specimen system (BSI) to communicate with the CIML. The CIML will coordinate the shipment of samples to Dr. David Fredricks at FHCRC or to designated CIMAC.

Site(s) Performing Correlative Study
Assays will be performed in collaboration with Dr. David Fredricks at FHCRC or other CIMAC collaborator.

9.2.8 Special Studies

9.2.8.1 *HLA Class I and Class II Typing*
DNA will be extracted from residual blood collected at baseline and processed as described in 9.2.6. Extracted DNA will be assayed at the laboratory of Dr. Dan Geraghty (FHCRC). The CIML will coordinate sample shipping to the Geraghty Lab.

10. STUDY CALENDAR

Baseline evaluations are to be conducted within 1 week before start of protocol therapy. Safety Labs are to be drawn within 10 days before the start of therapy. Scans and x-rays must be done <4 weeks before the start of therapy.

10.1 Mycosis Fungoides/Sézary Syndrome (Treatment Group 1)

Treatment Cycle[a] (Cycle Number)	Screening	Baseline/IFN Lead-In[s]	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	Response/ PD Assess or EOT [b,c]	Skin Flare Reaction[q]
Weeks (Week Numbers)			1-3	4-6	7-9	10-12	13-15	16-18	19-21	22-24	25-27	28-30	31-33	34-36	37-39	40-42	43-45	46-48	49-51	52-54		
Scheduling Window (days)			±3	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	
MK-3475 Administration[A]			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Interferon-G Administration[t]		X	X	X	X	X		X		X		X		X		X		X		X		
Administrative Procedures																						
Informed consent	X																					
Demographics	X																					
Medical history	X																					
Clinical Procedures/Assessments																						
Concurrent Medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
AE Assessment[d,e]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Limited Physical exam		X	X	X		X	X		X	X		X	X		X	X		X	X			
Comprehensive Physical Exam	X				X			X			X			X			X			X	X	X
Vital Signs & Weight[f]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Height	X																					
Electrocardiogram[g]	X																					
ECOG Performance status	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Pulmonary Function Testing[m]	X																					
Laboratory Assessments (Safety Labs)																						
CBC w/diff, plts[k]	X[h]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Serum chemistry[i,k]	X[h]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Urinalysis[k]	X[h]							X						X						X	X	
T3, FT4 and TSH[k]	X[h]							X						X						X	X	
Pregnancy Test[j,k]	X																					

Treatment Cycle[a] (Cycle Number)	Screening	Baseline/IFN Lead-In[s]	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	Response/ PD Assess or EOT [b,c]	Skin Flare Reaction[q]
Weeks (Week Numbers)			1-3	4-6	7-9	10-12	13-15	16-18	19-21	22-24	25-27	28-30	31-33	34-36	37-39	40-42	43-45	46-48	49-51	52-54		
Efficacy Measurements																						
Tumor Imaging (CT or CT/PET) for pts with extracutaneous disease[n]	X							X*				X				X				X	X	
Tumor Imaging for pts with cutaneous disease only	X																				X	
Circulating Sézary cells**		X		X				X*				X				X				X	X	X
mSWAT Scoring/Photography	X	X	X	X		X		X*		X		X		X		X		X		X	X	X
Tumor Biopsy/Correlative Blood and Stool Samples[l]																						
Skin Biopsy (See Section 9.1)[o]		X	X	X																	X	X[r]
Lymph Node Biopsy(Optional)[p]		X	X	X																	X	
Transcriptional Analysis (10mL)		X	X	X				X													X	X
WES, Neoantigens (90mL)		X		X				X													X	
Peripheral Immunophenotyping (CyTOF) (20mL)		X	X	X																		X
Cytokines/Chemokines (10mL)		X	X	X				X													X	X
TCR Sequencing (10mL)		X	X	X				X				X				X				X	X	X
Kyn/Trp Ratio (10mL)		X		X				X				X				X				X	X	X
Microbiome Analyses***		X																				
Biorepository (Sec. 9) (30mL)		X		X				X				X				X				X	X	X

A. The dose of MK-3475 is 200mg by IV infusion every 21 days. Interferon-gamma dose starts at 50mcg/m^2 thrice weekly (e.g., MWF or TTHS). Dose in mcg/m^2 may vary, see section 5.1.

a. In general, safety labs, assessments/procedures are to be performed on Day 1 and prior to the dose of MK-3475 for each cycle unless otherwise specified.

b. In subjects who discontinue study therapy without documented disease progression, every effort should be made to continue monitoring their disease status by Olsen assessment every 12 weeks (± 7 days) until (1) the start of new anticancer treatment, (2) documented disease progression, (3) death, or (4) the end of the study, whichever occurs first. If a previous assessment was obtained within 4 weeks prior to the date of discontinuation, then an additional assessment at treatment discontinuation isn't mandatory.

c. After the start of new anticancer treatment or documented disease progression, the subject should be contacted by telephone every 12 weeks (+/- 1 week) to assess for survival status.

d. AEs and laboratory safety measurements will be graded per NCI CTCAE version 5.0. All AEs will also be evaluated for seriousness.

e. Follow and document resolution of all AEs and SAEs for 30 days after the last dose of trial treatment.

f. Vital signs to include temperature, pulse, respiratory rate, weight and blood pressure.

g. Electrocardiogram at screening. Repeat only if clinically indicated.

Treatment Cycle[a] (Cycle Number)	Screening	Baseline/IFN Lead-In[s]	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	Response/ PD Assess or EOT [b,c]	Skin Flare Reaction[q]
Weeks (Week Numbers)			1-3	4-6	7-9	10-12	13-15	16-18	19-21	22-24	25-27	28-30	31-33	34-36	37-39	40-42	43-45	46-48	49-51	52-54		

h. Laboratory tests for screening are to be performed within 10 days prior to the first dose of trial treatment. After Cycle 1, lab samples can be collected up to 72 hours prior to the scheduled time point.
i. Tests to be included in the chemistries include: Albumin, alkaline phosphatase, total bilirubin, bicarbonate, BUN, calcium, chloride, creatinine, glucose, LDH, phosphorus, potassium, total protein, SGOT [AST], SGPT [ALT], sodium.
j. For women of reproductive potential, a urine pregnancy test should be performed within 72 hours prior to first dose of trial treatment.
k. Safety labs. These labs will be drawn, processed and resulted locally.
l. Baseline correlative samples may be obtained any time after confirmation of eligibility and before the first dose of IFN-G
m. PFT required at baseline for patients with a history of significant pulmonary disease, prolonged smoking history, or symptoms of respiratory dysfunction.
n. Presence of extracutaceous disease at screening: Scans will be performed at screening, C5-6 (before cycle 6), , C9-10 (before cycle 10), then every 4 cycles, to confirm CR/PR when suspect PD, EOT. Absent extracutaneous disease: Scans will be performed at screening, to confirm PR/CR, when suspect Progressive Disease and at EOT.
o. Skin biopsies will be performed prior to IFN-G lead-in, after IFN-G lead-in (C1D1), C2D1, for PD or appearance of a new lesion, skin flare & EOT. Biopsy for response (PR/CR) is optional.
p. Lymph node biopsies are at the same time points as skin biopsies however they are optional.
q. Visit for flare reaction may be scheduled or unscheduled. If flare is noticed during a regular visit the additional correlative studies and assessments must be performed at the time of the visit.
r. A research biopsy of the skin flare reaction is mandatory. Tissue for local review and patient management is also mandatory.
s. Procedures, assessments and tests for pre-IFN Lead-In only need to be performed once, prior to the first dose of IFN.
t. Interferon-gamma may be continued without break starting on cycle 7, according to Section 5.1.1
* The first global clinical assessment including mSWAT, CSCs (if indicated), and CT or PET/CT (for those with measurable or extracutaneous disease) will occur at Cycle #6 (before Pembro #6 is administered). For those with PD at Cycle #6 the same assessments will be repeated in a confirmatory fashion in ≥ 4 weeks. Those who do not have PD at Cycle #6 will have the same assessments repeated at Cycle #10, then every 4 cycles thereafter.
**CSC Testing: For extracutaneous disease at enrollment: CSC testing will be performed at pre-IFN, C2D1, C6D1, C10D1, then every 4 cycles thereafter then to confirm PR/CR, when suspect PD, EOT, skin flare. For patients with NO extracutaneous disease at enrollment perform CSC only at pre-IFN to confirm PR/CR, when suspect PD, EOT, skin flare.
***Fecal swab/storage devices and instructions must be given to patient; sample collection to be performed at home by patient and returned to clinical research site at the next study visit.

Treatment Cycle[a] (Cycle Number)	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	Response/ PD Assess or EOT [b,c]	Skin Flare Reaction[q]
Weeks (Week Numbers)	55-57	58-60	61-63	64-66	67-69	70-72	73-75	76-78	79-81	82-84	85-87	88-90	91-93	94-96	97-99	100-102		
Scheduling Window (days)	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	
Study Drug Administration																		
MK-3475 Administration[A]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Interferon-G Administration		X		X		X		X		X		X		X		X		
Clinical Procedures/Assessments																		
Concurrent Medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
AE Assessment[d,e]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Limited Physical exam	X	X		X	X		X	X		X	X		X	X		X		
Comprehensive Physical Exam			X			X			X			X			X		X	X

Treatment Cycle[a] (Cycle Number)	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	Response/ PD Assess or EOT [b,c]	Skin Flare Reaction[q]
Weeks (Week Numbers)	55-57	58-60	61-63	64-66	67-69	70-72	73-75	76-78	79-81	82-84	85-87	88-90	91-93	94-96	97-99	100-102		
Vital Signs & Weight[f]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Electrocardiogram[g]																		
ECOG Performance status	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Laboratory Assessments (Safety Labs)																		
CBC w/diff, plts[k]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Serum chemistry[i,k]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Urinalysis[k]						X						X					X	
T3, FT4 and TSH[k]						X						X					X	
Efficacy Measurements																		
Tumor Imaging (CT or CT/PET) for pts with extracutaneous disease[n]				X				X				X					X	
Tumor Imaging for pts with cutaneous disease only																	X	
Circulating Sézary cells**				X				X				X					X	X
mSWAT Scoring/Photography		X		X		X		X		X		X		X		X	X	X
Tumor Biopsy/Correlative Blood Samples[l]																		
Skin Biopsy[o] (See Section 9.1) [o]																	X	X[r]
Lymph Node Biopsy(Optional)[p]																	X	
Transcriptional Analysis (10mL)																	X	X
WES, Neoantigens (90mL)																	X	
Peripheral Immunophenotyping (CyTOF) (20mL)																		X
Cytokines/Chemokines (10mL)																	X	X
TCR Sequencing (10mL)				X				X				X					X	X
Kyn/Trp Ratio (10mL)				X				X				X					X	X
Biorepository (Sec. 9) (30mL)				X				X				X					X	X

A. The dose of MK-3475 is 200mg by IV infusion every 21 days. Interferon-gamma dose starts at 50mcg/m^2 thrice weekly (e.g., M/W/F or T/TH/S). Dose in mcg/m^2 may vary, see section 5.1.

a. In general, safety labs, assessments/procedures are to be performed on Day 1 and prior to the dose of MK3475 for each cycle unless otherwise specified.

b. In subjects who discontinue study therapy without documented disease progression, every effort should be made to continue monitoring their disease status by Olsen assessment every 12 weeks (± 7 days) until (1) the start of new anticancer treatment, (2) documented disease progression, (3) death, or (4) the end of the study, whichever occurs first. If a previous assessment was obtained within 4 weeks prior to the date of discontinuation, then an additional assessment at treatment discontinuation isn't mandatory.

c. After the start of new anticancer treatment or documented disease progression, the subject should be contacted by telephone every 12 weeks to assess for survival status.

d. AEs and laboratory safety measurements will be graded per NCI CTCAE version 5.0. All AEs will also be evaluated for seriousness.

e. Follow and document resolution of all AEs and SAEs for 30 days after the last dose of trial treatment.

f. Vital signs to include temperature, pulse, respiratory rate, weight and blood pressure.

g. Electrocardiogram at screening. Repeat only if clinically indicated.

Treatment Cycle[a] (Cycle Number)	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	Response/ PD Assess or EOT [b,c]	Skin Flare Reaction[q]
Weeks (Week Numbers)	55-57	58-60	61-63	64-66	67-69	70-72	73-75	76-78	79-81	82-84	85-87	88-90	91-93	94-96	97-99	100-102		

h. Laboratory tests for screening are to be performed within 10 days prior to the first dose of trial treatment. After Cycle 1, lab samples can be collected up to 72 hours prior to the scheduled time point.
i. Tests to be included in the chemistries include: Albumin, alkaline phosphatase, total bilirubin, bicarbonate, BUN, calcium, chloride, creatinine, glucose, LDH, phosphorus, potassium, total protein, SGOT [AST], SGPT [ALT], sodium.
j. For women of reproductive potential, a urine pregnancy test should be performed within 72 hours prior to first dose of trial treatment.
k. Safety labs. These labs will be drawn, processed and resulted locally.
l. Baseline correlative samples may be obtained any time after confirmation of eligibility and before the first dose of IFN-G
m. PFT required at baseline for patients with a history of significant pulmonary disease, prolonged smoking history, or symptoms of respiratory dysfunction.

n. Presence of extracutaceous disease at screening: Scans will be performed at screening C5-6 (before cycle 6), C9-10 (before cycle 10), then every 4 cycles, to confirm CR/PR when suspect PD, EOT. Absent extracutaneous disease: Scans will be performed at screening, to confirm PR/CR, when suspect Progressive Disease and at EOT.
o. Skin biopsies will be performed prior to INF-G lead-in, after IFN-G lead-in (C1D1), C2D1, for PD, or appearance of a new lesion, skin flare & EOT. Biopsy for response (PR/CR) is optional.
p. Lymph node biopsies are at the same time points as skin biopsies however they are optional
q. Visit for flare reaction may be scheduled or unscheduled. If flare is noticed during a regular visit the additional correlative studies and assessments must be performed at the time of the visit.
r. A research biopsy of the skin flare reaction is mandatory. Tissue for local review and patient management is also mandatory.
* The first global clinical assessment including mSWAT, CSCs (if indicated), and CT or PET/CT (for those with measurable or extracutaneous disease) will occur at Cycle #6 (before Pembro #6 is administered). For those with PD at Cycle #6 the same assessments will be repeated in a confirmatory fashion in ≥ 4 weeks. Those who do not have PD at Cycle #6 will have the same assessments repeated at Cycle #10, then every 4 cycles thereafter.
**CSC Testing: For extracutaneous disease at enrollment: CSC testing will be performed at pre-IFN, C2D1, C6D1, , C10D1, then every 4 cycles thereafter then to confirm PR/CR, when suspect PD, EOT, skin flare. For patients with NO extracutaneous disease at enrollment perform CSC only at pre-IFN to confirm PR/CR, when suspect PD, EOT, skin flare.

10.2 Synovial Sarcoma (Treatment Group 2)

Treatment Cycle	**Screening**	**Base line/ IFN lead-in**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**Subsequent Cycles (up to 2 years)**	**End of Tx and at documented progression**	**Post Treatment Follow-up**		
Weeks			1-3	4-6	7-9	10-12	13-15	16-18	19-21	22-24	25-27	28-30		At the time of D/C	Safety FU	Disease Assessment[a]	Survival FU
Scheduling window (days)	Within 7 days		+/-3d	+/- 7d	+/- 7d	+/- 7d	+/- 7d	+/- 7d	+/- 7d	+/- 7d	+/- 7d	+/- 7d			30 d +/- 5d post D/C	Every 12 +/- 1 weeks	Every 12 +/- 1 weeks
Interferon-gamma (ACTIMMUNE)[b]		X	X	X	X	X	X	X	X	X	X	X	X				
MK-3475 (pembrolizumab)[c]			X	X	X	X	X	X	X	X	X	X	X				
Administrative procedures																	
Informed consent	X																
Demographics	X																
Medical history	X																
Concurrent meds	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Clinical Procedures/Assessment																	
Physical exam	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Vital signs and weight	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Height	X																
ECOG Performance status	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
EKG[d]	X																
Adverse event assessment			X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Pulmonary function testing[e]	X																
Laboratory Assessments (Safety Labs)																	
CBC w/diff	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Serum chemistry[f]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Pregnancy test (urine or serum HCG)[g]	X																
Urinalysis	X							X					X[h]				
T3, FT4 and TSH	X							X					X[h]				

Treatment Cycle	**Screening**	**Base line/ IFN lead-in**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**Subsequent Cycles (up to 2 years)**	**End of Tx and at documented progression**	**Post Treatment Follow-up**		
Weeks			1-3	4-6	7-9	10-12	13-15	16-18	19-21	22-24	25-27	28-30		At the time of D/C	Safety FU	Disease Assessment[a]	Survival FU
Scheduling window (days)	Within 7 days		+/-3d	+/- 7d	+/- 7d	+/- 7d	+/- 7d	+/- 7d	+/- 7d	+/- 7d	+/- 7d	+/- 7d			30 d +/- 5d post D/C	Every 12 +/- 1 weeks	Every 12 +/- 1 weeks
Efficacy Measurements																	
Radiologic evaluation	X[i]						X				X		X[j]	X		X	
Tumor Biopsies/Archival Tissue Collection																	
Tumor biopsy	X[k]					X[l]											
Correlative Studies Blood Draws																	
Tetramer analyses by Flow Cytometry[m]		X[n]			X				X					X			
Whole Blood Multiparametric Flow cytometry[m]		X[n]	X		X				X								
ELISPOT[m]		X[n]			X				X					X			
Multiplex cytokines[m]		X[n]	X		X				X					X			
HLA Typing[o]		X[n]															
Stool Sample																	
Microbiome[p]		X															

a. Disease assessment per standard of care
b. Interferon Gamma-1b: 100 mcg/m^2 once per week, starting one week prior to the first MK-3475 (pembrolizumab) dose.
c. MK-3475 (pembrolizumab): 200 mg (≥18 years of age)/2 mg/kg (max=200mg) (<18years of age) every 3 weeks, starting cycle 1, week 1, day 1.
d. Electrocardiogram will be performed at screening. Repeat only if clinically indicated.
e. Pulmonary function testing required at baseline only for patients with a history of significant pulmonary disease, prolonged smoking history, or symptoms of respiratory dysfunction.
f. Albumin, alkaline phosphatase, total bilirubin, bicarbonate, BUN, calcium, chloride, creatinine, glucose, LDH, phosphorus, potassium, total protein, SGOT [AST], SGPT [ALT], sodium.
g. Pregnancy test (women of childbearing potential) must be performed within 72 hours of the initiation of study treatment.
h. Urinalysis and thyroid (T3, FT4 and TSH) function tests will be performed every 6th cycle.
i. Baseline radiographic assessment by CT scan must be done <2 weeks (14 days) before the initiation of study treatment.
j. Radiographic assessment by CT scan will occur every 12 weeks (+/- 1 week).
k. Baseline tumor biopsy (archival or fresh) is mandatory. Although there is no time limit on the pretreatment biopsy, the patient cannot have undergone a different therapy since its collection. Archival tissue can be used in lieu of a pretreatment biopsy if the patient has not undergone any treatment since that tissue was collected. If a fresh baseline biopsy is

Treatment Cycle	**Screening**	**Baseline/ IFN lead-in**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**Subsequent Cycles (up to 2 years)**	**End of Tx and at documented progression**	**Post Treatment Follow-up**		
Weeks			1-3	4-6	7-9	10-12	13-15	16-18	19-21	22-24	25-27	28-30		At the time of D/C	Safety FU	Disease Assessment[a]	Survival FU
Scheduling window (days)	Within 7 days		+/-3d	+/- 7d	+/- 7d	+/- 7d	+/- 7d	+/- 7d	+/- 7d	+/- 7d	+/- 7d	+/- 7d			30 d +/- 5d post D/C	Every 12 +/- 1 weeks	Every 12 +/- 1 weeks

obtained this should be collected any time after confirmation of eligibility and before the first dose of interferon gamma-1b.

l. The second biopsy is mandatory for participant ≥18 years of age, but will be performed only if deemed safe by the principal investigator. For participants <18 years of age a second biopsy is optional, and will be performed only if deemed safe by the principal investigator. The second biopsy will be performed after week 8, but before the patient's first scan at week 12.

m. Correlative blood samples must be drawn prior to administration of study agents on a dosing day.

n. Baseline correlative samples to be collected prior to the first dose of Interferon Gamma-1b.

o. HLA-typing is performed on residual material from the flow cytometry blood draws. There is no additional blood draw for this test.

p. Fecal swab/storage instructions must be given to patient; sample collection to be performed at home by patient and returned to clinical research site at the next study visit.

11. MEASUREMENT OF EFFECT

11.1 Mycosis Fungoides/Sézary Syndrome (Treatment Group 1)

11.1.1 Antitumor Effect – Solid Tumors

Mycosis Fungoides and Sézary Syndrome are unique in that some patients will not have disease that is measurable by CT or PET/CT. Patients who have cutaneous disease only will not have measurable disease by CT or PET/CT. Patients with measurable disease will have scans at the intervals specified in the study calendar. Patients who have nonmeasurable disease by CT and/or PET CT will have a scan at baseline (before study drug is initiated). This scan will be done as standard of care before study entry and will be used to determine the presence or absence or measurable disease. Subsequent scans in patients with nonmeasurable disease will only occur at CR, PR, PD/EOT.

There will be other criteria in addition to standard radiographic evaluation used in this study to determine progression or regression of disease including mSWAT (modified severity-weighted assessment tool) to determine response in skin. Flow cytometry will be used to determine the number of circulating sézary cells (CSC's) in the blood in order to evaluate response. Lastly, all of the measures including Skin (mSWAT), Lymph Nodes (CT or PET/CT), Visceral Disease (CT or PET/CT) and Blood (Flow Cytometry) will be combined to determine a Global Response Score. All of these evaluations, including the Global Response Score will be described in further detail in this section of the protocol.

Patients will be assessed (including scans for measurable disease, mSWAT and CSC, for extracutaneous disease) before study drug at Cycle 6, 10, then every 4 cycles thereafter. If progression is noted at an assessment, a confirmatory assessment will be repeated in ≥4 weeks. Assessments will also be performed at the time of CR/PR confirmation, PD and at EOT. Note: Only patients with extracutaneous disease (measurable by CT scan) will have scans done at these specified intervals. Those with nonmeasurable disease are only scanned at baseline, then at CR, PR, PD/EOT.

If a CR is achieved patients may stop study drug therapy after 2 additional cycles (each cycle is 3 weeks) have been given after 6 months of therapy have been completed. (*i.e.,* 6 months + 2 cycles). If patients who have stopped after a CR have disease recurrence, they may re-start therapy if they have not received additional therapy in the interim, if they are still eligible for the trial and the trial is still open to enrollment.

11.1.1.1 *Definitions*

Evaluable for toxicity. All patients will be evaluable for toxicity from the time of their first treatment with Interferon-gamma (given first as run-in before MK-3475 (pembrolizumab)).

Evaluable for objective response. As described above patients enrolled in this trial may not have disease that is measurable by CT and/or PET/CT however they can still

be objectively evaluated for disease response using parameters unique to Mycosis Fungoides/Sézary Syndrome.

11.1.1.2 *Disease Parameters: N/A*

11.1.1.3 *Tumor Imaging and Assessment of Disease*

The primary outcome is antitumor effect. Definitions for global response, CR, PR, PD, and SD (in skin/LN/viscera/blood) are detailed here.

Measurement Methods

- Skin: mSWAT.
- Lymph nodes: CT or PET/CT (Olsen criteria).
- Viscera: CT or PET/CT (Olsen criteria).
  - If using a PET/CT the CT should be of diagnostic quality
- Blood: Flow cytometry.

The skin compartment is the target of primary efficacy assessment, however in those subjects with extracutaneous disease, all involved compartments will be assessed separately and a global response will be determined.

Clinical response in the skin compartment will be assessed according to changes in the modified Severity-Weighted Assessment Tool (mSWAT) [Appendix E] and documented as SD, PR, complete clinical response, or PD as defined below. The response in the lymph node compartment will be assessed by IWG criteria, in blood by flow cytometry, and global response will be assigned adhering to the consensus criteria below. All objective response (PR or CR) and progression (PD) must be confirmed after 4 weeks. Digital copies of mSWAT photographs will be retained at sites for quality assurance or secondary review purposes.

Regardless of treatment delays, response assessment including mSWAT, circulating sézary cell count and imaging should always be performed on the aforementioned schedules. (*i.e.,* the imaging and mSWAT schedules do not change if there are treatment delays). Subjects with CR after receiving a minimum of 6 months of treatment with at least 2 doses since CR may discontinue therapy. Subjects with a CR who progress may be retreated if (1) no cancer treatment was administered since the last dose of MK-3475 (pembrolizumab), (2) subject continues to meet eligibility criteria, and (3) the trial is open. Subjects without symptomatic progression may receive up to a maximum of 2 years if radiologically and clinically improving or stable after 12 cycles.

11.1.1.4 *Initial Tumor Imaging*

Initial tumor imaging with a CT or PET/CT must be performed within 28 days before the first dose of trial treatment. For subjects with documented extracutaneous disease imaging will be repeated at the intervals specified in section 11.1. For consistency in interpretation, perform the same type of radiologic evaluation that was performed at screening. All subjects on the trial will have an EOT scan. 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. Imaging timing should follow calendar days and should not be adjusted for delays in cycle starts or extension of MK-3475 (pembrolizumab) cycle frequencies. The same imaging technique should be used in a subject throughout the trial. The site study team must review pre-trial images to confirm the subject has measurable disease per Olsen criteria **if the patient is going to be entered on trial with radiographically measurable disease**. Patients with only cutaneous disease (nonmeasurable by CT) are also eligible for the study.

11.1.1.5 *Tumor Imaging During Trial*

Tumor imaging may be performed by full-body CT or full-body PET/CT and the same imaging technique should be used in a subject throughout the trial as response will be assessed by Olsen criteria. Imaging should be performed if possible progression is considered or to confirm response. Imaging should not be delayed for delays in cycle starts or extension of MK-3475 (pembrolizumab) cycle intervals.

Measurement Methods

- Lymph nodes: CT or PET-CT (Olsen criteria).
- Viscera: CT or PET-CT (Olsen criteria).

If using a PET/CT the CT should be of diagnostic quality. Imaging should continue to be performed until documented disease progression, the start of new anticancer treatment, withdrawal of consent, death, or the end of the study, whichever occurs first. Disease progression should be confirmed at least 4 weeks after the first scan indicating PD in clinically stable subjects. Subjects who have unconfirmed disease progression may continue on treatment until progression is confirmed.

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 or less. If CT scans have slice thickness greater than 5 mm, 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).

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 accurate measurement. 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 tumor 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.

11.1.1.6 *Response Criteria*

Primary outcome measure is clinical response rate as assessed by the standard response criteria used in Mycosis Fungoides and Sézary Syndrome (skin, LN, viscera, blood, global).

Response in Skin*

Complete response (CR)	100% clearance of skin lesions[#]
Partial response (PR)	50-99% clearance of skin disease from baseline without new tumors (T_3) in subjects with T_1, T_2 or T_4 only skin disease
Stable disease (SD)	<25% increase to <50% clearance in skin disease from baseline without new tumors (T_3) in subjects with T_1, T_2 or T_4 only skin disease
Progressive disease (PD)[†]	(1) >25% increase in skin disease from baseline or (2) New tumors (T_3) in subjects with T_1, T_2 or T_4 only skin disease or (3) Loss of response: in those with CR or PR, increase of skin score of greater than the sum of nadir plus 50% baseline score
Relapse	Any disease recurrence in those with CR

*Based on mSWAT score.

A biopsy of normal appearing skin is unnecessary to assign a CR. However, a skin biopsy should be performed of a representative area of the skin if there is any question of residual disease where otherwise a CR would exist. If histologic features are suspicious or suggestive of Mycosis Fungoides/Sézary Syndrome (see histologic criteria for early MF7), the response should be considered a PR only.

[†]Whichever criterion occurs first.

Response in Lymph Nodes*

CR	All lymph nodes are now <1.5 cm in greatest transverse (long axis) diameter by method used to assess lymph nodes at baseline or biopsy negative for lymphoma. In addition, lymph nodes that were N3 classification and <1.5 cm in long axis diameter at baseline, must now be <1 cm in diameter of the short axis or biopsy negative for lymphoma
PR	(1) Cumulative reduction >50% of the SPD [sum of the maximum linear dimension (major axis) x longest perpendicular dimension (minor axis) of each abnormal lymph node at baseline and no new lymph node >1.5 cm or >1.0 cm in the short axis if long axis 1-1.5cm diameter.
SD	Fails to attain the criteria for CR, PR and PD
PD[†]	(1) >50% increase in SPD from baseline of lymph nodes or (2) Any new node >1.5 cm in greatest transverse diameter or >1 cm in short axis diameter if 1-1.5 cm in long axis that is proven to be N3 histologically or (3) Loss of response: in those with PR or CR, >50% increase from nadir in SPD of lymph nodes
Relapse	Any new lymph node >1.5cm in long axis diameter in those with CR

* Peripheral and central lymph nodes.

[†]Whichever criterion occurs first.

Response in Blood*

CR**	B_0
PR#	>50% decrease in quantitative measurements of blood tumor burden from baseline in those with high tumor burden at baseline (B_2)
SD	Fails to attain criteria for CR, PR or PD
PD†	(1) B_0 to B_2 or (2) >50% increase from baseline and at least 5,000 neoplastic cells/μL[42] or (3) Loss of response: in those with CR who were B_1 or B_2 at baseline, increase in neoplastic >1000 neoplastic cells/ μL or in those with PR who were originally B_2 at baseline, >50% increase from nadir and at least 5,000 neoplastic cells/μL
Relapse	Increase of neoplastic blood lymphocytes to ≥B_1 in those with CR

* As determined by absolute numbers of neoplastic cells/uL.

** If a bone marrow biopsy was performed at baseline and determined to unequivocally be indicative of lymphomatous involvement, then to confirm a global CR where blood assessment now meets criteria for B_0, a repeat bone marrow biopsy must show no residual disease or the response should be considered a PR only.

There is no PR in those with B_1 disease at baseline as the difference within the range of neoplastic cells that define B_1 is not considered significant and should not affect determination of global objective response.

†Whichever occurs first.

Response in Viscera

CR	Liver or spleen or any organ considered involved at baseline should not be enlarged on physical exam and should be considered normal by imaging. No nodules should be present on imaging of liver or spleen. Any post treatment mass must be determined to be biopsy to be negative for lymphoma
PR	>50% regression in any splenic or liver nodules, or in measurable disease (SPD) in any organs abnormal at baseline. No increase in size of liver or spleen and no new sites of involvement.
SD	Fails to attain the criteria for CR, PR or PD
PD†	(1) >50% increase in size (SPD) of any organs involved at baseline or (2) New organ involvement or (3) Loss of response: in those with PR or CR, >50% increase from nadir in the size (SPD) of any previous organ involvement
Relapse	New organ involvement in those with CR

†Whichever criterion occurs first.

Global Response Score

Global Score*	Definition	Skin	Nodes	Blood	Viscera
CR	Complete disappearance of all clinical evidence of disease	CR	All categories have CR/NI		

Global Score*	Definition	Skin	Nodes	Blood	Viscera
PR	Regression of measurable disease	CR	All categories do not have a CR/NI and no category has a PD		
		PR	No category has a PD and if any other category involved at baseline, at least one has a CR or PR		
SD	Failure to attain CR, PR or PD representative of all disease	PR	No category has a PD and if any other category involved at baseline, no CR or PR in any		
		SD	CR/NI, PR, SD in any category and no category has a PD		
PD	Progressive disease	PD in any category			
Relapse	Recurrence disease in prior CR	Relapse in any category			

NI= noninvolved

*It is recommended that not only the proportion of subjects who achieve a response or an unfavorable outcome be calculated but a life table account for the length of the interval.

After the first documentation of progression, it is at the discretion of the investigator to keep a clinically stable subject on trial treatment or to stop trial treatment until repeat imaging performed at least 28 days later confirms progression. A subject with *unconfirmed* progression of disease may continue trial treatment until progression of disease is confirmed. Subjects with suspected pseudoprogression should have biopsy proven confirmation of progression of disease during the 4-week interval between initial demonstration of progression and confirmation of progression of disease. Biopsy findings consistent with pseudoprogression, including evidence of a lymphoid infiltrate, necrotic tumor, without significant increase in viable tumor at site of suspected pseudoprogression, may justify continued treatment at the discretion of the PI.

Subjects may only receive study treatment while waiting for confirmation of PD versus pseudoprogression if the following criteria are met:

- Absence of signs and symptoms indicating disease progression
- Absence of rapid progression of disease
- Absence of progressive tumor at critical anatomical sites (*e.g.,* cord compression) requiring urgent alternative medical intervention

Disease assessments during the follow-up period is to be repeated every 12 weeks (± 7 days) for subjects who discontinue trial treatment for reasons other than disease progression until the subject experiences confirmed disease progression or starts a new antineoplastic therapy.

Local reading (investigator assessment with site radiology reading) will be used to determine subject eligibility and for subject management. Radiologic scans may be sent to a central vendor for evaluation.

11.1.1.7 *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 PD is objectively documented (taking as reference for PD 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 PD is objectively documented.

Duration of stable disease: SD 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.

ORR12: Patients who have a response duration of at least 12 months.

11.1.1.8 *Progression-Free Survival*

PFS is defined as the duration of time from start of treatment to time of progression or death, whichever occurs first.

11.1.1.9 *Response Review*

No review of response rate is contemplated. Investigator determined responses will be chronicled.

11.2 Synovial Sarcoma (Treatment Group 2)

11.2.1 Tumor Imaging and Assessment of Disease

The primary endpoint of the study will be the ORR. Clinical CT scans of the chest, abdomen and pelvis will be assessed and evaluated based on RECIST v. 1.1. If additional imaging is clinically necessary (e.g., MRI humerus) in addition to this CT scan, it should also be evaluated by RECIST criteria. If a patient's treating physician has a specific documented clinical reason to use a different imaging modality instead of CT chest, abdomen and pelvis, for a particular patient this will be allowed. Patients will come in for chest and/or abdomen scans, depending on clinical presentation, prior to treatment (within 14 days) and then at 12 week intervals at the discretion of the site principal investigator.

11.2.2 Response Criteria

CR	Disappearance of all lesions and no new lesion
PR	30% reduction in tumor size and no new lesions
SD	Fails to attain the criteria for CR, PR and PD
PD	20% increase in tumor size or at least one new lesion
Relapse	Any disease recurrence in those with CR

11.2.3 Progression-free Survival

Progression free survival (PFS) is defined as the duration of time from start of treatment to time of progression or death, whichever occurs first.

12. STUDY OVERSIGHT AND DATA REPORTING / REGULATORY REQUIREMENTS (TREATMENT GROUP 1 AND 2)

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

12.1 Study Oversight

This protocol is monitored at several levels, as described elsewhere in this section. The Protocol Principal Investigator is responsible for monitoring the conduct and progress of the clinical trial, including the ongoing review of accrual, patient-specific clinical and laboratory data, and routine and serious adverse events; reporting of expedited adverse events; and accumulation of reported adverse events from other trials testing the same drug(s). The Protocol Principal Investigator and statistician have access to the data at all times.

All Study Investigators at participating sites who register/enroll patients on a given protocol are responsible for timely submission of data via the mechanism described elsewhere in this section. All studies are also reviewed in accordance with the enrolling institution's data safety monitoring plan.

12.2 Data Reporting

Medidata Rave is a clinical data management system being used for data collection for this trial/study. Access to the trial in Rave is controlled through the CTEP-IAM system and role assignments. To access Rave via iMedidata:

- Site staff will need to be registered with CTEP and have a valid and active CTEP-IAM account; and
- Assigned one of the following Rave roles on the relevant Lead Protocol Organization (LPO) or Participating Organization roster at the enrolling site: Rave CRA, Rave Read Only, Rave CRA (LabAdmin), Rave SLA, or Rave Investigator. Refer to https://ctep.cancer.gov/investigatorResources/default.htm for registration types and documentation required.
    - To hold Rave CRA or Rave CRA (Lab Admin) role, site staff must hold a minimum of an AP registration type;
    - To hold Rave Investigator role, the individual must be registered as an NPIVR or IVR; and
    - To hold Rave Read Only role, site staff must hold an Associates (A) registration type.

If the study has a Delegation of Tasks Log (DTL), individuals requiring write access to Rave must also be assigned the appropriate Rave tasks on the DTL.

Upon initial site registration approval for the study in Regulatory Support System (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 staff 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. Site staff 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. If an eLearning is required and has not yet been taken, the link to the eLearning will appear under the study name in iMedidata instead of the *Rave EDC* link; once the successful completion of the eLearning has been recorded, access to the study in Rave will be granted, and a *Rave EDC* link will display under the study name.

Site staff 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, in the Rave section under the Rave resource materials (Medidata Account Activation and Study Invitation Acceptance). Additional information on iMedidata/Rave is available on the CTSU members' website in the Data Management > Rave section at www.ctsu.org/RAVE/ or by contacting the CTSU Help Desk at 1-888-823-5923 or by e-mail at ctsucontact@westat.com.

12.2.1 *Method*

This study will be monitored by the Clinical Data Update System (CDUS) Version 3.0. Cumulative protocol- and patient-specific CDUS data will be submitted electronically to CTEP on a quarterly basis by FTP burst of data. Reports are due January 31, April 30, July 31, and October 31. Instructions for submitting data using the CDUS can be found on the CTEP Web site (http://ctep.cancer.gov/reporting/cdus.html).

***Note**:* If your study has been assigned to CDUS-Complete reporting, **all** adverse events (both routine and expedited) that have occurred on the study and meet the mandatory CDUS reporting guidelines must be reported via the monitoring method identified above. If your study has been assigned to CDUS-Abbreviated reporting, no adverse event reporting (routine or expedited) is required to be reported via CDUS, but expedited adverse events are still required to be submitted via CTEP-AERS.

12.2.2 *Responsibility for Data Submission*

For CITN trials, it is the responsibility of the PI(s) at the site to ensure that all investigators at the CITN Sites understand the procedures for data submission for each CITN protocol and that protocol specified data are submitted accurately and in a timely manner to the CITN data management organization via the electronic data capture system, Medidata Rave.

Data are to be submitted via Medidata Rave to the CITN on a real-time basis, but no less than 72 hours after the data has been collected. The timeliness of data submissions and timeliness in resolving data queries will be tracked by the CITN data management organization. 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 CITN Coordinating Center and by the CITN data management organization on an ongoing basis as data is received. Queries will be issued by the CITN Data Management Organization directly within Rave. The queries will appear on the Task Summary Tab within Rave for the CRA at the clinical site to resolve. Onsite audits will be conducted 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 trials, which may be found on the CTEP (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/adverse_events.htm) and CTSU websites.

The CITN data management organization 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 CITN data management organization will prepare the eCRFs with built-in edit checks to the extent possible to promote data integrity.

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

See Section 12.2.1 for details on CDUS reporting. As the data management center for this trial, Axio is responsible for compiling and submitting CDUS data to CTEP for all participants and for providing the data to the Principal Investigator for review.

12.3 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.
- 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 CTEP PIO (PIO@ctep.nci.nih.gov) except for Group studies.

12.4 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 before 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 before 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 before submission, but in any case, before presentation at the meeting or publication in the proceedings. Press releases and other media presentations must also be forwarded to CTEP before release. Copies of any manuscript, abstract and/or press release/ media presentation should be sent to:

   Email: ncicteppubs@mail.nih.gov

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 Mycosis Fungoides/Sézary Syndrome (Treatment group 1)

13.1.1 Study Design/Endpoints

13.1.1.1 *Primary Objective*

To assess the overall response rate (ORR) of MK-3475 (pembrolizumab) and IFN-gamma (Actimmune®) combination immunotherapy in subjects with previously treated Mycosis Fungoides or Sézary Syndrome.

In this single stage phase II open label trial, we will have an interim futility analysis. When 12 patients have been followed for 6 months, we will perform the interim futility analysis. If ORR is less than 33% (4 or less CR+PR), the trial will stop and we will accept the null that combination therapy is no better than monotherapy. Otherwise, trial will continue until 30 patients accrue. If ORR is at least 57% (17 or

more CR+PR) at the final analysis, we will accept the alternative that combination therapy is significantly better than monotherapy.

***Hypothesis**:* Administration of MK-3475 (pembrolizumab) and IFN-gamma (Actimmune®) as a combination immunotherapy regimen to subjects with previously treated Mycosis Fungoides or Sézary Syndrome will result in a clinically meaningful ORR that is an improvement over the ORR of MK-3475 (pembrolizumab) or IFN-gamma as monotherapy.

13.1.1.2 *Secondary Objectives*

To explore the safety/tolerability and clinical activity of MK-3475 (pembrolizumab) and IFN-gamma (Actimmune®) in subjects with previously treated Mycosis Fungoides or Sézary Syndrome with respect to the following secondary endpoints:

Safety and tolerability

Interim safety review based on distinct patient SAE's following the first 3 doses of pembrolizumab (10 weeks of therapy) that are attributable to study drugs; We will allow 10% or less of patients to develop study drug related SAEs. If 4 or more patients amongst the first 12 evaluable patients for toxicity at pre-C4 (week 10) have experienced study drug related serious adverse events (SAEs), we will conclude that the combination immunotherapy regimen is too toxic and accrual will stop. If accrual is not stopped for either interim futility or safety reasons, a final safety evaluation will be conducted based on the percentage of the 30 patients who have experienced SAEs. We will consider the safety profile being acceptable if less than 6 patients have experienced study drug related SAEs. Otherwise, we will evaluate the tradeoff between safety and efficacy benefits based on the magnitude of ORR improvements.

Time to response (TTR)

Duration of response (DOR)

is defined as the time interval between the date of first response (CR/PR) and the date of progression.

Progression-free survival (PFS)

is defined as the time from enrollment to PD or death, whichever occurs earlier, based upon investigator assessment. Patients without documented PD/death will be censored at the last disease assessment date.

Event-free survival

(EFS events defined as termination due to toxicity, initiation of next significant treatment, progressive disease, or death of any cause)

ORR12

Percentage of all patients who have a response duration of at least 12 months (ORR12)

***Hypothesis**:* Combination immunotherapy of MK-3475 (pembrolizumab) and IFN-gamma (Actimmune®) will have acceptable safety/tolerability profile in previously treated Mycosis Fungoides/Sézary Syndrome population and meaningful clinical activity will be reflected in other clinical outcome parameters including DOR, PFS, EFS and ORR12.

13.1.1.3 *Exploratory Objectives*

To investigate the relationship between the following putative biomarkers for combination immunotherapy of MK-3475 (pembrolizumab) and IFN-gamma (Actimmune®) and clinical outcomes (as measured by safety/tolerability and ORR, DOR, PFS, EFS) in subjects with previously treated Mycosis Fungoides/Sézary Syndrome, including tumor/microenvironment (PD-1/PD-L1/PD-L2 expression, CTLs, Tregs, macrophages, DCs; nanostring gene expression profile), systemic immune response (flow cytometry, CyTOF, Luminex multiplexed cytokine profile), and molecular/genomic immune correlates (exome sequencing, high throughput sequencing (HTS) for TCR).

***Hypothesis**:* The putative biomarkers and immune regulators tested will be related to clinical response induced by combination immunotherapy of MK-3475 (pembrolizumab) and IFN-gamma (Actimmune®) and will help define actionable causes of not achieving CR.

The primary and key secondary endpoints, primary analysis population, and statistical methods that will be employed for the efficacy analyses are presented in the Table below.

Summary Analysis Strategy for Efficacy Endpoints

Endpoint/Variable (Description, Time Point)	**Statistical Method**	**Analysis Population**	**Missing Data Approach**
Primary:			
Overall response rate (ORR) per global assessment of Mycosis Fungoides and Sézary Syndrome (confirmed & investigator assessed)	Binomial proportion	Evaluable population as defined	Subjects without any efficacy evaluation will be excluded; if one compartment is missing data, that compartment will be considered non-response
Secondary:			
Time to Response (TTR)	Simple statistics	All responders	Non-responders are excluded in analysis
Duration of Response (DOR)	Kaplan-Meier method	All responders	Non-responders are excluded in analysis; censored at last f/u or start of new significant therapy
Progression-free survival	Kaplan-Meier method	All efficacy or safety evaluable patients	Censored at last f/u or start of new significant therapy

Endpoint/Variable (Description, Time Point)	Statistical Method	Analysis Population	Missing Data Approach
Event-free survival	Kaplan-Meier method	All efficacy or safety evaluable patients	Event is defined by early termination due toxicity, start of new significant therapy, PD, or death of any cause
Rate of overall response duration beyond 12 months (ORR12) per global assessment of Mycosis Fungoides and Sézary Syndrome (confirmed & investigator assessed)	Binomial distribution	Evaluable DOR beyond 12 months for evaluable population.	Subjects without any efficacy evaluation will be excluded; The ORR12 is the proportion of ORR times conditional probability of DOR beyond 12 months. If one compartment is missing data, that compartment will be considered non-response. Censored at last f/u. Start of new significant therapy before 12 months will be considered as failures.

13.1.1.4 *Interim Safety and Futility Analyses*

- One interim safety analysis will be performed in this study when 12 patients are evaluable for toxicity at pre-C4 (week 10) of the study. If at that time, 4 or more patients have experienced study drug related serious adverse events (SAEs), we will conclude that the combination immunotherapy regimen is too toxic and accrual will stop.
- The properties of interim safety stopping rule are given in the table below.

True Probability of Study Drug Related SAEs (ptox)	Probability of Stopping Early (pstop)
0.10	0.026
0.14	0.075
0.18	0.155
0.22	0.261
0.26	0.382
0.30	0.507

One interim futility analysis will be performed in this study. Results will be reviewed by the participating institutions/investigators, CITN, NCI/CTEP, and participating industry sponsors (Horizon and Merck).

The statistical criterion for success requires ORR that is greater than 37% (null) and at least 65% (alternative). This is a single stage trial. Patients will be recruited continuously. We will perform the interim futility analysis when 12 patients have been followed for 6 months. If ORR is less than 33% (4 or less CR+PR), the trial will stop and we will accept the null that combination therapy is no better than monotherapy. The probability of

stopping at interim futility analysis under the null and alternative are 52% and 2% respectively.

Otherwise, the trial will continue until we reach 30 patients. If ORR is at least 57% (17 or more CR+PR) at the final analysis, we will accept the alternative that combination therapy is significantly better than monotherapy. The type I error rate is 2%. The power is 87%.

Summary of Interim Safety and Futility Analyses Strategy

Key Endpoints for Interim Analysis	Timing of Interim Analysis	Purpose of Interim Analysis
Study drug related serious adverse events (SAEs)	12 subjects enrolled and received at least 1 dose of either IFN-g or MK-3475 (pembrolizumab), with 12th pt evaluable through interim safety assessment time point at pre-C4/week 10	Stop for significant safety concerns. Enrollment will not stop in order to wait for the 12th patient to reach week 10. New patient enrollment will continue as long as there are less than 4 study drug-related SAEs.
Overall response rate (ORR) per global assessment of Mycosis Fungoides and Sézary Syndrome (confirmed & investigator assessed)	12 subjects enrolled and received at least 1 dose of either IFN-g or MK-3475 (pembrolizumab); all 12 subjects followed for 6 months	Stop for futility of combination therapy relative to monotherapy.

13.1.2 *Exploratory Correlative Analyses*

Clinical response (as measured by the primary and secondary endpoints) to combination immunotherapy regimen as a function of biomarkers will be evaluated. All biomarker assays will be run on the clinical trial samples in a blinded manner.

Time to event endpoints (DOR, PFS, EFS) will be evaluated using Kaplan-Meier curves generated by biomarker scoring group using the log-rank test.

Exploratory outcomes will be summarized with descriptive statistics (primarily proportions and medians) for all biomarkers described above, and additionally, serum IL-10, regulatory T-cells, and activated CD8 T cells. Scatterplots and Kendall's tau estimates will be produced for estimating correlation of PD-1, PDL1, or PD-L2 expression measures and clinical outcome across compartments (skin, lymph node, blood). Comparison of tissue IHC markers between pre-treatment and with clinical response or disease progression will be assessed using Wilcoxon signed-rank test. A full panel of approximately ~600 mRNA transcripts will be measured using the Nanostring platform and will be evaluated using descriptive statistics.

13.1.3 Sample Size/Accrual Rate

13.1.3.1 *Power and Sample Size*

The statistical criterion for success requires ORR that is greater than 37% (null) and at least 65% (alternative). By adding an interim futility analysis, the sample size is 30

patients. The probability of stopping at interim futility analysis under the null and alternative are 52% and 2%, respectively. The type I error rate is 2%. The power is 87%. The expected sample sizes under the null and alternative are 21 and 30, respectively.

This is a single stage trial. Patients will be recruited continuously. We will perform the interim futility analysis when 12 patients have been followed for 6 months. If ORR is less than 33% (4 or less CR+PR), the trial will stop and we will accept the null that combination therapy is no better than monotherapy. Otherwise, the trial will continue until we reach 30 patients. If ORR is at least 57% (17 or more CR+PR) at the final analysis, we will accept the alternative that combination therapy is significantly better than monotherapy.

PLANNED ENROLLMENT REPORT

Racial Categories	Ethnic Categories				Total
	Not Hispanic or Latino		Hispanic or Latino		
	Female	Male	Female	Male	
American Indian/Alaska Native					
Asian	1	1			**2**
Native Hawaiian or Other Pacific Islander					
Black or African American	1	1			**2**
White	7	17	1	1	**26**
More Than One Race					
Total	**9**	**19**	**1**	**1**	**30**

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13.1.4 Stratification Factors

There is no planned stratification.

13.1.5 Reporting and Exclusions

13.1.5.1 *Evaluation of Toxicity*

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

13.1.5.2 *Evaluation of Response*

All patients included in the study must be assessed for response to treatment, even if there are major protocol treatment deviations or if they are ineligible. Each patient will be assigned one of the following categories: (1) complete response, (2) partial response, (3) stable disease, (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). [***Note:*** By arbitrary convention, category 9 usually designates the "unknown" status of any type of data in a clinical database.]

All of the patients who met the eligibility criteria (with the possible exception of those who received no study medication) should be included in the main analysis of the response rate. Patients in response categories 4-9 should be considered to have a treatment failure (disease progression). Thus, an incorrect treatment schedule or drug administration does not result in exclusion from the analysis of the response rate. Precise definitions for categories 4-9 will be protocol specific.

All conclusions should be based on all eligible patients. Subanalyses may then be performed on the basis of a subset of patients, excluding those for whom major protocol deviations have been identified (*e.g.,* early death due to other reasons, early discontinuation of treatment, major protocol violations, etc.). However, these subanalyses may not serve as the basis for drawing conclusions concerning treatment efficacy, and the reasons for excluding patients from the analysis should be clearly reported. The 95% confidence intervals should also be provided.

13.2 Synovial Sarcoma (Treatment Group 2)

13.2.1 Study Endpoints

The primary objective is to determine whether the combination of interferon gamma-1b (ACTIMMUNE®) and MK-3475 (pembrolizumab) improves the overall response rate (ORR) of pembrolizumab in patients with unresectable or metastatic synovial sarcoma.

The ORR of single agent pembrolizumab is ≤ 5%. Accordingly, a Simon 2-stage design will be used: Twelve patients will be enrolled initially. If 0 respond the study will be stopped for futility. Otherwise, an additional four patients will be enrolled. If three or more out of 16 patients respond, the treatment will be considered promising and would likely lead to widespread use of this regimen in the clinic.

The secondary objectives for the study are:

- To determine the progression-free survival (PFS) and overall survival (OS) for patients with advanced synovial sarcoma receiving interferon gamma-1b and MK-3475 (pembrolizumab).

- To determine the tolerability of the combination of interferon gamma-1b and MK-3475 (pembrolizumab) based on CTCAE version 5.0

The exploratory objectives are to investigate paired, serial biopsy specimens from pre-treatment and 8-12 weeks after starting treatment for the following:

- MHC class I expression (scored by pathologist)
- Number of infiltrating T cells per mm^2
- Tumor associated macrophage number and phenotype using multiplex immunohistochemistry
- T cell clonality
- Gene expression profiling

Additionally, the exploratory objectives include investigating peripheral blood samples from patients to determine:

- The number and phenotype of T cells specific for CT antigens and potential neo-antigens
- The phenotype of circulating monocytes
- Cytokines associated with response

The primary and key secondary endpoints, primary analysis population, and statistical methods that will be employed for the efficacy analyses are presented in the table below.

Summary Analysis Strategy for Efficacy Endpoints

Endpoint/Variable	**Statistical Method**	**Analysis Population**	**Missing Data Approach**
Primary:			
Overall Response Rate (ORR)	Binomial proportion	Evaluable population as defined	Subjects without any efficacy evaluation will be excluded; if one compartment is missing data, that compartment will be considered non-response.
Secondary:			
Progression-free survival (PFS)	Kaplan-Meier method	All efficacy or safety evaluable patients	Censored at last follow-up or start of new significant therapy
Overall survival (OS)	Kaplan-Meier method	All efficacy or safety evaluable patients	Event is death due to any cause, otherwise it is considered censored at last follow-up
Tolerability	Binomial proportion	All enrolled patients	All AEs and SAEs will be summarized

13.2.2 Interim Safety and Futility Analyses

One interim safety analysis will be performed in this study when 12 patients are evaluable for toxicity at pre-C4 (week 10) of the study. If at that time, 4 or more patients have experienced unexpected study drug related serious adverse events (SAEs), we will conclude that the combination immunotherapy regimen is too toxic and accrual will stop.

The properties of interim safety stopping rules are given in the table below.

True Probability of Study Drug-Related SAEs (ptox)	**Probability of Stopping Early**
0.10	0.026
0.14	0.075
0.18	0.155
0.22	0.261
0.26	0.382
0.30	0.507

One interim futility analysis will be performed in this study. A Simon 2-stage design will be used: Twelve patients will be enrolled initially. If 0 respond the study will be stopped for futility. The probabilities of stopping the trial for futility at this interim analysis are 54% and 3% under the null hypothesis (ORR=5%) and alternative hypothesis (ORR=25%) respectively.

Otherwise an additional four patients will be enrolled. If three or more out of 16 patients respond, the treatment will be considered promising and would likely lead to widespread use of this regimen in the clinic.

The overall type I error for the study is 4.3%, and the overall power of the study at the alternative hypothesis (ORR=25%) is 80.1%.

13.2.3 Exploratory/Correlative Analyses

The exploratory objectives are to investigate paired, serial biopsy specimens from pre-treatment and 8-12 weeks after starting treatment for the following:

- MHC class I expression (scored by pathologist)
- Number of infiltrating T cells per mm^2
- Tumor associated macrophage number and phenotype using multiplex immunohistochemistry
- T cell clonality
- Gene expression profiling

Additionally, the exploratory objectives include investigating peripheral blood samples from patients to determine:

- The number and phenotype of T cells specific for CT antigens and potential neo-antigens
- The phenotype and activation state of circulating monocytes and PBMC
- Cytokines associated with response

The exploratory outcomes will be summarized with descriptive statistics for all the biomarkers described above.

13.2.4 Sample Size and Power

A Simon 2-stage design will be used: Twelve patients will be enrolled initially. If 0 respond the study will be stopped for futility. The probabilities of stopping the trial for futility at this interim analysis are 54% and 3% under the null hypothesis (ORR=5%) and alternative hypothesis (ORR=25%) respectively.

Otherwise, an additional four patients will be enrolled. If three or more out of 16 patients respond, the treatment will be considered promising and would likely lead to widespread use of this regimen in the clinic. The overall type I error for the study is 4.3%, and the overall power of the study at the alternative hypothesis (ORR=25%) is 80.1%.

The patient demographics for the addendum is expected to be similar to the patient demographics of the original protocol. The planned enrollment report is given below.

13.2.5 Planned Enrollment Report

Racial Categories	**Ethnic Categories**				**Total**
	Not Hispanic or Latino		**Hispanic or Latino**		
	Female	**Male**	**Female**	**Male**	
American Indian/Alaska Native					
Asian	1	1			2
Native Hawaiian or other Pacific Islander					

Black or African American	1	1			2
White	5	5	1	1	12
More than one race					
Total					16

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APPENDIX A PERFORMANCE STATUS CRITERIA (TREATMENT GROUP 1 AND 2)

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 (TREATMENT GROUP 1 AND 2)

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.
- Before 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 before 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

Mycosis Fungoides/Sézary Syndrome (Treatment Group 1)

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]
Tissue PDL1 Expression PI: Dr. Rob Pierce Site: Fred Hutchinson Cancer Research Center	Chromagenic (Single-Color) IHC for PD-L1 CLIA: N	Exploratory Purpose: We will explore correlation of PDL1 expression with response. Two hypotheses will be explored: 1) Pre-treatment PDL1 expression correlates with response 2) Interferon-gamma mediated upregulation of PDL1 correlates with response	Tissue: Skin biopsy Timing: (M) Prior to IFN-gamma lead-in, Prior to Cycle 1, Prior to Cycle 2, w at progression or appearance of a new lesion, at end of treatment, and in the event of a Skin Flare Reaction (O) At response (PR/CR),	M	Funding for biomarkers will be from CITN with co-funding from Merck and Horizon. Additional funds will be sought from foundations and CTEP's CRADA with Merck
Spatial association of tumor cells and components of the tumor microenvironment PI: Dr. Rob Pierce Site: Fred Hutchinson Cancer Research Center	Multispectral immunohistochemistry CLIA: N	Exploratory Purpose: Hypothesis generating Multispectral immunohistochemistry IHC for PD1, PDL1, PDL2, CD3, CD4, CD8, Foxp3, CD163 will define the spatial relationship of the tumor infiltrate	Tissue: Skin biopsy Timing: (M) Prior to IFN-gamma lead-in, Prior to Cycle 1, Prior to Cycle 2, at progression or appearance of a new lesion, r, at end of treatment, and in the event of a Skin Flare Reaction (O) At response (PR/CR),	M	(see above)
High dimensional imaging of tumor microenvironment PI: Youn Kim Site: Stanford University	Multiplexed Ion Beam Imaging CLIA: N	Exploratory Purpose: Hypothesis generating Mass spectroscopy based imaging of ~30 parameters simultaneously to delineate expression of immune checkpoint molecules and activation markers on components of the tumor microenvironment	Tissue: Skin biopsy Timing: (M) Prior to IFN-gamma lead-in, Prior to Cycle 1, Prior to Cycle 2, , at progression or appearance of a new lesion, at end of treatment and in the event of a Skin Flare Reaction (O) At response (PR/CR).	M	(see above)

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]
Gene expression profiling PI: Dr. Rob Pierce Site: Fred Hutchinson Cancer Research Center	Nanostring immune panel CLIA: N	Exploratory Purpose: Hypothesis generating and will assess Th1 skewing of T cells after interferon gamma treatment	Tissue: Skin biopsy and peripheral blood mononuclear cells Timing: (M) Skin biopsy: Prior to IFN-gamma lead-in, Prior to Cycle 1, Prior to Cycle 2, at progression or appearance of a new lesion, at end of treatment and in the event of a Skin Flare Reaction Blood draw: Prior to IFN-gamma lead-in, Prior to Cycle 1, Prior to Cycle 2, Prior to Cycle 6, with a response, at progression or appearance of a new lesion, at end of treatment and in the event of a Skin Flare Reaction (O) Skin biopsy: At response (PR/CR),	M	(see above)
Peripheral blood immunophenotyping PI: Michael Khodadoust Site: Stanford University	Multiparametric flow cytometry and CyTOF CLIA: N	Exploratory Purpose: Hypothesis generating Phenotyping of normal T cell and Sezary cell populations pretreatment and post treatment. Functional phenotyping of T cells will be performed by testing cytokine production after stimulation.	Tissue: Peripheral blood mononuclear cells Timing: (M) Prior to IFN-gamma lead-in, Prior to Cycle 1, Prior to Cycle 2, and in the event of a Skin Flare Reaction.	M	(see above)
Serum cytokine and chemokine detection PI: Michael Khodadoust Site: Stanford University	Luminex multiplexed ELISA-based cytokine assay CLIA: N	Exploratory Purpose: Hypothesis generating Quantitative measurement of cytokines/chemokines pre and post treatment	Tissue: Serum Timing: (M) Prior to IFN-gamma lead-in, Prior to Cycle 1, Prior to Cycle 2, prior to Cycle 6, with response, or progression, at EOT and in the event of a Skin Flare Reaction.	M	(see above)

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]
Tumor genotyping and prediction of neoantigens PI: Michael Khodadoust Site: Stanford University	Whole exome sequencing CLIA: N	Exploratory Purpose: Hypothesis generating and will test the hypothesis that high neoantigen burden is associated with response	Tissue: Skin biopsy and peripheral blood Timing: (M) Skin biopsy: Prior to IFN-gamma lead-in, prior to cycle 1, prior to cycle 2, at progression or appearance of a new lesion, at EOT, and in the event of a Skin Flare reaction. Blood draw: Prior to IFN-gamma lead-in, Prior to Cycle 2, Prior to Cycle 6, with response, at progression, at EOT (O) Skin biopsy: At response (PR/CR).	M	(see above)
T cell receptor sequencing PI: Dr. Steven Fling/Dr. Rob Pierce Site: Fred Hutchinson Cancer Research Center	High throughput sequencing of TCR CLIA: N	Exploratory Purposes: Hypothesis generating and to assess responses through Response assessment through detection of malignant clone and characterization of the T cell repertoire.	Tissue: Skin biopsy and peripheral blood mononuclear cells Timing: (M) Skin biopsy: Prior to interferon gamma lead-in, Prior to Cycle 1, prior to Cycle 2, at progression or appearance of a new lesion, EOT, and in the event of a skin flare reaction. Blood draw: Prior to IFN-gamma lead-in, Prior to Cycle 1, Cycle 2, 6, 10, then every 4 cycles, with progression, response, EOT, and in the event of a Skin Flare Reaction. (O) Skin Biopsy: At response (PR/CR)	M	(see above)
Kyn/Trp PI: Dr. Steven Fling and TBD Site: Fred Hutchinson Cancer Research Center and Incyte Corp.	Mass Spec CLIA: N	Exploratory Purposes: Hypothesis generating and to assess whether IDO1 activity may be a mechanism leading to treatment failure.	Timing: (M) Blood draw: Prior to IFN-gamma lead-in, Prior to Cycle 2, 6, 10, then every 4 cycles, with progression, response, EOT, and in the event of a Skin Flare Reaction.	M	(see above)
Microbiome PIs: Dr. Steven Fling and Dr. David Fredricks Site: Fred Hutchinson Cancer Research Center	16S rRNA gene sequencing and WGS CLIA: N	Exploratory Purposes: Hypothesis generating and to understand the role of the microbiome in responses to immunotherapy	Timing: (M) Stool Sample: Prior to IFN-gamma	M	(see above)

Synovial Sarcoma (Treatment Group 2)

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]
Lymphocyte and Monocyte Phenotype Steven Fling, PhD CITN Central Immune Monitoring Laboratory (CIML)	Multiparametric Flow Cytometry CLIA: No	Exploratory To be used to assess the effect of IFNγ and pembrolizumab on circulating lymphocyte and monocyte numbers and phenotype	Whole Blood and PBMC Prior first IFNγ dose, Cycle 1, 3 and 7.	M	CITN/Horizon/Merck, possibly CIMAC
Flow cytometry for selected Class I HLA-Alleles and for phenotype assessment of antigen specific T cells Steven Fling, PhD CITN CIML and TBD Seth Pollack, MD FHCRC	Tetramer Flow cytometry CLIA: N	Integrated/Exploratory To evaluate for a change in the phenotype of circulating tumor specific T cells	Whole Blood and PBMC Prior first IFNγ dose, Cycle 3, 7 and EOT, and at time of documented failure	M	
Anti-Tumor Immune T cell Responses Steven Fling, PhD CITN CIML and TBD	Elispot CLIA: N	Exploratory To evaluate for the emergence and/or expansion of T-cells reactive to known tumor antigens (e.g. MAGE-A4, MAGE-A-9, NY-ESO-1, LAGE-1, PRAME)	Peripheral Blood Prior first IFNγ dose, Cycle 3, 7 and EOT and at time of documented failure	M	
Multiplex Cytokines FHCRC Shared Services and TBD or CIMAC	Affymatrix or Luminex CLIA: No	Exploratory To be used to explore whether reactive changes in cytokine levels correlates with toxicity & efficacy of IFNγ and pembrolizumab	Serum Prior first IFNγ dose, Cycle 1, 3, 7 and EOT and at time of documented failure	M	
PD-L1 baseline and post-treatment FHCRC (Rob Pierce) or Merck	IHC CLIA: No	Exploratory To be used to explore whether induction of this marker correlates with response	Tumor biopsy tissue Pre-therapy biopsy and Week 8-12		

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]**
Slide-Based Immune Phenotype Panel Immunohistochemistry for CD80, Arginase-1, CD3, CD4, CD8, CD20, PD1, CD68, FOXP3, PDL1, CD11b, CD137, CD45RO, HLA-DR, MHC class I, Rob Pierce MD in the FHCRC Core Laboratory CITN CIML and FHCRC Shared services	Multi-spectral Immunohistochemistry CLIA: N	Integrated/Exploratory To evaluate for a change in the immune profile of the tumor microenvironment towards a pro-inflammatory phenotype	Tumor biopsy tissue Pre-therapy biopsy and Week 8-12	M	
Immune Gene Expression Signature Steven Fling, PhD CITN CIML and/or NanoString Corp or CIMAC	NanoString® Gene Expression using the nCounter® Human Immunology V2 Panel and the nCounter® PanCancer Immune Profiling Panel CLIA: N	Integrated/Exploratory To evaluate for a change in the immune profile of the tumor microenvironment towards a pro-inflammatory phenotype	Tumor biopsy tissue Pre-therapy biopsy and Week 8-12	M	
TCR Clonality Adaptive Biotechnologies or CIMAC	TCR ImmunoSeq (Adaptive Biotechnologies) CLIA: N	Integrated/Exploratory To evaluate for evidence of the emergence and/or expansion of tumor specific T-cells within the TME	Tumor biopsy tissue Pre-therapy biopsy and Week 8-12	M	
Microbiome Dr. David Fredricks (FHCRC) or CIMAC	16S Ribosomal Sequencing and WGS CLIA: N	Integrated/Exploratory To evaluate the potential role of the microbiome in response to therapy and hypothesis generating	Fecal Stool Sample Pre-therapy	M	
HLA Class I and Class II Typing Dr. Dan Geraghty (FHRCR)	HLA Class I and Class II Typing		Peripheral Blood Pre-therapy	M	

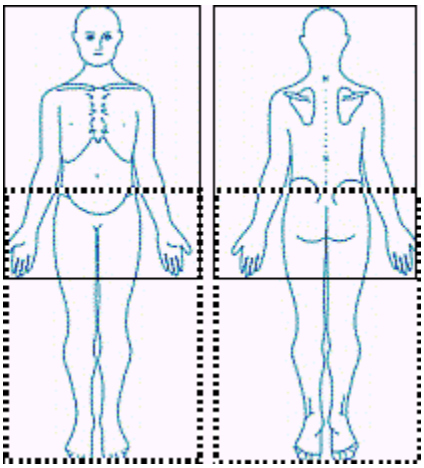
APPENDIX D STANDARDIZED MEDICAL PHOTOGRAPHY (TREATMENT GROUP 1)

Using a standard medical blue background and with the patient in anatomical position (palms placed anteriorly), the following photos will be taken of the study participant:

1. Global (full body).

2. Half-global (half body – anterior and posterior aspect).

3. Additional photographs will be taken at a short distance (1 foot) of biopsy sites.



APPENDIX E MODIFIED SEVERITY-WEIGHTED ASSESSMENT TOOL (MSWAT) (TREATMENT GROUP 1)

The mSWAT is an objective, quantitative, severity- weighted method to assess the extent of Mycosis Fungoides lesions. A SWAT score is derived by measuring each lesion as a percentage of total body surface area (%TBSA) and multiplying it by a severity-weighting factor (1 = patch, 2 = plaque, 4 = tumor). All individual numbers are then added to produce a total score.

The body is divided into 12 regions with pre-assigned %TBSA based on methodology used to assess burns. The extent of skin disease is assessed for each region and quantified by using the subject's palm as a "ruler" to measure the %TBSA involvement within each region.

Subject's palm with 4 fingers, including the thumb and measured from wrist to fingertips, is 1% of TBSA.

Subject's palm without fingers is 0.5% of TBSA.

Modified Severity Weighted Assessment Tool

Modified Severity Weighted Assessment Tool

Mycosis Fungoides lesion type	Elevation description	Erythema description
Patch	Abnormal skin not elevated from normal skin	Flat erythema or erythema with mild infiltration
Plaque	Abnormal skin elevated from normal skin by <5 mm	Elevated erythema or erythema with moderate infiltration
Tumor	Abnormal skin elevated from normal skin by ≥5 mm	Erythema with fissuring, ulceration, or tumor

SWAT Score Calculation

Sum of %TBSA from all body regions affected by patches x severity weighted factor of 1

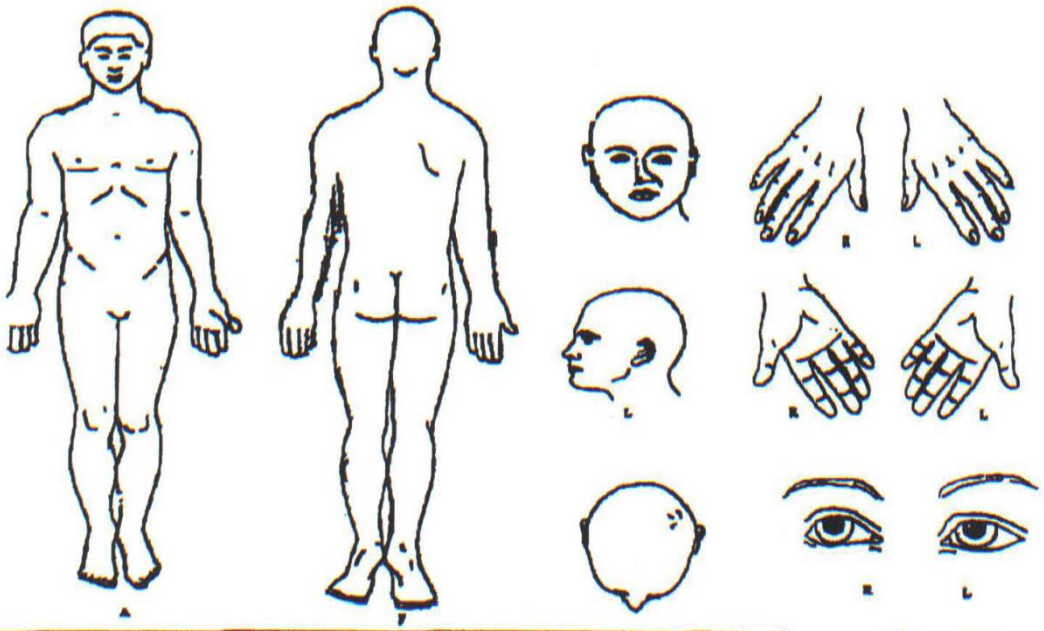
+ Sum of %TBSA from all body regions affected by plaques x severity weighted factor of 2

+ Sum of %TBSA from all body regions affected by tumors x severity weighted factor of 4

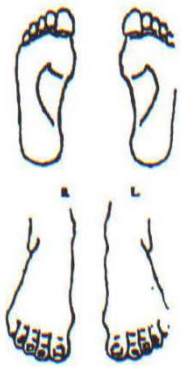
= TOTAL SWAT: (maximum score = 400)

Subject # ___ – ____ (site – subject) Initials ___ (F M L) Visit Date ___ (month) ___ (day) ____ (year)

BODY-SURFACE AREA ASSESSMENT



Area	%BSA for region	% BSA Patch	%BSA Plaque	%BSA Tumor
Head	7			
Neck	2			
Anterior Trunk	13			
Posterior Trunk	13			
Buttocks	5			
Genitalia	1			
Upper arms	8			
Forearms	6			
Hands	5			
Thighs	19			
Lower leg	14			
Feet	7			
Total	100			



Total BSA Involvement % BSA Patch _____

% BSA Plaque _____

% BSA Tumor _____

Total BSA Involvment % BSA = _____