SUMMARY OF CHANGES

For Protocol Amendment #4, Version 2.0

NCI Protocol #: CITN-10
Local Protocol #: CITN-10

Protocol Date: March 8, 2018

I. Comments Requiring a Response– Administrative & Editorial Issues:

#	Section	Comments
1.	**ICD Risks**	When updating risks outside of the CTEP process, they should be placed outside of the CTEP provided condensed risk list tables. That said, with an extensive set of changes, please contact CTEP in the future to discuss prior to making changes to the "Condensed Risk List." CTEP is undergoing a review of the latest (mid-October version) Investigator Brochure for MK-3475. A Request for Rapid Amendment is forthcoming, which could complicate any changes that CITN is contemplating. **PI Response:** Agree. See ICD Summary of Changes

II. Recommendations:

#	Section	Comments
2.	**8.1.1**	MK-3475 Storage: following "Store intact vials between 2°C - 8°C (36°F - 46°F). Do not freeze." please add: If a storage temperature excursion is identified, promptly return MK-3475 to between 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. **PI Response:** Agree. The recommended wording was added to section 8.1.1

III. Changes Recommended by CTEP

#	Section	Page(s)	Change
3.	8.1.1	63	**Information regarding MK-3475 storage was updated to include** "If a storage temperature excursion is identified, promptly return MK-3475 to between 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."

IV. Administrative Changes

#	Section	Page(s)	Change
4.	Throughout protocol	All pages	Updated version date in header
5.	Title Page	2	Updated protocol type, version number and version date. Date matches revised consent form.

V. Changes Requested by CTEP

#	Section	Page(s)	Change
6.	Title page	3	CTSU Regulatory Office mailing address change implemented
7.	4.2.2 Submitting Regulatory Documents	30	CTSU Regulatory Office mailing address change implemented
8.	Throughout	42	Updated CTCAE v4.0 to CTCAE v5.0 throughout document with the exception of the CAEPR (Section 7.1.1)
9.	7.2 Adverse Event Characteristics	57	Added language pertaining to timing of implementation of CTCAE v 5.0 reporting
10.	7.3.3 Expedited Reporting Guidelines	58	Revised language concerning expedited reporting of death due to progressive disease.
11.	7.3.3 Expedited Reporting Guidelines	59	Added language concerning reporting pregnancy loss.
12.	7.3.3 Expedited Reporting Guidelines	59	Added language concerning reporting neonatal death.

NCI Protocol #: CITN-10

Local Protocol #: CITN-10

TITLE: A Phase 2 Study of MK-3475 for the treatment of Relapsed/Refractory Mycosis Fungoides/Sézary Syndrome

Coordinating Center: Cancer Immunotherapy Trials Network, Fred Hutchinson Cancer Research Center

Principal Investigator (PI): Youn Kim, M.D.
Department of Dermatology, Stanford Univ.
School of Medicine
900 Blake Wilbur Drive, Room W1005
Stanford, CA 94305
CTEP Institution Organization ID#: CA141
Tel: (650) 721-7186
Email: younkim@stanford.edu

Participating Organizations : CITN – Cancer Immunotherapy Trials Network

Statistician:
Shufeng Li
Department of Dermatology, Stanford Univ. School of Medicine
900 Blake Wilbur Drive, Room 1080
Stanford, CA 94305
717-406-4371
shufeng@stanford.edu

Study Coordinator: N/A

Responsible Research Nurse: N/A

Responsible Data Manager: N/A

NCI-Supplied Agent: MK-3475, (SCH 900475) NSC# 776864/ Merck Sharp & Dohme Corp. a Subsidiary of Merck & Co. Inc.

IND #: 123635

IND Sponsor: DCTD, NCI

Protocol Type/Version #/Version Date: Amendment 4/Version 2/March 8, 2018

<table>
<tr><th colspan="3">CONTACT INFORMATION</th></tr>
<tr><th>To submit site registration documents:</th><th>For patient enrollments:</th><th>To submit study data</th></tr>
<tr><td>CTSU Regulatory Office
1818 Market Street, Suite 3000
Philadelphia, PA 19103
Phone – 1-866-651-CTSU
Fax – 215-569-0206
Email:
CTSURegulatory@ctsu.coccg.org (for submitting regulatory documents only)</td><td>Please refer to the patient enrollment section for instructions on using the Oncology Patient Enrollment Network (OPEN) 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 via Medidata Rave (FHCRC/AXIO Research, Inc.)Please refer to the data submission section of the protocol for Medidata Rave instructions.</td></tr>
<tr><td colspan="3">The current version of the study protocol and all supporting documents must be downloaded from the protocol-specific Web page of the CTSU Member Web site located at 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 user 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 RSS.</td></tr>
<tr><td colspan="3">For clinical questions (i.e., patient eligibility or treatment-related):
Contact the CITN Central Operations and Statistical Center at citn@fhcrc.org or 206-667-1216</td></tr>
<tr><td colspan="3">For nonclinical questions (i.e., unrelated to patient eligibility, treatment, or clinical data submission) contact the CTSU Help Desk by phone or e-mail:
CTSU General Information Line – 1-888-823-5923, or ctsucontact@westat.com. All calls and correspondence will be triaged to the appropriate CTSU representative.</td></tr>
<tr><td colspan="3">The CTSU Web site is located at https://www.ctsu.org.</td></tr>
</table>

SCHEMA

Abbreviated Title	MK-3475 For the Treatment Of Relapsed/Refractory Mycosis Fungoides/Sézary Syndrome (MF/SS)
Trial Phase	Phase II
Clinical Indication	Stage IB-IVB MF/SS, and who have relapsed, are refractory, or progressed after at least one standard systemic therapy
Trial Type	Nonrandomized, open-label, phase II, interventional study
Type of control	None
Route of administration	Intravenous (IV)
Trial Blinding	None
Treatment Groups	The dose level of MK-3475 proposed to be tested in this study will be 2 mg/kg administered by IV infusion q3w (21 [± 3] days). Treatment cycles will be 21 days with the first clinical response assessment at week 12 (after 4 doses of MK-3475 have been administered during week 1, 4, 7 and 10). If progression is seen at week 12 a confirmatory assessment will be performed at week 16. If progression is confirmed at week 16 or beyond, patients may continue to receive MK-3475 therapy if otherwise clinically stable. If no progression is seen at week 12, the next assessment will be at week 18, then every 2 cycles (every 6 weeks) through week #30. (Assessments will be performed at weeks 24 and 30). After week #30 study assessments will be reduced to every 4 cycles (every 12 weeks) and will be performed at weeks 42, 54, 66, 78, 90 and 104 (end of study). Not all MF/SS patients have disease that is measurable by computed tomography (CT) scan so the term "assessment" refers to the Olsen global assessments which include composite assessments of skin (assessed by mSWAT), lymph nodes (assessed by CT), viscera (by CT) and blood tumor burden of circulating Sézary cells (CSCs) via flow cytometry. At each assessment time point patients will receive CT scans (if they have measurable disease), mSWAT and flow cytometry for CSCs. 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, (2) subject continues to meet eligibility criteria, and (3) the trial is open. Subjects without confirmed progression of disease may receive up to a maximum of 2 years of therapy.

Number of trial subjects	In this Phase II trial, 9 subjects will be enrolled in Stage 1 and 15 subjects may be enrolled in Stage 2. In total a maximum of 24 subjects will be enrolled.
Estimated duration of trial	In this Phase II trial Stage 1 will enroll over 5-10 months, and Stage 2 will enroll over 10-20 months. In total the trial will be enrolled over 15-30 months.
Duration of Participation	First assessment of primary endpoint of clinical response at week 12. If progression, confirmatory assessment at week 16. If no progression, next assessment at week 18 and then every 6 weeks (every 2 cycles) through week #30. Assessments after week 30 will be every 4 cycles (every 12 weeks) including weeks 42, 54, 66, 78, 90 and 104 (end of study). Subjects are followed for overall response, progression free survival, duration of response, and overall survival. Immune response assays will be performed pre-study, following cycle 1 (on the first day of cycle #2) and then upon the first day of every 3rd cycle thereafter including cycles 5,8,11, etc.

SCHEMA (Continued)

CITN, multi-institution, non-randomized, open-label, phase II study of systemic intravenous infusion of MK-3475 in relapsed/refractory MF/SS. **Simon's Optimal Two-Stage Design:** **Stage 1** will enroll 9 patients. **Stage 2:** Will enroll an additional 15 patients (for a total of 24). If there are one or more responses (PR or CR) amongst the nine patients enrolled in Stage 1, Stage 2 enrollment will proceed. If there are no responses (PR or CR) amongst the nine patients enrolled in Stage 1, enrollment into Stage 2 will not proceed. The null hypothesis (H0) MK-3475 will show less than 5% overall response rate. The alternative hypothesis (H1) MK-3475 will show greater than 25% overall response rate (PR and CR).

TRIAL DIAGRAM

Relapsed/Refractory
MF and SS

Stage 1
N=9

- **Tx -** MK-3475 will be 2 mg/kg administered by IV infusion q3w (21 [± 3] days). Treatment cycles will be 21 days with first clinical response assessment at week 12, then again at either week 16 or 18, then after every 2 cycles (every 6 weeks) through week 30, then every 4 cycles (every 12 weeks) with treatment continued until confirmed progression by repeat assessment at least 4 weeks later. If progression is confirmed at week 16 or beyond, patients may continue to receive MK-3475 therapy if otherwise clinically stable. Subjects with CR after receiving a minimum of six months of treatment with at least two 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, (2) subject continues to meet eligibility criteria, and (3) the trial is open. Subjects may receive up to a maximum of 2 years of therapy if clinically improving or stable (Section 5.4).
- **Assessment –**
  - Clinical response – At week 12, then at either week 16 or 18, then every 6 weeks to week #30, then every 12 weeks thereafter.
  - Immune response – following cycle 1 and upon completion of every 3rd cycle. and at time of confirmed CR, PR, PD or EOT visit

With regard to efficacy/clinical response, in order to determine the sample size, we use an optimal 2-stage design since it minimizes the expected sample size given a poor response rate. The null hypothesis is set at 5% (p0 0.05), the alternative hypothesis is 25% (p1 0.25) and the desired significance level (α) and desired power (β) are 0.1 and 0.9, respectively. The total number of subjects for the trial will be 24 subjects, whereas 9 subjects will be accrued during stage 1 and 15 subjects accrued during stage 2. However, if no responses (CR or PR) are observed during the first stage, then further enrollment will be suspended. Patients currently on study who qualify will continue to be treated and followed.

Stage 2
N=15

- **Tx -** MK-3475 will be 2 mg/kg administered by IV infusion q3w (21 [± 3] days). Treatment cycles will be 21 days with first clinical response assessment at week 12, then again at either week 16 or week 18, then every 2 cycles to week #30, then every 4 cycles (every 12 weeks) with treatment continued until confirmed progression by repeat assessment at least 4 weeks later. If progression is confirmed at week 16 or beyond, patients may continue to receive MK-3475 therapy if otherwise clinically stable. Subjects with CR after receiving a minimum of six months of treatment with at least two 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, (2) subject continues to meet eligibility criteria, and (3) the trial is open. Subjects may receive up to a maximum of 2 years of therapy if clinically improving or stable.
- **Assessment –**
  - Clinical response – At week 12, then at either week 16 or 18, then every 6 weeks to week #30, then every 12 weeks thereafter.
  - Immune response – following cycle 1 and upon completion of every 3rd cycle. and at time of confirmed CR, PR, PD or EOT visit

Final Assessment:
With regard to efficacy/clinical response, in order to determine the sample size, we used an optimal 2-stage design since it minimizes the expected sample size given a poor response rate. The null hypothesis is set at 5% (p0 0.05), the alternative hypothesis is 25% (p1 0.25) and the desired significance level (α) and desired power (β) are 0.1 and 0.9, respectively. The total number of subjects for the trial will be 24 subjects, 15 subjects will be accrued during stage 2. However, if 3 or more responses (CR or PR) are observed during the first and second stage combined, the trial will be considered a success

TABLE OF CONTENTS

1. OBJECTIVES

1.1 Primary Objectives

To assess the response rate of MK-3475 in subjects with relapsed/refractory mycosis fungoides/Sézary syndrome (MF/SS).

Hypothesis: Administration of MK-3475 to subjects with relapsed/refractory MF and SS will result in a clinically meaningful objective response rate.

1.2 Secondary Objectives

To explore the clinical activity of MK-3475 in subjects with relapsed/refractory MF and SS with respect to the following endpoints:

- Duration of response (DOR)
- Progression-free survival (PFS)
- Overall survival (OS)

Hypothesis: Induction of a meaningful objective response rate with MK-3475 will be reflected in other clinical outcome parameters including DOR, PFS, and OS.

2. BACKGROUND

2.1 Relapsed/Refractory Mycosis Fungoides/Sézary Syndrome

Mycosis fungoides/Sézary syndrome is the most common type of cutaneous T-cell lymphoma (CTCL), a subset of mature non-Hodgkin lymphoma. MF exhibits an epidermotropic clonal expansion of cluster of differentiation 4–positive ($CD4^+$) T helper cells that induces pleomorphic skin lesions. MF 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. SS is a leukemic variant of CTCL in which subjects have generalized erythroderma and are at risk for lymph node and visceral disease. **MF/SS comprise the most common CTCLs, with continued increase in overall annual incidence** (currently approximately 0.9 per 100,000 persons in the United States) [Hoppe 1995]. 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). The cutaneous manifestations of MF are heterogeneous [Horwitz 2008].

Therapeutic options for MF and SS are primarily determined by the patient's clinical stage. The National Comprehensive Cancer Network (NCCN) has recently published consensus guidelines for stage-based treatment of MF/SS [NCCN]. The first-line treatment of early stage MF (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, approved by the U.S. Food and Drug Administration (FDA) based on improved response rates, vorinostat, interferons, extracorporeal photopheresis (ECP), denileukin diftitox, radiation therapy, traditional chemotherapeutic agents (methotrexate, doxorubicin, gemcitabine, and chlorambucil), and investigational agents. Despite a wide array of available therapeutic options, subjects with MF and SS remain largely incurable. **Response rates for most of these systemic agents are 30-40% with infrequent complete responses (CR); these clinical responses are often short-lived** with most approved agents yielding median DORs in the range of 6-12 months [Duvic 2001]; [Olsen 2001]; [Olsen 2007]; [Whittaker 2010].

The importance of intact immune surveillance in controlling outgrowth of neoplastic transformation has been known for decades [Disis 2010]. Accumulating evidence shows a correlation between tumor-infiltrating lymphocytes (TILs) in cancer tissue and favorable prognosis in various malignancies [Dong 2002]; [Sharpe 2002]; [Brown 2003]; [Thompson 2007]; [Francisco 2010]. In particular, the presence of $CD8^+$ T cells and the ratio of $CD8^+$ effector T cells/$FoxP3^+$ regulatory T cells (Tregs) seems to correlate with improved prognosis and long-term survival in many solid tumors.

There is mounting evidence that T cell immunity may be responsible for clinical antitumor activity in MF/SS:

2.1.1 *Tumor-infiltrating T cells are prognostic of survival.*

a. Hoppe et al. identified improved survival in MF subjects whose biopsies demonstrated $CD8^+$ TILs, even when controlling for stage [Hoppe 1995].

2.1.2 Therapies which augment T cell function are effective in MF/SS.

a. Interferon alpha has been shown in a number of studies to be a highly active agent in CTCL with overall response rates (ORRs) ranging from 40% to 80% with concurrent improvement in T cell cytotoxicity [Bunn 1986]; [Olsen 1995].

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

c. Early studies with high-dose interleukin 2 (IL-2) demonstrated activity in relapsed CTCL but with significant toxicity [Heald 1992]; [Heald 1990].

d. 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, and toxicities included myalgias, fatigue, and chills [Rook 2002]; [Rook 2001].

e. ECP is an immunomodulatory apheresis-based therapy that works directly on both subsets of T cells and on the precursors of maturing dendritic cells [Heald 1992]; [Heald 1990]; [Zic 1992]; [Prinz 1995]; [Owsianowski 1996]; [Di Renzo 1997] [Miracco 1997]; [Jiang 1999].

f. Other immunotherapy agents have been combined with photophoresis including retinoids, interferons, and cytokine growth factors.

i. Richardson and colleagues have reported high response rates in patients with the SS when ECP therapy was administration with immune adjuvant therapies, including interferon alpha (INF-α) and bexarotene [Rook 2002].

g. A modification of ECP known as transimmunization may improve tumor-targeted response.

i. Transimmunization involves co-incubating the apoptotic malignant T cells and the newly formed dendritic cells prior to reinfusion in order to optimize antigen processing and stimulate a more efficient induction of tumor-targeted immunity. The goal of treatment is to transfer the disease-associated antigens to antigen-presenting dendritic cells, thus initiating immunization against these antigens [Girardi 2002], [Girardi 2002], [Berger 2002], [Edelson 2001].

h. In a phase I study of 28 patients with recurrent or advanced CTCL who received CPG7909, the Toll-like receptor 9 (TLR9) agonist, in weekly subcutaneous doses of 0.08, 0.16, 0.24, or 0.28 mg/kg for 24 weeks, the ORR was 25% [Kim 2004]. Five patients (18%) achieved partial response (PR) and 2 (7%) achieved CR. Kim reported clinical responses in 5/15 subjects in an in-situ vaccination trial in which CPG (a TLR9 agonist) was combined with local radiation therapy [Kim 2012] validating the potential of T-cell responses and the likelihood of existent nascent T-cell responses.

i. Allogeneic stem cell transplantation (SCT) is superior to autologous. Allogeneic SCT in MF/SS demonstrates improved overall and event-free survival than autologous SCT recipients, possibly due to a graft versus lymphoma effect [Wu 2009], validating that T-cell responses can potentially eradicate the disease.

j. Alemtuzumab removes circulating T central memory cells, without effect on T effector memory cells, and Sézary cells from the circulation.

2.2 CTEP IND Agent: MK-3475

2.2.1 MK-3475

MK-3475 (SCH 900475) is a humanized immunoglobulin (Ig) G4 monoclonal antibody (mAb) which binds the programmed death 1 (PD-1) receptor, thus inhibiting the interaction with its ligands, PD-L1 or PD-L2 (Investigator's Brochure, 2014). PD-1 is an immune-checkpoint receptor expressed by T cells. When bound to either PD-L1 or PD-L2, the PD-1 pathway negatively regulates T-cell effector functions. The PD-1 pathway functions to limit unwanted or excessive immune responses, including autoimmune reactions. PD-L1 is typically expressed at low levels on various non-hematopoietic tissues, and PD-L2 is only detectably expressed on antigen-presenting cells in the lymphoid tissue or chronic inflammatory environments.

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

Immune-checkpoint inhibition of another inhibitory T-cell receptor, cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4), with the mAb ipilimumab demonstrated significant prolongation of overall survival (OS) in patients with melanoma in two phase 3 trials (Hodi *et al.*, 2010; Robert *et al.*, 2011; Ribas, 2012). As an immunotherapy target, PD-1 is distinct from CTLA-4 because it can be activated directly by the cancer and it regulates the effector phase of T-cell response, whereas CTLA-4 regulates the initial stage of T-cell activation (Pardoll, 2012; Ribas, 2012). Antibodies targeting the PD-1 pathway have demonstrated durable objective responses in phase 1 and 2 trials. Nivolumab showed an overall response rate (ORR) of approximately 28% in subjects with advanced melanoma, 27% in subjects with RCC, and 18% in subjects with non-small cell lung cancer (NSCLC) who had failed prior therapy (Topalian *et al.*, 2012). MK-3475 has shown an ORR of approximately 38% in patients with melanoma (Hamid *et al.*, 2013) and ~20% in patients with NSCLC (Investigator's Brochure, 2014).

2.2.1.1 Clinical Development of MK-3475

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

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

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

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

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

Part D: Advanced melanoma patients that are IPI-naïve. Patients in Part D receive MK-

3475 at 2 mg/kg Q3W and 10 mg/kg Q3W.

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

Pharmacokinetics

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

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

Anti-Drug Antibodies (ADA) Data

The occurrence of ADA has been observed in less than 1% of the patients screened, indicating a low potential of MK-3475 to elicit the formation of ADA (Investigator's Brochure, 2014). No impact of ADA on MK-3475 exposure has been observed.

Efficacy

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

The preliminary objective response rate for 38 patients with NSCLC (Part C) was 21%/24% by RECIST/investigator-assessed irRC, respectively (Investigator's Brochure, 2014).

Pharmacodynamics/Biomarkers

PD-L1 is being investigated as a predictive biomarker for MK-3475 treatment. At the 15th World Conference on Lung Cancer, Garon *et al.* presented preliminary data on a subset of patients suggesting that higher levels of tumor PD-L1 expression are associated with increased clinical activity (Garon *et al.*, 2013). Objective responses by RECIST 1.1 occurred in 4 out of 7 patients with higher levels of PD-L1 expression (57%, 95% confidence interval [CI] 18-90%) vs. 2 out of 22 patients with lower levels of PD-L1 expression (9%, 95% CI 1-29%). These data are extremely preliminary, and PD-L1 is not being used for patient selection.

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

2.2.1.2 Safety data

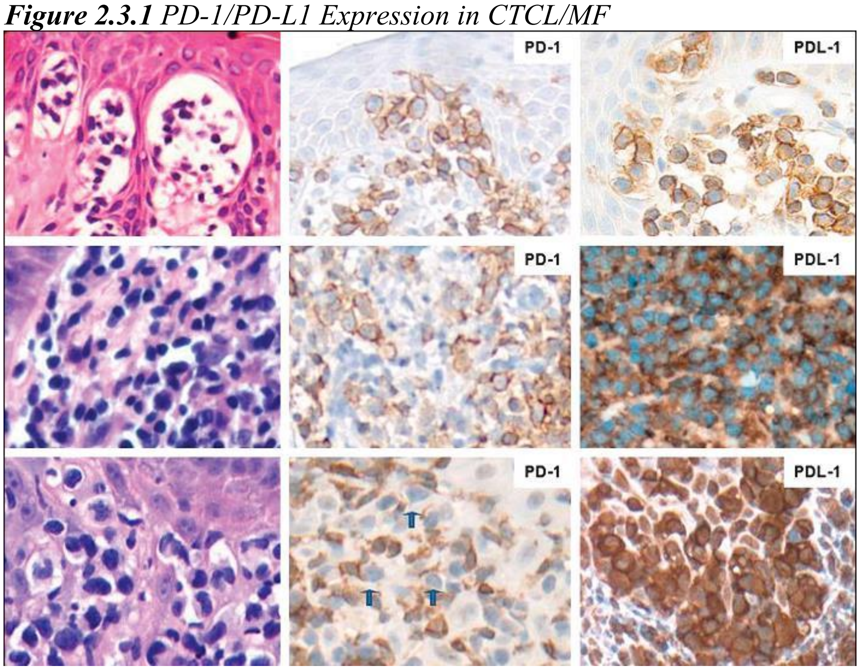
The most frequent treatment-related adverse events (AEs) were fatigue, nausea, cough, pruritus, diarrhea, and rash (Investigator's Brochure, 2014). Most AEs were not considered serious. The most commonly reported immune-related AEs were rash, pruritus, vitiligo, hypothyroidism, arthralgia, diarrhea,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

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

2.3 Rationale

Recent evidence of expression of PD-1 and PD-L1 in MF/SS has uncovered an additional mechanism of potential immune escape and a new therapeutic target. Current data suggest that the PD-1/PD-L1 may play a significant role in preventing immune-driven eradication of MF/SS tumor population. A 2012 study evaluated the expression of PD-1 and PD-L1 in various morphological subsets of MF ranging from patch/plaque to tumor stage with or without large cell transformation [Kantekure 2012] (Figure 2.3.1).

Figure 2.3.1 *PD-1/PD-L1 Expression in CTCL/MF*



PD-1 and PD-L1 expression at various stages of CTCL/MF: patch/plague (upper row), tumor (middle row), and large cell transformation (lower row). The formalin-fixed paraffin-embedded (FFPE) skin biopsy tissue sections were stained with H&E (left column) or antibodies against PD-1 (middle column) or PD-L1 (right column). The depicted images are representative of the 26 CTCL cases examined and were captured at the 4003 magnification. The blue arrows in the PD-1 stain of the large cell transformation case highlight the negative large lymphocytes).

A 2012 study evaluated the expression of PD-1 and PD-L1 in various morphological subsets of MF ranging from patch/plaque to tumor stage with or without large cell transformation [Kantekure 2012]. In this study, 9/9 patch/plaque and 5/6 tumor lesions showed >2% PD-1 expression of atypical lymphocytes via immunohistochemistry. In comparison, large transformed lymphocytes showed reduced expression of PD-1, with only 2/11 demonstrating >2% expression. On the other hand, PD-L1 expression was quite strong across all subsets, with 7/9 patch/plaque, 6/6 tumor stage, and 11/11 large transformed lymphocytes demonstrating >50% expression. In the 2/9 patch/plaque lesions with less than 50% PD-L1 expression, the staining was still greater than 2%.

Figure 2.3.2 *PD-1 Expression*

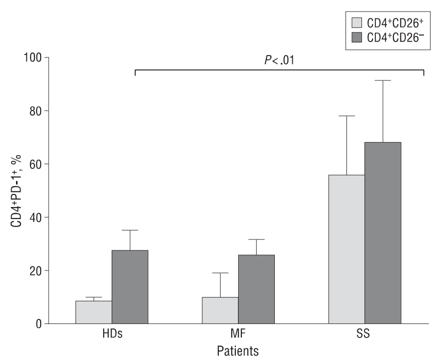
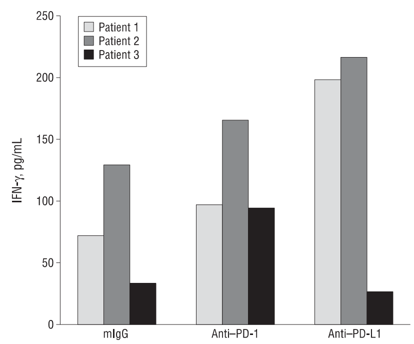


Figure 2.3.3 *Blocking PD-1 Increases INF-γ*



[Samimi 2010]; and [Rook 2002] also demonstrated higher expression of PD-1 and PD-L1 via flow cytometry on peripheral blood T cells in SS subjects [Samimi 2010] (See Figure 2.3.2. Increased expression of PD-1 on $CD4^{+}$ T cells from patients with SS. The peripheral blood mononuclear cells (PBMCs) from patients with SS (n=7), patients with MF (n=4), and healthy donors (n=4) were stained with anti-CD4, anti-PD-1, and anti-CD26, and were analyzed by flow cytometry. The percentage of $CD4^{+}PD\text{-}1^{+}$ is demonstrated according to patient population and CD26 status. Error bars indicate the standard deviation of uncertainty.)

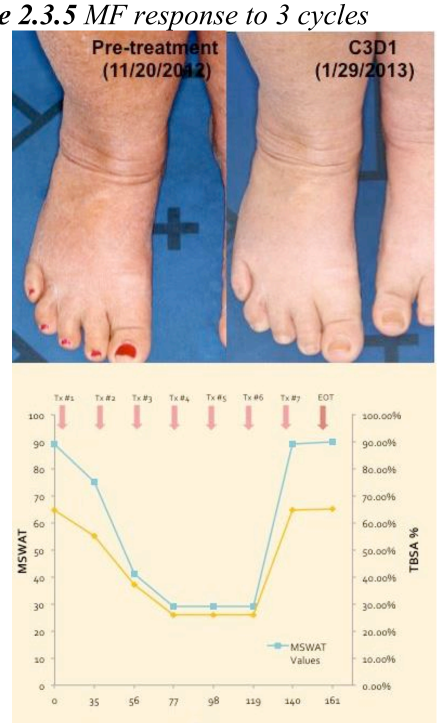
When blocking PD-1 and PD-L1 in vitro, interferon-γ (IFN-γ) production increased, perhaps indicating recovery of T-cell function after withdrawing the suppressive PD-1/PD-L1 signal (Figure 2.3.3.) Blocking the pathway of PD-1 and its ligand PD-L1 results in increased IFN-γ production by patients' PBMCs stimulated with anti-CD3/CD28. The PBMCs of patients with SS were cultured for 72 hours with either medium or anti-CD3/CD28 alone, and with the following: murine IgG (mIgG), anti-PD-1, or anti-PD-L1. Subsequently, culture supernatants were collected and tested for the presence of IFN-γ. Furthermore, PD-1 expression levels, along with the overall proportion of the malignant T-cell population, decreased as a SS patient improved clinically during treatment. Preliminary data supports the induction of PD-L1 by standard therapies in MF/SS including radiation, epigenetic therapies, and interferon.

Collectively, these data suggest that PD-1 and PD-L1 are expressed aberrantly on the malignant tumor cells of MF/SS, further augmented by current therapies, and that blockage of these signals may lead to reduced antitumor T-cell inhibition and thus tumor eradication.

Recent data of BMS-936558 have validated PD-1 as an attractive target for clinical intervention and have provided proof of concept for anti-PD-1 mAbs in melanoma and renal cell carcinoma (RCC) [Sznol 2010]. BMS-936558 has shown an ORR of approximately 30% in patients with advanced melanoma and RCC who had failed prior therapy [Sznol 2010]. In addition, ORR of near 20% was observed in patients with NSCLC [Brahmer 2012]; [Sznol 2010]. Importantly, responses were of long duration, and BMS-936558 was generally well tolerated. The repeat dose study tested multiple dose levels (0.1, 0.3, 1, 3, and 10 mg/kg every 2 weeks) [Sznol 2010]; [Robert 2011]. Importantly, as MF/SS appears to express a high level of PD-L1, the ability of PD-L1 to predict response to PD-1 targeted therapy is of relevance. In mixed tumor types including melanoma and NSCLC, among others, this observation has been reported and validated. In 3 recent reports, response rates among PD-L1–positive patients are 42%, 41%, and 34%, compared to 0%, 14%, and 16% among PD-L1–negative patients [Topalian 2012]. Additional biomarker analysis to predict response to PD-1 targeted therapies, demonstrated that patients with a history of or present tobacco use and thus a higher rate and number of mutations in NSCLC respond more frequently, 26%, than those without a tobacco history (10%). As MF/SS is considered a highly immunogenic and PD-L1–expressing tumor, it is likely to be responsive to PD-1 targeted therapy.

Figure 2.3.4 *MF response to 8 cycles*

Figure 2.3.5 *MF response to 3 cycles*



Finally, 2 recent cases of MF/SS enrolled on the MPDL3280A clinical trial of an IgG1 engineered mAb against PD-L1 both of whom obtained PRs support further testing of PD-1 targeted agents in this disease [Kohrt ASCO 2013]. The first patient was a 65-year-old man with Stage IB multiply relapsed MF (history of phototherapy: PUVA, bexarotene, anti-CD4 mAb, forodesine, CpG and radiation, lenalidomide, sapacitabine, enzastaurin, and total skin electron beam therapy) who obtained a PR at first assessment (following 2 cycles) and has maintained a deep PR following 16 cycles (1 year) of treatment. (See Figure 2.3.4. Lesion on right forearm pretreatment [top left] and following 8 cycles of therapy [top right]. Lesion on right upper thigh pretreatment [bottom left] and following 8 cycles of therapy [bottom right]). The second case was a 58-year-old woman with Stage IIIB multiply relapsed MF (history of photochemotherapy: PUVA + bexarotene, CpG and radiation, vorinostat, forodesine, bexarotene, sapacitabine, lenalidomide, enzastaurin, low-dose total skin electron beam therapy) who obtained a PR after 2 cycles of therapy with a reduction in Modified Severity-Weighted Assessment Tool (mSWAT) score (which scores extent and burden of disease in MF) from 90 at baseline to 42. Following 7 cycles of therapy, anti-PD-L1 was discontinued due to patient-reported profound fatigue and her disease progressed thereafter (See Figure 2.3.5. Lesion on right foot consistent with erythroderma prior to therapy [top left] and on day 1 of cycle 3 [top right]. mSWAT score over the course of treatment on clinical trial MPDL3280A [bottom]).

The primary endpoint of this current study (CITN-10) is clinical response. This endpoint will first be evaluated by clinical response (global) assessment per [Olsen] at week 12 (after 4 doses of MK-3475 during week 1, 4,7 and 10). If progressive disease (PD) is seen at week 12, a confirmatory assessment will be performed at week 16. If no progression is seen at week 12, subjects will be assessed again at week 18. After this, subjects will be assessed every 2 cycles (every 6 weeks) through week #30, then every 4 cycles (every 12 weeks) thereafter with the best response being assessed based on specific criteria relevant to the histologies of MF/SS:

1) Consensus response criteria in MF/SS [Olsen 2011]
2) Compartmental assessments of skin, blood, lymph nodes, and viscera, as appropriate (Olsen response criteria, see Protocol Section 11))
3) Global response will be determined from compartmental response, to determine ORR (Protocol Section 11)

If progression is determined at week 16 or beyond, patients will be eligible to receive continued MK-3475 if they are clinically stable as defined by the following criteria. (The maximum duration of therapy in this setting is the same as for other patients, 2 years).

- 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

The following assessment and stopping criteria apply to patients who continue MK-3475 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.

Patients being treated with MK-3475 for melanoma have experienced late responses with continued therapy. In the KEYNOTE-001 melanoma trial using MK-3475 there was an additional 3.6% response rate with continued therapy. This category of response in that trial was defined as an “unconventional response” with “delayed pseudoprogression: ≥25% increase in tumor burden at any assessment after week 12 that was not confirmed as progressive disease per irRC at the next assessment”. [Hodi, 2014].

Subjects will be assessed using the **modified SWAT** (mSWAT or modified skin weighted assessment tool) [see Appendix E] to capture percent body surface involvement with patches, plaques, or tumors. Patches will be multiplied × 1, plaques × 2, and tumors or nodules × 4. **Full-body and half-body photographs** will be taken at baseline, at each on-study evaluation visit, and at the end of treatment visit. Refer to Appendix C for full instructions. **Radiographic imaging** will be required with a full-body positron emission tomography(PET)/computed tomography (CT) with contrast performed prior to study entry and scored by Olsen criteria. Subjects without extracutaneous disease at screening (those with nonmeasureable disease by CT) will have repeat imaging at the discretion of the investigator for PD. Repeat imaging is not necessary for CR, PR, or stable disease (SD) in those patients with nonmeasurable disease. For subjects with known extracutaneous disease (those with measurable disease by CT), imaging will be performed at week 12 (after 4 doses of MK-3475). If progression is seen at week 12, a confirmatory scan will be repeated at week 16. If no progression is seen at week 12, imaging will be repeated at week 18 then every 6 weeks (every 2 cycles) through week #30, then every 4 cycles (every 12 weeks). At time of CR/PR confirmation or PD and end of therapy (EOT), an imaging study will be performed.

Immunotherapeutic agents such as MK-3475 may produce antitumor effects by potentiating endogenous cancer-specific immune responses, which may be functionally anergic. The response patterns seen with such an approach may extend beyond the typical time course of responses seen with cytotoxic agents and can manifest a clinical response after an initial increase in tumor burden or even the appearance of new lesions. Standard RECIST criteria may not provide a complete response assessment of immunotherapeutic agents such as MK-3475.

2.4 Correlative Studies Background

Cancer treatment has evolved significantly since the original introduction of nitrogen mustard during World War II for subjects with lymphoma [Alexander 2011]. Today mAbs are the standard of care for multiple tumor histologies [Dalle 2008], a dendritic cell vaccine is approved by the FDA for the treatment of hormone-resistant prostate cancer [Kantoff 2010], and an immunomodulating mAb is approved for melanoma [Hodi 2010], [Mellman 2011], [Topalian 2011]. This evolving field of immunotherapy provides the potential to eliminate cytotoxic, conventional chemotherapy, which results in significant toxicity to normal tissue in an effort to increase its antitumor efficacy. Uniquely, immunotherapy to date is well-tolerated or demonstrates predictable toxicity as a result of immunostimulation, such as the autoimmune AEs due to anti-CTLA4 or anti-PD-1 therapy [Attia 2005]; [Hodi 2010]. The drug development pipeline of both academic and pharmaceutical efforts appears rich in novel immunotherapeutics, suggesting that the field of immunotherapy is likely to be a mainstay of future cancer treatment. In contrast to the evolution of alkylating agents, topoisomerase inhibitors, and other conventional chemotherapies, the development of immunotherapy necessitates multiple shifts in the paradigm of cancer drug development. Development of new criteria to assess response to immunomodulating therapies is exemplary of the immunotherapy-specific shift [Alexander 2011]. This transition in response evaluation, though led by a single institution, is now implemented near-universally across U.S. and European institutions evaluating activity of immunotherapies. Similarly at the larger cooperative group and societal levels, efforts are ongoing to harmonize immune monitoring and immunologic biomarkers [Britten 2008]; [van der Burg 2011]. Despite immune-specific clinical trial monitoring, biomarkers, and response assessment, immunotherapy trials, to date, have yet to properly define immune-specific inclusion criteria. Defining which patient cohorts are responsive to immunotherapy or, more easily, excluding enrollment of subjects who have no likelihood of response based on an incompetent immune system will be of substantial significance to the field by (a) increasing the efficiency of immunotherapy trials, (b) reducing the needed sample size of early phase proof-of-concept studies, and (c) reducing the cost of clinical development by approximately 35%. The impact of this in-depth analysis of immune competency in cancer will provide mechanistic insight into the tumor-immune interactions, uncover biomarkers of response to therapy and patient prognosis, and ultimately aid in discovery of novel immunotherapeutics that improve patient survival while maintaining quality of life.

Anti-PD-1 therapy, as an immunotherapy, unlike conventional modalities of cancer treatment, targets and modulate the patient’s immune system. Tumor-immune interactions occur at the level of the tumor microenvironment, including TILs and systemic macroenvironment, including circulating lymphocytes that may be recruited to the tumor. The state of a patient’s immune system and its responsiveness to therapy influence the efficacy of immunotherapy. It is now well-established that tumor-induced immune suppression prevents the naturally protective antitumor immune response in subjects with cancer. The magnitude of immune suppression is heterogeneous dependent on disease histology, extent, duration, and prior therapies. Taken together, the efficacy of an immunotherapy is a balance that is dependent on the therapeutic and its ability to enhance an antitumor immune response and the patient’s immune system, which may be variably suppressed by cancer.

Current efforts to improve immunotherapy are focused on identifying and developing novel therapeutics. Due to the complexity, lack of in-depth methods, and limited incentive from a pharmaceutical perspective, little attention has been placed on thoroughly evaluating the immune competency of subjects with cancer. Unfortunately, therapeutics that appear highly promising, based on preclinical or early phase data, have failed in larger clinical application due, in part, to poor immune competency of the larger patient population [Houot 2009]; [Alexander 2011]; [Sznol 2012]. This leads to early abandoning of otherwise promising therapies.

MF skin lesions are often readily accessible with minimally invasive skin biopsies. Thus, from an exploratory biomarker perspective, this disease offers an almost unique opportunity to investigate the determinants of response and resistance to anti-PD-1 therapy as well as to discover additional molecular targets governing immune dysregulation in cancer. We anticipate that these studies will yield candidate biomarkers that will correlate with prognosis, have predictive value in the selection of which subjects benefit from anti-PD-1 mAb immunotherapy, and offer insight into new therapeutic approaches based on the mechanisms of immune suppression observed.

Our exploratory biomarker approach will focus on blood (98 mL total volume) and tissue sampling performed at screening, following cycle 1, and upon completion of every 3rd cycle as well as at time of confirmed CR, PR, PD, or EOT visit. In order to reduce the number of patient visits, the biomarkers "following cycle 1" will be drawn on the first day of cycle 2, prior to study drug administration. Biomarkers will then be drawn on the first day of every 3rd cycle thereafter including cycle 5, 8, 11, 14, 17, etc.

Biomarker and correlative studies for the CITN-10 trial will include the following:

2.4.1 *Chromogenic (Single-Color) Immunohistochemistry (IHC) for PD-L1*

PD-L1 expression has been identified as a potential biomarker for response to anti-PD-1 therapy. It is anticipated that FFPE samples will be sent to a clinical research organization (CRO) for staining with our 22C3 anti-PD-L1 assay. We will test whether PD-L1 expression correlates with MK-3475 response in the MF/SS population.

2.4.2 *Multiparametric (Two-Color) IHC*

Spatial association of PD-1$^+$ TILs and PD-L1$^+$ cells (tumor and myeloid cells) suggests "induction" of PD-L1. INF-γ production by antigen-specific PD-1$^+$ CD8$^+$ T cells is hypothesized to drive local intratumoral upregulation of PD-L1 on adjacent tumor and myeloid cells, leading to a "stalled cytotoxic T lymphocyte (CTL)" response, which may be predictive of response to MK-3475 therapy. By assessing both of the required elements (i.e., PD-L1 positive cells and PD-1$^+$ T cells), a two-color IHC assay may be a better predictor of response than PD-L1 positivity alone. Merck will perform this testing. Additional analytes may be assessed based upon funding. If so, an amendment to the protocol will be made.

2.4.3 *Transcriptional Analyses*

The Nanostring platform will be used to profile messenger RNA (mRNA) expression in archival biopsy material (and potentially PBMC material as well) to assess expression of over 650 genes and attempt to define a gene set critical for clinical response to MK-3475. The hypothesis to be tested is that MK-3475 responders will exhibit a "stalled CTL" response within the tumor reflected in the physical proximity between PD-1 and PD-L1 expression and the presence of an aborted (e.g., weak but discernible) INF-γ transcriptional program. Global profiling by next-generation sequencing (RNAseq) will also be pursued. The nanostring testing will be performed by Merck.

2.4.4 *Immunophenotyping and T cell function assays*

CyTOF and multiparametric flow cytomety will be employed to extensively immunophenotype circulating peripheral leukocytes both prior to and during MK-3475 treatment. We anticipate that these studies will provide a more granular view of the tolerized PD-1$^+$ target cell and its response to anti-PD-1 blockade, which will guide the future choice of rational immunomodulatory combination therapies. 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 MF/SS.

Table 2.4: Immunophenotype Studies

IMMUNOPHENOTYPE STUDIES

TCR Repertoire Analysis

- TCR Vβ repertoire comparison prior to and following vaccination

In vitro Stimulation *(autologous tumor antigen pulsed DCs)*

- Intracellular cytokines (IFNγ, TNFα, IL2)
- Intracellular cytotoxic enzymes (perforin, granzyme)
- Cell surface activation markers (CD137, ICOS, CD107, CD25)
- Cell surface markers of T cell subsets (CD4, CD8, CD45 RA/CD45RO, CD62L, CD127)

CYTOF

Phenotyping Panel		Cytokine Panel	Phospho-Flow Panel
Antibody	Antibody	Antibody	Antibody
CD3	CD85j	IL-2	pSTAT-1
CD4	CD94	IL-8	pSTAT-3
CD8	CD127	IL-17	pSTAT-5
CD14	CD161	GM-CSF	pErk-1/2
CD16	Perforin/granzyme	IFNγ	pP38
CD19	HLA-DR	TNFα	pPLCγ2
CD20	IgD	CD107a	pSLP76
CD24	TCRγδ	IL-4	pNFκB
CD25	CXCR3	IL-22	
CD27	CD11c	MIP-1β	
CD28	CD38	IL-10	
CD33	CD39		
CD38	CD123 (BDCA2)		
CD45RA/RO	CD203c		
CD56	CCR4		
CD62L	CCR6		
CXCR5	CCR7		
PD-L1	FoxP3		
PD-L2	CD137		
PD-1	CD278 (ICOS)		

Flow Cytometry

- Intracellular cytokines (IFNγ, TNFα, IL2)
- Intracellular cytotoxic enzymes (perforin, granzyme)
- Cell surface activation markers (CD137, ICOS, CD107, CD25)
- Cell surface markers of T cell subsets (CD4, CD8, CD45 RA/CD45RO, CD62L, CD127)
- Intracellular markers of Treg phenotype (foxP3).

Luminex/ NanoImmunoassay

- ELISA of 37 cytokines
- Oncogene protein analysis

Immunophenotyping will be augmented by assays of T cell function. Activation of discrete T cell subsets and/or combinations of T cells with putative "suppressor cells" will be assayed by intracellular cytokines, cell surface activation markers of proliferation when challenged with autologous tumor cells or autologous dendritic cells pulsed with tumor lysate.

2.4.5 ***Cytokine/Chemokine Analysis (serum enzyme-linked immunosorbent assay [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 (prior to treatment), on treatment, and at time of response assessment.

2.4.6 ***Whole Exome Sequencing and Neoantigen Identification***

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. Subsequent individualized testing of immune responses directed against candidate neoantigens may be performed. Depending on availability of resources, this may be limited to a subset of patients.

3. PATIENT SELECTION

3.1 Eligibility criteria

3.1.1 This trial will include subjects with Stage IB-IVB MF/SS (maximal stage since diagnosis will determine eligibility), and who have relapsed, are refractory, or progressed after at least one standard systemic therapy. Current disease stage at time of entry will also be documented but will not be used for eligibility.

3.1.2 Subjects must have the following minimum washout and AE recovery period from previous treatments without treatment between documentation of relapse/progression and enrollment of specifically:

a. ≥2 weeks for local radiation therapy.

b. ≥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 alemutuzumab for which the washout is at least 8 weeks.

c. ≥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).

d. ≥2 weeks from resolution (i.e., ≤ Grade 1 or at baseline) from AEs due to procedures performed or therapeutic agents administered.

e. ≥2 weeks for retinoids, interferons, vorinostat, romidepsin, denileukin diftitox, and therapeutic doses of oral corticosteroids (physiologic replacement doses of oral corticosteroids are allowed, topical corticosteroids are allowed).

f. ≥2 weeks for phototherapy.

g. ≥1 week for topical therapy (including retinoid, nitrogen mustard, or imiquimod).

3.1.3 Be ≥18 years of age on day of signing informed consent. Because no dosing or adverse event data are currently available on the use of MK-3475 in patients <18 years of age, children are excluded from this study, but will be eligible for future pediatric trials.

3.1.4 Have a performance status of 0 or 1 on the Eastern Cooperative Oncology Group (ECOG) Performance Scale.

3.1.5 Life expectancy of at least 6 months.

3.1.6 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**
– leukocytes	≥2,000/mcL
– absolute neutrophil count	≥1,500/mcL
– platelets	≥100,000/mcL

– hemoglobin	≥9 g/dL OR ≥5.6 mmol/L
– serum total bilirubin	≤1.5 X upper limit of normal (ULN) OR direct bilirubin ≤ ULN for patients with total bilirubin levels >1.5 ULN
– AST(SGOT)/ALT(SGPT)	≤2.5 × institutional ULN OR ≤5 X ULN for patients with liver metastases
– serum creatinine	≤1.5 X ULN
	OR
– Measured or calculated[a] creatinine clearance (CrCl) (Glomerular filtration rate [GFR] can also be used in place of creatinine or CrCl)	≥60 mL/min for subject with creatinine levels >1.5 X institutional ULN
– International Normalized Ratio (INR) or Prothrombin Time (PT)	≤1.5 X ULN unless subject is receiving anticoagulant therapy in which case the INR or PT must be within the therapeutic range of intended use for the anticoagulant.
– Activated Partial Thromboplastin Time (aPTT)	≤1.5 X ULN unless subject is receiving anticoagulant therapy in which case the aPTT must be within the therapeutic range of intended use for the anticoagulant.
- Thyroid Stimulating Hormone (TSH)	Within Institutional Limits (ie: Normal). If TSH is greater or less than institutional limits patients may participate if their T4 is WNL. Patients may be on a stable dose of replacement thyroid medication. Dose adjustments are allowed if needed.

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

3.1.7 Patients must provide tissue from a punch biopsy of the skin at baseline, at the time of a clinical event (at the time of response, progression or appearance of a new lesion) and at the end of treatment. Additional punch biopsies every 3 cycles are optional. An archival tissue sample is optional.

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

3.1.9 The effects of MK-3475 on the developing human fetus are unknown. For this reason and because anti-PD-1agents may be teratogenic, women of child-bearing potential and men must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) from the time of the pre-study visit, through the course of the study and for 120 days after the last dose of study medication.

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

Female patients of childbearing potential should be willing to use 2 methods of birth control or be surgically sterile, or abstain from heterosexual activity from the time of the pre-study visit, through the course of the study and for 120 days after the last dose of study medication. Patients of childbearing potential are those who have not been surgically sterilized or have not been free from menses for >1 year.

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

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

3.2 Exclusion Criteria

3.2.1 Patients who have had chemotherapy or targeted small molecule therapy within 4 weeks (6 weeks for nitrosoureas or mitomycin C) prior to entering the study or those who have not recovered from adverse events due to agents administered more than 4 weeks earlier.

-Note: Patients with ≤ Grade 2 neuropathy are an exception to this criterion and may qualify for the study.

-Note: If patients received major surgery, they must have recovered adequately from the toxicity and/or complications from the intervention prior to starting therapy.

3.2.2 Patients who are currently participating in or have participated in a study of an investigational agent or using an investigational device within 4 weeks of the first dose of treatment.

3.2.3 Has a diagnosis of immunodeficiency or is receiving therapeutic systemic steroid therapy or any other form of immunosuppressive therapy within 7 days prior to the first dose of trial treatment. See section 5.3.1.1 for additional information on acceptable and prohibited concomitant medications.

3.2.4 Has had a prior monoclonal antibody within 4 weeks prior to 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.

3.2.5 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, or *in situ* cervical cancer that has undergone potentially curative therapy.

3.2.6 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 for at least 4 weeks prior to the first dose of trial treatment and any neurologic symptoms have returned to baseline), have no evidence of new or enlarging brain metastases, and are not using steroids for at least 7 days prior to trial treatment.

3.2.7 History of allergic reactions attributed to compounds of similar chemical or biologic composition to MK-3475.

3.2.8 Has an active autoimmune disease requiring systemic treatment within the past 3 months or a documented history of clinically severe autoimmune disease, or a syndrome that requires systemic steroids or immunosuppressive agents. Patients with vitiligo or resolved childhood asthma/atopy would be an exception to this rule. Patients that require intermittent use of bronchodilators or local steroid injections would not be excluded from the study. The use of physiologic doses of corticosteroids may be approved after consultation with the Protocol PI and CITN. Patients with hypothyroidism stable on hormone replacement or Sjogren's syndrome will not be excluded from the study.

3.2.9 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.

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

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

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

3.2.13 History of other pulmonary disease such as emphysema or chronic obstructive pulmonary disease, (FEV_1<60% of predicted for height and age). Pulmonary function tests (PFTs) are required in patients with prolonged smoking history or symptoms of respiratory dysfunction.

3.2.14 Is pregnant or breastfeeding, or expecting to conceive or father children within the projected duration of the trial, starting with the pre-study visit through 120 days after the last dose of trial treatment. Pregnant women are excluded from this study because MK-3475 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*,* breastfeeding should be discontinued if the mother is treated with MK-3475.

MK-3475 may have adverse effects on a fetus in utero. Furthermore, it is not known if MK-3475 has 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 pre-screening or screening visit through 120 days after the last dose of trial treatment.

Men and non-pregnant, non-breast-feeding women may be enrolled if they are willing to use 2 methods of birth control or are considered highly unlikely to conceive. Highly unlikely to conceive is defined as 1) surgically sterilized, or 2) postmenopausal (a woman who is ≥45 years of age and has not had menses for greater than 1 year will be considered postmenopausal), or 3) not heterosexually active for the duration of the study.
The two birth control methods can be barrier method or a barrier method plus a hormonal method to prevent pregnancy. Patients should start using birth control from the time of the pre-study visit, through the course of the study and for 120 days after the last dose of study medication. The following are considered adequate barrier methods of contraception: diaphragm, condom (by the partner), copper intrauterine device, sponge, or spermicide. Appropriate hormonal contraceptives will include any registered and marketed contraceptive agent that contains an estrogen and/or a progestational agent (including oral, subcutaneous, intrauterine, or intramuscular agents).

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 they must adhere to the contraception requirement (described above) for the duration of the study and during the follow-up period defined in section 7.7-Reporting of Pregnancy and Lactation. 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.

Pregnancy: If a patient inadvertently becomes pregnant while on treatment with MK-3475, 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 as described in Section 7.7.

It is unknown whether MK-3475 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.

3.2.15 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.

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

3.2.17 Has received a live vaccine within 30 days prior to the first dose of trial treatment.

3.2.18 Has a known Human T-lymphotropic virus Type 1 (HTLV) infection.

3.2.19 Patient has a history of (non-infectious) pneumonitis that required steroids or current pneumonitis.

3.3 Inclusion of Women and Minorities

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

Table 3.3 Accrual Targets Table

Accrual Targets					
Ethnic Category	**Sex/Gender**				
	Females		**Males**		**Total**
Hispanic or Latino	1	+	1	=	2
Not Hispanic or Latino	9	+	13	=	22
Ethnic Category: Total of all subjects	10	+	14	=	(24)
Racial Category					
American Indian or Alaskan Native		+		=	
Asian	1	+	1	=	2
Black or African American	1	+	1	=	2
Native Hawaiian or other Pacific Islander		+		=	
White	8	+	12	=	20
Racial Category: Total of all subjects	10	+	14	=	(24)
	(A1 = A2)		(B1 = B2)		(C1 = C2)

4. REGISTRATION PROCEDURES

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 investigators participating in any NCI-sponsored clinical trial to register and to renew their registration annually.

Registration requires the submission of:

- a completed ***Statement of Investigator Form*** (FDA Form 1572) with an original signature
- a current Curriculum Vitae (CV)
- a completed and signed ***Supplemental Investigator Data Form*** (IDF)
- a completed ***Financial Disclosure Form*** (FDF) with an original signature

Fillable PDF forms and additional information can be found on the CTEP website at http://ctep.cancer.gov/investigatorResources/investigator_registration.htm. For questions, please contact the ***CTEP Investigator Registration Help Desk*** by email at pmbregpend@ctep.nci.nih.gov.

4.1.2 CTEP Associate Registration Procedures / CTEP-IAM Account

The Cancer Therapy Evaluation Program (CTEP) Identity and Access Management (IAM) application is a web-based application intended for use by both Investigators (i.e., all physicians involved in the conduct of NCI-sponsored clinical trials) and Associates (i.e., all staff involved in the conduct of NCI-sponsored clinical trials).

Associates will use the CTEP-IAM application to register (both initial registration and annual re-registration) with CTEP and to obtain a user account.

Investigators will use the CTEP-IAM application to obtain a user account only. (See CTEP Investigator Registration Procedures above for information on registering with CTEP as an Investigator, which must be completed before a CTEP-IAM account can be requested.)

An active CTEP-IAM user account is needed to access all CTEP and CTSU (Cancer Trials Support Unit) websites and applications, and is critical to the conduct of this study, including document access, patient enrollment, and clinical data submission.

Additional information can be found on the CTEP website at http://ctep.cancer.gov/branches/pmb/associate_registration.htm. For questions, please contact the ***CTEP Associate Registration Help Desk*** by email at ctepreghelp@ctep.nci.nih.gov.

4.1.3 For Questions and Support

For questions about Investigator Registration, please contact the CTEP Investigator Registration Help Desk: pmbregpend@ctep.nci.nih.gov.

For questions about Associate Registration or CTEP-IAM Account Creation, please contact the CTEP Registration Help Desk: ctepreghelp@ctep.nci.nih.gov.

4.2 Site Registration

This study is supported by the NCI Cancer Trials Support Unit (CTSU).

Each investigator or group of investigators at a clinical site must obtain Institutional Review Board (IRB) approval for this protocol and submit all required regulatory documents (including any protocol specific documents) to the CTSU Regulatory Office before they can be approved to enroll patients.

The CTSU Regulatory Office tracks receipt of these documents in the CTSU Regulatory Support System (RSS), reviews for compliance, and transmits site approval data to CTEP.

4.2.1 Downloading Regulatory Documents

Site registration forms may be downloaded from the CITN-10 protocol page located on the CTSU Web site. Permission to view and download this protocol is restricted and is based on person and site roster data housed in the CTSU RSS. To participate, Investigators and Associates must be associated with the Corresponding or Participating protocol organization in the RSS.

- Go to https://www.ctsu.org and log in using your CTEP IAM username and password
- Click on the Protocols tab in the upper left of your screen
- Click on the CITN link to expand, followed by protocol #CITN-10.
- Click on LPO Documents, select the Site Registration documents link, and download and complete the forms provided.

4.2.2 Submitting Regulatory Documents

Submit completed forms along with a copy of your IRB Approval and Model Informed Consent to the CTSU Regulatory Office, where they will be entered and tracked in the CTSU RSS.

CTSU Regulatory Office
1818 Market Street, Suite 3000
Philadelphia, PA 19103
Phone: 1-866-651-2878
Fax: 215-569-0206
E-mail: CTSURegulatory@ctsu.coccg.org (for regulatory document submission only)

4.2.3 Checking **Site** Registration Status

Sites can check the status of their registration packets by querying the Site Registration subtab of the members' section of the CTSU Web site. (Note: Sites will not receive formal notification of regulatory approval from the CTSU Regulatory Office.)

- Go to https://www.ctsu.org and log in using your CTEP IAM username and password.
- Click on the Regulatory tab at the top of your screen.
- Click on the Site Registration subtab.
- Enter your 5-character CTEP Institution Code and click on Go.

Note: If possible, please allow three working days for site registration approval before attempting to enroll your first patient.

4.3 Patient Registration

4.3.1 OPEN

Patient enrollment will be facilitated using the Oncology Patient Enrollment Network (OPEN). OPEN is a web-based registration system available to users on a 24/7 basis

All site staff will use OPEN to enroll patients to this study. It is integrated with the CTSU Enterprise System for regulatory and roster data and, upon enrollment, initializes the patient position in the Rave database.

All CITN member site staff will use OPEN to enroll patients to this study. OPEN can be accessed at https://open.ctsu.org or from the OPEN tab on the CTSU members' side of the website at https://www.ctsu.org.

Through both the first and second stages of this trial patient enrollment will be facilitated using the Slot-Reservation System in conjunction with the Patient Registration system in the Oncology Patient Enrollment Network (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 is obtained site staff will have 14 days to complete screening and to enroll the patient on study.

Prior to accessing OPEN CITN member site staff should verify the following:

- All eligibility criteria have been met within the protocol stated timeframes. Site staff should use the registration forms provided on the CTSU web site as a tool to verify eligibility.
- All patients have signed an appropriate consent form and HIPAA authorization form (if applicable).

Access requirements for OPEN:

- CITN member site staff will need to be registered with CTEP and have a valid and active CTEP-IAM account. This is the same account (user id and password) used for the CTSU members' web site.

- To perform registrations, the site user must have been assigned the ‘Registrar’ role on the CITN roster.

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

Further instructional information is provided on the OPEN tab of the CTSU members’ side of the CTSU website at https://www.ctsu.org or at https://open.ctsu.org. For any additional questions contact the CTSU Help Desk at 1-888-823-5923 or ctsucontact@westat.com.

4.4 General Guidelines

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

5. TREATMENT PLAN

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.

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

Trial Treatment

Drug	Dose/ Potency	Dose Frequency	Route of Administration	Regimen/ Treatment Period	Use
MK-3475	2mg/kg	q 3 weeks	IV infusion	Day 1 of each cycle	Experimental

The MK-3475 dosing interval may be increased due to toxicity as described in Section 6.

Note: Calculate the required dose amount based on dose level and subject weight. The dose amount should be recalculated if the subject's weight changes by more than 10% from the baseline measurement.

Trial treatment should begin on day 1 of treatment or as close as possible to the date on which treatment is enrolled.

5.1.1 MK-3475

Trial treatment should be administered on Day 1 of each cycle after all procedures/assessments have been completed. Trial treatment may be administered up to

3 days before or after the scheduled Day 1 of each cycle due to administrative reasons.

MK-3475 treatment will be administered on an outpatient basis.

MK-3475 will be administered as a 30 minute IV infusion (treatment cycle intervals may be increased due to toxicity as described in Section 6.1). Infusion timing should be as close to 30 minutes as possible; however, a window of -5 minutes and +10 minutes is permitted (*i.e.*, infusion time is 30 minutes: -5 min/+10 min).

5.2 Definition of Dose-Limiting Toxicity: N/A

5.3 General Concomitant Medication and Supportive Care Guidelines

5.3.1 MK-3475

5.3.1.1 MK-3475 Concomitant Medication

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

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

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

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:

- Anti-cancer systemic chemotherapy or biological therapy.
- Immunotherapy not specified in this protocol.
- Chemotherapy not specified in this protocol.
- Investigational agents other than MK-3475.
- Radiation therapy

    - Note: Radiation therapy to a symptomatic solitary lesion or to the brain may be allowed after consultation with the Protocol PI and CITN.
- Live vaccines within 30 days prior to the first dose of trial treatment and while participating in the trial. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, chicken pox, yellow fever, rabies, BCG, and typhoid (oral) vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed; however, intranasal influenza vaccines (*e.g.* Flu-Mist®) are live attenuated vaccines, and are not allowed. Both rabies and typhoid are also available as killed vaccines. The killed versions of rabies and typhoid vaccines are acceptable.
- Glucocorticoids for any purpose other than to modulate symptoms from an event of suspected immunologic etiology. The use of physiologic doses of corticosteroids may be approved after consultation with the Protocol PI and CITN.

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

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

5.3.2 *Supportive Care Guidelines*

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

- Nausea/vomiting: Nausea and vomiting should be treated aggressively, and consideration should be given in subsequent cycles to the administration of prophylactic antiemetic therapy according to standard institutional practice. Subjects should be strongly encouraged to maintain liberal oral fluid intake.
- Antiinfectives: Subjects with a documented infectious complication should receive oral or IV antibiotics or other antiinfective agents as considered appropriate by the treating investigator for a given infectious condition, according to standard institutional practice.

5.4 Duration of Therapy

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

- Disease progression warranting alternative systemic therapy and without evidence of clinical benefit from continued MK-3475,
- Patients who continue MK-3475 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,
- 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.

- Unacceptable adverse event(s), including:

    - Any Grade 2 drug-related uveitis or eye pain or blurred vision that does not respond to topical therapy and does not improve to Grade 1 severity within the re-treatment period OR requires systemic treatment.

    - Grade 3 drug-related autoimmune or inflammatory event including uveitis, pneumonitis, diarrhea, colitis, neurologic adverse events, hypersensitivity reaction, or infusion reaction of any duration requires discontinuation.

    - Any Grade 3 or 4 drug-related laboratory imbalance or electrolyte abnormality, not associated with underlying organ pathology and that do not require treatment except for electrolyte replacements do not require treatment discontinuation, with the following exceptions with approval of the Principal Investigator:

        - Hypophysitis or pan-hypopituitarism any grade should discontinue treatment.

        - Grade 4 amylase or lipase abnormalities that are not associated with DM, associated liver or gall bladder inflammation clinical manifestations of pancreatitis and which decrease to <Grade 4 within 1 week of onset may stay on study.

        - Any drug-related liver function test (LFT) abnormality that meets the following criteria requires discontinuation: Grade 3 AST or ALT (>5 x ULN) and total bilirubin >3 x ULN.

        - Grade 3 drug-related thrombocytopenia >7 days or associated with bleeding requires discontinuation.

- Any patient requiring therapeutic systemic steroid or other immunosuppressive treatment.

- For patients with skin-only toxicity, when symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. Discontinue MK-3475 if unable to reduce corticosteroid dose for irAEs to ≤10 mg. MK-3475 treatment may be restarted and the dose modified as specified in the protocol.

- Patients with peripheral thyroiditis and no other autoimmune/inflammatory event may be restarted after a short course of steroids on a stable replacement regimen.

- 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. Prior to re-initiating treatment in a subject 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.

5.5 Duration of Follow Up

All patients, regardless of reason for discontinuation from study, will be followed for AE/SAE resolution for 30 days after removal from study. Patients removed from study for unacceptable adverse event(s) will be followed every 12 weeks until progression is documented. All patients will be followed for survival either by in-person visit or by telephone assessment every 12 weeks until death.

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.

5.6 Criteria for Removal from Study

Patients will be removed from study when any of the applicable criteria, including progressive disease warranting alternative systemic therapy and without evidence of clinical benefit on study therapy, withdrawal, or inability to follow study protocol as listed in Section 5.4. The reason for study removal and the date the patient was removed must be documented in the Case Report Form.

5.7 Criteria to Resume Treatment

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

- Patients may resume treatment in the presence of Grade 2 fatigue.
- Patients with baseline Grade 1 AST/ALT or total bilirubin who require dose delays for reasons other than a 2-grade shift in AST/ALT or total bilirubin may resume treatment in the presence of Grade 2 AST/ALT OR total bilirubin.
- Patients with combined Grade 2 AST/ALT AND total bilirubin values meeting study parameters outlined in Section 5.4 should have treatment permanently discontinued.
- 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).

5.8 Treatment Beyond Progression

Immunotherapeutic agents such as MK-3475 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 approximately 4 weeks later in order to confirm PD with the option of continuing treatment per the instructions below while awaiting 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 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

If progression is determined at week 16 or beyond, patients will be eligible to receive continued MK-3475 if they are otherwise clinically stable as defined by the following criteria. (The maximum duration of therapy in this setting is the same as for other patients, 2 years).

- 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

The following assessment and stopping criteria apply to patients who continue MK-3475 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.

Patients being treated with MK-3475 for melanoma have experienced late responses with continued therapy. In the KEYNOTE-001 melanoma trial using MK-3475 there was an additional 3.6% response rate with continued therapy. This category of response in that trial was defined as an "unconventional response" with "delayed pseudoprogression: ≥25% increase in tumor burden at any assessment after week 12 that was not confirmed as progressive disease per irRC at the next assessment". [Hodi, 2014].

	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 MK-3475 therapy, repeat mSWAT every cycle. mSWAT, CT scans, for measurable disease, and	Patient may continue therapy with MK-3475.	No additional assessments required	N/A

	CSC, for patients who are positive, will be repeated every 4 cycles (every 12 weeks)			
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
Tumors will be assessed first at week 12, then every 6 weeks (42 ±3 days) until week 30. Subsequently, tumor imaging will be performed every 12 weeks (84 ±7 days).				

** Note: Mycosis Fungoides and Sézary Syndrome may not be measurable by CT scan. Disease assessments will include 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 MF/SS. In the table above PD, SD, PR and CR will be determined by Global Response Assessment as described in section 11.

5.9 Discontinuation of Treatment Following Complete Response

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 and had at least two treatments with MK-3475 beyond the date when the initial CR was declared.

5.10 Treatment Up to 2 Years

Treatment with MK-3475 monotherapy will continue for up to two years. Treatment will be discontinued for documented disease progression in patients warranting other systemic therapy as described above, 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 MK-3475 Dose Modifications

6.1.1 General MK-3475 Dose Modifications

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

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

General Dose Modification Guidelines for Drug-Related Adverse Events.

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

In case toxicity does not resolve to Grade 0-1 within 12 weeks after last infusion, trial treatment should be discontinued. With Principal Investigator agreement, subjects with a laboratory adverse event still at Grade 2 after 12 weeks may continue treatment in the trial only if asymptomatic and controlled. Patients who experience a recurrence of the same severe or life-threatening event at the same grade or greater with re-challenge of MK-3475 should be discontinued from trial treatment.

Additionally, immune-related adverse events (irAEs), defined as adverse events of unknown etiology, associated with drug exposure and consistent with an immune phenomenon, may be predicted based on the nature of the MK-3475 compound, its mechanism of action, and reported experience with immunotherapies that have a similar mechanism of action. Special attention should be paid to AEs that may be suggestive of potential irAEs. An irAE can occur shortly after the first dose or several months after the last dose of treatment. All AEs of unknown etiology associated with drug exposure should be evaluated to determine if they are possibly immune-related. If an irAE is suspected, efforts should be made to rule out neoplastic, infectious, metabolic, toxin or other etiologic causes prior to labeling an adverse event as an irAE.

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

General Dose Modification Guidelines for Drug-Related Immune-Related Adverse Events

irAE	Withhold/Discontinue MK-3475?	Supportive Care
Grade 1	No action	Provide symptomatic treatment
Grade 2	May withhold MK-3475	Consider systemic corticosteroids in addition to appropriate symptomatic treatment
Grade 3 and Grade 4	Withhold MK-3475 Discontinue if unable to reduce corticosteroid dose to < 10 mg per day prednisone equivalent within 12 weeks of toxicity	Systemic corticosteroids are indicated in addition to appropriate symptomatic treatment. May utilize 1 to 2 mg/kg prednisone or equivalent per day. Steroid taper should be considered once symptoms improve to Grade 1 or less and tapered over at least 4 weeks.

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

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

AE-Specific Dose Modification Guidelines for Drug-Related Adverse Events

Event(s)	CTCAE v5.0 Grade	Management / Next Dose for MK-3475	Action / Supportive Care Guidelines	Symptoms[a]	Differential Diagnosis
Colitis events • **Bowel obstruction** • **Colitis** • **Colitis microscopic** • **Enterocolitis** • **Enterocolitis hemorrhagic** • **Gastrointestinal (GI) perforation** • **Necrotizing colitis** **Diarrhea** *All patients who experience diarrhea should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion.*	≤Grade 1	No change in dose	• For diarrhea, treat symptomatically (loperamide, oral hydration, electrolyte substitution and ADA colitis diet). Endoscopy is recommended if symptoms persist. • Grade 1 diarrhea that persist for >1 week should be treated with the addition of oral diphenoxylate hydrochloride and atropine sulfate four times daily and budesonide 9 mg daily.	Symptoms may include (but not limited to): • Abdominal pain, cramping and/or bloating • Blood and/or mucus in stool with or without fever • Constipation • Diarrhea • Ileus • Nausea and/or vomiting • Peritoneal signs consistent with bowel perforation • Rectal bleeding • With or without fever Patients with diarrhea should be carefully monitored for signs and symptoms of enterocolitis (such as diarrhea, abdominal pain, blood or mucus in stool, with or without fever) and of bowel perforation (such as	All attempts should be made to rule out other causes such as metastatic disease, bacterial or parasitic infection, viral gastroenteritis, or the first manifestation of an inflammatory bowel disease by examination for stool leukocytes, stool cultures, and a *Clostridium difficile* titer.
	Grade 2	Hold until ≤Grade 1. Resume at same dose level. May increase dosing interval by 1 week if it takes more than 4 weeks for toxicities to resolve.	• GI consultation and endoscopy is recommended to confirm or rule out colitis for grade 2 diarrhea that persists >1 week or grade 1-2 diarrhea with rectal bleeding (additional guidelines for the treatment of persistent colitis are provided below). • Grade 2 diarrhea should be treated with the addition of oral diphenoxylate hydrochloride and atropine sulfate four times daily and budesonide 9 mg daily. • Grade 2 diarrhea with diffuse ulceration and bleeding seen on endoscopy may require oral steroids with prolonged taper and represent an increased risk for the development of bowel perforation. • When symptoms improve to grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. • In patients with Grade 2 enterocolitis, MK-3475 should be withheld and anti-diarrheal treatment should be started. If symptoms are persistent for more than one week, systemic corticosteroids should be initiated (*e.g.*, 0.5 mg/kg/day of prednisone or equivalent). When symptoms improve to Grade 1 or less, corticosteroid taper should be started and continued over at least 1 month.		

Event(s)	CTCAE v5.0 Grade	Management / Next Dose for MK-3475	Action / Supportive Care Guidelines	Symptoms[a]	Differential Diagnosis
	Grade 3-4	Withhold MK-3475 Discontinue if unable to reduce corticosteroid dose to <10 mg per day prednisone equivalent within 12 weeks of toxicity	• In patients with Grade 3 enterocolitis, MK-3475 will be permanently discontinued and treatment with systemic corticosteroids should be initiated at a dose of 1 to 2 mg/kg/day of prednisone or equivalent. When symptoms improve to Grade 1 or less, corticosteroid taper should be started and continued over at least 1 month. For Grade 3-4 diarrhea (or Grade 2 diarrhea that persists after initial steroid treatment), • Rule out bowel perforation. Imaging with plain films or computed tomography (CT) can be useful. • Consider consultation with gastroenterologist and confirmation biopsy with endoscopy. • Treat with intravenous (IV) steroids (methylprednisolone 125 mg) followed by high-dose oral steroids (prednisone 1-2 mg/kg once per day or dexamethasone 4 mg every 4 hours). When symptoms improve to grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. Taper over 6-8 weeks in patients with diffuse and severe ulceration and/or bleeding. • If IV steroids followed by high-dose oral steroids does not reduce initial symptoms within 48-72 hours, consider treatment with infliximab at 5 mg/kg once every 2 weeks. Discontinue infliximab upon symptom relief and initiate a prolonged steroid taper over 45-60 days. If symptoms worsen during steroid reduction, initiate a retapering of steroids starting at a higher dose of 80 or 100 mg followed by a more prolonged taper and administer infliximab. CAUTION: infliximab is contraindicated in patients with bowel perforation or sepsis[b]. • If symptoms persist despite the above treatment a surgical consult should be obtained.	peritoneal signs and ileus). In symptomatic patients, infectious etiologies should be ruled out, and if symptoms are persistent and/or severe, endoscopic evaluation should be considered.	

Event(s)	CTCAE v5.0 Grade	Management / Next Dose for MK-3475	Action / Supportive Care Guidelines	Symptoms[a]	Differential Diagnosis
Endocrine events • **Hyperthyroidism** • **Hypophysitis** • **Hypopituitarism** • **Hypothyroidism** • **Thyroid disorder** • **Thyroiditis**	Grade 1-2	No change in dose	• Monitor thyroid function or other hormonal level tests and serum chemistries more frequently until returned to baseline values.	Symptoms may include (but not limited to): • Abdominal pain • Abnormal thyroid function tests and/or serum chemistries (Thyroid-stimulating hormone increased [decreased], Free thyroxine increased, Tri-iodothyronine increased.) • Arrhythmias[c] • Cold or heat intolerance • Fatigue • Fever • Headache • Hypotension[c] • Loss of appetite • Mental status and/or behavior changes • Nausea and/or vomiting • Unusual bowel habits • Vision disturbances • Weakness	All attempts should be made to rule out other causes such as brain metastases, sepsis, and/or infection. An endocrinology consultation is recommended.
	Grade 3-4	Hold/discontinue MK-3475.	• Consider endocrine consultation. • Rule out infection and sepsis with appropriate cultures and imaging. • Treat with an initial dose of methylprednisolone 1-2 mg/kg IV followed by oral prednisone 1-2 mg/kg per day. When symptoms improve to grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. Replacement of appropriate hormones may be required as the steroid dose is tapered.		
Endocrine events • **Adrenal insufficiency** • **Hypophysitis** • **Pan-hypopituitarism**	Grade 1-4	Discontinue MK-3475.	• Thyroid hormone and/or steroid replacement therapy to manage adrenal insufficiency. • If Grade 1-2 hypophysitis is considered, pituitary gland imaging should be considered (magnetic resonance imaging [MRIs] with gadolinium and selective cuts of the pituitary can show enlargement or heterogeneity and confirm the diagnosis). • Grade 3-4 hypophysitis with clinically significant adrenal insufficiency and hypotension, dehydration, and electrolyte abnormalities (such as hyponatremia and hyperkalemia) constitutes adrenal crisis. Hospitalization and IV methylprednisolone should be initiated.		
Eye event • **Uveitis**	Grade 1	Discontinue MK-3475 **if** symptoms persist despite treatment with topical immunosuppressive therapy	• Evaluation by an ophthalmologist is strongly recommended. • Treat with topical steroids such as 1% prednisolone acetate suspension and iridocyclitics.	Symptoms may include (but not limited to): • Blurred vision • Diffuse erythema and a prominent blush on the sclerae • Dryness of the eyes	All attempts should be made to rule out other causes such as metastatic disease, infection, or other ocular

Event(s)	CTCAE v5.0 Grade	Management / Next Dose for MK-3475	Action / Supportive Care Guidelines	Symptoms[a]	Differential Diagnosis
	Grade 2	Discontinue MK-3475 **if** symptoms persist despite treatment with topical immunosuppressive therapy and does not improve to Grade 1 within the re-treatment period OR requires systemic treatment.	• Evaluation by an ophthalmologist is strongly recommended. • Treat with topical steroids such as 1% prednisolone acetate suspension and iridocyclitics.	• Pain • Photophobia	disease (*e.g.*, glaucoma or cataracts).
	Grade 3-4	Discontinue MK-3475.	• Treat with systemic corticosteroids such as prednisone at a dose of 1-2 mg/kg per day. When symptoms improve to ≤Grade 1, steroid taper should be started and continued over no less than 4 weeks.		
Hepatic events • **Hepatitis** • **Hepatitis, Autoimmune**	Grade 1-2	No change in dose	• Monitor liver function tests more frequently until returned to baseline values.	Symptoms may include (but not limited to): • Elevations in: ○ AST >2.5 times ULN ○ ALT >2.5 times ULN ○ Total bilirubin >1.5 X ULN • Fever • Malaise • Upper quadrant abdominal pain	All attempts should be made to rule out other causes such as metastatic disease, progressive liver disease, viral hepatitis, alternative drug toxicity, infectious causes and/or myositis.
	Grade 3-4	Discontinue MK-3475 when AST or ALT >5.0 times ULN and/or total bilirubin >3.0 times ULN.	• Consider appropriate consultation and liver biopsy to establish etiology of hepatic injury, if necessary. • Treat with high-dose IV glucocorticosteroids for 24-48 hours. When symptoms improve to grade 1 or less, a steroid taper with dexamethasone 4 mg every 4 hours or prednisone at 1-2 mg/kg should be started and continued over no less than 4 weeks. • If serum transaminase levels do not decrease 48 hours after initiation of systemic steroids, oral mycophenolate mofetil 500 mg every 12 hours may be given. Infliximab is not recommended due to its potential for hepatotoxicity[b]. • Several courses of steroid tapering may be necessary as symptoms may worsen when the steroid dose is decreased .		

Event(s)	CTCAE v5.0 Grade	Management / Next Dose for MK-3475	Action / Supportive Care Guidelines	Symptoms[a]	Differential Diagnosis
Nausea	≤Grade 1	No change in dose	• Nausea should be treated aggressively, and consideration should be given in subsequent cycles to the administration of prophylactic antiemetic therapy according to standard institutional practice. Patients should be strongly encouraged to maintain liberal oral fluid intake.		
	Grade 2	Hold until ≤Grade 1. Resume at same dose level. May increase dosing interval by 1 week if it takes more than 4 weeks for toxicities to resolve.			
	Grade 3	Hold until <Grade 2. May increase dosing interval by 1 week for each occurrence. Discontinue if toxicities do not resolve within 12 weeks.			
	Grade 4	Off protocol therapy			
Neutropenia	≤Grade 1	No change in dose			
	Grade 2	No change in dose			
	Grade 3	No change in dose			
	Grade 4	Hold until resolves to ≤Grade 1. May increase the dosing interval by 1 week. Discontinue if toxicities do not resolve within 12 weeks.			

Event(s)	CTCAE v5.0 Grade	Management / Next Dose for MK-3475	Action / Supportive Care Guidelines	Symptoms[a]	Differential Diagnosis
Pneumonitis events • **Pneumonitis** • **Interstitial lung disease** • **Acute interstitial pneumonitis**	Grade 1	MK-3475 may be continued with close monitoring.	• Radiologic findings should be followed on serial imaging studies. • Consider pulmonary consultation and/or bronchoscopy if clinically indicated.	Symptoms may include (but not limited to): • Abnormal breath sounds • Chest pain and/or tightness[c] • Dyspnea[c] • Dry cough • Fatigue • Fever • Hemoptysis	All attempts should be made to rule out other causes such as metastatic disease, bacterial or viral infection.
	Grade 2	Hold MK-3475	**To rule out other causes such as infection:** • Consider pulmonary consultation with bronchoscopy and biopsy/bronchoalveolar lavage (BAL). • Consider pulmonary function tests. **If the patient is determined to have study drug associated pneumonitis:** • Treat with systemic corticosteroids at a dose of 1-2 mg/kg/day prednisone or equivalent. When symptoms improve to grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. • Treatment with MK-3475 may be resumed if the event improves to ≤Grade 1 within 12 weeks and corticosteroids have been reduced to the equivalent of methylprednisolone 10 mg by mouth daily or less. Repeat chest imaging monthly as clinically indicated. **For Grade 2 pneumonitis that improves to ≤Grade 1 within 12 weeks, the following rules should apply:** • First episode of pneumonitis: May increase dosing interval by one week in subsequent cycles. • Second episode of pneumonitis: Discontinue MK-3475 if upon rechallenge the patient develops a second episode of ≥Grade 2 pneumonitis.		

Event(s)	CTCAE v5.0 Grade	Management / Next Dose for MK-3475	Action / Supportive Care Guidelines	Symptoms[a]	Differential Diagnosis
	Grade 3-4	Discontinue MK-3475.	• Consider pulmonary function tests with pulmonary consult. • Bronchoscopy with biopsy and/or BAL is recommended. • Treat with IV steroids (methylprednisolone 125 mg). When symptoms improve to grade 1 or less, a high-dose oral steroid (prednisone 1-2 mg/kg once per day or dexamethasone 4 mg every 4 hours) taper should be started and continued over no less than 4 weeks. • If IV steroids followed by high-dose oral steroids does not reduce initial symptoms within 48-72 hours, treat with infliximab at 5 mg/kg once every 2 weeks. Discontinue infliximab upon symptom relief and initiate a prolonged steroid taper over 45-60 days. If symptoms worsen during steroid reduction, initiate a retapering of steroids starting at a higher dose of 80 or 100 mg followed by a more prolonged taper and administer infliximab.		
Renal events • **Nephritis** • **Nephritis autoimmune** • **Renal failure** • **Renal failure, Acute**	Grade 1	Consider withholding MK-3475 **if** Grade 1 does not improve with symptomatic treatment	• Provide symptomatic treatment.	Symptoms may include (but not limited to): • Fatigue • High blood pressure • Increased serum creatinine • Swelling	All attempts should be made to rule out other causes such as obstructive uropathy, progression of disease, or injury to other chemotherapy agents. A renal consultation is recommended.
	Grade 2	Consider withholding MK-3475.	• Systemic corticosteroids may be indicated.		
	Grade 3-4	Discontinue MK-3475.	• Renal consultation with consideration of ultrasound and/or biopsy as appropriate. • Treat with systemic corticosteroids at a dose of 1-2 mg/kg prednisone or equivalent once per day. • When symptoms improve to grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. • Discontinue MK-3475 if unable to reduce corticosteroid dose for irAEs to ≤10 mg. • MK-3475 treatment may be restarted and the dose modified as specified in the protocol.		

Event(s)	CTCAE v5.0 Grade	Management / Next Dose for MK-3475	Action / Supportive Care Guidelines	Symptoms[a]	Differential Diagnosis
Skin events • **Dermatitis exfoliative** • **Erythema multiforme** • **Stevens-Johnson syndrome** • **Toxic epidermal necrolysis** If they are considered to be immune related, ≥Grade 3 or result in dose modification or discontinuation: • **Pruritus** • **Rash** • **Rash generalized** • **Rash maculo-papular** • **Vitiligo**	Grade 1-2	No change in dose	• Symptomatic treatment should be given such as topical glucocorticosteroids (*e.g.*, betamethasone 0.1% cream or hydrocortisone 1%) or urea-containing creams in combination with oral antipruritics (e.g., diphenhydramine HCl or hydroxyzine HCl). • Treatment with oral steroids is at investigator discretion for grade 2 events.		All attempts should be made to rule out other causes such as metastatic disease, infection, or allergic dermatitis.
	Grade 3	Hold MK-3475.	• Consider dermatology consultation and biopsy for confirmation of diagnosis. • Treatment with oral steroids is recommended, starting with 1 mg/kg prednisone or equivalent once per day or dexamethasone 4 mg four times orally daily. When symptoms improve to grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.		
	Grade 4	Permanently discontinue MK-3475.	• Dermatology consultation and consideration of biopsy and clinical dermatology photograph. • Initiate steroids at 1-2 mg/kg prednisone or equivalent. When symptoms improve to grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.		
Thrombocytopenia	≤Grade 1	No change in dose			
	Grade 2	No change in dose			
	Grade 3	No change in dose	• Grade 3 drug-related thrombocytopenia >7 days or associated with bleeding requires discontinuation.		
	Grade 4	Hold MK-3475 until resolves to ≤Grade 1. May increase the dosing interval by 1 week.	• Grade 4 drug-related thrombocytopenia >7 days or associated with bleeding requires discontinuation.		
Vomiting	≤Grade 1	No change in dose	• Vomiting should be treated aggressively, and consideration		

Event(s)	CTCAE v5.0 Grade	Management / Next Dose for MK-3475	Action / Supportive Care Guidelines	Symptoms[a]	Differential Diagnosis
	Grade 2	Hold until ≤Grade 1. Resume at same dose level. May increase dosing interval by 1 week if it takes more than 4 weeks for toxicities to resolve.	should be given in subsequent cycles to the administration of prophylactic antiemetic therapy according to standard institutional practice. Patients should be strongly encouraged to maintain liberal oral fluid intake.		
	Grade 3	Hold until <Grade 2. May increase dosing interval by 1 week for each occurrence. Discontinue if toxicities do not resolve within 12 weeks.			
	Grade 4	Off protocol therapy			

Event(s)	CTCAE v5.0 Grade	Management / Next Dose for MK-3475	Action / Supportive Care Guidelines	Symptoms[a]	Differential Diagnosis
Other events • **Autoimmune neuropathy** • **Demyelinating polyneuropathy** • **Guillain-Barre** • **Myasthenia gravis-like syndrome** • **Non-infectious myocarditis** • **Non-infectious pericarditis** • **Pancreatitis** • **Rapid onset of grade 3 fatigue in the absence of disease progression**	Grade 1	Consider withholding MK-3475 for Grade 1 that does not improve with symptomatic treatment.	• Provide symptomatic treatment.		All attempts should be made to rule out other causes. Therapeutic specialists should be consulted as appropriate.
	Grade 2	Consider withholding MK-3475.	• Systemic corticosteroids may be indicated. • Consider biopsy for confirmation of diagnosis.		
	Grade 3-4	Discontinue MK-3475.	• Treat with systemic corticosteroids at a dose of 1-2 mg/kg prednisone or equivalent once per day. • When symptoms improve to grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. • Discontinue MK-3475 if unable to reduce corticosteroid dose for irAEs to ≤10 mg. • MK-3475 treatment may be restarted and the dose modified as specified in the protocol.		

[a] The signs and symptoms may be associated with any of the diagnoses in the associated “Event(s)” column.
[b] Janssen Biotech, Inc.: REMICADE (Infliximab) prescribing information revised September 2011.
http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.Label_ApprovalHistory#labelinfo
[c] If symptoms indicate possible new or worsening cardiac abnormalities, additional testing and/or a cardiology consultation should be considered.

6.1.3 Treatment Guidelines for Infusion Reactions

Acute infusion reactions (which can include cytokine release syndrome, angioedema, or anaphylaxis) are different from allergic/hypersensitive reactions, although some of the manifestations are common to both AEs. Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion.

Signs/symptoms may include: Allergic reaction/hypersensitivity (including drug fever); Arthralgia (joint pain); Bronchospasm; Cough; Dizziness; Dyspnea (shortness of breath); Fatigue (asthenia, lethargy, malaise); Headache; Hypertension; Hypotension; Myalgia (muscle pain); Nausea; Pruritis/itching; Rash/desquamation; Rigors/chills; Sweating (diaphoresis); Tachycardia; Tumor pain (onset or exacerbation of tumor pain due to treatment); Urticaria (hives, welts, wheals); Vomiting.

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

Treatment Guidelines for Infusion Reactions

NCI CTCAE Grade	Treatment	Premedication at subsequent dosing
Grade 1 Mild reaction; infusion interruption not indicated; intervention not indicated	Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator.	None
Grade 2 Requires infusion interruption but responds promptly to symptomatic treatment (*e.g.*, antihistamines, NSAIDS, narcotics, IV fluids); prophylactic medications indicated for ≤24 hours	**Stop Infusion and Monitor Symptoms.** Additional supportive care, as per institutional guidelines. Appropriate medical therapy may include but is not limited to: IV fluids Antihistamines NSAIDS Acetaminophen Narcotics Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator. If symptoms resolve within one hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (*e.g.* from 100 mL/hr to 50 mL/hr). **Please note:** prior to restarting the infusion, confirm that the 4 hour room temperature stability from the time of the IV bag preparation will not be exceeded. Otherwise dosing will be held until symptoms resolve and the subject should be premedicated for the next scheduled dose. **Subjects who develop Grade 2 toxicity upon rechallenge despite adequate premedication should be permanently discontinued from further trial treatment administration.**	Subject may be premedicated 1.5h (± 30 minutes) prior to infusion of MK-3475 with: Diphenhydramine 50 mg PO (or equivalent dose of antihistamine). Acetaminophen 500-1000 mg PO (or equivalent dose of antipyretic).

NCI CTCAE Grade	Treatment	Premedication at subsequent dosing
Grades 3 or 4 Grade 3: Prolonged (*i.e.*, not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (*e.g.*, renal impairment, pulmonary infiltrates) Grade 4: Life-threatening; pressor or ventilatory support indicated	**Stop Infusion and Monitor Symptoms. Subject is permanently discontinued from further trial treatment administration.** Dexamethasone should be administered at a dose of at least 24 mg per day (8 mg every 8 hours PO or IV) for up to three days. The dexamethasone dose will then be reduced step-wise over up to four days. Additional supportive care, as per institutional guidelines. Appropriate medical therapy may include but is not limited to: IV fluids Antihistamines NSAIDS Acetaminophen Narcotics Oxygen Pressors Corticosteroids Epinephrine Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator. Hospitalization may be indicated.	No subsequent dosing
Appropriate resuscitation equipment should be available in the room and a physician readily available during the period of drug administration. For Further information, please refer to the Common Terminology Criteria for Adverse Events v4.0 (CTCAE) at http://ctep.cancer.gov		

7. ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS

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

7.1 Comprehensive Adverse Events and Potential Risks List (CAEPR)

The Comprehensive Adverse Event and Potential Risks list (CAEPR) provides a single list of reported and/or potential 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 via CTEP-AERS (except as noted below). Refer to the 'CTEP, NCI Guidelines: Adverse Event Reporting Requirements' http://ctep.cancer.gov/protocolDevelopment/adverse_effects.htm for further clarification.

Note: The highest grade currently reported is noted in parentheses next to the AE in the SPEER.

Report **ONLY** AEs higher than this grade expeditiously via CTEP-AERS. 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

7.1.1.1 CAEPR for 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, NSC 776864).

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

Version 2.3, March 9, 2017[1]

Adverse Events with Possible Relationship to MK-3475 (pembrolizumab) (CTCAE 4.0 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]		
CARDIAC DISORDERS			
		Myocarditis[2]	
		Pericarditis[2]	
ENDOCRINE DISORDERS			
	Adrenal insufficiency[2]		
	Endocrine disorders - Other (hypophysitis, hypopituitarism)[2]		
	Endocrine disorders - Other (thyroiditis)[2]		
	Hyperthyroidism[2]		
	Hypothyroidism[2]		
EYE DISORDERS			
		Uveitis[2]	
GASTROINTESTINAL DISORDERS			

Adverse Events with Possible Relationship to MK-3475 (pembrolizumab) (CTCAE 4.0 Term) [n= 3793]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
	Colitis[2]		
	Diarrhea[2]		***Diarrhea[2] (Gr 2)***
	Mucositis oral[2]		
	Nausea		***Nausea (Gr 2)***
	Pancreatitis[2]		
	Small intestinal mucositis[2]		
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
	Chills[2]		
Fatigue			***Fatigue (Gr 2)***
	Fever[2]		
	Infusion related reaction		
HEPATOBILIARY DISORDERS			
	Hepatobiliary disorders - Other (autoimmune hepatitis)[2]		
IMMUNE SYSTEM DISORDERS			
		Anaphylaxis[2]	
		Cytokine release syndrome[2]	
		Immune system disorders - Other (hemophagocytic lymphohistiocytosis)[2]	
	Immune system disorders - Other (immune thrombocytopenic purpura)[2]		
	Immune system disorders - Other (pseudoprogression/tumor inflammation)[2]		
		Serum sickness[2]	
INFECTIONS AND INFESTATIONS			
	Infection[3]		
INVESTIGATIONS			
	Alanine aminotransferase increased[2]		
	Alkaline phosphatase increased		
	Aspartate aminotransferase increased[2]		
	Blood bilirubin increased		
	CPK increased		
		GGT increased	
		Serum amylase increased	
METABOLISM AND NUTRITION DISORDERS			
	Anorexia		
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS			
	Arthralgia[2]		***Arthralgia[2] (Gr 2)***
	Arthritis[2]		
	Avascular necrosis[2]		
	Joint effusion[2]		
	Joint range of motion decreased		
	Musculoskeletal and connective tissue disorder - Other (tenosynovitis)[2]		
	Myalgia[2]		

Adverse Events with Possible Relationship to MK-3475 (pembrolizumab) (CTCAE 4.0 Term) [n= 3793]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
	Myositis[2]		
NERVOUS SYSTEM DISORDERS			
		Nervous system disorders - Other (Guillain-Barre syndrome)[2]	
		Nervous system disorders - Other (myasthenic syndrome)[2]	
		Nervous system disorders - Other (neuromyopathy)[2]	
		Nervous system disorders - Other (polyneuropathy)[2]	
		Paresthesia	
		Peripheral motor neuropathy[2]	
RENAL AND URINARY DISORDERS			
		Renal and urinary disorders - Other (autoimmune nephritis)[2]	
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
	Pleuritic pain[2]		
	Pneumonitis[2]		
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
	Bullous dermatitis[2]		
		Erythema multiforme[2]	
	Erythroderma		
	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[2]	
	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. Adverse events potentially related to MK-3475 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, administration of corticosteroids and supportive care.

[3]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; Abdominal pain; 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); General disorders and administration site conditions - Other (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; Hyponatremia; Hypophosphatemia; Metabolism and nutrition disorders - Other (failure to thrive); Tumor lysis syndrome
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Back pain; Bone pain; Generalized muscle weakness; Musculoskeletal and connective tissue disorder - Other (groin pain); Pain in extremity
NERVOUS SYSTEM DISORDERS - Aphonia; Depressed level of consciousness; Dysarthria; Edema cerebral; Encephalopathy; Headache; Hydrocephalus; Lethargy; Meningismus; Nervous system disorders - Other (brainstem herniation); Seizure; Syncope; Tremor
PSYCHIATRIC DISORDERS - Agitation; Confusion
RENAL AND URINARY DISORDERS - Acute kidney injury; Proteinuria; Renal and urinary disorders - Other (hydronephrosis); Renal and urinary disorders - Other (nephrotic syndrome); Urinary incontinence; Urinary tract pain
REPRODUCTIVE SYSTEM AND BREAST DISORDERS - Pelvic pain
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Cough; Dyspnea; Hypoxia; Laryngeal inflammation; Pleural effusion; Pneumothorax; Respiratory failure
SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Alopecia; Dry skin; Skin and subcutaneous tissue disorders - Other (drug eruption)
VASCULAR DISORDERS - Hypertension; Peripheral ischemia; Thromboembolic event

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

7.2 Adverse Event Characteristics

- **CTCAE term (AE description) and grade:** The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized until March 31, 2018 for AE reporting. CTCAE version 5.0 will be utilized for AE reporting beginning April 1, 2018. All appropriate treatment areas should have access to a copy of the CTCAE version 5.0. A copy of the CTCAE version 5.0 can be downloaded from the CTEP web site http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

- **For expedited reporting purposes only:**
  - AEs for the agent that are ***bold and italicized*** in the CAEPR (i.e., those listed in the SPEER column, Section 7.1.1) should be reported through CTEP-AERS only if the grade is above the grade provided in the SPEER.
  - Other AEs for the protocol that do not require expedited reporting are outlined in section 7.3.4.
- **Attribution** of the AE:
  - Definite – The AE *is clearly related* to the study treatment.
  - Probable – The AE *is likely related* to the study treatment.
  - Possible – The AE *may be related* to the study treatment.
  - Unlikely – The AE *is doubtfully related* to the study treatment.
  - Unrelated – The AE *is clearly NOT related* to the study treatment.

7.3 Expedited Adverse Event Reporting

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 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, the local treating physician, and the Reporter and Submitter. CTEP-AERS provides a copy feature for other e-mail recipients.

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

7.3.3 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 CTEPAERS 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.

Late Phase 2 and Phase 3 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 AdEERS within the timeframes detailed in the table below.

Hospitalization	Grade 1 Timeframes	Grade 2 Timeframes	Grade 3 Timeframes	Grade 4 & 5 Timeframes
Resulting in Hospitalization ≥24 hrs	10 Calendar Days			24-Hour 5 Calendar Days
Not resulting in Hospitalization ≥24 hrs	Not required		10 Calendar Days	

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 reported via AdEERS 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 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 4, and Grade 5 AEs

Expedited 10 calendar day reports for:

- Grade 2 adverse events resulting in hospitalization or prolongation of hospitalization
- Grade 3 adverse events

[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*

For this protocol only, the AEs/grades listed below do not require expedited reporting via CTEP-AERS. However, they still must be reported through the routine reporting mechanism (Section 7.4):

CTCAE SOC	Adverse Event	Grade	Hospitalization/ Prolongation of Hospitalization	Attribution	Comments

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.

7.5 Secondary Malignancy

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

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

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

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

7.6 Second Malignancy

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

7.7 Reporting of Pregnancy and Lactation to the Sponsor

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

8. PHARMACEUTICAL INFORMATION

A list of the AEs and potential risks associated with the investigational agent administered in this study can be found in Section 7.1.

8.1 CTEP IND Agent(s) (MK-3475)

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

Other Names: SCH 900475

Classification: Anti-PD-1 MAb

Molecular Weight: 148.9-149.5 KDa

CAS Number: 1374853-91-4

Mode of Action: The programmed cell death 1 (PD-1) receptor is an inhibitory receptor expressed by T cells. When bound to either of its ligands, PD-L1 or PD-L2, activated PD-1 negatively regulates T-cell activation and effector function. The pathway may be engaged by tumor cells to suppress immune control. MK-3475 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 is a humanized MAb of the IgG4/kappa isotype.

How Supplied: MK-3475 is supplied by Merck & Co., Inc. and distributed by the Pharmaceutical Management Branch, CTEP/DCTD/NCI as single-use 50 mg vials containing a sterile, non-pyrogenic white to off-white lyophilized powder formulated in 10mM histidine buffer, pH 5.2-5.8, containing 7% sucrose and 0.02% polysorbate 80.

Preparation: Allow the required number of MK-3475 vials to equilibrate to room temperature. Reconstitute the lyophilized powder by adding 2.3 mL of Sterile Water for Injection (SWFI) to the vial to yield 2.4 mL of solution containing 25 mg/mL of MK-3475. The vial contains an excess fill of 10 mg (0.4 mL) to ensure recovery of 50 mg (2 mL) per vial. Add SWFI along the walls of the vial to avoid foaming. Swirl the vial, do not shake. Discard vial if extraneous particulate matter other than translucent to white proteinaceous particles is observed. Do not use if discolored. To prepare the final solution for IV administration add the dose volume of MK-3475 to an infusion bag containing 0.9% Sodium Chloride Injection, USP and 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

Calculate the required dose amount based on dose level and subject weight. The dose amount should be recalculated if the subject's weight changes by more than 10% from the baseline measurement.

Storage: Store intact vials between 2°C - 8°C (36°F - 46°F). Do not freeze. If a storage temperature excursion is identified, promptly return MK-3475 to between 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 20 hours. MK-3475 solutions may be stored at room temperature for a cumulative time of up to 4 hours. This includes room temperature storage of reconstituted solution in vials, room temperature storage of admixture solutions in the IV bags, and the duration of infusion.

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

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

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 is an investigational agent supplied to investigators by the Division of Cancer Treatment and Diagnosis (DCTD), NCI.

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

8.1.2 N/A

8.1.3 Agent Ordering and Agent Accountability

8.1.3.1 NCI-supplied agents may be requested by the Principal Investigator (or their authorized designee) at each participating institution. Pharmaceutical Management Branch (PMB) policy requires that agent be shipped directly to the institution where the patient is to be treated. PMB does not permit the transfer of agents between institutions (unless prior approval from PMB is obtained). The CTEP-assigned protocol number must be used for ordering all CTEP-supplied investigational agents. The responsible investigator at each participating institution must be registered with CTEP, DCTD through an annual submission of FDA Form 1572 (Statement of Investigator), Curriculum Vitae, Supplemental Investigator Data Form (IDF), 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.

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 (https://eapps-ctep.nci.nih.gov/OAOP/pages/login.jspx). Access to OAOP requires the establishment of a CTEP Identity and Access Management (IAM) account (https://eapps-ctep.nci.nih.gov/iam/) and the maintenance of an "active" account status and a "current" password. For questions about drug orders, transfers, returns, or accountability, call (240) 276-6575 Monday through Friday between 8:30 am and 4:30 pm (ET) or email PMBAfterHours@mail.nih.gov anytime.

8.1.3.2 Agent Inventory Records – The investigator, or a responsible party designated by the investigator, must maintain a careful record of the inventory and disposition of all agents received from DCTD using the NCI Drug Accountability Record Form (DARF). (See the NCI Investigator's Handbook for Procedures for Drug Accountability and Storage.)

9. BIOMARKER, CORRELATIVE, AND SPECIAL STUDIES

This study will require approximately 500 mL of blood to be drawn during the first 3 cycles (9 weeks) of therapy. After this, approximately 250 mL of blood will be drawn every 9 weeks. These quantities include blood drawn for safety labs, research labs, and for 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. The results of the CBC will be reviewed and the following blood volumes will be drawn based upon the patient hemoglobin level:

- For a hemoglobin over 10.0, draw the full volume of blood for safety labs, research labs, and for the biorepository. The biorepository volume of 100 mL will include 10 mL for plasma, and 90 mL of whole blood to be used for cells.
- For a hemoglobin between 9.0 and 10.0, draw the full volume of blood for safety labs and research labs, however draw only 30 mL for the biorepository as opposed to drawing the full 100 mL. The 30 mL will include 10 mL for plasma and 20 mL of whole blood to be used for cells.
- For a hemoglobin less than 9.0, only draw the safety labs which will include a CBC and a Comprehensive Metabolic Panel.

9.1 Biomarker Studies

To assess the immune response and pre-determined correlative studies a skin biopsy will be collected and peripheral blood (98mL total) collected at baseline. Blood samples will also be collected after cycle 1 (on the first day of cycle 2, prior to dosing) then on the first day of every 3rd cycle thereafter, prior to dosing (i.e., day 1 cycle 5, day 1 cycle 8, day 1 cycle 11, etc.), and at time of confirmed CR or PR, & at PD or EOT visit. After the skin punch biopsy at baseline patients must also provide a biopsy at the time of a clinical event (at the time of response, progression or appearance of a new lesion) and at the end of treatment. Additional punch biopsies every 3 cycles are optional. An archival tissue sample is optional.

All patients will have an additional 10ml of blood drawn at each of the above specified intervals for Kyn/Trp ratio testing. We have listed this test as a “Special Correlative Study” as opposed to a Biomarker Study because we will be testing Kyn/Trp ratio as a potential mechanism of resistance.

Table 9.1 Tumor Tissue and Blood Collection

	Screening/Post cycle 1 (day 1 of cycle 2, prior to dosing)/Post every 3rd cycle (day 1 of every 3rd cycle, prior to dosing, day 1 cycle 5,8,11, etc.)	**Response/PD**	**EOT**
5 mm punch biopsy (#1)*	**Required at baseline** – (Sent to CITN Central Lab in formalin) ***Biopsies at other “every 3rd cycle” time points are optional.***	**Required at response, progression or appearance of a new lesion** –(Sent to CITN Central Lab in formalin)	**Required** – (Sent to CITN Central Lab in formalin)
5 mm punch biopsy – immediately adjacent (#2)*	***Optional*** – (To CITN Central Lab in formalin)	***Optional*** **-**(To CITN Central Lab in formalin)	***Optional*** –(To CITN Central Lab in formalin)
FNA + Core Biopsy (subjects with known LN disease only)	***Optional*** – (FNA to Stanford in RPMI, Core biopsy to CITN Central Laboratory in Formalin)	***Optional*** – (FNA to Stanford in RPMI, Core biopsy to CITN Central Laboratory in Formalin)	***Optional*** – (FNA to Stanford in RPMI, Core biopsy to CITN Central Laboratory in Formalin)
Biomarkers (blood)	**Required** (Sent to CITN	**Required** (Sent to CITN Central Lab)	**Required** (Sent to CITN Central Lab)

	Central Lab)		
Kyn/Trp Ratio, 1GTT (10 mL)	**Required** (Frozen plasma sent to CITN Central Lab)	**Required** (Frozen plasma sent to CITN Central Lab)	**Required** (Frozen Plasma sent to CITN Central Lab)
Biorepository: 110ml total volume with 100ml used for cells (PBMC's) and 10ml used for serum with reduced volumes in anemic patients. Hgb > 10, draw the full 110ml. Hgb 9-10, draw only 30ml (10ml Serum, 20ml cells). Hgb < 9.0, no Biorepository volumes drawn.	**Optional** (Sent to CITN Central Lab)	**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 *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 will be sent to the CITN Central Laboratory where slides will be made and shipped to Qualtek for Chromogenic (Single-Color) IHC for PD-L1 and to Merck, Palo Alto, for Multiparametric (Two-Color) IHC and Transcriptional Analyses using the Nanostring platform. If archival tissue is not available it is important to review the pathology report and confirm the diagnosis.

Skin specimens may be obtained at other study visits depending on principal investigator decision. At the response/PD visit and the end of treatment visit, 2 side-by-side 5-mm punch biopsies may be optionally obtained from each [anatomical] site biopsied at screening. Biopsies will be obtained at the respective Cancer Center clinics according to their clinical SOPs.

If a patient has known lymph node disease an optional Fine Needle Aspiration (FNA) of the lymph node and an optional core biopsy of the lymph node will be obtained at screening, after cycle 1, after every 3rd cycle, at response/PD visit, and end of treatment visit. Patients may refuse the lymph node biopsies and still participate in the trial. Patients may agree to only one type of lymph node biopsy (FNA or Core) if they are uncomfortable providing both and still participate in the trial. Lymph node biopsies and core biopsies will be obtained at the respective Cancer Center according to their clinical SOP's.

9.1.2 *Laboratory Procedures/Assessments*

9.1.2.1 *Laboratory Safety Evaluations (Hematology, Chemistry and Urinalysis)*

Laboratory tests for hematology, chemistry, urinalysis, and others are specified below:

Table 9.2: Laboratory Tests

Hematology	Chemistry	Urinalysis	Other
Hematocrit	Albumin	Blood	Serum β-human chorionic gonadotropin (β-hCG)*
Hemoglobin	Alkaline phosphatase	Glucose	PT (INR)
Platelet count	Alanine aminotransferase (ALT)	Protein	aPTT
WBC (total and differential)	Aspartate aminotransferase (AST)	Specific gravity	Total thriiodothyronine (T3)
Red Blood Cell Count	Lactate dehydrogenase (LDH)	Microscopic exam, if abnormal results are noted	Free thyroxin (T4)
	Blood Urea Nitrogen (BUN)		
Absolute Neutrophil Count	Carbon Dioxide (CO_2 or bicarbonate)	Urine pregnancy test*	Thyroid stimulating hormone (TSH)
Absolute Lymphocyte Count	Creatinine		
	Uric Acid		
	Calcium		Blood for correlative studies
	Chloride		
	Glucose		
	Phosphorus		
	Potassium		
	Sodium		
	Magnesium		
	Total Bilirubin		
	Direct Bilirubin, if total bilirubin is elevated above the upper limit of normal		
	Total protein		
	Blood Urea Nitrogen		

* Perform on women of childbearing potential only. If urine pregnancy results cannot be confirmed as negative, a serum pregnancy test will be required.

After Cycle 1, pre-dose laboratory procedures can be conducted up to 72 hours prior to dosing. Results must be reviewed by the investigator or qualified designee and found to be acceptable prior to each dose of trial treatment.

9.1.2.2 ***Circulating Tumor Cells (will be referred to as circulating Sézary cells or CSCs in this protocol).***

In this protocol Sézary cells are defined as T cells which are either $CD4^+CD7^-$ **OR** CD4+CD26-. For an individual patient only one of the phenotypes will be used, not both. The protocol allows the use of either $CD4^+CD7^-$ or $CD4^+CD26^-$ T cells since there is variation in which phenotype best represents an individual patient's Sézary phenotype. The Olsen Criteria for response assessment include the use of either phenotype. [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 of Circulating Sézary Cells). This test is considered Standard-of-Care for patients with MF/SS so the flow cytometry for CSC testing will take place at the individual research sites. Since this test will be used as part of the disease assessment it will be performed at the same time points as the CT scans (for those with measurable disease) and mSWAT testing. Circulating Sézary Cell (CSC) burden will be determined at baseline then again at week 12 (after 4 doses of MK-3475). If progression is seen at week 12 CSC will be repeated at week 16. If no progression is seen at week 12 CSC will be repeated at week 18. CSC will be repeated every 2 cycles (every 6 weeks) out to week #30 (including week 24 and week 30). Repeat CSC after week 30 will take place every 4 cycles (every 12 weeks) including week 42, 54, 66, 78, 90 and 104 (end of study).

All patients who are positive for CSC's in blood at baseline should receive continued CSC testing at the intervals described above. Those patients who have measurable disease by CT scan (either LN or viscera) should receive continued CSC testing per the above schedule EVEN if they are negative at baseline. Those patients who do NOT have measurable disease by CT scan should NOT have regular, ongoing, CSC testing if they are negative at baseline however these patients will have repeat CSC testing for CR, PR, PD or EOT. As a quality assurance tool for this trial we will obtain data from all CSC results and send the data to Stanford University for central review by their pathologists.

9.2 Laboratory Correlative Studies

The biomarker and correlative studies that will be performed at the time points described above are as follows:

9.2.1 ***Chromogenic (Single-Color) IHC for PD-L1 - Laboratory Correlative Study #1.*** PD-L1 expression has been identified as a potential biomarker for response to anti-PD-1 therapy. We will test whether PD-L1 expression correlates with MK-3475 response in the MF/SS population.

9.2.1.1 ***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

9.2.1.1.1. Timing of specimen collection will include a biopsy at baseline, at the time of a clinical event (at the time of response, progression or appearance of a new lesion) and at the end of treatment. Additional punch biopsies every 3 cycles are optional.

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

9.2.1.3 ***Shipping of Specimen(s).*** Participating sites will send biopsy tissue in formalin for overnight delivery to the CITN Central Laboratory. The CITN Central Laboratory or designate will prepare FFPE blocks then prepare slides. Slides will be sent to Qualtek for staining with anti-22C3 anti-PD-L1 IHC Assay.

9.2.1.4 ***Site(s) Performing Correlative Study.*** Merck CRO, Qualtek, will perform the testing using the slides sent by the CITN Central Laboratory.

9.2.2 ***Multiparametric (Two-Color) IHC – Laboratory Correlative Study #2.***
Spatial association of PD-1^+ TILs and PD-$L1^+$ cells (tumor and myeloid cells) suggests "induction" of PD-L1. Interferon-gamma production by antigenspecific PD-1^+ $CD8^+$ T cells is hypothesized to drive local intratumoral upregulation of PD-L1 on adjacent tumor and myeloid cells, leading to a "stalled CTL" response which may be predictive of response to MK-3475 therapy. By assessing both of the required elements, i.e., PD-L1 positive cells and PD-1^+ T cells, a two-color IHC assay may be a better predictor of response than PD-L1 positivity alone. Immunohistochemical staining for CD3 and CD8 may also be performed if funds become available.

9.2.2.1 ***Collection of Specimen(s)***

9.2.2.1.1. Specimens will include archived and prospectively obtained tumor biopsies from skin and/or lymph nodes including possible punch and/or core biopsies

9.2.2.1.2. Timing of specimen collection will include a biopsy at baseline, at the time of a clinical event (at the time of response, progression or appearance of a new lesion) and at the end of treatment. Additional punch biopsies every 3 cycles are optional.

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

9.2.2.3 ***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 Merck, Palo Alto, where multiparametric immunohistochemical assays will be performed to identify and enumerate key cellular components and immunoregulatory molecules to include PD-1, PD-L1, among other analytes.

9.2.2.4 ***Site(s) Performing Correlative Study.*** Merck, Palo Alto, will perform the testing using the slides sent by the CITN Central Laboratory.

9.2.3 ***Transcriptional Analyses – Laboratory Correlative Study #3.***
The Nanostring platform will be used to profile mRNA expression in archival material, to assess expression of approximately 650 genes and attempt to define a gene set critical for clinical response to MK-3475. The hypothesis to be tested is that MK-3475 responders will exhibit a "stalled Cytotoxic T Lymphocyte (CTL)" response within the tumor reflected in the physical proximity between PD-1 and PD-L1 expression and the presence

of an aborted (e.g., weak but discernible) INF-γ transcriptional program.

9.2.3.1 ***Collection of Specimen(s)***

9.2.3.1.1. Specimens will include archived and prospectively obtained tumor biopsies including skin and/or lymph nodes including possible punch and/or core biopsies

9.2.3.1.2. Timing of specimen collection will include a biopsy at baseline, at the time of a clinical event (at the time of response, progression or appearance of a new lesion) and at the end of treatment. Additional punch biopsies every 3 cycles are optional.

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

9.2.3.3 ***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 Merck, Palo Alto for Nanostring analysis and global profiling by next-generation sequencing (RNAseq).

9.2.3.4 ***Site(s) Performing Correlative Study.*** Merck, Palo Alto, will perform the testing using the slides sent by the CITN Central Laboratory.

9.2.4 ***Immunophenotyping & T cell function assays-Laboratory Correlative Study #4.*** CyTOF and multiparametric flow cytomety will be employed to extensively immunophenotype the tumor and associated immune infiltrates both prior to and during MK-3475 treatment. We anticipate that these studies will provide a more granular view of the tolerized PD-1$^+$ target cell and its response to anti-PD-1 blockade, which will guide the future choice of rational immunomodulatory combination therapies. 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 MF/SS.

Immunophenotyping will be augmented by assays of T cell function. Activation of discrete T cell subsets and/or combinations of T cells with putative “suppressor cells” will be assayed by intracellular cytokines, cell surface activation markers of proliferation when challenged with autologous tumor cells or autologous dendritic cells pulsed with tumor lysate.

9.2.4.1 ***Collection of Specimens***

9.2.4.1.1. Whole blood will be collected into heparinized tubes. For patients with lymph node disease who agree to the optional Fine Needle Aspiration (FNA), the sample will be obtained locally using routine clinic SOP's.

9.2.4.1.2. Timing of specimen collection will include mandatory collection prior to treatment, post cycle 1 (on the 1st day of cycle 2 just prior to dosing), on the first day of every 3rd cycle thereafter, prior to dosing (i.e., day 1 of cycle 5, 8, 11, etc), response/PD visit and end of treatment visit.

9.2.4.2 ***Handling of Specimen(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. FNA samples will be placed in RPMI and will be shipped to the Stanford Laboratory overnight for flow cytometry.

9.2.4.3 ***Shipping of Specimens***

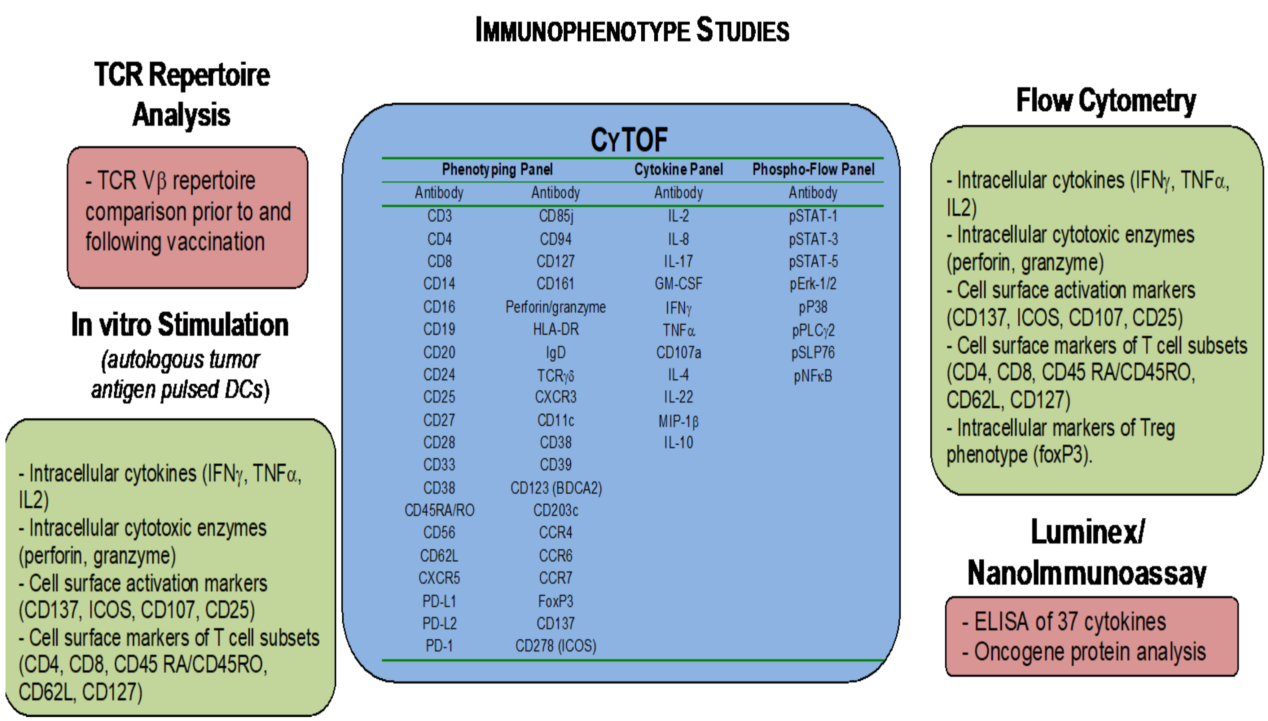
Frozen PBMCs and FNA samples in RPMI will be shipped to Stanford University.

9.2.4.4 ***Site(s) Performing Correlative Study.***

All sites will provide samples for analysis to be performed at Stanford University.

9.2.5 ***Cytokine/Chemokine Analysis (serum ELISA)-Laboratory Correlative Study #5.***

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 (prior to treatment), on treatment, and at time of response assessment.



9.2.5.1 ***Collection of Specimens***

9.2.5.1.1. Whole blood will be collected into red-top tubes.

9.2.5.1.2. Timing of specimen collection will include mandatory collection prior to treatment, post cycle 1 (on the 1st day of cycle 2 just prior to dosing), on the first day of every 3rd cycle thereafter, prior to dosing (i.e., day 1 of cycle 5, 8, 11, etc), response/PD visit and end of treatment visit.

9.2.5.2 ***Handling of Specimen(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, Kohrt Laboratory. Aliquots will be thawed and analyzed by Luminex.

9.2.5.3 ***Shipping of Specimens***

Frozen serum will be shipped by the CITN Central Laboratory to Stanford University.

9.2.5.4 ***Site(s) Performing Correlative Study.*** All sites will provide samples for analysis to be performed at Stanford University.

9.2.6 ***Whole Exome Sequencing and Neoantigen Identification (Laboratory Correlative Study #6):*** We propose performing whole exome sequencing of pre-treatment samples using paired germline/tumor DNA. Depending on availability of resources, this may be limited to a subset of patients. Subsequent bioinformatic prediction of neoantigens and individualized testing of immune responses directed against candidate neoantigens may be performed.

9.2.6.1 ***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.

9.2.6.2 ***Handling of Specimen(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.

9.2.6.3 ***Shipping of Specimens***

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.

9.2.6.4 ***Site(s) performing correlative study***

The Stanford Laboratory of Dr. Michael Khodadoust (or an equivalent laboratory) will perform the Exome Sequencing and neoantigen identification.

9.3 Special Studies (Kyn/Trp Ratio)

9.3.1 *Special Correlative Study #1: Whole Blood Kyn/Trp Ratios*

Kyn/Trp ratios will be assayed in patients receiving a regimen of MK-3475 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. It is postulated that enhanced IDO expression may occur in patients who fail anti-PD-1 therapy. IDO catabolizes the conversion of Tryptophan to Kynurenine, which has potent immunosuppressant properties. An increase in Kynurenine levels over time, relative to Tryptophan levels, in patients who are failing anti-PD-1 therapy would indicate that IDO expression may be leading to treatment failure. This mechanism of resistance could potentially be overcome with an IDO inhibitor.

9.3.1.1 *Collection of Specimens*

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

9.3.1.1.2. Timing of specimen collection will include mandatory collection prior to treatment, post cycle 1 (on the 1st day of cycle 2 just prior to dosing), on the first day of every 3rd cycle thereafter, prior to dosing (i.e., day 1 of cycle 5, 8, 11, etc), response/PD visit and end of treatment visit.

9.3.1.2 *Handling of Specimen(s)*

Frozen vials of plasma will be batch shipped to the CITN Central Laboratory.

9.3.1.3 *Shipping of Specimens*

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

9.3.1.4 *Site(s) Performing Correlative Study*

The Kyn/Trp analysis will be conducted at Incyte Corporation.

10. STUDY CALENDAR

Baseline evaluations are to be conducted within 1 week prior to start of therapy. Scans and x-rays must be done ≤4 weeks prior to the start of therapy.

Treatment Cycle[a] (Cycle Number)	Pre-Study	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	Response/ PD Assess or at discon.	Off Study[b,c] EOT
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	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±7
MK-3475 Administration[A]		X	X	X	X	X	X	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
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
Limited Physical exam		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
Height	X																				
12 Lead Electrocardiogram[g]	X	X							X											X	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
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
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
Urinalysis[k]	X[h]						X						X						X	X	X
T3, FT4 and TSH[k]	X[h]						X						X						X	X	X
Pregnancy Test[j,k]	X																				
PT/INR, aPTT[k,l]	X[h]																			X	X

Treatment Cycle[a] (Cycle Number)	Pre-Study	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	Response/ PD Assess or at discon.	Off Study[b,c] EOT
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/PET) for pts with measurable disease[n]	X				X*± 3		X*± 3		X*± 3		X*± 3				X*± 7				X*± 7	X	X
Tumor Imaging for pts with nonmeasurable disease	X																				
Circulating Sézary cells**	X				X*± 3		X*± 3		X*± 3		X*± 3				X*± 7				X*± 7	X	X
mSWAT Scoring/Photography	X				X*± 3		X*± 3		X*± 3		X*± 3				X*± 7				X*± 7	X	X
Tumor Biopsy/Correlative Blood Samples																					
Skin Biopsy[o] (See Section 9.1)	X		X			X			X			X			X			X		X	X
Lymph Node Biopsy[o](Optional)	X		X			X			X			X			X			X		X	X
Blood Samples (Biomarkers)[o]	X		X			X			X			X			X			X		X	X
Kyn/Trp Ratio[o]	X		X			X			X			X			X			X		X	X
Biorepository (Section 9)	X		X			X			X			X			X			X		X	X

Treatment Cycle[a] (Cycle Number)	Pre-Study	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	Response/ PD Assess or at discon.	Off Study[b,c] EOT
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		

A: The dose of MK-3475 is 2mg/kg q 21 days.

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. Height will be measured at visit 2 only.

g. ECG should be performed at baseline, within 30 minutes of the end of infusion after dosing for Cycle 1 and Cycle 8 and at discontinuation.

h. Laboratory tests for screening are to be performed within 10 days prior to the first dose of trial treatment. See table 9.2 for details regarding laboratory tests. 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 are found in table 9.2.

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. Coagulation factors (PT/INR and aPTT) should be tested as part of the screening procedures for all subjects.

m. PFT required at baseline for patients with a history of pulmonary disease, prolonged smoking history, or symptoms of respiratory dysfunction.

n. For scan schedules see section 11.1. For mSWAT and CSC see section 11.1.3. ***Note:*** mSWAT and CSCs will be measured during the same weeks as CT scans.

o. Blood for biomarkers will be drawn during screening (within 28 days), again after the first cycle (day 1 of cycle 2, prior to study drug infusion), then prior to study drug infusion on day 1 of every 3rd cycle (i.e., day 1, cycle 5, 8, 11, 14, etc.) then again for a confirmed CR or PR and at the time of PD and at EOT. Mandatory and optional biopsies will be performed at these same time points.

* The first clinical assessment including mSWAT, CSCs, and CT or PET/CT (for those with measurable or extracutaneous disease) will occur at week 12. For those with PD at week 12 the same assessments will be repeated in a confirmatory fashion at week 16. Those who do not have PD at week 12 will have the same assessments repeated at week 18, then every 2 cycles (every 6 weeks) through week #30, then every 4 cycles (12 weeks) for the duration of the study. Assessments will occur at week 12, (16 for PD), 18, 24, 30, 42, 54, 66, 78, 90 and 104 (EOS). If patients continue with MK-3475 therapy after confirmed progression, mSWAT frequency will increase to every cycle. CT or PET/CT and CSC (both, if indicated) will continue every 4 cycles,.

**CSC Testing will be performed at the individual research sites with central review of results at Stanford University. Refer to section 9.1.2.2 for additional CSC testing information.

Study Calendar (Continued)

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 at discon.	Off Study[b,c] EOT
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)	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±7
Study Drug Administration																		
MK-3475 Administration[A]	X	X	X	X	X	X	X	X	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
Vital Signs & Weight[f]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
12 Lead Electrocardiogram[g]								X									X	X
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	X
T3, FT4 and TSH[k]						X						X					X	X
PT/INR, aPTT[k,l]																	X	X
Efficacy Measurements																		
Tumor Imaging (CT/PET) for pts with measurable disease[n]				X±7				X±7				X±7					X	X (wk 104)
Tumor Imaging for pts with nonmeasurable disease																		
Circulating Sézary cells**				X±7				X±7				X±7					X	X (wk 104)
mSWAT Scoring/Photography				X±7				X±7				X±7					X	X (wk 104)

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 at discon.	Off Study[b,c] EOT
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		
Tumor Biopsy/Correlative Blood Samples																		
Skin Biopsy[o] (See Sectin 9.1)		X			X			X			X			X			X	X
Lymph Node Biopsy[o](Optional)		X			X			X			X			X			X	X
Blood Samples (Biomarkers)[o]		X			X			X			X			X			X	X
Kyn/Trp Ratio[o]		X			X			X			X			X			X	X
Biorepository (Section 9)		X			X			X			X			X			X	X

A: The dose of MK-3475 is 2mg/kg q 21 days.

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. Subjects with CR after receiving a minimum of 6 months of treatment with at least 2 doses since CR may discontinue therapy. Subjects without symptomatic progression may receive up to a maximum of 2 years.
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 scan was obtained within 4 weeks prior to the date of discontinuation, then a scan 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. Record all AEs and SAEs occurring within 30 days after the last dose of trial treatment.
f. Vital signs to include temperature, pulse, respiratory rate, weight and blood pressure. Height will be measured at visit 2 only.
g. ECG should be performed within 30 minutes of the end of infusion after dosing for Cycle 1 and Cycle 8 and at discontinuation.
h. Laboratory tests for screening are to be performed within 10 days prior to the first dose of trial treatment. See table 9.2 for details regarding laboratory tests. 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 are found in table 9.2.
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. Coagulation factors (PT/INR and aPTT) should be tested as part of the screening procedures for all subjects.
m.
n. For scan schedules see section 11.1. For mSWAT and CSC see section 11.1.3. ***Note:*** mSWAT and CSCs will be measured during the same weeks as CT scans so that all assessments are done at the same time. mSWAT and CSC may be done on the same day as the CT scans or they may be done another day that week if needed for patient convenience. If patients continue therapy after progression, mSWAT will increase to every cycle. CT or PET/CT and CSC (both, if indicated) will continue every 4 cycles.
o. Blood for biomarkers will be drawn during screening (within 28 days), again after the first cycle (day 1 of cycle 2, prior to study drug infusion), then prior to study drug infusion on day 1 of every 3rd cycle (i.e., day 1, cycle 5, 8, 11, 14, etc.) then again for a confirmed CR or PR and at the time of PD and at EOT. Mandatory and optional biopsies will be performed at these same time points

**CSC Testing will be performed at the individual research sites with central review of results at Stanford University. Refer to section 9.1.2.2 for additional CSC testing information.

11. MEASUREMENT OF EFFECT

11.1 Antitumor Effect – Solid Tumors

MF and SS 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 who have extracutaneous disease will have disease that is measurable by CT or PET/CT. Patients with measurable (extracutaneous) disease will have scans at the intervals specified in the paragraph below. 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 the discretion of the investigator. Patients with nonmeasurable disease will not be required to have repeat scans for CR, PR or SD.

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), Visceral Disease (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.

The tests other than radiographic scans will include mSWAT and flow cytometry for CSCs. These tests will be performed on all patients (those with and without measurable disease) at the same intervals as CT scans described in the next paragraph for patients with measurable disease. All assessments including CT scans (for patients with measurable disease), mSWAT, and CSC will be performed at the same intervals and time points. Assessments for patients with measurable disease will include radiologic scans, mSWAT and CSC. Assessments for patients with nonmeasurable disease will consist of mSWAT and CSC (if indicated).

For the purposes of this study, patients will first be assessed for response at week 12 (after 4 cycles of MK-3475). If progression is seen at week 12, confirmatory assessments will be repeated at week 16. If no progression is seen at week 12, assessments will be repeated at week 18. Assessments will then be repeated every 2 cycles (every 6 weeks) until week #30. (Assessments will be repeated at week 24 and week 30). Repeat assessments after week 30 will take place every 4 cycles (every 12 weeks) including week #42, 54, 66, 78, 90 and 104 (end of study). Assessments will also be performed at the time of CR/PR confirmation, or PD. ***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 the discretion of the investigator. Patients with nonmeasurable disease will not be required to have repeat scans for CR, PR, or SD.

If a CR is achieved patients may stop study drug therapy after 2 additional cycles 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. Patients who are treated again after a CR will have scans, tests, procedures, biopsies and study drug administration at intervals just like a new patient beginning protocol therapy.

11.1.1 ***Definitions***

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

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 MF/SS.

11.1.2 ***Disease Parameters*** N/A

11.1.3 ***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.

11.1.3.1 ***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.

Subjects will have a skin evaluation (mSWAT) at screening, then again at week 12 (after 4 cycles of MK-3475). mSWAT will be repeated at week 16 if patients have progressive disease (PD) at week 12. If no PD is seen at week 12, the mSWAT will be repeated at week 18. mSWAT will then be repeated every 2 cycles (every 6 weeks) to week #30 including assessments at week 24 and week 30. After week 30 mSWAT will be repeated every 4 cycles (every 12 weeks) including week 42, 54, 66, 78, 90 and 104 (end of study). 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.

Regardless of treatment delays, response assessment including mSWAT 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, (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.

11.1.4 *Initial Tumor Imaging*

Initial tumor imaging with a CT or PET/CT must be performed within 28 days prior to 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 prior to 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 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.

11.1.5 *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 as described in section 11.1.3 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 cycle intervals.

11.1.5.1 *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 provided they have met the conditions detailed in Section 5.8.

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.

11.1.6 *Response Criteria*

Primary outcome measure is clinical response rate as assessed by the standard response criteria used in MF and SS (skin, LN, viscera, blood, global) [23].

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) $\geq$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 MF/SS (see histologic criteria for early MF[7]), 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 N_3 classification and <1.5 cm in long axis diameter at baseline, must now be $\leq$1 cm in diameter of the short axis or biopsy negative for lymphoma
PR	(1) Cumulative reduction $\geq$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 $\geq$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 $\geq$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 N_3 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 measureable 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		
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		

Global Score*	Definition	Skin	Nodes	Blood	Viscera
			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 as long as section 5.8 criteria are met. 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, 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: "Section 5.8 Criteria"

- 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

If at the subsequent response assessment a patient is noted to have confirmed, continued, progression of disease by global response criteria, the patient may not continue on MK-3475.

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.

11.1.7 ***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.

11.1.8 ***Progression-Free Survival***

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

11.1.9 ***Response Review***

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

11.2 Antitumor Effect – Hematologic Tumors: N/A

11.3 Other Response Parameters: N/A

12. DATA REPORTING/REGULATORY REQUIREMENTS

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

12.1 Data Reporting

Data collection for this study will be done exclusively through Medidata Rave. Access to the trial in Rave is granted through the iMedidata application to all persons with the appropriate Rave roles in the CTSU Regulatory Support System (RSS). To access iMedidata/Rave the site user must have an active CTEP IAM account (https://eapps-ctep.nci.nih.gov/iam). In addition, site users that are members of the CITN must have the appropriate Rave roles (Rave CRA, Site PI, or Site co-PI) in RSS at the enrolling site.

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

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

12.1.1 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, either by FTP burst of data or via the CDS web application. 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).

12.1.2 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 data management organization on a real-time basis, but no less than 72 hours after data has been collected. (ie: 72 hours after a visit). 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 clinical 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 12.1.1 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.

12.2 CTEP Multicenter Guidelines

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

- The Principal Investigator/Coordinating Center is responsible for distributing all IND Action Letters or Safety Reports received from CTEP to all participating institutions for submission to their individual IRBs for action as required. Submit documentation of reportable adverse events to CTSUprotocol@westat.com and state in the subject line "Safety Report for *NCI protocol #*" or "Action Letter for *NCI protocol #*", as appropriate. A brief summary cover page on Coordinating Center letterhead is encouraged. These documents will be posted to the CTSU protocol web page and included in the next CTSU bi-monthly broadcast.

- Except in very unusual circumstances, each participating institution will order DCTD-supplied agents directly from CTEP. Agents may be ordered by a participating site only after the initial IRB approval for the site has been forwarded to the CTSU Regulatory Office as detailed in the Site Registration section of this protocol. The CTSU Regulatory Office will enter and track IRB approval information in the CTSU Regulatory Support System (RSS) where it will be transmitted to CTEP for fulfillment of agent requests.

12.3 Collaborative Agreements Language

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

1. Agent(s) may not be used for any purpose outside the scope of this protocol, nor can Agent(s) be transferred or licensed to any party not participating in the clinical study. Collaborator(s) data for Agent(s) are confidential and proprietary to Collaborator(s) and shall be maintained as such by the investigators. The protocol documents for studies utilizing Agents contain confidential information and should not be shared or distributed without the permission of the NCI. If a copy of this protocol is requested by a patient or patient's family member participating on the study, the individual should sign a confidentiality agreement. A suitable model agreement can be downloaded from: http://ctep.cancer.gov.

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

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

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

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

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

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

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

6. Any manuscripts reporting the results of this clinical trial must be provided to CTEP by the Group office for Cooperative Group studies or by the principal investigator for non-Cooperative Group studies for immediate delivery to Collaborator(s) for advisory review and comment prior to submission for publication. Collaborator(s) will have 30 days from the date of receipt for review. Collaborator shall have the right to request that publication be delayed for up to an additional 30 days in order to ensure that Collaborator's confidential and proprietary data, in addition to Collaborator(s)'s intellectual property rights, are protected. Copies of abstracts must be provided to CTEP for forwarding to Collaborator(s) for courtesy review as soon as possible and preferably at least 3 days prior to submission, but in any case, prior to presentation at the meeting or publication in the proceedings. Press releases and other media presentations must also be forwarded to CTEP prior to release. Copies of any manuscript, abstract and/or press release/ media presentation should be sent to:

Email: 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

This section outlines the statistical analysis strategy and procedures for the study. If, after the study has begun, but prior to the conduct of any analysis, changes are made to primary and/or key secondary hypotheses, or the statistical methods related to those hypotheses, then the protocol will be amended (consistent with ICH Guideline E-9). Changes to exploratory or other nonconfirmatory analyses made after the protocol has been finalized, along with an explanation as to when and why they occurred, will be listed in the Clinical Study Report (CSR) for the study. Post hoc exploratory analyses will be clearly identified in the CSR. No separate Statistical Analysis Plan (SAP) will be issued for this study.

13.1 Responsibility for Analyses

The statistical analysis of the data obtained from this study will be the responsibility of the Fred Hutchinson Cancer Research Center as part of the Cancer Immunotherapy Trials Network (CITN).

This trial is being conducted as an open-label study (i.e., patients, investigators, and trial personnel will be aware of patient treatment).

A single interim analysis will be conducted at the end of Stage 1: **Stage 1** will enroll 9 patients. **Stage 2:** Will enroll an additional 15 patients (for a total of 24). If there are one or more responses (PR or CR) amongst the nine patients enrolled in Stage 1, Stage 2 enrollment will proceed. If there are no responses (PR or CR) amongst the nine patients enrolled in Stage 1, enrollment into Stage 2 will not proceed. The null hypothesis (H0) MK-3475 will show less than 5% overall response rate. The alternative hypothesis (H1) MK-3475 will show greater than 25%

overall response rate (PR and CR).

13.2 Study Design/Endpoints

13.2.1 *Primary Objective*

To determine the clinical efficacy of MK-3475 for the treatment of relapsed or refractory MF or SS.

The primary endpoint will be Objective Response Rate (ORR) as measured by the global assessment standard response criteria for MF and SS [Olsen 2011]. Response is defined as a confirmed PR or a confirmed CR with the confirmation assessment no less than 4 weeks after criteria for response is first met.

13.2.2 *Secondary Objectives*

To determine the clinical activity of MK-3475 for the treatment of patients with relapsed or refractory MF or SS.

The secondary endpoints will be PFS, DOR, and OS, as measured by the global assessment standard response criteria for MF and SS [Olsen 2011]. PFS is defined as the time from allocation to the first documented disease progression or death due to any cause, whichever comes first.

13.3 Analysis Endpoints

13.3.1 *Efficacy Endpoints*

The primary and secondary efficacy endpoints are described below.

Objective response rate (ORR): is defined as the proportion of patients who have achieved CR or PR according to the global assessment standard response criteria for MF and SS [Olsen 2011].

Progression-free Survival (PFS): is defined as the time from enrollment to PD or death, whichever occurs earlier, based upon investigator assessment using RECIST 1.1. Patients without documented PD/death will be censored at the last disease assessment date.

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

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

13.3.2 *Safety Endpoints*

The primary safety endpoints are AEs graded using CTCAE (Version 5.0) criteria. Safety will be assessed by quantifying the toxicities and grades experienced by subjects who have received MK-3475 including AEs and SAEs. Safety will be monitored by cumulative data reviews throughout the trial.

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

Note: patients discontinuing MK-3475 due to toxicity will still be considered evaluable for response.

13.4 Analysis Populations

13.4.1 *Efficacy Analysis Population*

The population of eligible subjects who receive at least 1 dose of treatment will serve as the primary population for the analysis of efficacy data in this study.

13.4.2 *Safety Analysis Population*

The All Subjects as Treated (ASaT) population will be used for the analysis of safety data in this study. The ASaT population consists of all patients who received at least 1 dose of study treatment. Patients who do not receive the study treatment will be excluded from analysis.

At least one laboratory or vital sign measurement obtained subsequent to at least 1 dose of study treatment is required for inclusion in the analysis of each specific parameter. To assess change from baseline, a baseline measurement is also required.

13.5 Statistical Methods

The protocol has a standard Simon two stage design. The null hypothesis that the true response rate is 5% will be tested against a one-sided alternative. **Stage 1** will enroll 9 patients. **Stage 2:** Will enroll an additional 15 patients (for a total of 24). If there are one or more responses (PR or CR) amongst the nine patients enrolled in Stage 1, Stage 2 enrollment will proceed. If there are no responses (PR or CR) amongst the nine patients enrolled in Stage 1, enrollment into Stage 2 will not proceed. The null hypothesis (H0) MK-3475 will show less than 5% overall response rate. The alternative hypothesis (H1) MK-3475 will show greater than 25% overall response rate (PR and CR). The null hypothesis will be rejected if 3 or more responses are observed in 24 patients. This design yields a type I error rate of 0.1 and power of 0.9 when the true response rate is 25%.

Unless otherwise stated, all statistical tests will be conducted at the α=0.05(1-sided) level.

13.5.1 *Statistical Methods for Efficacy Analyses*

13.5.1.1 *ORR*

ORR will be estimated as the number of responders as a percent of the number of eligible participants who received at least 1 dose of treatment. If a substantial amount of primary endpoint data are missing (at least 1 value missing from more than 20% of participants), using nonparametric estimation to estimate the ORR requires the missing completely at random assumption may give misleading results. In this situation, analyses of the primary endpoint at the primary time-point will be performed using parametric generalized linear models fit by maximum likelihood. These methods provide unbiased estimation and inferences under the parametric modeling assumptions and the assumption that the missing data are missing at random (MAR). MAR assumes that the probability of an observation being missing may depend upon the observed responses and upon observed covariates, but not upon any unobserved factors. A generalized linear model for the objective response rate will use a binomial error distribution. The model will include as covariates all available baseline predictors of the missing outcomes.

Note: Patients who progress on MK-3475 but remain on study with continued MK-3475 therapy will be considered to have progressive disease. Any delayed responses with continued therapy in this group will be chronicled and reported.

13.5.1.2 ***PFS, DOR and OS***

Survival curves for PFS, DOS and OS will be estimated using the Kaplan-Meier method.

For PFS, subjects without documented PD/death will be censored at the last disease assessment date. Any subject who is lost to follow-up will be included in the analysis and their PFS time will be censored on the last date that the subject was known to be progression free, defined as the date of the last tumor assessment not indicating progression. As a sensitivity analysis the primary analysis of PFS will be performed reconsidering subjects without documented PD or death who discontinued treatment or received new anticancer therapy, to have been progressed at the date of treatment discontinuation or initiation of new anticancer therapy, whichever occurs later.

For OS, subjects without documented death at the time of analysis will be censored at the date last known to be alive.

For DOR, subjects who have not yet progressed by the last disease assessment will be censored at the last disease assessment" – this is intended to describe censoring rules for the analysis where only responders are used.

Table 13.5 Analysis Strategy for Key Efficacy Variables

Endpoint/Variable (Description, Timepoint)	**Statistical Method**	**Analysis Population**	**Missing Data Approach**
Primary Hypothesis			
ORR	Simon Two Stage design analysis	Eligible subjects who receive at least 1 dose of treatment	See 13.5.1.
Secondary Objectives			
PFS	Estimation: Kaplan-Meier method for PFS curve estimation	Eligible subjects who receive at least 1 dose of treatment	Model based (censored at last assessment)

DOR	Summary statistics using Kaplan-Meier method	All responders	Nonresponders are excluded in analysis
OS	Summary statistics using Kaplan-Meier method	Eligible subjects who receive at least 1 dose of treatment	Model based (censored at last date)

Note: PD after 1 or more missed visits will be counted as PD as of the date of documented disease progression. An additional sensitivity analysis will be performed where subjects with 2 or more missed visits prior to progression will be censored at the last disease assessment prior to the ≥2 missed disease assessments.

13.5.2 *Statistical Methods for Safety Analyses*

Safety and tolerability will be assessed by clinical review of all relevant parameters including adverse experiences (AEs), laboratory tests, vital signs, and ECG measurements.

Adverse experiences will be summarized as counts and frequencies by toxicity grade. Summary statistics (median and range) for time to onset of first drug-related toxicity will be provided.

Laboratory assessments, vital signs, and other safety endpoints will be summarized using descriptive statistics as appropriate.

13.5.3 *Summaries of Baseline Characteristics, Demographics, and Other Analyses*

The number and percentage of subjects enrolled, and the primary reason for discontinuation will be displayed. Demographic variables (such as age) and baseline characteristics will be summarized either by descriptive statistics or categorical tables. No statistical hypothesis tests will be performed on these characteristics.

13.6 Multiplicity

No multiplicity adjustment will be applied.

13.7 Sample Size/Accrual Rate and Power Calculations

This study will enroll between 9 and 24 subjects to receive MK-3475 in a two-stage Simon design with 90% power to reject the null hypothesis of a 5% true response rate against a one-sided alternative when the true response rate is 25%. The study will enroll the first 9 patients over a 6 month period, followed by enrollment of 15 more subjects over 10 months.

In the first stage, 9 patients will be accrued. If there are no responses in these 9 patients, further enrollment will be suspended. If there are one or more responses amongst the first nine patients an additional 15 patients will be accrued for a total of 24. The null hypothesis will be rejected if 3 or more responses are observed in 24 patients. This design yields a type I error rate of 0.1 and power of 0.9 when the true response rate is 25%.

13.8 Stratification Factors- N/A

13.9 Interim Analyses

There will be one interim analysis at the end of Stage 1, on the first 9 patients. If there are no responses in these 9 patients further enrollment will be suspended however patients who are actively being treated on study will continue therapy and will continue to be followed for response. If there are one or more responses amongst the first nine patients we will proceed on to Stage 2 and enroll an additional 15 subjects for a total of 24.

13.10 Compliance (Medication Adherence)

Drug accountability data for trial treatment will be collected during the study. Compliance with trial treatment administration will be measured by subjects: (1) receiving unscheduled study agent infusions/injections; (2) missing an infusion/injection. Numbers and percentages of subjects and infusion/injection visits with any deviation in these measures will be reported for the eligible subjects

13.11 Extent of Exposure

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

13.12 Analysis of Secondary Endpoints

Analysis of secondary endpoints is addressed in Section 13.2

13.13 Reporting and Exclusions

13.13.1 *Evaluation of Toxicity*

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

13.13.2 *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) CR, (2) PR, (3) SD, (4) PD, (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 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.

14. STUDY STATUS UPDATES AND STUDY CLOSURE

14.1 Definitions of Study Status Changes

14.1.1 Temporarily Closed to Accrual

The study status is Temporarily Closed to Accrual when no patient slots are currently available, but there is the possibility that the trial will re-open for accrual (patient slots become available). Sites are not permitted to accrue additional patients until CTEP is notified of Re-Activation.

Study status will need to be changed to Temporarily Closed to Accrual when any of the following criteria are met:

- Sites are notified by CTEP (via Request for Rapid Amendment [RRA]) of changes in the risk/benefit ratio that necessitate changes to the patient Informed Consent document. Requested changes will be specified in the RRA and must be reviewed by the study's IRB.
- CTEP and the lead investigator agree that unacceptable toxicities necessitate a discussion to change the dosing/regimen.
- A protocol-defined benchmark has been achieved (such as an interim analysis before proceeding to the next stage).

14.1.2 Closed to Accrual

The study status is (permanently) Closed to Accrual when no more patient enrollment slots are available, and at least one patient is still actively receiving the study treatment. Sites are no longer permitted to enroll additional patients.

Patient slots are no longer available when the following criteria are met:

- The pre-specified number of evaluable patients has been successfully enrolled, treated, and evaluated.
- The study treatment has failed to meet the pre-specified efficacy goal at the stage 1 interim analysis.
- CTEP and the investigators agree that unacceptable toxicities preclude further

enrollment.

14.1.3 Closed to Accrual and Treatment

The study status is Closed to Accrual and Treatment when no more patient enrollment slots are available and no patients are currently receiving the study treatment. Patients may still be enrolled on the protocol only for the purposes of follow-up.

Patient accrual and treatment will be permanently halted when any of the following criteria are met:

- Enrollment was previously closed (study status of "Closed to Accrual"), and no patients are receiving the study treatment.
- CTEP and the investigators agree that unacceptable toxicities preclude further enrollment. In this case, CTEP and the investigators must collaborate to alter the regimen or to halt the study treatment altogether as soon as it can be safely done for patients currently receiving treatment.

CTEP and Axio **must be notified** when patients are no longer receiving treatment [*i.e.*, when the last patient(s) to be receiving treatment is/are no longer receiving the study regimen for any reason].

14.1.4 Closed to Follow-Up

The study is considered Closed to Follow-Up when all protocol-defined follow-up procedures have been completed for all patients who have not been removed from the study for other reasons. That is, there are no outstanding follow-up procedures to be performed as mandated by the protocol.

CTEP does **not** need to be notified of a status change to "Closed to Follow Up."

14.1.5 Complete

Study is considered Complete if it has been at least thirty (30) days since the last patient follow-up evaluation.

A citation to a final study report (manuscript, meeting abstract, etc.) is required with the submission of the Protocol Status Update Form to CTEP PIO.

14.2 Responsibility for Filing Protocol Status Update Forms

CTEP must be notified of all study status changes in Section 14.1 (except for Closed to Follow-Up) by the Corresponding Organization via Protocol Status Update Form, available from the CTEP website at http://ctep.cancer.gov/protocolDevelopment/default.htm#amendments.

Axio must be notified as soon as all patients are off treatment (*i.e.*, when study status changes to Closed to Accrual and Treatment). Axio will produce a report within 90 days of this notification.

REFERENCES

Al-Shibli KI, Donnem T, Al-Saad S, Persson M, Bremnes RM, Busund LT (2008). Prognostic effect of epithelial and stromal lymphocyte infiltration in non-small cell lung cancer. *Clin Cancer Res* 14(16): 5220-5227.

Alexander MA (2011). *Immune-based cancer treatment: the T lymphocyte response*. Boca Raton, FL Enfield, N.H., CRC Press; Science Publishers.

Attia P, Phan GQ, Maker AV, Robinson MR, Quezado MM, Yang JC, et al. (2005). Autoimmunity correlates with tumor regression in patients with metastatic melanoma treated with anti-cytotoxic T-lymphocyte antigen-4. *J Clin Oncol* 23(25): 6043-6053.

Berman, D.M., J. Wolchok, J. Weber*, et al.* (2009). Association of peripheral blood absolute lymphocyte count (ALC) and clinical activity in patients (pts) with advanced melanoma treated with ipilimumab. *JClin Oncol*. 27:A3020.

Berger CL, Longley J, Hanlon D, et al. (2001). The clonotypic T cell receptor is a source of tumor-associated antigens in cutaneous T cell lymphoma. *Ann N Y Acad Sci* 941:106–22.

Berger CL, Hanlon D, Kanada D, et al. (2001). Transimmunization, a novel approach for tumor immunotherapy. Transfus Apher Sci 2002;26:205–16. Edelson RL. Cutaneous T cell lymphoma: the helping hand of dendritic cells. *Ann N Y Acad Sci* 941:1–11.

Britten CM, Janetzki S, van der Burg SH, Gouttefangeas C, Hoos A (2008). Toward the harmonization of immune monitoring in clinical trials: quo vadis? *Cancer Immunol Immunother* 57(3): 285-288.

Brown JA, Dorfman DM, Ma FR, Sullivan EL, Munoz O, Wood CR, et al. (2003). Blockade of programmed death-1 ligands on dendritic cells enhances T cell activation and cytokine production. *J Immunol* 170(3): 1257-1266.

Bunn Jr PA, Ihde DC, Foon KA, et al. (1986). The role of recombinant interferon alfa-2a in the therapy of cutaneous T-cell lymphomas. *Cancer* 57:1689–95.

Di Renzo M, Rubegni P, De Aloe G, et al. (1997). Extracorporeal photochemotherapy restores Th1/Th2 imbalance in patients with early stage cutaneous T-cell lymphoma. *Immunology* 92:99–103.

Dalle S, Thieblemont C, Thomas L, Dumontet C (2008). Monoclonal antibodies in clinical oncology. *Anticancer Agents Med Chem* 8(5): 523-532.

Deschoolmeester V, Baay M, Van Marck E, Weyler J, Vermeulen P, Lardon F, et al. (2010). Tumor infiltrating lymphocytes: an intriguing player in the survival of colorectal cancer patients. *BMC Immunol* 11: 19.

Diez M, Pollan M, Enriquez JM, Dominguez P, Santana A, Tobaruela E, et al. (1998). Histopathologic prognostic score in colorectal adenocarcinomas. *Anticancer Res* 18(1B): 689-694.

Disis ML (2010). Immune regulation of cancer. *J Clin Oncol* 28(29): 4531-4538.

Dong H, Strome SE, Salomao DR, Tamura H, Hirano F, Flies DB, et al. (2002). Tumor-associated B7-H1 promotes T-cell apoptosis: a potential mechanism of immune evasion. *Nat*

Med 8(8): 793-800.

Duvic M, Hymes K, Heald P, Breneman D, Martin AG, Myskowski P, et al. (2001). Bexarotene is effective and safe for treatment of refractory advanced-stage cutaneous T-cell lymphoma: multinational phase II-III trial results. *J Clin Oncol* 19(9): 2456-2471.

Francisco LM, Sage PT, Sharpe AH (2010). The PD-1 pathway in tolerance and autoimmunity. *Immunol Rev* 236: 219-242.

Galon J, Costes A, Sanchez-Cabo F, Kirilovsky A, Mlecnik B, Lagorce-Pages C, et al. (2006). Type, density, and location of immune cells within human colorectal tumors predict clinical outcome. *Science* 313(5795): 1960-1964.

Gao, Q., X.Y. Wang, S.J. Qiu, *et al.* (2009). Overexpression of PD-L1 significantly associates with tumor aggressiveness and postoperative recurrence in human hepatocellular carcinoma. *Clin Cancer Res.* 15:971-979.

Garon, E.B., A. Balmanoukian, O. Hamid*, et al.* (2013). Preliminary clinical safety and activity of MK-3475 monotherapy for the treatment of previously treated patients with non-small cell lung cancer (NSCLC). *J Thor Oncol*. 8 Suppl 2:S364-365.

Girardi M, Schechner J, Glusac E, et al. (2002). Transimmunization and the evolution of extracorporeal photochemotherapy. *Transfus Apher Sci* 26:181–90.

Girardi M, Berger C, Hanlon D, et al. (2002) Efficient tu.mor antigen loading of dendritic antigen presenting cells by transimmunization. *Technol Cancer Res Treat* 1:65–9.

Hamanishi, J., M. Mandai, M. Iwasaki, *et al.* (2007). Programmed cell death 1 ligand 1 and tumor-infiltrating CD8+ T lymphocytes are prognostic factors of human ovarian cancer. *Proc Natl Acad Sci USA*. 104:3360-3365.

Hamid, O., S.D. Chasalow, Z. Tsuchihashi, *et al*. (2009). Association of baseline and on-study tumor biopsy markers with clinical activity in patients (pts) with advanced melanoma treated with ipilimumab. *J Clin Oncol*. 27:A9008.

Hamid O, Robert C, Daud A, Hodi FS, Hwu WJ, Kefford R, et al. (2013). Safety and tumor responses with lambrolizumab (anti-PD-1) in melanoma. *N Engl J Med* 369(2): 134-144.

Heald P, Rook A, Perez M, et al (1992). Treatment of erythrodermic cutaneous T-cell lymphoma with extracorporeal photochemotherapy. *J Am Acad Dermatol* 27:427–33.

Heald PW, Perez MI, McKiernan G, et al. (1990). Extracorporeal photochemotherapy for CTCL. *Prog Clin Biol Res* 337: 443–7.

Zic J, Arzubiaga C, Salhany KE, et al (1992). Extracorporeal pho- topheresis for the treatment of cutaneous T-cell lymphoma. *J Am Acad Dermatol* 27:729–36.

Hillen F, Baeten CI, van de Winkel A, Creytens D, van der Schaft DW, Winnepenninckx V, et al. (2008). Leukocyte infiltration and tumor cell plasticity are parameters of aggressiveness in primary cutaneous melanoma. *Cancer Immunol Immunother* 57(1): 97-106.

Hiraoka N (2010). Tumor-infiltrating lymphocytes and hepatocellular carcinoma: molecular biology. *Int J Clin Oncol* 15(6): 544-551.

Hodi FS, Dranoff G (2010). The biologic importance of tumor-infiltrating lymphocytes. *J Cutan*

Pathol 37 Suppl 1: 48-53.

Hodi FS, O'Day SJ, McDermott DF, Weber RW, Sosman JA, Haanen JB, et al. (2010). Improved survival with ipilimumab in patients with metastatic melanoma. *N Engl J Med* 363(8): 711-723.

Hodi FS, Ribas A, Daud A, Hamid O, Robert C, Kefford R, Hwu W, Gangadhar TC, Joshua AM, Hersey P, Weber J, Dronca R, Gammage L, Hille D, Xue D, Kang SP, Chun P, Ebbinghaus S, Perrone A, Wolchok JD. Evaluation of immune-related response criteria (irRC) in patients with advanced melanoma treated with the anti-PD-1 monoclonal antibody MK-3475. *J Clin Oncol*. 2014;32:5s (suppl; abstr 3006).

Hoppe RT, Medeiros LJ, Warnke RA, Wood GS (1995). CD8-positive tumor-infiltrating lymphocytes influence the long-term survival of patients with mycosis fungoides. *J Am Acad Dermatol* 32(3): 448-453.

Horwitz SM, Olsen EA, Duvic M, Porcu P, Kim YH (2008). Review of the treatment of mycosis fungoides and sezary syndrome: a stage-based approach. *J Natl Compr Canc Netw* 6(4): 436-442.

Houot R, Levy R (2009). T-cell modulation combined with intratumoral CpG cures lymphoma in a mouse model without the need for chemotherapy. *Blood* 113(15): 3546-3552.

Investigator's Brochure. (2014). MK-3475. Merck Sharp & Dohme Corp., a Subsidiary of Merck & Co.,Inc.

Jiang SB, Dietz SB, Kim M, et al. (1999). Extracorporeal photochemotherapy for cutaneous T-cell lymphoma: a 9.7-year experience. *Photodermatol Photoimmunol Photomed* 15:161–5.

Kantekure K, Yang Y, Raghunath P, Schaffer A, Woetmann A, Zhang Q, et al. (2012). Expression patterns of the immunosuppressive proteins PD-1/CD279 and PD-L1/CD274 at different stages of cutaneous T-cell lymphoma/mycosis fungoides. *Am J Dermatopathol* 34(1): 126-128.

Kantoff PW, Higano CS, Shore ND, Berger ER, Small EJ, Penson DF, et al. (2010). Sipuleucel-T immunotherapy for castration-resistant prostate cancer. *N Engl J Med* 363(5): 411-422.

Kaplan EH, Rosen ST, Norris DB, et al. (1990). Phase II study of recombinant human interferon gamma for treatment of cutaneous T-cell lymphoma. *J Natl Cancer Inst* 82: 208–12.

Kim Y, Girardi M, Duvic M, et al. (2004). TLR9 agonist immunomodulator treatment of cutaneous T-cell lymphoma (CTCL) with CPG7909. *Blood* 104:743.

Kim EJ, Hess S, Richardson SK, Newton S, Showe LC, Benoit BM, et al. (2005). Immunopathogenesis and therapy of cutaneous T cell lymphoma. *J Clin Invest* 115(4): 798-812.

Kim YH, Gratzinger D, Harrison C, Brody JD, Czerwinski DK, Ai WZ, et al. (2012). In situ vaccination against mycosis fungoides by intratumoral injection of a TLR9 agonist combined with radiation: a phase 1/2 study. *Blood* 119(2): 355-363.

Klemke CD, Dippel E, Assaf C, et al. (1999). Follicular mycosis fungoides. *Br J Dermatol* 141:137–40.

Kloor M (2009). Lymphocyte infiltration and prognosis in colorectal cancer. *Lancet Oncol* 10(9):

840-841.

Koyama T, Chen H (2008). Proper inference from Simon's two-stage designs. *Stat Med* 27(16): 3145-3154.

Lee HE, Chae SW, Lee YJ, Kim MA, Lee HS, Lee BL, et al. (2008). Prognostic implications of type and density of tumour-infiltrating lymphocytes in gastric cancer. *Br J Cancer* 99(10): 1704-1711.

Leffers N, Gooden MJ, de Jong RA, Hoogeboom BN, ten Hoor KA, Hollema H, et al. (2009). Prognostic significance of tumor-infiltrating T-lymphocytes in primary and metastatic lesions of advanced stage ovarian cancer. *Cancer Immunol Immunother* 58(3): 449-459.

Liotta F, Gacci M, Frosali F, Querci V, Vittori G, Lapini A, et al. (2011). Frequency of regulatory T cells in peripheral blood and in tumour-infiltrating lymphocytes correlates with poor prognosis in renal cell carcinoma. *BJU Int* 107(9): 1500-1506.

Mellman I, Coukos G, Dranoff G (2011). Cancer immunotherapy comes of age. *Nature* 480(7378): 480-489.

Miracco C, Rubegni P, De Aloe G, et al. (1997). Extracorporeal photochemotherapy induces apoptosis of infiltrating lymphoid cells in patients with mycosis fungoides in early stages. A quantitative histological study. *Br J Dermatol* 137: 549–57.

NCCN, National Comprehensive Cancer Network (2014). Clinical practice guidelines in oncology: non-Hodgkin's lymphoma v2.2014. NCCN web site. www.nccn.org. Published March 27, 2014. Accessed March 28, 2014.

Nishimura H, Honjo T, Minato N (2000). Facilitation of beta selection and modification of positive selection in the thymus of PD-1-deficient mice. *J Exp Med* 191(5): 891-898.

Nobili C, Degrate L, Caprotti R, Franciosi C, Leone BE, Trezzi R, et al. (2008). Prolonged survival of a patient affected by pancreatic adenocarcinoma with massive lymphocyte and dendritic cell infiltration after interleukin-2 immunotherapy. Report of a case. *Tumori* 94(3): 426-430.

Nomi, T., M. Sho, T. Akahori, *et al.* (2007). Clinical significance and therapeutic potential of the programmed death-1 ligand/programmed death-1 pathway in human pancreatic cancer. *Clin Cancer Res.* 13:2151-2157.

Olsen EA, Bunn PA. (1995). Interferon in the treatment of cutaneous T-cell lymphoma. *Hematol Oncol Clin North Am* 9: 1089–107.

Olsen E, Duvic M, Frankel A, Kim Y, Martin A, Vonderheid E, et al. (2001). Pivotal phase III trial of two dose levels of denileukin diftitox for the treatment of cutaneous T-cell lymphoma. *J Clin Oncol* 19(2): 376-388.

Olsen EA, Kim YH, Kuzel TM, Pacheco TR, Foss FM, Parker S, et al. (2007). Phase IIb multicenter trial of vorinostat in patients with persistent, progressive, or treatment refractory cutaneous T-cell lymphoma. *J Clin Oncol* 25(21): 3109-3115.

Olsen EA, Whittaker S, Kim YH, Duvic M, Prince HM, Lessin SR, et al. (2011). Clinical end points and response criteria in mycosis fungoides and Sezary syndrome: a consensus statement of the International Society for Cutaneous Lymphomas, the United States Cutaneous Lymphoma

Consortium, and the Cutaneous Lymphoma Task Force of the European Organisation for Research and Treatment of Cancer. *J Clin Oncol* 29(18): 2598-2607.

Owsianowski M, Garbe C, Ramaker J, et al. (1996). Therapeutic experiences with extracorporeal photopheresis. Technical procedure, follow-up and clinical outcome in 31 skin diseases. *Hautarzt* 47:114–23.

Pardoll, D.M. (2012). The blockade of immune checkpoints in cancer immunotherapy. *Nat Rev Cancer*. 12:252-264.

Prinz B, Behrens W, Holzle E, et al. (1995). Extracorporeal photoph- eresis for the treatment of cutaneous T-cell lymphoma – the Dusseldorf and Munich experience. *Arch Dermatol Res* 287:621–6.

Ribas, A. (2012). Tumor immunotherapy directed at PD-1. *N Engl J Med*. 366:2517-2519.

Robert C, Thomas L, Bondarenko I, O'Day S, M DJ, Garbe C, et al. (2011). Ipilimumab plus dacarbazine for previously untreated metastatic melanoma. *N Engl J Med* 364(26): 2517-2526.

Rook AH, Zaki MH, Wysocka M, et al. (2001). The role for interleukin- 12 therapy of cutaneous T cell lymphoma. *Ann N Y Acad Sci* 941:177–84.

Rook AH, Junkins-Hopkins JM, McGinnis KS, et al. (2002). Cytokines and other biologic agents as immunotherapeutics for cutane- ous T-cell lymphoma. *Adv Dermatol* 18:29–43.

Samimi S, Benoit B, Evans K, Wherry EJ, Showe L, Wysocka M, et al. (2010). Increased programmed death-1 expression on $CD4^+$ T cells in cutaneous T-cell lymphoma: implications for immune suppression. *Arch Dermatol* 146(12): 1382-1388.

Sharpe AH, Freeman GJ (2002). The B7-CD28 superfamily. *Nat Rev Immunol* 2(2): 116-126.

Sznol M (2012). Advances in the treatment of metastatic melanoma: new immunomodulatory agents. *Semin Oncol* 39(2): 192-203.

Talmadge JE, Donkor M, Scholar E (2007). Inflammatory cell infiltration of tumors: Jekyll or Hyde. *Cancer Metastasis Rev* 26(3-4): 373-400.

Thompson RH, Dong H, Lohse CM, Leibovich BC, Blute ML, Cheville JC, et al. (2007). PD-1 is expressed by tumor-infiltrating immune cells and is associated with poor outcome for patients with renal cell carcinoma. *Clin Cancer Res* 13(6): 1757-1761.

Topalian SL, Weiner GJ, Pardoll DM (2011). Cancer immunotherapy comes of age. *J Clin Oncol* 29(36): 4828-4836.

Topalian SL, Hodi FS, Brahmer JR et al. (2012). Safety, activity, and immune correlates of anti-PD-1 antibody in cancer. *N Engl J Med* 366(26)**:** 2443-54.

Usubutun A, Ayhan A, Uygur MC, Ozen H, Toklu C, Ruacan S (1998). Prognostic factors in renal cell carcinoma. *J Exp Clin Cancer Res* 17(1): 77-81.

van der Burg SH, Kalos M, Gouttefangeas C, Janetzki S, Ottensmeier C, Welters MJ, et al. (2011). Harmonization of immune biomarker assays for clinical studies. *Sci Transl Med* 3(108): 108ps144.

Whittaker SJ, Demierre MF, Kim EJ, Rook AH, Lerner A, Duvic M, et al. (2010). Final results from a multicenter, international, pivotal study of romidepsin in refractory cutaneous T-cell lymphoma. *J Clin Oncol* 28(29): 4485-4491.

Wu PA, Kim YH, Lavori PW, Hoppe RT, Stockerl-Goldstein KE (2009). A meta-analysis of patients receiving allogeneic or autologous hematopoietic stem cell transplant in mycosis fungoides and Sezary syndrome. *Biol Blood Marrow Transplant* 15(8): 982-990.

Zou, W., and L. Chen. (2008). Inhibitory B7-family molecules in the tumour microenvironment. *Nat Rev Immunol*. 8:467-477.

APPENDIX A PERFORMANCE STATUS CRITERIA

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

APPENDIX B CTEP MULTICENTER GUIDELINES

If an institution wishes to collaborate with other participating institutions in performing a CTEP sponsored research protocol that does **not** use the CTSU/OPEN rostered model, then the following guidelines 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 AEs to ensure safety of the patients.
- The Protocol Chair will be responsible for the review of and timely submission of data for study analysis.

Responsibilities of the Coordinating Center

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

IRB approval documents, NCI Drug Accountability Record forms, patient registration lists, response assessments scans, x-rays, etc. available for the audit.

Inclusion of Multicenter Guidelines in the Protocol

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

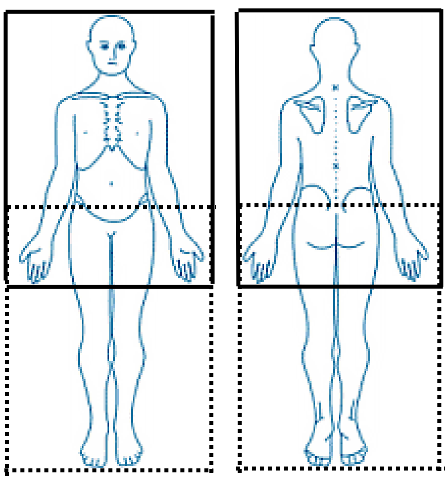
Agent Ordering

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

APPENDIX C STANDARDIZED MEDICAL PHOTOGRAPHY

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 D BIOASSAY TEMPLATES

Biomarker name (Lead PI and Site)	Assay & Method/Template/SOP & Hypothesis	Tissue/Body Fluid Tested & Timing of Assay	Prioritization & Funding
Tissue PD-L1 Expression Holbrook Kohrt, MD PhD (Stanford University) Testing to be performed by Qualtek, a Merck CRO.	• Chromogenic (Single-Color) IHC for PD-L1 • Hypothesis: A direct correlation exists between tissue PD-L1 expression and clinical efficacy endpoints.	Tissue: • Tumor Biopsy including skin and/or lymph node Timing: • Prior to treatment, following the 1st cycle, then following every 3rd cycle thereafter, at the time of response and EOT.	1 Merck
TIL gene expression profile Holbrook Kohrt, MD PhD (Stanford University) Testing to be performed by Merck, Palo Alto.	• Nanostring platform will be used to profile mRNA expression in archival material, to assess expression of approximately 650 genes • Merck SOP • Hypothesis: A Th1 inflammatory T cell gene expression profile directly correlates with clinical efficacy endpoints.	Tissue: • Tumor Biopsy including skin and/or lymph node Timing: • Prior to treatment, following the 1st cycle, then following every 3rd cycle thereafter, at the time of response and EOT.	2 Merck
Cytokine & chemokine analysis Holbrook Kohrt, MD PhD Testing to be performed at Stanford University	• Luminex multiplexed ELISA-based platform • Stanford Human Immune Monitoring Core SOP • Hypothesis: A Th1 cytokine profile directly correlates with clinical efficacy endpoints.	Tissue: • Blood Timing: • Prior to treatment, following the 1st cycle, then following every 3rd cycle thereafter, at the time of response and EOT.	3 Merck
Spatial association of PD-1$^+$ TILs and PD-L1$^+$ cells Holbrook Kohrt, MD PhD (Stanford University) Testing performed by Merck, Palo Alto	• Multiparametric immunohistochemical assays will be performed to include PD-1 and PD-L1. • Merck SOP	Tissue: • Tumor Biopsy including skin and/or lymph node Timing: • Prior to treatment, following the 1st cycle, then following every 3rd cycle thereafter, at the time of response and EOT.	4 Merck

Biomarker name (Lead PI and Site)	Assay & Method/Template/SOP & Hypothesis	Tissue/Body Fluid Tested & Timing of Assay	Prioritization & Funding
T cell immunophenotype Holbrook Kohrt, MD PhD Testing to be performed at Standord University	• CyTOF and multiparametric flow cytometry • Stanford Human Immune Monitoring Core SOP	Tissue: • PBMC Timing: • Prior to treatment, following the 1st cycle, then following every 3rd cycle thereafter, at the time of response and EOT.	5 Merck
T cell receptor sequencing Holbrook Kohrt, MD PhD (Stanford University)	• Next-generation sequencing of T cell-specific CDR rearrangements will be performed to analyze the breadth of the CD4 and CD8 repertoire • Stanford Human Immune Monitoring Core SOP	Tissue: • PBMC Timing: • Prior to treatment, at the end of cycle 1, following every 3rd cycle, at end of treatment, at follow-up visits	6 Merck ***Note:*** This is an exploratory assay that will be performed should funding become available.

TIL, tumor-infiltrating lymphocyte

APPENDIX E MODIFIED SEVERITY-WEIGHTED ASSESSMENT TOOL (MSWAT)

The mSWAT is an objective, quantitative, severity- weighted method to assess the extent of MF 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

MF 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

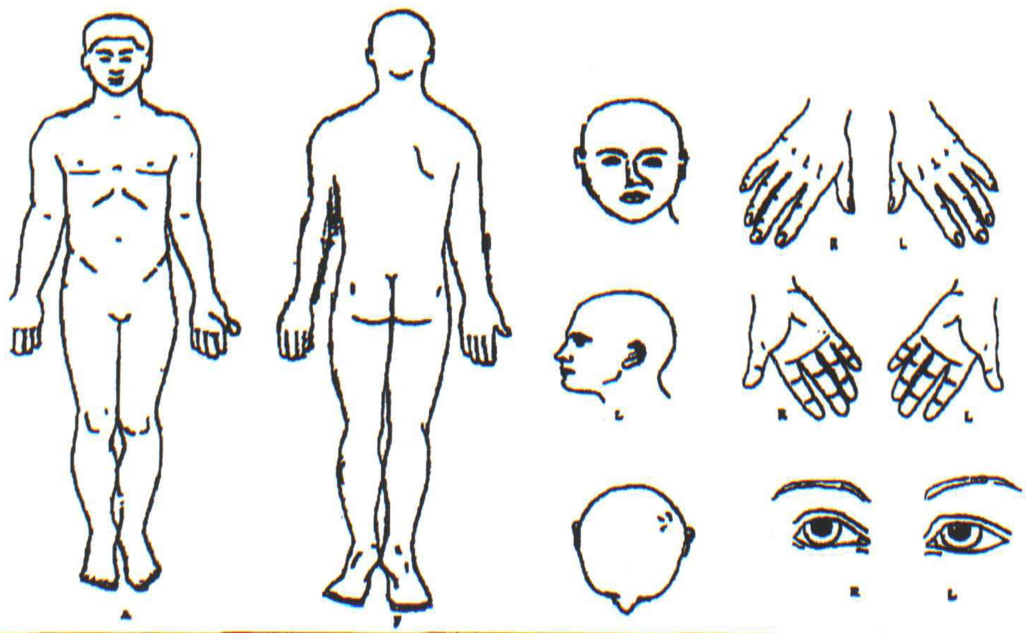
+ Sum of %TBSA from all body regions affected by **plaques x** severity weighted factor of 2

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

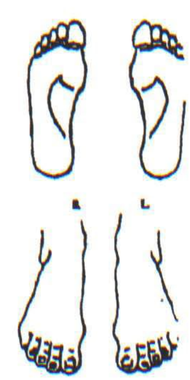
= TOTAL SWAT: (maximum score = 400)

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 = ________

APPENDIX F TNMB CLASSIFICATION AND STAGING OF MYCOSIS FUNGOIDES AND SÉZARY SYNDROME

National Comprehensive Cancer Network®

NCCN Guidelines™ Version 2.2011
Mycosis Fungoides/Sezary Syndrome

NCCN Guidelines Index
NHL Table of Contents
Discussion

TNMB[f]		TNMB Classification and Staging of Mycosis Fungoides and Sezary Syndrome[g]
Skin	T1	Limited patches,[h] papules and/or plaques[i] covering < 10 % of the skin surface
	T2	Patches,[h] papules and/or plaques[i] covering ≥ 10 % of the skin surface
	T3	One or more tumors[j] (≥ 1 cm in diameter)
	T4	Confluence of erythema ≥ 80 % body surface area
Node	N0	No clinically abnormal peripheral lymph nodes; biopsy not required[k]
	N1	Clinically abnormal peripheral lymph nodes; histopathology Dutch Gr 1 or NCI LN 0-2
	N2	Clinically abnormal peripheral lymph nodes; histopathology Dutch Gr 2 or NCI LN 3
	N3	Clinically abnormal peripheral lymph nodes; histopathology Dutch Gr 3-4 or NCI LN 4
	NX	Clinically abnormal peripheral lymph nodes; no histologic confirmation
Visceral	M0	No visceral organ involvement
	M1	Visceral involvement (must have pathology confirmation[l] and organ involved should be specified)
Blood	B0	Absence of significant blood involvement: ≤ 5 % of peripheral blood lymphocytes are atypical (Sezary) cells[m]
	B1	Low blood tumor burden: > 5 % of peripheral blood lymphocytes are atypical (Sezary) cells but does not meet the criteria of B2
	B2	High blood tumor burden: ≥ 1000/mcL Sezary cells[l]

[f] Olsen E, Vonderheid E, Pimpinelli N, et al. Blood 2007;110:1713-1722.

[g] Sezary syndrome (B2) is defined as a clonal rearrangement of the TCR in the blood (clones should be relevant to clone in the skin) and either 1000/mcL or increased CD4 or CD3 cells with CD4/CD8 of 10 or more or increase in CD4 cells with an abnormal phenotype (40% CD4/CD7 or 30% CD4/CD26).

[h] Patch = Any size skin lesion without significant elevation or induration. Presence/absence of hypo- or hyperpigmentation, scale, crusting and/or poikiloderma should be noted.

[i] Plaque = Any size skin lesion that is elevated or indurated. Presence or absence of scale, crusting and/or poikiloderma should be noted. Histological features such as folliculotropism or large cell transformation (≥ 25 % large cells), CD30+ or CD30- and clinical features such as ulceration are important to document.

[j] Tumor = at least one > 1 cm diameter solid or nodular lesion with evidence of depth and/or vertical growth. Note total number of lesions, total volume of lesions, largest size lesion, and region of body involved. Also note if histological evidence of large cell transformation has occurred. Phenotyping for CD30 is encouraged.

[k] Abnormal peripheral lymph node(s) = any palpable peripheral node that on physical examination is firm, irregular, clustered, fixed or ≥ 1.5 cm in diameter. Node groups examined on physical examination = cervical, supraclavicular, epitrochlear, axillary and inguinal. Central nodes, which are not generally amenable to pathologic assessment, are not currently considered in the nodal classification unless used to establish N3 histopathologically.

[l] Spleen and liver may be diagnosed by imaging criteria.

[m] Sezary cells are defined as lymphocytes with hyperconvoluted cerebriform nuclei. If Sezary cells are not able to be used to determine tumor burden for B2, then one of the following modified ISCL criteria along with a positive clonal rearrangement of the TCR may be used instead. (1) expanded CD4+ or CD3+ cells with CD4/CD8 ratio ≥ 10, (2) expanded CD4+ cells with abnormal immunophenotype including loss of CD7 or CD26.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

MFSS-2

NCCN practice guidelines for Non-Hodgkin's Lymphomas Guidelines 2.2011. National Comprehensive Cancer Network. www.nccn.org. Accessed: March 24, 2011.