

MD Anderson IND Sponsor Cover Sheet	
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Protocol Title	A phase I/II study of pembrolizumab (MK-3475) in combination with romidepsin in patients with relapsed or refractory peripheral T-cell lymphoma
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Protocol PI	Swaminathan Iyer
Department	Lymphoma/Myeloma
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IND #	136194

TITLE: A phase I/II study of pembrolizumab (MK-3475) in combination with romidepsin in patients with relapsed or refractory peripheral T-cell lymphoma

Institution

University of Texas, MD Anderson Cancer Center
1515 Holcombe Blvd Unit 429
Houston, TX 77030

Principal Investigator:

Swaminathan Iyer, MD
Department of Lymphoma and Myeloma
(713) 792-2860
spiyer@mdanderson.org

Biostat collaborator:

Lei Feng
Department of Biostatistics
713-794-4169
lfeng@mdanderson.org

IND NUMBER: 136194

1.0 TRIAL SUMMARY

Abbreviated Title	Pembrolizumab in combination with romidepsin in patients with relapsed or refractory peripheral T-cell lymphoma
Trial Phase	Phase 1/2
Clinical Indication	Relapsed or refractory peripheral T-cell lymphoma
Trial Type	Single center, open-label single arm
Type of control	None
Route of administration	• Pembrolizumab is given intravenously at a fixed dose of 200mg every 3 weeks • Romidepsin is given intravenously at a specified dose per cohort on days 1 and 8 every 3 weeks. In Phase 2, C1D1-Romidepsin will be omitted.
Trial Blinding	None
Treatment Groups	Single arm
Number of trial subjects	21-39
Estimated enrollment period	3 years
Estimated duration of trial	3.5 years
Duration of Participation	3.5 years
Estimated average length of treatment per patient	6 months

2.0 TRIAL DESIGN

2.1 Trial Design

This is a single center, single arm, nonrandomized trial of pembrolizumab (MK-3475) in combination with romidepsin in subjects with relapsed or refractory peripheral T-cell lymphoma (PTCL) that have failed to achieve a complete response or progressed after at least one systemic treatment regimen. Approximately 21-39 subjects will be enrolled in this trial to examine the safety and efficacy of pembrolizumab 200 mg fixed dose administered every 3 weeks (Q3W) in combination with romidepsin. The safety of the combination is tested in the lead-in phase I study. The toxicity profiles of pembrolizumab and romidepsin have limited overlap, and thus, to maximize the efficacy of the both drugs, it is considered safe and reasonable to test the combination of the two drugs at their optimal dose as a single agent for the first testing dose. Therefore, the strategy for the phase I study is dose de-escalation, rather than dose escalation. The starting dose of romidepsin 14mg/m² on days 1 and 8. At the dose considered to be safe, phase II study will be performed. Adverse events will be monitored throughout the trial and graded in severity according to the guidelines outlined in the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. Treatment will

continue up to a maximum of 36 cycles per subject or until documented disease progression, unacceptable adverse event(s), intercurrent illness that prevents further administration of treatment, investigator's decision to withdraw the subject, subject withdraws consent, pregnancy of the subject, noncompliance with trial treatment or procedure requirements, or administrative reasons.

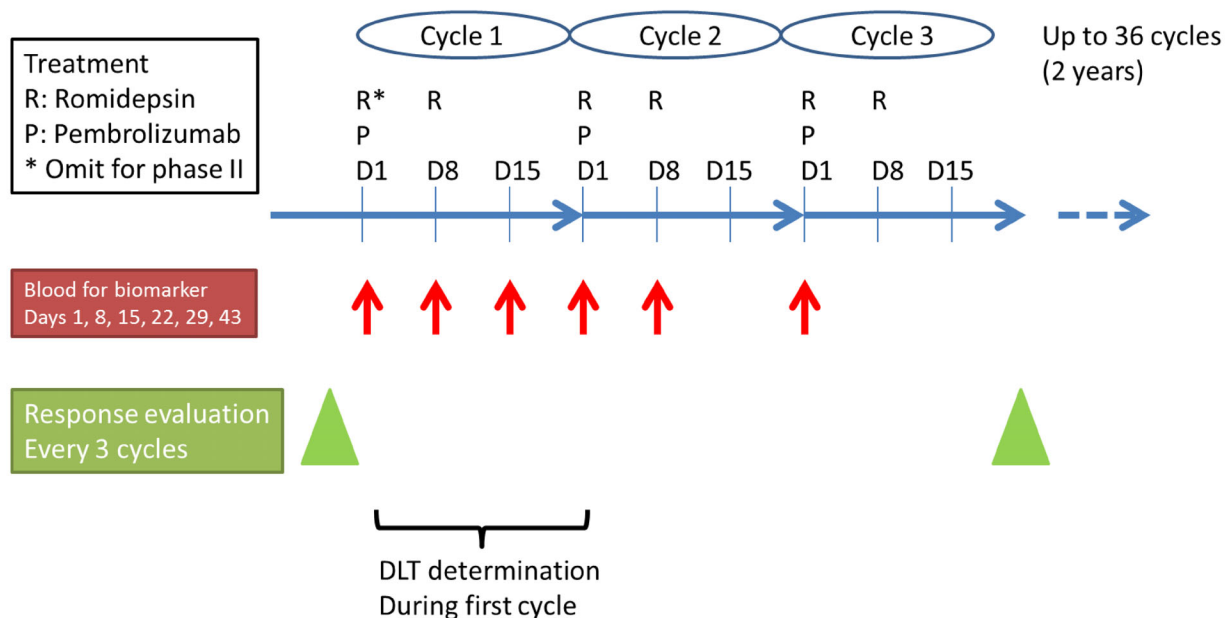
Per the investigator's discretion subjects who attain an investigator-determined confirmed complete response (CR) may consider stopping trial treatment after receiving at least 24 weeks of therapy. At least two doses must be received after CR is documented. After the end of treatment, each subject will be followed for 90 days for adverse event monitoring. But in addition, beyond 90 days the patients are to be carefully monitored for early evidence of transplant-related complications, such as hyperacute graft-versus-host disease (GVHD), severe acute GVHD, steroid-requiring febrile syndrome, hepatic veno-occlusive disease and other immune mediated adverse reactions. Subjects who discontinue treatment for reasons other than disease progression will have post-treatment follow-up for disease status until disease progression, initiating a non-study cancer treatment, withdrawing consent, or becoming lost to follow-up. All subjects will be followed by telephone contact for overall survival until death, withdrawal of consent or the end of the study, whichever comes first.

The primary objectives of the trial are to determine safety, tolerability, and overall response rate (ORR) of pembrolizumab in combination with romidepsin in subjects with relapsed and/or refractory PTCL. Secondary objectives include further analysis of various efficacy parameters [complete remission rate (CRR), progression free survival (PFS), overall survival (OS) and duration of response (DOR)]. We will also assess secondary endpoints such as, overall response rate (ORR) event-free survival (EFS), and failure-free survival (FFS).

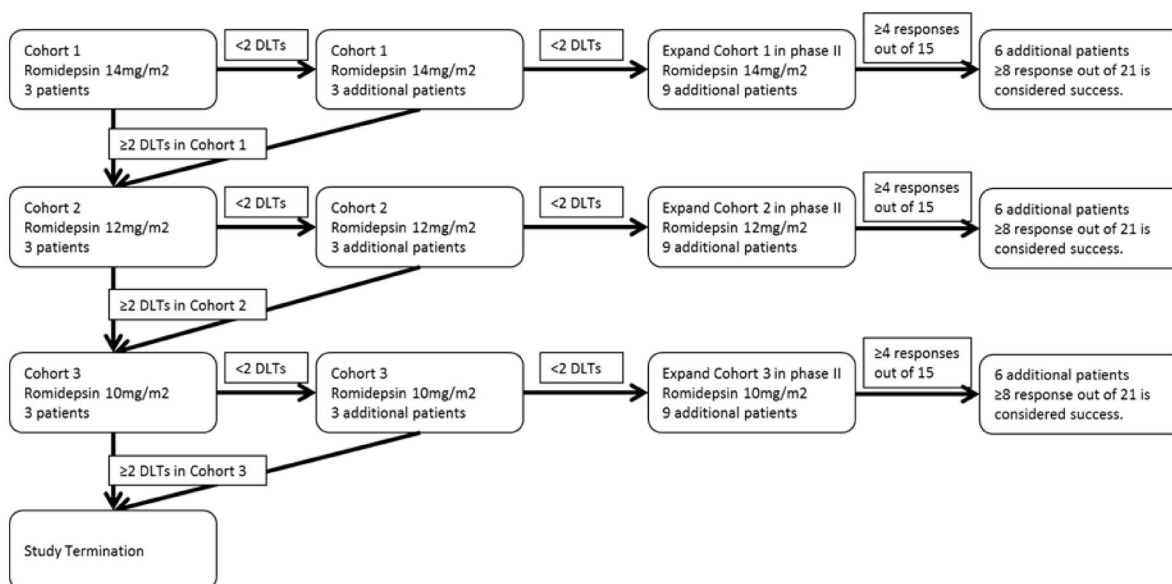
Response assessment is performed utilizing Lugano Revised Response Criteria,¹ and PD-L1 expression will be assessed by immunohistochemistry in the primary lymphoma tissue and exploratory analysis of its association with response is performed. Changes in peripheral blood T-cell repertoire will be assessed primarily by flow cytometry.

2.2 Trial Diagram

2.2.1 Treatment



2.2.2 Cohort



3.0 OBJECTIVES & HYPOTHESES

3.1 Primary Objectives

Objectives:

- (1) Evaluate the safety of pembrolizumab in combination with romidepsin.
- (2) Estimate the response rate of the combination therapy in refractory or recurrent PTCL

3.2 Secondary Objectives

Objectives:

- (1) Estimate progression free survival (PFS).
- (2) Estimate overall survival (OS).
- (3) Estimate complete response (CR) and duration of response (DOR).
- (4) Estimate the event-free survival (EFS) and the failure free survival (FFS)
- (5) Estimate the overall response rate (ORR) per Lugano criteria.

3.3 Exploratory Objectives

Objectives:

- (1) Assess activation of T-cells after treatment in peripheral blood and tumor microenvironment.
- (2) Correlate features of peripheral blood T-cell activation with toxicities, clinical response, and PFS.

4.0 BACKGROUND & RATIONALE

4.1 Background

4.1.1. Peripheral T-cell lymphoma

The management of recurrent or refractory T-cell lymphoma is challenging. The outcome of patients with such condition is dismal, short of stem cell transplant option. According to the report from British Columbia Cancer Agency, the median overall survival of this population was 5.5 months³. Also in MDACC experience, while autologous stem cell transplant is often considered for patients who experienced recurrence of the disease, the efficacy is moderate at best; 3 year overall survival is less than 30%. Allogeneic stem cell transplant therefore is

considered for young patients with recurrent disease, but this approach is with significant treatment related morbidity and mortality. ⁴

4.1.2. Romidepsin

Romidepsin is a histone deacetylase inhibitor that has shown a clinical anti-tumor activity against T-cell lymphoma, and has been approved for the treatment of relapsed or refractory peripheral T-cell lymphoma and cutaneous T-cell lymphoma. ⁵ While the drug was generally well tolerated, the response rate in PTCL is only 25%, and the median progression free survival is 4 months after starting romidepsin. ⁵ Other recently approved drugs for the same disease, including pralatrexate ⁶ and belinostat, ⁷ generally have only similar response rate and progression free survival. Novel therapeutic approaches with better efficacy and tolerability are needed.

The known adverse events of romidepsin are summarized below.

>10%:

Cardiovascular: ST-T wave changes (2% to 63%), hypotension (7% to 23%)

Central nervous system: Fatigue (53% to 77%), fever (20% to 47%), headache (15% to 34%), chills (11% to 17%)

Dermatologic: Pruritus (7% to 31%), dermatitis/exfoliative dermatitis (4% to 27%)

Endocrine & metabolic: Hypocalcemia (4% to 52%), hyperglycemia (2% to 51%), hypoalbuminemia (3% to 48%), hyperuricemia ($\leq 33\%$), hypomagnesemia (22% to 28%), hypermagnesemia ($\leq 27\%$), hypophosphatemia ($\leq 27\%$), hypokalemia (6% to 20%), hyponatremia ($\leq 20\%$)

Gastrointestinal: Nausea (56% to 86%; grades 3/4: 2% to 6%), anorexia (23% to 54%), vomiting (34% to 52%; grades 3/4: $\leq 10\%$), taste alteration (15% to 40%), constipation (12% to 40%), diarrhea (20% to 36%), weight loss (10% to 15%), abdominal pain (13% to 14%)

Hematologic: Anemia (19% to 72%; grades 3/4: 3% to 28%), thrombocytopenia (17% to 72%; grades 3/4: $\leq 36\%$), neutropenia (11% to 66%; grades 3/4: 4% to 47%), lymphopenia (4% to 57%; grades 3/4: $\leq 37\%$), leukopenia (4% to 55%; grades 3/4: $\leq 45\%$)

Hepatic: AST increased (3% to 28%), ALT increased (3% to 22%)

Neuromuscular & skeletal: Weakness (53% to 77%)

Respiratory: Cough (18% to 21%), dyspnea (13% to 21%)

Miscellaneous: Infection (46% to 54%; grades 3/4: 11% to 33%)

1% to 10%:

Cardiovascular: Peripheral edema (6% to 10%), tachycardia ($\leq 10\%$), chest pain, DVT, edema, QT prolongation, supraventricular arrhythmia, syncope, ventricular arrhythmia

Dermatologic: Cellulitis

Endocrine & metabolic: Dehydration

Gastrointestinal: Stomatitis (6% to 10%)

Hematologic: Neutropenic fever

Hepatic: Hyperbilirubinemia

Respiratory: Hypoxia, pneumonia, pneumonitis, pulmonary embolism

Miscellaneous: Central line infection, hypersensitivity, sepsis, tumor lysis syndrome (1% to 2%)

$\leq 1\%$ (Limited to important or life-threatening):

Acute renal failure, acute respiratory distress syndrome, atrial fibrillation, bacteremia, candida infection, cardiopulmonary failure, cardiogenic shock, Epstein-Barr virus reactivation, multiorgan failure, septic shock

4.1.3. Pembrolizumab (MK-3475)

Immune check point modulation is becoming an important strategy to manage cancer. One of the most effective approaches is PD1 blockade with monoclonal antibodies. Especially in Hodgkin lymphoma, PDL1 expression is observed nearly all cases, and anti-PD1 antibody therapy has shown significant efficacy in early studies.^{8,9}

PDL1 expression is also observed in PTCL. In a recent report, PDL1 expression is observed in 5-17% of tumor cells in PTCL-NOS or AITL, and 43%-57% in stromal histiocytes, and the expression of PDL1 suppresses host immunity.¹⁰ In addition, PTCL often carries multiple gene mutations in epigenetic modifier genes (TET2, IDH2, DNMT3A) and others (RHOA, FYN) that may impair immunogenicity and promote immune escape.¹¹⁻¹⁴

Multiple trials exploring PD-1 blockade in hematological malignancies are ongoing. Published data supports its safety and efficacy of such an approach. In a phase I study of nivolumab in patients with hematologic malignancies,⁹ a total of 81 patients were treated (follicular lymphoma, n = 10; diffuse large B-cell lymphoma, n = 11; other B-cell lymphomas, n = 10; mycosis fungoides, n = 13; peripheral T-cell lymphoma, n = 5; other T-cell lymphomas, n = 5;

multiple myeloma, n = 27). Patients had received a median of three (range, one to 12) prior systemic treatments. Drug-related adverse events occurred in 51 (63%) patients, and most were grade 1 or 2. Objective response rates were 40%, 36%, 15%, and 40% among patients with follicular lymphoma, diffuse large B-cell lymphoma, mycosis fungoides, and peripheral T-cell lymphoma, respectively. Median time of follow-up observation was 66.6 weeks (range, 1.6 to 132.0+ weeks). Durations of response in individual patients ranged from 6.0 to 81.6+ weeks.

While “active” immunotherapy by immune checkpoint blockade might not be applicable to all subtypes of PTCL, an additional anti-lymphoma effect of PD-1 antibodies by “passive” immune mechanisms could be postulated for PTCL with high PD-1 expression (e.g. AITL). For this subgroup of patients with high PD-1 expression, binding of the PD-1 monoclonal antibody (mAb) could lead to direct cytotoxicity, although with an IgG4 mAbs such as pembrolizumab less antibody-dependent (ADCC) or complement mediated cytotoxicity is expected than with IgG1 mAbs.

With this background, a phase I study enrolling multiple different hematologic malignancy revealed that 2 out of 5 patients with PTCL experienced objective response. Based on this study, a phase II single agent study of pembrolizumab is ongoing targeting patients with PTCL. While this is a very attractive treatment approach, above mentioned response is still considered inadequate. Additional strategies are needed to make this approach more effective to produce higher response rate with durable response duration.

Refer to the Investigator’s Brochure (IB)/approved labeling for detailed background information on pembrolizumab.

4.1.4 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 tyrosine-based switch motif

(ITSM). Following T-cell stimulation, PD-1 recruits the tyrosine phosphatases SHP-1 and SHP-2 to the ITSM motif within its cytoplasmic tail, leading to the dephosphorylation of effector molecules such as CD3 ζ , PKC θ 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 States for the treatment of patients with unresectable or metastatic melanoma and disease progression following ipilimumab and, if BRAF V600 mutation positive, a BRAF inhibitor.

4.1.5 Preclinical and Clinical Trial Data

Refer to the Investigator's Brochure for Preclinical and Clinical data.

4.2 Rationale

4.2.1 Rationale for the Trial and Selected Subject Population

Peripheral T-cell lymphoma

The management of recurrent or refractory T-cell lymphoma is challenging. The outcome of patients with such condition is dismal, short of stem cell transplant option. According to the report from British Columbia Cancer Agency, the median overall survival of relapsed or refractory PTCL was 5.5 months³. Also in MDACC experience, while autologous stem cell transplant is often considered for patients who experienced recurrence of the disease, the

efficacy is moderate at best; 3 year overall survival is less than 30%. Allogeneic stem cell transplant therefore is considered for young patients with recurrent disease, but this approach is with significant treatment related morbidity and mortality.⁴ As mentioned in 4.1.3., preliminary result of anti-PD1 antibody therapy in relapsed or refractory PTCL has shown promising result (response seen in 2 of 5 patients treated).

Combination of pembrolizumab with romidepsin

There are data supporting the rationale to combine histone deacetylase inhibitor with PD-1 blockade. Histone deacetylase blockage upregulates certain cancer testis antigens thereby makes the tumor more immunogenic. In addition, histone deacetylase promote expression of T-cell recruiting chemokines in the tumor. These effect of histone deacetylase inhibitor promote the immune reactivity leading to synergistic tumor eradication when combined with anti-PD1 antibody.^{15,16} In addition, histone deacetylase inhibitor induces PDL1 expression in cancer cell lines.¹⁷ Induction of PDL1 may be one of the mechanisms of resistance to HDAC inhibitor therapy, given the fact that HDAC inhibitors have anti-tumor activity but many would eventually become resistant clinically. Blocking immune checkpoints such as PD-1 may promote or unleash the endogenous antitumor immune responses and augment the efficacy of other therapeutic approaches.¹⁵⁻¹⁷

Based on above, here we propose a clinical trial combining romidepsin, which is an approved drug for PTCL, with fixed dose of pembrolizumab (200mg IV Q3W), to exert anti-lymphoma activity. The first part of the study serves as a phase I study to confirm the safety of combination, then a phase II study is to be performed for PTCL at the recommended phase II dose.

4.2.2 Rationale for Dose Selection/Regimen/Modification

An open-label Phase I trial (Protocol 001) is being 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. This first in human study of pembrolizumab showed evidence of target engagement and objective evidence of tumor size reduction at all dose levels (1 mg/kg, 3 mg/kg and 10 mg/kg Q2W). No maximum tolerated dose (MTD) has been identified to date. 10.0 mg/kg Q2W, the highest dose tested in PN001, will be the dose and schedule utilized in Cohorts A, B, C and D of this protocol to test for initial tumor activity. 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 pharmacodynamic 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.

4.2.3 Rationale for Endpoints

4.2.3.1 Toxicity Endpoints

The primary safety objective of this study is to characterize the safety and tolerability of pembrolizumab plus romidepsin in subjects with relapsed or refractory T-cell Lymphoma. The primary safety analysis will be based on subjects who experienced toxicities as defined by CTCAE criteria v4.0. Safety will be assessed by quantifying the toxicities and grades experienced by subjects who have received pembrolizumab and romidepsin, including serious adverse events (SAEs) and events of clinical interest (ECIs). Safety will be assessed by reported adverse experiences using CTCAE, Version 4.0. The attribution to drug, time-of-onset, duration of the event, its resolution, and any concomitant medications administered will be recorded. AEs will be analyzed including but not limited to all AEs, SAEs, fatal AEs, and laboratory changes. Furthermore, the occurrence of a Grade 2 or higher immune-related adverse events will be collected and designated as immune-related events of clinical interest (irAEs).

Dose limiting Toxicity (DLT) will be considered if it occurs during the first cycle (3 weeks) of treatment and is considered possibly related to the treatment. Dose limiting toxicity is defined by the following.

- Hematological DLTs:

Grade 4 neutropenia (absolute neutrophil count [ANC] $<500/\mu\text{L}$) for >7 days despite use of growth factor, or Grade ≥ 3 febrile neutropenia (ANC $<1000/\mu\text{L}$ with fever $>38.5^{\circ}\text{C}$ [101°F])

Grade 4 thrombocytopenia for >7 days, or grade ≥ 3 thrombocytopenia associated with bleeding

- Non-Hematological DLTs:

Grade ≥ 3 non-hematologic toxicity with exception of: Grade ≥ 3 diarrhea or nausea that resolve to $\leq$ Grade 2 within 48 hours with appropriate symptomatic treatment. In Phase I, treatment delay of ≥ 14 days due to unresolved toxicity

4.2.3.2 Efficacy Endpoints

The primary efficacy objective of this study is to evaluate the anti-tumor activity of pembrolizumab plus romidepsin in subjects with relapsed or refractory PTCL. Immunotherapeutic agents such as pembrolizumab may produce antitumor effects by potentiating endogenous cancer-specific immune responses, which may be functionally anergic. The response patterns seen with such an approach may extend beyond the typical time course of responses seen with cytotoxic agents, and can manifest a clinical response after an initial increase in tumor burden or even the appearance of new lesions. Standard response assessment criteria may not provide a comprehensive response assessment of

immunotherapeutic agents such as pembrolizumab. Therefore in the setting where a subject assessment shows PD, study drug may be continued, at the discretion of the PI, until the next disease response assessment provided the subjects' clinical condition is stable. However, imaging study or any other response assessment should occur at any time where there is clinical suspicion of progression. Patients will be assessed for responses by CT scans or PET-CT scans every 3 cycles. Patients with bone marrow involvement at baseline will require follow-up bone marrow examination to document a complete response.

Response assessment in CTCL will be done as per the modified Severity Weighted Assessment Tool (mSWAT). Additionally, CT scan will be done in the CTCL patients with lymph node and visceral involvement. CTCL patients with subcutaneous lesions which cannot be measured by mSWAT will be assessed by change in PET-CT avid lesions. Bone marrow biopsy will be performed in patients with B2 blood involvement. In these patients, Sezary cell count will be quantified by flow cytometry or morphology in blood/bone marrow.

4.2.3.3 Biomarker Research

Blood samples and tumor biopsies will be obtained from consenting patients at baseline and/or on treatment from subjects enrolled on the study at the indicated time points shown in the Trial Flow Chart indicated at 2.2.1. The overall goal of the biomarker studies is to identify predictive, surrogate, mechanistic, and pharmacodynamic biomarkers of pembrolizumab plus romidepsin therapy. Peripheral blood mononuclear cells (PBMC) and plasma will be isolated from blood samples and cryopreserved for batched analysis.

PBMC samples will be analyzed by up to 14-color multiparametric flow cytometry to determine alteration in effector and regulatory T cell subsets and to determine expression of various co-stimulatory and co-inhibitory receptors on T cells. Plasma samples will be analyzed for alteration in various cytokines and chemokines. Tumor biopsies will be analyzed by whole genome gene expression profiling (GEP), whole exome sequencing, immunohistochemistry (IHC), and/or flow cytometry. IHC/flow cytometry assessment will include PD-1, PD-L1, and PD-L2 expression besides evaluation of effector and regulatory T cell subsets. We will also assess the predictive significance of the intratumoral effector T cell gene signature.

5.0 METHODOLOGY

5.1 Entry Criteria

5.1.1 Diagnosis/Condition for Entry into the Trial

1. Patients with peripheral T-cell lymphoma (including but not limited to PTCL-NOS, angioimmunoblastic T-cell lymphoma, anaplastic large T-cell lymphoma). Patients with mycosis fungoides with large cell transformation with measurable disease are eligible.
2. Disease status defined as refractory to or relapsed after ≥ 1 prior treatment lines.

3. Patients irrespective of transplant eligibility status can be enrolled; however patients can be seen by SCT team in anticipation for SCT. 4. Subjects with ALK+ ALCL should have been treated with, be ineligible for, or have refused chemotherapy and brentuximab prior to enrollment on the current study.

5. Patients with a measurable disease, defined by a node or mass with the longest diameter $\geq$ 1.5cm.

5.1.2 Subject Inclusion Criteria

In order to be eligible for participation in this trial, the subject must:

1. Be willing and able to provide written informed consent/assent for the trial.
2. Be $\geq$ 18 years of age on day of signing informed consent.
3. Patients with PTCL should have radiographically measurable disease $\geq$ 1.5cm.
4. Be willing to provide tissue from a newly obtained core or excisional biopsy of a tumor lesion. *Newly-obtained is defined as a specimen obtained up to 12 weeks(84 days) prior to initiation of treatment on Day 1. Subjects for whom newly-obtained samples cannot be provided (e.g. inaccessible or subject safety concern) may submit an archived specimen.*
5. Have a performance status of 0, 1 or 2 on the ECOG Performance Scale.
6. Demonstrate adequate organ function as defined in Table 1, all screening labs should be performed within 14 days of treatment initiation.

Table 1 Adequate Organ Function Laboratory Values

System	Laboratory Value
Hematological	
Absolute neutrophil count (ANC)	$\geq$ 1000 /mcL
Platelets	$\geq$ 100,000 / mcL. If bone marrow is involved, platelets should be at least 50K and ANC 750 / mcL
Hemoglobin	$\geq$ 8g/dL without transfusion or EPO dependency (within 7 days of assessment)
Renal	
Serum creatinine <u>OR</u>	$\leq$ 1.5 X upper limit of normal (ULN) <u>OR</u>

Measured or calculated ^a creatinine clearance (GFR can also be used in place of creatinine or CrCl)	≥60 mL/min for subject with creatinine levels > 1.5 X institutional ULN
Hepatic	
Serum total bilirubin	≤ 1.5 X ULN OR
	Direct bilirubin ≤ ULN for subjects with total bilirubin levels > 1.5 ULN
AST (SGOT) and ALT (SGPT)	≤ 2.5 X ULN OR ≤ 5 X ULN for subjects with liver metastases
Albumin	≥ 2 mg/dL
Coagulation	
International Normalized Ratio (INR) or Prothrombin Time (PT)	≤1.5 X ULN unless subject is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants
Activated Partial Thromboplastin Time (aPTT)	≤1.5 X ULN unless subject is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants
^a Creatinine clearance should be calculated per institutional standard.	

7. Female subject of childbearing potential should have a negative urine or serum pregnancy within 72 hours prior to receiving the first dose of study medication. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required.
8. Female subjects of childbearing potential (Section 5.7.2) must be willing to use an adequate method of contraception as outlined in Section 5.7.2 – Contraception, for the course of the study through 120 days after the last dose of study medication.

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

9. Male subjects of childbearing potential (Section 5.7. .2 must agree to use an adequate method of contraception as outlined in Section 5.7. .2- Contraception, starting with the first dose of study therapy through 120 days after the last dose of study therapy.

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

10. Relapsed/refractory Cutaneous T cell Lymphomas (CTCL) patients with transformed and aggressive T Cell with predominant lymph node involvement and those that are

measurable by standard T Cell criteria. These patients require failure of at least one prior systemic therapy for the transformed lymphoma.

5.1.3 Subject Exclusion Criteria

The subject must be excluded from participating in the trial if the subject:

1. Is currently receiving study therapy or has participated in a study of an investigational agent and received study therapy or used an investigational device within 4 weeks of the first dose of treatment.
2. Has a diagnosis of immunodeficiency, is receiving systemic steroids above physiologic dose ($>10\text{mg/day}$ prednisone or equivalent) within 5 half lives after the last dose of steroid of start of therapy or is receiving any other form of immunosuppressive therapy.
3. Has a known history of active TB (Bacillus Tuberculosis)
4. Hypersensitivity to pembrolizumab or any of its excipients.
5. Has had a prior anti-cancer monoclonal antibody (mAb) within 4 weeks prior to study Day 1 or who has not recovered (i.e., $\leq$ Grade 1 or at baseline) from adverse events due to agents administered more than 4 weeks earlier.
6. Has had prior chemotherapy, targeted small molecule therapy, or radiation therapy within 2 weeks prior to study Day 1 or who has not recovered (i.e., $\leq$ Grade 1 or at baseline) from adverse events due to a previously administered agent.
 - Note: Subjects with $\leq$ 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.
7. Has a known additional malignancy that is progressing or requires active treatment within the last 3 years Exceptions include basal cell carcinoma of the skin, resected renal cell cancer or squamous cell carcinoma of the skin that has undergone potentially curative therapy or in situ cervical cancer.
8. Has known active central nervous system (CNS) metastases and/or carcinomatous meningitis. Subjects with previously treated brain metastases may participate provided they are stable (without evidence of progression by imaging for at least four weeks prior to the first dose of trial treatment and any neurologic symptoms have returned to

baseline), have no evidence of new or enlarging brain metastases, and are not using steroids for at least 7 days prior to trial treatment. This exception does not include carcinomatous meningitis which is excluded regardless of clinical stability.

9. 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). Replacement therapy (e.g., thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency, etc.) is not considered a form of systemic treatment.
10. Has known history of non-infectious pneumonitis that required systemic steroid use, or has active pneumonitis.
11. Has an active infection requiring systemic therapy.
12. 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.
13. Has known psychiatric or substance abuse disorders that would interfere with cooperation with the requirements of the trial.
14. Is pregnant or breastfeeding, or expecting to conceive or father children within the projected duration of the trial, starting with the pre-screening or screening visit through 120 days after the last dose of trial treatment.
15. Has received prior therapy with an anti-PD-1, anti-PD-L1, or anti-PD-L2 agent.
16. Has a known history of Human Immunodeficiency Virus (HIV) (HIV 1/2 antibodies).
17. Has known active Hepatitis B (e.g., HBsAg reactive) or Hepatitis C (e.g., HCV RNA [qualitative] is detected).
18. Baseline EKG shows QTcF > 470 msec
19. Concomitant use of strong CYP3A4 inhibitors and inducers.
20. Has received a live vaccine within 30 days of planned start of study therapy.

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.
21. Has undergone prior allogenic hematopoietic stem cell transplantation any time.

5.2 Trial Treatments

All trial treatments will be administered on an outpatient basis.

Phase 1: On Day 1 of each cycle, romidepsin is given first, followed by pembrolizumab.

Phase 2: The exception is the cycle 1 day 1 in the phase II study, where only pembrolizumab is to be given for biomarker analysis.

Treatment is every 21 day cycle, up to 35 cycles in the absence of progression or serious toxicity.

After disease evaluation with imaging on (+/-3days) on C4- if patient achieves CR, Romidepsin on subsequent Day 8 can be given by local Oncologist. On next imaging, if above patient is still on CR, Day 8 can be skipped per Principal Investigators discretion. Patient will continue with treatment until 35 cycles.

If patients achieved PR or stable disease on (+/-3days) on C4- Romidepsin on subsequent Day 8 can be given by local Oncologist or at MD Anderson. On next imaging if above patient has achieved CR, patient will continue to receive Romidepsin for 2 more cycles, then Day 8 can be skipped per Principal Investigators discretion. Day 8 Romidepsin can be restarted at any time in subsequent cycles after discussion with the Principal Investigator. Patient will continue with treatment until 35 cycles.

The treatment to be used in this trial is outlined below in Table 2

Table 2 Trial Treatment

Drug	Dose/Potency	Dose Frequency	Route of Administration	Regimen/Treatment Period	Use
Pembrolizumab	200 mg	Q3W	IV infusion	Day 1 of each 3 week cycle	Experimental
Romidepsin	Dose level 0 = 14 mg/m ² Dose level - 1 = 10 mg/m ²	Q3W	IV infusion 4 hours	Day 1 and 8 of each 3 week cycle (with the exception of Phase 2, C1D1	

Drug	Dose/Potency	Dose Frequency	Route of Administration	Regimen/Treatment Period	Use
	Dose level -2 = 8 mg/m ²			when Romidepsin is omitted)	

5.2.1 Dose Selection/Modification

5.2.1.1 Dose Selection

5.2.1.1.1 Romidepsin

The toxicity profile of pembrolizumab and romidepsin have limited overlap, as reviewed in 4.1.2 and 4.1.3. To maximize the efficacy of both drugs, it is considered safe and reasonable to test the combination of the two drugs at their optimal dose as a single agent. Therefore, the strategy for the phase I study is dose de-escalation, rather than dose escalation.

Romidepsin is given according to the institutional guideline of romidepsin. EKG should be performed on day 1 of each cycle within 6 hours prior to romidepsin infusion, and confirm QTcF ≤ 470 msec.

Dose level 0 = 14 mg/m²

Dose level -1 = 10 mg/m²

Dose level -2 = 8 mg/m²

Dose level 0 = 14mg/m²: First, 3 patients are to be treated at this dose. If 2 or more patients out of first 3 patients experience DLT, this dose is considered exceeding MTD, and the dose level -1 is to be evaluated. Otherwise, 6 patients are to be treated at the dose. If 2 or more out of the 6 patients experience DLT, this dose is considered exceeding DLT, and the level -1 is to be tested. If 0 or 1 patient experienced DLT in 6 patients, this dose is the MTD and can be evaluated in the phase II study.

Dose level -1 = 10mg/m²: The same strategy is to be applied to evaluate this dose, if needed..

Dose level -2 = 8mg/m²: The same strategy is to be applied to evaluate this dose. If this dose is to be considered exceeding MTD, the study is to be terminated.

Following the above scheme, MTD is defined as the highest dose level in which 6 patients have been treated with less than 2 instances of DLT. Recommended phase 2 dose (RP2D) will be a dose level at MTD or lower than MTD with similar efficacy.

The 6 patients tested in the phase I at the dose finally determined as RP2D will be included in the response assessment of phase II study.

Of note, once in phase II study, cycle 1 day 1 romidepsin will be omitted (i.e. pembrolizumab lead in time). This way, day 8 blood sample will be able to assess the host response by pembrolizumab alone. Romidepsin will be started from cycle 1 day 8.

5.2.1.1.2 Pembrolizumab

The rationale for selection of doses to be used in this trial is provided in Section 4.0 – Background and Rationale.

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

5.2.1.2 Dose Modification (Escalation/Titration/Other)

Adverse events (both non-serious and serious) associated with pembrolizumab exposure may represent an immunologic etiology. These adverse events may occur shortly after the first dose or several months after the last dose of treatment. Pembrolizumab must be withheld for drug-related toxicities and severe or life-threatening AEs as per Table 3 below. See Section 5.6 for supportive care guidelines, including use of corticosteroids.

Table 3 Dose Modification Guidelines for Drug-Related Adverse Events

Toxicity	Hold Treatment For Grade	Timing for Restarting Treatment	Treatment Discontinuation
Diarrhea/Colitis	2-3	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks
	4	Permanently discontinue	Permanently discontinue
	2	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose

Toxicity	Hold Treatment For Grade	Timing for Restarting Treatment	Treatment Discontinuation
AST, ALT, or Increased Bilirubin	3-4	Permanently discontinue (see exception below) ^a	Permanently discontinue
Type 1 diabetes mellitus (if new onset) or Hyperglycemia	T1DM or 3-4	Hold pembrolizumab for new onset Type 1 diabetes mellitus or Grade 3-4 hyperglycemia associated with evidence of beta cell failure	Resume pembrolizumab when patients are clinically and metabolically stable
Hypophysitis	2-4	Toxicity resolves to Grade 0-1. Therapy with pembrolizumab can be continued while endocrine replacement therapy is instituted	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks
Hyperthyroidism	3	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks
	4	Permanently discontinue	Permanently discontinue
Hypothyroidism		Therapy with pembrolizumab can be continued while thyroid replacement therapy is instituted	Therapy with pembrolizumab can be continued while thyroid replacement therapy is instituted
Infusion Reaction	2 ^b	Toxicity resolves to Grade 0-1	Permanently discontinue if toxicity develops despite adequate premedication
	3-4	Permanently discontinue	Permanently discontinue
Pneumonitis	2 ^c	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks
	3-4	Permanently discontinue	Permanently discontinue
Renal Failure or Nephritis	2	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks
	3-4	Permanently discontinue	Permanently discontinue
	3 or Severe	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to

Toxicity	Hold Treatment For Grade	Timing for Restarting Treatment	Treatment Discontinuation
All Other Drug-Related Toxicity ^d			10 mg or less of prednisone or equivalent per day within 12 weeks
	4	Permanently discontinue	Permanently discontinue

Note: Permanently discontinue for any severe or Grade 3 drug-related AE that recurs or any life-threatening event.

^a For patients with liver metastasis who begin treatment with Grade 2 AST or ALT, if AST or ALT increases by greater than or equal to 50% relative to baseline and lasts for at least 1 week then patients should be discontinued.

^b If symptoms resolve within one hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (e.g., from 100 mL/hr to 50 mL/hr). Otherwise dosing will be held until symptoms resolve and the subject should be premedicated for the next scheduled dose; Refer – Infusion Treatment Guidelines for further management details.

^c Should grade 2 pneumonitis recur, patient will be removed from study.

^d Patients with intolerable or persistent Grade 2 drug-related AE may hold study medication at physician discretion. Permanently discontinue study drug for persistent Grade 2 adverse reactions for which treatment with study drug has been held, that do not recover to Grade 0-1 within 12 weeks of the last dose.

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

5.2.2 Timing of Dose Administration

Trial treatment should be administered on Day 1 of each cycle after all procedures/assessments have been completed as detailed on the Trial Flow Chart (Section 6.0). Trial treatment may be administered up to 3 days before or after the scheduled Day 1 of each cycle.

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.

Above mentioned immune mediated toxicity criteria for pembrolizumab must be met to start the next cycle of treatment. In addition, all other non-hematologic toxicities must have recovered to grade 2 or better, absolute neutrophil count (ANC) must be $\geq 0.75 \times 10^9/\text{L}$ and platelets must be $\geq 75 \times 10^9/\text{L}$ to administer romidepsin.

On day 8, all non-hematologic toxicities must have recovered to grade 2 or better, and platelets must be $\geq 50 \times 10^9/\text{L}$ to administer romidepsin. There is no requirement for ANC for day 8 romidepsin.

5.2.3 Trial Blinding/Masking

This is an open-label trial; therefore, Merck, IND office, investigator and subject will know the treatment administered.

5.3 Randomization or Treatment Allocation

There is no randomization.

5.4 Stratification

There is no stratification.

5.5 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.

5.5.1 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 EMR (EPIC) including all prescription, over-the-counter (OTC), herbal supplements, and IV medications and fluids. If changes occur during the trial period, documentation of drug dosage, frequency, route, and date may also be included on the CRF.

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

5.5.2 Prohibited Concomitant Medications

Subjects are prohibited from receiving the following therapies during the Screening and Treatment Phase:

- 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 systemic glucocorticoids is acceptable premedication for contrast CT scans if patients are allergic to intravenous contrast. The use of physiologic doses of corticosteroids may be approved after consultation with the principal investigator.
- 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.
- Medications which have a risk of causing Torsades de Pointes ventricular arrhythmia, namely strong CYP3A4 inhibitors (Appendix A) should be avoided.

Concomitant use of moderate CYP3A4 inhibitors and p-glycoprotein inhibitors (Appendix A) should be used with caution when administered with romidepsin.

Table 4. Medications which have a risk of causing Torsades de pointes to be avoided

All Class IA antiarrhythmics including but not limited to • quinidine • procainamide

• disopyramide
All Class III antiarrhythmics including but not limited to amiodarone sotalol bretylium disopyramide dofetilide ibutilide
Antibiotics Macrolide antibiotics* • erythromycin • clarithromycin • telithromycin Quinolone antibiotics* sparfloxacin
Antipsychotics thioridazine mesoridazine chlorpromazine pimozide
Antimalarials • halofantrine • chloroquine
Miscellaneous drugs • arsenic trioxide • astemizole • bepridil • domperidone • levomethadyl • methadone • pentamidine • droperidol
*Note: azithromycin, ciprofloxacin, levofloxacin, pefloxacin, ofloxacin, tosylfloxacin, difloxacin, temafloxacin, fleroxacin, acrosoxacin, nalidixic acid and enoxacin are allowed.

This is not a comprehensive list of medications which may prolong the QT interval or have a risk of causing Torsades de pointes. The following website may be referenced as a supplemental guide for drugs which have been associated with Torsades de pointes or prolonging the QT interval but at this point lack substantial evidence for causing Torsades de pointes:

<https://www.crediblemeds.org/pdftemp/pdf/CompositeList.pdf>

Medications listed on the website which do not appear in this Table above may be used with caution at the discretion of the investigators. The serotonin (5HT3) antagonists, often used as antiemetics, such as ondansetron dolasetron, (also are known CYP2D6 substrates, see Table 3-1), or granisetron have been associated with Torsades de points and QT prolongation but have not been shown to cause Torsades de pointes. Therefore, 5HT3 antagonists are not per se prohibited but close monitoring for signs and symptoms of QT prolongation is recommended. Caution is to be exercised when using these or other agents that may prolong QT intervals.

There are no prohibited therapies during the Post-Treatment Follow-up Phase.

5.6 Rescue Medications & Supportive Care

5.6.1 Supportive Care Guidelines

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

Note: if after the evaluation the event is determined not to be related, the investigator does not need to follow the treatment guidance (as outlined below). Refer to Section 5.2.1 for dose modification.

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

- **Pneumonitis:**

- For **Grade 2 events**, treat with systemic corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.
- For **Grade 3-4 events**, immediately treat with intravenous steroids. Administer additional anti-inflammatory measures, as needed.
- Add prophylactic antibiotics for opportunistic infections in the case of prolonged steroid administration.

- **Diarrhea/Colitis:**

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

- All subjects who experience diarrhea/colitis should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion. For Grade 2 or higher diarrhea, consider GI consultation and endoscopy to confirm or rule out colitis.
- For **Grade 2 diarrhea/colitis**, administer oral corticosteroids.
- For **Grade 3 or 4 diarrhea/colitis**, treat with intravenous steroids followed by high dose oral steroids.
- When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.
- **Type 1 diabetes mellitus (if new onset, including diabetic ketoacidosis [DKA]) or $\geq$ Grade 3 Hyperglycemia, if associated with ketosis (ketonuria) or metabolic acidosis (DKA)**
 - For **T1DM** or **Grade 3-4 Hyperglycemia**
 - Insulin replacement therapy is recommended for Type I diabetes mellitus and for Grade 3-4 hyperglycemia associated with metabolic acidosis or ketonuria.
 - Evaluate patients with serum glucose and a metabolic panel, urine ketones, glycosylated hemoglobin, and C-peptide.
- **Hypophysitis:**
 - For **Grade 2** events, treat with corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. Replacement of appropriate hormones may be required as the steroid dose is tapered.
 - For **Grade 3-4** events, treat with an initial dose of IV corticosteroids followed by oral corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. Replacement of appropriate hormones may be required as the steroid dose is tapered.
- **Hyperthyroidism or Hypothyroidism:**

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

 - **Grade 2** hyperthyroidism events (and **Grade 2-4** hypothyroidism):

- In hyperthyroidism, non-selective beta-blockers (e.g. propranolol) are suggested as initial therapy.
 - In hypothyroidism, thyroid hormone replacement therapy, with levothyroxine or liothyronine, is indicated per standard of care.
- **Grade 3-4** hyperthyroidism
 - Treat with an initial dose of IV corticosteroid followed by oral corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. Replacement of appropriate hormones may be required as the steroid dose is tapered.
- **Hepatic:**
 - For **Grade 2** events, monitor liver function tests more frequently until returned to baseline values (consider weekly).
 - Treat with IV or oral corticosteroids
 - For **Grade 3-4** events, treat with intravenous corticosteroids for 24 to 48 hours.
 - When symptoms improve to Grade 1 or less, a steroid taper should be started and continued over no less than 4 weeks.
- **Renal Failure or Nephritis:**
 - For **Grade 2** events, treat with corticosteroids.
 - For **Grade 3-4** events, treat with systemic corticosteroids.
 - When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.
- **Management of Infusion Reactions:** Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion.

Below shows treatment guidelines for subjects who experience an infusion reaction associated with administration of pembrolizumab.

Table 4 Infusion Reaction Treatment Guidelines

NCI CTCAE Grade	Treatment	Premedication at subsequent dosing
<u>Grade 1</u> Mild reaction; infusion interruption not	Increase monitoring of vital signs as medically indicated until the subject is deemed medically	None

NCI CTCAE Grade	Treatment	Premedication at subsequent dosing
indicated; intervention not indicated	stable in the opinion of the investigator.	
<u>Grade 2</u> Requires infusion interruption but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDS, narcotics, IV fluids); prophylactic medications indicated for < =24 hrs	Stop Infusion and monitor symptoms. Additional appropriate medical therapy may include but is not limited to: IV fluids Antihistamines NSAIDS Acetaminophen Narcotics Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator. If symptoms resolve within one hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (e.g., from 100 mL/hr to 50 mL/hr). Otherwise dosing will be held until symptoms resolve and the subject should be premedicated for the next scheduled dose. Subjects who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further trial treatment administration.	Subject may be premedicated 1.5h ($\pm$ 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 antipyretic).
<u>Grades 3 or 4</u> Grade 3: Prolonged (i.e., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following	Stop Infusion. Additional appropriate medical therapy may include but is not limited to: IV fluids Antihistamines NSAIDS Acetaminophen Narcotics	No subsequent dosing

NCI CTCAE Grade	Treatment	Premedication at subsequent dosing
initial improvement; hospitalization indicated for other clinical sequelae (e.g., renal impairment, pulmonary infiltrates) Grade 4: Life-threatening; pressor or ventilatory support indicated	Oxygen Pressors Corticosteroids Epinephrine Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator. Hospitalization may be indicated. Subject is permanently discontinued from further trial treatment administration.	
Appropriate resuscitation equipment should be available in the room and a physician readily available during the period of drug administration.		

5.7 Diet/Activity/Other Considerations

5.7.1 Diet

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

5.7.2 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.

5.7.3 Use in Pregnancy

If a subject inadvertently becomes pregnant while on treatment with pembrolizumab, the subject will immediately be removed from the study. The site will contact the subject at least monthly and document the subject's status until the pregnancy has been completed or terminated. The outcome of the pregnancy will be reported within 2 working days to Merck if the outcome is a serious adverse experience (e.g., death, abortion, congenital anomaly, or other disabling or life-threatening complication to the mother or newborn).

The study investigator will make every effort to obtain permission to follow the outcome of the pregnancy and report the condition of the fetus or newborn to Merck. If a male subject impregnates his female partner the study personnel at the site must be informed immediately and the pregnancy reported to Merck and followed as described above and in Section 7.2.2.

5.7.4 Use in Nursing Women

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

5.8 Subject Withdrawal/Discontinuation Criteria

Subjects may withdraw consent at any time for any reason or be dropped from the trial at the discretion of the investigator should any untoward effect occur. In addition, a subject may be withdrawn by the investigator if enrollment into the trial is inappropriate, the trial plan is violated, or for administrative and/or other safety reasons. Specific details regarding discontinuation or withdrawal are provided in Section 7.1.4 – Other Procedures.

A subject must be discontinued from the trial for any of the following reasons:

- The subject or legal representative (such as a parent or legal guardian) withdraws consent.
- Confirmed radiographic disease progression

Note: For unconfirmed radiographic disease progression, please see Section 5.2.2

Note: A subject may be granted an exception to continue on treatment with confirmed radiographic progression if clinically stable or clinically improved, Unacceptable adverse experiences as described in Section 5.2.1.2

- Intercurrent illness that prevents further administration of treatment
- Investigator's decision to withdraw the subject
- The subject has a confirmed positive serum pregnancy test
- Noncompliance with trial treatment or procedure requirements
- The subject is lost to follow-up
- Completed 35 cycles of uninterrupted treatment with pembrolizumab or 35 administrations of study medication, whichever is later.
- *Note: 35 cycles of study medication is calculated from the date of first dose.*
Administrative reasons

The End of Treatment and Follow-up visit procedures are listed in Section 6 (Protocol Flow Chart) and Section 7.1.4.3 (Visit Requirements). After the end of treatment, each subject will be followed for 30 days for adverse event monitoring (serious adverse events will be collected

for 90 days after the end of treatment as described in Section 7.2.3.1). But in addition, beyond 90 days the patients are to be carefully monitored for early evidence of transplant-related complications, such as hyperacute graft-versus-host disease (GVHD), severe acute GVHD, steroid-requiring febrile syndrome, hepatic veno-occlusive disease and other immune mediated adverse reactions. Subjects who discontinue for reasons other than progressive disease will have post-treatment follow-up for disease status until disease progression, initiating a non-study cancer treatment, withdrawing consent or becoming lost to follow-up. After documented disease progression each subject will be followed by telephone for overall survival until death, withdrawal of consent, or the end of the study, whichever occurs first.

5.8.1 Discontinuation of Study Therapy after CR

Discontinuation of treatment may be considered for subjects who have attained a confirmed CR that have been treated for at least 24 weeks with pembrolizumab. Subject Replacement Strategy

For phase I portion of the study, if a subject did not complete the first cycle for reasons other than DLT, a subject is replaced with another subject for toxicity evaluation.

For phase II portion of the study, if a subject terminates study treatment without adequate response evaluation (either clinical or radiographic) at 3 cycles, a subject is considered as inevaluable for efficacy evaluation.

5.9 Clinical Criteria for Early Trial Termination

Early trial termination will be the result of the criteria specified below:

1. Quality or quantity of data recording is inaccurate or incomplete
2. Poor adherence to protocol and regulatory requirements
3. Incidence or severity of adverse drug reaction in this or other studies indicates a potential health hazard to subjects
4. Plans to modify or discontinue the development of the study drug

In the event of Merck decision to no longer supply study drug, ample notification will be provided so that appropriate adjustments to subject treatment can be made.

6.0 TRIAL FLOW CHART

6.1 Study Flow Chart

Trial Period:	Screening Phase	Treatment Cycles +/- 3 days for treatment												End of Treatment (EOT) ^f	Post-Treatment		
		C1 D1	C1 D8	C1 D15	C2 D1	C2 D8	C3 D1	C3 D8			C4	C5	C6	C7			
Treatment Cycle/Title:	Main Study Screening (Visit 2)																Survival Follow-Up
Scheduling Window (Days):	-28 to -1	± 1	± 1	± 1	±3	±1	±3	±1							At time of Discon	Every 12 weeks post discon	Survival Follow-Up Every 12 weeks
Administrative Procedures																	
Informed Consent	x																
Inclusion/Exclusion Criteria	x																
Demographics and Medical History	x																
Prior and Concomitant Medication Review		x	x		x	x	x	x			x	x	x	x	x		
Romidepsin administration ^a		x	x		x	x	x	x			x	x	x	x			
Pembrolizumab administration																	
Post-study anticancer therapy status																x	x
Survival Status																	x
Clinical Procedures/Assessments																	
Review Adverse Events		x						x			x	x	x	x			

	Screening Visit	C1 D1	C1 D8	C1 D15	C2 D1	C2 D8	C3 D1	C3 D8	C4	C5	C6	C7	At time of Discontinuation	Safety Follow up	Follow up Visits (every 12 weeks)	Survival Follow up
Full Physical Examination	x	x			x		x		x	x	x	X				
Directed Physical Examination ^b			x					x								
Vital Signs	x	x	x		x	x	x	x	x	x	x	X				
ECOG Performance Status	x	x	x		x	x	x	x	x	x	x	X				
Laboratory Procedures/Assessments: analysis performed by LOCAL laboratory																
Pregnancy Test – Urine or Serum Beta-HCG (Day 1 of each cycle)	x	x			x		x		x	x	x	X				
PT/INR and aPTT	x															
CBC with Differential ^c	x	x	x	x	x	x	x	x	x	x	x	X	x	x	x	
Comprehensive Serum Chemistry Panel, Mg, Phos, Uric Acid, LDH	x	x	x	x	x		x	x	x	x	x	X	x	x	x	
Urinalysis	x															
T3, FT4 and TSH (every 2 cycles)	x				x				x		X		x		x	
Pulmonary function tests	x															
EBV/PCR	x															
Efficacy Measurements																
Imaging (CT or PET/CT, every 3 cycles) ^e	x								X			X			x	
EKG Assessment ^d		x	x		x		x	x	x	x	x	X				
Tumor Biopsies/Archival Tissue Collection/Correlative Studies Blood																
Archival or Newly Obtained Tissue Collection	x															
Correlative Studies Blood Collection	x	x	x	x	x	x		x								

^a Romidepsin will be given on days 1 and 8 of all cycles, except on Phase II, where it will be given on day 8 only during C1..

^b Directed Exams will be done on day 8 of Cycles 1, 2, and 3; then day 8 of succeeding cycles.

^c CBC and Comprehensive serum chemistry be taken every Day 8 of each cycle

^d . Phase 1 - EKG will be done on day 1 of each cycle. Phase 2 EKG will be done on C1D8 and on day 1 of all subsequent cycles.

^e Imaging will be done (-3 days) every 3 cycles. C4, C7, C10, and onward.

^f Patient with rapidly progressive disease will be tested with relevant laboratory and scans at EOT.

7.0 TRIAL PROCEDURES

7.1 Trial Procedures

The Trial Flow Chart - Section 6.0 summarizes the trial procedures to be performed at each visit. Individual trial procedures are described in detail below. It may be necessary to perform these procedures at unscheduled time points if deemed clinically necessary by the investigator.

Furthermore, additional evaluations/testing may be deemed necessary by the IND Office and/or Merck for reasons related to subject safety. In some cases, such evaluation/testing may be potentially sensitive in nature (e.g., HIV, Hepatitis C, etc.), and thus local regulations may require that additional informed consent be obtained from the subject. In these cases, such evaluations/testing will be performed in accordance with those regulations.

7.1.1 Administrative Procedures

7.1.1.1 Informed Consent

The Investigator must obtain documented consent from each potential subject prior to participating in a clinical trial.

7.1.1.2 Inclusion/Exclusion Criteria

All inclusion and exclusion criteria will be reviewed by the investigator or qualified designee to ensure that the subject qualifies for the trial.

7.1.1.3 Medical History

A medical history will be obtained by the investigator or qualified designee. Medical history will include all active conditions, and any condition diagnosed within the prior 10 years that are considered to be clinically significant by the Investigator. Details regarding the disease for which the subject has enrolled in this study will be recorded separately and not listed as medical history.

7.1.1.4 Prior and Concomitant Medications Review

7.1.1.4.1 Prior Medications

The investigator or qualified designee will review prior medication use, including any protocol-specified washout requirement, and record prior medication taken by the subject within 28 days before starting the trial. Treatment for the disease for which the subject has enrolled in this study will be recorded separately and not listed as a prior medication.

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7.1.1.4.2 Concomitant Medications

The investigator or qualified designee will record medication, if any, taken by the subject during the trial. All medications related to reportable SAEs and ECIs should be recorded as defined in Section 7.2.3.

7.1.1.5 Disease Details and Treatments

7.1.1.5.1 Disease Details

The investigator or qualified designee will obtain prior and current details regarding disease status.

7.1.1.5.2 Prior Treatment Details

The investigator or qualified designee will review all prior cancer treatments including systemic treatments, radiation and surgeries.

7.1.1.5.3 Subsequent Anti-Cancer Therapy Status

The investigator or qualified designee will review all new anti-neoplastic therapy initiated after the last dose of trial treatment. If a subject initiates a new anti-cancer therapy within 30 days after the last dose of trial treatment, Follow-up visit must occur on or before the first dose of the new therapy. Once new anti-cancer therapy has been initiated or moved to SCT the subject will move into survival follow-up.

7.1.1.6 Assignment of Screening Number

Consecutive numbers starting from 001 are assigned to patients in the order they were registered for the clinical trial.

7.1.1.7 Assignment of Randomization Number

There is no randomization.

7.1.1.8 Trial Compliance (Medication/Diet/Activity/Other)

7.1.2 Clinical Procedures/Assessments

7.1.2.1 Adverse Event (AE) Monitoring

The investigator or qualified designee will assess each subject to evaluate for potential new or worsening AEs as specified in the Trial Flow Chart and more frequently if clinically indicated. Adverse experiences will be graded and recorded throughout the study and during the follow-up period according to NCI CTCAE Version 4.0 (see Section 11.2). Toxicities will be characterized in terms regarding seriousness, causality, toxicity grading, and action taken with regard to trial treatment.

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Please refer to section 7.2 for detailed information regarding the assessment and recording of AEs.

7.1.2.2 Full Physical Exam

The investigator or qualified designee will perform a complete physical exam during the screening period. Clinically significant abnormal findings should be recorded as medical history. A full physical exam should be performed during screening,

7.1.2.3 Directed Physical Exam

For cycles that do not require a full physical exam per the Trial Flow Chart, the investigator or qualified designee will perform a directed physical exam as clinically indicated prior to trial treatment administration.

7.1.2.4 Vital Signs

The investigator or qualified designee will take vital signs at screening, prior to the administration of each dose of trial treatment and at treatment discontinuation as specified in the Trial Flow Chart (Section 6.0). Vital signs should include temperature, pulse, respiratory rate and blood pressure.

7.1.2.5 Eastern Cooperative Oncology Group (ECOG) Performance Scale

The investigator or qualified designee will assess ECOG status (see Section 11.1) at screening, prior to the administration of each dose of trial treatment and discontinuation of trial treatment as specified in the Trial Flow Chart.

7.1.2.6 Tumor Imaging and Assessment of Disease

The tumor assessment is based on IWG criteria (Cheson 2014) primarily by PET scan as defined by the protocol schedule. Bone marrow biopsy and other non-measurable lesions (such as cutaneous or gastrointestinal diseases) are performed as needed.

7.1.2.7 Tumor Tissue Collection and Correlative Studies Blood Sampling

Blood samples and core needle biopsies will be obtained at baseline and on treatment from patients enrolled. Blood samples will be collected pre-dose for peripheral blood mononuclear cell (PBMC) and serum at baseline and day 1, day 8, day 15, day 22 (C2D1), day 29(C2D8), day 43 (C3D1) and at progression/relapse.

Core needle biopsies will be obtained at baseline and approximately on day 15 (optional) and at progression/relapse (optional).

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Biomarker studies: The overall goal of the correlative studies is to identify predictive, surrogate, mechanistic and pharmacodynamic biomarkers of pembrolizumab plus romidepsin therapy. PBMC samples will be analyzed by 10-color multiparametric flow cytometry to determine alteration in effector and regulatory T cell subsets and to determine expression of various co-stimulatory and co-inhibitor receptors (described in Westin et al... Neelapu, Lancet Oncol, 2014). Receptor occupancy by pembrolizumab will also be determined.

Serum samples will be analyzed for alteration in various cytokines and chemokines. Core needle biopsies and FNA of tumors will be analyzed by whole genome GEP, immunohistochemistry (IHC), and flow cytometry. IHC/flow cytometry assessment will include PD-1, PD-L1, and PD-L2 expression besides evaluation of effector and regulatory T cell subsets and expression of various co-stimulatory and coinhibitory receptors.

Laboratory Procedures/Assessments

Details regarding specific laboratory procedures/assessments to be performed in this trial are provided.

Laboratory tests for hematology, chemistry, urinalysis, and others are specified in Table 6.

Pregnancy Test will be performed on women of childbearing potential only. If urine pregnancy results cannot be confirmed as negative, a serum pregnancy test will be required. This will be performed on screening and Day 1 of each cycle.

Table 5 Laboratory Tests

Hematology	Chemistry	Urinalysis	Other
Hematocrit	Albumin	Blood	Serum β -human chorionic gonadotropin [†]
Hemoglobin	Alkaline phosphatase	Glucose	(β -hCG) [†]
Platelet count	Alanine aminotransferase (ALT)	Protein	PT (INR)
WBC (total and differential)	Aspartate aminotransferase (AST)	Specific gravity	aPTT
Red Blood Cell Count	Lactate dehydrogenase (LDH)	Microscopic exam (<i>If abnormal</i>)	Total triiodothyronine (T3)
Absolute Neutrophil Count	Carbon Dioxide ‡	results are noted	Free thyroxine (T4)
Absolute Lymphocyte Count	(CO_2 or <i>biocarbonate</i>)	Urine pregnancy test †	Thyroid stimulating hormone (TSH)
	Uric Acid		Pulmonary function tests
	Calcium		Epstein-Barr Virus (EBV) antibodies
	Chloride		Polymerase Chain Reaction (PCR) test for EBV
	Glucose		Blood for correlative studies
	Phosphorus		
	Potassium		
	Sodium		
	Magnesium		
	Total Bilirubin		
	Direct Bilirubin		
	Total protein		
	Blood Urea Nitrogen		
† Perform on women of childbearing potential only. If urine pregnancy results cannot be confirmed as negative, a serum pregnancy test will be required.			
‡ If considered standard of care in your region.			

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

7.1.2.8 Pharmacokinetic/Pharmacodynamic Evaluations

7.1.2.8.1 Blood Collection for Serum Pembrolizumab

There will be blood collection.

7.1.2.8.2 Blood Collection for Anti-Pembrolizumab Antibodies

7.1.3 None NA Other Procedures

7.1.3.1 Withdrawal/Discontinuation

When a subject discontinues/withdraws prior to trial completion, all applicable activities scheduled for the final trial visit should be performed at the time of discontinuation. Any adverse events which are present at the time of discontinuation/withdrawal should be followed in accordance with the safety requirements outlined in Section 7.2 - Assessing and Recording Adverse Events. After discontinuing treatment following assessment of CR, these subjects should return to the site for a Safety Follow-up Visit (described in Section 7.1.5.3.1) and then proceed to the Follow-Up Period of the study (described in Section 7.1.5.4).

7.1.3.2 Blinding/Unblinding

There is no blinding procedure in this trial.

7.1.4 Visit Requirements

Visit requirements are outlined in Section 6.0 - Trial Flow Chart. Specific procedure-related details are provided above in Section 7.1 - Trial Procedures.

7.1.4.1 Screening

7.1.4.1.1 Screening Period

Subjects will be screened within 28 days prior to protocol treatment. Study procedures and information regarding the nature of the study will be reviewed with potential subjects and written informed consent will be obtained prior to any study related procedures. Screening procedures are described in Section 6.0 – Trial Flow Chart

7.1.4.2 Treatment Period

Subjects will be treated every 3 weeks with pembrolizumab and romidepsin for up to 35 cycles. During the treatment phase patients will be evaluated prior to any treatment dose of

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pembrolizumab for toxicities and every 3 months for disease progression as outlined in detail in Section 6.0 – Trial Flow Chart.

In the event that Pembrolizumab is held, patients will be allowed to continue Romidepsin provided that it is not the cause of the toxicity.

7.1.4.2.1 Outside Physician Participation During Treatment

1. MDACC Physician communication with the outside physician is required prior to the patient returning to the local physician. This will be documented in the patient record. CBC, Serum creatinine, Mg, Phos, Uric acid and LDH may be performed locally. Physical Exam, Weight, Performance status (ECOG) and Toxicity notatopn will be assessed
2. A letter to the local physician outlining the patient's participation in a clinical trial (Dear Doctor Letter) will request local physician agreement to supervise the patient's care.
3. Protocol required evaluations outside MDACC will be documented by telephone, fax or e-mail. Fax and/or e-mail will be dated and signed by the MDACC physician, indicating that they have reviewed it.
4. A copy of the informed consent, protocol, treatment schema and evaluation during treatment will be provided to the local physician.
5. Documentation to be provided by the local physician will include progress notes, reports of protocol required laboratory and diagnostic studies and documentation of any hospitalizations.
6. The home physician will be requested to report to the MDACC physician investigator all life threatening events within 24 hours of documented occurrence.
7. Day 1 of each cycle will be performed at MDACC. Physical exam including but not limited to Vital signs, Performance Status (ECOG), Weight as well as laboratory assessments (CBC, Serum chemistry, Mg, Phos, Uric acid and LDH) will be evaluated. Romidepsin and Pembrolizumab will be administered per protocol. Response assessment will be performed every 3 cycles.
8. Changes in drug dose and/or schedule must be discussed with and approved by the MDACC physician investigator, or their representative prior to initiation, and will be documented in the patient record.
9. The patient should return to MD Anderson Cancer Center after 2 weeks of receiving Romipedsin locally to start Day 1 of the succeeding cycle.

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7.1.4.3 Post-Treatment Visits

7.1.4.3.1 Safety Follow-Up Visit

The mandatory Safety Follow-Up Visit should be conducted approximately 30 days after the last dose of trial treatment or before the initiation of a new anti-cancer treatment, whichever comes first. All AEs that occur prior to the Safety Follow-Up Visit should be recorded. Subjects with an AE of Grade > 1 will be followed until the resolution of the AE to Grade 0-1 or until the beginning of a new anti-neoplastic therapy, whichever occurs first. SAEs that occur within 30 days of the end of treatment or before initiation of a new anti-cancer treatment should also be followed and recorded.

7.1.4.3.2 Follow-up Visits

Subjects who discontinue trial treatment for a reason other than disease progression will move into the Follow-Up Phase and should be assessed every 12 weeks (42 ± 7 days) by radiologic imaging to monitor disease status. Every effort should be made to collect information regarding disease status until the start of new anti-neoplastic therapy, disease progression, death, end of the study. Information regarding post-study anti-neoplastic treatment will be collected if new treatment is initiated.

7.1.4.3.3 Survival Follow-up

Once a subject experiences confirmed disease progression starts a new anti-cancer therapy, or moves to SCT, the subject moves into the survival follow-up phase and should be contacted by telephone every 12 weeks to assess for survival status until death, withdrawal of consent, or the end of the study, whichever occurs first.

Retreatment is not considered in this clinical trial once a subject is taken off study.

7.2 Assessing and Recording Adverse Events

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

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Changes resulting from normal growth and development that do not vary significantly in frequency or severity from expected levels are not to be considered adverse events. Examples of this may include, but are not limited to, teething, typical crying in infants and children and onset of menses or menopause occurring at a physiologically appropriate time.

Merck product includes any pharmaceutical product, biological product, device, diagnostic agent or protocol-specified procedure, whether investigational (including placebo or active comparator medication) or marketed, manufactured by, licensed by, provided by or distributed by Merck for human use.

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

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

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

From the time of treatment through 30 days following cessation of treatment, all adverse events must be reported by the investigator. Such events will be recorded at each examination on the Adverse Event case report forms/worksheets. The reporting timeframe for adverse events meeting any serious criteria is described in section 7.2.3.1. The investigator will make every attempt to follow all subjects with non-serious adverse events for outcome.

Adverse events will not be collected for subjects during the pre-screening period (for determination of archival tissue status) as long as that subject has not undergone any protocol-specified procedure or intervention. If the subject requires a blood draw, fresh tumor biopsy etc., the subject is first required to provide consent to the main study and AEs will be captured according to guidelines for standard AE reporting.

The investigator (or physician designee) is responsible for verifying and providing source documentation for all adverse events and assigning the attribution for all adverse events for subjects enrolled.

RedCAP and/or CORE will be used for data entry. REDCap and/or CORE will be the AE database. Concomitant medications will be captured in the medical record.

Recommended Adverse Event Recording Guidelines for phase 1 and phase 2 trials

Attribution	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Unrelated	-	-	Record	Record	Record
Unlikely	-	-	Record	Record	Record
Possible	Record	Record	Record	Record	Record
Probable	Record	Record	Record	Record	
Definitive	Record	Record	Record	Record	Record

7.2.1 Definition of an Overdose for This Protocol and Reporting of Overdose

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

If an adverse event(s) is associated with (“results from”) the overdose of 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 2 working days hours to Merck Global Safety. (Attn: Worldwide Product Safety; FAX 215 993-1220)

7.2.2 Reporting of Pregnancy and Lactation

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

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

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

Such events must be reported within 2 working days to Merck Global Safety. (Attn: Worldwide Product Safety; FAX 215 993-1220)

7.2.3 Immediate Reporting of Adverse Events

7.2.3.1 Serious Adverse Events

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

- Results in death;
- Is life threatening;
- Results in persistent or significant disability/incapacity;
- Results in or prolongs an existing inpatient hospitalization;
- Is a congenital anomaly/birth defect;
- Is another important medical event

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

Refer to Table 6 for additional details regarding each of the above criteria.

For the time period beginning when the consent form is signed, any serious adverse event, or follow up to a serious adverse event, including death due to any cause other than progression of the cancer under study (reference Section 7.2.3.3 for additional details) that occurs to any subject must be reported within 2 working days to Merck Global Safety if it causes the subject to be excluded from the trial, or is the result of a protocol-specified intervention, including but

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not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure.

For the time period beginning through 90 days following cessation of treatment, or 90 days following cessation of treatment if the subject initiates new anticancer therapy, whichever is earlier, any serious adverse event, or follow up to a serious adverse event, including death due to any cause other than progression of the cancer under study (reference Section 7.2.3.3 for additional details), whether or not related to the Merck product, must be reported within 2 working days to Merck Global Safety.

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

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

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

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. (Attn: Worldwide Product Safety; FAX 215 993-1220) at the time of submission to FDA.

7.2.3.2 Serious Adverse Event (SAE) Reporting

An adverse event or suspected adverse reaction is considered “serious” if, in the view of either the investigator or the IND office, it results in any of the following outcomes:

- Death
- A life-threatening adverse drug experience – any adverse experience that places the patient, in the view of the initial reporter, at immediate risk of death from the adverse experience as it occurred. It does not include an adverse experience that, had it occurred in a more severe form, might have caused death.
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
- A congenital anomaly/birth defect.

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Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate 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. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse (21 CFR 312.32).

- Important medical events as defined above, may also be considered serious adverse events. Any important medical event can and should be reported as an SAE if deemed appropriate by the Principal Investigator or, IND Office.
- All events occurring during the conduct of a protocol and meeting the definition of a SAE must be reported to the IRB in accordance with the timeframes and procedures outlined in “The University of Texas M. D. Anderson Cancer Center Institutional Review Board Policy for Investigators on Reporting Serious Unanticipated Adverse Events for Drugs and Devices”. Unless stated otherwise in the protocol, all SAEs, expected or unexpected, must be reported to the IND Office, regardless of attribution (within 5 working days of knowledge of the event).
- All life-threatening or fatal events, that are unexpected, and related to the study drug, must have a written report submitted within 24 hours (next working day) of knowledge of the event to the Safety Project Manager in the IND Office.
- Unless otherwise noted, the electronic SAE application (eSAE) will be utilized for safety reporting to the IND Office and MDACC IRB.
- Serious adverse events will be captured from the time of the first protocol-specific intervention, until 30 days after the last dose of drug, unless the participant withdraws consent. Serious adverse events must be followed until clinical recovery is complete and laboratory tests have returned to baseline, progression of the event has stabilized, or there has been acceptable resolution of the event.
- Additionally, any serious adverse events that occur after the 90day time period that are related to the study treatment must be reported to the IND Office. This may include the development of a secondary malignancy.

Reporting to FDA:

- Serious adverse events will be forwarded to FDA by the IND office (Safety Project Manager IND Office) according to 21 CFR 312.32.

It is the responsibility of the PI and the research team to ensure serious adverse events are reported according to the Code of Federal Regulations, Good Clinical Practices, the protocol guidelines, the Merck guidelines, and Institutional Review Board policy.

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7.2.3.3 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. (Attn: Worldwide Product Safety; FAX 215 993-1220).

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

For the time period beginning when the consent form is signed through 30 days following cessation of treatment, or 30 days following cessation of treatment if the subject initiates new anticancer therapy, whichever is earlier, any ECI, or follow up to an ECI, whether or not related to Merck product, must be reported within 2 working days to Merck Global Safety.

Events of clinical interest for this trial include:

1. An overdose of Merck product, as defined in Section 7.2.1 - Definition of an Overdose for This Protocol and Reporting of Overdose to the IND Office, that is not associated with clinical symptoms or abnormal laboratory results.
2. An elevated AST or ALT lab value that is greater than or equal to 3X the upper limit of normal and an elevated total bilirubin lab value that is greater than or equal to 2X the upper limit of normal and, at the same time, an alkaline phosphatase lab value that is less than 2X the upper limit of normal, as determined by way of protocol-specified laboratory testing or unscheduled laboratory testing.*

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

7.2.3.4 Protocol-Specific Exceptions to Serious Adverse Event Reporting

Efficacy endpoints as outlined in this section will not be reported to Merck as described in Section 7.2.3- Immediate Reporting of Adverse Events to Merck, unless there is evidence suggesting a causal relationship between the drug and the event. Any such event will be submitted to Merck Global Safety within 2 working days either by electronic or paper media.

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

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

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

7.2.5 Evaluating Adverse Events

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

Given that the combination of pembrolizumab and romidepsin is novel and no combinations of drugs of the same class has been tested, all events, regardless of grade or attribution, should be recorded.

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

Table 6 Evaluating Adverse Events

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

V4.0 CTCAE Grading	Grade 1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
	Grade 2	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL.
	Grade 3	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation or hospitalization indicated; disabling; limiting self-care ADL.
	Grade 4	Life threatening consequences; urgent intervention indicated.
	Grade 5	Death related to AE
Seriousness	A serious adverse event is any adverse event occurring at any dose or during any use of Merck product that:	
	†Results in death; or	
	†Is life threatening; or places the subject, in the view of the investigator, at immediate risk of death from the event as it occurred (Note: This does not include an adverse event that, had it occurred in a more severe form, might have caused death.); or	
	†Results in a persistent or significant disability/incapacity (substantial disruption of one’s ability to conduct normal life functions); or	
	†Results in or prolongs an existing inpatient hospitalization (hospitalization is defined as an inpatient admission, regardless of length of stay, even if the hospitalization is a precautionary measure for continued observation. (Note: Hospitalization for an elective procedure to treat a pre-existing condition that has not worsened is not a serious adverse event. A pre-existing condition is a clinical condition that is diagnosed prior to the use of a Merck product and is documented in the patient’s medical history.); or	
	†Is a congenital anomaly/birth defect (in offspring of subject taking the product regardless of time to diagnosis);or	
	Is a new cancer (that is not a condition of the study) (although not serious per ICH definition, is reportable to Merck within 2 working days to meet certain local requirements); or	

	Is an overdose (whether accidental or intentional). Any adverse event associated with an overdose is considered a serious adverse event for collection purposes. An overdose that is not associated with an adverse event is considered a non-serious event of clinical interest and must be reported to Merck within 2 working days.	
	Other important medical events that may not result in death, not be life threatening, or not require hospitalization may be considered a serious adverse event when, based upon appropriate medical judgment, the event may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed previously (designated above by a †).	
Duration	Record the start and stop dates of the adverse event. If less than 1 day, indicate the appropriate length of time and units	
Action taken	Did the adverse event cause Merck product to be discontinued?	
Relationship to Merck Product	Did Merck product cause the adverse event? The determination of the likelihood that Merck product caused the adverse event will be provided by an investigator who is a qualified physician. The investigator's signed/dated initials on the source document or worksheet that supports the causality noted on the AE form, ensures that a medically qualified assessment of causality was done. This initialed document must be retained for the required regulatory time frame. The criteria below are intended as reference guidelines to assist the investigator in assessing the likelihood of a relationship between the test drug and the adverse event based upon the available information. The following components are to be used to assess the relationship between Merck product and the AE; the greater the correlation with the components and their respective elements (in number and/or intensity), the more likely Merck product caused the adverse event (AE):	
	Exposure	Is there evidence that the subject was actually exposed to Merck product such as: reliable history, acceptable compliance assessment (pill count, diary, etc.), expected pharmacologic effect, or measurement of drug/metabolite in bodily specimen?
	Time Course	Did the AE follow in a reasonable temporal sequence from administration of Merck product? Is the time of onset of the AE compatible with a drug-induced effect (applies to trials with investigational medicinal product)?
	Likely Cause	Is the AE not reasonably explained by another etiology such as underlying disease, other drug(s)/vaccine(s), or other host or environmental factors

Relationship to Merck Product (continued)	The following components are to be used to assess the relationship between the test drug and the AE: (continued)	
	Dechallenge	Was Merck product discontinued or dose/exposure/frequency reduced? If yes, did the AE resolve or improve? If yes, this is a positive dechallenge. If no, this is a negative dechallenge. (Note: This criterion is not applicable if: (1) the AE resulted in death or permanent disability; (2) the AE resolved/improved despite continuation of the Merck's product; or (3) the trial is a single-dose drug trial); or (4) Merck's product(s) is/are only used one time.)
	Rechallenge	Was the subject re-exposed to Merck product in this study? If yes, did the AE recur or worsen? If yes, this is a positive rechallenge. If no, this is a negative rechallenge. (Note: This criterion is not applicable if: (1) the initial AE resulted in death or permanent disability, or (2) the trial is a single-dose drug trial); or (3) Merck's product(s) is/are used only one time). NOTE: IF A RECHALLENGE IS PLANNED FOR AN ADVERSE EVENT WHICH WAS SERIOUS AND WHICH MAY HAVE BEEN CAUSED BY MERCK PRODUCT, OR IF REEXPOSURE TO MERCK PRODUCT POSES ADDITIONAL POTENTIAL SIGNIFICANT RISK TO THE SUBJECT, THEN THE RECHALLENGE MUST BE APPROVED IN ADVANCE BY THE IND office AS PER DOSE MODIFICATION GUIDELINES IN THE PROTOCOL.
	Consistency with Trial Treatment Profile	Is the clinical/pathological presentation of the AE consistent with previous knowledge regarding Merck product or drug class pharmacology or toxicology?

The assessment of relationship will be reported on the case report forms /worksheets by an investigator who is a qualified physician according to his/her best clinical judgment, including consideration of the above elements.	
Record one of the following	Use the following scale of criteria as guidance (not all criteria must be present to be indicative of Merck product relationship).
Yes, there is a reasonable possibility of Merck product relationship.	There is evidence of exposure to Merck product. The temporal sequence of the AE onset relative to the administration of Merck product is reasonable. The AE is more likely explained by Merck product than by another cause.
No, there is not a reasonable possibility of Merck product relationship	Subject did not receive the Merck product OR temporal sequence of the AE onset relative to administration of Merck product is not reasonable OR the AE is more likely explained by another cause than the Merck product. (Also entered for a subject with overdose without an associated AE.)

8.0 STATISTICAL ANALYSIS PLAN

Outcome measures

The adverse events are recorded according to CTCAE criteria version 4.0, and the detailed plan is described in section 7.2. The primary endpoint of phase I study is dose limiting toxicity. Response is defined by the best response during the therapy, as defined by the schedule of response evaluation. If the treating physician determines that the patient is clinically progressing and the patient is to be taken off study, that day will be defined as day of progression.

Response assessment is performed utilizing Lugano Revised Response Criteria.¹

Progression free survival (PFS) duration is calculated as the time interval from the date of study registration and the date of progression, recurrence, or death without progression, whichever comes first. Patients alive without progression are censored at the date they were last known to be without progression or recurrence and alive for PFS. The overall survival (OS) duration is calculated as the time interval from the date of study registration to the date of death from any cause.

Event-free survival (EFS) duration will be calculated as the time interval from the date of study registration to the earliest date of the following events: disease progression according to the Lugano classification, recurrence, death from any cause, or start of new therapy for lymphoma therapy excluding patients with a best response of stable disease or better. Other patients will be censored at the last follow-up or start of new therapy for lymphoma therapy for patients with a best response of CR/PR/SD.

Failure-free survival duration will be calculated as the time interval from the date of study registration to the earliest date of the following events: disease progression according to the Lugano classification, recurrence, death from lymphoma, or start of new therapy for lymphoma excluding patients with a best response of stable disease or better. Patients died of cause other than lymphoma will be censored at the death date. Other patients will be censored at the last follow-up or start of new therapy for lymphoma therapy for patients with a best response of CR/PR/SD.

Statistical Analysis Plan Summary

- 8.1 The phase I portion of the study follows standard 3+3 design. The 6 patients tested in the phase I at the dose finally determined as RP2D will be included in the response assessment of phase II study. The primary endpoint for phase II is overall response (OR: CR+PR). The phase II study is based on Simon's minimax design ($\alpha = 0.05$, $\beta = 0.1$, poor response rate = 25% (response rate of romidepsin for PTCL), good response rate = 50%). If response at 3 cycles is observed in 4 or less patients among the first 16 evaluable patients**

(including 6 from phase I), the combination is considered not to be pursued further. If 5 or more responses are observed in the first 16 evaluable patients, the study continues to accrue 17 additional evaluable patients. A total of 33 evaluable patients are to be assessed for response, and 13 or more responses are considered success of the study. To ensure a total of 33 evaluable patients for the efficacy assessment in the phase II (including 6 treated at the RP2D in Phase I), up to 39 patients will be enrolled in phase I and phase II. Patients are considered to be evaluable if they have the response assessment at 3 cycles.

Statistical Analysis Plan

The primary endpoint in the phase I study is to determine if the suggested combination is safe without DLT related to treatment, and the doses are only to be de-escalated if needed. The primary endpoint in the phase II study is to determine the efficacy of the combination therapy. The patients who were enrolled in the phase I study at the recommended phase II dose (RP2D) will be included in the assessment in phase II study for efficacy.

The probability of early stopping under the null hypothesis is 63%. If the number of responses required for moving the trial to next stage has not been achieved, the patient enrollment will be halted until enough responses observed. We will evaluate the toxicity data and make dose adjustment whenever we observe >33% of the patients experienced DLT within cycle 1.

Secondary objectives of the study are to determine CR, DOR, PFS, OS, EFS, FFS. We will also assess ORR with CR, PR, SD and SD will be broken down into SD>90 days and SD<90 days. All responses will have Duration of ORR, Duration of CR and Duration of PR.1

Summary statistics will be provided for continuous variables and categorical variables. The CR and OR rates and their 95% confidence intervals will be reported. Fisher's exact test will be used to evaluate the association between two categorical variables. Wilcoxon rank sum test will be used to assess the difference in a continuous variable between patient groups. The distribution of time-to-event endpoints including DOR, PFS, and OS will be estimated using the method of Kaplan and Meier.

Toxicity data will be summarized by type and severity for all patients who received the treatment regardless of the eligibility nor the duration or dose of the treatment received.

The Investigator is responsible for completing toxicity/efficacy summary reports and submitting them to the IND Office Medical Affairs and Safety Group, for review. These should be submitted as follows:

- Phase I:

After the first 3 evaluable subjects per cohort, complete cycle 1 of study treatment, and every 3 evaluable subjects thereafter, prior to changing dose levels, or advancing to Phase 2. Enrollment should be held until IND Office approval is obtained.

Phase 2:

- Phase 2:

After the first 5 evaluable subjects complete 1 cycle of study treatment and every 5 patients thereafter. Efficacy summary will be submitted after the first 16 patients (including the 6 treated at MTD), complete 3 cycles of treatment and at the end of enrollment. Enrollment should be held until the efficacy summary is approved by the IND Office.

9.0 LABELING, PACKAGING, STORAGE AND RETURN OF CLINICAL SUPPLIES

9.1 Investigational Product

The investigator shall take responsibility for and shall take all steps to maintain appropriate records and ensure appropriate supply, storage, handling, distribution and usage of investigational product in accordance with the protocol and any applicable laws and regulations.

Clinical Supplies will be provided by Merck as summarized in Table 7.

Table 7 Product Descriptions

Product Name & Potency	Dosage Form
Pembrolizumab 50 mg	Lyophilized Powder for Injection
Pembrolizumab 100 mg/ 4mL	Solution for Injection

9.2 Packaging and Labeling Information

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

9.3 Clinical Supplies Disclosure

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

9.4 Storage and Handling Requirements

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

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

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

9.5 Returns and Reconciliation

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

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

10.0 ADMINISTRATIVE AND REGULATORY DETAILS

10.1 Confidentiality

10.2 Compliance with Financial Disclosure Requirements

Financial Disclosure requirements are outlined in the US Food and Drug Administration Regulations, Financial Disclosure by Clinical Investigators (21 CFR Part 54). It is the IND Office's responsibility to determine, based on these regulations, whether a request for Financial Disclosure information is required. It is the investigator's/subinvestigator's responsibility to comply with any such request. The investigator/subinvestigator(s) agree, if requested by the IND Office in accordance with 21 CFR Part 54, to provide his/her financial interests in and/or arrangements with the IND Office to allow for the submission of complete and accurate certification and disclosure statements. The investigator/subinvestigator(s) further agree to provide this information on a Certification/Disclosure Form, commonly known as a financial disclosure form, provided by the IND Office or through a secure password-protected electronic portal provided by the IND Office. The investigator/subinvestigator(s) also consent to the transmission of this information to the IND Office in the United States for these purposes. This may involve the transmission of information to countries that do not have laws protecting personal data.

10.3 Compliance with Law, Audit and Debarment

This study will be conducted in accordance with local, state and Federal regulations and according to accepted good clinical practice guidelines.

10.4 Compliance with Trial Registration and Results Posting Requirements

Under the terms of the Food and Drug Administration Modernization Act (FDAMA) and the Food and Drug Administration Amendments Act (FDAAA), the IND Office is solely

responsible for determining whether the trial and its results are subject to the requirements for submission to the Clinical Trials Data Bank, <http://www.clinicaltrials.gov>. Information posted will allow subjects to identify potentially appropriate trials for their disease conditions and pursue participation by calling a central contact number for further information on appropriate trial locations and trial site contact information.

10.5 Quality Management System

The principal investigator is responsible for implementing and maintaining a quality management system with written development procedures and functional area standard operating procedures (SOPs) to ensure that trials are conducted and data are generated, documented, and reported in compliance with the protocol, accepted standards of Good Clinical Practice, and all applicable federal, state, and local laws, rules and regulations relating to the conduct of the clinical trial.

10.6 Data Management

The principal investigator or qualified designee is responsible for recording and verifying the accuracy of subject data.

11.0 APPENDICES

11.1 ECOG Performance Status

Grade	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. 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.: <i>Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. Am J Clin Oncol</i> 5:649-655, 1982. The Eastern Cooperative Oncology Group, Robert Comis M.D., Group Chair.	

11.2 Common Terminology Criteria for Adverse Events V4.0 (CTCAE)

The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for adverse event reporting. (<http://ctep.cancer.gov/reporting/ctc.html>)

11.3 Response Evaluation Criteria

Revised Lugano Revised Response Criteria and ISCL/EORTC Lymphoma Response Criteria

NOTE: These criteria are based upon the criteria from the Lugano Revised Response Criteria and ISCL/EORTC for Malignant Lymphoma,¹ The criteria use the following categories of response: Complete Response (CR), Partial Response (PR), Stable Disease (SD), Relapse and Progression (PD). In the case of stable disease, follow-up assessments must have met the SD criteria at least once after study entry at a minimum interval of six weeks. The following guidelines are to be used for establishing tumor measurements at baseline and for subsequent comparison:

- Up to six dominant nodes or extranodal masses can be identified if present at baseline.
- If there are 6 or fewer nodes and extranodal masses, all must be listed as dominant

- If there are more than 6 involved nodes or extranodal masses, the 6 largest dominant nodes or extranodal masses should be selected according to the following features: a) they should be clearly measurable in at least two perpendicular measurements; b) they should be from as disparate regions of the body as possible; and c) they should include mediastinal and retroperitoneal areas of disease whenever these sites are involved.
- Measurements for all dominant nodes and extranodal masses will be reported at baseline. Measurements on non-dominant nodes are not required.
- The lymph nodes or extranodal masses selected for measurement should be measured in two perpendicular diameters, one of which is the longest perpendicular diameter. The lymph nodes should be measured in centimeters to the nearest one tenth of a centimeter (e.g., 2.0 cm, 2.1 cm, 2.2 cm, etc.)
- The two measured diameters of each lymph node site or extranodal mass should be multiplied giving a product for each nodal site or extranodal mass. The product of each nodal site should be added, yielding the sum of products of the diameters (SPD). The SPD will be used in determining the definition of response for those who have less than a complete response.
- Patients should be assessed with PET CTs. Where PET is not available, response should be assessed as above, but only using CT scans. However, residual masses should not be assigned CRu status, but should be considered partial responses.

11.3.1 Complete Response

Complete disappearance of all detectable clinical evidence of disease, and disease-related symptoms if present prior to therapy.

- In patients with a typically FDG-avid lymphoma with no pre-treatment PET scan, or for lymphomas for which the PET scan was positive prior to therapy: a post-treatment residual mass of any size is permitted as long as it is PET-negative.
- For variably FDG-avid lymphomas without a pretreatment PET scan, or if a pretreatment PET scan was negative: all lymph nodes and extranodal masses must have regressed on CT to normal size (≤ 1.5 cm in their greatest transverse diameter for nodes > 1.5 cm prior to therapy). Previously involved nodes that were 1.1-1.5 cm in their long axis and > 1.0 cm in their short axis prior to treatment must have decreased to ≤ 1 cm in their short axis after treatment.
- The spleen and/or liver, if considered enlarged prior to therapy on the basis of a physical examination or CT scan, should not be palpable on physical examination, and nodules related to lymphoma should disappear. However, no normal size can be specified because of the difficulties in accurately evaluating splenic and hepatic size and involvement. For instance, a spleen considered normal size may contain lymphoma, whereas an enlarged spleen may not necessarily reflect the presence of lymphoma, but variations in anatomy, blood volume, the use of hematopoietic growth factors, or other causes.

11.3.2 Partial Response (PR)

- The designation of PR requires all of the following: A $\geq$ 50% decrease in sum of the product of the diameters (SPD) of up to 6 of the largest dominant nodes or extranodal masses.
- No increase in the size of other nodes, liver or spleen.
- No new sites of disease.
- For a typically FDG-avid lymphoma with no pretreatment PET scan or one that was PET-positive prior to therapy, the post-treatment PET should be positive at any previously involved sites.
- For variably FDG-avid lymphomas/FDG-avidity unknown, without a pre-treatment PET scan, or if a pretreatment PET scan was negative, CT scan criteria should be used.
- Patients who achieve a CR by the above criteria, but who have persistent morphologic bone marrow involvement will be considered partial responders.
- When the bone marrow was involved before therapy and a clinical CR was achieved, but with no bone marrow assessment after treatment, patients should be considered partial responders.

11.3.3 Stable Disease (SD)

- Failing to attain the criteria needed for a PR or CR, but not fulfilling those for progressive disease (see below).
- Typically FDG-avid lymphomas: The PET should be positive at prior sites of disease with no new areas of involvement on the post-treatment CT or PET.
- For variably FDG-avid lymphomas/FDG-avidity unknown: For patients without a pretreatment PET scan or if the pre-treatment PET was negative, there must be no change in the size of the previous lesions on the post-treatment CT scan.

11.3.4 Progression (PD) and Relapse

- For determination of relapsed and progressive disease, lymph nodes should be considered abnormal if the long axis is more than 1.5 cm, regardless of the short axis. If a lymph node has a long axis of 1.1 to 1.5 cm, it should only be considered abnormal if the short axis is more than 1 cm. Lymph nodes $\leq 1 \times \leq 1$ cm will not be considered as abnormal for relapse or progressive disease.
- Treatment decisions in patients with presumed refractory, relapsed or progressive disease should not be made solely on the basis of a single PET scan without histologic confirmation.
- Appearance of any new lesion more than 1.5 cm in any axis during or at the end of therapy, even if other lesions are decreasing in size.

- Increased FDG uptake in a previously unaffected site should only be considered relapsed or progressive disease after confirmation with other modalities. In patients with no prior history of pulmonary lymphoma, new lung nodules identified by CT are mostly benign. Thus, a therapeutic decision should not be made solely on the basis of the PET without histologic confirmation.
- At least a 50% increase from nadir in the SPD of any previously involved nodes or extranodal masses, or in a single involved node or extranodal mass, or the size of other lesions (e.g. splenic or hepatic nodules). To be considered progressive disease, a lymph node or extranodal mass with a diameter of the short axis of less than 1.0 cm must increase by $\geq 50\%$ and to a size of 1.5 cm x 1.5 cm or more than 1.5 cm in the long axis.
- At least a 50% increase in the longest diameter of any single previously identified node or extranodal mass more than 1 cm in its short axis.
- Lesions should be PET positive if observed in a typical FDG-avid lymphoma or the lesion was PET positive before therapy unless the lesion is too small to be detected with current PET systems (< 1.5 cm in its long axis by CT).
- Measurable extranodal disease should be assessed in a manner similar to that for nodal disease. For these response criteria, the spleen is considered nodal disease. Disease that is only assessable (e.g., pleural effusions, bone lesions) will be recorded as present or absent only, unless, while an abnormality is still noted by imaging studies or physical examination, it is found to be histologically negative.

11.3.5 11Response Endpoints

All tumor assessments will be made using Revised Response criteria.¹ Pembrolizumab is expected to trigger immune-mediated responses, which require activation of the immune system prior to the observation of clinical responses. Such immune activation may take weeks to months to be evident. Some patients may experience tumor flare with objective volume increase of tumor lesions or other disease parameters (based on study indication, ie, hematologic malignancies) within 12 weeks following the start of pembrolizumab dosing. Such patients may not have had sufficient time to develop the required immune activation or, in some patients, tumor volume or other disease parameter increases may represent infiltration of lymphocytes into the original tumor or blood. In conventional studies, such tumor volume or relevant laboratory parameter increases during the first 12 weeks of the study would constitute PD and lead to discontinuation of imaging to detect response, thus disregarding the potential for subsequent immune-mediated clinical response.

Therefore if at the first imaging time point (9 weeks after initiating treatment) patients demonstrate up to 2 new lesions, with sum of all lesions $< 70\%$ greater than baseline by SPD, or decreasing in size, and stable without evidence of rapid clinical deterioration, patients may be continue to be treated with pembrolizumab and clinically observed with imaging repeated after 1 month. If at that time there is Progression of Disease (POD) by standard Revised Response Criteria patients will be removed from study. For patients in whom investigators consider that tumor flare may be playing a role in the response seen on initial imaging, this must be documented at time of scan, and discussed with Study Chair. This may improve the overall assessment of the clinical activity of pembrolizumab and more likely capture its true potential to induce clinical responses. In regards to PFS analysis, the date of progression for patients who were initially considered to have tumor flare, but had further progression of

disease (POD) on the repeat image after 1 month, will be the time of first imaging in which new lesions were originally detected.

Data Confidentiality Plan for Management and Protection

All laboratory and clinical data gathered in this protocol will be stored in a password-protected database. All patient information will be handled using anonymous identifiers. Linkage to patient identity is only possible after accessing a password-protected database. Access to the database is only available to individuals directly involved in the study.

Information gathered for this study will not be reused or disclosed to any other person or entity, or for other research. Once the research has been completed, identifiers will be retained for as long as is required by law and by institutional regulations, and at that point will be destroyed.

Appendix A

List of Relevant Cytochrome P450 Inhibitors and Inducers

Strong CYP2C19 Inhibitors		
fluconazole	fluvoxamine	ticlopidine
Moderate CYP3A4 Inhibitors		
amprenavir	darunavir/ritonavir	fosamprenavir
aprepitant	Diltiazem	grapefruit juice (a)
atazanavir	erythromycin	imatinib
ciprofloxacin	fluconazole	verapamil
Strong CYP3A4 Inhibitors		
boceprevir	ketoconazole	ritonavir
clarithromycin	lopinavir/ritonavir	saquinavir
conivaptan	mibefradil (b)	telaprevir
grapefruit juice (a)	nefazodone	telithromycin
indinavir	Nelfinavir	voriconazole
itraconazole	posaconazole	
Clinically Significant Enzyme Inducers		
carbamazepine	Rifabutin	St. John's Wort
phenobarbital	Rifampin	
phenytoin	rifapentine	

Note that these lists are not exhaustive.

(a) The effect of grapefruit juice varies widely among brands and is concentration-, dose-, and preparation-dependent. Studies have shown that it can be classified as a "strong CYP3A inhibitor" when a certain preparation was used (eg, high dose, double strength) or as a "moderate CYP3A inhibitor" when another preparation was used (eg, low dose, single strength).

(b) Withdrawn from the United States market because of safety reasons.

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