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Novel immuno-epigenetic based platform for patients with peripheral T-cell lymphoma (PTCL) and cutaneous T-cell lymphoma (CTCL): an international phase Ib study of pembrolizumab combined with decitabine and/or pralatrexate

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TITLE: **Novel immuno-epigenetic based platform for patients with peripheral T-cell lymphoma (PTCL) and cutaneous T-cell lymphoma (CTCL): an international phase Ib study of pembrolizumab combined with decitabine and/or pralatrexate.**

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STATEMENT OF COMPLIANCE

The trial will be conducted in accordance with International Conference on Harmonisation Good Clinical Practice (ICH GCP), applicable United States (US) Code of Federal Regulations (CFR). The Principal Investigator will assure that no deviation from, or changes to the protocol will take place without prior agreement from the Investigational New Drug (IND) sponsor, and documented approval from the Institutional Review Board (IRB), except where necessary to eliminate an immediate hazard(s) to the trial participants. All personnel involved in the conduct of this study have completed Human Subjects Protection.

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the IRB for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. All changes to the consent form will be IRB approved; a determination will be made regarding whether a new consent needs to be obtained from participants who provided consent, using a previously approved consent form.

Sponsor/Lead Principal Investigator

_____	_____	_____
Name (print)	**Signature**	**Date**

Investigator

_____	_____	_____
Name (print)	**Signature**	**Date**

1.0 TRIAL SUMMARY

Abbreviated Title	PDP (pembrolizumab plus decitabine plus pralatrexate) phase Ib study in relapsed/refractory PTCL and CTCL.
Trial Phase	Phase Ib
Clinical Indication	Relapsed, refractory peripheral T-cell Lymphoma (PTCL) and cutaneous T-cell lymphoma (CTCL).
Trial Type	Dose-escalation.
Type of control	N/A
Route of administration	Intra-venous (IV)
Trial Blinding	Open-label
Treatment Groups	Arm A (pembrolizumab plus pralatrexate); Arm B (pembrolizumab plus pralatrexate plus decitabine); Arm C (pembrolizumab plus decitabine).
Number of trial subjects	Maximum of 38
Estimated enrollment period	6-10 months
Estimated duration of trial	2 years
Duration of Participation	2 years plus
Estimated average length of treatment per patient	6 months

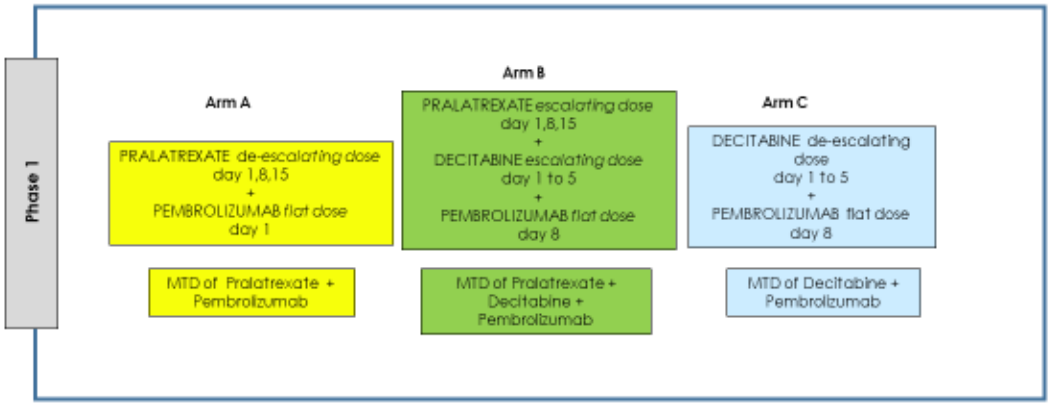
2.0 TRIAL DESIGN

2.1 Trial Design

This is an international, multicenter, multi-arm, phase Ib, model-based dose-escalation study. The primary objectives of the study in each arm is to determine the maximum tolerated dose (MTD), recommended phase 2 dose (RP2D), dose limiting toxicities (DLTs) and to evaluate the clinical efficacy at the MTD of various combinations of pembrolizumab, pralatrexate and decitabine.

The safety and toxicity of these combinations will be evaluated throughout the entire study. Dose allocation in Arms A and C will be based upon a continual reassessment method (CRM)[1], and combination allocation in Arm B will be conducted using a DLT-adapted partial order continual reassessment method (POCRM) for dose-finding with combinations of agents[2].

2.2 Trial Diagram



*Pembrolizumab Day above (e.g. Day 1 and Day 8) refers only to cycle 1 of treatment. Pembrolizumab will be continued every 3 weeks following the first administration. Please refer to Section 8.0 for detail.

3.0 OBJECTIVES & HYPOTHESIS

3.1 Primary Objectives & Hypothesis

- Determine the maximum tolerated dose (MTD), recommended phase 2 dose (RP2D) and dose limiting toxicity (DLT) of the combinations of pembrolizumab and pralatrexate (Arm A), pralatrexate, decitabine and pembrolizumab (Arm B), and decitabine and pembrolizumab (Arm C) in patients with relapsed/refractory PTCL and CTCL.
- Evaluate the safety and toxicity of the combination of pembrolizumab and pralatrexate (Arm A), pralatrexate, decitabine and pembrolizumab (Arm B), and decitabine and pembrolizumab (Arm C) in patients with relapsed/refractory PTCL and CTCL.

- Evaluate the efficacy, as determined by the ORR (complete + partial response), of the combination of pembrolizumab and pralatrexate (Arm A), pralatrexate, decitabine and pembrolizumab (Arm B), and decitabine and pembrolizumab (Arm C) in patients with relapsed/refractory PTCL and CTCL.

Hypothesis: If pralatrexate and/or decitabine functions in an immunomodulatory fashion **then** priming and modulating the malignant cells and the microenvironment will enhance the antitumor activity of pembrolizumab in patients with PTCLs and CTCLs.

3.2 Secondary Objectives

- Describe the anti-tumor activity of the combinations of pembrolizumab and pralatrexate (Arm A), pralatrexate, decitabine and pembrolizumab (Arm B), and decitabine and pembrolizumab (Arm C) in patients with relapsed/refractory PTCL and CTCL.
- Evaluate the efficacy, as determined by the overall response rate (ORR), progression free survival (PFS), and duration of response (DOR), of the study population receiving the combinations of pembrolizumab and pralatrexate (Arm A), pralatrexate, decitabine and pembrolizumab (Arm B), and decitabine and pembrolizumab (Arm C) in patients with relapsed/refractory PTCL and CTCL.
- Evaluate pharmacodynamic markers of drug effect in paired tissue biopsies (pre- and post-treatment).
- Establish pharmacokinetic profile for pembrolizumab when administered with pralatrexate (Arm A), with decitabine (Arm C) and when given as a combination (Arm B) during cycle 1 only.
- Obtain additional information regarding adverse events within the selected dose range.

- Estimate the OS, PFS of the combination in patients with relapsed/refractory PTCL and CTCL.
- Estimate the DOR of patients with relapsed/refractory PTCL and CTCL on study.
- Identify potential biomarkers of response to treatment.

3.3 Exploratory Objective

We will determine the treatment related effects on host immune function and identify potential biomarker of response through the objectives below:

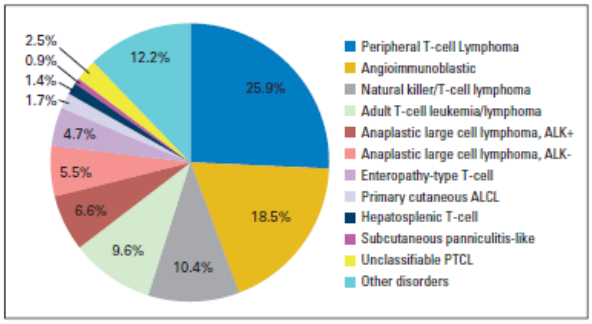
Objectives:

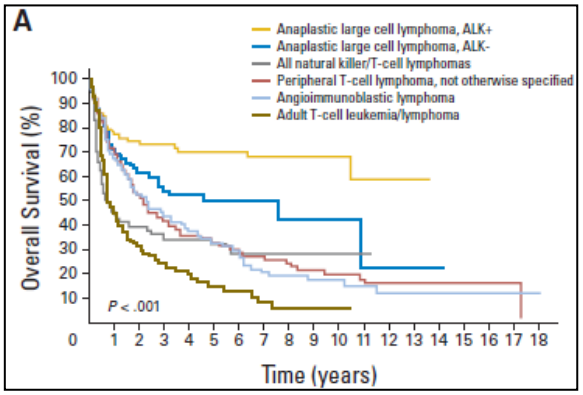
(1) Analyze the changes in the T cell repertoire in peripheral blood and primary tumor samples as a function of treatment with pembrolizumab and pralatrexate (Arm A), pembrolizumab, decitabine and pralatrexate (Arm B), pembrolizumab and decitabine (Arm C) in order to assess the contribution of epigenetic priming with decitabine in patients receiving treatment with pembrolizumab and pralatrexate.

(2) Elucidate the immunomodulatory effect of the combinations of pembrolizumab with pralatrexate (Arm A), pralatrexate and decitabine (Arm B), and decitabine (Arm C) and identify biomarkers of response

4.0 BACKGROUND & RATIONALE

4.1 Background





Mature T cell lymphomas, also known as peripheral T cell lymphomas (PTCL), comprise a heterogeneous group of lymphoid malignancies characterized by their rare frequency and unique clinicopathologic features[3,4]. The annual prevalence of non-Hodgkin lymphomas in the US is estimated to be 72,580, or approximately 4.3% of all newly diagnosed malignancies. The mature T cell lymphomas represent about 5-10% of all newly diagnosed NHLs. The most common subtypes of PTCL are PTCL Not Otherwise specified (NOS) and angioimmunoblastic lymphoma (AILT), which when combined represent approximately 45% of all PTCLs (see figure above). Peripheral T-cell lymphomas also include the cutaneous T-cell lymphomas (CTCL) which are a mature post-thymic T-cell lymphoma. The two most common forms of CTCL are mycosis fungoides (MF) and Sézary syndrome (SS). Between 2,000 and 3,000 new cases of CTCL occur in the United States each year. MF is categorized as limited stage (IA, IB, and IIA) or plaque/patch disease localized within the skin, and advanced stage (IIB to IVB), characterized by cutaneous tumors and involvement of the blood, lymph nodes, bone marrow, or visceral organs. SS is characterized by generalized erythroderma and the presence of abnormal lymphoid cells in the blood.

The largest study conducted to date to evaluate the outcomes of patients with PTCL was the International T-cell Lymphoma project[5]. This retrospective study of more than 1300 patients from North America, Europe and Asia revealed that outcomes of patients with PTCL were dismal, with the majority of patients dying from their disease (as noted in the Kaplan-Meier curve on the right). What was particularly important was the fact that majority of patients included in this study were treated with chemotherapeutic regimens that

were borrowed from B- cell lymphoma treatment paradigms such as CHOP and CHOP-like regimens. For CTCL patients, those with limited-stage disease may be effectively treated with skin-directed therapies including topical nitrogen mustard or psoralen plus ultraviolet A. However, in patients with an advanced disease, control is often short lived, and the disease is relentlessly progressive. Although response rates to cytotoxic chemotherapy range from 60 to 80% in patients with advanced disease, the median duration of response is usually measured in months.

Clearly, there is an unmet need for novel therapeutic agents for both PTCL and advanced stage CTCL. Several newer medications have been approved by the FDA for treatment of PTCL and CTCL, including vorinostat[6], romidepsin[7,8], belinostat[9] and pralatrexate[10-12]. The response for these single agents are seen in up to 1/3 of the patients despite having heavily treated disease. Possible strategies directed at improving their efficaciousness include combining novel agents in an effort to design new backbone (T cell specific regimen, analogous to CHOP for B cell aggressive lymphomas), and/or to identify novel biological agents that can complement their activity in a relative non-toxic fashion (in an attempt to replicate what rituximab has done for B cell NHL within a T cell lymphoma).

4.2 Rationale and Preclinical Data

The peripheral T-cell lymphomas (PTCLs) are rare subtypes of Non-Hodgkin lymphoma (NHL) with unique clinicopathologic features and very unfavorable prognosis. Recently it has been demonstrated that PTCLs are characterized by recurrent mutations in epigenetic operators (e.g. *TET2*, *DNMT3A*, and *IDH2*) and escape from immune surveillance.

4.2.1 Deciphering mechanisms of action of pralatrexate in PTCLs.

In order to clarify the mechanism of action of pralatrexate compared to methotrexate, we performed gene expression profiling on multiple cell lines treated with equimolar concentrations of methotrexate and pralatrexate. Preliminary data produced by our group revealed that when using GEP profiling, pralatrexate induces radically different patterns of gene expression compared to methotrexate.

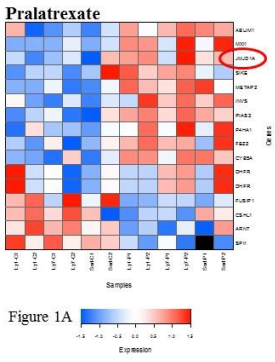


Figure 1A

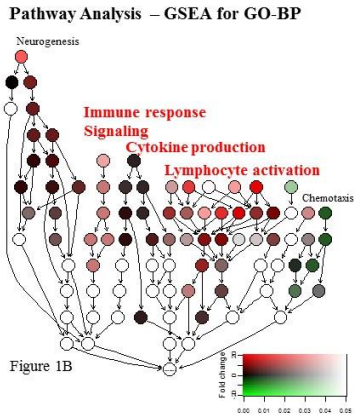
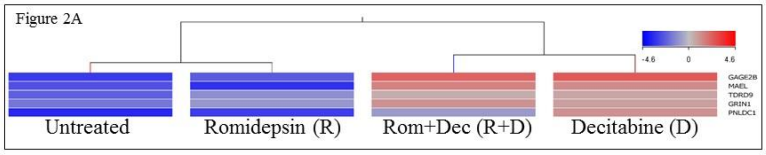


Figure 1B

Firstly, we demonstrated that pralatrexate induces differential expression of multiple genes including KDM3A, alias JMJD1A. KDM3A is a histone demethylase that specifically demethylates Lysine-9 residue of histone H3 (H3-K9), and plays a central role in the histone code (figure 1A). Existing data shows that epigenetic regulation through methylation and demethylation of H3-K9 at the locus encoding for interferon γ regulates T-helper differentiation and signaling. Furthermore, other evidence supports the notion that H3-K9 demethylation contributes to transcriptional depression of the promoter region for the MAGE gene family, inducing expression of MAGE A2.

Secondly, when we performed pathway analysis comparing methotrexate and pralatrexate we confirmed the hypothesis that pralatrexate specifically affects immune response signaling, cytokine production and lymphocyte activation pathways (figure 1B). We are presently expanding the repertoire of T-cell lymphomas treated with methotrexate and pralatrexate, to further elucidate the immunomodulatory functions of pralatrexate. This data provides the basis for our hypothesis that pralatrexate would potently interact with the immune checkpoint inhibitor, pembrolizumab in restoring cytotoxic T-cell response affecting both the microenvironment and the tumor cells and would synergize with the HMA, decitabine, inducing interferon-mediated response and re-expression of MAGE family genes.

4.2.2 Epigenetic Priming with the HMA, decitabine



Preclinical data recently published by our group have added even more credence that these epigenetic drugs cooperate through both basic pathway interruption as well as through numerous immunologically mediated processes[13,14]. We demonstrated major class effects between HDAC inhibitors and HMAs, where the IC10-20 of each drug in combination produced astounding synergy with synergy coefficients ranging between 0.0007 and 0.9. Interestingly, the synergy was more dependent on the concentration of the HDAC inhibitor, rather than the hypomethylating agent, owing to the fact that higher doses of HMA kill cells primarily through a DNA damage response, while lower doses predominantly work by inhibiting DNMT3. These observations were also validated in a SCID beige mouse model of T-cell lymphoma. We further investigated the effects of the various treatments on the gene expression and methylation profile. Whole genome gene expression profiling (GEP) and genome wide methylation analysis was performed through collaboration with the Bologna group. Our final analysis of this data demonstrated that the combination of romidepsin and decitabine 'reversed' the malignant GEP signature of all the T-cell lymphoma cell lines studied, with each individual drug having only a partial effect on the gene expression signature (published data, not shown here). These results served as the basis for a phase I/II clinical trial using oral 5-azacitidine and romidepsin in patients with relapsed or refractory PTCL that is currently ongoing (https://clinicaltrials.gov/show/NCT01998035). Interestingly, 4 of 5 patients with chemotherapy refractory and many with HDAC inhibitor refractory PTCL responded to the treatment, with 2 of the 4 responses being complete remission. However, when we analyzed the methylation profile induced by either drug alone and in the combination, we found that decitabine produced a profound effect, inducing demethylation of 190 different gene regions corresponding to 175 genes and an additional 335 loci. Consistent with previous findings, the 5 top ranked genes in terms of both gene expression and methylation modification upon treatment turned out to be predominantly affected by decitabine (figure 2A). A search for genes modulated by both gene expression and methylation found only 5 genes in common, which were mostly cancer testis antigens (GAGE2B, MAEL, TDRD9, GRIN1 and PNLDC1). Four out of five genes were also confirmed by RT-PCR (figure 2B). These genes modulated almost uniquely by decitabine, suggesting that the addition of the HDAC inhibitor could be avoided. Interestingly, other detailed studies of antigen presentation on the tumor cells revealed that another HMA, azacytidine, increased expression of multiple cancer testis antigens including multiple MAGE family proteins, whose expression have been shown to be suppressed by promoter hypermethylation. This finding is nearly identical to the one made by our group following treatment of T-cell lymphoma cell lines by the combination of romidepsin and decitabine. In addition, recent data has demonstrated that low dose decitabine elicits an anti-tumor cytotoxic T lymphocyte response by the induction of CD80 expression via demethylation of CpG dinucleotide sites in the promoter of CD80 gene in preclinical model of T-cell lymphoma[15]. We hypothesize that prior exposure to HMA combined with pralatrexate can enhance "the priming effect" on patients undergoing treatment with the immune checkpoint inhibitor, pembrolizumab, increasing the expression of neoantigens on the surface of the neoplastic cells, restoring the T-cell cytotoxic response through upregulation of T-cell co-stimulatory molecules, inducing expression of the MAGE family proteins, de-repressing the transcription of human endogenous retrovirus (HERV) genes[16] and modulating the malignant cells and the microenvironment to become more vulnerable to PD-1 blockade.

4.2.3 Pralatrexate potently synergizes with epigenetic drugs in models of T-cell lymphoma.

Accumulating work from our group continues to confirm that pralatrexate favorably combines with a number of drugs very active in PTCL, including bortezomib[17], gemcitabine, and romidepsin[18]. The latter combination of pralatrexate and romidepsin is simply based on the empiric observation that these two drugs were the first approved for the treatment of patients with relapsed or refractory PTCL, with single agent activity that appears to be lineage specific. Mice treated at the MTD of each drug exhibited some regression

of tumor, with the best response seen with pralatrexate in this model. However, when given at 50% of the MTD for the single agent, the combination of pralatrexate and romidepsin induced complete remission not seen with single agents, and produced an overall survival benefit only for mice in the combination cohort. Given pre-clinical evidence of synergism, our group initiated a phase I/II trial of combined pralatrexate and romidepsin (https://clinicaltrials.gov/show/NCT01947140). Among 25 patients enrolled in phase 1 study, the combination was found to be highly tolerable, and produced an ORR in PTCL patients with very chemotherapy resistant disease of 77%, including 38% CR.

4.2.4 Hypothesis

We hypothesize that if pralatrexate serves as an immunomodulatory agent able to induce interferon-mediated T-helper response signaling and contributes to promoter de-repression of MAGE family genes through KDM3A and decitabine induces the expression of T-cell co-stimulatory molecules (e.g. CD 80), MAGE family proteins, and triggers type-I interferon-mediated response through viral mimicry as described above[19], then priming and modulating the malignant cells and the microenvironment with pralatrexate and decitabine before exposure to the PD-1 blockade with pembrolizumab will restore and enhance immune surveillance and ultimately augment the antitumor activity in patients with PTCL and CTCL.

4.2.5 Rationale for the Trial and Selected Subject Population

The peripheral T-cell lymphomas (PTCLs) are rare subtypes of Non-Hodgkin lymphoma (NHL) with unique clinicopathologic features and very unfavorable prognosis. Recently it has been demonstrated that PTCLs are characterized by recurrent mutations in epigenetic operators (e.g. *TET2*, *DNMT3A*, and *IDH2*) and escape from immune surveillance. The immune checkpoint inhibitor, pembrolizumab has shown marked activity as single agent in patients with PTCL and CTCL.

4.3 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 CD3ζ, PKCθ and ZAP70 which are involved in the CD3 T-cell signaling cascade. The mechanism by which PD-1 down modulates T-cell responses is similar to, but distinct from that of CTLA-4 as both molecules regulate an overlapping set of signaling proteins. PD-1 was shown to be expressed on activated lymphocytes including peripheral CD4+ and CD8+ T-cells, B-cells, T regs and Natural Killer cells. Expression has also been shown during thymic development on CD4-CD8- (double negative) T-cells as well as subsets of macrophages and dendritic cells. The ligands for PD-1 (PD-L1 and PD-L2) are constitutively expressed or can be induced in a variety of cell types, including non-hematopoietic tissues as well as in various tumors. Both ligands are type I transmembrane receptors containing both IgV- and IgC-like domains in the extracellular region and contain short cytoplasmic regions

with no known signaling motifs. Binding of either PD-1 ligand to PD-1 inhibits T-cell activation triggered through the T-cell receptor. PD-L1 is expressed at low levels on various non-hematopoietic tissues, most notably on vascular endothelium, whereas PD-L2 protein is only detectably expressed on antigen-presenting cells found in lymphoid tissue or chronic inflammatory environments. PD-L2 is thought to control immune T-cell activation in lymphoid organs, whereas PD-L1 serves to dampen unwarranted T-cell function in peripheral tissues. Although healthy organs express little (if any) PD-L1, a variety of cancers were demonstrated to express abundant levels of this T-cell inhibitor. PD-1 has been suggested to regulate tumor-specific T-cell expansion in subjects with melanoma (MEL). This suggests that the PD-1/PD-L1 pathway plays a critical role in tumor immune evasion and should be considered as an attractive target for therapeutic intervention.

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

The peripheral T-cell lymphomas (PTCLs) are rare subtypes of Non-Hodgkin lymphoma (NHL) with unique clinicopathologic features and very unfavorable prognosis. Recently it has been demonstrated that PTCLs are characterized by recurrent mutations in epigenetic operators (e.g. *TET2*, *DNMT3A*, and *IDH2*) and escape from immune surveillance. The immune check point inhibitor, pembrolizumab has shown marked activity as single agent in patients with PTCL and CTCL.

We hypothesize that if pralatrexate serves as an immunomodulatory agent able to induce interferon-mediated T-helper response signaling and contributes to promoter de-repression of MAGE family genes through KDM3A and decitabine induces the expression of T-cell co-stimulatory molecules (e.g. CD 80), MAGE family proteins, and triggers type-I interferon-mediated response through viral mimicry, then priming and modulating the malignant cells and the microenvironment with pralatrexate and decitabine before exposure to the PD-1 blockade with pembrolizumab will restore and enhance immune surveillance and ultimately augment the antitumor activity in patients with PTCL and CTCL.

4.3.1 Pembrolizumab

An open-label Phase I trial (Protocol 001) is being conducted to evaluate the safety and clinical activity of single agent MK-3475. 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 MK-3475 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 MTD has been identified to date. 10.0 mg/kg Q2W, the highest dose tested in PN001, was the dose and schedule utilized in Cohorts A, B, C and D of this protocol to test for initial tumor activity. More recent data from other clinical studies within the MK-3475 program has shown that a lower dose of MK-3475 and a less frequent schedule may be sufficient for target engagement and clinical activity.

PK data analysis of MK-3475 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 MK-3475 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. MK-3475 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 MK-3475 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 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.

4.3.2 Pralatrexate

Overview
Pralatrexate is presently approved for the treatment of relapsed or refractory PTCL. O'Connor el at in the pivotal study PROPEL showed that pralatrexate produced an overall response rate of 29% and a median duration of response of 10.4 months in a heavily pretreated group of patients. Pralatrexate is a novel antifolate that has been rationally designed to have increased affinity for the reduced folate carrier (RFC-1), allowing for better internalization into the cell. Pralatrexate is also a better substrate for polyglutamation by FPGS (folylpolyglutamyl synthetase) allowing for better retention in the cell compared to MTX. In addition, the polyglutamate chains formed by pralatrexate tend to be longer than those formed on MTX, which appears to improve the inhibition of the target enzyme dihydrofolate reductase (DHFR). Collectively, these pharmacological attributes render pralatrexate a more potent cytotoxic agent in vitro and in vivo compared to MTX across a broad panel of lymphoma cell lines. Clinical trials to assess the efficacy of pralatrexate in other forms of lymphoma are ongoing including CTCL and B-cell malignancies. Interestingly, initial clinical experiences seemed to suggest that pralatrexate was more active in T- over B-cell lymphomas, though; admittedly few patients with B-cell lymphoma have been treated. Dedicated studies exploring the activity of pralatrexate in B-cell neoplasms on a weekly schedule are now ongoing [11].
Some data has suggested that the activity in different lymphoid neoplasms may correlate with higher levels of RFC-1 in sensitive cells, suggesting that RFC-1 could be an important biomarker of activity. While many laboratory studies are now ongoing to explore these relationships, it is clear that any up-regulation of RFC-1 could lead to marked improvement in the activity of pralatrexate. Such pharmacologic strategies could lead to the generation of rational synergistic combinations.
The regulation of RFC-1 is complex. The promoter site of RFC is known to be epigenetically regulated and known be hypermethylated in many tumor types [20]. This observation has led to the hypothesis that RFC expression can be pharmacologically modulated by histone deacetylase inhibitors and hypomethylating

agents, both of which are known to influence the epigenetic regulation of many genes. These biological features of RFC regulation suggest that rational combinations of select agents known (or suspected of regulating RFC expression) may provide a basis for exploring the potential synergistic combinations of pralatrexate and HDACI or hypomethylating agents.

Mechanism of Action

Pralatrexate is a unique antifolate that has been rationally designed to have a high affinity for the reduced folate receptor (RFC-1) and the enzyme folylpolyglutamy synthetase [21]. This allows the drug to be selectively accumulated in tumor cells. RFC expression is induced by various oncogenes, including H-*ras* and c-*myc,* which results in an increase in the rate of internalization of radio-labeled antifolate[11]. Several studies have shown greater cytotoxic properties for pralatrexate compared to methotrexate, but its precise mechanism of action and T-cell specificity remain objects of research. Preliminary gene expression profiling and pathway analysis comparing methotrexate and pralatrexate demonstrated that pralatrexate specifically affects immune response signaling, cytokine production and lymphocyte activation pathways.

Clinical Pharmacokinetics

Non-compartmental and population PK (POPPK) analyses showed that pralatrexate *R* and *S* diastereomers follow apparent first-order PK with the area under the curve to infinity (AUC∞) increasing in a near linear manner with dose. Total, renal, and non-renal clearance as well as volume of distribution were constant within (nominal) doses ranging from 30 mg/m^2 to 325 mg/m^2. Comparing the 2 diastereomers, plasma exposures of the *R* diastereomer exceed those of the *S* diastereomer by approximately 2-fold; the reason for this is unclear at this point. *S* and *R* diastereomer clearance were reduced by 0.128 and 0.0778 L/hour per 1 mL/min reduction in creatinine clearance for patients with a creatinine clearance less than 80 mL/min. Although the estimated effects of creatinine clearance appeared to be clinically insignificant, few patients with moderate to severe renal impairment were enrolled in these studies, making characterization of the effects of renal impairment on pralatrexate disposition difficult. Based on clearance parameters, it appears that renal tubular and hepatobiliary drug transporters may play an important role in the elimination of pralatrexate.

In vitro plasma protein binding studies showed that pralatrexate was 67-86% bound to human plasma protein, with human serum albumin being a significant contributor to the total binding. Pralatrexate did not compete with plasma protein binding of 6 drugs that were selected as reference compounds for different plasma protein binding sites. These studies suggest that pralatrexate at clinically relevant concentrations is not likely to cause displacement of other drugs from plasma proteins. Of note is that the reciprocal study also showed that 6 selected reference agents did not displace pralatrexate from plasma proteins. These results collectively suggest that a plasma protein binding displacement drug interaction is unlikely.

Safety

The most frequent AEs, regardless of causality, reported in single-agent studies of hematologic malignancies were fatigue (n=86, 47%), nausea (n=74, 41%), mucosal inflammation (n=67, 37%), stomatitis (n=66, 36%), and constipation (n=65, 36%).

Patients with ATLL and HTLV-1 will be closely monitored by both the principle investigator and the DSMB.

Patients receiving pralatrexate should be monitored closely because AEs may occur at any time during therapy. For detailed information about the safety profile of pralatrexate, refer to the current pralatrexate IB and/or package insert.

Efficacy in Non-Hodgkin's Lymphoma

Pralatrexate is FDA approved for the treatment of PTCL. There are data published by our group that suggest that pralatrexate is strongly synergistic in combination with bortezomib and other agents including romidepsin and hypomethylating agents in the treatment of PTCLs. Pralatrexate used in combination with romidepsin and hypomethylating agents represent a novel and potentially important platform for the

treatment of T-cell malignancies. Early clinical phase I/II trials exploring the value of the doublet combination of pralatrexate plus romidepsin and azacytidine plus romidepsin are currently ongoing with very promising results.

4.3.3 Decitabine

Decitabine (5-aza-2'-deoxycytidine) is a hypomethylating agent thought to exert its antineoplastic effects after phosphorylation and direct incorporation into DNA. This process leads to DNA methyltransferase irreversible inhibition, causing hypomethylation of DNA and resulting in cellular differentiation or apoptosis. Decitabine inhibits DNA methylation *in vitro*, which is achieved at concentrations that do not cause major suppression of DNA synthesis. Decitabine-induced hypomethylation in neoplastic cells may restore normal function to genes that are critical for the control of cellular differentiation and proliferation. In rapidly dividing cells, the cytotoxicity of decitabine may also be attributed to the formation of covalent adducts between DNA methyltransferase and decitabine incorporated into DNA. Nonproliferating cells are relatively insensitive to decitabine.

Mechanism of Action of Decitabine
Decitabine is believed to exert its antineoplastic effects after phosphorylation and direct incorporation into DNA and inhibition of DNA methyltransferase, causing hypomethylation of DNA and cellular differentiation or apoptosis. Decitabine inhibits DNA methylation in vitro, which is achieved at concentrations that do not cause major suppression of DNA synthesis. Decitabine-induced hypomethylation in neoplastic cells may restore normal function to genes that are critical for the control of cellular differentiation and proliferation. In rapidly dividing cells, the cytotoxicity of decitabine may also be attributed to the formation of covalent adducts between DNA methyltransferase and decitabine incorporated into DNA. Non-proliferating cells are relatively insensitive to decitabine.

Nonclinical Pharmacology of Decitabine - pharmacodynamics and pharmacokinetics
Decitabine has been shown to induce hypomethylation both in vitro and in vivo. However, there have been no studies of decitabine-induced hypomethylation and pharmacokinetic parameters. Pharmacokinetic parameters were evaluated in patients. Eleven patients received 20 mg/m2 infused over 1 hour intravenously (treatment Option 2). Fourteen patients received 15 mg/m2 infused over 3 hours (treatment Option 1). PK parameters are shown in Table 3. Plasma concentration-time profiles after discontinuation of infusion showed a biexponential decline. The CL of decitabine was higher following treatment Option 2. Upon repeat doses there was no systemic accumulation of decitabine or any changes in PK parameters. Population PK analysis (N=35) showed that the cumulative AUC per cycle for treatment Option 2 was **2.3.2.** The exact route of elimination and metabolic fate of decitabine is not known in humans. One of the pathways of elimination of decitabine appears to be deamination by cytidine deaminase found principally in the liver but also in granulocytes, intestinal epithelium and whole blood.

Nonclinical Toxicology of Decitabine
Carcinogenicity studies with decitabine have not been conducted. The mutagenic potential of decitabine was tested in several *in vitro* and *in vivo* systems. Decitabine increased mutation frequency in L5178Y mouse lymphoma cells, and mutations were produced in an Escherichia coli lac-I transgene in colonic DNA of decitabine-treated mice. Decitabine caused chromosomal rearrangements in larvae of fruit flies. The effect of decitabine on postnatal development and reproductive capacity was evaluated in mice administered a single 3 mg/m^2 IP injection (approximately 7% the recommended daily clinical dose) on day 10 of gestation. Body weights of males and females exposed in utero to decitabine were significantly reduced relative to controls at all postnatal time points. No consistent effect on fertility was seen when female mice exposed in utero were mated to untreated males. Untreated females mated to males exposed in utero showed decreased fertility at 3 and 5 months of age (36% and 0% pregnancy rate, respectively). In male mice given IP injections of 0.15, 0.3 or 0.45 mg/m^2 decitabine (approximately 0.3% to 1% the recommended clinical

dose) 3 times a week for 7 weeks, decitabine did not affect survival, body weight gain or hematological measures (hemoglobin and WBC counts). Testes weights were reduced, abnormal histology was observed and significant decreases in sperm number were found at doses ≥0.3 mg/m^2. In females mated to males dosed with ≥0.3 mg/m^2 decitabine, pregnancy rate was reduced, and preimplantation loss was significantly increased.

Safety of Decitabine
Most common adverse reactions (>50%) are neutropenia, thrombocytopenia, anemia, and pyrexia.
Following the first cycle of DACOGEN treatment, if any of the following non-hematologic toxicities are present, DACOGEN treatment should not be restarted until the toxicity is resolved: 1) serum creatinine ≥2 mg/dL; 2) SGPT, total bilirubin ≥2 times ULN; 3) and active or uncontrolled infection.

Efficacy of Decitabine
A randomized open-label, multicenter, controlled trial evaluated 170 adult patients with myelodysplastic syndromes (MDS) meeting French American-British (FAB) classification criteria and International Prognostic Scoring System (IPSS) High-Risk, Intermediate-2 and Intermediate-1 prognostic scores. Eighty-nine patients were randomized to DACOGEN therapy plus supportive care (only 83 received DACOGEN), and 81 to Supportive Care (SC) alone. Patients with Acute Myeloid Leukemia (AML) were not intended to be included. Of the 170 patients included in the study, independent review (adjudicated diagnosis) found that 12 patients (9 in the DACOGEN arm and 3 in the SC arm) had the diagnosis of AML at baseline. Baseline demographics and other patient characteristics in the Intent-to-Treat (ITT) population were similar between the 2 groups. Patients randomized to the DACOGEN arm received DACOGEN intravenously infused at a dose of 15 mg/m^2 over a 3-hour period, every 8 hours, for 3 consecutive days. This cycle was repeated every 6 weeks, depending on the patient's clinical response and toxicity. Supportive care consisted of blood and blood product transfusions, prophylactic antibiotics, and hematopoietic growth factors. The study endpoints were overall response rate (complete response + partial response) and time to AML or death. Responses were classified using the MDS International Working Group (IWG) criteria; patients were required to be RBC and platelet transfusion independent during the time of response. The overall response rate (CR+PR) in the ITT population was 17% in DACOGEN-treated patients and 0% in the SC group ($p<0.001$). The overall response rate was 21% (12/56) in DACOGEN-treated patients considered evaluable for response (i.e., those patients with pathologically confirmed MDS at baseline who received at least 2 cycles of treatment). The median duration of response (range) for patients who responded to DACOGEN was 288 days (116-388) and median time to response (range) was 93 days (55-272). All but one of the DACOGEN-treated patients who responded did so by the fourth cycle. Benefit was seen in an additional 13% of DACOGEN-treated patients who had hematologic improvement, defined as a response less than PR lasting at least 8 weeks, compared to 7% of SC patients. DACOGEN treatment did not significantly delay the median time to AML or death versus supportive care. All patients with a CR or PR were RBC and platelet transfusion independent in the absence of growth factors. Responses occurred in patients with an adjudicated baseline diagnosis of AML.

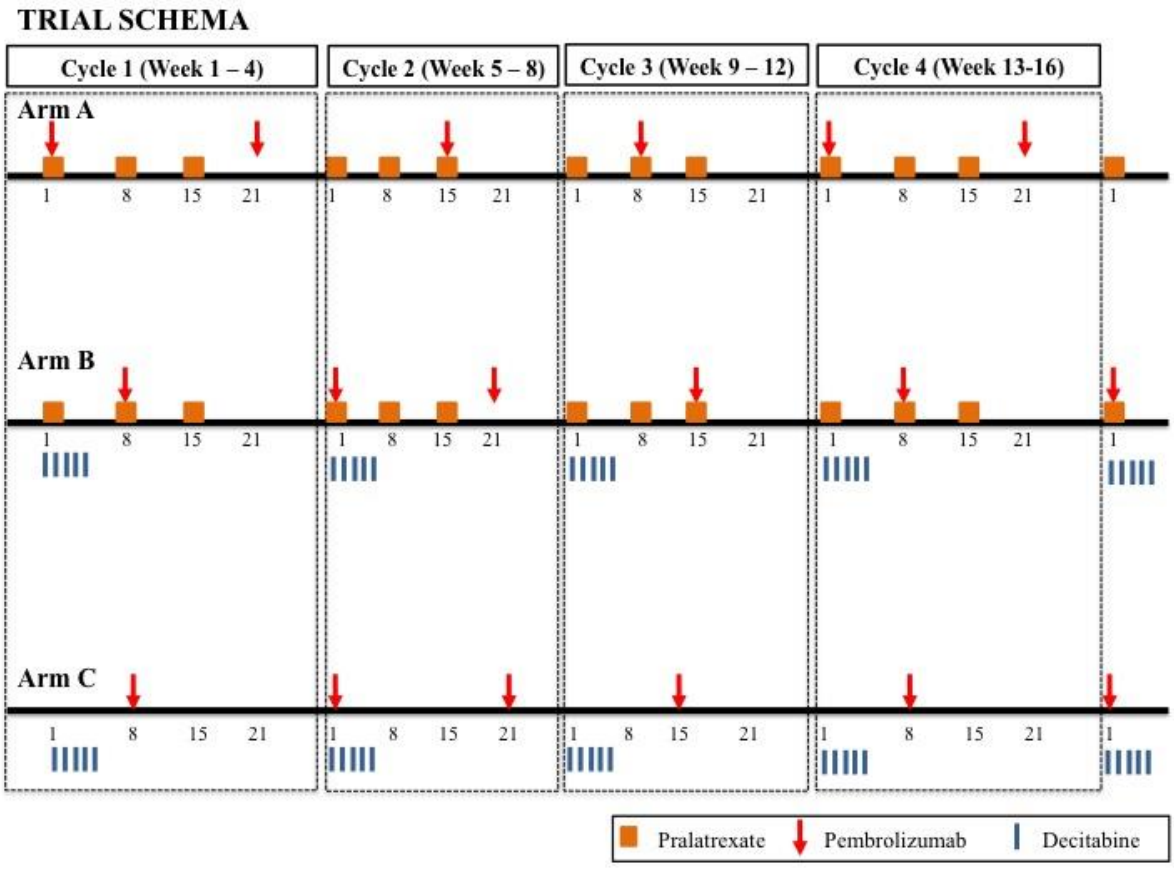
5.0 TREATMENT PLAN

5.1 Study Design
In Arm A and Arm C, because there are non-overlapping toxicities between pralatrexate or decitabine and pembrolizumab, a classic 3 x 3 dose escalation design will not be applied. Rather, in Arm A and Arm C, we will start at the known MTD for each drug and use a CRM design for dose escalation and de-escalation. In Arm B, a CRM design for escalation of more than one agent (POCRM) will be applied.

Pralatrexate and decitabine will be administered as described every 28 days (Q4W).

Pembrolizumab will be administered at the fixed dose of 200 mg every 3 weeks (Q3W) 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 patient exposure in the exposure range established in melanoma that are well tolerated and safe. As noted above, the different drugs used in this trial will be administered following different schedule, every 3 weeks (Q3W) for pembrolizumab and every 4 weeks (Q4W) for pralatrexate and decitabine. Each cycle is 28 days. The trial schema for the first 12 weeks of treatment is provided below.

Participants will be enrolled only onto Arms A and C until the required number of patients are accrued to both arms. Enrollment onto Arm A or Arm C will be based on investigators' choice. Once enrollment onto Arm A or Arm C is completed, the next participant(s) will be assigned to the open Arm (A or C). Arm B will be the last Arm enrolling patients as important toxicity information could be learned from treating patients on the doublet combinations in Arm A and Arm C.



5.2 Agents Administration

Details regarding study drug administrations are reported in the sections below (Section 5.2.1, Section 5.2.2 and Section 5.2.3). Dose modifications are detailed in Section 7.3.

Refer to FDA approved package insert and//or investigator's brochure for each study drug for anything not specifically mentioned in the protocol.

5.2.1 Pembrolizumab

Pembrolizumab will be administered at the fixed dose of 200 mg every 3 weeks (Q3W) in all the study arms. In Arm A, pembrolizumab will be started on day 1 of cycle 1. In Arm B and Arm C, pembrolizumab administration will be started on day 8 of cycle 1 to allow respectively sensitization with pralatrexate and decitabine.

5.2.2 Pralatrexate

In Arm A, pralatrexate will be administered at the entry dose of 30 mg/m^2 day 1, 8, 15 Q4W which represents the MTD identified in the PROPEL trial. Allocation of participants to doses of Pralatrexate will be conducted according to the study design described in Section 10: Statistical Considerations.
In Arm B, pralatrexate will be administered at the entry dose of 20 mg/m^2 day 1, 8, 15 Q4W and subsequently de-escalated (if applicable) following the study design described in the Statistical Considerations.
All patients receiving pralatrexate will receive folic acid at the dose of 1,000 mg orally daily and vitamin B_{12} intramuscularly every 2 cycles (8 weeks) as recommended in the package insert of the product. The vitamin supplementation will start prior to the first dose of pralatrexate as recommended in the drug package insert. Leucovorin will be used to decrease the risk of mucositis in all patients receiving treatment with pralatrexate. Leucovorin will be given at the dose of 15 mg orally twice daily and should be held the day before, the day of and the day after pralatrexate treatment. Leucovorin is mandatory for patients on trial.

5.2.3 Decitabine

In Arm B, decitabine will be administered at the entry dose of 10 mg/m^2 day 1 to day 5 (day 1 -> day 5) Q4W and de-escalated (if applicable) following the study design described in the Statistical Considerations.
In Arm C, decitabine will be administered at the entry dose of 20 mg/m^2 day 1 to day 5 (day 1 -> day 5) Q4W and allocation of participants to doses of decitabine will be conducted according to the study design outlined in the Statistical Considerations.
For any additional information refer to FDA-approved package insert.

5.3 Dose Limiting Toxicities

A dose limiting toxicity (DLT) is defined as any toxicity that occurs that is considered at least "possibly related to the study drug administration". Only DLT's that occur prior to initiation of cycle 2 will be used to determine dose escalation/de-escalation decisions.
DLT criteria are defined as follows:

1. Any non-hematologic toxicity greater and/or equal to grade 3, except for:
    - Alopecia
    - Untreated nausea or vomiting;
    - Untreated constipation or diarrhea;
    - Untreated dehydration or fatigue uncontrolled;
    - Any liver function test including AST/ALT, GGT, Alkaline phosphatase elevation that has returned to grade 1 or baseline by day1 of cycle 2;

2. Grade 4 neutropenia lasting more than 5 days despite GCS-F support;
3. Febrile neutropenia (ANC < 1000/mm^3 with a single temperature of > 38.3°C or sustained temperature of ≥ 38°C for over one hour);
4. Any grade 4 thrombocytopenia or grade 3 thrombocytopenia with clinically significant bleeding or any grade-3 thrombocytopenia requiring platelet transfusion
5. Grade 4 anemia unexplained by underlying disease involvement;

6. Failure to meet the required blood parameters for cycle 2 day 1.

Management and dose modifications associated with adverse events will be described in the following sections 7.0, 7.1, 7.2 (Dose selection, dose delays, dose modification).

5.4 Required Blood Parameters and Other Investigations Prior to Each Treatment

Before the start of each cycle, patients should be reassessed, and the following criteria must be fulfilled:

- Absolute neutrophil count (ANC) > 1000/μL
- Platelet count ≥ 50,000/μL
- Serum creatinine concentration ≤ 2.0 × institutional ULN or ≤ baseline, or creatinine clearance > 50 ml/min or baseline
- AST and ALT ≤ 2.0 × ULN or ≤ 3.0 × institutional ULN or baseline in presence of demonstrable lymphoma involvement of liver
- Bilirubin concentration ≤ 1.5 x ULN or direct bilirubin ≤ULN for patients with total bilirubin levels >1.5 × ULN
- Recovery of any drug-related non-hematological AE to grade ≤ 1, unless otherwise indicated
- The above blood parameters are required to start day 1 treatment of every cycle with decitabine but do not need to be evaluated on day 2, day 3, day 4 and day 5 of each cycle unless clinically indicated.

5.5 Efficacy Endpoints

The primary endpoints of this study are safety, tolerability, and efficacy (anti-tumor activity) that will be obtained at completion of the study. The study will provide additional data regarding safety, anti-tumor activity and efficacy of the combinations and will suggest possible biomarkers of response.

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The plan is to evaluate the overall response rate (ORR), progression free survival (PFS), and duration of response (DOR) of the study population receiving the combinations of pembrolizumab and pralatrexate (Arm A), pralatrexate, decitabine and pembrolizumab (Arm B), and decitabine and pembrolizumab (Arm C).

5.6 Biomarker Research

The trial will aim to identify biomarkers that may correlate with clinical activity of pembrolizumab through the following steps:

- Analyze the changes on T cell repertoire in peripheral blood and primary tumor samples as a function of treatment with pralatrexate, decitabine and pembrolizumab and assess the contribution of epigenetic priming with decitabine in patients receiving treatment with pembrolizumab and pralatrexate.

Standard flow cytometry to assess CD3, CD4, CD8, CD25, CD80, PD1, PD-L1, PD-L2 and Foxp3 will be performed in peripheral blood mononuclear cells. In addition, peripheral blood T lymphocytes will be analyzed by flow cytometry for CD45 RA, CCR7, CD62L to understand changes in the T cell repertoire. Correlation in between changes and response to treatment will be made.

Paraffin embedded primary tumor samples will be obtained pre- and post-treatment as defined below and OpalMultiplexing “MANTRA” will be performed. MANTRA is a tissue evaluation technique, which uses a fluorescent signal amplification probe to permit serial immunohistochemistry and compared to conventional immunohistochemistry permits multiplex detection. Opal Multiplexing MANTRA will be used to determine changes in the microenvironment (TILs, NK-cell and antigen-presenting cells) as a function of treatment. The following set of 6 markers will be analyzed on each tissue biopsy: CD3, CD7, CD4, CD8, PGM1, IDO; CD3, CD7, CD4, CD8, CD20, FOXP3; CD3, CD7, CD4, CD8, PD-1, PD-L1; CD3, CD7, CD4, CD8, CD56, Granzyme B.

- Elucidate the immune modulatory effect of pralatrexate and decitabine and identify biomarker of response accounting for heterogeneity and dynamic changes.

Gene expression profiling (GEP) analysis will be obtained on primary tumor samples pre- and post-treatment. Changes of gene expression profiling as a function of treatment with pralatrexate and decitabine will be analyzed. Specific attention will be placed on defined gene-signature already described and predictive of response to pembrolizumab (e.g. interferon-γ-related genes including CXCL9, CXCL10, IDO1, IFNG, HLA-DRA, STAT1). Additional signature associated with clinical outcome will be investigated.

Genome wide methylation analysis will be performed to identify and quantify changes in methylation pre- and post-treatment. Specific attention will be placed on decitabine contribution in de-repressing and inducing transcription of multiple DNA hypermethylated human endogenous retrovirus (HERV) genes triggering a type I interferon-response.

GEP and methylation wide methylation profiling will be analyzed, and correlation will be made to identify biomarkers of response. The data gathered from the GEP and genome wide methylation will be used to create an algorithm of regulatory networks within PTCLs. The analysis of these data will provide information on etiology of PTCLs and will suggest possible targetable oncogenic pathways.

6.0 METHODOLOGY

6.1 Diagnosis/Condition for Entry into the Trial

Patients must have histologically confirmed diagnosis of relapsed and refractory (R/R) peripheral T-cell lymphoma (PTCL) or cutaneous T-cell lymphoma (CTCL).

6.1.1 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 ≥ 18 years of age on day of signing informed consent.
3. Have measurable disease as defined by the Lugano Criteria for PTCL (Cheson et al., 2014)[22] and by the Global Response Score for CTCL (Olsen et al., 2011)[23].
4. Patient must have histologically confirmed relapsed or refractory Peripheral T-cell lymphoma (PTCL) or cutaneous T-cell Lymphoma (CTCL) as per WHO criteria and TNMB classification and staging.
5. There is no upper limit for the number of prior therapies. Patient may have relapsed after prior autologous stem cell transplant.
6. Patients who had prior treatment for their disease, as long as there is radiographic evidence of refractory or relapsed disease and the patient meets all other clinical and laboratory criteria for study treatment.
7. Be willing to provide tissue from a newly obtained core or excisional biopsy of a tumor lesion. Be willing to provide FNA of a tumor lesion. *Newly-obtained is defined as a specimen obtained up to 6 weeks (42 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 only upon agreement from the Sponsor.*
8. Have a performance status of 0 or 1 on the ECOG Performance Scale.
9. Demonstrate adequate organ function as defined in Table 6, all screening labs should be performed within 10 days of treatment initiation.

Table 6: Adequate Organ Function Laboratory Values.

System	Laboratory Value
Hematological	
Absolute neutrophil count (ANC)	≥1,000 /mcL
Platelets	≥75,000 / mcL
Hemoglobin	≥9 g/dL or ≥5.6 mmol/L without transfusion or EPO dependency (within 7 days of assessment)
Renal	
Serum creatinine **OR** Measured or calculated[a] creatinine clearance (GFR can also be used in place of creatinine or CrCl)	≤1.5 X upper limit of normal (ULN) **OR** ≥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	≥2.5 mg/dL
Coagulation	
International Normalized Ratio (INR) or Prothrombin Time (PT) 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 ≤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.	

10. Female subjects 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.
11. Female subjects of childbearing potential (Section 7.7.9.2) must be willing to use an adequate method of contraception as outlined in Section 7.9.2 – 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.

12. Male subjects of childbearing potential (Section 7.9.2) must agree to use an adequate method of contraception as outlined in Section 7.9.2- 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.

6.1.2 Subject Exclusion Criteria

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

1. Has lack of resolution of adverse events (AE) due to previously administered antineoplastic therapy to grade 1 or less according to National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE), version 5.0
2. Had prior therapy with PD-1 inhibitors.

3. Has a diagnosis of immunodeficiency or has been receiving any immunosuppressive therapy within 7 days prior to the first dose of trial treatment. Use of steroid equivalent to prednisone 10 mg/day does not constitute an exclusion criterion.
4. Has a known history of active TB (Bacillus Tuberculosis)
5. Hypersensitivity to pralatrexate, or decitabine or pembrolizumab or any of its excipients.
6. Has received prior allogeneic stem cell transplant.
7. Has a known additional malignancy that is progressing or requires active treatment. Exceptions include basal cell carcinoma of the skin 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. The following are exceptions to this criterion: subjects with vitiligo or alopecia; subjects with hypothyroidism (e.g., following Hashimoto syndrome) stable on hormone replacement; subjects with psoriasis not requiring systemic treatment; patients with autoimmune phenomena secondary to active lymphoma.
10. Has known history of, or any evidence of non-infectious pneumonitis/interstitial lung disease that required steroids or has current pneumonitis/interstitial lung disease.
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. Has received a live vaccine or live-attenuated vaccine within 30 days of planned start of study therapy. Administration of killed vaccines is allowed.
    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.

6.2 Trial Treatments

The treatment arms to be used in this trial are outlined in Table 7, Table 8 and Table 9 below.

Table 7: Trial Treatment – Arm A

Agent	Premedication Precautions	Dose	Route	Schedule A	Cycle Length
Pembrolizumab	N/A	200 mg (flat dose)	IV Administered first during cycle 1	Days 1*	Q3W
Pralatrexate	B12 and Folate supplementation (to be started within one week before initiation of treatment), and leucovorin (LV) as outlined	20 or 30 mg/m^2**	IV push	Days 1, 8, 15	Q4W

**Day 1 for pembrolizumab administration refers only to cycle 1 of treatment. Pembrolizumab will be continued every 3 weeks following the first administration.*
*** Doses as appropriate for assigned dose level. Pralatrexate dose will be calculated using weight at cycle 1 day 1, unless weight has changed more that 10%. If so, the total dose should be calculated on the updated weight.*

Table 8: Trial Treatment – Arm B

Agent	**Premedication Precautions**	**Dose**	**Route**	**Schedule B**	**Cycle Length**
Decitabine	Antiemetic	10 mg/m^2*	IV	Days 1, 2,3,4,5	*Q4W*
Pralatrexate	B12 and Folate supplementation (to be started within one week before initiation of treatment) and leucovorin (LV)	20 mg/m2 *	IV push	Days 1,8,15	
Pembrolizumab	N/A	200 mg (Flat dose)	IV	Day 8**	*Q3W*

** Doses as appropriate for assigned dose level. Pralatrexate and decitabine dose will be calculated using weight at cycle 1 day 1, unless weight has changed more that 10%. If so, the total dose should be calculated on the updated weight.*
***Day 8 for pembrolizumab administration refers only to cycle 1 of treatment. Pembrolizumab will be continued every 3 weeks following the first administration.*

Table 9: Trial Treatment – Arm C

Agent	Premedication Precautions	Dose	Route	Schedule C	Cycle Length
Pembrolizumab	N/A	200 mg (flat dose)	IV (Administered first during cycle 1)	Days 8*	*Q3W*
Decitabine	Antiemetic	20 mg/m^2 **	IV	Days 1,2, 3, 4, 5	*Q4W*
**Day 8 for pembrolizumab administration refer only to cycle 1 of treatment. Pembrolizumab will be continued every 3 weeks following the first administration.* ***Doses as appropriate for assigned dose level. Decitabine dose will be calculated using weight at cycle 1 day 1, unless weight has changed more that 10%. If so, the total dose should be calculated on the updated weight.*					

All patients receiving pralatrexate will receive folic acid at the dose of 1,000 mg orally daily and vitamin B_{12} intramuscularly every 2 cycles (8 weeks) as recommended in the package insert of the product. The vitamin supplementation will start prior to the first dose of pralatrexate as recommended in the drug package insert. If leucovorin is being used for rescue, this should be used at the dose of 15 mg orally twice daily and should be held the day before, of and after pralatrexate.

Trial treatment should begin on the day of randomization or as close as possible to the date on which treatment is allocated/assigned.

7.0 DOSE SELECTION/DELAYS/MODIFICATION

7.1 Dose Selection

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

7.2 Dose Delays

These dose delays apply to all drugs and patients on all study arms. Additional delays may apply for specific drugs (see sections 7.3.1 and 7.3.2 below).

- Study drugs can be administered within 48 hours of their scheduled time.
- Study drugs will be held for DLT and any grade 3/4 toxicity not addressed in section 5.3 until the AE returns to grade ≤ 2 unless otherwise specified in the sections below.
- If the interruption lasts for more than 14 days, study treatment will be discontinued.

7.3 Dose Modification

If the administration of a study drug combination (Arm A, Arm B, or Arm C) leads to a toxicity beyond cycle 1 at a given dose level, dose modifications may occur in accordance with the drug FDA approved package insert, or as outlined in the dose de-escalation tables. This post-cycle 1 DLT will not count towards the overall determination of MTD for this study.

7.3.1 Immune Related Adverse Events

Adverse events (both non-serious and serious) associated with pembrolizumab exposure, including coadministration with additional compounds, may represent an immunologic etiology. These adverse events may occur shortly after the first dose or several months after the last dose of pembrolizumab/combination treatment and may affect more than one body system simultaneously. Therefore, early recognition and initiation of treatment is critical to reduce complications. Based on

existing clinical study data, most irAEs were reversible and could be managed with interruptions of pembrolizumab/combination treatment, administration of corticosteroids and/or other supportive care. For suspected irAEs, ensure adequate evaluation to confirm etiology or exclude other causes. Additional procedures or tests such as bronchoscopy, endoscopy, skin biopsy may be included as part of the evaluation. Dose modification and toxicity management guidelines for irAEs associated with pembrolizumab/combination treatment are provided in Table 10 below. See Section 7.8 for supportive care guidelines, including use of corticosteroids.

Attribution of Toxicity:
When study interventions are administered in combination, attribution of an adverse event to a single component is likely to be difficult. Therefore, while the investigator may attribute a toxicity event to the assigned treatment combination, to pralatrexate alone (Arm A or B), to decitabine alone (Arm B or C) or to pembrolizumab alone, for adverse events listed in Table 10, both (all, for Arm B) interventions must be held according to the criteria in Table 10 Dose Modification and Toxicity Management Guidelines for Immune-Related Adverse Events.

Holding Study Interventions:
When study interventions are administered in combination, if the AE is considered immune-related, both (all for Arm B) interventions should be held according to recommended dose modifications.

Restarting Study Interventions:
Participants may not have any dose modifications (no change in dose or schedule) of pembrolizumab in this study, as described in Table 10.

- If the toxicity does not resolve or the criteria for resuming treatment are not met, the participant must be discontinued from all study interventions.
- If the toxicities do resolve and conditions are aligned with what is defined in Table 10, the assigned treatment combination (based on Arm assignment) may be restarted at the discretion of the investigator. In these cases where the toxicity is attributed to the assigned treatment combination, to only the combination of decitabine and pralatrexate (Arm B only), or to decitabine or pralatrexate alone, re-initiation of pembrolizumab either as a monotherapy or, for Arm B only, combined with decitabine or pralatrexate if the AE is not attributed to one of the drugs, may be considered if the principal investigator's agrees.

Table 10: Dose Modification Guidelines for Immune-Related Adverse Events Associated with Monotherapy and IO Combinations. For further details please see section 7.8.2

General instructions:

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

Immune-related AEs	Toxicity grade (CTCAE v5.0)	Action with pembrolizumab	Corticosteroid and/or other therapies	Monitoring and follow-up
Pneumonitis	Grade 2	Withhold	• Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper • Add prophylactic antibiotics for opportunistic infections	• Monitor participants for signs and symptoms of pneumonitis • Evaluate participants with suspected pneumonitis with radiographic imaging and initiate corticosteroid treatment
	Grade 3 or 4, or recurrent Grade 2	Permanently discontinue		
Diarrhea / Colitis	Grade 2 or 3	Withhold	• Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper	• Monitor participants for signs and symptoms of enterocolitis (ie, diarrhea, abdominal pain, blood or mucus in stool with or without fever) and of bowel perforation (ie, peritoneal signs and ileus). • Participants with ≥ Grade 2 diarrhea suspecting colitis should consider GI consultation and performing endoscopy to rule out colitis. • Participants with diarrhea/colitis should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion.
	Recurrent Grade 3, or Grade 4	Permanently discontinue		
AST / ALT elevation or Increased	Grade 2[a]	Withhold	• Administer corticosteroids (initial dose of	• Monitor with liver function tests (consider weekly or more frequently until liver enzyme

bilirubin			0.5- 1 mg/kg prednisone or equivalent) followed by taper	value returned to baseline or is stable
	Grade 3[b] or 4[c]	Permanently discontinue	• Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper	
Type 1 diabetes mellitus (T1DM) or Hyperglycemia	New onset T1DM or Grade 3 or 4 hyperglycemia associated with evidence of β-cell failure	Withhold[d]	• Initiate insulin replacement therapy for participants with T1DM • Administer anti-hyperglycemic in participants with hyperglycemia	• Monitor participants for hyperglycemia or other signs and symptoms of diabetes.
Hypophysitis	Grade 2	Withhold	• Administer corticosteroids and initiate hormonal replacements as clinically indicated.	• Monitor for signs and symptoms of hypophysis's (including hypopituitarism and adrenal insufficiency)
	Grade 3 or 4	Withhold or permanently discontinue[d]		
Hyperthyroidism	Grade 2	Continue	• Treat with nonselective beta-blockers (e.g., propranolol) or thionamides as appropriate	• Monitor for signs and symptoms of thyroid disorders.
	Grade 3 or 4	Withhold or permanently discontinue[d]		
Hypothyroidism	Grade 2, 3 or 4	Continue	• Initiate thyroid replacement hormones (e.g., levothyroxine or liothyronine) per standard of care	• Monitor for signs and symptoms of thyroid disorders.

Nephritis grading according to increased creatinine or acute kidney injury	Grade 2	Withhold	• Administer corticosteroids (prednisone 1-2 mg/kg or equivalent) followed by taper.	• Monitor changes of renal function
	Grade 3 or 4	Permanently discontinue		
Neurological Toxicities	Grade 2	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 3 or 4	Permanently discontinue		
Myocarditis	Grade 1	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 2, 3 or 4	Permanently discontinue		
Exfoliative Dermatologic Conditions	Suspected SJS, TEN, or DRESS	Withhold	• Based on type and severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Confirmed SJS, TEN, or DRESS	Permanently discontinue		
All other irAEs	Persistent Grade 2	Withhold	• Based on type and severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 3	Withhold or discontinue based on the event[e]		
	Grade 4 or recurrent Grade 3	Permanently discontinue		

AE(s)=adverse event(s); ALT= alanine aminotransferase; AST=aspartate aminotransferase; CTCAE=Common Terminology Criteria for Adverse Events; DRESS=Drug Rash with Eosinophilia and Systemic Symptom; GI=gastrointestinal; IO=immuno-oncology; ir=immune related; IV=intravenous; SJS=Stevens-Johnson Syndrome; T1DM=type 1 diabetes mellitus; TEN=Toxic Epidermal Necrolysis; ULN=upper limit of normal.

Note: Non-irAE will be managed as appropriate, following clinical practice recommendations.

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

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

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

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

[e] Events that require discontinuation include, but are not limited to: encephalitis, and other clinically important irAEs (e.g. vasculitis and sclerosing cholangitis).

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 Sponsor. The reason for interruption should be documented in the patient's study record.

7.3.2 Pralatrexate

Patient treated with pralatrexate are at risk of developing mucositis. The risk of developing mucositis can be lowered by pretreating patient with leucovorin 15 mg PO BID that has to be held the day before, day of and day after pralatrexate administration. The treatment with leucovorin will be given with treatment as noted above but can be given at the treating physician's discretion for pralatrexate related mucositis (i.e. in schedule delays). Pralatrexate and decitabine can induce hematologic toxicity that should be address with Neupogen/Neulasta support at the treating physician's discretion and as suggested in Table 12 and Table 13.

Doses may be omitted or reduced based on patient tolerance. Omitted doses will not be made up for at the end of the cycle; once a dose reduction occurs for toxicity, there will be no re-escalation. For dose modifications and omissions, use the suggested guidelines in Table 11, Table 12 and Table 13 below.

Table 11: Suggested Guidelines for Pralatrexate Dose Modifications for Mucositis after Cycle 1

Mucositis Grade[a] on the Day of Treatment	**Action**	**Dose upon recovery to Grade ≤ 1**
Grade 2	Omit dose	Maintain dose level
Grade 2 recurrence	Omit dose	Reduce to one dose level below
Grade 3	Omit dose	Reduce to one dose level below
Grade 4	Stop therapy	No further treatment with pralatrexate

[a] Per NCI CTCAE, Version 3.0

Table 12: Suggested Guidelines for Pralatrexate Dose Modifications for Hematologic Toxicities

Blood Counts on the Day of Treatment	**Duration of Toxicity**	**Action**	**Dose upon re-start**
Platelets < 50,000/μL	1 week	Omit dose	Continue prior dose
	2 weeks	Omit dose	Reduce to one dose level below
	>2 weeks	Stop therapy	No further pralatrexate
ANC 500-1,000/μL and no fever	1 week	Omit dose	Continue prior dose
ANC 500-1,000/μL with fever (a single temperature of > 38.3°C or sustained temperature of ≥ 38°C for over one hour) or ANC <500/μL	1 week	Omit dose, give G-CSF or GM-CSF	Continue prior dose with G-CSF or GM-CSF support
	2 weeks or recurrence	Omit dose, give G-CSF or GM-CSF	Reduce to one dose level below with G-CSF or GM-CSF support
	>2 weeks or 2nd recurrence	Stop therapy	No further pralatrexate

Table 13: Suggested Guidelines for Pralatrexate Dose Modifications for All Other Treatment Related Toxicities

Toxicity Grade [a] on the Day of Treatment	**Action**	**Dose upon recovery to Grade ≤ 2**
Grade 3	Omit dose	Reduce to one dose level below
Grade 4	Stop therapy	No further pralatrexate

[a] Per NCI CTCAE, Version 3.0)

7.4 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 8.0). Trial treatment may be administered up to 2 days before or after the scheduled Day 1 of each cycle due to administrative reasons.

All trial treatments will be administered on an outpatient basis.

Pembrolizumab 200 mg will be administered as 30-minute IV infusion every 3 weeks (21 days). 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). Pralatrexate will be administered as a 3-5 minute IV infusion at day 1, day 8 and day 15 of a 28-day cycle. Decitabine will be administered as a 1-hour (+ 60 minutes) IV continuous infusion from day 1 to day 5 of a 28-day cycle.
In Arm A, pembrolizumab should precede the administration of pralatrexate on the days that both infusions are scheduled (refer to trial schema in section 5.1). In Arm B, decitabine should be infused first, pembrolizumab second and pralatrexate third when the three drugs are given together. On days where pembrolizumab is not due, decitabine should precede pralatrexate. When only two drugs are scheduled on the same day, decitabine should be infused first followed by pembrolizumab and pralatrexate should always be infused last (refer to trial schema 5.1). In Arm C, decitabine should precede the administration of pembrolizumab (refer to trial schema 5.1).
The Pharmacy Manual contains specific instructions for the preparation of the pembrolizumab infusion fluid and administration of infusion solution.

7.5 Trial Blinding/Masking

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

7.6 Randomization and Treatment Allocation

Participants will be enrolled only onto Arms A and C until the required number of patients are accrued to both arms. Enrollment onto Arm A or Arm C will be based on investigators' choice. Once enrollment onto Arm A or Arm C is completed, the next participant(s) will be assigned to the open Arm (A or C). Enrollment to Arm B will begin once enrollment onto Arms A and C is completed.

7.7 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.

7.7.1 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 on the case report form (CRF) including all prescription, over the counter (OTC), herbal supplements, and IV medications and fluids. If changes occur during the trial period, documentation of drug dosage, frequency, route, and date may also be included on the CRF.
Systemic glucocorticoids are allowed within 4 weeks of study treatment, as long as the steroids are stopped or reduced to a dose of no more than prednisone 10 mg/day or equivalent within 10 days of study drug initiation.
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 9.2.

7.7.2 Prohibited Concomitant Medications

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

- Antineoplastic systemic chemotherapy or biological therapy
- Immunotherapy not specified in this protocol
- Chemotherapy not specified in this protocol

- Investigational agents other than pembrolizumab or pralatrexate (for participants assigned to an arm including pralatrexate)
- 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.

Subjects who, in the assessment by the investigator, require the use of any of the aforementioned treatments for clinical management should be removed from the trial. Subjects may receive other medications that the investigator deems to be medically necessary.
The Exclusion Criteria describes other medications which are prohibited in this trial.
There are no prohibited therapies during the Post-Treatment Follow-up Phase.

7.8 Rescue Medications & Supportive Care

7.8.1 Prophylactic Measurements and Supportive Care

Patients will be permitted to receive appropriate supportive care measures as deemed necessary by the treating physician including but not limited to the items outlined below:

- **Diarrhea:** Diarrhea should be treated promptly as it could represent an immune-related adverse event due to pembrolizumab administration. Please follow section 7.8.2 for supportive care guidelines for immune-related adverse events in case of diarrhea.
- **Nausea/vomiting:** Nausea and vomiting should be treated aggressively, with agents such as prochlorperazine, metoclopramide, 5-HT-3 inhibitors, or benzodiazepines. Patients should be strongly encouraged to maintain liberal oral fluid intake during therapy, especially during the initial 14 days of each treatment cycle.
- **Fatigue:** May be cumulative with increasing cycles of therapy. Can be treated as recommended in the NCCN Guidelines 2017 available online.
- **Anemia:** Transfusions or erythropoietin may be utilized as clinically indicated for the treatment of symptomatic anemia but should be clearly noted as concurrent medications.
- **Thrombocytopenia:** Transfusion of platelets may be used if clinically indicated. Dose modification for thrombocytopenia is allowed. Prophylactic folic acid and vitamin B12 supplements may be necessary to reduce hematologic toxicity as indicated in section and should be used as detailed in section 5.2.2.
- **Neutropenia:** Prophylactic use of colony-stimulating factors including granulocyte colony stimulating factor (G-CSF), pegylated G-CSF or granulocyte-macrophage colony stimulating factor (GM-CSF) may be utilized if clinically indicated and as suggested in Table 12 and Table 13.
- **Hypokalemia or hypomagnesemia** should be corrected prior to administration of study drugs, and consideration should be given to monitoring potassium and magnesium in patients experiencing side effects potentially affecting serum electrolytes (e.g. patients with nausea, vomiting, diarrhea, fluid imbalance or cardiac symptoms.)
- **Oral Mucositis:** Pralatrexate may cause mucositis, including stomatitis or mucosal inflammation of gastrointestinal and genitourinary tracts; prophylactic folic acid and vitamin B_{12} supplements are necessary to reduce treatment-related mucositis; dosage modification may be required. Please see section 5.2.2 and the FDA approved package insert for any clarification.
- **Hepatotoxicity:** Liver function test abnormalities have been observed with pralatrexate use. Persistent abnormalities may indicate hepatotoxicity and may require dosage modification as indicated in table 13 and in the FDA package insert.

7.8.2 Supportive Care Guidelines for Immune-related AEs

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 (see section 7.3.1).

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 5.0 and 7.0 for dose modification, escalation and de-escalation rules.

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

- **Pneumonitis**:
  - **Grade 2 events** withhold treatment and 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 and recurrent grade 2**, immediately treat with intravenous steroids. Permanently discontinue treatment. 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,** withhold treatment and administer oral corticosteroids.
  - For **Grade 3 or 4 diarrhea/colitis,** treat with intravenous steroids followed by high dose oral steroids. Permanently discontinued treatment.
  - 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 ≥ Grade 3 Hyperglycemia, if associated with ketosis (ketonuria) or metabolic acidosis (DKA)**
  - For **T1DM** or **Grade 3-4** Hyperglycemia
    - Withhold treatment. 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, withhold treatment and 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. Withhold or permanently discontinue treatment, at discretion of the investigator or treating physician. 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) or thinamides, as appropriate, are suggested as initial therapy. Continue treatment.
    - In hypothyroidism, thyroid hormone replacement therapy, with levothyroxine or liothyroinine, is indicated per standard of care.
  - **Grade 3-4** hyperthyroidism
    - Treat with an initial dose of IV corticosteroid followed by oral corticosteroids. Withhold or permanently discontinue treatment, at discretion of the investigator or treating physician. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.

- **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. Permanently discontinue treatment for grade 4 or grade 3 toxicity.
  - 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, withhold treatment and treat with corticosteroids.
  - For **Grade 3-4** events, treat with systemic corticosteroids. Permanently discontinue treatment.
  - When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks

- For other immune related adverse events (IRAE) including myocarditis, encephalitis and Gullian-Barre and further clarification of the above mention IRAE refer to table 10 and section 7.3.1**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.

Treatment guidelines for subjects who experience an infusion reaction associated with administration of pembrolizumab are in Table 14 below.

Table 14: Infusion Reaction Treatment Guidelines

NCI CTCAE Grade	Treatment	Premedication at subsequent dosing
Grade 1 Mild reaction; infusion interruption not indicated; intervention not indicated	Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator.	None
Grade 2 Requires infusion	**Stop Infusion and monitor symptoms.**	Subject may be premedicated 1.5h (± 30 minutes) prior to infusion of

NCI CTCAE Grade	Treatment	Premedication at subsequent dosing
interruption but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDS, narcotics, IV fluids); prophylactic medications indicated for < =24 hrs.	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.**	pembrolizumab (MK-3475) 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 initial improvement; hospitalization indicated for other clinical sequelae (e.g., renal impairment, pulmonary infiltrates) Grade 4: Life-threatening; pressor or ventilatory support indicated	**Stop Infusion.** Additional appropriate medical therapy may include but is not limited to: IV fluids Antihistamines NSAIDS Acetaminophen Narcotics Oxygen Pressors Corticosteroids Epinephrine Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator. Hospitalization may be indicated. **Subject is permanently discontinued from further trial**	No subsequent dosing

NCI CTCAE Grade	Treatment	Premedication at subsequent dosing
	treatment administration.	
Appropriate resuscitation equipment should be available in the room and a physician readily available during the period of drug administration.		

7.9 Diet/Activity/Other Considerations

7.9.1 Diet

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

7.9.2 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.
Both pralatrexate and decitabine can cause fetal harm when administered to a pregnant woman. There are no adequate and well-controlled studies of either agent in pregnant women.
Women of childbearing potential will be advised to avoid becoming pregnant while receiving treatment with pembrolizumab combined with pralatrexate and/or decitabine.
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, symptom-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.

7.9.3 Use in Pregnancy

If a subject inadvertently becomes pregnant while on treatment with pembrolizumab, pralatrexate and/or decitabine the subject will immediately be removed from the study treatment. 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 to the Sponsor and to Merck without delay and within 24 hours to the Sponsor and within 2 working days to Merck if the outcome is a serious adverse experience (e.g., death, abortion, congenital anomaly, or other disabling or life-threatening complication to the mother or newborn).
The study investigator will make every effort to obtain permission to follow the outcome of the pregnancy and report the condition of the fetus or newborn to the Sponsor. If a male subject impregnates his female partner the study personnel at the site must be informed immediately and the pregnancy reported to the Sponsor/UVA CC/GTcLC within 24 hours of awareness of the event (see study reference manual) and to Merck (see section 9.2.1.1) and followed as described above and in Section 9.2.2.

7.9.4 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.

7.10 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 or the Sponsor 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 9.1.8– 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 LYRIC criteria

  Note: A subject may be granted an exception to continue on treatment with confirmed radiographic progression if clinically stable or clinically improved, please see Section 7.11
- Unacceptable adverse experiences as described in Section 7.3
  a. Note: if any drug in the combination for the assigned arm is discontinued and/or is required to be held for an adverse event per section 7.0 for >2 weeks, all study treatment should be discontinued.
- Treatment needs to be held (based on section 7.0) for an adverse event delaying treatment for > 2 weeks
- 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 24 months of uninterrupted treatment with pembrolizumab or 35 administrations of pembrolizumab, whichever is later.
- Administrative reasons

The End of Treatment and Follow-up visit procedures are listed in Section 8.0 (Protocol Flow Chart) and Section 9.1.9 (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 9.2.1). 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.

7.10.1 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 and had at least two treatments with pembrolizumab beyond the date when the initial CR was declared.

7.11 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 drugs

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

8.0 TRIAL FLOW CHART

STUDY FLOW CHART – ARM A		**Treatment Cycles**[1]										**Post-treatment**		
Treatment Cycle/Title:	Screening (Visit 1)	1&4				2&5			3&6			Discon	Safety Follow-up	Follow Up Visits
Scheduling Window (Days) ± 2 :		D1	D8	D15	D22	D1	D8	D15	D1	D8	D15	At time of Discon	30 days post discon	Every 8 weeks post discon
Informed Consent	x													
Inclusion/Exclusion Criteria	x													
Demographics and Medical History	x													
Prior and Concomitant Medication Review	x	x----------x										x	x	
Post-study anticancer therapy status													x	x[12]
Review Adverse Events		x----------x										x	x	x[15]
Physical Examination	x	x[2]	x[2]	x[2]	x[2]	x			x			x	x	
Vital Signs and Weight	x	x-----on all days with physical exam or infusion-------x										x	x	
ECOG Performance Status	X	x[3]	x[3]	x[3]	x[3]	x[3]			x			x	x	
Pregnancy Test – Urine or Serum β-HCG	X													
PT/INR and aPTT	X	x[10]				x			x					
CBC with Differential	x	x[10]	x	x	x	x	x	x	x	x	x	x	x	

STUDY FLOW CHART – ARM A		**Treatment Cycles**[1]										**Post-treatment**		
Treatment Cycle/Title:	Screening (Visit 1)	1&4				2&5			3&6			Discon	Safety Follow-up	Follow Up Visits
Scheduling Window (Days) ± 2 :		D1	D8	D15	D22	D1	D8	D15	D1	D8	D15	At time of Discon	30 days post discon	Every 8 weeks post discon
Chemistry[13]	x	x[10]	x	x	X	x	x	x	x	x	x	x	x	
EBV PCR	x													
Urinalysis	x													
T3, FT4 and TSH	x	x[10, 14]				x[14]			x[14]			x	X	
Tumor Imaging[4]	x[4]					x[4]			x[4]					
mSWAT and photograph of skin involvement[5]	x[5]	x[5]				x[5]			x[5]					
Archival/Newly Obtained Tissue Collection	x[6]								x[7]					
Correlative Studies Blood Collection		x	x[11]	x[11]		x			x			X		
Pharmacokinetics (PKs)[8]		x	x[11]	x[11]										
Pralatrexate IV push		x	x	x		x	x	x	x	x	x			
Pembrolizumab Infusion		x[9]			X			x		x				

X[1] After cycle 6, cycle 7 will follow the calendar for cycle 1&4, cycle 8 will follow the calendar for cycle 2&5, cycle 9 will follow the calendar for cycle 3&6 etcetera

X[2] Physical exam will be performed weekly ONLY during cycle 1. Physical Exam will be performed only at D1 of each subsequent cycle beyond cycle 1.

X[3] ECOG will be performed weekly ONLY during cycle 1. ECOG will be performed only at D1 of each subsequent cycle beyond cycle 1.

X[4] CT/PET or CT will be performed at screening within 4 weeks from treatment start date and after cycle 2; then it will be repeated every 3 to 4 cycles at the discretion of the treating physician.

X[5] mSWAT and standardized photographs of skin involvement are strongly recommended at screening or cycle 1 day 1 not at both timepoints. mSWAT is required to be performed after cycle 2 and then it will be repeated every 3 to 4 cycles at the discretion of the treating physician. mSWAT will be performed along with CT/PET or CT evaluation.

X[6] Blood samples and tissue collection should be obtained in the screening phase of the study

X[7] Tissue collection of the tumor lesion (including possible FNA or ultrasound when indicated per standard care) should be obtained, if possible, at screening or within Cycle 1 (please refer to section 6.1.1: Subject Inclusion Criteria number 7). An optional biopsy may be performed post Cycle 3 or 4.

X[8] Pharmacokinetics (PKs) blood draws are only for patients at UVA. See *section 9.1.7.3* for details.

X[9] Pembrolizumab will be administered every 3 weeks (Q3W). In Arm A, pembrolizumab administration will be started on day 1 of cycle 1 as described in section 5.2.1.

X[10] For cycle 1 day 1, laboratory screening tests can be considered valid for treatment on cycle 1 day 1 as long as they are performed within the screening laboratory test window (10 days). After Cycle 1, pre-dose laboratory procedures can be conducted up to 72 hours prior to dosing.

X[11] Pharmacokinetics (PKs) and correlative study blood draws at Days 8 and 15 in a cycle are only for Cycle 1 (not cycles 4, 7, etc.)

X[12] For subjects who have an allogeneic SCT within 24 months of last study treatment, transplant parameters will be collected and specific events will be collected for 18 months from the date of the allogeneic transplant to include graft-versus-host-disease (acute and/or chronic), veno-occlusive disease, febrile syndrome (a steroid-requiring febrile illness without an infectious cause), and encephalitis, for all grades, and regardless of relationship to study drug. Additional medically important adverse events post-allogeneic SCT may be submitted at the Investigator's discretion.

X[13]See table in *section 9.1.7* for list of tests to include (not just the comprehensive metabolic panel)

X[14]Thyroid blood tests are only required every other cycle (e.g. day 1 only for odd cycles)

X[15]After 30 day safety visit, only new SAEs considered related to study intervention need to be collected and assessments (as applicable) may be by phone or videoconference. Active AEs at the time of 30 day safety visit should be followed through resolution or stability.

STUDY FLOW CHART – ARM B		**Treatment Cycles**[1]											**Post-treatment**		
Treatment Cycle/Title:	Screening (Visit 1)	1&4				2&5				3&6			Discon	Safety Follow-up	Follow Up Visits
Scheduling Window (Days) ± 2 :		D1	D8	D15	D22	D1	D8	D15	D22	D1	D8	D15	At time of Discon	30 days post discon	Every 8 weeks post discon
Informed Consent	X														
Inclusion/Exclusion Criteria	X														
Demographics and Medical History	X														
Prior and Concomitant Medication Review	X	x----------x											x	x	
Post-study anticancer therapy status														x	x[14]
Review Adverse Events		x----------x											x	x	x[17]
Physical Examination	X	x[2]	x[2]	x[2]		x				x			x	x	
Vital Signs and Weight	X	x-----on all days with physical exam or infusion----x											x	x	
ECOG Performance Status	X	x[3]	x[3]	x[3]		x				x			x	x	
Pregnancy Test – Urine or Serum β-HCG	X														
PT/INR and aPTT	X	x[12]				x				x					
CBC with Differential	X	x[12]	x	x	x[19]	x	x	x	x	x	x	x	x	x	
Chemistry [18]	X	x[12]	x	x		x	x	x	x[16]	x	x	x	x	x	
EBV PCR	x														

STUDY FLOW CHART – ARM B		**Treatment Cycles**[1]											**Post-treatment**		
Treatment Cycle/Title:	Screening (Visit 1)	1&4				2&5				3&6			Discon	Safety Follow-up	Follow Up Visits
Scheduling Window (Days) ± 2 :		D1	D8	D15	D22	D1	D8	D15	D22	D1	D8	D15	At time of Discon	30 days post discon	Every 8 weeks post discon
Urinalysis	x														
T3, FT4 and TSH	x	x[12, 15]				x[15]				x[15]			x	x	
Tumor Imaging[4]	x[4]					x[4]				x[4]					
mSWAT and photograph of skin involvement[5]	x[5]	x[5]				x[5]				x[5]					
Archival/Newly Obtained Tissue Collection	x[6]									x[7]					
Correlative Studies Blood Collection		x	x[13]	x[13]		x				x			X		
Pharmacokinetics (PKs)[8]		x[9]	x[13]	x[13]											
Pralatrexate		x	x	x		x	x	x		x	x	x			
Decitabine		x[10]				x[10]				x[10]					
Pembrolizumab			x[11]			x			x			x			

X[1] After cycle 6, cycle 7 will follow the calendar for cycle 1&4, cycle 8 will follow the calendar for cycle 2&5, cycle 9 will follow the calendar for cycle 3&6 etcetera.

X[2] Physical exam will be performed weekly only during cycle 1. It will be performed ONLY at D1 of each subsequent cycle beyond cycle 1.

X[3] ECOG should be only performed at D1 of each cycle beyond cycle 4.

X[4] CT/PET or CT will be performed at screening within 4 weeks from treatment start date and after cycle 2;, then it will be repeated every 3 to 4 cycles at the discretion of the treating physician.

X[5] mSWAT and standardized photographs of skin involvement are strongly recommended at screening or cycle 1 day 1 not at both timepoints. mSWAT is required to be performed after cycle 2 and then it will be repeated every 3 to 4 cycles at the discretion of the treating physician. mSWAT will be performed along with CT/PET or CT evaluation

X[6] Blood samples and tissue collection should be obtained in the screening phase of the study.

X[7] Tissue collection of the tumor lesion (including possible FNA or ultrasound when indicated per standard care) should be obtained, if possible, at screening or within Cycle 1 (please refer to section 6.1.1: Subject Inclusion Criteria number 7). An optional biopsy may be performed post Cycle 3 or 4.

X[8] The pharmacokinetics (PKs) blood draw are only for patients at UVA. See *section 9.1.7.3* for details. .

X[9] Cycle 1 only. Additional pharmacokinetics sample (only for patients at UVA) will be obtained at day 5 to determine drug steady state.

X[10] Decitabine will be given from day 1 to day 5 (or day 3, depending on dose level) of each cycle as described in section 5.2.3

X[11] Pembrolizumab will be administered every 3 weeks (Q3W). In Arm B, pembrolizumab administration will be started on day 8 of cycle 1 as described in section 5.2.1.

X[12] For cycle 1 day 1, laboratory screening tests can be considered valid for treatment on cycle 1 day 1 as long as they are performed within the screening laboratory test window (10 days). After Cycle 1, pre-dose laboratory procedures can be conducted up to 72 hours prior to dosing.

X[13] Pharmacokinetics (PKs) and correlative study blood draws at Days 8 and 15 in a cycle are only for Cycle 1 (not cycles 4, 7, etc.)

X[14] For subjects who have an allogeneic SCT within 24 months of last study treatment, transplant parameters will be collected and specific events will be collected for 18 months from the date of the allogeneic transplant to include graft-versus-host-disease (acute and/or chronic), veno-occlusive disease, febrile syndrome (a steroid-requiring febrile illness without an infectious cause), and encephalitis, for all grades, and regardless of relationship to study drug. Additional medically important adverse events post-allogeneic SCT may be submitted at the Investigator's discretion.

X[15] Thyroid blood tests are only required every other cycle (e.g. day 1 only for odd cycles)

X[16] After cycle 2, the day 22 CBC with differential is not required (e.g. not for cycles 5, 8, etc.)

X[17]After 30 day safety visit, only new SAEs considered related to study intervention need to be collected and assessments (as applicable) may be by phone or videoconference. Active AEs at the time of 30 day safety visit should be followed through resolution or stability.

X[18]See table in *section 9.1.7* for list of tests to include (not just the comprehensive metabolic panel)

X[19]CBC with differential at Day 22 is for cycle 1 only (e.g. not for cycles 4, 7, etc)

STUDY FLOW CHART – ARM C		**Treatment Cycles**[1]								**Post-treatment**			
Treatment Cycle/Title:	Screening (Visit 1)	1&4				2&5		3 &6		Discon	Safety Follow-up	Follow Up Visits	
Scheduling Window (Days) ± 2 :		D1	D8	D15	D22	D1	D22	D1	D15	At time of discon	30 days post discon	Every 8 weeks post discon	
Informed Consent	x												
Inclusion/Exclusion Criteria	x												
Demographics and Medical History	x												
Prior and Concomitant Medication Review	x		x----------x							x		x	x
Post-study anticancer therapy status											x	x[14]	
Review Adverse Events			x----------x							x		x	x[17]
Physical Examination	x	x[2]	x[2]			x		X		x	x		
Vital Signs and Weight	x		x-on all days with physical exam or infusion-x							x		x	
ECOG Performance Status	x	x[3]	x			x		X		x	x		
Pregnancy Test – Urine or Serum β-HCG	x												
PT/INR and aPTT	x	x[12]				x		X					
CBC with Differential	x	x[12]	x	X[13]	x[19]	x	x[15]	x	X	x	x		
Chemistry[18]	x	x[12]	x	X[13]		x	X	x	X	x	x		
EBV PCR	x												

STUDY FLOW CHART – ARM C		**Treatment Cycles**[1]								**Post-treatment**		
Treatment Cycle/Title:	Screening (Visit 1)	1&4				2&5		3 &6		Discon	Safety Follow-up	Follow Up Visits
Scheduling Window (Days) ± 2 :		D1	D8	D15	D22	D1	D22	D1	D15	At time of discon	30 days post discon	Every 8 weeks post discon
Urinalysis	x											
T3, FT4 and TSH	x	x[12, 16]				x[16]		x[16]		x	x	
Tumor Imaging[4]	x[4]					x[4]		x[4]				
mSWAT and Photograph of skin involvement[5]	x[5]	x[5]				x[5]		x[5]				
Archival/Newly Obtained Tissue Collection	x[6]							x[7]				
Correlative Studies Blood Collection		x	x[13]	x[13]		x		X		x		
Pharmacokinetics (PKs)[8]		x[9]										
Decitabine		x[10]				x[10]		x[10]				
Pembrolizumab			x[11]			x[11]	x[11]		x[11]			

X[1] After cycle 6, cycle 7 will follow the calendar for cycle 1&4, cycle 8 will follow the calendar for cycle 2&5, cycle 9 will follow the calendar for cycle 3&6 etcetera

X[2] Physical exam should be performed ONLY at D1 of each cycle beyond cycle 4

X[3] ECOG should be only performed at D1 of each cycle beyond cycle 4

X[4] CT/PET or CT will be performed at screening within 4 weeks from treatment start date and after cycle 2; then it will be repeated every 3 to 4 cycles at the discretion of the treating physician.

X[5] mSWAT and standardized photographs of skin involvement are strongly recommended at screening or cycle 1 day 1 not at both timepoints. mSWAT is required to be performed after cycle 2 and then it will be repeated every 3 to 4 cycles at the discretion of the treating physician. mSWAT will be performed along with CT/PET or CT evaluation.
X[6] Blood samples and tissue collection should be obtained in the screening phase of the study.
X[7] Tissue collection of the tumor lesion (including possible FNA or ultrasound when indicated per standard care) should be obtained, if possible, at screening or within Cycle 1 (please refer to section 6.1.1: Subject Inclusion Criteria number 7). An optional biopsy may be performed post Cycle 3 or 4.
X[8] The pharmacokinetics (PKs) blood draw are only for patients at UVA. See *section 9.1.7.3* for details. X[9] Cycle 1 only. Additional pharmacokinetics sample (only for patients at UVA) will be obtained on the final day (in Cycle 1) of scheduled treatment for the participant to determine drug steady state. See *section 9.1.7.3* for details.
X[10] Decitabine will be given from day 1 to day 5 (or day 3, depending on dose level) of each cycle as described in section 5.2.3
X[11] Pembrolizumab will be administered every 3 weeks (Q3W). In Arm C, pembrolizumab administration will be started on day 8 of cycle 1 as described in section 5.2.1.
X[12] For cycle 1 day 1, laboratory screening tests can be considered valid for treatment on cycle 1 day 1 as long as they are performed within the screening laboratory test window (10 days). After Cycle 1, pre-dose laboratory procedures can be conducted up to 72 hours prior to dosing.

X[13] Correlative study blood draws at Days 8 and 15 in a cycle are only for Cycle 1 (not cycles 4, 7, etc.). Labs (CBC with differential and Chemistry) on day 15 are for cycle 1 only.

X[14] For subjects who have an allogeneic SCT within 24 months of last study treatment, transplant parameters will be collected and specific events will be collected for 18 months from the date of the allogeneic transplant to include graft-versus-host-disease (acute and/or chronic), veno-occlusive disease, febrile syndrome (a steroid-requiring febrile illness without an infectious cause), and encephalitis, for all grades, and regardless of relationship to study drug. Additional medically important adverse events post-allogeneic SCT may be submitted at the Investigator's discretion.

X[15] After cycle 2, the day 22 CBC with differential is not required (e.g. not for cycles 5, 8, etc.)

X[16]Thyroid blood tests are only required every other cycle (e.g. day 1 only for odd cycles)

X[17]After 30 day safety visit, only new SAEs considered related to study intervention need to be collected and assessments (as applicable) may be by phone or videoconference. Active AEs at the time of 30 day safety visit should be followed through resolution or stability.

X[18]See table in *section 9.1.7* for list of tests to include (not just the comprehensive metabolic panel)

X[19]CBC with differential at Day 22 is for cycle 1 only (e.g. not for cycles 4, 7, etc)

9.0 TRIAL PROCEDURES

9.1 Trial Procedures

The Trial Flow Chart - Section 8.0 summarizes the trial procedures to be performed at each visit. Individual trial procedures are described in detail below. Study treatment is expected up to two years. 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 Sponsor 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.

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site investigator. The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data.

Clinical data (including adverse events (AEs), concomitant medications, and expected adverse reactions data) and clinical laboratory data will be entered into Forte EDC, a password-protected data capture system provided by the UVA Coordinating Center / GTcLC. Clinical data will be entered directly from the source documents.

9.1.1 Administrative Procedures

9.1.1.1 Informed Consent

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

9.1.1.2 General Informed Consent

Consent must be documented by the subject's dated signature or by the subject's legally acceptable representative's dated signature on a consent form along with the dated signature of the person conducting the consent discussion.

A copy of the signed and dated consent form should be given to the subject before participation in the trial.

The initial informed consent form, any subsequent revised written informed consent form and any written information provided to the subject must receive the IRB/ERC's approval/favorable opinion in advance of use. The subject or his/her legally acceptable representative should be informed in a timely manner if new information becomes available that may be relevant to the subject's willingness to continue participation in the trial. The communication of this information will be provided and documented via a revised consent form or addendum to the original consent form that captures the subject's dated signature or by the subject's legally acceptable representative's dated signature.

Specifics about a trial and the trial population will be added to the consent form template at the protocol level.

The informed consent will adhere to IRB/ERC requirements, applicable laws and regulations and Sponsor requirements.

9.1.2 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.

9.1.3 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.

9.1.4 Prior and Concomitant Medications Review

9.1.4.1 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.

9.1.4.2 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 9.2.

9.1.5 Disease Details and Treatments

Disease Details

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

Prior Treatment Details

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

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, the 30-day Safety Follow-up visit must occur before the first dose of the new therapy. Once new anti-cancer therapy has been initiated the subject will move into survival follow-up.

9.1.6 Clinical Procedures/Assessments

9.1.6.1 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 5.0 (see *Section 11.3*). Toxicities will be characterized in terms regarding seriousness, causality, toxicity grading, and action taken with regard to trial treatment.

Please refer to *section 9.2* for detailed information regarding the assessment and recording of AEs.

9.1.6.2 Physical Exam

The investigator or qualified designee will perform a physical exams according to standard clinical care during the study period. Clinically significant abnormal findings at screening/baseline should be recorded as medical history.

9.1.6.3 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 8.0). Vital signs should include temperature, pulse, respiratory rate, weight and blood pressure. Height will be measured at screening only.

9.1.6.4 Eastern Cooperative Oncology Group (ECOG) Performance Scale

The investigator or qualified designee will assess ECOG status as outlined in the study flow chart (see Section 8.0).

9.1.6.5 Tumor Imaging and Assessment of Disease

The primary objectives are to evaluate the safety, tolerability, and efficacy of the study drugs. All patients will be assessed by standard criteria for clinical response. Patients with measurable disease will be assessed by standard criteria. For patients with PTCL, response will be evaluated with physical exam, computerized tomography (CT) and tissue biopsies as defined by the lymphoma response to immunomodulatory therapy criteria or LYRIC (Cheson *et al.,* 2016)[24]. Positron emission tomography / computerized tomography (PET/CT) will be utilized if available (optional).

For patients with CTCL and PTCL with skin involvement, we recommend skin assessments using mSWAT, preferably by the same investigator at all times (to limit inter-observer variability) during the screening period and during the treatment period as defined in Study Flow Chart[23]. Please find mSWAT worksheet in *section 11.2*. Additional assessments will be performed as clinically indicated at investigator discretion.
In particular, we strongly recommend standardized photographs of the skin involvement to document the appearance of skin lesions at baseline (screening or Cycle 1 day 1) and as defined in Study Flow Chart. Blood involvement assessments will be performed for only CTCL patients at the same time as the skin assessments.
Evaluable for objective response. Patients who have received at least one cycle of therapy will be considered evaluable for response. These patients will have their response classified according to the definitions stated below. Patients who exhibit objective disease progression prior to the end of cycle 1 will also be considered.
The following disease parameters will be assessed.
Measurable disease. Measurable lesions are defined as those that can be accurately measured in two dimensions (longest diameter to be recorded) as $\geq$20 mm with conventional techniques (PET/CT, MRI, x-ray) or as $\geq$10 mm with spiral CT scan. All tumor measurements will be recorded in millimeters (or decimal fractions of centimeters). Tumor volume will be recorded as the sum of the product of the diameters (SPD) of the largest predominant target lesions. FDG avidity is based on comparison with background tissues. There is no specific SUV value that is considered a cut-off.
Non-measurable disease (evaluable disease). All other lesions (or sites of disease), including small lesions (<10 mm using spiral CT scan), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonitis,

inflammatory breast disease, abdominal masses (not followed by CT or MRI), and cystic lesions are all non-measurable.

Target lesions. All measurable lesions up to a maximum of 6 lesions total, representative of all involved organs, should be identified as target lesions and recorded and measured at baseline. Target lesions should be selected on the basis of their SUV avidity (High SUV lesions will be prioritized, even if not the largest lesions) and size (lesions with the largest SPD diameter) and their suitability for accurate repeated measurements (either by imaging techniques or clinically). An SPD for all target lesions will be calculated and reported as the baseline sum SPD. The baseline sum SPD will be used as reference by which to characterize the objective tumor response based on CT criteria.

Non-target lesions. All other lesions (or sites of disease) including any measurable lesions over and above the 6 target lesions should be identified as non-target lesions and should also be recorded at baseline. Measurements of these lesions are not required, but the presence or absence of each should be noted throughout follow-up.

The guidelines to assess response will be based on the Olsen (Olsen et al., 2011)[23] and the Lymphoma Response to Immunomodulatory Therapy Criteria or LYRIC (Cheson et al., 2016)[24].

9.1.7 Laboratory Procedures/Assessments

Details regarding specific laboratory procedures/assessments to be performed in this trial are provided below. Laboratory tests for hematology, chemistry, urinalysis, and others are specified in Table 15.

Table 15: 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 *(If abnormal)*	Total thriiodothyronine (T3)
Absolute Neutrophil Count	Carbon Dioxide ‡	results are noted	Free tyroxine (T4)
Absolute Lymphocyte Count	*(CO_2 or bio carbonate)*	Urine pregnancy test †	Thyroid stimulating hormone (TSH)
	Uric Acid		PK
	Calcium		EBV PCR
	Chloride		Blood for correlative studies
	Glucose		
	Phosphorus		
	Potassium		
	Sodium		
	Magnesium		
	Total Bilirubin		
	Direct Bilirubin *(If total bilirubin is elevated above the upper limit of normal)*		
	Total protein		
	Blood Urea Nitrogen		
	Creatinine		

† 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.

Laboratory test before every day 1 of treatment, except cycle 1 day 1, should be performed within 72 hours prior to study treatment.
For cycle 1 day 1 laboratory screening tests can be considered valid for treatment on cycle 1 day 1 as long as they are performed within the screening laboratory test window (10 days). After Cycle 1, pre-dose laboratory procedures can be conducted up to 72 hours prior to dosing. Results must be reviewed by the investigator or qualified designee and found to be acceptable prior to each dose of trial treatment.

9.1.7.1 Tumor Tissue Collection and Correlative Studies Blood Sampling

The following exploratory parameters will be assessed:

9.1.7.2 Biomarkers from tumor tissue and peripheral blood

1. Standard flow cytometry to assess CD3, CD4, CD8, CD25, CD80, PD1, PD-L1, PD-L2 and Foxp3 in peripheral blood mononuclear cells and in addition we will analyze peripheral blood T lymphocytes by flow cytometry for CD45 RA, CCR7, CD62L to understand changes in the T cell repertoire. Correlation in between changes and response to treatment will be made.

2. Paraffin embedded primary tumor samples will be obtained pre- and post-treatment as defined below and OpalMultiplexing "MANTRA" will be performed. MANTRA is a tissue evaluation technique, which uses a fluorescent signal amplification probe to permit serial immunohistochemistry and compared to conventional immunohistochemistry permits multiplex detection. We will use Opal Multiplexing MANTRA to determine changes in the microenvironment (TILs, NK-cell and antigen-presenting cells) as a function of treatment. The following set of 6 markers will be analyzed on each tissue biopsy: CD3, CD7, CD4, CD8, PGM1, IDO; CD3, CD7, CD4, CD8, CD20, FOXP3; CD3, CD7, CD4, CD8, PD-1, PD-L1; CD3, CD7, CD4, CD8, CD56, Granzyme B.
3. Gene expression profiling (GEP) analysis will be obtained on primary tumor samples pre- and post-treatment. Changes of gene expression profiling as a function of treatment with pralatrexate and decitabine will be analyzed. Specific attention will be placed on defined gene-signature already described and predictive of response to pembrolizumab (e.g. interferon-γ-related genes including CXCL9, CXCL10, IDO1, IFNG, HLA-DRA, STAT1). Additional signature associated with clinical outcome will be investigated.
4. Genome wide methylation analysis will be performed to identify and quantify changes in methylation pre- and post-treatment. Specific attention will be placed on decitabine contribution in de-repressing and inducing transcription of multiple DNA hypermethylated human endogenous retrovirus (HERV) genes triggering a type I interferon-response.
5. GEP and methylation wide methylation profiling will be analyzed, and correlation will be made to identify biomarkers of response. The data gathered from the GEP and genome wide methylation will be used to create an algorithm of regulatory networks within PTCLs. The analysis of these data will provide information on etiology of PTCLs and will suggest possible targetable oncogenic pathways.

9.1.7.3 Pharmacokinetic/Pharmacodynamic Evaluations

Pharmacokinetic evaluation will be performed at UVA ONLY.
The pharmacokinetics (PKs) blood draw for most timepoints can be performed with a +/- 30 minutes window. Exceptions include:

1. The 24 hour after end of administration timepoint may be performed with a +/- 90 minute window.
2. End of infusion (EOI) draw should be within 10 minutes following completion of infusion
3. 30 minutes post completion of infusion draw should be +/- 5 minutes

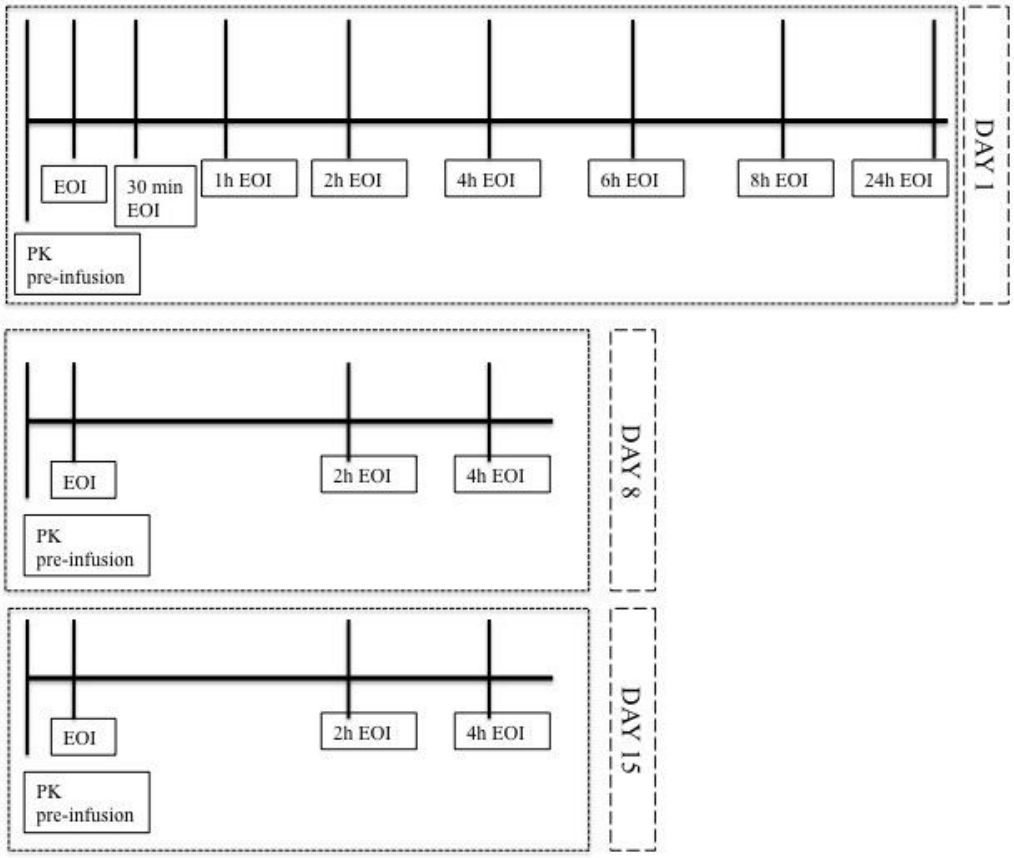
Pharmacokinetic evaluation will be performed only during cycle 1.

- Pharmacokinetics will be assessed as followed in Arm A:

On day 1 of cycle 1, blood samples will be obtained from patients at fixed time intervals after administration of pralatrexate to determine the plasma level of both pralatrexate and pembrolizumab. This will be compared to the known pharmacokinetic data for the individual agents in order to identify any possible effect of the combination.

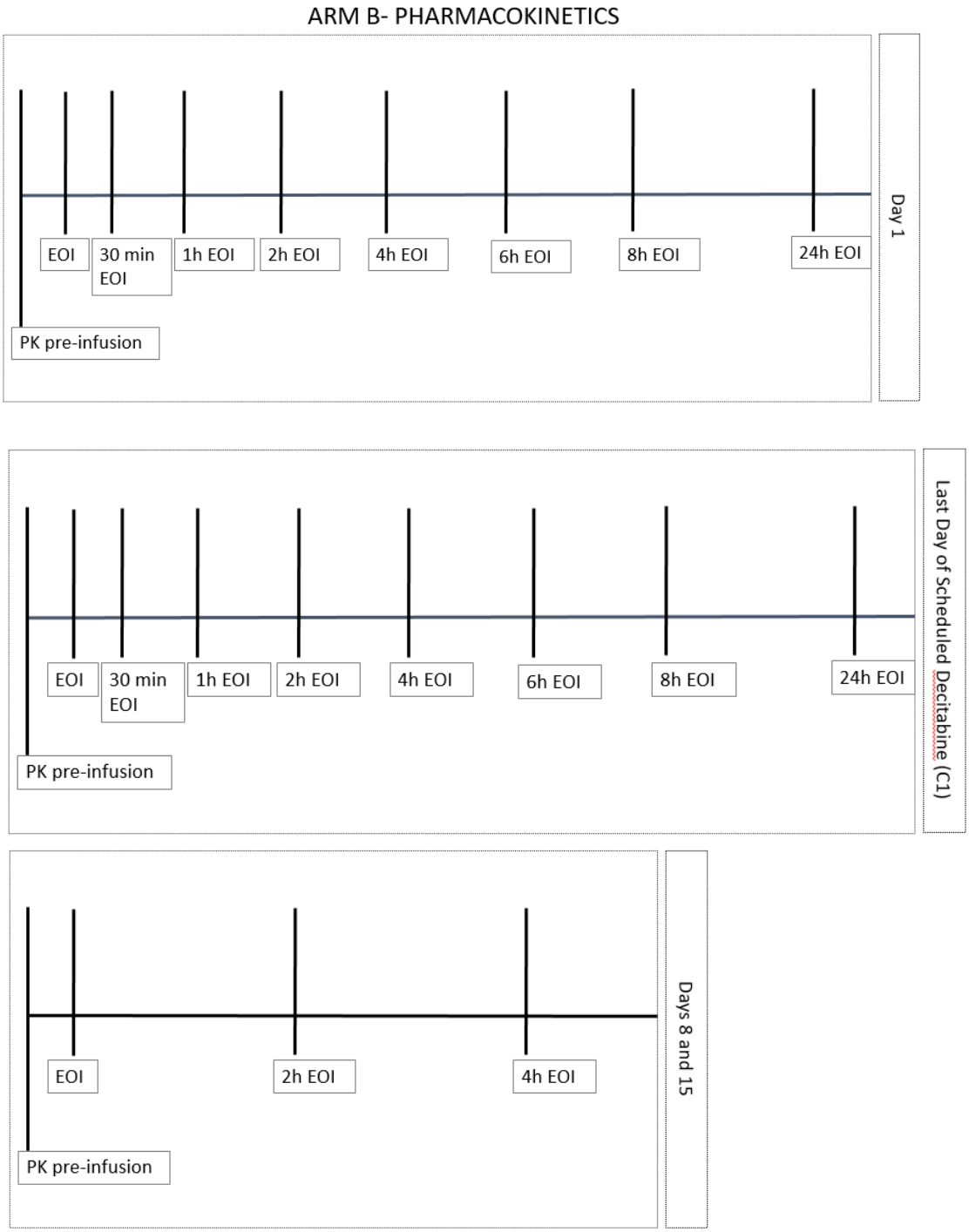
Specifically, blood samples will be obtained at day 1 pre-administration, end of administration (EOA), 30 minutes, 1 hour, 2 hours, 4 hours, 6 hours, 8 hours, and 24 hours after the end of administration. On day 8 and day 15 of cycle 1, blood samples will be obtained pre-administration, EOA, 2 hours and 4 hours after the end of administration.

ARM A - PHARMACOKINETICS



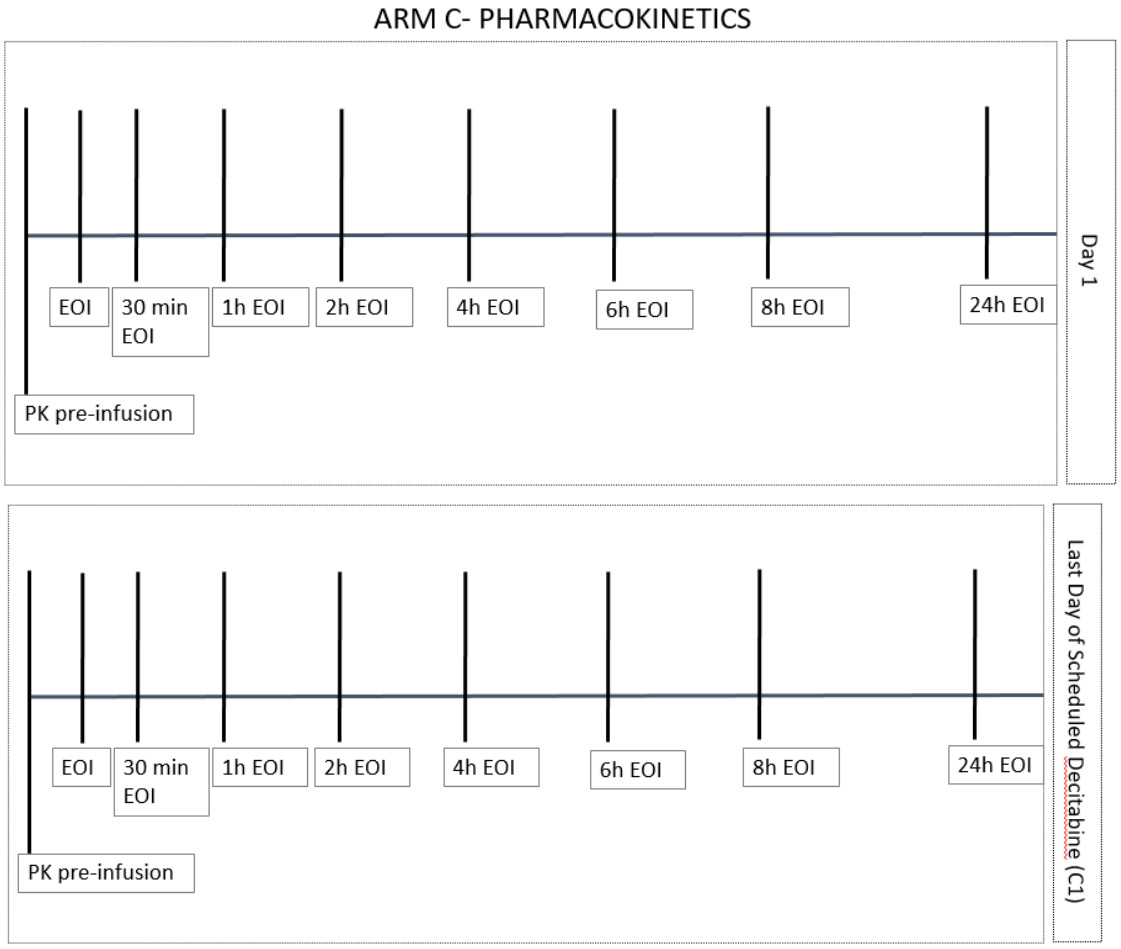
- Pharmacokinetics will be assessed as followed in Arm B:

On day 1 of cycle 1, blood samples will be obtained from patients at fixed time intervals after administration of decitabine and pralatrexate to determine the plasma level of pralatrexate, decitabine and pembrolizumab. This will be compared to the known pharmacokinetic data for the individual agents in order to identify any possible effect of the combination. Specifically, blood samples will be obtained at day 1 and day 5 (day 3 if dose level is for decitabine on days 1-3) of cycle 1 pre-administration, end of administration (EOA), 30 minutes, 1 hour, 2, 4, 6, 8, and 24 hours after EOA. On day 8 and day 15 of cycle 1 blood sample will be obtained pre-administration, EOA, 2 and 4 hours after EOA.



- Pharmacokinetics will be assessed as followed in Arm C:

On day 1 of cycle 1, blood samples will be obtained from patients at fixed time intervals after administration of decitabine to determine the plasma level of decitabine. This will be compared to the known pharmacokinetic data for the individual agents in order to identify any possible effect of the combination. Specifically, blood samples will be obtained at day 1 of cycle 1 pre-infusion, end of infusion (EOI), 30 minutes, 1 hour, 2, 4, 6, 8 and 24 hours after EOI. On day 5 of cycle 1 (day 3 if dose level is for decitabine on days 1-3), blood samples will be obtained pre-infusion, end of infusion (EOI), 30 minutes after EOI, 1 hour after EOI, 2 hours after EOI, 4 hours after EOI, 6 hours after EOI and 8 hours after EOI.



Pharmacodynamics evaluation will be performed as described in detail in the laboratory manual.

9.1.8 Other Procedures

9.1.8.1 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 9.2.

9.1.9 Visit Requirements

Visit requirements are outlined in Section 8.0- Trial Flow Chart. Specific procedure-related details are provided above in Section 9.1- Trial Procedures.

9.1.9.1 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 90 days of the end of treatment or before initiation of a new anti-cancer treatment should also be followed and recorded.

For subjects who have an allogeneic SCT within 24 months of last study treatment, transplant parameters will be collected and specific events will be collected for 18 months from the date of the allogeneic transplant to include graft-versus-host-disease (acute and/or chronic), veno-occlusive disease, febrile syndrome (a steroid-requiring febrile illness without an infectious cause), and encephalitis, for all grades, and regardless of relationship to study drug. Additional medically important adverse events post-allogeneic SCT may be submitted at the Investigator's discretion. If available and relevant to an event post-allogeneic SCT, concomitant medications and/or laboratory results may also be reported.

9.1.10 Subject Registration and Randomization

All participants must sign the consent form prior to determination of eligibility for this study.
When a site is ready to enroll a patient, the following documentation must be scanned and emailed to the UVA Coordinating Center:

- Patient and staff signed signature page of the current informed consent form (ICF)
- Completed Inclusion/Exclusion checklist demonstrating subject eligibility
- Supporting documentation needed to confirm eligibility (lab results, scan results etc.)

Consult the Study Reference Manual for instructions on sending this information. The Coordinating Center will consult with the Overall Study PI if questions arise in confirming eligibility. The UVA Coordinating Center will communicate the subject number and treatment dose assignment to the enrolling site.

Registration will occur following verification of eligibility by the treating physician.

Participants who are consented and accrued to the study should be registered in OnCore in accordance with the Clinical Trial Management System Policy via the UVa OnCore Resources link in Oncore. General guidelines are available in the OnCore User Manual and Data Entry Guide.
Participants should receive their first study treatment within 2 weeks of registration.

Treatment allocation will be discussed with participants during the process of informed consent and will occur after registration. Treatment allocation will be based upon the study design until a safety bound has been triggered or target accrual has been met. Arm allocation slots are generated by the coordinating center. Treatment allocation will occur after registration and within 2 weeks of the start of treatment.
This study does not involve any blinding or masking procedures. Subjects will be told which treatment they are receiving.

9.2 DATA REPORTING / REGULATORY REQUIREMENTS

The Global T-cell Lymphoma Consortium (GTcLC) consist of centers across the globe whose specialty is conducting clinical research studies in T-cell Lymphoma. The data and safety monitoring plan will adhere to the Data Safety Monitoring Board of the UVA Cancer Center for investigator-initiated studies. When a UVA faculty member holds an IND for a study UVA will be the coordinating center. All other sites under the GTcLC will be participating centers.
When an industry study is being conducted under the auspices of the consortium the industry sponsor will be responsible for monitoring the study. UVA will continue to report any needed SAE, deviations, or toxicities as required by the institution and FDA. For any investigator-initiated study within the consortium where the IND is held at another institution that institution will be the coordinating center and all other sites will be the participating centers. Each member site within the consortium will follow the guidelines of each individual institutional or FDA guidelines as well as local ethical standards.

The definitions of an AE or SAE, as well as the method of recording, evaluating, and assessing causality of AE and SAE and the procedures for completing and transmitting AE, SAE, and other reportable safety event reports can be found in *section 11.5*.

Adverse events, SAEs, and other reportable safety events will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

The investigator and any designees are responsible for detecting, documenting, and reporting events that meet the definition of an AE or SAE as well as other reportable safety events. Investigators remain responsible for following up AEs, SAEs, and other reportable safety events for outcome.

The investigator, who is a qualified physician, will assess events that meet the definition of an AE or SAE as well as other reportable safety events with respect to seriousness, intensity/toxicity and causality.

9.2.1 Time Period and Frequency for Collecting AE, SAE, and Other Reportable Safety Event Information

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

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

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

9.2.1.1 Reporting to Merck

All initial and follow-up AEs, SAEs, and other reportable safety events will be recorded and reported to Merck within the time frames as indicated in

Table 16.

Table 16 Reporting Time Periods and Time Frames for Adverse Events and Other Reportable Safety Events

Type of Event	**Reporting Time Period: Consent to Randomization/ Allocation**	**Reporting Time Period: Randomization/ Allocation through Protocol-specified Follow-up Period**	**Reporting Time Period: After the Protocol-specified Follow-up Period**	**Time Frame to Report Event and Follow-up Information to Merck:**
Serious Adverse Event (SAE) including Cancer and Overdose	Report if: - due to protocol-specified intervention - causes exclusion - participant is receiving placebo run-in or other run-in treatment	Report all	Report if: - drug/vaccine related. (Follow ongoing to outcome)	Within 2 business days but no longer than 3 calendar days of learning of event
Pregnancy/Lactation Exposure	Report if: - due to intervention - causes exclusion	Report all	Previously reported – Follow to completion/termination; report outcome	Within 2 business days but no longer than 3 calendar days of learning of event
Event of Clinical Interest (require regulatory reporting)	Report if: - due to intervention - causes exclusion	Report - potential drug-induced liver injury (DILI) - require regulatory reporting	Not required	Within 2 business days but no longer than 3 calendar days of learning of event

9.2.1.2 Adverse Event Reporting to Sponsor/UVA CC/GTcLC/DSMC

The UVA Cancer Center Data Safety Monitoring Committee (DSMC) will oversee conduct of the study, patient safety and all interim analyses as specified in the data analysis plan. Detailed guidelines regarding the structure, function and decision-making mechanisms for the Data Safety Monitoring Committee are provided in the DSMC charter.

The Global T-cell Lymphoma Consortium (GTcLC) at UVA will be the coordinating center. All participating centers will report all serious adverse events to the UVA Cancer Center's DSMC and to local ethics committees.

AEs must be recorded into the study's case report forms per the following guidelines.
In the event of a DLT prior to initiation of cycle 2, site staff must report the occurrence to the UVA CC/GTcLC via the DLT CRF within 24 hours from the time the study team receives knowledge of the event. DLT's that are deemed serious will also be submitted according to the reporting guidelines in *section 9.2.* DLTs occurring after the initiation of cycle 2 do not need to be submitted on the DLT CRF, but should be reported as AEs/SAEs accordingly.

Table 17 : High Risk Studies Reporting requirements for AEs that occur within 30 days of the last dose of protocol specified treatment								
	Grade 1	Grade 2		Grade 3				Grade 4 & 5
	Expected and unexpected	Expected	Unexpected	Expected		Unexpected		Expected and Unexpected
				Without hospitalization	With hospitalization	Without hospitalization	With hospitalization	
Unrelated Unlikely	30 days	30 days	30 days	30 days	15 days	30 days	15 days	7 days
Possible Probable Definite	30 days	30 days	15 days	30 days	15 days	7 days	7 days	(24-hrs)* 7 days
*Enter into Cancer Center database within 24 hours if unexpected and definitely related to protocol specified treatment Hospitalization defined as an inpatient hospital stay or prolongation of a hospital stay equal to or greater than 24 hours								

9.2.1.3 Serious Adverse Event Reporting to Sponsor/UVA CC/GTcLC /DSMC/IRB

The study clinician will report to the sponsor (see Study Reference Manual for contact information and instructions) any serious adverse event, whether or not considered study intervention related, including those listed in the protocol, package insert or investigator brochure and must include an assessment of whether there is a reasonable possibility that the study intervention caused the event.

All serious adverse events (SAEs) will be followed until satisfactory resolution or until the site investigator deems the event to be chronic or the participant is stable. Other supporting documentation of the event may be requested by the UVA Coordinating Center (UVA CC/GTcLC /Sponsor) and should be provided as soon as possible.

Any event deemed serious

- Report to the UVA CC/GTcLC within 24 hours from the time the study team received knowledge of the event according to UVA CC/GTcLC requirements.
    - Additional follow-up reports should be sent according to the Study Reference Manual
- Report to your IRB in accordance with your IRB guidelines.

Sponsor Reporting Requirements

- The Sponsor is responsible for notifying the UVA IRB-HSR of any event resulting in death that is deemed DEFINITELY related to (caused by) study within 24 hours from the time the study team received knowledge of the event. Report using IRB Online and by telephone.

- The Sponsor is responsible for notifying the Food and Drug Administration (FDA) of any unexpected fatal or life-threatening adverse event that is at least possibly related to study intervention as soon as possible, but in no case later than 7 calendar days after the sponsor's initial receipt of the information. Report using the FDA Form 3500a.

- The Sponsor is responsible for notifying the UVA IRB-HSR of any serious, unexpected, related adverse event within 7 calendar days from the time the study team receives knowledge of the event. Timeline includes submission of signed hardcopy of AE form. Report using IRB online.

- The Sponsor is responsible for notifying the FDA and all participating investigators in an Investigational New Drug (IND) safety report of potential serious risks, from clinical trials or any other source, as soon as possible, but in no case later than 15 calendar days after the sponsor determines that the information qualifies for reporting (21 CFR 312.32 (c)(1)). Other adverse event information should be sent to the FDA in the IND annual report.

9.2.2 Pregnancy and Exposure During Breastfeeding

Although pregnancy and infant exposure during breastfeeding are not considered AEs, any pregnancy or infant exposure during breastfeeding in a participant (spontaneously reported to the investigator or their designee) that occurs during the study are reportable to Merck and to the UVA CC/GTcLC /Sponsor (see section 9.2.
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.

9.2.3 Events of Clinical Interest

Selected nonserious and SAEs are also known as ECIs and must be reported to Merck.
Events of clinical interest for this study include:

1. An overdose of pembrolizumab that is not associated with clinical symptoms or abnormal laboratory results. For purposes of this study, an overdose of pembrolizumab will be defined as any dose of 1,000 mg or greater (≥5 times the indicated dose). No specific information is available on the treatment of overdose of pembrolizumab. In the event of overdose, the participant should be observed closely for signs of toxicity. Appropriate supportive treatment should be provided if clinically indicated. If an adverse event(s) is associated with ("results from") the overdose of a Merck product, the adverse event(s) is reported as a serious adverse event, even if no other seriousness criteria are met.

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

9.2.4 Unanticipated Problems

9.2.4.1 Definition of Unanticipated Problems (UP)

The Office for Human Research Protections (OHRP) considers unanticipated problems (UPs)(may include a data breach) involving risks to participants or others to include, in general, any incident, experience, or outcome that meets **all** of the following criteria:

- Unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the Institutional Review Board (IRB)-approved research protocol and informed consent document; and (b) the characteristics of the participant population being studied;
- Related or possibly related to participation in the research ("possibly related" means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
- Suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

9.2.4.2 Unanticipated Problem Reporting

Site Reporting Requirements

- UPs that are SAEs will be reported in accordance with the guidelines for SAE reporting.
- UPs that are not adverse events, protocol deviations or data breaches (see *section 9.2.5* for reporting for data breaches) should be reported as follows:
    - Report to the UVA CC/GTcLC within 2 calendar days from the time the study team receives knowledge of the event.
    - Report to your IRB of record in accordance with your IRB guidelines.

Sponsor/UVA CC/GTcLC Reporting Requirements

- Report UPs that are not adverse events, protocol deviations or data breaches to the UVA IRB-HSR within 7 calendar days from the time the study team receives knowledge of the event. Report using the Unanticipated Problem Report form.

All UPs will be reported to appropriate institutional officials (as required by an institution's written reporting procedures), the supporting agency head (or designee), and the Office for Human Research Protections (OHRP) in accordance with institutional policies.

9.2.5 Data Breaches

9.2.5.1 Definition of a Data Breach

An unauthorized acquisition, access, or use of protected health information (PHI) that compromises the security or privacy of such information.

9.2.5.2 Reporting a Data Breach

Site Reporting Requirements

- Report to the Sponsor/UVA CC/GTcLC within 24 hours from the time the study team receives knowledge of the event.
- Report to your IRB of record in accordance with your IRB guidelines.

Sponsor/UVA CC/GTcLC Reporting Requirements

- Report to the UVA Corporate Compliance and Privacy Office as soon as possible and no later than 24 hours from the time the incident is identified. Report by telephone.

- Report to ITC if the breach involves electronic data. Report as soon as possible and no later than 24 hours from the time the incident is identified. Refer to the following for details: http://security.virginia.edu/report-information-security-incident.

- Report to UVA police if the breach includes such things as stolen computers. Report by telephone.

9.2.6 Protocol Violations or Deviations

9.2.6.1 Definition of a Protocol Violation/Deviation

A protocol deviation is defined as any change, deviation, or departure from the study design or procedures of a research project that is NOT approved by the institution's IRB prior to its initiation or implementation, OR deviation from standard operating procedures, Good Clinical Practices (GCPs), federal, state or local regulations. Protocol violations may or may not be under the control of the study team or UVa staff. These protocol violations may be major or minor violations.

9.2.6.2 Emergency Protocol Deviation/Violation

When an emergency occurs that requires a violation of the protocol for a subject, this will be made only for that subject. A decision will be made as soon as possible to determine whether or not the subject (for whom the violation of, the protocol was affected) is to remain on study. This decision will be made by Dr. Owen O'Connor the IND holder. The subject's medical records will completely describe the violation of, the protocol and state the reasons thereof. In addition, the Investigator will notify the IRB/EC and the FDA as applicable in writing of such violation of, the protocol.

9.2.6.3 Non-Emergency Protocol Deviation/Violations

Non-emergency minor violations of the protocol (i.e., deviations) will be permitted with approval of the PI.

It is the responsibility of the site investigator to use continuous vigilance to identify and report deviations.

9.2.6.4 Reporting of Protocol Deviations/Violations

Site Reporting Requirements

- Report major deviations to the UVA CC/GTcLC within 4 calendar days from the time the study team receives knowledge of the event. All deviations must be addressed in study source documents. Refer to the Study Reference Manual for instructions on recording minor deviations.
- Report to your IRB of record in accordance with your IRB guidelines.

Sponsor/UVA CC/GTcLC Reporting Requirements

- Report to the UVA IRB-HSR major deviations within 7 calendar days from the time the study team received knowledge of the event. Report using the Protocol Deviation and Protocol Exception Reporting Form.
- Minor deviations do not need to be reported to the UVA IRB-HSR.

9.2.7 Method of Detecting AEs, SAEs, and Other Reportable Safety Events

Care will be taken not to introduce bias when detecting AEs and/or SAEs and other reportable safety events. Open-ended and nonleading verbal questioning of the participant is the preferred method to inquire about AE occurrence.

9.2.8 Follow-up of AE, SAE, and Other Reportable Safety Event Information

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All AEs, SAEs, and other reportable safety events including pregnancy and exposure during breastfeeding, events of clinical interest (ECIs), cancer, and overdose will be followed until resolution, stabilization, until the event is otherwise explained, or the participant is lost to follow-up.. In addition, the investigator will make every attempt to follow all nonserious AEs that occur in randomized participants for outcome. Further information on follow-up procedures is given in *section 11.5*.

9.2.9 Sponsor Responsibility for Reporting Adverse Events

All Adverse Events will be reported to regulatory authorities, IRB/IECs and investigators in accordance with all applicable country specific regulatory requirements, global laws and regulations.

9.3 Other Regulatory, Monitoring and Quality Assurance/Quality Control Considerations

9.3.1 Foreign Sites

All studies conducted under an IND will obtain a waiver of Institutional Review Board (IRB) requirements under 21CFRPart 56. The clinical parameters, data collection, data quality, and clinical trial conduct must adhere to U.S. regulations to be considered in the evaluation of a new drug application.

Reference to:

ICH guidance *E5 Ethnic Factors in the Acceptability of Foreign Clinical Data:*
https://www.fda.gov/downloads/Drugs/Guidances/ucm073120.pdf
Guidance for Industry and FDA staff: *FDA Acceptance of Foreign Clinical Studies Not Conducted Under an IND Frequently Asked Questions*.

https://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM294729.pdf
Guidance for Industry: *Investigator Responsibilities – Protecting the Rights, Safety, and Welfare of Study Subjects*.

https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM187772.pdf

Office of Scientific Investigations.
https://www.fda.gov/aboutfda/centersoffices/officeofmedicalproductsandtobacco/cder/ucm090085.htm

9.3.2 Compliance & Monitoring

The Global T-cell Lymphoma Consortium consists of a network of physicians whose expertise in T-cell Lymphoma whose mission is to advance the standards of care for patients with these complex diseases.
The consortium's three Principal Investigators represent three geographic sectors; Asia, North America, and Europe. Columbia University Medical Center (CUMC) will be the central reporting administration for the consortium. In this capacity the consortium will function similar to that of a clinical research organization (CRO).
Each global center will have a monitor at the site level who will follow the guidelines outlined in this document. A copy of monitoring reports will be made available to the Coordinating Center.
Each individual site will continue to follow their individual institution's guidelines for reporting purposes in addition to reporting these events to the centralized reporting administration of the consortium. The consortium central reporting administration will utilize the UVA Data Safety Monitoring Committee (DSMC) reporting templates for both serious adverse events and risk assessment. Reporting of SAEs will be in real time for each center using a 24 hour fax & email system. All necessary documentation will be sent including any pertinent labs and clinic /hospital notes. The necessary reporting to the UVA DSMC, IRB, and FDA will be the responsibility of the IND holder. When a protocol is conducted under an IND, the holder of that IND will follow their institutional guidelines in addition to reporting to the central reporting administration of the consortium. Each site within the Consortium will utilize their Institutional DSMB (DSMC or DMB) committee within each geographical sector. This is intended to satisfy the policies and recommendations of the U.S. Food and Drug Administration (FDA) and local ethics boards.

9.3.3 Study Monitoring

Clinical site monitoring is conducted to ensure that the rights and well-being of trial participants are protected, that the reported trial data are accurate, complete, and verifiable, and that the conduct of the trial is in compliance with the currently approved protocol/amendment(s), with International Conference on Harmonisation Good Clinical Practice (ICH GCP), and with applicable regulatory requirement(s).

- The UVA Coordinating Center will implement ongoing monitoring activities for this study to ensure that Participating Institutions are complying with regulatory and protocol requirements, data quality, and subject safety. Monitoring will occur before the clinical phase of the protocol begins, continue during protocol performance and through study completion.

- Monitoring may be conducted either remotely or on-site. For remote visits, each institution will be required to provide redacted source documents for review or appropriate access to the EMR. The UVA CC/GTcLC will provide the Participating Institution with a follow-up letter following completion of the monitoring visit which should be maintained in the site regulatory files. The schedule for monitoring may be adjusted according to subject accrual and data quality. The Investigator will be notified in advance of each visit.

- Independent audits may be conducted by each institution according to institutional guidelines. Results of these audits may be requested by the UVA Coordinating Center.

Investigator responsibilities are set out in the ICH guideline for Good Clinical Practice (GCP) and in the US Code of Federal Regulations.

The University of Virginia Cancer Center Data and Safety Monitoring Committee (CC DSMC) will provide oversight of the conduct of this study. The CC DSMC will report to the UVA Protocol Review Committee (PRC).

The UVA Cancer Center DSMC will review the following:

- All adverse events
- Audit results
- Application of study designed stopping/decision rules
- Whether the study accrual pattern warrants continuation/action
- Protocol violations

Whenever a PAM audit (described in the next paragraph) is conducted, the results will be provided to the DSMC Chair for review. The UVA Cancer Center DSMC will meet every month for aggregate review of data. Tracking reports of the meetings are available to the PI for review. Issues deemed of immediate concern by the DSMC are brought to the attention of the sponsor (and if appropriate to the PRC and UVA IRB-HSR) and a formal response from the sponsor is requested. Per the UVA Cancer Center NIH approved institutional plan, this study will be audited (post-approval monitoring) approximately every 6 months. The audit may include direct access to source data/documents.

Any study conducted at UVA and under the purview of the University of Virginia HSR-IRB is subject to review of UVA documents. Studies are chosen for Post-approval Monitoring (PAM) either a) at random or b) requested by a study team member or any member of the IRB-HSR.

The purpose of Post-approval Monitoring audits is to ensure that documentation of clinical research studies is of the highest quality, verify protocol adherence, and ensure that all Federal and local rules concerning clinical research are being fulfilled. Post-approval monitoring is done by staff within the office of the Vice President for Research (VPR) in accordance with their Standard Operating Procedures. The conduct of an on-site review may include but is not limited to:

- requests for progress reports from investigators,
- examinations of research records, including signed informed consent documents, protocol modifications, and unexpected, serious, and/or related adverse experience reports,
- contacts with research subjects, or

- observation of the consent process and/or research procedures. Examples of when observation of the consent process could occur are:
    - Full board IRB determines during review of a project that a conflict of interest exists such that the informed consent process should be observed by a neutral party;
    - IRB is made aware of a complaint or concern with regard to the informed consent process; or

IRB determines as a result of the monitoring process that the consent process is insufficient and education/training is required for conduct of consent.

Investigators must enter study data onto CRFs or other data collection system. The Investigator will permit study-related audits by UVA Cancer Center or its representatives, IRB/EC review, and regulatory inspection(s) (e.g., FDA, EMEA, TPP), providing direct access to the facilities where the study took place, to source documents, to CRFs, and to all other study documents.

9.3.3.1 Quality Assurance and Quality Control

Each clinical site will perform internal quality management of study conduct, data and biological specimen collection, documentation and completion according to institutional policies.]

Quality control (QC) procedures will be implemented beginning with the data entry system and data QC checks that will be run on the database will be generated. Any missing data or data anomalies will be communicated to the site(s) for clarification/resolution.

Following written Standard Operating Procedures (SOPs), the monitors will verify that the clinical trial is conducted and data are generated and biological specimens are collected, documented (recorded), and reported in compliance with the protocol, International Conference on Harmonisation Good Clinical Practice (ICH GCP), and applicable regulatory requirements (e.g., Good Laboratory Practices (GLP), Good Manufacturing Practices (GMP)).

The investigational site will provide direct access to all trial related sites, source data/documents, and reports for the purpose of monitoring and auditing by the sponsor, and inspection by local and regulatory authorities.

9.3.4 Study Records Retention

Study documents should be retained for a minimum of 2 years after the last approval of a marketing application in an International Conference on Harmonisation (ICH) region and until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the study intervention. These documents should be retained for a longer period, however, if required by local regulations. No records will be destroyed without the written consent of the sponsor, if applicable. It is the responsibility of the sponsor to inform the investigator when these documents no longer need to be retained. Record retention will be in accord with drug 21 CFR 312.62 and HIPAA regulations.

10.0 STATISTICAL CONSIDERATIONS

10.1 Study Design

This is a Phase Ib study evaluating the safety and efficacy of pembrolizumab combined with pralatrexate (Arm A) or decitabine (Arm C) or decitabine and pralatrexate (Arm B) in patients with peripheral T-cell lymphoma (PTCL) and cutaneous T-cell lymphoma (CTCL). In all arms, toxicity will be assess according to the NCI Common Toxicity Criteria for Adverse Events (CTCAE), version 5.0. Dose-limiting toxicity (DLT) is a binary outcome (yes/no) and will be determined by adverse events occurring during the first cycle of treatment (see Section 5.3 for DLT definition). In all arms, the maximum tolerated dose (MTD) is defined as the dose combination with a DLT rate closest to the target DLT rate of 25%. The study will accrue participants in cohorts of size 1 in all arms. After accrual of a participant to an arm, the accumulating DLT data will be used to update the model-based estimated DLT

probabilities for each dose level. These estimates will then be used to update the recommended dose level for the next participant accrued to that arm of the study.

Arms A and C:
The primary objectives of Arms A and C is to determine the MTD, defined by acceptable toxicity, of decitabine (Arm C) or pralatrexate (Arm A) (plus a fixed dose of pembrolizumab) from among the 3 study dose levels in the following tables, and to evaluate efficacy, as determined by overall response rate, at the estimated MTD.

Arm A		
Dose Level	**Pralatrexate**	**Pembrolizumab***
Level 1 (start)	**30 mg/m^2 day 1, 8, 15**	**200 mg day 1**
Level -1	30 mg/m^2 day 1, 15	200 mg day 1
Level - 2	20 mg/m^2 day 1, 15	200 mg day 1

Arm C		
Dose Level	**Decitabine**	**Pembrolizumab***
Level 1 (start)	**20 mg/m^2 day 1->5**	**200 mg day 8**
Level -1	20 mg/m^2 day 1->3	200 mg day 8
Level -2	10 mg/m^2 day 1->3	200 mg day 8

Based on the accumulated data from the previous 5 subjects (1 observed DLT) accrued to Arm A, the first eligible subject in Arm A will be entered onto Level 1. Based upon the accumulated data from the previous 4 subjects (2 observed DLTs) accrued to Arm C, the first eligible subject in Arm C will be entered onto Level -1.

Arm B:
The primary objective of Arm B is to determine the MTD, defined by acceptable toxicity, of pembrolizumab combined with decitabine and pralatrexate from among the six study dose combinations in the following table, and to evaluate efficacy, as determined by overall response rate, at the estimated MTD. In a previous version of the protocol (dated 14 Dec 2022), fifteen dose combinations were considered for Part B. While the current protocol version reduces the number of dose combinations to six, we have maintained the original combination labels to maintain consistency with the original dose levels for each combination.

Combination designation			
Pralatrexate	20mg/m^2 1,8,15	**Combination 6**	**Combination 8**
	20mg/m^2 1,15	**Combination 3**	**Combination 5**
	15mg/m^2 1,15	**Combination 1**	**Combination 2**
		10mg/m^2 1-3	10mg/m^2 1-5
		Decitabine	

Based on the accumulated data from the first 4 subjects (1 observed DLT) accrued to Combination 8 in Arm B, the next eligible subject in Arm B will be entered onto Combination 8.

10.2 Dose allocation

Arms A and C

Dose allocation in Arms A and C will be based upon a continual reassessment method (CRM), which uses a model for the probability of DLT and the accumulated DLT data at each dose level to sequentially allocate each new patient cohort[1]. Toxicity assessment is based on the occurrence of DLTs, and the minimum follow-up for determination of escalation is one cycle of treatment. The DLT probabilities are modeled using a one-parameter working model $R(d_i) = Pr(\text{DLT at dose level } i) \approx \alpha_i^{\exp(a)}$, where α_i is the skeleton of the working model. The skeleton values are pre-specified constants and were chosen according to the algorithm of Lee and Cheung[25], which yields a working model that results in well-performing operating characteristics in a broad range of scenarios. For this study, the skeleton values are $\alpha_i = (0.08, 0.15, 0.25)$. Based on the available DLT data $D = \{(y_i, n_i); i = 1, \ldots, 3\}$, where where y_i is the number of DLT's and n_i is the number of subjects treated on study dose level i, the likelihood is given by $L(a) \propto \prod_{i=1}^{3} \left(\alpha_i^{\exp(a)}\right)^{y_i} \left(1 - \alpha_i^{\exp(a)}\right)^{n_i - y_i}$.

After accrual of each patient into the trial, the DLT probability estimates, $\tilde{R}(d_i)$, are updated via $\tilde{R}(d_i) = \alpha_i^{\exp(\tilde{a})}; \quad \tilde{a} = \arg\max L(a)$.

These estimates are used to sequentially allocate patients to the dose indicated by the modeling to have the estimated DLT rate closest to 25%. The study will accrue participants in cohorts of size 1 and dose levels will not be skipped. The coherence principle will be used, where the next patient will not be treated at a dose level higher than the current dose level if the current patient experiences a DLT[26]. Additionally, the next patient will not be treated at a dose level lower than the current dose level if the current patient does not experience a DLT. The study will sequentially repeat the estimation procedure after the enrollment and follow-up of each cohort. The allocation procedure will be repeated until sufficient information about the MTD has been obtained according to the stopping rules described below.

Arm B

Dose combination allocation in Arm B will be conducted using a DLT-adapted partial order continual reassessment method (POCRM) for dose-finding with combinations of agents[2]. The study will accrue eligible participants in cohorts of size 1 and will be based upon a modeling approach that uses (a) a selected set of five possible orderings for the DLT probabilities and (b) a skeleton for the DLT probabilities under each ordering. In drug combination studies, the toxicity relationship between some of the combinations being studied may be uncertain. If a combination involves increasing the dose of one agent while decreasing the dose of the other agent relative to another combination, then it may not be known which is more toxic. For example, combination 2 is an increase in the dose of decitabine and a decrease in the dose of pralatrexate relative to combination 3, which creates uncertainty in the ordering of DLT probabilities between combination 2 and combination 3. The specification of multiple possible orderings of DLT probabilities accounts for these types of uncertainty in the modeling approach.

Possible orderings of DLT probabilities
1) 1-2-3-5-6-8
2) 1-2-3-6-5-8
3) 1-3-2-5-6-8
4) 1-3-2-6-5-8
5) 1-3-6-2-5-8

Skeleton of DLT probabilities under each ordering**						
	Combination labels					
Order	1	2	3	5	6	8
1	0.012	0.03	0.062	0.11	0.174	0.25
2	0.012	0.03	0.062	0.174	0.11	0.25
3	0.012	0.11	0.03	0.174	0.062	0.25
4	0.012	0.062	0.03	0.174	0.11	0.25
5	0.012	0.062	0.03	0.11	0.174	0.25
**Skeleton values were chosen according to the algorithm of Lee and Cheung (*Clin Trials*, 2009)[25]						

Within each ordering, the CRM is fit to estimate DLT probabilities using that ordering's working model and the accumulated data. For each possible ordering, $m = 1, \cdots, 5$ in the table above, the DLT probabilities are modeled via a one-parameter power model $R(d_i) = \Pr(\text{DLT at combination } i) \approx p_{mi}^{\exp(\theta_m)}$, where the p_{mi} are the skeleton values for order m given in the table above. Uniform prior weights $\tau(m) = 1/m$ are placed on each possible ordering so that each ordering/skeleton is considered equally likely a priori. After accrual of each patient into the trial, the parameter θ_m is estimated for each ordering by maximum likelihood estimation where the likelihood is given by

$$L_m(\theta_m) = \prod_{i \in (1,2,3,5,8)} \left(p_{mi}^{\exp(\theta_m)}\right)^{y_i} \left(1 - p_{mi}^{\exp(\theta_m)}\right)^{n_i - y_i},$$

y_i= the number of DLTs, and n_i=the number of treated patients in combination i. The ordering h with the largest likelihood is chosen and, within this ordering, DLT probability estimates are updated for each combination. If there is a tie between the likelihood values of two or more orderings, then the selected ordering h is randomly chosen from among the tied orderings. After accrual of each patient cohort into the trial, the DLT probability estimates, $\tilde{R}(d_i)$, are updated via

$$\tilde{R}(d_i) = p_{hi}^{\exp(\tilde{\theta}_h)}; \qquad \tilde{\theta}_h = \arg\max L_h(\theta_h).$$

The DLT probability estimates are used to sequentially allocate participants according to the following rules:

1. If the most recent participant accrued to the study **does not** experience a DLT, then the recommended combination for the next participant will be the combination indicated by the model to have an estimated DLT rate closest to 25%. Escalation of both agents simultaneously or escalation of more than one dose level of either agent is not allowed.
2. If the most recent participant accrued to the study **does** experience a DLT:
    a. If the DLT is mucositis *or* thrombocytopenia *or* mucositis plus neutropenia and/or thrombocytopenia, then the recommended combination for the next participant will be restricted to either the current combination administered to the most recent participant or to de-escalation of one dose level of Pralatrexate, based on which combination has an estimated DLT rate closest to 25%.
    b. If the DLT is neutropenia or neutropenia and thrombocytopenia, then the recommended combination for the next participant will be restricted to either the current combination administered to the most recent participant or to de-escalation of one dose level of Decitabine, based on which combination has an estimated DLT rate closest to 25%

The study will sequentially repeat the estimation procedure after the enrollment and follow-up of each cohort. The allocation procedure will be repeated until sufficient information about the MTD has been obtained according to the stopping rules described below.

10.3 Stopping rules and MTD definition

Arms A and C

Accrual to Arms A and C will be halted and trigger a review by the study investigators and the DSMC to determine if the study should be modified, or permanently closed to further accrual according to the following:

1. Stop the study for safety if the observed DLT rate at the lowest study dose level (Level -2) ≥ the following number of DLTs out of the following number of patients treated at the lowest study dose level. These stopping guidelines are based on whether the lower limit of an Agresti-Coull[27] binomial confidence interval (with 80% confidence) for the lowest study dose level exceeds the target DLT rate. The following bounds were generated using the web application at http://uvatrapps.uvadcos.io/crmb/]. Note that, given the accrual of previous participants to dose level 1 in Arms A and C, at most 4 participants can be accrued to Level -2 before the maximum sample size is reached.

Stopping guidelines for DLTs at the lowest dose level	
Number of participants	Boundary
2-3	≥ 2
4	≥ 3

2. If the recommendation is to assign the next patient to a dose level that already has 7 participants treated at the dose level, enrollment to the arm is stopped and the recommended dose level is declared the MTD.
3. Otherwise, the MTD is defined as the dose level that is recommended after the maximum sample size of 10 participants for the arm.

Arm B

Accrual to Arm B will be halted and trigger a review by the study investigators and the DSMC to determine if the study should be modified, or permanently closed to further accrual according to the following:

1. Stop the study for safety if the observed DLT rate at the lowest combination (Combination 1) ≥ the following number of DLTs out of the following number of patients treated at the lowest combination. These stopping guidelines are based on whether the lower limit of an Agresti-Coull binomial confidence interval (with 80% confidence) for the lowest combination exceeds the target DLT rate[27]. The following bounds were generated using the web application at http://uvatrapps.uvadcos.io/pocrm/].

Stopping guidelines for DLTs at the lowest combination	
Number of participants	Boundary
2-3	≥ 2
4-6	≥ 3
7	≥ 4

2. If the recommendation is to assign the next patient to a combination that already has 7 participants treated on the combination, the study is stopped and the recommended combination is declared the MTD.
3. Otherwise, the MTD is defined as the combination that is recommended after the maximum target sample size of 30 participants are accrued to the study.

10.4 Sample size and accrual

A maximum target accrual of 5 additional eligible participants is planned in Arm A (total accrual n=10) and 6 additional eligible participants in Arm C (total accrual n=10). A maximum target accrual of 26 additional eligible participants is planned in Arm B (total accrual n=30), but simulation results below indicate that the average estimated

sample size needed to complete accrual to Arm B is between 3.5 (total accrual n=7.5) and 11.3 (total accrual n=15.3) additional participants. Maximum total sample size for all arms is estimated to be approximately 23 additional participants (total accrual n=36). For estimation of ORR at the MTD, a sample size of 7 at the MTD produces a two-sided 80% binomial confidence interval with a width equal to 0.556 when the sample proportion is 0.5. Additional subjects will be enrolled to replace any subjects who are enrolled, but do not receive treatment. Accrual is estimated at 2 participants per month. Adjusting for an approximate 5% drop-out/ineligibility rate, maximum target accrual should not exceed 38 participants.

10.5 Operating characteristics

Arms A and C

Simulations were run to display the performance of the design characteristics in Arms A and C using the R statistical programming language. For each scenario, 5000 simulated trials were run using a random seed of 322348. The confidence level used to define the safety stopping guidelines was 80%. Each table reports the true DLT probability at each dose level, the percentage of trials in which each dose level was recommended as the MTD, the average number of participants treated at each dose level, and the percentage of trials stopped early for safety. The results displayed in the following tables were based upon a maximum target accrual of 10 subjects.

Operating characteristics in Arm A for the continual reassessment method with cohorts of size 1. **Bold** font indicates the level that is the MTD corresponding to a target DLT rate of 25%. Previously, there were 5 participants accrued (1 observed DLT) on dose level 3. Sample size for each scenario is n=10 total (previous plus additional) participants.

Scenario		Dose level 1	Dose level 2	Dose Level 3	% stopped for safety
1	True DLT prob:	0.05	0.15	**0.25**	0.0
	MTD selection %	5.7	22.6	**71.7**	
	Avg # of patients	0.1	0.6	**9.3**	
2	True DLT prob:	0.15	**0.25**	0.40	0.24
	MTD selection %	18.9	**36.2**	44.7	
	Avg # of patients	0.3	**1.0**	8.7	
3	True DLT prob:	**0.25**	0.40	0.55	1.24
	MTD selection %	**41.2**	34.0	23.5	
	Avg # of patients	**0.6**	1.4	8.0	

Operating characteristics in Arm C for the continual reassessment method with cohorts of size 1. **Bold** font indicates the level that is the MTD corresponding to a target DLT rate of 25%. Previously, there were 4 participants accrued (1 observed DLT) on dose level 3. Sample size for each scenario is n=10 total (previous plus additional) participants.

Scenario		Dose level 1	Dose level 2	Dose Level 3	% stopped for safety
1	True DLT prob:	0.05	0.15	**0.25**	0.0
	MTD selection %	6.9	3.1	**62.1**	
	Avg # of patients	0.3	1.2	**8.5**	
2	True DLT prob:	0.15	**0.25**	0.40	0.52
	MTD selection %	23.6	**43.7**	32.2	
	Avg # of patients	0.7	**1.8**	7.5	
3	True DLT prob:	**0.25**	0.40	0.55	2.24
	MTD selection %	**50.1**	35.4	12.2	

	Avg # of patients	**1.5**	2.0	6.5	

Arm B

Simulations were run to display the performance of the design characteristics in Arm B using the R statistical programming language. For each scenario, 5000 simulated trials were run using a random seed of 322348. The confidence level used to define the safety stopping guidelines was 80%. Simulation results include the true DLT probability at each combination, the percentage of trials in which each combination was recommended as the MTD, the average number of participants treated at each combination, the average sample size, and the percentage of trials stopped early for safety. The results displayed in the following tables were based upon a maximum target accrual of 30 participants where accrual was stopped when 7 participants were treated on the recommended combination.

Operating characteristics summary for proposed design over five scenarios					
	Scenario 1	**Scenario 2**	**Scenario 3**	**Scenario 4**	**Scenario 5**
Observed % DLTs	20.25%	21.38%	17.38%	27.27%	31.59%
Average sample size	8.42	8.84	7.51	12.44	15.32
MTD selection % ±5% of target*	92.50%	90.38%	98.70%	22.34%	37.28%
Avg # of pts treated ±5% of target*	6.93	6.91	6.99	2.8	4.4
% of early stopping for safety	0.00%	0.02%	0.00%	0.52%	1.84%
* Includes combination with highest DLT rate if true DLT probability for all combinations is below 5% of the target					

Operating Characteristics						
	True DLT probabilities		**MTD Selection Percentage**		**Average Number of Patients Treated**	
Scenario 1						
20mg/m^2 1,8,15	0.15	0.20	1.36	92.50	0.25	6.93
20mg/m^2 1,15	0.09	0.14	0.22	5.60	0.08	1.00
15mg/m^2 1,15	0.07	0.07	0.06	0.26	0.02	0.15
Scenario 2						
20mg/m^2 1,8,15	0.14	0.25	1.94	90.38	0.33	6.91
20mg/m^2 1,15	0.10	0.14	0.26	6.64	0.10	1.28
15mg/m^2 1,15	0.09	0.10	0.04	0.72	0.03	0.20
Scenario 3						
20mg/m^2 1,8,15	0.08	0.10	0.30	98.70	0.09	6.99
20mg/m^2 1,15	0.06	0.07	0.00	0.98	0.01	0.39
15mg/m^2 1,15	0.05	0.05	0.00	0.02	0.00	0.03
Scenario 4						
20mg/m^2 1,8,15	0.40	0.47	5.00	57.16	0.87	6.52
20mg/m^2 1,15	0.18	0.25	6.38	22.34	0.89	2.77
15mg/m^2 1,15	0.15	0.18	1.62	6.98	0.32	1.07
Scenario 5						
20mg/m^2 1,8,15	0.47	0.55	6.12	34.72	1.25	6.09
20mg/m^2 1,15	0.25	0.47	18.38	13.10	2.09	2.53
15mg/m^2 1,15	0.15	0.25	6.94	18.90	1.06	2.31
Pralatrexate	10mg/m^2 1-3	10mg/m^2 1-5	10mg/m^2 1-3	10mg/m^2 1-5	10mg/m^2 1-3	10mg/m^2 1-5
	Decitabine					

10.6 Data Analysis Plan

All subjects who are put on-study will be assessed for inclusion in the final report. All subjects who receive any protocol treatment will be monitored for adverse events. Adverse events will be described and coded based upon the NCI CTCAE v5.0. A DLT is defined in Section 5.3. Occurrence of DLTs will contribute to escalation and stopping decisions. Adverse events will be summarized by frequency and magnitude of event. Incidence of DLTs will be monitored against the safety bounds above. The bounds are non-binding, and provide a guideline that may result in study modification or closure. At study conclusion frequency, proportion and severity of adverse events, and DLTs by study dose level, as well as by arm, will be tabulated. Point estimates and 90% Agresti-Coull[27] binomial confidence intervals will be calculated for dichotomous endpoints (AEs, DLTs, overall response). For longitudinal measurements (i.e., immunologic and pharmacodynamic markers; see Sections 3 and 5.6), graphical methods will be used to display the data and exploratory repeated measures models will be used to describe changes over time. For continuous variables (i.e., duration of response), means, medians, and variability measures will be summarized with point estimates and 95% confidence intervals. PFS and OS distributions will be estimated by the product limit method of Kaplan and Meier.

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.: Toxicity And Response Criteria of The Eastern Cooperative Oncology Group. Am J Clin Oncol 5:649-655, 1982.* The Eastern Cooperative Oncology Group, Robert Comis M.D., Group Chair.	

11.2 Modified Severity Weighted Assessment Tool (mSWAT) Worksheet

Subject Number: _____
Visit Name: _____
Date of Assessment: _____ / _____ / _____

Body Region	% BSA in Body Region	% BSA Patch*	% BSA Plaque†	% BSA Tumor‡
Head	7			
Neck	2			
Anterior trunk	13			
Arms	8			
Forearms	6			
Hands	5			

Body Region	% BSA in Body Region	% BSA Patch*	% BSA Plaque†	% BSA Tumor‡
Posterior trunk	13			
Buttocks	5			
Thighs	19			
Legs	14			
Feet	7			
Groin	1			
% BSA by Involvement Category (Subtotal of each lesion type)	100			
Weighting factor		×1	×2	×4
Subtotal lesion BSA × weighting factor (multiply % BSA by Involvement Category and weighting factor for each lesion type)				

*Any size lesion without induration or significant elevation above the surrounding uninvolved skin; poikiloderma may be present.
†Any size lesion that is elevated or indurated; crusting, ulceration, or poikiloderma may be present.
‡Any solid or nodular lesion ≥ 1 cm in diameter with evidence of deep infiltration in the skin and/or vertical growth.

Total Score of Target Lesions (sum of lesion BSA × weighting factor subtotals): _____

11.3 Common Terminology Criteria for Adverse Events V5.0 (CTCAE)

The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for adverse event reporting. (http://ctep.cancer.gov/reporting/ctc.html)

11.4 Response Evaluation Criteria in Lymphoid Malignancies and CTCL

Overall response rates will be evaluated using clinical parameters, CT scan (PET/CT scan is allowable, if available) and bone marrow biopsy, as outlined by the 2007 International Harmonization Project criteria and revised criteria (Lugano 2014)[22,28]

11.5 Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

11.5.1 Definition of AE

AE definition

- An AE is any untoward medical occurrence in a clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention.
- NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a study intervention.
- NOTE: For purposes of AE definition, study intervention (also referred to as Merck product) includes any pharmaceutical product, biological product, vaccine, diagnostic agent, or protocol specified procedure whether investigational or marketed (including placebo, active comparator product, or run-in intervention), manufactured by, licensed by, provided by, or distributed by Merck for human use in this study.

Events meeting the AE definition

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator.
- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication.
- For all reports of overdose (whether accidental or intentional) with an associated AE, the AE term should reflect the clinical symptoms or abnormal test result. An overdose without any associated clinical symptoms or abnormal laboratory results is reported using the terminology "accidental or intentional overdose without adverse effect."

Events NOT meeting the AE definition

- Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.
- Surgery planned prior to informed consent to treat a pre-existing condition that has not worsened.

11.5.2 Definition of SAE

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met.

An SAE is defined as any untoward medical occurrence that, at any dose:

a. Results in death

b. Is life-threatening

- The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

c. Requires inpatient hospitalization or prolongation of existing 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 an SAE. A pre-existing condition is a clinical condition that is diagnosed prior to the use of a Merck product and is documented in the participant's medical history.

d. Results in persistent or significant disability/incapacity

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.
- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) that may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect

- In offspring of participant taking the product regardless of time to diagnosis.

f. Other important medical events

- Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent 1 of the other outcomes listed in the above definition. These events should usually be considered serious.
- Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

11.5.3 Additional Events Reported in the Same Manner as SAE

Additional events that require reporting in the same manner as SAE

In addition to the above criteria, AEs meeting either of the below criteria, although not serious per ICH definition, are reportable to Merck in the same time frame 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 of pembrolizumab

11.5.4 Recording AE and SAE

AE and SAE recording

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory, and diagnostics reports) related to the event.
- The investigator will record all relevant AE/SAE information on the AE CRFs/worksheets at each examination.
- There may be instances when copies of medical records for certain cases are requested by the Merck. In this case, all participant identifiers, with the exception of the participant number, will be blinded on the copies of the medical records before submission to the Merck.

- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of intensity/toxicity

- An event is defined as "serious" when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, not when it is rated as severe.

1. The investigator will make an assessment of intensity for each AE and SAE (and other reportable safety event) according to the NCI Common Terminology for Adverse Events (CTCAE), version 5. Any AE that changes CTCAE grade over the course of a given episode will have each change of grade recorded on the AE CRFs/worksheets.
    - 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 activities of daily living (ADL).
    - Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL.
    - Grade 4: Life threatening consequences; urgent intervention indicated.
    - Grade 5: Death related to AE.

Assessment of causality

1. Did Merck product cause the AE?

2. The determination of the likelihood that Merck product caused the AE 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 product and the AE based upon the available information.

3. The following components are to be used to assess the relationship between Merck's 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 AE:

    - **Exposure:** Is there evidence that the participant 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 studies 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.

- **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 product; (3) the study is a single-dose drug study; or (4) Merck product(s) is/are only used 1 time.)
- **Rechallenge:** Was the participant 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 study is a single-dose drug study; or (3) Merck product(s) is/are used only 1 time.)

NOTE: IF A RECHALLENGE IS PLANNED FOR AN AE THAT WAS SERIOUS AND MAY HAVE BEEN CAUSED BY MERCK PRODUCT, OR IF RE-EXPOSURE TO MERCK'S PRODUCT POSES ADDITIONAL POTENTIAL SIGNIFICANT RISK TO THE PARTICIPANT THEN THE RECHALLENGE MUST BE APPROVED IN ADVANCE BY THE SPONSOR AS PER DOSE MODIFICATION GUIDELINES IN THE PROTOCOL, AND IF REQUIRED, THE INIRB/IEC.

4. **Consistency with study intervention profile:** Is the clinical/pathological presentation of the AE consistent with previous knowledge regarding Merck product or drug class pharmacology or toxicology?

5. 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.

6. 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 the 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:

- Participant did not receive the Merck product OR temporal sequence of the AE onset relative to administration of the Merck product is not reasonable OR the AE is more likely explained by another cause than the Merck product. (Also entered for a participant with overdose without an associated AE.)

7. For each AE/SAE, the investigator must document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.

8. There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to the Merck. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to Merck.

9. The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.

10. The causality assessment is 1 of the criteria used when determining regulatory reporting requirements.

11. For studies in which multiple agents are administered as part of a combination regimen, the investigator may attribute each AE causality to the combination regimen or to a single agent of the combination. In general, causality attribution should be assigned to the combination regimen (ie, to all agents in the regimen). However, causality attribution may be assigned to a single agent if in the investigator's opinion, there is sufficient data to support full attribution of the AE to the single agent.

Follow-up of AE and SAE

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- New or updated information will be recorded in the CRF.
- The investigator will submit any updated SAE data to Merck within 2 business days but no longer than 3 calendar days of receipt of the information.

11.5.4.1 Reporting of AEs, SAEs, and Other Reportable Safety Events to the Merck

SAE reports and any other relevant safety information are to be forwarded to the Merck Global Safety facsimile number: +1-215-661-6229

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 215-661-6229) at the time of submission to FDA.

12.0SUMMARY OF CHANGES

From 12/14/2022 to 04/12/2024

Section(s)	Change	Justification
1.0, 5.2.2, 5.2.3, 10.1, 10.2, 10.3, 10.4, 10.5	Multiple dose levels of both pralatrexate and decitabine were removed from the possibilities for Arm B. Starting dose level will still be Combination 8. As a result of this revision, the maximum sample size (and estimated sample size for Arm B) were also decreased.	Based on the safety data collected in Arms A and C, higher doses were removed from the possible combinations for Arm B
Throughout	Minor formatting changes	To increase readability

From 03/28/22 to 12/14/2022

Section(s)	Change	Justification
Title page	The Mayo Clinic and Samsung University were removed from the list of participating sites	Mayo Clinic and Samsung University will not be participating in the study going forward
7.4 Timing of drug administration	Switch window for decitabine from 1 hour to 1 hour + 60 minutes	Commercial admin of decitabine usually ranges from 1-3 hours depending on dose, increases over an hour are not a safety issue, per IDS and infusion nurses
5.1 Study Design 7.6 Randomization and Treatment Allocation	Revised to allow investigator's choice between Arms A and C until required accrual is reached	Treatment arms are not being compared on this study, but for safety, participants should not be enrolled on Arm B until Arms and C are completed. The additional flexibility will allow participants (until an arm is closed) who have already received an included drug to try something different, which may be more effective for them.
8.0 Trial Flowchart	Updated footnotes related to pks to refer to section, which provides varying windows depending on timepoint Updated footnotes pertaining to decitabine administration and pk timing to refer to the final day for the cycle (since days of treatment/cycle will vary based on dose level) Removed physical exam requirement for Arm C, cycles 2&5, Day 22 Corrected footnote reference on Arm C to refer to Arm C (not Arm B)	Clarification and consistency
9.1.7.3 Pharmacokinetics/ Pharmacodynamics Evaluations	For Arms B and C, added "(day 3 if dose level is for decitabine on days 1-3)" and updated graphic accordingly to accommodate all dose levels	To accommodate all dose levels (consistency)
10.2 Dose allocation	Additional language was added to indicate that	To prevent a drastic reduction in

	dose levels will not be skipped (e.g. the dose will not decrease from dose level 2 to -1) and that the coherence principle will be used.	dose level after some toxicity

From 09/28/21 to 03/28/22

SECTION(S)	Change	Justification
Title page	Beth Israel Medical Center was removed from the list of participating sites	BIMC will not be participating in the study going forward
3.1 Primary Objectives & Hypothesis	Removed "de novo and" from the third primary objective in this section	Internal consistency with initially stated objectives
5.3 Dose Limiting Toxicities	Updated "during cycle 1" to "prior to initiation of cycle 2"	Clarity with intended meaning
6.1.2 Subject Exclusion Criteria 9.1.6.1 Adverse Event (AE) Monitoring 11.3 Common Terminology Criteria for Adverse Events V5.0 (CTCAE)	CTCAE "version 4.0" was updated to "version 5.0"	Internal consistency.
6.2 Trial Treatments	In the Arm C table (Table 9), updated decitabine dosing from 10 mg/m^2 to 20 mg/m^2	Internal consistency
7.3.2 Pralatrexate	CTCAE "version 4.0" was updated to "version 3.0"	Correction, as version 3.0 is used in the pralatrexate package insert
7.8.1 Prophylactic Measurements and Supportive Care	Removed restriction on G-CSF / GM-CSF during the first cycle of study treatment	Internal consistency (section 5.3, Dose-Limiting Toxicities) indicates this use is acceptable
8.0 Trial Flowchart 9.1.7.3 Pharmacokinetic/ Pharmacodynamic Evaluations	In all footnotes related to a window for pharmacokinetics, the +/- 30 minute window was updated to refer to the pharmacokinetic section (9.1.7.3) Section 9.1.7.3 was revised to provide exceptions to the 30 minute window for the End of Infusion (EOI) draw and the 30 minutes following EOI draw	Clarification on windows for pharmacokinetic blood collection
8.0 Trial Flowchart	A column for cycle 1 day 22 was added for Arms B and C to require a CBC with differential at this timepoint Footnote for cycle 1 day 22 CBC with differential lab was removed, as pembrolizumab is given at this timepoint, so CBC with differential should be collected at this timepoint consistently.	Improved safety for earlier intervention as needed
9.2.1 Time Period and Frequency for Collecting AE, SAE, and Other Reportable Safety Event Information	Removed some nonsense letters/numbers (a typo) from the section (EM5YT). These numbers/letters (the PI's username) was accidentally added in a previous amendment. Language was added to limit DLT reporting: DLTs prior to cycle 2 need to be reported to the UVA CC within 24 hours of identification of the DLT. DLTs occurring during/after Cycle 2 only	Correction and clarity on reporting expectations

	need to be reported as AEs.	
9.2.1.2 Adverse Event Reporting to Sponsor/UVA CC/GTcLC/DSMC	Renamed table from Table A to Table 17 Removed "Oncore", as AEs will be reported in Advarra	Internal consistency
10.1 Study Design, 10.5 Operating Characteristics	In Arm B, flat dosing was updated to be per m^2 throughout tables	Internal consistency

From 4/13/2021 to 09/28/2021

Section(s) revised	**Change(s)**
Title page	Updated site PI information for Beth Israel Deaconess Medical Center
Rationale: Update	
8.0 Trial Flow Chart	Removed columns where there were no assessments Merged columns for AE assessment and concomitant medications Removed concomitant medication review from long term follow-up Limited AE assessment in long term follow-up Added footnote to refer to section to make sure that all chemistry assessments are included and renamed to "Chemistry" Simplified vital signs line to be collected on days when either a physical exam is completed or treatment is received Removed labs from days that do not have drug administration or a physical exam (except in Cycle 1)
Rationale: AE assessment and reviews of concomitant medications is ongoing during study treatment, simplification and streamlining to collect all data that is needed for analysis (but not other data that aren't needed for analysis	

From 11/23/2020 to 04/13/2021

Section(s) revised	**Change(s)**
Title page	Dr. John Lister's information was updated Dr. O'Connor's role was updated to Co-Principal Investigator
Rationale: Corrections	
Statement of Compliance	Added a signature page
Rationale: To incorporate the signature page into the document	
6.1.2 Subject Exclusion Criteria	Exclusions #10 (pneumonitis/interstitial lung disease) and #18 (vaccines) were updated
Rationale: To be consistent with current pembrolizumab risks and Merck template language	
6.2 Trial Treatments 8.0 Trial Flowchart 7.3Pharmacokinetic/ Pharmacodynamic Evaluations	Updated to clarify that pralatrexate is administered by IV push (not infusion)
Rationale: Clarification	
7.3.1 Immune Related Adverse Events	Section title was revised Section was considerably revised to clarify stopping/holding rules for immune related adverse events
Rationale: To be consistent with risks associated with pembrolizumab and combinations including pembrolizumab according to the Merck template	

9.1.7.3 Pharmacokinetic/ Pharmacodynamic Evaluations	"and 48 hours" was removed from the text regarding timepoints for Arm A A sentence was added to allow a 90 minute window for the 24 hour after end of administration timepoint.
Rationale: Correction for consistency and a little more flexibility for the 24 hour timepoint	

From 11/03/2020 to 11/23/2020

Section(s) revised	**Change(s)**
2.1 Trial Design 3.1 Primary Objectives & Hypothesis 5.5 Efficacy Endpoints 9.1.6.5 Tumor Imaging and Assessment of Disease 10.1 Study Design	Efficacy, as assessed by ORR, has been moved to be a co-primary objective.
10.1 Study Design	Text has been added to clarify how participants will be assigned a dose level based on past DLTs and modeling The number of DLTs noted on Arm C so far was corrected and therefore the dose level that the next subject would be assigned was corrected Also, there were some changes to the table for clarity and to decrease confusion
10.2 Dose allocation	Additional text was added for clarification of the purpose of the table describing ordering of DLT probabilities
10.5 Operating characteristics	Tables have been reformatted for clarity

From 09/23/2020 to 11/03/2020 (11/03/2020 version reviewed by IRB as part of version date 11/23/2020)

Section(s) revised	**Change(s)**
1.0 Trial Summary	Number of trial subjects was revised to indicate "Maximum of 45"
2.1 Trial Design	Updated to indicate model-based dose escalation study with arms A & C based and combination allocation in Arm B will be conducted using a DLT-adapted partial order continual reassessment method upon a continual reassessment method. Removed references to 3x3 design and expansion phase.
2.2 Trial Diagram	Updated to reflect removal of expansion phase.
3 Objectives & Hypothesis	Shifted primary objectives from the expansion phase to secondary objectives. Removed references to Phase I, Expansion Phase, and de novo. Added "the efficacy, as determined by" in the second secondary objective.
5.1 Study Design	Updated to indicate CRM design. Removed references to 3+3 design and phase 1.
5.2.2 Pralatrexate	Updated to refer to section 10 for pralatrexate dosing.
5.2.3 Decitabine	Updated to refer to section 10 for decitabine dosing.
5.3 Dose Escalation and De-escalation Schema and Rule	Removed previous section in its entirety.
5.5 Efficacy Endpoints	Removed references phase 1 and expansion phase.
6.1.1 Subject Inclusion Criteria	Removed references to Phase I, Expansion Phase, de novo PTCL and de novo CTCL.
9.1.6.5 Tumor Imagin and Assessment of Disease	Removed references phase 1.
10 Statistical Considerations	Replaced previous Statistical Analysis Plan Section in its entirety.
Rationale: to reflect revised statistical analyses for a model-based phase I dose escalation study with no expansion phase.	

7.3 Resuming Administration of study drug	Removed previous section in its entirety.
Rationale: this section is redundant with section 7.2 bullet point two.	
Section 8.0	Clarified footnote 7 for all calendars to indicate that pretreatment biopsy would be collected per standard care and that post treatment biopsy would be optional. Removed concomitant medication review on Arm B calendar D22 cycles 1 & 4 as there are no other study activities required at that time point. Added the superscript 16 to address footnote 16 for Arm B calendar D22 cycles 2 & 5.
Section 13.0	Replaced references section previously omitted.
Section references, table references, and section headers were updated throughout the protocol document	
Rationale: Internal consistency	

From 08/25/2020 to 09/23/2020 (footer was also added to pages where it was missing)

Section(s) revised	**Change(s)**
Title page	Coordinating Center was updated to "Global T-cell Lymphoma Consortium (GTcLC) at the University of Virginia" "Participating Centers" was removed "Co-Investigator and Sponsor" was updated to "Co-Investigator and IND Holder" U.S. Subsites was updated to "Participating Sites" and UVA was added to this list The separate "Site Principal Investigators" section was removed and the Korea site was incorporated into the "Participating Sites" section. The Italian site was removed from the list.
Rationale: Most of the changes were made for clarification of what sites will participate and Dr. O'Connor's role as the IND Holder, since "Sponsor" can be interpreted to be the funding source. The Italian site will not be participating in the study after all.	
1.0 Trial Summary	"to maximum of 21" was added to the expansion phase for number of trial subjects
Rationale: At the request for this information by the UVA IRB-HSR	
8.0 Trial Flow Chart	Study Flowchart-Arm C, footnote 12 was updated to a black font color
Rationale: Readability	
9.2.1.3 Serious Adverse Event Reporting to Sponsor/UVA CC/GTcLC/DSMC/IRB 9.2.4.2 Unanticipated Problem Reporting 9.2.5.2 Reporting a Data Breach 9.2.6.4 Reporting of Protocol Deviations/Violations	Text relating to sites relying on UVA IRB-HSR was removed, as no outside sites will rely on UVA IRB-HSR
Rationale: Clarification	

From 11/20/2019 to 08/25/2020

Section(s) revised	**Change(s)**
Title Page 8.0 Trial Flowchart 9.1 Trial Procedures 9.1.7.3 Pharmacokinetic/ Pharmacodynamic Evaluations 9.1.10 Subject Registration	Site affiliation for Enrica Marchi, MD., Ph.D. and Owen O'Connor has been updated to UVA (University of Virginia) Enrica Marchi was updated to be the PI rather than Owen O'Connor. Owen O'Connor will remain as the IND Sponsor With Drs. Marchi and O'Connor at UVA, the Coordinating Center was transferred to UVA. Safety reporting requirements, data collection/entry and instructions for safety reporting were updated based on the UVA template

and Randomization 9.2 Data Reporting / Regulatory Requirements 9.3.2 Compliance & Monitoring 9.3.3 Study Monitoring (and subsection) 9.3.4 Study Records Retention Throughout	As CUMC was previously the coordinating site and PKs were only collected for CUMC participants, now with UVA being the coordinating site, PKs are only collected for UVA participants (trial Flowchart and 9.1.7.3) CUMC was revised to UVA in multiple sections
Rationale: The PI has changed and the new PI and Sponsor are now both affiliated with UVA. Accordingly, the coordinating center has also been moved to UVA so all safety reporting needed to be updated.	
9.1.8.1 Withdrawal/ Discontinuation 9.2 Data Reporting / Regulatory Requirements and subsections 11.5 Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting (and subsections)	Updated to current Merck template but removed option for retreatment and corresponding protocol section
Rationale: Participants will not have the option for retreatment, so this was revised for accuracy, and the safety reporting sections of the new Merck template were used as they fit better with safety UVA reporting.	
2.2 Trial Diagram	Statement was added to clarify that the days for pembrolizumab shown in the figure reflected cycle 1 only,
Rationale: For clarification : Pembrolizumab is given every 3 weeks, though the study is based on 4 week cycles.	
3.3 Exploratory objective 4.3.1 Pembrolizumab	“pembrolizumab” was corrected to “pralatrexate” Minor corrections to language for clarity
Rationale: Accuracy	
4.3.2 Pralatrexate 5.2 Agents Administration	Areas where “investigator’s brochure” or “package insert” are used were updated to include both terms where applicable.
Rationale: Clarification, as both options are available for some of the drugs used in this study.	
5.3 Dose Escalation and De-escalation Schema and Rule 5.4 Dose Limiting Toxicities	DLT definition was amended to remove the requirement for the DLT to occur in Cycle 1, though only cycle 1 DLTs will be used for the purposes of dose escalation and de-escalation
Rationale: Revised for accuracy, as AEs that meet the definition of a DLT should cause a dose delay, regardless of when they occur during study treatment.	
5.4 Dose Limiting Toxicities 5.5 Required Blood Parameters and Other Investigations Prior to Each Treatment	Revised for internal consistency and corrected based on AEs that may exist at the time of enrollment
Rationale: Internal consistency and accuracy	
7.2 Dose Delays 7.3 Resuming Administration of Study Drugs 7.4 Dose Modification (and subsections)	Revised for internal consistency: 2 week delay means study treatment discontinuation, so references to 3 and 12 weeks being cause for discontinuation of an individual drug were updated, “or baseline” was added to make these sections consistent with one another and the DLT definition, “or mucositis” was removed, as this exception is not true for pralatrexate, and febrile neutropenia specifics were added.

Rationale: Internal consistency	
7.8.2 Prohibited Concomitant Medications	"or pralatrexate (for participants assigned to an arm including pralatrexate)" was added as an exception to the prohibition of investigational agents for participants assigned to an arm that includes pralatrexate
Rationale: Correction for internal consistency	
7.10.3 Use in Pregnancy	Some reporting information was added to this section and a reference to a different section for reporting to Merck was added
Rationale: Updating to current Merck and UVA reporting templates	
7.11 Subject Withdrawal/Discontinuation Criteria 7.12 Clinical Criteria for Early Trial Termination	Notes were added to clarify that participants that are off any study treatment for >2 weeks for an adverse event are off all study treatment Corrected an incorrect section reference Corrected "study medication" to "pembrolizumab" as there are multiple study medications in this study.
Rationale: Internal consistency	
7.11 Subject Withdrawal/Discontinuation Criteria 7.11.1 Discontinuation of Study Therapy after CR	Removed references to the option of re-starting study treatment after completion of initial round of study medications
Rationale: Correction, as re-treatment following study treatment discontinuation is not an option for this study	
7.12 Clinical Criteria for Early Trial Termination	"study drug" was updated to "pembrolizumab" as Merck is only providing pembrolizumab for this study
Rationale: Accuracy	
8.0 Trial Flowchart	Multiple revisions to be internally consistent and improve safety monitoring: 1. Physical exam, vital signs and weight, CBC with differential, comprehensive serum chemistry panel, thyroid blood tests and ECOG status were added to the visit at discontinuation of treatment and 30-day safety follow-up 2. ECOG was added to day 1 for cycles 3,6,9,12, etc. 3. Thyroid testing was updated to occur at Day 1 of every other cycle (not every cycle). Footnotes were added/revised to 1. Include that laboratory screening tests do not need to be repeated at C1D1 if they are performed in the 10 day window and at other cycles they may be completed in the 72 hours prior to treatment. (Previously only elsewhere in the protocol) 2. Clarify that PKs are only required for UVA participants and that correlative blood draws on Day 8 and 15 only need to occur during cycle 1 3. Include requirements for data collection for participants that have an allogeneic SCT following participation. (Previously only elsewhere in the protocol) 4. Remove the need for CBC at Day 22 in later cycles (only where indicated for cycle 1 (or cycle 2 for Arms B and C)
Rationale: For internal consistency and adequate safety monitoring	
9.1.6.2 Physical Exam (previously "Full" Physical Exam)	The section was renamed and revised --level of physical exams (full vs directed) should be consistent with standard clinical care
Rationale: For consistency with standard clinical care. No designations for full vs. directed were included before this version either.	
9.3.2 Compliance and Monitoring	Some minor details were removed

Rationale: This level of detail may vary by site and these details will be available in a separate study reference manual	
10.0 Statistical Analysis Plan	Minor revisions were made for accuracy
Rationale: Accuracy	
Throughout document	Minor grammatical corrections Formatting of headers was corrected Section numbers were made into cross references/links and were corrected as necessary
Rationale: Internal consistency, readability and easier navigation	

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