Mayo Clinic Cancer Center

A Phase II, Open-label, Single-Arm trial Using KEYTRUDA (pembrolizumab) as Initial Systemic Therapy in the Treatment of Advanced Mycosis Fungoides

Sponsor/Principal Investigator: [redacted]

Co-Investigators: [redacted]

Statistician: [redacted]

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Drug Company Supplied: Pembrolizumab

√Study contributor(s) not responsible for patient care

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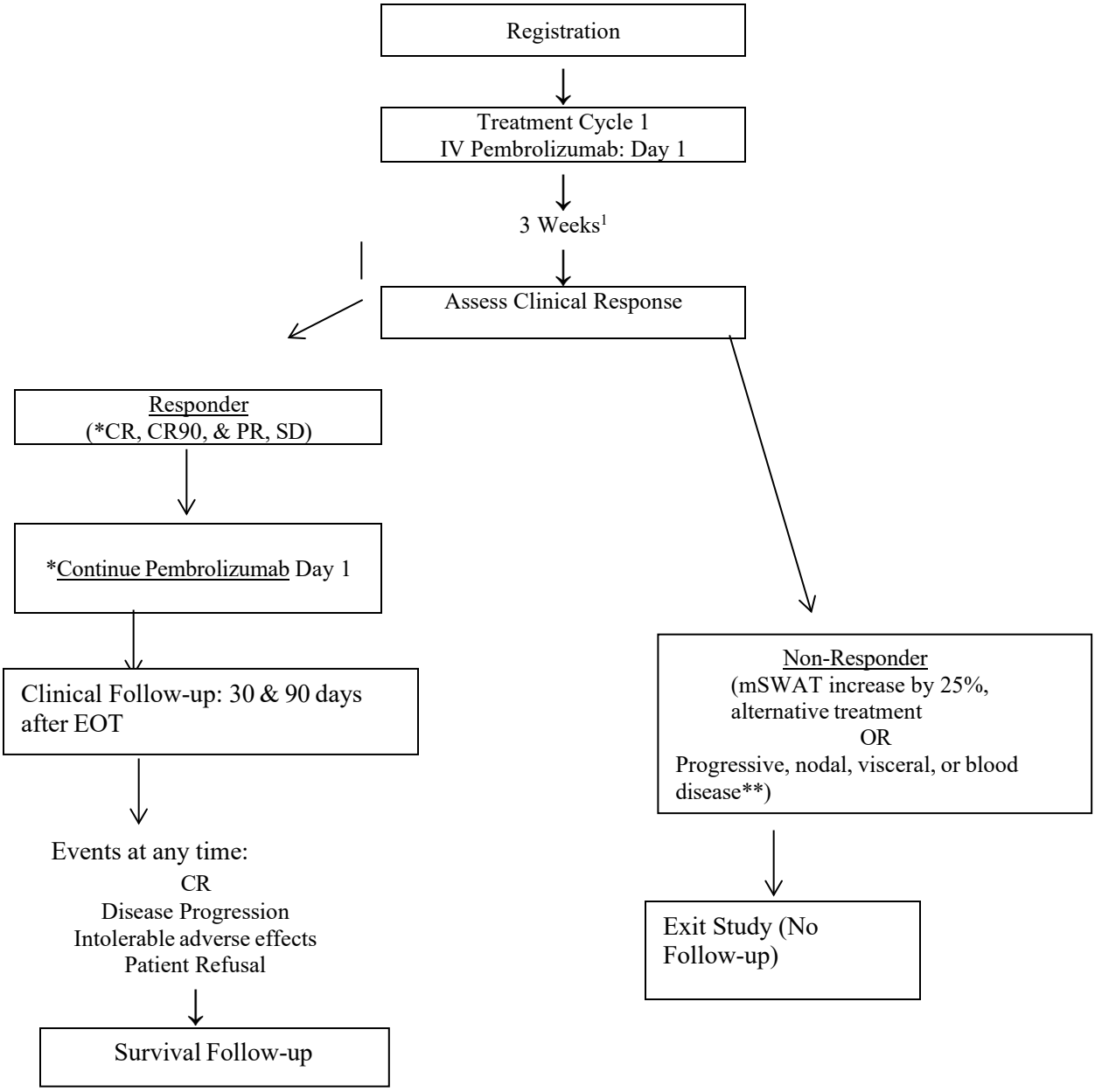
Protocol Resources

Questions:	Contact Name:
Patient eligibility*, test schedule, treatment delays/interruptions/adjustments, dose modifications, adverse events, forms completion and submission	[redacted]
Forms completion and submission	
Protocol document, consent form, regulatory issues	
Non-paraffin biospecimens	
Serious Adverse Event Reporting	

*No waivers of eligibility allowed

Table of Contents

Schema



Cycle = 21 days

Window for all visits = ± 3 days

[1]Patients who go off protocol treatment during Cycle 1 for reasons other than PD or CR, will continue to Survival follow-up.

*The maximum duration of therapy is 24 months. If the patient achieves CR during this period, further , pembrolizumab cycles will be discontinued and the patient will proceed to survival followup.

**Non-responders include patients with progressive, nodal, visceral, or blood disease as assessed by repeat staging after Cycle 4 and at the end of treatment visit.

Generic name: pembrolizumab, MK-3475 Brand name(s): Keytruda™ Mayo Abbreviation: MK3475 Availability: Mayo Clinic Pharmacy

1.0 Background

Mycosis fungoides (MF) is an incurable extranodal, T-cell non-Hodgkin lymphoma that accounts for 80% of all primary cutaneous lymphomas. Affected individuals initially develop pruritic patches initially in sun protected anatomic sites. Most presentations are indolent but 20% progress in a stepwise fashion from patch disease to raised plaque and nodular skin lesions with variable degrees of lymph node, blood, and visceral organ involvement (Wilcox, 2017).

Patients who fail skin directed therapies receive systemic therapy with bexarotene, interferon, extracorporeal photopheresis, deacetylase inhibitors, methotrexate, pralatexate, gemcitabine, pegylated liposomal doxorubicin, bortezomib, and denileukin diftitox (Devata et al., 2016; Trautinger, 2017). These agents may be combined after the failure of monotherapy or rotated therapeutically if toxicity or efficacy limits use.

Patients with advanced stage disease have a 5-year survival of 17-40%, and ultimately die of lymphoma and infectious complications associated with disease progression after 2-3 lines of systemic therapy.

Pembrolizumab, an immune checkpoint inhibitor of PD-1, has been recently reported to have clinical activity in MF previously treated with one systemic agent and also in patients with Sézary syndrome (SS) (Khodadoust et al., 2016).

Pembrolizumab is presently FDA approved for the treatment of unresectable or metastatic melanoma, as first-line treatment of patients with metastatic non-small cell lung cancer (NSCLC) with high PD-L1 expression, recurrent or metastatic head and neck squamous cell carcinoma (HNSCC) with disease progression, and in refractory classical Hodgkin lymphoma (cHL) who have relapsed after three or more prior lines of therapy.

1.1 Pharmaceutical and Therapeutic Background

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

The PD-1 receptor-ligand interaction is a major pathway hijacked by tumors to suppress immune control. The normal function of PD-1, expressed on the cell surface of activated T-cells under healthy conditions, is to down-modulate unwanted or excessive immune responses, including autoimmune reactions. PD-1 (encoded by the gene Pdcd1) is an Ig superfamily member related to CD28 and CTLA-4 which has been shown to negatively regulate antigen receptor signaling upon engagement of its ligands (PD-L1 and/or PD-L2).

The structure of murine PD-1 has been resolved. PD-1 and family members are type I transmembrane glycoproteins containing an Ig Variable-type (V-type) domain responsible for ligand binding and a cytoplasmic tail which is responsible for the binding of signaling molecules. The cytoplasmic tail of PD-1 contains 2 tyrosine-based signaling motifs, an immunoreceptor tyrosine-based inhibition motif (ITIM) and an immunoreceptor tyrosinebased switch motif (ITSM).

Following T-cell stimulation, PD-1 recruits the tyrosine phosphatases SHP-1 and SHP-2 to the ITSM motif within its cytoplasmic tail, leading to the dephosphorylation of effector molecules such as CD3ζ, PKCθ and ZAP70 which are involved in the CD3 T-cell signaling cascade. The mechanism by which PD-1 down modulates T-cell responses is similar to, but distinct from that of CTLA-4 as both molecules regulate an overlapping set of signaling proteins. PD-1 was shown to be expressed on activated lymphocytes including peripheral CD4+ and CD8+ T-cells, B-cells, T regs and Natural Killer cells. Expression has also been shown during thymic development on CD4-CD8- (double negative) T-cells as well as subsets of macrophages and dendritic cells. The ligands for PD-1 (PD-L1 and PD-L2) are constitutively expressed or can be induced in a variety of cell types, including non-hematopoietic tissues as well as in various tumors. Both ligands are type I transmembrane receptors containing both IgV- and IgC-like domains in the extracellular region and contain short cytoplasmic regions with no known signaling motifs.

Binding of either PD-1 ligand to PD-1 inhibits T-cell activation triggered through the T-cell receptor. PD-L1 is expressed at low levels on various non-hematopoietic tissues, most notably on vascular endothelium, whereas PD-L2 protein is only detectably expressed on antigen-presenting cells found in lymphoid tissue or chronic inflammatory environments.

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

Pembrolizumab is a potent and highly selective humanized monoclonal antibody (mAb) of the IgG4/kappa isotype designed to directly block the interaction between PD-1 and its ligands, PD-L1 and PD-L2. KeytrudaTM (pembrolizumab) has recently been approved in the United Stated for the treatment of patients with unresectable or metastatic melanoma and disease progression following ipilumumab and, if BRAF V600 mutation positive, a BRAF inhibitor.

1.2 Rationale

1.21 Rationale for the Trial and Selected Subject Population

There is no evidence-based algorithm for the treatment of MF, but therapies have been conventionally divided into skin-directed therapy and systemic therapy. Patients with early stage disease (patch/plaque disease without nodal or visceral involvement) are treated with topical corticosteroids, topical cytostatic agents, topical retinoids, superficial radiotherapy, and phototherapy. These modalities are rarely remittive but may temporarily clear involved skin and improve pruritus.

For progressive early stage MF, high risk early-stage MF (thick plaques or follicular involvement), advanced-stage MF (presence of tumors, nodal involvement, erythroderma, visceral involvement), or SS, systemic therapy is the standard of care. Biologic response modifying agents such as IFN-alpha, bexarotene, or HDAC inhibitors are considered first line, as systemic multi-agent chemotherapy provides no survival advantage.

However, the optimal treatment sequence is unknown and there is no clear evidence that sequential or step-wise combination systemic therapy is more efficacious or contributes to long-term survival or cure. Early/initial use of pembrolizumab in the treatment of advanced MF is postulated to have a unique therapeutic synergy, whereby the direct reduction of tumor burden by pembrolizumab further enhances the baseline endogenous host anti-tumor response that is subsequently amplified with additional scheduled treatments. This rationale supports the use of pembrolizumab as initial first line systemic therapy, as the endogenous anti-tumor host response is more robust earlier in the disease course and is thus more likely to produce clinical clearance of lesional skin.

1.22 Rationale for Dose Selection, Regimen, and Modification

Multiple prior studies have been conducted to evaluate the safety and clinical activity of single agent pembrolizumab. The dose escalation portion of this trial evaluated three dose levels, 1 mg/kg, 3 mg/kg, and 10 mg/kg, administered every 2 weeks (Q2W) in subjects with advanced solid tumors. All three dose levels were well tolerated and no dose limiting toxicities were observed.. Recent data from other clinical studies within the pembrolizumab program has shown that a lower dose of pembrolizumab and a less frequent schedule may be sufficient for target engagement and clinical activity.

PK data analysis of pembrolizumab administered Q2W and Q3W showed slow systemic clearance, limited volume of distribution, and a long half-life (refer to IB). Pharmacodynamic data (IL-2 release assay) suggested that peripheral target engagement is durable (>21 days). This early PK and pharmacodynamics data provides scientific rationale for testing a Q2W and Q3W dosing schedule.

A population pharmacokinetic analysis has been performed using serum concentration time data from 476 patients. Within the resulting population PK model, clearance and volume parameters of pembrolizumab were found to be dependent on body weight. The relationship between clearance and body weight, with an allometric exponent of 0.59, is within the range observed for other antibodies and would support both body weight normalized dosing or a fixed dose across all body weights. pembrolizumab has been found to have a wide

therapeutic range based on the melanoma indication. The differences in exposure for a 200 mg fixed dose regimen relative to a 2 mg/kg Q3W body weight based regimen are anticipated to remain well within the established exposure margins of 0.5 – 5.0 for pembrolizumab in the melanoma indication. The exposure margins are based on the notion of similar efficacy and safety in melanoma at 10 mg/kg Q3W vs. the proposed dose regimen of 2 mg/kg Q3W (i.e. 5-fold higher dose and exposure). The population PK evaluation revealed that there was no significant impact of tumor burden on exposure. In addition, exposure was similar between the NSCLC and melanoma indications. Therefore, there are no anticipated changes in exposure between different indication settings.

The rationale for further exploration of 2 mg/kg and comparable doses of pembrolizumab in solid tumors is based on: 1) similar efficacy and safety of pembrolizumab when dosed at either 2 mg/kg or 10 mg/kg Q3W in melanoma patients, 2) the flat exposure-response relationships of pembrolizumab for both efficacy and safety in the dose ranges of 2 mg/kg Q3W to 10 mg/kg Q3W, 3) the lack of effect of tumor burden or indication on distribution behavior of pembrolizumab (as assessed by the population PK model) and 4) the assumption that the dynamics of pembrolizumab target engagement will not vary meaningfully with tumor type.

The choice of the 200 mg Q3W as an appropriate dose for the switch to fixed dosing is based on simulations performed using the population PK model of pembrolizumab showing that the fixed dose of 200 mg every 3 weeks will provide exposures that 1) are optimally consistent with those obtained with the 2 mg/kg dose every 3 weeks, 2) will maintain individual patient exposures in the exposure range established in melanoma as associated with maximal efficacy response and 3) will maintain individual patients exposure in the exposure range established in melanoma that are well tolerated and safe.

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

1.23 Rationale for Endpoints

The proposed primary and secondary efficacy endpoints conform to recommended consensus definitions of the International Society for Cutaneous Lymphomas (ISCL), the United States Cutaneous Lymphoma Consortium (USCLC), and the Cutaneous Lymphoma Task Force of the European Organization for Research and Treatment of Cancer (EORTC) and will permit a relative comparison to other published work using these definitions.

The Primary efficacy endpoint will be the overall cutaneous response rate at week 27 by the Modified Skin Severity Assessment (mSWAT) score.

The mSWAT is calculated using body surface area (BSA) of each MF lesion (palm plus fingers of the patient ≈ 1% BSA) in each of 12 areas of the body, multiplying the sum of the BSA of each lesion type by a weighting factor (patch=1, plaque=2, and tumor =4) and generating a sum of the subtotals of each lesion subtype.

Hypothesis: Biopsies in MF reveal an abnormal accumulation of clonal CD4+ helper T-cells initially in the epidermis and later in the dermis and subcutis. There is also a characteristic anti-tumor host response of infiltrating CD8+/TIA-1+ cytotoxic T-lymphocytes in lesional skin. Histologically, the intensity of this infiltrate diminishes with disease progression from patch, plaque to tumor disease and has been postulated to reflect the suppressive effects of TH2 cytokine production and CD25+ TReg phenotypic induction by the malignant CD4+ T-cells (Phillips et al., 2016; Rozati et al., 2016).

Pembrolizumab is a humanized monoclonal IgG4 antibody directed against the receptor PD-1 (programmed cell death-1) expressed on the surface of activated T cells (Nguyen et al., 2017; Warren et al., 2017).

We hypothesize PD-1 inhibition will preserve and enhance the anti-tumor responses in MF through effector T cell activation and TReg inhibition. (Wang et al., 2018)
We have also conducted a preliminary analysis of PD-1/CD279 expression in a representative group of patch, plaque, and tumor MF biopsy specimens and found expression in nearly all cases; this finding further supports the hypothesis that pembrolizumab may have value in the management of all stages of MF.

1.3 Correlative Research

1.31 This study proposes to characterize the histologic features of the anti-tumor host response before and after treatment with pembrolizumab. Prior to the initial dose of pembrolizumab, a 6 mm punch skin biopsy of the most common presenting morphology (i.e. patch, plaque, or tumor) will be obtained for each study participant; at the second cycle (week 6), an additional 6 mm punch skin biopsy of the same morphologic type will be obtained. Immunohistochemistry will then be used to assess the levels of CD4, CD8, PD-1/CD279, and PD-L1 expression before and after treatment with pembrolizumab.

2.0 Goals

2.1 Primary Goal

To evaluate the antitumor activity of pembrolizumab in patients with advanced MF as initial systemic therapy.

2.2 Secondary Goals

2.21 To evaluate safety of pembrolizumab in this patient population.

2.22 To evaluate response rates of pembrolizumab in this patient population.

2.23 To determine the progression free survival, duration of response, time to response and overall survival of pembrolizumab in this patient population .

2.3 Correlative Research

To characterize the histologic features of the anti-tumor response in patients with advanced MF before and after treatment with pembrolizumab.

3.0 Registration Patient Eligibility

3.1 Registration – Inclusion Criteria

3.11 Age ≥ 18 years.

3.12 Histological confirmation of one of the following:

- Stage IIB-IV Mycosis Fungoides not previously treated with systemic therapy
- Stage IB/IIA Mycosis Fungoides with mSWAT ≥ 20 with high risk morphologic features defined as thick plaque disease and/or follicular involvement who have failed one form of skin-directed therapy.
- Sézary Syndrome patients not previously treated with systemic therapy.

3.13 Measurable disease based on mSWAT and/or RECIST 1.1 (see Section 11.0).

3.14 Be willing to provide tissue from a newly obtained core or excisional biopsy of a tumor lesion. Note: Newly-obtained is defined as a specimen obtained up to 6 weeks (42 days) prior to registration. Exception: Subjects for whom newly-obtained samples cannot be provided (e.g. inaccessible or subject safety concern) may submit an archived specimen only upon agreement from the Sponsor.

3.15 ECOG Performance Status (PS)0 or 1 (Appendix I).

3.16 The following laboratory values obtained ≤28 days prior to registration.

- Absolute neutrophil count (ANC) ≥1,500 /mcL
- Platelet count ≥100,000/mcL
- Hemoglobin ≥9.0 g/dL or ≥5.6 mmol/L without transfusion or EPO dependency (within 7 days of assessment)
- Serum total bilirubin ≤ 1.5 X ULN OR Direct bilirubin ≤ ULN for subjects with total bilirubin levels > 1.5 ULN
- Aspartate transaminase (AST) and Alanine transaminase (ALT) ≤ 2.5 X ULN OR ≤ 5 X ULN for subjects with liver metastases
- Albumin >2.5 mg/dL
- Serum creatinine <=1.5 x upper limit of normal (ULN) OR Measured or calculated creatinine clearance >=60 ml/min for subject with creatinine levels >1.5 x institutional ULN.
- PT/INR and PTT ≤1.5 X ULN OR if patient is receiving anticoagulant therapy and PT/INR or PTT is within therapeutic range of intended use of coagulants

3.17 Negative urine or serum pregnancy test done ≤ 28 days prior to registration and ≤ 72 hours prior to receiving the first dose of study medication, for women of childbearing potential only.

3.18 Female subjects of childbearing potential must be willing to use an adequate method of contraception for the course of the study through 120 days after the last dose of the study medication.

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

3.19 Male subjects of childbearing potential must agree to use an adequate method of contraception for the course of the study through 120 days after the last dose of the study medication.

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

3.20a Provide written informed consent.

3.20b Willing to return to enrolling institution for follow-up (during the Active Monitoring Phase of the study).

3.20c Willing to provide tissue samples for correlative research purposes (see Section 17*).*

3.2 Registration – Exclusion Criteria

3.21 Any of the following because this study involves:
an agent that has known genotoxic, mutagenic and teratogenic effects:

- Pregnant women
- Nursing women
- Men or women of childbearing potential who are unwilling to employ adequate contraception

3.22 Is currently participating and receiving study therapy or have participated in a study of an investigational agent and received study therapy or used an investigational device <= 4 weeks prior to registration.

3.23 Has a diagnosis of immunodeficiency or is receiving systemic steroid therapy or any other form of immunosuppressive therapy <= 7 days prior to registration.

3.24 Has a known history of active TB (Bacillus Tuberculosis).

3.25 Hypersensitivity to pembrolizumab or any of its excipients.

3.26 Has had a prior anti-cancer monoclonal antibody (mAb) <= 4 weeks prior to registration or who has not recovered (i.e., ≤ Grade 1 or at baseline) from adverse events due to agents administered more than 4 weeks earlier.

3.27 Has had prior chemotherapy, targeted small molecule therapy, or radiation therapy <= 2 weeks prior to registration or who has not recovered (i.e., ≤ Grade 1 or at baseline) from adverse events due to a previously administered agent.

- Note: Subjects with ≤ Grade 2 neuropathy are an exception to this criterion and may qualify for the study.
- Note: If subject received major surgery, they must have recovered adequately from the toxicity and/or complications from the intervention prior to starting therapy.

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

3.29 Has known active central nervous system (CNS) metastases and/or carcinomatous meningitis. Exceptions:subjects with previously treated brain metastases may participate provided they are stable (without evidence of progression by imaging <= 4 weeks prior to registration 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 registration. This exception does not include carcinomatous meningitis which is excluded regardless of clinical stability.

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

3.31 Has a history of non-infectious pneumonitis that required steroids or has current pneumonitis.

3.32 Has an active infection requiring systemic therapy.

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

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

3.35 Is pregnant or breastfeeding, or expecting to conceive or father children within the projected duration of the trial, starting with the screening visit through 120 days after the last dose of trial treatment.

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

3.37 Has a known history of Human Immunodeficiency Virus (HIV) (HIV 1/2 antibodies).

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

3.39 Has received a live vaccine <= 30 days prior to registration.

Note: Seasonal influenza vaccines for injection are generally inactivated flu vaccines and are allowed; however intranasal influenza vaccines (e.g., Flu-Mist®) are live attenuated vaccines, and are not allowed.

3.39a Sezary syndrome patients with high blood burden requiring immediate cytoreduction.

4.0 Test Schedule

4.1 Test schedule for Mycosis Fungoides

Tests and procedures	*≤ 28 days prior to registration*	Active Monitoring Phase*			Follow-up*	
		prior to treatment Day 1, Cycles 2-4[7]	*prior to treatment Day 1, Cycles 5 and beyond*[7]	*End of treatment (21 days after last dose)*	*Clinical Follow-up (30 days after EOT)*	*Clinical Follow-up visit (90 days after EOT)*
Main study Informed Consent	X					
Inclusion/Exclusion Criteria	X					
Demographics, medical history	X				X	
Ht and Wt**	X	X		X		
Vital signs Blood pressure Pulse Temperature	X	X	X	X		
Prior and Concomitant Medication Review	X				X	
Post-study Anticancer therapy status					X	X
Adverse event assessment	X	X	X	X	X	X
Physical Exam	X	X	X	X		
Dermatology Exam[R]	X	X	X	X	X	X
Standardized Clinical Photography[R]	X	X	X	X	X	X
Skin Biopsy	X	X[R]				
ECOG PS	X			X		X
mSWAT	X	X	X	X	X	X
Pregnancy test[1]	X					
Hematology group CBC with Diff	X	X	X	X	X	
Chemistry group[2]	X	X	X	X	X	
Urinalysis	X					
PT/INR and PTT	X					
T3, FT4, and TSH[3]	X	X	X	X	X	
Tumor Imaging[4]	X		X	X		
T and B-cell Quantitation[5]	X		X[R]	X[R]		
Mandatory Research tissue specimens (see Section 17.0) [6,R],	X	X				

Cycle = 21 days

***Window for all visits = ± 3 days**

1. For women of childbearing potential only. Must be done ≤ 72hrs prior to treatment and if clinically

indicated.

2. Chemistry panel: Albumin, total bilirubin, direct bilirubin, calcium, carbon dioxide (bicarbonate), chloride, creatinine, glucose, alkaline phosphatase , potassium, total protein, sodium, aspartate amino transferase (AST) (SGOT), alanine amino transferase (ALT) (SGPT), urea nitrogen (BUN)
3. Repeat every other cycle starting on Day 1, Cycle 2.
4. Whole body CT/PET. 1 Week after the end of Cycle 4 during course of treatment and then, at the End of Treatment Visit.
5. 1 Week after the end of Cycle 4 during course of treatment and then, at the End of Treatment Visit.
6. Tissue specimens (Skin Biopsy) will be collected and submitted after registration and Cycle 2, Day 15 only. (See Section 17.0)
7. Cycle 1 day 1 prior to treatment is recorded as baseline, Prior to treatment Day 1 Cycles 2-4 is recorded in the data base as end of cycles 1-3, Prior to treatment Day 1 Cycles 5 and beyond is recorded in the database as end of cycle 4 and beyond.

**Ht not required after registration.

R Research funded (see Section 19.0)

4.2 Survival Follow-up

	Survival Follow-up				
	q. 3 months until PD	At PD	After PD q. 3 months	Death	New Primary
Survival Follow-up	X	X	X	X	At each occurrence

1. If a patient is still alive 2.5 year after registration, no further follow-up is required.

5.0 Stratification Factors OR Grouping Factor:

None.

6.0 Registration Procedures

6.1 Registration:

6.11 Registering a patient

To register a patient, access the Mayo Clinic Cancer Center (MCCC) web page and enter the registration/randomization application. The registration/ randomization application is available 24 hours a day, 7 days a week. Back up and/or system support contact information is available on the website. If unable to access the website, call the MCCC Registration Office at [redacted] between the hours of 8 a.m. and 4:30 p.m. Central Time (Monday through Friday).

The instructions for the registration/randomization application are available on the MCCC web page [redacted] and detail the process for completing and confirming patient registration. Prior to initiation of protocol treatment, this process must be completed in its entirety and an MCCC subject ID number must be available as noted in the instructions. It is the responsibility of the individual registering the patient to confirm the process has been successfully completed prior to release of the study agent. Patient registration via the registration/randomization application can be confirmed in any of the following ways:

- Contact the MCCC Registration Office [redacted] If the patient was fully registered, the MCCC Registration Office staff can access the information from the centralized database and confirm the registration.
- Refer to “Instructions for Remote Registration” in section “Finding/Displaying Information about A Registered Subject.”

6.2 Verification of materials

Prior to accepting the registration, registration/randomization application will verify the following:

- IRB approval at the registering institution
- Patient eligibility
- Existence of a signed consent form
- Existence of a signed authorization for use and disclosure of protected health information

6.3 Documentation of IRB approval

Documentation of IRB approval must be on file in the Registration Office before an investigator may register any patients.

In addition to submitting initial IRB approval documents, ongoing IRB approval documentation must be on file (no less than annually) at the Registration Office (fax: [redacted]). If the necessary documentation is not submitted in advance of attempting patient registration, the registration will not be accepted and the patient may not be enrolled in the protocol until the situation is resolved.

When the study has been permanently closed to patient enrollment, submission of annual IRB approvals to the Registration Office is no longer necessary.

6.4 Correlative Research

A mandatory correlative research component is part of this study, the patient will be automatically registered onto this component (see Sections 17.1*)*.

6.5 Treatment on protocol

Treatment on this protocol must commence at Mayo Clinic Florida under the supervision of a dermatologist and medical oncologist.

6.6 Treatment start

Treatment cannot begin prior to registration and must begin ≤28 days after registration.

6.7 Pretreatment

Pretreatment tests/procedures (see Section 4.0) must be completed within the guidelines specified on the test schedule.

6.8 a Baseline symptoms

All required baseline symptoms (see Section 10.6) must be documented and graded.

6.8b Study drug

Study drug is available on site.

6.8c Study Conduct

The clinical trial will be conducted in compliance with regulations (21 CFR 312, 50, and 56), guidelines for Good Clinical Practice (ICH Guidance E6), and in accordance with general ethical principles outlined in the Declaration of Helsinki; informed consent will be obtained from all participating patients; the protocol and any amendments will be subject to approval by the designated IRB prior to implementation, in accordance with 21 CFR 56.103(a); and subject records will be stored in a secure location and subject confidentiality will be maintained. The investigator will be thoroughly familiar with the appropriate use of the study drug as described in the protocol and Investigator's Brochure. Essential clinical documents will be maintained to demonstrate the validity of the study and the integrity of the data collected. Master files should be established at the beginning of the study, maintained for the duration of the study and retained according to the appropriate regulations.

7.0 Protocol Treatment

7.1 Treatment Schedule

Agent	Dose	Route	Day	Cycles
Pembrolizumab	200 mg	IV	Day 1	q3 weeks until disease progression, intolerable toxicity, or CR for a maximum duration of 24 months

Protocol treatment should be administered on Day 1 of each cycle after all procedures/assessments have been completed as detailed on the Test Schedule (Section 4.0). Trial treatment may be administered up to 3 days before or after the scheduled Day 1 of each cycle due to administrative reasons.

All trial treatments will be administered on an outpatient basis.

Pembrolizumab 200 mg will be administered as a 30 minute IV infusion every 3 weeks. Sites should make every effort to target infusion timing to be as close to 30 minutes as possible. However, given the variability of infusion pumps from site to site, a window of -5 minutes and +10 minutes is permitted (i.e., infusion time is 30 minutes: -5 min/+10 min).

The Pharmacy Manual contains specific instructions for the preparation of the pembrolizumab infusion fluid and administration of infusion solution.

8.0 Dosage Modification Based on Adverse Events

Strictly follow the modifications in this table for the first **two** cycles, until individual treatment tolerance can be ascertained. Thereafter, these modifications should be regarded as guidelines to produce mild-to-moderate, but not debilitating, side effects. If multiple adverse events are seen, administer dose based on greatest reduction required for any single adverse event observed. Reductions or increases apply to treatment given in the preceding cycle and are based on adverse events observed since the prior dose.

→ ALERT: ADR reporting may be required for some adverse events (See Section 10.0) ←

→ → Use the NCI Common Terminology Criteria for Adverse Events (CTCAE) current version 5.0* unless otherwise specified ← ←

* Located at [redacted]

8.1 Dose Modifications Based on Adverse Events

CTCAE System/Organ/Class (SOC)	ADVERSE EVENT	AGENT	ACTION**
Cardiac disorders	Myocarditis	pembrolizumab	Hold if grade 1 or 2. Administer corticosteroids as clinically indicated. Discontinue if Grade 3 or 4. Pembrolizumab should be permanently discontinued if AE does not resolve within 12 weeks of last dose or corticosteroids cannot be reduced to ≤ 10 mg prednisone or equivalent per day within 12 weeks and continue to survival follow-up.
Endocrine disorders	Hyperthyroidism	pembrolizumab	Continue if grade 2. Treat with non-selective beta-blockers (e.g. propranolol) or thionamides as appropriate. [1]Hold or discontinue if grade 3 or 4. If discontinue, continue to survival follow-up. Pembrolizumab should be permanently discontinued if AE does not resolve within 12 weeks of last dose and continue to survival follow-up.
	Hypophysitis	pembrolizumab	Hold if grade 2. Administer corticosteroids and initiate hormonal replacements as clinically indicated. [1]Hold or discontinue if grade 3 or 4. Pembrolizumab should be permanently discontinued if AE does not resolve within 12 weeks of last dose or corticosteroids cannot be reduced to ≤ 10 mg prednisone or equivalent per day within 12 weeks and continue to survival follow-up.
	Hypothyroidism	pembrolizumab	Continue if grade 2-4. Initiate thyroid replacement hormones (e.g. levothyroxine or liothyroinine) per standard of care. Pembrolizumab should be permanently discontinued if AE does not resolve within 12 weeks of last dose and continue to survival follow-up.

CTCAE System/Organ/Class (SOC)	ADVERSE EVENT	AGENT	ACTION**
Gastrointestinal disorders	Diarrhea or Colitis	pembrolizumab	Hold if grade 2-3. Discontinue if Grade 4 or if AE does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less prednisone or equivalent per day within 12 weeks and continue to survival follow-up.
Immune System disorders	All other immune-related AEs	pembrolizumab	Hold if intolerable/persistent grade 2. Administer corticosteroids as clinically indicated. Hold if grade 3 AE, unless the event is Gullian-Barre Syndrome and/or Encephalitis, then, pembrolizumab should be discontinued. If AE does not resolve within 12 weeks of last dose or corticosteroids cannot be reduced to ≤ 10 mg prednisone or equivalent per day within 12 weeks and continue to survival follow-up. Pembrolizumab should be discontinued if grade 4 AE or recurrent grade 3.
Investigations	AST / ALT elevation or Increased Bilirubin	pembrolizumab	Hold if grade 2. Administer corticosteroids (initial dose of 1-2mg/kg prednisone or equivalent) followed by taper. Discontinue if Grade 3 or 4 or if AE does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less prednisone or equivalent per day within 12 weeks and continue to survival follow-up.
Metabolism and nutrition disorders	Type 1 diabetes mellitus (T1DM) or Hyperglycemia	pembrolizumab	Hold if Newly onset T1DM or Grade 3 or 4 hyperglycemia associated with evidence of β-cell failure. Initiate insulin replacement therapy for subjects with T1DM. Administer anti-hyperglycemic in subjects with hyperglycemia. Discontinue if AE does not resolve within 12 weeks of last dose and continue to survival follow-up.

CTCAE System/Organ/Class (SOC)	ADVERSE EVENT	AGENT	ACTION**
Renal and urinary disorders	Nephritis	pembrolizumab	Hold if grade 2. Administer corticosteroids (prednisone 1-2mg/kg or equivalent) followed by taper. Discontinue if grade 3 or 4 or if AE does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less prednisone or equivalent per day within 12 weeks and continue to survival follow-up.
Respiratory, thoracic and mediastinal disorders	Pneumonitis	pembrolizumab	Hold if grade 2. Administer corticosteroids (initial dose of 1-2mg/kg prednisone or equivalent) followed by taper. Discontinue if recurrent grade 2, if grade 3 or 4, or if AE does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less prednisone or equivalent per day within 12 weeks and continue to survival follow-up.
Skin and subcutaneous tissue disorders	Stevens-Johnson syndrome/ toxic epidermal necrolysis	pembrolizumab	Hold if grade 3. Discontinue if grade 4. Discontinue if AE does not resolve within 12 weeks of last dose and continue to survival follow-up.

** Use the following to describe actions in the Action column:

- **Omit** = The current dose(s) for the specified drug(s) during a cycle is skipped. The patient does not make up the omitted dose(s) at a later time.
- **Hold/Delay** = The current dose(s) of all drugs during a cycle is delayed. The patient does make up the delayed dose(s) when the patient meets the protocol criteria to restart drugs.
- **Discontinue** = The specified drug(s) are totally stopped.

NOTES:

- [1]Withhold or permanently discontinue pembrolizumab is at the discretion of the investigator or treating physician.
- For subjects with Grade 3 or 4 immune-related endocrinopathy where withhold of pembrolizumab is required, pembrolizumab may be resumed when AE resolves to ≤ Grade 2 and is controlled with hormonal replacement therapy or achieved metabolic control (in case of T1DM)

9.0 Ancillary Treatment/Supportive Care

9.1 Full supportive care

Patients should receive full supportive care while on this study. This includes blood product support, antibiotic treatment, and treatment of other newly diagnosed or concurrent medical conditions. All blood products and concomitant medications such as antidiarrheals, analgesics, and/or antiemetics received from the first day of study treatment administration until 30 days after the final dose will be recorded in the medical records.

9.2 Blood products and growth factors

Blood products and growth factors should be utilized as clinically warranted and following institutional policies and recommendations. The use of growth factors should follow published guidelines of the Journal of Clinical Oncology, Volume 33, No 28 (October 1), 2015: pp. 3199-3212 (WBC growth factors) AND Journal of Clinical Oncology, Volume 28, No 33 (November 20), 2010: pp. 4955-5010 (darbepoetin/epoetin).

9.3 Antiemetics

Antiemetics may be used at the discretion of the attending physician.

9.4 Diarrhea

Diarrhea could be managed conservatively with loperamide. The recommended dose of loperamide is 4 mg at first onset, followed by 2 mg every 2-4 hours until diarrhea free (maximum 16 mg/day).

In the event of Grade 3 or 4 diarrhea, the following supportive measures are allowed: hydration, octreotide, and antidiarrheals.

If diarrhea is severe (requiring intravenous rehydration) and/or associated with fever or severe neutropenia (Grade 3 or 4), broad-spectrum antibiotics must be prescribed. Patients with severe diarrhea or any diarrhea associated with severe nausea or vomiting **should be hospitalized** for intravenous hydration and correction of electrolyte imbalances.

9.5 Concomitant Medications/Vaccinations (allowed & prohibited)

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

9.51 Acceptable Concomitant Medications

All treatments that the investigator considers necessary for a subject’s welfare may be administered at the discretion of the investigator in keeping with the community standards of medical care. All concomitant medication will be recorded in the medical record 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 in the medical record. All concomitant medications received within 28 days before the first dose of trial treatment and 30 days after the last dose of trial treatment should be recorded. Concomitant medications

administered after 30 days after the last dose of trial treatment should be recorded for SAEs and ECIs.

9.52 Prohibited Concomitant Medications

Subjects are prohibited from receiving the following therapies during the Screening and Treatment Phase (including retreatment of patients who develop new skin disease after achieving a complete cutaneous response) of this trial:

- Antineoplastic systemic chemotherapy or biological therapy
- Immunotherapy not specified in this protocol
- Chemotherapy not specified in this protocol
- Investigational agents other than pembrolizumab
- Radiation therapy
    - Note: Radiation therapy to a symptomatic solitary lesion or to the brain may be allowed at the investigator's discretion.
- 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, varicella/zoster, yellow fever, rabies, BCG, and typhoid vaccine.
- Systemic glucocorticoids for any purpose other than to modulate symptoms from an event of clinical interest of suspected immunologic etiology. The use of physiologic doses of corticosteroids may be approved after consultation with the sponsor.

Subjects 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. Subjects 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.

9.6a Toxicity management for immune-related AEs associated with pembrolizumab

AEs associated with pembrolizumab exposure may represent an immunologic etiology. These immune-related AEs (irAEs) may occur shortly after the first dose or several months after the last dose of pembrolizumab treatment and may affect more than one body system simultaneously. Therefore, early recognition and initiation of treatment is critical to reduce complications. Based on existing clinical trial data, most irAEs were reversible and could be managed with interruptions of pembrolizumab, administration of corticosteroids and/or other supportive care. For suspected irAEs, ensure adequate evaluation to confirm etiology or exclude other causes. Additional procedures or tests such as bronchoscopy, endoscopy, skin biopsy may be included as part of the evaluation. Based on the severity of irAEs, withhold or permanently discontinue pembrolizumab and administer corticosteroids. Dose modification and toxicity management guidelines for AEs associated with pembrolizumab are provided in the table in Section 8.1.

9.6b Toxicity management of infusion-reactions related to pembrolizumab

Pembrolizumab may cause severe or life threatening infusion-reactions including severe hypersensitivity or anaphylaxis. Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion. Dose modification and toxicity management guidelines on pembrolizumab associated infusion reaction are provided in the table below.

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 therapy or infusion interruption but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for ≤24 hrs	**Stop Infusion.** Additional appropriate medical therapy may include but is not limited to: IV fluids Antihistamines NSAIDs Acetaminophen Narcotics Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator. If symptoms resolve within 1 hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (e.g. from 100 mL/hr to 50 mL/hr). Otherwise dosing will be held until symptoms resolve and the subject should be premedicated for the next scheduled dose. **Subjects who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further study drug treatment**	Subject may be premedicated 1.5h (± 30 minutes) prior to infusion of pembrolizumab with: Diphenhydramine 50 mg po (or equivalent dose of antihistamine). Acetaminophen 500-1000 mg po (or equivalent dose of analgesic).
Grades 3 or 4 Grade 3: Prolonged (i.e., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (e.g., renal impairment, pulmonary infiltrates) Grade 4: Life-threatening; pressor or ventilatory support indicated	**Stop Infusion.** Additional appropriate medical therapy may include but is not limited to: Epinephrine** IV fluids Antihistamines NSAIDs Acetaminophen Narcotics Oxygen Pressors Corticosteroids 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. **In cases of anaphylaxis, epinephrine should be used immediately. **Subject is permanently discontinued from further study drug treatment.**	No subsequent dosing

Appropriate resuscitation equipment should be available at the bedside and a physician readily available during the period of drug administration.
For further information, please refer to the Common Terminology Criteria for Adverse Events v5.0 (CTCAE) at [redacted]

Other allowed dose interruption for pembrolizumab

Pembrolizumab may be interrupted for situations other than treatment-related AEs such as medical / surgical events or logistical reasons not related to study therapy. Subjects should be placed back on study therapy within 3 weeks of the scheduled interruption, unless otherwise discussed with the Sponsor. The reason for interruption should be documented in the patient's study record.

9.6c Diet

Subjects should maintain a normal diet unless modifications are required to manage an AE such as diarrhea, nausea or vomiting.

9.6d Contraception

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

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

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

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

OR

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

OR

(3) has a congenital or acquired condition that prevents childbearing. Female and male subjects of reproductive potential must agree to avoid becoming pregnant or impregnating a partner, respectively, while receiving study drug and for 120 days after the last dose of study drug by complying with one of the following:

(1) practice abstinence† from heterosexual activity;

OR

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

Acceptable methods of contraception are‡:
Single method (one of the following is acceptable):

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

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

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

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

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

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

9.6e Use in Pregnancy

If a patient inadvertently becomes pregnant while on treatment with pembrolizumab, the patient will immediately be removed from the study. The site will contact the patient at least monthly and document the patient's status until the pregnancy has been completed or terminated. The outcome of the pregnancy will be reported to Mayo Clinic and to Merck without delay and within 24 hours to Mayo Clinic and within 2 working days to Merck if the outcome is a serious adverse experience (e.g., death, abortion, congenital anomaly, or other disabling or life-threatening complication to the mother or newborn).

The study investigator will make every effort to obtain permission to follow the outcome of the pregnancy and report the condition of the fetus or newborn. If a male subject impregnates his female partner the study personnel at the site must be informed immediately and the pregnancy reported to Mayo Clinic and to Merck and followed as described above.

9.6f Use in Nursing Women

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. Specific additional information follows for individual agents used in this trial.

9.6f1 Pembrolizumab

It is unknown whether pembrolizumab is excreted in human milk.

10.0 Adverse Event (AE) Monitoring and Reporting

The site principal investigator is responsible for reporting any/all serious adverse events to the sponsor as described within the protocol, regardless of attribution to study agent or treatment procedure.

The sponsor/sponsor-investigator is responsible for notifying FDA and all participating investigators in a written safety report of any of the following:

- Any suspected adverse reaction that is both serious and unexpected.
- Any findings from laboratory animal or *in vitro* testing that suggest a significant risk for human subjects, including reports of mutagenicity, teratogenicity, or carcinogenicity.
- Any findings from epidemiological studies, pooled analysis of multiple studies, or clinical studies, whether or not conducted under an IND and whether or not conducted by the sponsor, that suggest a significant risk in humans exposed to the drug
- Any clinically important increase in the rate of a serious suspected adverse reaction over the rate stated in the protocol or Investigator's Brochure (IB).

Summary of SAE Reporting for this study
(please read entire section for specific instructions):

WHO:	WHAT form:	WHERE to send:
Mayo Clinic Sites	Pregnancy Reporting [redacted]	Mayo Sites – attach to MCCC Electronic SAE Reporting Form [redacted] Will automatically be sent to [redacted]
Mayo Clinic Sites	Mayo Clinic Cancer Center SAE Reporting Form [redacted] AND attach MedWatch 3500A: [redacted]	Will automatically be sent to [redacted]
Mayo Clinic Sites	Merck Global Safety Form Merck AE Fax Form	Submit to Merck Global Safety Attn: Worldwide Product Safety; FAX [redacted]

Definitions

Adverse Event
Any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related.

Suspected Adverse Reaction
Any adverse event for which there is a reasonable possibility that the drug caused the adverse event.

Expedited Reporting
Events reported to sponsor within 24 hours, 5 days or 10 days of study team becoming aware of the event.

Routine Reporting
Events reported to sponsor via case report forms

Events of Interest
Events that would not typically be considered to meet the criteria for expedited reporting, but that for a specific protocol are being reported via expedited means in order to facilitate the review of safety data (may be requested by the FDA or the sponsor).

10.1 Adverse Event Characteristics

CTCAE term (AE description) and grade: The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for AE reporting. 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:
[redacted]

a. Identify the grade and severity of the event using the CTCAE version 5.0.
b. Determine whether the event is expected or unexpected (see Section 10.2).
c. Determine if the adverse event is related to the study intervention (agent, treatment or procedure) (see Section 10.3).
d. Determine whether the event must be reported as an expedited report. If yes, determine the timeframe/mechanism (see Section 10.4).
e. Determine if other reporting is required (see Section 10.5).
f. Note: All AEs reported via expedited mechanisms must also be reported via the routine data reporting mechanisms defined by the protocol (see Sections 10.6 and 18.0).

NOTE: A severe AE is NOT the same as a serious AE, which is defined in Section 10.4.

10.2 Expected vs. Unexpected Events

Expected events - are those described within the Section 15.0 of the protocol, the study specific consent form, package insert (if applicable), and/or the investigator brochure, (if an investigator brochure is not required, otherwise described in the general investigational plan).

Unexpected adverse events or suspected adverse reactions are those not listed in Section 15.0 of the protocol, the study specific consent form, package insert (if applicable), or in the investigator brochure (or are not listed at the specificity or severity that has been observed); if an investigator brochure is not required or available, is not consistent with the risk information described in the general investigational plan.

Unexpected also refers to adverse events or suspected adverse reactions that are mentioned in the investigator brochure as occurring with a class of drugs but have not been observed with the drug under investigation.
An investigational agent/intervention might exacerbate the expected AEs associated with a commercial agent. Therefore, if an expected AE (for the commercial agent) occurs with a higher degree of severity or specificity, expedited reporting is required.
NOTE: *The consent form may contain study specific information at the discretion of the Principal Investigator; it is possible that this information may NOT be included in the protocol or the investigator brochure. Refer to protocol or IB for reporting needs.

10.3 Attribution to agent(s) or procedure

When assessing whether an adverse event (AE) is related to a medical agent(s) medical or procedure, the following attribution categories are utilized:

Definite - The AE *is clearly related* to the agent(s)/procedure.
Probable - The AE *is likely related* to the agent(s)/procedure.
Possible - The AE *may be related* to the agent(s)/procedure.
Unlikely - The AE *is doubtfully related* to the agent(s)/procedure.
Unrelated - The AE *is clearly NOT related* to the agent(s)/procedure.

10.31 **EXPECTED Serious Adverse Events: Protocol Specific Exceptions to Expedited Reporting**

For this protocol only, the following Adverse Events/Grades are expected to occur within this population and do not require Expedited Reporting. These events must still be reported via Routine Reporting (see Section 10.6).*

*Report any clinically important increase in the rate of a serious suspected adverse reaction (at your study site) over that which is listed in the protocol or investigator brochure as an expedited event.

*Report an expected event that is greater in severity or specificity than expected as an expedited event.

*Specific protocol exceptions to expedited reporting should be reported expeditiously by investigators **ONLY** if they exceed the expected grade of the event.

CTCAE System Organ Class (SOC)	**Adverse event/ Symptoms**	**CTCAE Grade at which the event will not be reported via expedited mechanisms[1]**
Blood and lymphatic system disorders	Anemia	≤Grade 4
Gastrointestinal disorders	Vomiting	≤Grade 3
	Nausea	≤Grade 3
	Diarrhea	≤Grade 3
General disorders and administrations site conditions	Fatigue	≤Grade 3
	Malaise	≤Grade 3
Investigations	Neutrophil count decreased	≤Grade 4
	White blood cell count decreased	≤Grade 4
	Lymphocyte count decreased	≤Grade 4
	Platelet count decreased	≤Grade 4

CTCAE System Organ Class (SOC)	Adverse event/ Symptoms	CTCAE Grade at which the event will not be reported via expedited mechanisms[1]
Skin and subcutaneous tissue disorders	Rash (acneiform or maculopapular)	≤Grade 4

[1] These exceptions only apply if the adverse event does not result in hospitalization. If the adverse event results in hospitalization, then the standard expedited adverse events reporting requirements must be followed.

The following hospitalizations are not considered to be SAEs because there is no "adverse event" (*i.e.*, there is no untoward medical occurrence) associated with the hospitalization:

- Hospitalizations for respite care
- Planned hospitalizations required by the protocol
- Hospitalization planned before informed consent (where the condition requiring the hospitalization has not changed post study drug administration)
- Hospitalization for elective procedures unrelated to the current disease and/or treatment on this trial
- Hospitalization for administration of study drug or insertion of access for administration of study drug
- Hospitalization for routine maintenance of a device (*e.g.*, battery replacement) that was in place before study entry
- Hospitalization, or other serious outcomes for signs and symptoms of progression of the cancer.

10.4 Expedited Reporting Requirements for IND Agents

10.41 Late Phase 2 and Phase 3 Studies: Expedited Reporting Requirements for Adverse Events that Occur on Studies under an IND 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 **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 sponsor 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	7 Calendar Days			24-Hour 3 Calendar Days

Not resulting in Hospitalization ≥24 hrs	Not required	7 Calendar Days	

Expedited AE reporting timelines are defined as:

- "24-Hour; 3 Calendar Days" - The AE must initially be reported within 24 hours of learning of the AE, followed by a complete expedited report within 3 calendar days of the initial 24-hour report.
- "7 Calendar Days" - A complete expedited report on the AE must be submitted within 7 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 3 calendar days for:

- All Grade 4, and Grade 5 AEs

Expedited 7 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

NOTE: Refer to Section 10.31 for exceptions to Expedited Reporting

10.42 General reporting instructions

The Mayo IND and/or MCCC Compliance will assist the sponsor-investigator in the processing of expedited adverse events and forwarding of suspected unexpected serious adverse reactions (SUSARs) to the FDA and IRB.

Use Mayo Expedited Event Report form [redacted] for investigational agents or commercial/investigational agents on the same arm.

Submit to Merck Global Safety Attn: Worldwide Product Safety; [redacted]

Use Sponsor provided forms available in the forms packet and attach to the Mayo Expedited Event Report form.

10.43 Reporting of re-occurring SAEs

ALL SERIOUS adverse events that meet the criteria outlined in table10.41 MUST be immediately reported to the sponsor within the timeframes detailed in the corresponding table. This reporting includes, but is not limited to SAEs that re-occur again after resolution.

10.5 Other Required Reporting

10.51 Unanticipated Problems Involving Risks to Subjects or Others (UPIRTSOS)

Unanticipated Problems Involving Risks to Subjects or Others (UPIRTSOS) in

general, include any incident, experience, or outcome that meets **all** of the following criteria:

1. Unexpected (in terms of nature, severity, or frequency) given (a) the research procedures that are described in the protocol-related documents, such as the

IRB-approved research protocol and informed consent document; and (b) the characteristics of the subject population being studied;

2. Related or possibly related to participation in the research (in this guidance document, possibly related means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
3. Suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

Some unanticipated problems involve social or economic harm instead of the physical or psychological harm associated with adverse events. In other cases, unanticipated problems place subjects or others at increased *risk* of harm, but no harm occurs.

Note: If there is no language in the protocol indicating that pregnancy is not considered an adverse experience for this trial, and if the consent form does not indicate that subjects should not get pregnant/impregnate others, then any pregnancy in a subject/patient or a male patient's partner (spontaneously reported) which occurs during the study or within 120 days of completing the study should be reported as a UPIRTSO.

Mayo Clinic Cancer Center (MCCC) Institutions:

If the event meets the criteria for IRB submission as a Reportable Event/UPIRTSO, provide the appropriate documentation and use the Mayo Clinic Cancer Center Expedited Event Report form [redacted] The Mayo Clinic Compliance Unit will review and process the submission to the Mayo Clinic IRB and work with the IND Coordinator for submission to FDA.

10.52 Death

Note: A death on study requires both routine and expedited reporting regardless of causality, unless as noted below. Attribution to treatment or other cause must be provided.

Any death occurring within 30 days of the last dose, regardless of attribution to an agent/intervention under an IND requires expedited reporting within 24-hours.

Any death occurring greater than 30 days with an attribution of possible, probable, or definite to an agent/intervention under an IND requires expedited reporting within 24-hours.

Reportable categories of Death

- Death attributable to a CTCAE term.
- Death Neonatal: A disorder characterized by cessation of life during the first 28 days of life.
- Death NOS: A cessation of life that cannot be attributed to a CTCAE term associated with Grade 5.
- Sudden death NOS: A sudden (defined as instant or within one hour of the onset of symptoms) or an unobserved cessation of life that cannot be attributed to a CTCAE term associated with Grade 5.
- Death due to progressive disease that cannot be attributed to a CTCAE term associated with Grade 5 should be reported as **Grade 5 "Disease progression"** under the system organ class (SOC) of 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.

10.53 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.
- All secondary malignancies that occur following treatment with an agent under an IND will be reported. Three options are available to describe the event:
  - Leukemia secondary to oncology chemotherapy (e.g., Acute Myeloctyic 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.

10.54 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 reporting unless otherwise specified.

10.55 Pregnancy, Fetal Death, and Death Neonatal

If a female subject (or female partner of a male subject) taking investigational product becomes pregnant, the subject taking should notify the Investigator, and the pregnant female should be advised to call her healthcare provider immediately. The patient should have appropriate follow-up as deemed necessary by her physician. If the baby is born with a birth defect or anomaly, a second expedited report is required.

Prior to obtaining private information about a pregnant woman and her infant, the investigator must obtain consent from the pregnant woman and the newborn infant's parent or legal guardian before any data collection can occur. A consent form will need to be submitted to the IRB for these subjects if a pregnancy occurs. If informed consent is not obtained, no information may be collected.

In cases of fetal death, miscarriage or abortion, the mother is the patient. In cases where the child/fetus experiences a serious adverse event other than fetal death, the child/fetus is the patient.

NOTE: When submitting Mayo Expedited Adverse Event Report reports for "Pregnancy", "Pregnancy loss", or "Neonatal loss", the potential risk of exposure of the fetus to the investigational agent(s) or chemotherapy agent(s) should be documented in the "Description of Event" section. Include any available medical documentation. Include this form:

[redacted]

10.551 Pregnancy

Pregnancy should be reported in an expedited manner as **Grade 3 "Pregnancy, puerperium and perinatal conditions - Other (pregnancy)"** under the Pregnancy, puerperium and perinatal conditions SOC. Pregnancy should be followed until the outcome is known.

10.552 Fetal Death

Fetal death is defined in CTCAE as "A disorder characterized by death in utero; failure of the product of conception to show evidence of respiration, heartbeat, or definite movement of a voluntary muscle after expulsion from the uterus, without possibility of resuscitation."

Any fetal death should be reported expeditiously, as **Grade 4 "Pregnancy, puerperium and perinatal conditions - Other (pregnancy loss)"** under the Pregnancy, puerperium and perinatal conditions SOC.

10.553 Death Neonatal

Neonatal death, defined in CTCAE as "A disorder characterized by cessation of life occurring during the first 28 days of life" that is felt by the investigator to be at least possibly due to the investigational agent/intervention, should be reported expeditiously.

A neonatal death should be reported expeditiously as **Grade 4 "General disorders and administration - Other (neonatal loss)"** under the General disorders and administration SOC.

10.6 Required Routine Reporting

10.61 **Baseline and Adverse Events Evaluations**

Pretreatment symptoms/conditions to be graded at baseline and adverse events to be graded at each evaluation.
Grading is per CTCAE v5.0 **unless** alternate grading is indicated in the table below:

CTCAE SYSTEM ORGAN CLASS	Adverse event/Symptoms	Baseline	Each evaluation
Blood and lymphatic system disorders	Febrile neutropenia	X	X
Eye disorders	Retinal detachment	X	X
	Retinal vascular disorder (RVO)	X	X
General disorders and administration site conditions	Fatigue	X	X
Gastrointestinal disorders	Nausea	X	X
	Vomiting	X	X
	# of Stools	X	
	Diarrhea		X
	Constipation	X	X
Infections and infestations	Sepsis	X	X
Investigations	CPK (CK) increased	X	X
	Creatinine increased	X	X
	Neutrophil count decreased	X	X
	Platelet count decreased	X	X
Nervous system disorders	Peripheral sensory neuropathy	X	X
	Peripheral motor neuropathy	X	X
Skin and subcutaneous tissue disorders	Rash, acneiform	X	X
	Rash, maculo-papular	X	X
Vascular disorders	Hypertension	X	X

10.62 All other AEs

Submit via appropriate MCCC Case Report Forms (i.e., paper or electronic, as applicable) the following AEs experienced by a patient and not specified in Section 10.6:

10.621 Grade 2 AEs deemed *possibly, probably, or definitely* related to the study treatment or procedure.

10.622 Grade 3 and 4 AEs regardless of attribution to the study treatment or procedure.

10.623 Grade 5 AEs (Deaths)

10.6231 Any death within 30 days of the patient's last study treatment or procedure regardless of attribution to the study treatment or procedure.

10.6232 Any death more than 30 days after the patient's last study treatment or procedure that is felt to be at least possibly treatment related must also be submitted as a Grade 5 AE, with a CTCAE type and attribution assigned.

10.7 Late Occurring Adverse Events

Refer to the instructions in the Forms Packet (or electronic data entry screens, as applicable) regarding the submission of late occurring AEs following completion of the Active Monitoring Phase (i.e., compliance with Test Schedule in Section 4.0).

10.8 Additional Event Reporting Instruction (Merck)

10.81 All AEs, SAEs and other reportable safety events that occur after the consent form is signed but before treatment allocation must be reported by the investigator if the participant is receiving placebo run-in or other run-in treatment, if the event cause the participant to be excluded from the study, or is the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, or a procedure.

- All AEs from the time of treatment allocation/randomization through 30 days following cessation of study treatment must be reported by the investigator.
- All AEs meeting serious criteria, from the time of treatment allocation/randomization through 90 days following cessation of study treatment, or 30 days following cessation of study treatment if the participant initiates new anticancer therapy, whichever is earlier must be reported by the investigator.
- All pregnancies and exposure during breastfeeding, from the time of treatment allocation/randomization through 120 days following cessation of study treatment, or 30 days following cessation of study treatment if the participant initiates new anticancer therapy must be reported by the investigator.
- Additionally, any SAE brought to the attention of an investigator at any time outside of the time period specified above must be reported immediately by the investigator if the event is considered to be drug-related.

Investigators are not obligated to actively seek AE or SAE or other reportable safety events in former study participants. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study treatment or study participation, the investigator must promptly notify Merck.

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

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

If an adverse event(s) is associated with ("results from") the overdose of a Merck product, the adverse event(s) is reported as a serious adverse event, even if no other seriousness criteria are met.

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

All reports of overdose with and without an adverse event must be reported within 24 hours to the Sponsor and within 2 working days to Merck Global Safety. [redacted]

10.83 Reporting of Pregnancy and Lactation to Merck

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

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

Pregnancies and infant exposures during breastfeeding that occur from the time of treatment allocation/randomization through 120 days following cessation of Sponsor's product, or 30 days following cessation of treatment if the participant initiates new anticancer therapy, whichever is earlier, must be reported by the investigator. All reported pregnancies must be followed to the completion/termination of the pregnancy. Pregnancy outcomes of spontaneous abortion, missed abortion, benign hydatidiform mole, blighted ovum, fetal death, intrauterine death, miscarriage and stillbirth must be reported as serious events (Important Medical Events). If the pregnancy continues to term, the outcome (health of infant) must also be reported.

Such events must be reported within 24 hours to the Sponsor and within 2 working days to Merck Global Safety. [redacted]

10.84 Immediate Reporting of Adverse Events to the Sponsor and to Merck

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

- Results in death;
- Is life threatening;
- Results in persisten or significant disability/incapacity;
- Results in or prolongs an existing inpatient hospitalization;
- Is a congenital anomaly/birth defect;
- Is an other important medical event
- **Note:** In addition to the above criteria, adverse events meeting either of the below criteria, although not serious per ICH definition, are reportable to the Merck in the same timeframe as SAEs to meet certain local requirements. Therefore, these events are considered serious by Merck for collection purposes.
    - Is a new cancer (that is not a condition of the study);
    - Is associated with an overdose.

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

For the time period beginning at treatment allocation/randomization through 90 days following cessation of treatment, or 30 days following cessation of treatment if the participant initiates new anticancer therapy, whichever is earlier, any serious adverse event, or follow up to a serious adverse event, including death due to any cause whether or not related to the Merck product, must be reported within 24 hours to the Sponsor and within 2 working days to Merck Global Safety.

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

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

SAE reports and any other relevant safety information are to be forwarded to the Merck Global Safety facsimile number: [redacted]

A copy of all 15 Day Reports and Annual Progress Reports is submitted as required by FDA, European Union (EU), Pharmaceutical and Medical Devices agency (PMDA) or other local regulators. Investigators will cross reference this submission according to local regulations to the Merck Investigational Compound Number (IND, CSA, etc.) at the time of submission. Additionally investigators will submit a copy of these reports to Merck & Co., Inc. [redacted]

[redacted] at the time of submission to FDA.

10.85 Events of Clinical Interest

Selected non-serious and serious adverse events are also known as Events of Clinical Interest (ECI) and must be reported within 2 working days to Merck Global Safety. [redacted]

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

For the time period beginning at treatment allocation/randomization through 90 days following cessation of treatment, or 30 days following cessation of treatment if the participant initiates new anticancer therapy, whichever is earlier, any ECI, or follow up to an ECI, whether or not related to Merck product, must be reported within 2 working days to Merck Global Safety.

Events of clinical interest for this trial include:

1. An overdose of Merck product, as defined in Section10.82, that is not associated with clinical symptoms or abnormal laboratory results.
2. An elevated AST or ALT lab value that is greater than or equal to 3X the upper limit of normal and an elevated total bilirubin lab value that is greater than or equal to 2X the upper limit of normal and, at the same time, an alkaline phosphatase lab value that is less than 2X the upper limit of normal, as determined by way of protocol-specified laboratory testing or unscheduled laboratory testing.*

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

11.0 Treatment Evaluation/Measurement of Effect

Patients must have measurable disease.

The primary endpoint is the evaluation of cutaneous disease as measured by mSWAT (5). Disease progression will also be measured by lymph nodes, visceral disease and blood.

11.1 Definitions of Measurable

11.11 Measurable Disease

11.111 A primary cutaneous lesion is measurable if detectable through standard full body skin examination. Documentation by color photography is required.

11.112 A visceral lesion is considered measurable if its longest diameter can be accurately measured as 2.0 cm with chest x-ray, or as ≥1.0 cm with CT scan, CT component of a PET/CT, or MRI.

11.113 A malignant lymph node is considered measurable if its short axis is ≥1.5 cm when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm).

11.2 Evaluation of Measurable Disease

11.21 Evaluation of primary cutaneous lesion

mSWAT is calculated using body surface area (BSA) of each MF lesion (palm plus fingers of the patient ≈ 1% BSA) in each of 12 areas of the body, multiplying the sum of the BSA of each lesion type by a weighting factor (patch=1, plaque=2, and tumor =4) and generating a sum of the subtotals of each lesion subtype.

11.211 Measurement of effect

- Overall cutaneous response rate (ORR) = proportion of patients with a 50% or greater reduction of baseline mSWAT score
- Complete cutaneous response rate (CR) = proportion of patients with a 100% reduction of baseline mSWAT score
- Cutaneous 90 response rate (CR90) = proportion of patients with a 90% or greater reduction of baseline mSWAT score without the development of new tumors
- Cutaneous partial response rate (PR) = proportion of patients with a 50-90% baseline reduction of mSWAT score without the development of new tumors
- Progressive cutaneous disease (PD) = greater than 25% increase in baseline mSWAT or the development of new tumors. However, if in the judgement of the investigator, the increase in mSWAT is the result of inflammation due to treatment and/or the unmasking of subclinical skin involvement, this increase in mSWAT shall not be considered evidence of progressive cutaneous disease and the patient shall otherwise be classified as stable cutaneous disease (SD).
- Stable cutaneous disease (SD) = <25% increase to <50% reduction in baseline mSWAT without the development of new tumors ; or patients with a greater than 25% increase baseline mSWAT due to

the result of inflammation due to treatment and/or the unmasking of subclinical skin involvement.
- Relapsed cutaneous disease = Any disease recurrence in those with complete response

11.22 Evaluation of target visceral lesions or target lymph nodes

11.223 Identification of target lesions
- Measurable lesions (as defined in Section 11.1) up to a maximum of 5 representative of all involved organs, should be identified as "Target Lesions" and recorded and measured at baseline.
- Target visceral lesions and target lymph nodes should be selected on the basis of their size, be representative of all involved sites of disease, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion (or malignant lymph node) does not lend itself to reproducible measurements in which circumstance the next largest lesion (or malignant lymph node) which can be measured reproducibly should be selected.

11.224 Measurement Methods
- All measurements should be recorded in metric notation (i.e., decimal fractions of centimeters) using a ruler or calipers.
- The same method of assessment and the same technique must be used to characterize each identified and reported lesion at baseline, at the end of cycle 4 and at the end of treatment.

11.225 Acceptable modality
- Tumor imaging will be performed using a full body PET-CT. If the site can document that the CT performed as part of a PET-CT is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast), then the CT portion of the PET-CT can be used for RECIST measurements.

11.226 Evaluation of target lesions
- Baseline Sum of Dimensions (BSD): A sum of the longest diameter for all target visceral lesions plus the sum of the short axis of all the target lymph nodes will be calculated and reported as the baseline sum of dimensions (BSD). The BSD will be used as reference to further characterize any objective tumor response in the measurable dimension of the disease.
- Post-Baseline Sum of the Dimensions (PBSD): A sum of the longest diameter for all target visceral lesions plus the sum of the short axis of all the target lymph nodes will be calculated and reported as the post-baseline sum of dimensions (PBSD). If the radiologist is able to provide an actual measure for the target visceral lesion (or target lymph node), that should be recorded, even if it is below 0.5 cm. If the target visceral lesion (or target lymph node) is believed to be present and is faintly seen but too small to measure, a default value of 0.5 cm should be assigned. If it is the opinion of the radiologist that the target visceral lesion or target lymph node has likely disappeared, the measurement should be recorded as 0 cm.

- The minimum sum of the dimensions (MSD) is the minimum of the BSD and the PBSD.

11.227 Measurement of effect

- Complete Response (CR):All of the following must be true:
  a. Disappearance of all visceral lesions.
  b. Each target lymph node must have reduction in short axis to <1.0 cm.
- Partial Response (PR): At least a 30% decrease in PBSD (sum of the longest diameter for all target visceral lesions plus the sum of the short axis of all the target lymph nodes at current evaluation) taking as reference the BSD (see Section 11.226).
- Progression (PD): At least one of the following must be true:
  a. At least one new malignant lesion, which also includes any lymph node that was normal at baseline (<1.0 cm short axis) and increased to ≥1.0 cm short axis during follow-up.
  b. At least a 20% increase in PBSD (sum of the longest diameter for all target visceral lesions plus the sum of the short axis of all the target lymph nodes at current evaluation) taking as reference the MSD (Section 11.41). In addition, the PBSD must also demonstrate an absolute increase of at least 0.5 cm from the MSD.
- Stable Disease (SD): Neither sufficient shrinkage to qualify for PR, nor sufficient increase to qualify for PD taking as reference the MSD.

11.3 Evaluation of peripheral blood

T and B-cell Quantitation will be utilized to evaluate peripheral blood. CD4 and CD8 test results will be collected and the ratio CD4:CD8 will be compiled.

11.31 Measurement effect

- Complete Response (CR): No blood involvement.
- Partial Response (PR): 50% decrease in CD4 count or CD4:CD8 ratio ≤10.
- Progressive Disease (PD): 50% increase from baseline (≥5,000 CD4+cells in blood or CD4:CD8 ratio ≥15).
- Stable Disease (SD): Not CR, PR or PD.

11.4 Measurement at Follow-up Evaluations

11.41 Cutaneous lesions

- mSWAT will be collected at baseline, end of every cycle of treatment and during clinical follow-up at 30 and 90 days.
- mSWAT response will be recorded as per Section 11.211.

11.42 Target visceral lesions and lymph nodes.

- Subsequent PET-CT scans must be obtained after cycle 4 and the end of treatment visit following initial documentation of objective cutaneous response status of either complete response (CR) or partial response (PR).
- In the case of stable disease (SD), follow-up measurements must have met the SD criteria at least once after study entry at a minimum interval of 3 weeks.
- The cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment when the measurable tumor has met criteria for response or stable disease is mandatory to differentiate between response or stable disease (an effusion may be a side effect of the treatment) and progressive disease.

11.43 Peripheral blood

T and B-Cell Quantitation will be performed at baseline, end of cycle 4, and at end of treatment.

11.5 Overall Objective Status

Overall systemic response rate is defined as 50% or greater reduction of baseline mSWAT score without evidence of progressive nodal, visceral, or blood involvement.

12.0 Descriptive Factors

12.1 None.

13.0 Treatment/Follow–up Decision at Evaluation of Patient

Reason Off Treatment (from the Off Treatment Form)	*Go to CFU, SFU, or end folder rollout*
1 = Treatment (Intervention) Completed Per Protocol Criteria	CFU
2 = Patient Withdrawal/Refusal After Beginning Protocol Therapy (Intervention)	SFU
3 = Adverse Events/Side Effects/Complications	SFU
4 = Disease Progression, Relapse During Active Treatment (Intervention)	SFU
5 = Alternative Therapy	No follow-up
6 = Patient Off-Treatment (Intervention) For Other Complicating Disease	SFU
7 = Death On Study	No follow-up
8 = Other	SFU
10 = Disease Progression Before Active Treatment (Intervention)	No follow-up
24 = Patient Withdrawal/Refusal Prior To Beginning Protocol Therapy (Intervention)	No follow-up

13.1 Continuation of treatment

Patients who are CR90, PR, or SD will continue treatment per protocol up to a maximum duration of 24 months. .

13.2 Progressive disease (PD)

Patients who develop PD (non-responders) during cycle 1 will exit the study (no follow-up). Patients who develop PD subsequent while receiving therapy will complete the End of Treatment visit at the time of PD and repeat staging per protocol, then proceed to survival follow-up (Section 4.2).

13.3 Off protocol treatment

Patients who do not develop PD during cycle 1 and go off protocol treatment for reasons other than PD within any cycle will proceed to survival follow-up. Note: This does not apply to patients receiving alternative therapy. Patients who go off treatment for alternative therapy will exit the study (no follow-up).

Patients who achieve CR at any time will proceed to survival follow-up.

13.4 Clinical Follow-up

Patients achieving CR90, PR, or SD, and who have completed 24 months of treatment will be observed for clinical follow-up at 30 and 90 days after the end of treatment, and then proceed to survival follow-up.

13.5 Duration of therapy for CR

The maximum duration of therapy is 24 months. Patients who achieve CR during this period will be removed from active treatment and will proceed to survival follow-up, thus duration of therapy for CR will be 24 months or less.

13.6 Duration of therapy for CR90, PR or SD

Patients who achieve CR90, PR, or SD will continue on therapy up to a maximum duration of 24 months.. After 24 months,, the patients will continue to clinical follow-up at 30 and 90 days after the last treatment and then proceed to survival follow-up (see 13.4 above). Subsequent treatment is at the discretion of their attending.

13.7 Ineligible

A patient is deemed *ineligible* if after registration, it is determined that at the time of registration, the patient did not satisfy each and every eligibility criteria for study entry. If the patient received treatment, the patient may continue treatment at the discretion of the physician as long as there are not safety concerns. The patient will continue in the Active Monitoring/Treatment phase of the study, as per section 4.0 of the protocol.

- If the patient never received treatment, on-study material must be submitted. Survival Follow-up will be required per Section 4.0 of the protocol.

13.8 Major violation

A patient is deemed a *major violation*, if protocol requirements regarding treatment in cycle 1 of the initial therapy are severely violated that evaluability for primary end point is questionable. If the patient received treatment, the patient may continue treatment at the discretion of the physician as long as there are no safety concerns. The patient will continue in the Active Monitoring/Treatment phase of the study, as per section 4.0 of the protocol.

13.9 Cancel

A patient is deemed a *cancel* if he/she is removed from the study for any reason before any study treatment is given. On-study material and the End of Active Treatment/Cancel Notification Form must be submitted. No further data submission is necessary.

14.0 Body Fluid Biospecimens

None.

15.0 Drug Information

IND number (139381)

- Investigator brochure
  Industry-supplied:
  (drug company contact: : [redacted]

15.1 Pembrolizumab (MK-3475, SCH 900475, Keytruda®)

15.11 **Background**: Pembrolizumab is a potent humanized IgG4 monoclonal antibody with high specificity of binding to the PD-1 receptor, thus inhibiting its interaction with PD-L1 and PD-L2. Based on preclinical *in vitro* data, pembrolizumab has high affinity and potent receptor blocking activity for PD-1.

15.12 **Formulation**:

Pembrolizumab is available as a liquid 25 mg/mL, 100 mg/vial.

15.13 **Preparation and storage**:

Vials should be stored in the refrigerator at temperatures between 2-8°C.

Drug concentrate is further diluted with normal saline (or 5% dextrose) in the concentration range of 1 to 10 mg/mL. The infusion solution in the IV bag should be immediately administered. Diluted pembrolizumab solutions may be stored at room temperature for a cumulative period of up to 46 hours. This includes room temperature storage of admixture solutions in the IV bags and the duration of infusion. The product can also be stored under refrigeration at 2°C to 8°C for no more than 96 hours from the time of dilution. If refrigerated, the diluted solution must be allowed to come to room temperature prior to administration. The solution must be discarded after 6 hours at room temperature or 96 hours under refrigeration.

15.14 **Administration:** Pembrolizumab is administered by intravenous infusion over 30 minutes via a 0.22 micron in-line filter. The final infusion volume must be between 1 and 10 mg/mL. Maximum rate of infusion should not exceed 6.7 mL/minute through a peripheral or indwelling catheter. Flush the line with 0.9% NaCL following the completion of the infusion.

15.15 **Pharmacokinetic information**:
a) Absorption –Because pembrolizumab is administered intravenously, it is immediately and completely bioavailable. Steady-state concentrations of pembrolizumab are reached by 16 weeks of repeated dosing with a Q3W regimen and the systemic accumulation is 2.1-fold. The peak concentration, trough concentration, and area under the plasma concentration versus time curve at steady state of pembrolizumab increased dose proportionally in the dose range of 2 to 10 mg/kg Q3W.
b) Distribution – Pembrolizumab has a limited volume of distribution.

c) Excretion – CL is approximately 23% lower after achieving maximal change at steady state compared with the first dose. The terminal elimination half-life (t½) is estimated to be 22 days at steady state.
d) Metabolism - Pembrolizumab is catabolized through non-specific pathways; metabolism does not contribute to its CL.

There are limited clinical studies on the subcutaneous formulation. Model-based analysis showed an estimated bioavailability of 64% (95% CI: 54% to 74%; variability, 128% CV). This is consistent with the reported bioavailability for other mAbs (range: 50% to 85%) given SC. Clearance was the same for the IV and SC formulations. The mean time to achieve maximum concentration (Tmax) with pembrolizumab SC was estimated to be 5.5 days (range: 3 days to 14 days).

15.16 **Potential Drug Interactions:** There are no known significant drug interactions.

15.17 **Known potential adverse events**:
Very common known potential toxicities, ≥ 10%:
Gastrointestinal disorders: diarrhea, nausea
Cardiovascular: cardiac arrythmia, peripheral edema
Dermatologic: pruritis, skin rash, vitiligo
Endocrine and metabolic: decreased serum bicarbonate, hypercalcemia, hypercholesterolemia, hyperglycemia, hyperkalemia, hypertriglyceridemia, hypoalbuminemia, hypocalcemia, hypoglycemia, hypokalemia, hypomagnesemia, hyponatremia, hypophosphatemia, hypothyroidism, weight loss, constipation, decreased appetite, vomiting
Genitourinary: hematuria, urinary tract infection
Hematologic and oncologic: anemia, hemorrhage, increased INR, leukopenia, lymphocytopenia, neutropenia, prolonged partial thromboplastin time, thrombocytopenia Hepatic: hyperbilirubinemia, increased serum alanine aminotransferase, increased serum alkaline phosphatase, increased serum aspartate aminotransferase
Infection: infection
Nervous system: fatigue, headache, pain, peripheral neuropathy
Neuromuscular & skeletal: arthralgia, asthenia, back pain, musculoskeletal pain, myalgia
Renal: increased serum creatinine
Respiratory: cough, dyspnea, flu-like symptoms, pneumonia, pneumonitis, upper respiratory tract infection
Miscellaneous: fever

Common known potential adverse events, ≥1% to < 10
Cardiovascular: acute myocardial infarction, cardiac tamponade, facial edema, ischemic heart disease, myocarditis, pericardial effusion, pericarditis, pulmonary embolism
Endocrine & metabolic: hyperthyroidism, thyroiditis
Gastrointestinal: colitis, dysphagia, stomatitis
Hematologic & oncologic: febrile neutropenia, tumor flare

Hepatic: ascites, hepatitis
Immunologic: antibody development
Infection: herpes virus infection, herpes zoster infection, sepsis
Nervous system: altered mental status, confusion, dizziness, insomnia
Neuromuscular & skeletal: arthritis, myositis, neck pain
Ophthalmic: uveitis
Renal: acute kidney injury
Respiratory: nasopharyngitis, oropharyngeal pain, pleural effusion, respiratory

failure
Miscellaneous: fistula, infusion related reaction

Uncommon known potential adverse events , ≥0.1% to <1%:
Cardiovascular: Vasculitis
Endocrine & metabolic: adrenocortical insufficiency, diabetic ketoacidosis, hypoparathyroidism, hypophysitis, type 1 diabetes mellitus
Gastrointestinal: duodenitis, gastritis, increased serum amylase, increased serum lipase, pancreatitis
Hematologic & oncologic: aplastic anemia, hemolytic anemia, immune thrombocytopenia, immunological signs and symptoms (hemophagocytic lymphohistiocytosis), lymphadenitis (histiocytic necrotizing lymphadenitis [Kikuchi lymphadenitis]), sarcoidosis
Hypersensitivity: anaphylaxis
Immunologic: organ transplant rejection (solid)
Infection: Systemic inflammatory response syndrome
Nervous system: demyelinating disease, encephalitis, exacerbation of myasthenia gravis, Guillain-Barre syndrome, meningitis, myasthenia (myasthenic syndrome), myasthenia gravis, neuropathy (autoimmune), paresis (nerve)
Neuromuscular & skeletal: myelitis, polymyalgia rheumatica, polymyositis, rhabdomyolysis
Ophthalmic: iritis
Renal: nephritis

The risk profile for pembrolizumab also includes two important potential risks: a) myasthenic syndrome, and b) an increased risk of severe complications (such as early severe graft versus host disease and veno-occlusive disease) of allogeneic transplant in patients with hematologic malignancies who have previously been treated with PD-1 inhibitors.

Since the last IB, Edition 21, a new identified risk of hypoparathyroidism has been added to the warnings and precautions section of the CCDS based on routine pharmacovigilance.

Per IB, Edition 23 a new risk of optic neuritis has been added to the Postmarketing Experience Adverse Reactions section of the CCDS based on routine pharmacovigilance.

Patients with multiple myeloma who were treated with pembrolizumab in combination with either pomalidomide or lenalidomide and dexamethasone, had an increased number of serious side effects and deaths as compared to patients who received only dexamethasone and either pomalidomide or lenalidomide. The benefit-risk profile is unfavorable for the combination of pembrolizumab, pomalidomide, and dexamethasone in relapsed refractory multiple myeloma, and the combination of pembrolizumab, lenalidomide, and dexamethasone in newly diagnosed treatment-naive multiple myeloma.

Post marketing reports have identified additional adverse reactions, including arthritis, Vogt-Koyanagi-Harada syndrome and hemophagocytic lymphohistiocytosis. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

15.18 Drug procurement:

Pembrolizumab will be provided free of charge to study participants by Merck.

15.19 Nursing guidelines

15.191 Pembrolizumab side effects vary greatly from those of traditional chemotherapy and can vary in severity from mild to life threatening. Instruct patients to report any side effects to the study team immediately. Side effects may be immediate or delayed up to months after discontinuation of therapy. Most side effects are reversible with prompt intervention of corticosteroids.

15.192 Diarrhea can be seen however is less common than that seen with anti-CTLA-4 agents. However it can be severe, leading to colonic perforation. Instruct patients to report ANY increase in the number of stools and/or change in baseline, blood in the stool, abdominal pain to the study team immediately.

15.193 Rash/pruritus/dermatitis is seen. Patients should report any rash to the study team. Treat per section 9.0 and monitor for effectiveness.

15.194 Monitor LFT's closely as elevations in these levels could indicate early onset autoimmune hepatitis. Patients should also be instructed to report any jaundice, or right upper quadrant pain to the study team immediately.

15.195 Pneumonitis can be seen and may be mild (only seen on imaging) to severe. Patients should be instructed to report any SOB, dyspnea, cough, chest pain, etc. to the study team immediately. Patients reporting these symptoms should have a pulse ox checked and consider immediate imaging per the treating MD.

15.196 Endocrinopathies (including hypopituitarism, hypothyroidism, hypophysistis, and adrenal insufficiency) are seen with this agent. Patients may present only with the vague sense of fatigue and "not feeling well" . Additional symptoms may be that of nausea, sweating and decreased activity tolerance. Instruct patients to report these signs or symptoms immediately and obtain appropriate labs as ordered by MD.

15.197 Patients who are started on steroid therapy for any side effects of pembrolizimab toxicity should be instructed to take the steroids as ordered, and not to discontinue abruptly as symptoms may return and be severe. Patients may be on steroid therapy for weeks. Instruct patients to report any increase or change in side effects with any dosage decrease as patients may need a slower taper.

15.198 Fatigue is common and may or may not be associated with immune related side effects. Assess patient's fatigue level prior to each cycle of therapy and report any changes to the study team.

15.199a Patients should avoid receiving live vaccines within 30 days of study drug administration or per other study guidelines.

15.199b Patients who have undergone an allogenic bone marrow transplant, have an increased risk of severe complications including early GVHD, and venoocclusive disease, if they have previously been treated with pembrolizumab

15.199c Myocarditis has been reported and associated with pembrolizumab. Instruct patients to report chest pain, SOB, or dyspnea to study team immediately and/or seek emergency medical attention.

15.199d Autoimmune hematologic disorders including ITP and hemolytic anemia have been reported. Monitor blood counts closely and report any abnormalities to the study team.

15.199e Rare neurologic disorders including Guillian-Barre syndrome and myasthenia gravis have been reported. Instruct patients to report any neurologic symptoms including weakness, parasthesias or numbness, tingling to the study team immedicately.

16.0 Statistical Considerations and Methodology

16.1 Overview

This is a phase II study designed to assess the overall cutaneous response rate at cycle 9 in MF patients treated with pembrolizumab. It is a single one-stage design with an interim analysis based on the Simon optimal design with 85% power and 10% Type I error.

NOTE: As per Amendment 4, accrual will cease after the enrollment of 10 patients due to sponsor decision on funding. Thus, the study power and type I error will not be appropriate for the analysis, as the study will not be able to go to full accrual. The study will be analyzed at the pre-defined interim step.

16.11 Endpoint:

The primary endpoint is overall cutaneous response (cutaneous complete response (CR), cutaneous 90 response (CR90) or cutaneous partial response (PR)) as defined using the mSWAT score as stated in section 11.0. Throughout Section 16.0, CR, CR90 or PR will be considered synonymous with "success", unless specified otherwise. All patients meeting the eligibility criteria who have signed a consent form and have begun treatment will be evaluable for response.

16.2 Statistical Design

16.21 Design: The largest success proportion where the proposed treatment regimen would be considered ineffective in this population is 15%, and the smallest success proportion that would warrant subsequent studies with the proposed regimen in this patient population is 35%. This design uses 28 evaluable patients to test the null hypothesis that the true complete response rate is at most 15%.

16.22 Interim Analysis: Enter 10 evaluable patients to the study. If there are less than 2 successes in the first 10 evaluable patients, we will consider this regimen ineffective in this patient population and terminate this study. Otherwise, if the number of successes is at least 2, we will continue accrual.

16.23 **N/A as per Amendment 4:** Final Decision rule: If 6 or fewer successes are observed in the first 28 evaluable patients, we will consider this regimen ineffective in this patient population. Otherwise, if the number of successes is at least 7, this will be considered evidence of promising activity and the treatment may be recommended for further testing in subsequent studies.

16.24 **N/A as per Amendment 4:** NOTE: We will not suspend accrual at the interim analysis to allow the first 10 patients to become evaluable, unless undue toxicity is observed. Given the limited overall sample size and the inclusion of an adverse events stopping rule, we feel it is ethical to not halt accrual for the interim analysis. However, if accrual is extremely rapid, we may temporarily suspend accrual in order to obtain safety data on these patients before re-opening accrual to further patients.

16.3 Sample Size, Accrual Rate and Power and Significance Level

16.31 Sample Size: This study is expected to require a minimum of 10 and a maximum of 28 evaluable patients. We anticipate accruing 3 (10%) additional patients to account for ineligibility, cancellation, major treatment violation, or other reasons. Therefore, the study is expected to accrue a maximum of 31 patients overall. **As per Amendment 4, accrual will cease at 10 patients.**

16.32 Accrual Rate and Study Duration: The anticipated accrual rate is 10 evaluable patients per year. Therefore, the accrual period is expected to be 3.1 years. The

primary endpoint will be evaluated approximately 3.75 years after the trial opens, or after the last patient accrued has received 24 months of treatment.

16.33 Power and Significance Level: Assuming that the number of successes is binomially distributed, the significance level is .10, i.e. there is a 10% chance of finding the drug to be effective when it truly is not. The probability of declaring that this regimen warrants further study (i.e. statistical power) under various

success proportions and the probability of stopping accrual after the interim analysis can be tabulated as a function of the true success proportion.

If the true success proportion is...	0.15	0.20	0.25	0.30	0.35
Then the probability of declaring that the regimen warrants further study is…	0.456	0.624	0.756	0.851	0.914
and the probability of stopping after the interim analysis is …	0.544	0.376	0.244	0.149	0.086

16.34 Other considerations: Adverse events, quality/duration of response, and patterns of treatment failure observed in this study, as well as scientific discoveries or changes in standard care will be taken into account in any decision to terminate the study.

16.4 Analysis Plan

16.41 Primary Outcome Analysis: The mSWAT score at baseline and cycle 9 will be used for change in baseline calculations. All calculated values will use the last-observation-carried forward for any participants who withdraw, are lost to follow up, or exit the study per protocol. The proportion of successes will be estimated by the number of successes divided by the total number of evaluable patients will be analysed using Mann–Whitney U for nonparametric data and the student t-test. Confidence intervals for the true success proportion will be calculated according to the approach of Duffy and Santner (Duffy D 1987).

16.42 Secondary Outcome Analysis: These analyses will include all patients meeting the eligibility criteria who have signed a consent form and have begun treatment, including patients who fail to achieve a complete or partial response.

Adverse Events: All eligible patients that have initiated treatment will be considered evaluable for assessing adverse event rate(s). The maximum grade for each type of adverse event will be recorded for each patient, and frequency tables will be reviewed to determine patterns. Additionally, the relationship of the adverse event(s) to the study treatment will be taken into consideration.

Response Rates:

Changes in mSWAT scores from baseline will be evaluated at cycle 9. Summary statistics will be calculated.

Patients will be assigned response based on the mSWAT criteria in section 11.0. Proportions of patients will be calculated and described using summary statistics. Proportions of interest are patients having CR, CR90 and PR; patients having stable subcutaneous disease; patients having progressive cutaneous disease; and patients having an overall systemic response rate.

Progression free survival time is defined for all evaluable patients as the time from registration to relapse or death due to any cause. Patients are censored if they have not achieved a progression at the time of analysis. The distribution of progression-free survival will be estimated using the method of Kaplan-Meier. In addition, the progression-free survival rate at 5 years after registration will be reported.

Duration of response is defined for all evaluable patients who have achieved a CR, CR90 or PR as the date at which the patient's objective status is first noted to be a CR, CR90 or PR to the earliest date relapse is documented. The distribution of duration of complete response will be estimated using the method of Kaplan-Meier.

Time to response is defined as the time from registration to CR, CR90 or PR. The distribution of survival time will be estimated using the method of Kaplan-Meier (Kaplan and Meier 1958).

Overall survival time is defined as the time from registration to death due to any cause. Patients are censored if they are alive at the time of analysis. The distribution of survival time will be estimated using the method of Kaplan-Meier (Kaplan and Meier 1958). In addition, the overall survival rate at 2 years after registration will be reported.

Additional Analyses: All endpoints may be analysed using patient characteristics to explore possible associations of demographics with the endpoints. Possible characteristics include clinical stage, gender and prior treatments.

16.43 Correlative Analyses
Immunohistochemistry will be used to quantify levels of CD4, CD8, PD-1/CD279, and PD- L1 expression before and after treatment with pembrolizumab and will be used for change in baseline calculations at baseline and end of cycle 2. Qualitative measures of the strength of PD-1 and PD-L1 expression will use published standardized grading scales for categorical classification purposes.

16.5 Primary Endpoint Completion Date for [redacted] Reporting

For purpose of [redacted] reporting, the Primary Endpoint Completion Date (PECD) for this study is the time the last patient registered has been followed for at least 7 months.

16.6 Data Safety and Monitoring

16.61 The study statistician will review the study weekly to monitor accrual, endpoints and adverse events. Additionally, the Mayo Clinic Cancer Center (MCCC) Data Safety Monitoring Board (DSMB) is responsible for reviewing accrual and safety data for this trial at least twice a year, based on reports provided by the MCCC Statistical Office.

16.62 This study will be monitored by the Clinical Data Update System (CDUS) version 2.0. A full report containing cumulative CDUS data will be submitted quarterly to CTEP by electronic means. Reporting time points are: January 31, April 30, July 31, and October 31.

16.63 Adverse Event Stopping Rules: The stopping rules specified below are based on the knowledge available at study development. We note that the Adverse Event Stopping Rule may be adjusted in the event of either (1) the study re-opening to accrual or (2) at any time during the conduct of the trial and in consideration of newly acquired information regarding the adverse event profile of the treatment(s) under investigation. The study team may choose to suspend accrual

because of unexpected adverse event profiles that have not crossed the specified rule below.

Accrual will be temporarily suspended to this study if at any time we observe events considered at least possibly related to study treatment (i.e. an adverse event with attribute specified as "possible," "probable," or "definite") that satisfy one of the following:

- if 2 or more patients in the first 10 treated patients (20%) experience a grade 4 or higher non-hematologic adverse event at least possibly related to treatment.
- if after the first 10 patients have been treated, 20% of all patients experience a grade 4 or higher non-hematologic adverse event at least possibly related to treatment.

We note that we will review grade 4 and 5 adverse events deemed "unrelated" or "unlikely to be related", to verify their attribution and to monitor the emergence of a previously unrecognized treatment-related adverse event.

16.63 Accrual Stopping Rule

The study design assumes that 2 patients will accrue per month, leading to a 26-month total accrual. At 6 months, if the total accrual is below 50% of the expected (fewer than 6 patients) then the significance and power will be much better than designed for and a sample size reduction may be called for. Consequently, we will update the design and may adjust sample size and/or duration of follow-up. At 6 months, if the total accrual is above 200% (more than 24 patients) then we may have lost significance and/or power and an increase in sample size or a lengthening of total observation time may be necessary. Consequently, we may pause accrual or update the design and may adjust the sample size to achieve the desired significance and power.

16.7 Inclusion of Women and Minorities

16.71 This study will be available to all eligible patients, regardless of race, gender, or ethnic origin.

16.72 There is no information currently available regarding differential effects of this regimen in subsets defined by race, or ethnicity, and there is no reason to expect such differences to exist. Therefore, although the planned analysis will, as always, look for differences in treatment effect based on race, the sample size is not increased in order to provide additional power for subset analyses.

16.73 The geographical region served by MCCC has a population which includes approximately 3% minorities. Based on prior MCCC studies involving similar disease sites, we expect about 3-5% of patients will be classified as minorities by race and about 30% of patients will be women. Expected sizes of racial by gender subsets are shown in the following table:

Accrual Estimates by Gender/Ethnicity/Race

	Sex/Gender			
Ethnic Category	Females	Males	Unknown	Total
Hispanic or Latino	5	4	0	9
Not Hispanic or Latino	11	11	0	22

Ethnic Category	Sex/Gender			
	Females	Males	Unknown	Total
Ethnic Category: Total of all subjects	16	15	0	31
Racial Category				
American Indian or Alaskan Native	0	0	0	0
Asian	0	0	0	0
Black or African American	4	5	0	9
Native Hawaiian or other Pacific Islander	0	0	0	0
White	12	10	0	22
Racial Category: Total of all subjects	**16**	**15**	**0**	**31**

Ethnic Categories:

Hispanic or Latino – a person of Cuban, Mexican, Puerto Rico, South or Central American, or other Spanish culture or origin, regardless of race. The term "Spanish origin" can also be used in addition to "Hispanic or Latino."

Not Hispanic or Latino

Racial Categories:

American Indian or Alaskan Native – a person having origins in any of the original peoples of North, Central, or South America, and who maintains tribal affiliations or community attachment.

Asian – a person having origins in any of the original peoples of the Far East, Southeast Asia, or the Indian subcontinent including, for example, Cambodia, China, India, Japan, Korea, Malaysia, Pakistan, the Philippine Islands, Thailand, and Vietnam. (Note: Individuals from the Philippine Islands have been recorded as Pacific Islanders in previous data collection strategies.)

Black or African American – a person having origins in any of the black racial groups of Africa. Terms such as "Haitian" or "Negro" can be used in addition to "Black or African American."

Native Hawaiian or other Pacific Islander – a person having origins in any of the original peoples of Hawaii, Guam, Samoa, or other Pacific Islands.

White – a person having origins in any of the original peoples of Europe, the Middle East, or North Africa.

17.0 Pathology Considerations/Tissue Biospecimens

17.1 Summary Table of Research Tissue Specimens to be collected for this Protocol

Research Study (Section for more information)	Specimen Purpose (check all that apply)	Mandatory or Optional	Type of Tissue to Collect	Block, Slides, Core, etc. (# of each to submit)	After registration	Cycle 2 Day 15	Process at site? (Yes or No)
Histopathologic and immunohistochemical analysis	☒ Correlative ☐ Eligibility Confirmation ☐ Banking ☐ Other (specify)	Mandatory	FFPE	H&E Slides and 4-unstained slides of 5 microns	X	X	Yes

17.2 Diagnostic Slides from Original and /or Recurrent Tissue

Prior to the initial dose of pembrolizumab, a 6 mm punch skin biopsy of the most common presenting morphology (i.e. patch, plaque, or tumor) will be obtained for each study participant; at Cycle 2, Day 15, an additional 6 mm punch skin biopsy of the same morphologic type will be obtained.

Please see the number of required unstained slides for each test in the table. Slides should be sent to BAP lab in Jacksonville

17.3 Correlative Tissue Collection

17.31 Tissue Kits will not be provided for this protocol..

17.32 Paraffin Embedded Tissue

17.321 Submit H&E as well as uncharged, unstained slides – see table. Do not use coverslips, do not bake. 5 micron thick sections on uncharged slides at ambient temperature.

17.4 Background and Methodology

17.41 The use of formalin-fixed paraffin embedded tissue for standard histology is a well-established modality in the diagnosis of treatment of cutaneous lymphoma. Histologic factors such as epidermotropism, the extensive of dermal involvement, and cytomorphologic features are all of import. Immunohistochemistry is additionally routinely utilized in classifying the nature of the atypical mononuclear infiltrate and in the assessment of large cell transformation. Histopathology will be used for diagnostic confirmation and to assess for evidence of histologic regression of tumor with treatment. Immunohistochemistry will be used to quantify levels of CD4, CD8, PD-1/CD279, and PD-L1 expression before and after treatment with pembrolizumab and will be used for change in baseline calculations at after registration and Cycle 2, Day 15. Qualitative measures of the strength of PD-1 and PD-L1 expression will use published standardized grading scales for categorical classification purposes.

18.0 Records and Data Collection Procedures

18.1 Submission Timetable

Data submission instructions for this study can be found in the Data Submission Schedule.

18.2 Survival Follow-up

See Section 4.

18.3 CRF completion

This study will use Medidata Rave for remote data capture (rdc) of all study data. Data collection for this study will be done exclusively through the Medidata Rave clinical data management system. Access to the trial in Rave is granted through the iMedidata application to all persons with the appropriate roles assigned in Regulatory Support System (RSS). To access Rave via iMedidata, the site user must have an active account and the appropriate Rave role (Rave CRA, Read-Only, Site Investigator) on either the organization roster at the enrolling site.

18.4 Site responsibilities

Each site will be responsible for insuring that all materials contain the patient's initials, MCCC registration number, and MCCC protocol number. Patient's name must be removed.

18.5 Supporting documentation

This study requires supporting documentation for diagnosis and progression prior to study entry as well as for evidence of response to study therapy and progression after study therapy.

Supporting documentation for diagnosis will include a pathology report from the most recent tumor tissue biopsy, dermatology exam clinical note, imaging report, and T & B-cell Quantitation lab report, if blood involved by tumor. These documents should be uploaded into the Supporting Documentation: Baseline form in the Medidata Rave system within 14 days of registration.

For response to treatment, supporting documentation includes a dermatology exam clinical note, imaging report, and T & B-cell Quantitation lab report, if blood involved with tumor.

For patients who progress, supporting documentation of all sites of progression is required and can include dermatology exam clinical note, imaging report, or T & B-cell Quantitation lab report, if blood involved with tumor.

18.6 Labeling of materials

Each site will be responsible for insuring that all materials contain the patient's initials, MCCC registration number, and MCCC protocol number. Patient's name must be removed.

18.7 Overdue lists

A list of overdue forms and outstanding queries will be available in Rave through the Rave Task Summary. In addition to this, the Overdue Materials report is available on the Cancer Center Systems homepage.

19.0 Budget

19.1 Costs charged to patient: routine clinical care

19.2 Tests to be research funded: Tumor Biopsy at Cycle 2, Day 15, Dermatology exam, Standardized Clinical photography, T and B-cell Quantitation after Cycle 4 during course of treatment and at the End of Treatment Visit, and research tissue. Drug provided free of charge.

19.3 Other budget concerns:

Merck will provide Mayo Clinic with funding to support the costs of running this study.

20.0 References

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10. Warren, S., et al. (2017). Unrelated immunodeficiency states may impact outcomes and immune checkpoint molecule expression in patients with mycosis fungoides: A clinicopathologic case-control study. *Journal of the American Academy of Dermatology*, 78(3) 530-539.
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Appendix I ECOG Performance Status

ECOG PERFORMANCE STATUS*

Grade	ECOG
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours.
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair.
5	Dead

*As published in Am. J. Clin. Oncol.:
Oken, M.M., Creech, R.H., Tormey, D.C., Horton, J., Davis, T.E., McFadden, E.T., Carbone, P.P.: Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. Am J Clin Oncol 5:649-655, 1982.

The ECOG Performance Status is in the public domain therefore available for public use. To duplicate the scale, please cite the reference above and credit the Eastern Cooperative Oncology Group, Robert Comis M.D., Group Chair.

From [redacted]