CITY OF HOPE
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DEPARTMENT OF HEMATOLOGY AND HEMATOPOIETIC CELL TRANSPLANTATION

TITLE: A Phase 1/2 Study of Pembrolizumab plus Pralatrexate for Treatment of Relapsed or Refractory Peripheral T-cell Lymphomas

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DISEASE SITE: Peripheral T-cell Lymphoma

STAGE: Relapsed/Refractory

MODALITY(IES):

TYPE: Phase 1/2

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Clinical Trial Protocol

A Phase 1/2 Study of Pembrolizumab plus Pralatrexate for Treatment of Relapsed or Refractory Peripheral T-cell Lymphomas

Version Date:	05/25/2021
Protocol Version:	05
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Agents:	Pembrolizumab, Pralatrexate
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NCT Number:	NCT03598998
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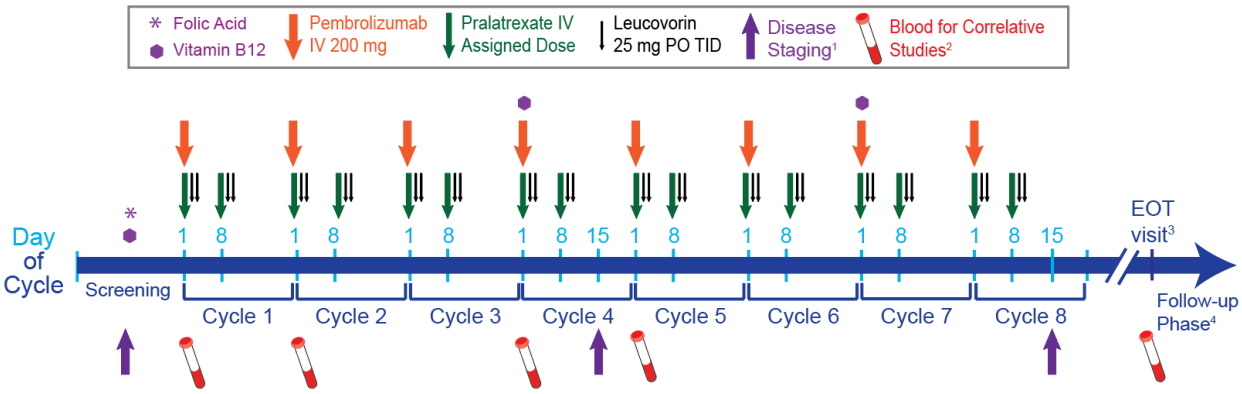
EXPERIMENTAL DESIGN SCHEMA



Each cycle = 21 days. Maximum duration of protocol therapy is 24 months.

Folic acid and Vitamin B12 supplementation is standard of care for pralatrexate therapy.

Folic acid is given daily during the course of therapy. Vitamin B12 is given every 3 cycles.

[1] Disease staging is performed at screening and every 4 cycles until disease progression or off study therapy. Disease staging will be by either PET/CT (preferred) or CT scan, but, if disease is FDG-avid, will be PET/CT at baseline, Cycle 4 and every 8 cycles thereafter. Refer to Study calendar and Section 11.1 for details.

2 Peripheral blood for correlative studies will be collected on C1D1, C2D1, C4D1, C5D1, and at EOT (refer to Table 9.3.1 for additional details).

[3] End of treatment visit.

[4] Follow-up Phase for patients who have completed treatment without disease progression will include staging every 12 weeks for the first year and every 18 weeks thereafter, until disease progression or off study.

PROTOCOL SYNOPSIS

Protocol Title

A Phase 1/2 Study of Pembrolizumab plus Pralatrexate for Treatment of Relapsed or Refractory Peripheral T-cell Lymphomas

Study Detail

Population/Indication(s):	Relapsed/Refractory Peripheral T-cell Lymphomas
Phase:	1/2
Sample Size:	Expected: 30 evaluable (Phase 1: 12 evaluable, Phase 2: 24 evaluable (including up to 6 patients from Phase 1 at RP2D) Maximum: 40
Estimated Accrual Duration:	48 months
Estimated Study Duration	6 years
Participant Duration:	Until progression, unacceptable toxicity, or withdrawal
Participating Sites:	• City of Hope Duarte, CA • University of Nebraska, NE • Emory University, GA
Study Agents:	Pembrolizumab, Pralatrexate
Sponsor:	City of Hope
Industry Partner:	Merck, Acrotech Biopharma, LLC

Rationale for this Study

Outcomes of patients with relapsed or refractory PTCL are dismal. Current therapies available for relapsed or refractory PTCL, including novel agents, are associated with poor response rates and short median progression-free survival, and few patients are salvaged by stem cell transplantation.[1-5] Novel therapies for relapsed or refractory PTCL are urgently needed. Because of inadequate response rates using novel therapies as single agents in PTCL, we anticipate that novel therapeutic combinations will be necessary to impact these aggressive and difficult-to-treat diseases.

In early studies evaluating PD-1/PD-L1 pathway inhibitors in PTCL and MF/CTCL, response rates of 15-40% have been observed. Therefore, these well-tolerated immunotherapy agents with a different mechanism of action compared to all other available drugs for treating T-cell lymphomas are a potential backbone on which to build a novel therapy combination. One logical combination partner for a PD-1/PD-L1 inhibitor in PTCL is the antifolate drug, pralatrexate. Antifolate agents, like pemetrexed, have immunologic effects which may result in synergy with PD-1 blockade, including activation of IFNγ-producing NK cells and, potentially, activation of CD8+ T-cells.[6,7] There is already clinical evidence of potential synergy between PD-1 inhibitors and anti-folate drugs. In a randomized phase II trial of patients with metastatic non-small cell lung cancer (NSCLC), patients treated with a PD-1 inhibitor, pembrolizumab, plus with carboplatin and an antifolate chemotherapy, pemetrexed, had a higher ORR (71%) than patients treated with pembrolizumab combined with carboplatin and paclitaxel (ORR 50%). (Gadgeel, ASCO 2015; Papadimitrakopoulou, ASCO 2014). We propose a phase 1/2 study to evaluate the safety and efficacy of combining pralatrexate with pembrolizumab for the treatment of relapsed or refractory aggressive PTCL.

Objectives

Primary Objective

- Evaluate the safety and tolerability of a regimen combining pembrolizumab and pralatrexate in patients with relapsed or refractory PTCL.
- Establish the maximum tolerated dose (MTD) and recommended phase II dose (RP2D) of the combined pralatrexate and pembrolizumab regimen.
- Estimate the overall response rate (ORR) according to the Lugano Classification[8] in patients treated with

pembrolizumab plus pralatrexate at the RP2D.

Secondary Objective

- Estimate the complete response (CR) rate according to the Lugano Classification,[8] duration of response (DOR), overall survival (OS) and progression-free survival (PFS) in patients treated with pembrolizumab plus pralatrexate.
- Estimate the ORR and CR rate according to the International Harmonization Project response criteria (Cheson 2007).[9]
- Evaluate responses and disease progression according to the Lymphoma Response to Immunomodulatory therapy Criteria (LYRIC).[10]

Exploratory Objective

- Explore immunologic and genomic biomarkers of response to pembrolizumab plus pralatrexate therapy.

Study Design

This is a prospective, single-arm, multi-center, open-label phase 1/2 study of pembrolizumab (MK-3475) plus pralatrexate in subjects with relapsed or refractory peripheral T-cell lymphomas (PTCL) that have failed at least one prior line of therapy.

The phase 1 dose-escalation portion of the study, with 2 dose levels and 1 possible de-escalation dose level, will determine the MTD and RP2D of the combination therapy. The starting dose will be 20 mg/m2 of pralatrexate on days 1 and 8 and 200 mg IV of pembrolizumab every 21 days, administered in 21-day cycles. The planned dose levels in the Phase 1 portion of the study are outlined in the table below. The phase 1 portion will use a modified rolling 6 design allowing 3 patients to be treated and evaluated for dose-limiting toxicity simultaneously, with up to 6 patients per dose level.

Dosing regimen and schedule

Dose level	Pembrolizumab (Day 1)	Pralatrexate (Days 1 and 8)
-1	200 mg IV	15 mg/m^2 IV
1	200 mg IV	20 mg/m^2 IV
2	200 mg IV	30 mg/m^2 IV

In the phase 2 portion, pembrolizumab will be administered at a dose of 200 mg IV and pralatrexate at the RP2D selected in the phase 1 portion following the same schedule. The phase 2 portion will use a Gehan two-stage design with advancement to the second stage based on ORR in the first stage.

In both phases, patients will receive up to 24 months of combined pembrolizumab and pralatrexate therapy. In both phases, Vitamin B12, Folic acid and Leucovorin will be administered as indicated in the study calendar and Section 5.13.2.

Evaluation Criteria and Endpoints

Response/progression

Disease response/progression will be evaluated using 2014 Lugano Classification[8,11]. Participants who meet the definition of progressive disease per Lugano Classification[8] should be evaluated using the LYRIC criteria[10]. The ORR and CR rate will also be estimated according to the International Harmonization Project response criteria (Cheson 2007).[9]

Primary Endpoints

- Dose limiting toxicity (DLT) (defined in Section 5.5). The DLT observation period will be 2 cycles. Toxicities will be graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE, Version 5.0).
- Overall response rate (ORR), per the Lugano classification.[8]

Secondary Endpoints

- Complete Response (CR) rate per the Lugano classification.[8]
- ORR and CR rate according to the International Harmonization Project response criteria (Cheson 2007).[9]
- Duration of Response (DOR).
- Overall Survival (OS).
- Progression-Free Survival (PFS).
- Toxicity: Toxicity and adverse events will be recorded using the NCI CTCAE 5.0 scale. Observed toxicities will be summarized by type (organ affected or laboratory determination such as absolute neutrophil count), severity (by NCI CTCAE v5.0 and nadir or maximum values for lab measures), date of onset, duration, reversibility, and attribution.
- Unacceptable Toxicity (defined in Section 11.2)

Statistical Considerations

Phase 1 portion

During the Phase 1 portion of the study, a modified, more conservative version of the Rolling 6 design of Skolnik et al will be employed. In this design, at most, 3 patients will be under observation for DLT on the current test dose level at any time. DLT observation period is 2 cycles. Patients who did not receive the doses of pembrolizumab during DLT period (not due to DLT), or those who missed any doses of pralatrexate during DLT period (not due to DLT) will be replaced. Once 3 patients are evaluable with no patient at that dose level experiencing a DLT, the dose can be escalated, or up to 3 additional patients may be treated at the current dose level. No more than 6 evaluable patients will be accrued to any dose level. Escalation will terminate as soon as ≥ 2 patients experience DLT at a given dose level. If 1/6 patients experience DLT at the current dose level, the dose will be escalated to the next higher level. If more than 1/6 patients experience DLT, then the next lower dose will be expanded. MTD will be declared the highest dose level at which 6 evaluable patients have been treated and, at most, 1/6 patients experiences DLT. The MTD will be considered the RP2D, unless the PI chooses a lower dose level, based on toxicity in subsequent cycles.

Phase 2 portion

In the phase 2 portion, patients will be treated at the RP2D. The phase 2 portion of this study will implement a Gehan two-stage design to estimate the ORR and to evaluate the activity of the combined regimen. Patients treated during the Phase 1 portion at the RP2D will be included in the Phase 2 evaluations if they are evaluable for response, defined as patients who received at least 1 dose of pembrolizumab and at least 1 dose of pralatrexate and had at least 1 disease assessment. The sample size is based on the desire to estimate the response rate with approximately 10% standard error, and early stopping if the combination is unexpectedly ineffective. In the pivotal PROPEL trial, the overall response rate (ORR) in 109 evaluable patients who received pralatrexate as a single agent was 29%, including 12 (11%) complete responses (CR) and 20 (18%) partial responses (PR).[5]

The phase 2 portion of the study is expected to evaluate a minimum of 7 and a maximum of 24 patients evaluable for response, including the patients treated at RP2D during the Phase 1 portion. At stage 1, if 0 responses are seen in the first 7 patients (including up to 6 patients enrolled during the Phase 1 portion that are evaluable for response), the study will be terminated and the true ORR will be declared ≤35%. If at least 1 patient responds, the trial will continue to the second stage. At stage 2, a total of 24 patients will be evaluated (including up to 6 patients enrolled during the Phase 1 portion that are evaluable for response).

This design provides for estimation of the response rate with approximately 10% standard error. The standard error will be 9.4%-10.2% after 24 patients if the ORR rate is 30%-70%. Under this design if the ORR is >35%, there would be ≥95% chance of at least one response among the first 7 patients.

Safety Analysis and Stopping Rules for Excessive Toxicity or Rapid Disease Progression

Because of the unique immune-related adverse events (IrAEs) observed with checkpoint inhibitors, we will monitor for "Unacceptable toxicity" (defined in Section 11.2) and treatment-related mortality at any time during study treatment with this new combination of drugs. This monitoring will include all patients treated on the study regardless of the dose levels they were on. The expected rate of "unacceptable toxicity" should not be >33%. If the rate of "unacceptable toxicity" is >33% after at least 6 patients are treated on study at any bi-annual safety review, or if a 2nd death that is at least possibly related to study treatment occurs regardless of the number of patients on study, accrual will be halted and a full review of these events will be performed by the City of Hope Data Safety Monitoring Committee (DSMC). Patient accrual will not resume until approved by the DSMC to do so. These rules are in addition to the bi-annual review of all toxicities submitted to the City of Hope Data Safety Monitoring Committee (DSMC). Patients with ongoing toxicity will be followed until resolution or stability.

In addition, because of the evidence that PD-1 may act as a tumor suppressor in preclinical T-cell lymphoma models and the recent reports of rapid disease progression in patients with ATLL, a subtype of PTCL, we will also monitor for rapid progression of disease. If at any bi-annual safety review during the conduct of the study, and after at least 3 patients are treated on study, > 33% of patients who received at least one dose each of pembrolizumab and pralatrexate experience rapid progression, the study accrual will be halted and a full review of these events will be performed by the City of Hope Data Safety Monitoring Committee (DSMC). Patient accrual will not resume until approved by the DSMC to do so.

Abbreviated Eligibility Criteria

Main Inclusion Criteria

- Age 18 or older

- ECOG performance status of 0 or 1.

- Patients must have a histologically confirmed diagnosis of mature peripheral T-cell or NK-cell lymphoma according to the WHO classification, including transformed mycosis fungoides, with hematopathology review at the participating institution. Refer to Section 3.1 for a full list of eligible histologies.

- Patients must have failed at least one prior regimen.

- Patient must have measurable disease by CT or PET scan, with one or more sites of disease ≥ 1.5cm in longest dimension.

- Be willing to provide tissue from a fresh core or excisional biopsy (performed as standard of care) of a tumor lesion prior to starting study therapy or from archival tissue of a biopsy that was performed after the most recent systemic therapy. Exception can be granted by the PI if a biopsy is not feasible and/or safe.

- Patients must have received one dose of Vitamin B12 (1 mg IM) within 10 weeks prior to first dose of

pralatrexate, and must have begun folic acid supplementation (1 mg orally, once daily) within 10 days of first dose of pralatrexate. Note: if folic acid was not started but MMA and HCY levels were checked and are in normal range at screening, the investigator can decide to start study therapy immediately. Vitamin B12 and folic acid supplementation is standard of care for pralatrexate therapy.

- Adequate hematological, renal, and hepatic function.

- Female of childbearing potential: negative urine or serum pregnancy test within 72 hours prior to receiving the first dose of study medication.

- Agreement to use effective methods of contraception for both women of childbearing potential and male patients during the study and through 6 months post-last dose of pralatrexate for women and 3 months post-last dose of pralatrexate for man, and 120 days post-last dose of pembrolizumab for both women and men.

Main Exclusion Criteria

- Patients with adult T-cell leukemia/lymphoma.

Prior Therapy and Concomitant Therapy

- Prior allogeneic hematopoietic stem cell transplantation within the last 5 years.

- Prior autologous hematopoietic stem cell transplant within the last 60 days.

- Patients who received prior therapy with an anti-PD-1, anti-PD-L1, or anti-PD-L2 agent without having had evidence of objective response.

- Patients who received prior therapy with pralatrexate without having had evidence of objective response.

- Investigational agent or anti-cancer monoclonal antibody (mAb) within 21 days prior to Day 1 of therapy or who has not recovered (i.e. ≤1 or at baseline) from adverse events due to agents administered more than 21 days earlier.

- Prior chemotherapy, targeted small molecule therapy, or radiation therapy within 14 days prior to Day 1 of therapy or who has not recovered (i.e. ≤1 or at baseline) from adverse events due to a previously administered agent. Note: Subjects with ≤ Grade 2 neuropathy are an exception and may qualify for the study.

- Antineoplastic biologic therapy or major surgery within 21 days of the first dose of trial medication. If subjects received major surgery more than 21 days ago, they must have recovered adequately from the toxicity and/or complications from the intervention prior to starting therapy.

- Received live vaccine or live-attenuated vaccine within 30 days prior to Day 1 of protocol therapy. Administration of killed vaccines is allowed.

- Systemic steroid therapy or on any other form of immunosuppressive therapy within 7 days prior to the first dose of trial treatment.

Other Illnesses and Conditions

- Diagnosis of immunodeficiency.

- 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.

- Congestive heart failure Class III/IV according to the New York Heart Association (NYHA) Functional Classification.

- Known severe hypersensitivity reaction to pembrolizumab, pralatrexate, leucovorin or any excipients.

- Active autoimmune disease that has required systemic treatment in the past 2 years (replacement therapies for hormone deficiencies are allowed). Hemolytic anemia associated with the lymphoma does not exclude a patient from the study.

- Known history of HIV (HIV ½ antibodies).

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

- History of active TB infection (Bacillus Tuberculosis).

- Active central nervous system (CNS) involvement by lymphoma, including parenchymal and/or lymphomatous meningitis.

- Has a history of (non-infectious) pneumonitis/interstitial lung disease that required steroids or current pneumonitis/interstitial lung disease

- Active, uncontrolled infection requiring systemic therapy.

- Female: Pregnant or breastfeeding

- 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

Investigational Product Dosage and Administration

- Pembrolizumab 200 mg IV on Day 1 of each cycle.
- Pralatrexate 15, 20, or 30 mg/m^2 (according to dose level) on Days 1 and 8 of each cycle.
- 1 cycle = 21 Days.

Clinical Observations and Tests to be Performed

- Medical history and physical exam
- Safety assessments (CBCs with differential, comprehensive chemistry panel, thyroid function and coagulation)
- PET-CT
- CT/ MRI scans
- Correlative tumor tissue and blood samples.

TABLE OF CONTENTS

LIST OF TABLES AND FIGURES

ABBREVIATIONS

Abbrevation	Meaning
AE	Adverse Event
ALT	Alanine Aminotransferase
ANC	Absolute Neutrophil Count
AST	Aspartate Aminotransferase
C	Cycle
CFR	Code of Federal Regulations
COH	City of Hope
CR	Complete Response
CRA	Clinical Research Associate
CRF	Case Report Form
CTCAE	Common Terminology Criteria for Adverse Events
CTEP	Cancer Therapy Evaluation Program
CTMS	Clinical Trial Management System
DSMC	Data Safety Monitoring Committee
ECOG	Eastern Cooperative Oncology Group
EOT	End of Treatment
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HCY	Homocysteine
IB	Investigator Brochure
ICF	Informed Consent Form
IND	Investigational New Drug
IR	Indeterminate Response
irAE	Immune-related adverse event
IRB	Institutional Review Board
IV	Intravenous
LYRIC	Lymphoma Response to Immunomodulatory Therapy Criteria
MMA	Methylmalonic acid
PD	Progressive Disease
PFS	Progression-Free Survival
PI	Principal Investigator
PMT	Protocol Monitoring Team
PR	Partial Response
PTCL	Peripheral T-Cell Lymphoma
SAE	Serious Adverse Event
SD	Stable Disease
WHO	World Health Organization

1.0 OBJECTIVES

1.1 Primary Objectives

- Evaluate the safety and tolerability of a regimen combining pembrolizumab and pralatrexate in patients with relapsed or refractory PTCL.
- Establish the maximum tolerated dose (MTD) and recommended phase II dose (RP2D) of the combined pralatrexate and pembrolizumab regimen.
- Estimate the overall response rate (ORR) according to the Lugano Classification[8] in patients treated with pembrolizumab plus pralatrexate at the RP2D.

1.2 Secondary Objectives

- Estimate the complete response (CR) rate according to the Lugano Classification[8], duration of response (DOR), overall survival (OS) and progression-free survival (PFS) in patients treated with pembrolizumab plus pralatrexate.
- Estimate the ORR and CR rate according to the International Harmonization Project response criteria (Cheson 2007).[9]
- Evaluate responses and disease progression according to the Lymphoma Response to Immunomodulatory therapy Criteria (LYRIC).[10]

1.3 Exploratory Objectives

- Explore immunologic and genomic biomarkers of response to pembrolizumab plus pralatrexate therapy.

2.0 BACKGROUND

2.1 Introduction/Rationale for Development

2.1.1 Disease Under Study: Peripheral T-cell Lymphoma

Peripheral T-cell lymphomas (PTCL) are an uncommon group of disorders, accounting for about 10% of all non-Hodgkin lymphomas (NHL). EBV-associated extranodal NK/T-cell lymphoma (NKTCL) is more common in parts of Asia and South America, while angioimmunoblastic T-cell lymphoma (AITL) and peripheral T-cell lymphoma, not otherwise specified (PTCL NOS) are more common in Western countries.[12] TCLs are generally associated with poor outcomes after standard therapy, with variation in prognosis according to disease subtype.[12] ALK-expressing anaplastic large cell lymphomas (ALCL) have a favorable prognosis with 5-year survival exceeding 80%, though some studies suggest outcomes in ALCL are dependent on age rather than ALK status.[12-14] Anthracycline-based induction combination chemotherapy is standard upfront treatment for patients with PTCL; however, with the exception of ALK-positive ALCL, relapse rates are high.[15-17] Autologous hematopoietic stem cell transplantation (ASCT) is widely used as consolidation for PTCL patients in first remission to reduce the risk of relapse. Single-arm prospective and retrospective studies of consolidative ASCT for TCLs in 1st remission report improvements in survival compared to historical controls, but progression-free survival (PFS) remains low, ranging from 44-58% at 3-5 years.[2,18-21] Outcomes are poorer in patients who undergo ASCT with relapsed PTCL, with 3-5 year PFS ranging from 32-41%.[1,2]

Current approved therapies available for relapsed or refractory TCLs include histone deacetylase inhibitors (romidepsin and belinostat), pralatrexate, and brentuximab vedotin (for ALCL). With the exception of brentuximab vedotin for ALCL, these agents are associated with low response rates and short median progression free survival.[3-5]

In the pivotal PROPEL trial, 115 heavily pre-treated PTCL patients (median 3 prior systemic therapies) received pralatrexate as a single agent. The overall response rate (ORR) in 109 evaluable patients was 29%, including 12 (11%) complete responses (CR) and 20 (18%) partial responses (PR), with a median remission duration of 10.1 months. Median PFS and OS were 3.5 and 14.5 months, respectively. The most common grade 3/4 adverse events were thrombocytopenia (32%), mucositis (22%), neutropenia (22%), and anemia (18%).[5]

Romidepsin is a histone deacetylase (HDAC) inhibitor that has been approved for the treatment of PTCL and cutaneous T-cell lymphoma (CTCL). Of the 131 patients enrolled in the pivotal phase II trial, 130 had histologically confirmed PTCL by central review. The objective response rate was 25% (33 of 130), including 15% (19 of 130) with CR/CRu. The median duration of response was 17 months, with the longest response ongoing at 34+ months. Of the 19 patients who achieved CR/CRu, 17 (89%) had not experienced disease progression at a median follow-up of 13.4 months. The most common grade ≥ 3 adverse events were thrombocytopenia (24%), neutropenia (20%), and infections (all types, 19%).[3]

Belinostat is a potent hydroxamic acid-derived pan-HDAC inhibitor. It was evaluated in an open-label phase II study. A total of 129 relapsed/refractory PTCL patients received 1000 mg/m^2 belinostat infusion on days 1–5 of every 3-week cycle. Among 120 evaluable patients, the ORR was 26%, including 10% CR, and median response duration was 8.3 months. The most common grade 3–4 AEs were thrombocytopenia (13%), neutropenia (13%), and anemia (10%). This agent can be used even in patients who have a decreased platelet count.[22]

Brentuximab vedotin is FDA-approved for relapsed CD30 expressing systemic anaplastic large cell lymphoma.[23] Of 58 patients treated in the study, 50 patients (86%) achieved an objective response, 33 patients (57%) achieved a complete remission (CR), and 17 patients (29%) achieved a partial remission. The median durations of overall response and CR were 12.6 and 13.2 months, respectively. Grade 3 or 4 adverse events in ≥10% of patients were neutropenia (21%), thrombocytopenia (14%), and peripheral sensory neuropathy (12%).

With high relapse rates after standard therapy including ASCT and inadequate second line treatment options, novel therapies are for relapsed or refractory PTCL are urgently needed.

2.1.2 PD-1/PD-L1 Pathway in Lymphoma

The programmed death receptor-1 (PD-1) pathway is an immune checkpoint that normally serves to dampen immune responses in tissues. PD-1 is expressed on activated T-cells and binds its ligands, PD-L1 and PD-L2, on tissue cells or antigen presenting cells to decrease T-cell activation, proliferation, and survival.[24] Tumor cells can co-opt this pathway to evade attack by the host immune system.[24] A wide range of hematologic malignancies express PD-1 or PD-L1, including Hodgkin's lymphoma (HL),[25] diffuse large B-cell lymphoma (DLBCL),[26] primary mediastinal B-cell lymphoma (PMBCL),[25,27] follicular lymphoma (FL),[28] chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL),[29] peripheral T-cell lymphomas (PTCL),[30-34] multiple myeloma (MM),[35] acute myelogenous leukemia (AML),[36,37] and myelodysplastic syndrome (MDS).[38,39] In addition, molecular analyses have demonstrated that genetic alterations involving

PD-L1 and its overexpression are critical in the pathogenesis of HL, PMBCL, and Epstein-Barr virus-associated post-transplant lymphoproliferative disorders.[25,40]

Inhibitors of PD-1 and PD-L1 have produced clinical responses in early-phase studies in patients with a range of lymphomas, including HL, DLBCL, and FL. Pidilizumab (CureTech, Yavne, Israel) produced responses as a single-agent in patients with rel/ref FL, CLL, and HL, in a phase I study,[41] and yielded a 66% ORR when used in combination with rituximab in patients with relapsed or refractory FL in a phase II study.[42] A phase Ib study of nivolumab demonstrated an 87% overall response rate (ORR) and 100% clinical benefit rate in 23 patients with relapsed or refractory HL.[43] A subsequent phase II study of nivolumab in 80 patients who failed ASCT as well as prior brentuximab vedotin confirmed a high ORR of 66%, with 9% of patients having a complete response per independent review. Notably, the majority of responders remained in remission at the time of censoring, thus a significant proportion of responses appear to be durable.[44] A phase Ib study of pembrolizumab in 31 patients with rel/ref HL who failed prior brentuximab vedotin demonstrated a 65% ORR with 16% of patients achieving CR.[45] A phase II study of pembrolizumab in patients with rel/ref HL is ongoing, but interim reports have demonstrated an ORR of 70%.[46] Similarly, in a phase Ib study of nivolumab, a 36% ORR was observed in patients with rel/ref DLBCL, and a 40% ORR was observed in patients with rel/ref FL.[47] In an early interim analysis, the PD-L1 inhibitor, atezolizumab, in combination with obinutuzumab produced a 15% ORR in patients with rel/ref DLBCL or FL. 23 patients with T-cell lymphoma were enrolled in the phase I study of nivolumab, including 13 patients with mycosis fungoides (MF)/CTCL and 5 patients with relapsed or refractory peripheral PTCL. The ORR was 40% in relapsed or refractory PTCL and 15% in CTCL. However, 69% of CTCL patients had stable disease, resulting in a clinical benefit rate of 84%. In addition, interim results from a phase 2 study of pembrolizumab in patients with MF/CTCL were presented at ASH 2016 by Khodadoust et al., and pembrolizumab produced a 38% ORR in patients with MF/CTCL.

2.2 Pembrolizumab

Pembrolizumab is a monoclonal antibody that binds PD-1 and inhibits the interaction between PD-1 and its ligands. The programmed death receptor-1 (PD-1) pathway is an immune checkpoint that normally serves to dampen immune responses in tissues. PD-1 is expressed on activated T-cells and binds its ligands, PD-L1 and PD-L2, on tissue cells or antigen presenting cells to decrease T-cell activation, proliferation, and survival[24]. Tumor cells can co-opt this pathway to evade attack by the host immune system[24]. Phase I studies of pembrolizumab in solid tumors and hematologic malignancies have demonstrated that the medication is safe, well-tolerated, and effective for treating classical Hodgkin lymphoma [Moskowitz, ASH 2014]. The ongoing KEYNOTE-013 study is evaluating pembrolizumab for treatment of other lymphoma subtypes, myelodysplastic syndrome, and multiple myeloma.

The PD-1 pathway is an attractive therapeutic target in PTCLs:

- PD-1 or PD-L1 are over-expressed in angioimmunoblastic T-cell lymphoma (AITL), peripheral T-cell lymphoma, not otherwise specified (PTCL-NOS), ALCL, extranodal NK/T-cell lymphoma, and HTLV-associated adult T-cell lymphoma/leukemia[30-34].
- PD-1 inhibitors have produced clinical responses in early-phase studies in patients with a range of lymphomas, including PTCL [41-43,48-50].
- Interim results from a phase 1 study of Nivolumab (Bristol-Myers Squibb, New York, NY) presented at the 2014 ASH annual meeting demonstrated a 40% ORR (2/5 patients) in relapsed or refractory PTCLs (Lesokhin, ASH 2014).

While responses to PD-1/PD-L1 inhibition have been observed in patients with NHL, there is room for improvement. The reported ORRs to single-agent PD-1/PD-L1 inhibition are ~35-40%, with a low CR rate (~0-10%). Given the responses to PD-1/PD-L1 inhibition observed across lymphoma subtypes, the addition of synergistic agents may result in deeper and more durable responses.

However, it should be noted that a recent report described evidence of rapid progression of disease after treatment with an anti-PD-1 antibody in patients with adult T-cell leukemia-lymphoma (ATLL), which is a subtype of PTCL. All 3 patients with ATLL treated on a phase 2 clinical trial of nivolumab experienced rapid clinical progression of disease with leukocytosis, hypercalcemia, renal dysfunction, and elevated lactate dehydrogenase levels. Concurrently, HTLV-1 proviral loads were noted to be increased in 2 patients and 2 patients also developed circulating atypical lymphocytes and hyperbilirubinemia.[51] In a separate study, using a mouse model of human T-cell lymphoma, it was demonstrated that PD-1 can function as a tumor suppressor.[52] Although, thus far, this phenomenon of rapid progression after anti-PD-1 therapy has only been described in ATLL, it is theoretically possible in other PTCL subtypes.

2.3 Pralatrexate

Pralatrexate is a potent antifolate that is FDA-approved for the treatment of relapsed or refractory PTCL. In the pivotal PROPEL trial, pralatrexate resulted in an ORR of 29% in heavily pre-treated PTCL patients, including 11% complete responses (CR) and 18% partial responses (PR), with a median remission duration of 10.1 months.
Pralatrexate is a folate analogue metabolic inhibitor that competitively inhibits the enzyme dihydrofolate reductase (DHFR). The activity of DHFR is critical to catalyze the reduction of dihydrofolate (DHF) to tetrahydrofolate (THF), which in turn is required for deoxyribonucleic acid (DNA) synthesis. This mechanism of action results in a potential for broad spectrum cytotoxic activity against tumor cells and rapidly dividing nucleated cells.

<u>Treatment-limiting toxicity with pralatrexate:</u>
Mucositis is the most frequent and treatment-limiting adverse event (AE) associated with the administration of pralatrexate. In the pivotal PDX-008 study in the approved R/R PTCL indication (n=111), the ORR was 27%. Overall, mucositis was observed in approximately 70% of patients (Grade 1 or 2=50%, Grade 3 or 4=21%) and generally occurred early in the first cycle of treatment. Dose omissions and reductions due to mucositis occurred in 41% of patients with Grade 1 or 2 mucositis and in 23% of patients with Grade 3 or 4 mucositis.[53] Mucositis was also observed at pralatrexate doses as low as 15 mg/m2 given 3 weeks out of 4 weeks in Study PDX-010 (n=29), in which 59% of patients with cutaneous T-cell lymphoma (CTCL) developed mucositis (Grade 1 or 2=38%, Grade 3=21%). Study PDX-010 also tested a pralatrexate dose of 10 mg/m2, which was deemed to be a suboptimal starting dose. Among the 10 patients treated at this dose, 50% experienced Grade 1 or 2 mucositis, but no severe (Grade 3 or 4) mucositis was reported.[54] Given these results, mucositis is considered a serious treatment-limiting toxicity observed with pralatrexate treatment at doses ≥15 mg/m2.

No biomarker or other prognostic indicator has been identified to predict a patient's likelihood of developing mucositis with pralatrexate treatment. Homocysteine (Hcy) and methylmalonic acid (MMA) levels at Baseline have been studied for correlation with subsequent development of mucositis. In one study, the investigators found that MMA levels were a predictor of the grade of mucositis that

developed,[55] but results from other studies have been inconclusive.[56] For additional information, see the current Investigator's Brochure for pralatrexate.[57]

Leucovorin, which is approved as an antidote for the toxicity from folic acid antagonists, including pralatrexate, will thus be administered. Vitamin B12 and Folic acid supplementation will be given as well.

2.4 Leucovorin

Leucovorin is the reduced form of a racemic mixture of diasterioisomers of folic acid, which is readily converted to other reduced folic acid derivatives (eg, tetrahydrofolate).[58] Because leucovorin does not require reduction by DHFR as folic acid does, leucovorin is not affected by blockage of DHFR by folic acid antagonists, including pralatrexate. This allows purine and thymidine synthesis to take place in the presence of pralatrexate or other DHFR inhibitors (eg, MTX), and thus DNA, RNA, and protein synthesis can occur. Leucovorin may also limit pralatrexate action on normal cells by competing with pralatrexate for the same transport processes into the cell. Leucovorin is approved as an antidote for the toxicity from folic acid antagonists, including pralatrexate. Allergic sensitization, including anaphylactoid reactions and urticaria, has been reported following the administration of both oral and parenteral leucovorin.[58] The use of leucovorin as a reactive rescue treatment for pralatrexate-induced mucositis has been evaluated in patients with PTCL.[59] Patients with Grade 2+ mucositis received leucovorin 25 mg orally (PO) every 6 hours for 5 days in the week of pralatrexate-induced mucositis and treatment was stopped at least 48 hours prior to the administration of the next pralatrexate dose. All interventions (n=17) resulted in subjective improvement of mucositis by Day 4 following leucovorin treatment and 94% (16 of the 17) of interventions resulted in complete resolution of the mucositis by Day 7. None of these patients discontinued treatment with pralatrexate due to mucositis.[59] In addition, there is evidence that proactively treating patients with leucovorin (50 mg IV) 24 hours after pralatrexate administration could prevent or reduce pralatrexate-induced oral mucositis. Three patients with CTCL, who were preemptively treated with single IV doses of leucovorin, 24 hours after pralatrexate administration, showed no mucositis.[60]

2.5 Overview and Rationale of Study Design

<u>Rationale for study combination:</u>

Outcomes of patients with relapsed or refractory PTCL are dismal. Current therapies available for relapsed or refractory PTCL, including novel agents, are associated with poor response rates and short median progression-free survival, and few patients are salvaged by stem cell transplantation.[1-5] Novel therapies for relapsed or refractory PTCL are urgently needed. Because of inadequate response rates using novel therapies as single agents in PTCL, we anticipate that novel therapeutic combinations will be necessary to impact these aggressive and difficult-to-treat diseases.

In early studies evaluating PD-1/PD-L1 pathway inhibitors in PTCL and MF/CTCL, response rates of 15-40% have been observed. Therefore, these well-tolerated immunotherapy agents with a different mechanism of action compared to all other available drugs for treating T-cell lymphomas are a potential backbone on which to build a novel therapy combination. One logical combination partner for a PD-1/PD-L1 inhibitor in PTCL is the antifolate drug, pralatrexate. Antifolate agents, like pemetrexed, have immunologic effects which may result in synergy with PD-1 blockade, including activation of IFNγ-producing NK cells and, potentially, activation of CD8+ T-cells.[6,7] There is already clinical evidence of potential synergy between PD-1 inhibitors and anti-folate drugs. In a randomized phase II trial of patients with metastatic non-small cell lung cancer (NSCLC), patients treated with a PD-1 inhibitor, pembrolizumab, plus with carboplatin and

an antifolate chemotherapy, pemetrexed, had a higher ORR (71%) than patients treated with pembrolizumab combined with carboplatin and paclitaxel (ORR 50%). (Gadgeel, ASCO 2015; Papadimitrakopoulou, ASCO 2014). We propose a phase 1/2 study to evaluate the safety and efficacy of combining pralatrexate with pembrolizumab for the treatment of relapsed or refractory aggressive PTCL.

3.0 ELIGIBILITY CRITERIA

Participant MRN (COH Only):	Participant Initials (F, M, L):
Institution:	

Participants must meet all of the following criteria on screening examination to be eligible to participate in the study:

3.1 Inclusion Criteria

Informed Consent and Willingness to Participate

__1. Documented willingness and ability to sign an informed consent of the participant and/or Legally Authorized Representative

Age Criteria and Performance Status

__2. Age 18 or older

__3. ECOG performance status of 0 or 1.

Nature of Illness and Disease Status Criteria

__4. Patients must have a histologically confirmed diagnosis of mature peripheral T-cell or NK-cell lymphoma according to the WHO classification, with hematopathology review at the participating institution. Eligible histologies are:

- Peripheral T-cell lymphoma, not otherwise specified
- Anaplastic large cell lymphoma, ALK-negative
- Anaplastic large cell lymphoma, ALK-positive
- Angioimmunoblastic T-cell lymphoma
- Nodal peripheral T-cell lymphoma with TFH phenotype
- Follicular T-cell lymphoma
- Indolent T-cell lymphoproliferative disorder of the GI tract
- Extranodal NK-/T-cell lymphoma
- Enteropathy-associated T cell lymphoma
- Monomorphic epitheliotropic intestinal T-cell lymphoma
- Hepatosplenic T-cell lymphoma
- Subcutaneous panniculitis-like T-cell lymphoma
- Transformed mycosis fungoides

__5. Patients must have failed at least one prior regimen, including:

- Recurrence of disease after a documented complete response (CR)
- Progression of disease after a partial response (PR) to the prior regimen
- Partial response, stable disease (SD) or progressive disease (PD) at the completion of the prior treatment regimen. If a patient has PR to prior regimen without PD, there must be biopsy-proven* residual disease that is measurable (see #6 below)

  * Exception can be granted by the PI if a biopsy is not feasible and/or safe.

__6. Patient must have measurable disease by CT or PET scan, with one or more sites of disease ≥ 1.5cm in longest dimension.

__7. Be willing to provide tissue from a fresh core or excisional biopsy (performed as standard of care) of a tumor lesion prior to starting study therapy or from archival tissue of a biopsy that was performed after the most recent systemic therapy. Exception can be granted by the PI if a biopsy is not feasible and/or safe.

Participant MRN (COH Only):	Participant Initials (F, M, L):
Institution:	

__8. Patients must have received one dose of Vitamin B12 (1 mg IM) within 10 weeks prior to first dose of pralatrexate, and must have begun folic acid supplementation (1 mg orally, once daily) within 10 days of first dose of pralatrexate. Note: if folic acid was not started but MMA and HCY levels were checked and are in normal range at screening, the investigator can decide to start study therapy immediately. Vitamin B12 and folic acid supplementation is standard of care for pralatrexate therapy.

Clinical Laboratory Criteria

__9. ANC ≥ 1,000/mm^3. In Phase 2 portion of study, ANC < 1000/mm^3 but ≥ 500/mm^3 is allowable if patients have demonstrated bone marrow involvement by lymphoma. **NOTE:** Growth factor is not permitted within 7 days of ANC assessment unless cytopenia is secondary to disease involvement.	ANC:	Date:
__10. Platelets ≥ 75,000/mm^3. In Phase 2 portion of study, Platelets < 75,000/mm^3 but ≥ 25,000/mm^3 is allowable if patients have demonstrated bone marrow involvement by lymphoma. **NOTE:** Platelet transfusions are not permitted within 7 days of platelet assessment unless cytopenia is secondary to disease involvement.	Plts:	Date:
__11. Total serum bilirubin ≤ 1.5X ULN OR Direct bilirubin ≤ ULN for subjects with total bilirubin levels > 1.5 ULN, unless has Gilbert's disease or hepatic involvement by lymphoma	ULN: Bil:	Date:
__12. AST ≤ 2.5 x ULN OR ≤ 5 X ULN for subjects with hepatic involvement by lymphoma as the etiology of transaminase elevation	ULN: AST:	Date:
__13. ALT ≤ 2.5 x ULN OR ≤ 5 X ULN for subjects with hepatic involvement by lymphoma as the etiology of transaminase elevation	ULN: ALT:	Date:
__14. Creatinine clearance of ≥ 60 mL/min per the Cockcroft-Gault formula. If CrCl is ≥ 60 mL/min as measured by 24 hour urine collection, this will be allowable. $\text{CrCl (mL/min)} = \frac{(140\text{-age}) \times \text{actual body weight (kg)}}{72 \times \text{serum creatinine (mg/dL)}}$ **(x 0.85 for females)** **Or** $\text{CrCl (mL/min)} = \frac{(140\text{-age}) \times \text{actual body weight (kg)}}{0.8136 \times \text{serum creatinine (umol/L)}}$ **(x 0.85 for females)**	Cr Clearance:	Date:
__15. **If not receiving anticoagulants**: International Normalized Ratio (INR) OR Prothrombin (PT) ≤ 1.5 x ULN **If on anticoagulant therapy**: PT must be within therapeutic range of intended use of anticoagulants	ULN: INR: PT:	Date:
__16. **If not receiving anticoagulants**: Activated Partial Thromboplastin Time (aPTT) ≤ 1.5 x ULN **If on anticoagulant therapy**: aPTT must be within therapeutic range of intended use of anticoagulants	ULN: aPTT:	Date:

Participant MRN (COH Only):	Participant Initials (F, M, L):
Institution:	

__17. **Female of childbearing potential**: negative urine or serum pregnancy test 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	Urine:	Serum:	Date:

Contraception

__18. *Woman of childbearing potential (WOCBP)*: use two effective methods of contraception (hormonal or barrier method) or be surgically sterile, or abstain from heterosexual activity for the course of the study through 6 months post last dose of pralatrexate and 120 days post last dose of pembrolizumab. WOCBP defined as not being surgically sterilized or have not been free from menses for >1 year.
Male: use two effective methods of contraception (barrier method) or abstain from heterosexual activity with the first dose of study therapy through 3 months post last dose of pralatrexate and 120 days post last dose of pembrolizumab.

Refer to Appendix E for Contraception Guidelines.

3.2 Exclusion Criteria

Nature of Illness and Disease Status Criteria

__1. Patients with adult T-cell leukemia/lymphoma

Prior Therapy and Concomitant Therapy

__2. Prior allogeneic hematopoietic stem cell transplantation within the last 5 years.

__3. Prior autologous hematopoietic stem cell transplant within the last 60 days.

__4. Patients who received prior therapy with an anti-PD-1, anti-PD-L1, or anti-PD-L2 agent without having had evidence of objective response.

__5. Patients who received prior therapy with pralatrexate without having had evidence of objective response.

__6. Investigational agent or anti-cancer monoclonal antibody (mAb) within 21 days prior to Day 1 of therapy or who has not recovered (i.e. ≤1 or at baseline) from adverse events due to agents administered more than 21 days earlier.

__7. Prior chemotherapy, targeted small molecule therapy, or radiation therapy within 14 days prior to Day 1 of therapy or who has not recovered (i.e. ≤1 or at baseline) from adverse events due to a previously administered agent. Note: Subjects with ≤ Grade 2 neuropathy are an exception and may qualify for the study.

__8. Antineoplastic biologic therapy or major surgery within 21 days of the first dose of trial medication. If subjects received major surgery more than 21 days ago, they must have recovered adequately from the toxicity and/or complications from the intervention prior to starting therapy.

__9. Received live vaccine or live-attenuated vaccine within 30 days prior to Day 1 of protocol therapy. Administration of killed vaccines is allowed.

__10. Systemic steroid therapy or on any other form of immunosuppressive therapy within 7 days prior to the first dose of trial treatment.

Participant MRN (COH Only):	Participant Initials (F, M, L):
Institution:	

Other Illnesses and Conditions

__11. Diagnosis of immunodeficiency.

__12. 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.

__13. Congestive heart failure Class III/IV according to the New York Heart Association (NYHA) Functional Classification.

__14. Known severe hypersensitivity reaction to pembrolizumab, pralatrexate, leucovorin or any excipients.

__15. Active autoimmune disease that has required systemic treatment in the past 2 years (replacement therapies for hormone deficiencies are allowed). Hemolytic anemia associated with the lymphoma does not exclude a patient from the study.

__16. Known history of HIV (HIV ½ antibodies).

__17. Known active Hepatitis B (e.g., HBsAg reactive) or Hepatitis C (e.g., HCV RNA [qualitative] is detected).

__18. History of active TB infection (Bacillus Tuberculosis).

__19. Active central nervous system (CNS) involvement by lymphoma, including parenchymal and/or lymphomatous meningitis. Subjects with prior CNS involvement by lymphoma must have a baseline MRI and lumbar puncture at screening that demonstrate no active lymphoma in the CNS.

__20. Has a history of (non-infectious) pneumonitis/interstitial lung disease that required steroids or current pneumonitis/interstitial lung disease.

__21. Active, uncontrolled infection requiring systemic therapy.

__22. Female: Pregnant or breastfeeding

__23. 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

__24. Has known psychiatric or substance abuse disorders that would interfere with cooperation with the requirements of the trial.

__25. 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.

__26. Any other condition that would, in the Investigator's judgment, contraindicate the patient's participation in the clinical study due to safety concerns with clinical study procedures.

Participant MRN (COH Only):	Participant Initials (F, M, L):
Institution:	

Noncompliance

__27. Prospective participants who, in the opinion of the investigator, may not be able to comply with all study procedures (including compliance issues related to feasibility/logistics).

Eligibility Confirmed* by (Choose as applicable):	**Print Name**	**Signature**	**Date**
☐ Site PI			
☐ Authorized study MD			
☐ Study Nurse			
☐ Study CRA/ CRC			
☐ Other:_____			
*Eligibility should be confirmed per institutional policies.			

4.0 PARTICIPANT ENROLLMENT

NOTE: Sites must meet activation requirements prior to enrolling participants.

4.1 Pre-Enrollment Informed Consent and Screening Procedures

Diagnostic or laboratory studies performed exclusively to determine eligibility will be done only after obtaining written informed consent. Studies or procedures that are performed for clinical indications (not exclusively to determine study eligibility) may be used for baseline values and/or to determine pre-eligibility, even if the studies were done before informed consent was obtained. The informed consent process is to be fully documented (see Section 16.4), and the prospective participant must receive a copy of the signed informed consent document. Screening procedures are listed in Section 10.0.

4.2 Participant Enrollment

Eligible participants will be registered on the study centrally by the Data Coordinating Center (DCC) at City of Hope. DCC staff are **available between the hours of 8:00 a.m. and 5:00 p.m. PST, Monday through Friday (except holidays).**

- E-mail: DCC@coh.org

4.2.1 Slot verification and reservation

Issues that would cause treatment delays should be discussed with the Study PI.

A designated study team member should email the DCC to verify current slot availability, and to reserve a slot for a specific prospective subject (provide DCC with subject initials), including a tentative treatment date. Slots can only be held for a limited time, at the discretion of the study PI.

The DCC should be notified of cancellations of prospective participants holding slots as soon as possible.

4.2.2 Registration Process

Allow up to 24 hours for the DCC to review. To register a participant, the following procedure must be followed:

1. The study team should contact the DCC via email to provide notification regarding the pending registration and communicate desired timeline of the registration, especially if it must be completed promptly to meet the registration window.
2. The study team will email a **Complete Registration Packet** to the DCC, which consists of a copy of the following documents:
    - Registration Cover Sheet (Appendix F)
    - Completed Eligibility Checklist (printed from Section 3.0 of the protocol) with required signature(s)
    - Signed informed consent
    - Signed HIPAA authorization form (if separate from informed consent)
    - Signed subject's Bill of Rights (California only)

3. In some cases, the DCC may request additional documentation prior to registration. Please refer to the Work Instruction – Reviewing Packets and Registering Subjects for more information. A copy of this work instruction can be provided by the DCC, upon request.

4. When all documents are received, the DCC will review and work with the study team to resolve any missing elements. Any missing documents may delay registration. A participant failing to meet all requirements will not be registered and the study team will be immediately notified.

5. The DCC will send a Confirmation of Registration Form, including the subject study number and cohort assignment to:
    - The study team: Site Lead Investigator, treating physician/sub-investigator, protocol nurse, CRC and pharmacy (as needed)
    - The COH Study PI and COH study team designees (including but not limited to study monitor(s) and statistician(s)).
6. Upon receipt of the Confirmation of Registration Form, COH study team will register the patient in OnCore. DCC will register non-COH patients in OnCore.

4.3 Screen Failures and Registered Participants Who Do Not begin Study Treatment

Notify the DCC immediately if the participant screen fails after registration or if the participant does not start treatment.

For non-COH sites, the reason for screen failure will be documented in the registration coversheet (see Appendix F) and submitted to the DCC.

Issues that would cause treatment delays should be discussed with the Study Principal Investigator.

4.4 Dose Level Assignment

During the Phase 1 portion, eligible participants will be assigned a dose level (Section 5.3). Once the recommended phase 2 dose (RP2D) is defined, participants will enroll at the RP2D dose (Section 5.6).

5.0 TREATMENT PROGRAM

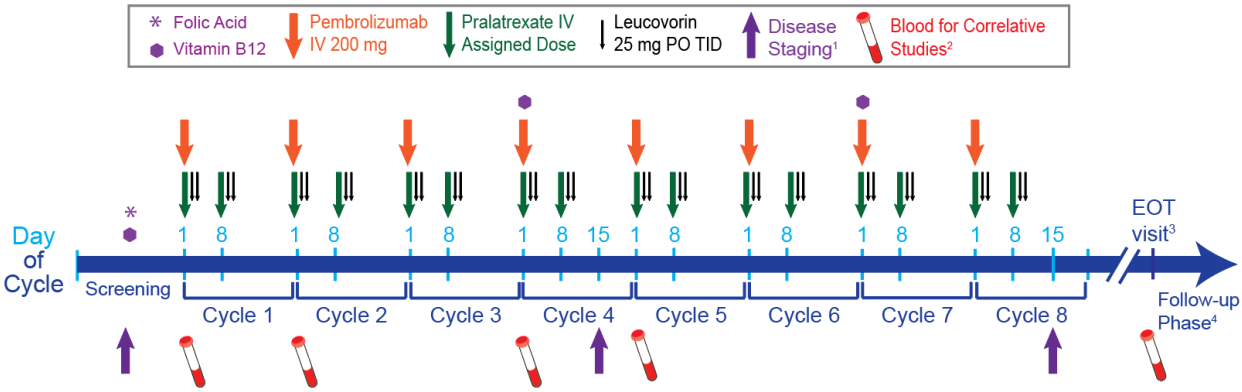
5.1 Study Overview

This is a prospective, single-arm, multi-center, open-label phase 1/2 study of pembrolizumab (MK-3475) plus pralatrexate in subjects with relapsed or refractory peripheral T-cell lymphomas (PTCL) that have failed at least one prior line of therapy.

In the phase 1 portion, pembrolizumab will be administered at a constant dose of 200 mg IV and pralatrexate will be dose-escalated (range from 15-30 mg/m^2 IV). The phase I portion will use a modified rolling 6 design allowing 3 patients to be treated and evaluated for dose-limiting toxicity simultaneously, with up to 6 patients per dose level. An MTD and RP2D will be selected based on toxicity and tolerability data.

In the phase 2 portion, pembrolizumab will be administered at a dose of 200 mg IV and pralatrexate at the RP2D selected in the phase 1 portion following the same schedule. The phase 2 portion will use a Gehan two-stage design with advancement to the second stage based on ORR in the first stage.

In both phases, patients will receive up to 24 months of combined pembrolizumab and pralatrexate therapy. In both phases, Vitamin B12, Folic acid and Leucovorin will be administered as indicated in the study calendar and Section 5.13.



Each cycle = 21 days. Maximum duration of protocol therapy is 24 months.

Folic acid and Vitamin B12 supplementation is standard of care for pralatrexate therapy.

Folic acid is given daily during the course of therapy. Vitamin B12 is given every 3 cycles.

[1] Disease staging is performed at screening and every 4 cycles until disease progression or off study. Disease staging will be by either PET/CT (preferred) or CT scan, but, if disease is FDG-avid, will be PET/CT at baseline, Cycle 4 and every 8 cycles thereafter. Refer to Study calendar and Section 11.1 for details.

2 Peripheral blood for correlative studies will be collected on C1D1, C2D1, C4D1, C5D1, and at EOT (refer to Table 9.3.1 for additional details).

[3] End of treatment visit.

[4] Follow-up Phase for patients who have completed treatment without disease progression will include staging every 12 weeks for the first year and every 18 weeks thereafter, until disease progression or off study.

5.2 Treatment Cycle Definition

In the absence of a delay due to toxicity, each treatment cycle lasts 21 days ± 3 days. Day 1 of a cycle is defined as the administration of pembrolizumab.

5.3 Treatment Plan

For a tabular view of the treatment, monitoring, and follow-up schedule, see study calendar in Section 10.

This is a phase 1/2 study, including a phase 1 dose-escalation portion of the study with 2 dose levels and 1 possible de-escalation dose level, for a total of 3 possible dose levels. The starting dose will be 20 mg/m^2 of pralatrexate on days 1 and 8 and 200 mg IV of pembrolizumab every 21 days, administered in 21-day cycles. The planned dose levels in the Phase 1 portion of the study are outlined in the table below.

Table 5.3 Dosing regimen and schedule

Dose level	Pembrolizumab (Day1)	Pralatrexate (Days 1 and 8)
-1	200 mg IV	15 mg/m^2 IV
1	200 mg IV	20 mg/m^2 IV
2	200 mg IV	30 mg/m^2 IV

In the phase 2 portion of the study, subjects will receive therapy at the RP2D.

Intrapatient dose escalation is permitted in patients enrolled to dose level 1 if and only if the study proceeds to dose level 2 and dose level 2 is determined to be the RP2D. In that case, once dose level 2 is deemed safe and the study proceeds to the phase 2 portion of the study, patients who were enrolled to dose level 1 and are continuing to receive therapy can escalate to dose level 2 in their subsequent cycle of therapy. Patients must meet the criteria for initiation of subsequent cycles of therapy detailed in Section 5.4 of the protocol.

5.4 Eligibility criteria for initiation of subsequent treatment cycles

Prior to initiation of Cycle 2 or any subsequent cycle, and based on the dose delay/modification guidelines provided in Section 6.3 and Section 6.4, patients will need to meet the following eligibility criteria:

- Mucositis ≤ grade 1
- Platelet count ≥ 25,000/µL
- ANC between 500-1,000/µL with no fever, or ANC ≥ 1000/µL
- AST and ALT ≤ 3 ULN OR ≤ 5 ULN for subjects with hepatic involvement by lymphoma as the etiology of transaminase elevation
- Total serum bilirubin ≤ 1.5 ULN OR Direct bilirubin ≤ ULN for subjects with total bilirubin levels > 1.5 ULN, unless has Gilbert's disease or hepatic involvement by lymphoma.
- No ongoing ≥ grade 3 pralatrexate-related toxicity
- No ≥ grade 2 pneumonitis, diarrhea/colitis, hypophysitis, nephritis/renal dysfunction, or intolerable/persistent immune-related AE
- No ≥ grade 3 hyperthyroidism
- No evidence of myocarditis or newly onset type I diabetes mellitus
- No ≥ grade 3 hyperglycemia associated with evidence of β-cell failure

5.5 Definition of Dose-Limiting Toxicity

The dose-limiting toxicity (DLT) observation period will be 2 cycles of therapy, from the start of Cycle 1 through the start of Cycle 3, including any delays (regardless of cause) to start of C3. It will be 42 days if there is no delay. If C3D1 is shorter than 42 days from C1D1, DLT will be evaluated through prior to administration of study therapy on C3D1.

Toxicities will be graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE, Version 5.0) accessible at:

https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_50

DLT will be defined as one of the following AEs that is **at least possibly related** to study treatment:

Hematologic

- Grade 4 neutropenia lasting > 7 days (despite the use of growth factor support).
- Grade 4 thrombocytopenia lasting > 7 days or requiring platelet transfusion.
- Grade 3 or 4 thrombocytopenia associated with grade 2 or higher bleeding.
- Grade 4 anemia not associated with lymphoma.
- Any Grade 5 AE.

Non-hematologic

- Grade ≥ 3 pneumonitis without suspected infectious cause.
- Any ≥ grade 3 AE that does not resolve to grade ≤ 1 within 7 days with the exception of:
    - Grade ≥ 3 asymptomatic laboratory abnormalities, including lipase or amylase, that do not require hospitalization or delay of treatment.
    - Grade 3 nausea or vomiting, that improves to grade ≤ 2 within 7 days with supportive measures.
    - Grade 3 fatigue that improves to grade ≤ 2 within 14 days with supportive measures.
    - Grade 3 asymptomatic endocrinopathy of any duration.
    - Grade 3 fatigue related to endocrinopathy that resolves within 7 days of hormone-replacement or corticosteroid therapy.
    - Grade 3 inflammatory response attributed to local antitumor response of any duration.
    - Vitiligo or alopecia of any grade and duration.
- Any Grade 5 AE

5.6 Definition of the MTD and Recommended Phase 2 Dose

Dose escalation will proceed according to the schema outlined in Table 5.3. The maximum tolerated dose (MTD) is defined as the highest dose level at which < 2 out of 6 evaluable subjects experienced DLT. The MTD will be considered the recommended phase 2 dose (RP2D), however the principal investigator may ultimately choose a lower dose level as the RP2D, depending on toxicity considerations, dose reduction on subsequent cycles, and other considerations.

5.7 Replacement of Subjects

During the Phase 1 portion of the study, subjects will be replaced for any of the following:

- Missed any doses of pralatrexate during the DLT period (not due to DLT).
- Did not receive the doses of pembrolizumab during the DLT period (not due to DLT).

Subjects who are replaced for missed doses may continue to receive study treatment if there is clear clinical benefit, but will not be included in DLT analysis.

During the Phase 2 portion of the study, subjects who did not receive at least 1 dose of pembrolizumab and 1 dose of pralatrexate, or who did not have a tumor response assessment (except due to progression of disease prior to the first tumor response assessment) will be replaced. If a patient discontinues study treatment prior to the first response assessment due to progressive disease, the treating physician is encouraged to obtain imaging to confirm progression.

5.8 Agent Administration

5.8.1 Pembrolizumab

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

Pembrolizumab (200 mg) will be administered as a 30-minute IV infusion on Day 1 of each 21-day cycle.

The final concentration of the diluted solution should be 1 mg/mL - 10 mg/mL and administered IV over 30 minutes, through an intravenous line containing a sterile, non-pyrogenic, low-protein binding 0.2 micron to 5 micron in-line or add-on filter.

Every effort should be made to target infusion timing to be as close to 30 minutes as possible. However, given the variability of infusion pumps, a window of -5 minutes and +10 minutes is permitted (i.e., infusion time is 30 minutes: -5 min/+10 min).

The pembrolizumab dose is fixed at 200 mg. There are no dose reductions. Management and dose delays associated with pembrolizumab AEs are outlined in Section 6.3.

Pembrolizumab will always be given first (before pralatrexate).

5.8.2 Pralatrexate

Pralatrexate will be administered by intravenous (IV) push according to dose levels, over 3 to 5 minutes, via the side port of a free-flowing 0.9% sodium chloride injection on Days 1 and 8 of each cycle.

Pralatrexate dosing should be based on baseline body surface area (BSA). Patients with a BSA>2m^2 can be treated either at the actual BSA or at BSA=2m^2, at the Investigator's discretion. The patient will receive the same dose of pralatrexate (based on the BSA calculated at baseline) throughout treatment unless the patient's actual weight changes by ≥10% (in that case the dose will be adjusted accordingly).

5.9 Assessments and Special Monitoring

Section 10 summarizes the trial procedures to be performed. **Note:** Protocol therapy should be administered on Day 1 of each cycle after all procedures/safety assessments have been completed.

It may be necessary to perform study procedures at unscheduled time points if deemed clinically necessary by the investigator.

5.9.1 Special Monitoring for pembrolizumab.

Adverse events (both non-serious and serious) associated with pembrolizumab exposure may represent an immunologic etiology. These adverse events may occur shortly after the first dose or several months after the last dose of pembrolizumab.

Diarrhea/colitis

- Participants 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).

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.

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.
- Appropriate resuscitation equipment should be available in the room and a physician readily available during the period of drug administration.

5.9.2 Monitoring for pralatrexate.

Oral mucositis is common and mucositis should be graded at each study visit. Oral mucositis will be graded according to the CTCAE v5.0 and pralatrexate dose delay/modification guidelines in section 6.4 should be adhered to.

5.10 Duration of Therapy and Criteria for Removal from Protocol Therapy

Participants will receive protocol therapy until one of the below criteria are met:

- Disease progression
- **Note:** Following consultation with the Study PI, participants who meet progression per 2014 Lugano classification [8] but who meet the criteria of "indeterminate response" (IR) according to the provisional modification to the 2014 Lugano Classification, the LYRIC criteria [10] (Appendix C), and are deriving clinical benefit may continue to receive protocol therapy beyond progression as long as they meet the following criteria:
  - Continue to meet treatment criteria
  - Investigator-assessed clinical benefit
  - Tolerance of study drug
  - Stable performance status
  - Treatment beyond progression will not delay an imminent intervention to prevent serious complications of disease progression (e.g., CNS metastases)
- *If the patient has IR per LYRIC criteria and is receiving therapy beyond progression*:
  - A confirmatory PET-CT should be performed within 12 weeks after initial progression to determine whether the patient meets PD criteria according to the LYRIC criteria [10].
  - Further progression is defined according to the LYRIC criteria
  - Protocol therapy should be discontinued permanently upon documentation of PD per the LYRIC criteria
- Unacceptable toxicity despite dose delay/ modification

- **Note:** If one agent is delayed due to toxicity, then participants many continue with monotherapy for the other agent.
- Completed protocol therapy.
  - General or specific changes in the participant's condition (including intercurrent illness) which render the participant unacceptable for further treatment in the judgment of the investigator
  - Withdrawal of consent for further protocol therapy by the participant (See Section 16.5)

Once participants meet criteria for removal from protocol therapy, the participant should then proceed to End of Protocol Therapy assessments and follow-up.

Documentation of the reason for discontinuing protocol therapy and the date effective should be made in the medical record and appropriate eCRF. The COH DCC and the Study PI should be promptly notified of the change in participant status.

5.11 Follow-Up

Following completion of protocol therapy, all participants will enter follow-up after ending protocol treatment. This is comprised of:

- **Safety Follow-up**- 30 days post-last dose of protocol therapy through to (a) 90 days post-last dose of protocol therapy or (b) until initiation of a new anticancer therapy (whichever occurs sooner)
- Note: the period for safety follow-up will be extended until stabilization or resolution for all reportable AEs (per the agreement of the Study PI) and accompanying follow-up safety report.
- **Response Follow-up-** for those who have yet to have disease progression.
- **Survival Follow-up-** for those who progressed or completed Response Follow-up.

  This follow-up will be performed typically via medical record review. It will entail (a) Disease status (for those who have yet to progress) (b) Vital status (all participants).

Assessment time points and windows are detailed in Section 10.0.

5.12 Duration of Study Participation

Study participation may conclude when any of the following occur:

- Completion of study activities
- Withdrawal of consent (See Section 16.5)
- Participant is lost to follow-up. All attempts to contact the participant must be documented.
- At the discretion of the investigator for safety, behavioral, study termination or administrative reasons

Documentation of the reason for discontinuing study participation and the date effective should be made in the medical record and appropriate eCRF. The COH DCC should be promptly notified of the change in participant status.

5.13 Supportive Care, Prohibited Medications and Concomitant Therapy

Participants must be instructed not to take any additional medications (including over-the-counter products) during the trial without prior consultation with the investigator.

If concomitant therapy must be added or changed, including over-the-counter medications or alternative therapies, the reason and name of the agent/therapy should be recorded in the eCRF and the medical record.

5.13.1 Prohibited concomitant medication and medications to use with caution

The following are **prohibited** from Day 1 of protocol therapy until end of protocol therapy (last day of study agent or decision to end study agent(s) whichever occurs later):

- Antineoplastic systemic chemotherapy or biological therapy
- Immunotherapy not specified in this protocol
- Chemotherapy not specified in this protocol
- Other investigational agents other than pembrolizumab and pralatrexate
- Live vaccines
- Systemic glucocorticoids for any purpose other than to modulate symptoms from an event of clinical interest of suspected immunologic etiology. The use of physiologic doses of corticosteroids may be approved after consultation with the PI.

Participants who, in the assessment by the investigator, require the use of any of the aforementioned treatments for clinical management should be removed from the study.

The following medications should be **used with caution**:

- “Sulfa” antibiotics
- Non-steroidal anti-inflammatory drugs
- Probenecid

When administering pralatrexate to patients receiving probenecid or other drugs that may affect relevant transporter systems (eg, NSAIDs), monitor patients closely for signs of systemic toxicity due to increased drug exposure.

5.13.2 Specific supportive care guidelines for pralatrexate

5.13.2.1 Leucovorin

Mucositis is the most frequent and treatment-limiting adverse event (AE) associated with the administration of pralatrexate. Leucovorin (*d,l*-folinic acid) is a reduced form of a racemic mixture of diasterioisomers of folic acid and is well-recognized and approved as rescue therapy for high-dose methotrexate (MTX) therapy, mitigating gastrointestinal lining and bone marrow cell toxicity [3]. It is also indicated to treat MTX or other folic acid antagonist overdose and is used in combination with fluorouracil to treat cancer of the colon. Leucovorin is approved as an antidote for the toxicity from folic acid antagonists, including pralatrexate. In the present study it is thus used to prevent or reduce mucositis resulting from pralatrexate treatment.

Leucovorin (25 mg tablets) will be administered orally three times daily (every 8 hours) for 2 days for a total of 6 doses (150 mg cumulative weekly dose) beginning 24h (+/- 2h) after each dose of pralatrexate is administered.

The patient will be instructed to take the first dose of leucovorin 24 hours (±2 hours) after the administration of pralatrexate, and to continue to take the leucovorin three times daily (every 8 hours) for 2 days. At each weekly treatment visit, the patient will be asked whether they have taken leucovorin as instructed and will be supplied with a prescription to obtain additional doses.

5.13.2.2 Folic Acid supplementation/Premedication (Standard of care for pralatrexate therapy)

Folic acid (1 mg orally, once daily) supplementation is to begin within 10 days (as early as possible) prior to the first dose of pralatrexate administration (per pralatrexate product insert). However, if folic acid was not taken but MMA (methylmalonic acid) and HCY (homocysteine) levels were checked and are in normal range at screening, the investigator can decide to start study therapy immediately. Administration should continue during the full course of pralatrexate therapy and for 30 days after the last dose of pralatrexate.

5.13.2.3 Vitamin B12 supplementation/Premedication (Standard of care for pralatrexate therapy)

Vitamin B12 (1 mg IM) will be administered anytime within 10 weeks prior to initiation of pralatrexate (per pralatrexate product insert) and can be administered during screening, and will be administered every 3 cycles. Administration should continue during the full course of pralatrexate therapy and for 30 days after the last dose of pralatrexate.

5.13.3 General Supportive Care Guidelines

Participants 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 or pralatrexate** administration.

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

Myocarditis

- For suspected immune-mediated myocarditis, ensure adequate evaluation to exclude other etiologies.
- Administer corticosteroids as appropriate.

Pneumonitis

- Add prophylactic antibiotics for opportunistic infections in the case of prolonged steroid administration.

Grade 2

- Administer systemic corticosteroids.
- When symptoms improve to ≤ Grade 1, steroid taper should be started and continued over no less than 4 weeks.

Grade 3 or 4

- Immediately treat with IV steroids.
- Administer additional anti-inflammatory measures, as needed.

Diarrhea/colitis

- All participants 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.

Grade 2 diarrhea/colitis

- Administer oral corticosteroids.
- When symptoms improve to ≤ Grade 1, steroid taper should be started and continued over no less than 4 weeks.

Grade 3 or 4 diarrhea/colitis

- IV steroids followed by high dose oral steroids
- When symptoms improve to ≤ Grade 1, steroid taper should be started and continued over no less than 4 weeks.

Type 1 diabetes mellitus* OR ≥ Grade 3 hyperglycemia*

- *if new onset, including diabetic ketoacidosis [DKA])
- **if associated with ketosis (ketonuria) or metabolic acidosis (DKA)

*For **T1DM** or **Grade 3-4** hyperglycemia*

- Insulin replacement therapy is recommended.
- Evaluate patients with serum glucose and a metabolic panel, urine ketones, glycosylated hemoglobin, and C-peptide.

Hypophysitis

Grade 2 (i.e. symptomatic)

- Treat with corticosteroids.
- When symptoms improve to ≤ Grade 1, 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.

Grade 3 or 4

- Treat with an initial dose of IV corticosteroids followed by oral corticosteroids.
- When symptoms improve to ≤ Grade 1, 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

*Grade 2 **Hyper**thyroidism*

- Non-selective beta-blockers (e.g. propranolol) are suggested as initial therapy.

*Grade 3 or 4 **Hyper**thyroidism*

- Treat with an initial dose of IV corticosteroid followed by oral corticosteroids.
- When symptoms improve to ≤ Grade 1, 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

*Grades 2-4 **Hypo**thyroidism*

- Thyroid hormone replacement therapy, with levothyroxine or liothyroinine, is indicated per standard of care.

Hepatic

Grade 2

- Monitor liver function tests more frequently until returned to baseline values (consider weekly).
- Treat with IV or oral corticosteroids

Grade 3 or 4

- Treat with intravenous corticosteroids for 24 to 48 hours.
- When symptoms improve to ≤ Grade 1, steroid taper should be started and continued over no less than 4 weeks

Renal failure or nephritis

Grade 2

- Treat with corticosteroids

Grade 3 or 4

- Treat with systemic corticosteroids.
- When symptoms improve to ≤ Grade 1, steroid taper should be started and continued over no less than 4 weeks

Management of infusion reactions

- Pembrolizumab may cause severe or life threatening infusion-reactions including severe hypersensitivity or anaphylaxis. Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion.

Dose modification and toxicity management guidelines on pembrolizumab associated infusion reaction are provided in Table 5.13.3.

Table 5.13.3 Pembrolizumab Infusion Reaction Dose modification and 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 participant is deemed medically stable in the opinion of the investigator.	None
Grade 2 Requires therapy or infusion interruption but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for ≤24 hrs	**Stop Infusion.** Additional appropriate medical therapy may include but is not limited to: IV fluids Antihistamines NSAIDs Acetaminophen Narcotics Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator. If symptoms resolve within 1 hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (e.g. from 100 mL/hr to 50 mL/hr). Otherwise dosing will be held until symptoms resolve and the participant should be premedicated for the next scheduled dose. **Participants who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further study drug treatment**	Participant may be premedicated 1.5h (± 30 minutes) prior to infusion of pembrolizumab with: Diphenhydramine 50 mg po (or equivalent dose of antihistamine). Acetaminophen 500-1000 mg po (or equivalent dose of analgesic).

Grades 3 or 4 Grade 3: Prolonged (i.e., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (e.g., renal impairment, pulmonary infiltrates) Grade 4: Life-threatening; pressor or ventilatory support indicated	**Stop Infusion.** Additional appropriate medical therapy may include but is not limited to: Epinephrine** IV fluids Antihistamines NSAIDs Acetaminophen Narcotics Oxygen Pressors Corticosteroids Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator. Hospitalization may be indicated. **In cases of anaphylaxis, epinephrine should be used immediately. **Participant is permanently discontinued from further study drug treatment.**	**No subsequent dosing**
Appropriate resuscitation equipment should be available at the bedside and a physician readily available during the period of drug administration. For further information, please refer to the Common Terminology Criteria for Adverse Events v5.0 (CTCAE) at http://ctep.cancer.gov		

5.13.4 Other Considerations

Refer to Appendix E for contraception related guidance.

6.0 ANTICIPATED TOXICITIES & DOSE MODIFICATION/ DELAY GUIDELINES

6.1 Anticipated Toxicities

6.1.1 Pembrolizumab

Per the IB the expected toxicities for pembrolizumab are as follows (asterisk signifies ≥ 10%; no asterisk signifies 1-10%, † signifies < 1%, and ^ signifies unknown frequency):

Blood and lymphatic system disorders (includes investigations)	Anemia, neutropenia†, thrombocytopenia†, leukopenia†, lymphopenia†, eosinophilia†, hemolytic anemia†,immune thrombocytopenic purpura†
Cardiac	Myocarditis †
Endocrine	Hyperthyroidism, hypothyroidism, hypophysitis †, adrenal insufficiency †, thyroiditis †
Eye	Uveitis †, dry eye †, Vogt-Koyanagi-Harada disease ^
Gastrointestinal	Diarrhea*, nausea *, abdominal pain, vomiting, colitis, constipation, dry mouth, pancreatitis †, small intestine perforation †
General Disorders and Administration Site	Fatigue *, asthenia, edema, pyrexia, influenza-like illness, chills
Hepatobiliary	Hepatitis †, sclerosing cholangitis ^
Immune system	Infusion related reactions, severe infusion reactions †, sarcoidosis †, solid organ transplant rejection ^, GvHD (potential risk), haemophagocytic lymphohistiocytosis †
Investigations (excluding hematologic)	AST/ALT increased, blood alkaline phosphatase increased, blood creatinine increased, low sodium levels†, low potassium levels†, low calcium levels†, blood bilirubin increased†, amylase increased†, increased calcium †
Metabolism and Nutrition	Decreased appetite, type 1 diabetes mellitus †
Musculoskeletal and Connective Tissue	Arthralgia, back pain, myositis, musculoskeletal pain, arthritis, pain in extremity, tenosynovitis †
Nervous system	Headache, dizziness, dysgeusia, epilepsy †, lethargy †, Guillian-Barré syndrome†, peripheral neuropathy†, myasthenic syndrome †, encephalitis †, myelitis†
Psychiatric disorders	Insomnia †
Renal and urinary	Nephritis †
Respiratory, Thoracic and Mediastinal	Cough, pneumonitis, dyspnoea
Skin and Subcutaneous Tissue	Pruritus*, rash*, vitiligo, dry skin, erythema, hair color change †, eczema †, alopecia †, severe skin reactions†, Steven-Johnson Syndrome†, toxic epidermal necrolysis†
Vascular Disorders	Hypertension †, vasculitis †

6.1.2 Pralatrexate

Per package insert: the most common adverse reactions (>35%) are mucositis, thrombocytopenia, nausea, and fatigue. Most common serious adverse reactions are pyrexia, mucositis, sepsis, febrile neutropenia, dehydration, dyspnea, and thrombocytopenia.

Bone Marrow Suppression

Pralatrexate can suppress bone marrow function, manifested by thrombocytopenia, neutropenia, and anemia.

Mucositis

Treatment with pralatrexate may cause mucositis.

Dermatologic Reactions

Pralatrexate has been associated with severe dermatologic reactions, which may result in death. Dermatologic reactions have been reported in clinical studies and post-marketing safety reports in patients treated with pralatrexate. Dermatologic reactions have included skin exfoliation, ulceration, and toxic epidermal necrolysis (TEN) (post-marketing reports). These reactions may be progressive and increase in severity with further treatment, and may involve skin and subcutaneous sites of known lymphoma.

Tumor Lysis Syndrome

Tumor lysis syndrome has been reported in patients with lymphoma receiving pralatrexate in post-marketing reports.

Hepatic Toxicity

Hepatic toxicity and liver function test abnormalities have been observed after pralatrexate administration. Persistent liver function test abnormalities may be indicators of liver toxicity.

Risk of Increased Toxicity in the Presence of Impaired Renal Function

Patients with moderate to severe renal function impairment may be at greater risk for increased exposure and toxicity. Serious adverse drug reactions including TEN (post-marketing reports) and mucositis were reported in patients with end stage renal disease (ESRD) undergoing dialysis who were administered FOLOTYN therapy.

Pregnancy and Breastfeeding

Pralatrexate can cause fetal harm when administered to a pregnant woman. Pralatrexate was embryotoxic and fetotoxic in rats and rabbits.

6.2 Dose Delay/ Modification - General instructions

If pembrolizumab administration is held for toxicity, and the toxicity is most likely attributed to pembrolizumab and not attributed to pralatrexate, administration of pralatrexate may continue.

If pralatrexate administration is held for toxicity, and the toxicity is most likely attributed to pralatrexate and not attributed to pembrolizumab, administration of pembrolizumab may continue.

In the event that attribution of a treatment-emergent toxicity is unclear, but is at least possibly related to both study medications, both drugs should be delayed/modified according to the most conservative dose delay criteria. The most conservative dose delay criteria should be observed for any particular AEs called out in the dose delay/modification tables (Tables 6.3, 6.4.1, 6.4.2, or 6.4.3) or according to the general "all other IrAE" guidelines in Table 6.3 for unspecified immune-related AEs or the "all other pralatrexate-related" AE guidelines in Table 6.4.3 for non-immune related AEs.

6.3 Dose Delay/ Modification Guidelines for Pembrolizumab-associated Adverse Events

- Toxicities will be graded using the NCI CTCAE Version 5.0.
- Baseline values are from the last values obtained prior to treatment.

AEs associated with pembrolizumab exposure may represent an immunologic etiology. These immune-related AEs (irAEs) may occur shortly after the first dose or several months after the last dose of pembrolizumab treatment and may affect more than on 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, administration of corticosteroids and/or other supportive care. For suspected irAEs, ensure adequate evaluation to confirm etiology or exclude other causes. Additional procedures or tests such as bronchoscopy, endoscopy, skin biopsy may be included as part of the evaluation. Based on the severity of irAEs, withhold or permanently discontinue pembrolizumab and administer corticosteroids. Dose modification and toxicity management guidelines for irAEs associated with pembrolizumab are provided in Table 6.3.

Table 6.3 Dose Modification and toxicity management for irAEs typically associated with pembrolizumab

General instructions:

1. Corticosteroid taper should be initiated upon AE improving to Grade 1 or less and continue to taper over at least 4 weeks.
2. For situations represented in Table 6.3 where pembrolizumab has been withheld, pembrolizumab can be resumed after AE has been reduced to Grade 1 or 0 and corticosteroid has been tapered. Pembrolizumab should be permanently discontinued if AE does not resolve within 12 weeks of last dose or corticosteroids cannot be reduced to ≤10 mg prednisone or equivalent per day within 12 weeks.
3. For situations represented in Table 6.3 where pralatrexate has been withheld, pralatrexate can be resumed at prior dose after AE improves to grade 1 or 0. If the investigator feels that the AE was related to pralatrexate, the pralatrexate dose can be reduced by one level after discussion with the overall study PI.

Exceptions:

- For patients who develop severe renal impairment (eGFR or CrCl 15 to < 30 mL/min/1.73m^2) while on treatment with pralatrexate at the 30 mg/m^2 dose level, the dose of pralatrexate upon recovery will be reduced to 15 mg/m^2.
- For patients who develop severe renal impairment (eGFR or CrCl 15 to < 30 mL/min/1.73m^2) while on treatment with pralatrexate at the 20 mg/m^2 dose level or lower, pralatrexate will be permanently discontinued.

4. For severe and life-threatening irAEs, IV corticosteroid should be initiated first followed by oral steroid. Other immunosuppressive treatment should be initiated if irAEs cannot be controlled by corticosteroids.

Immune-related AEs	Toxicity grade or conditions (CTCAE v5.0)	Action taken to pembrolizumab and/or pralatrexate	irAE management with corticosteroid and/or other therapies	Monitor and follow-up
Pneumonitis	Grade 2	• Withhold pembrolizumab • Consider holding pralatrexate	• 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 pembrolizumab • Hold pralatrexate		
Diarrhea / Colitis	Grade 2 or 3	• Withhold pembrolizumab • Hold pralatrexate	• 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.
	Grade 4, or recurrent Grade 3	• Permanently discontinue pembrolizumab • Hold pralatrexate		
AST / ALT elevation or Increased bilirubin	Grade 2	• Withhold pembrolizumab • Hold pralatrexate	• Administer corticosteroids (initial dose of 0.5- 1 mg/kg prednisone or equivalent) followed by taper	• Monitor with liver function tests (consider weekly or more frequently until liver enzyme value returned to baseline or is stable
	Grade 3 or 4	• Permanently discontinue pembrolizumab • Hold pralatrexate	• Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper	

Type 1 diabetes mellitus (T1DM) or Hyperglycemia	Newly onset T1DM or Grade 3 or 4 hyperglycemia associated with evidence of β-cell failure	• Withhold pembrolizumab	• 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 pembrolizumab	• Administer corticosteroids and initiate hormonal replacements as clinically indicated.	• Monitor for signs and symptoms of hypophysitis (including hypopituitarism and adrenal insufficiency)
	Grade 3 or 4	• Withhold or permanently discontinue pembrolizumab[1]		
Hyperthyroidism	Grade 2	Continue pembrolizumab	• Treat with non-selective beta-blockers (eg, propranolol) or thionamides as appropriate	• Monitor for signs and symptoms of thyroid disorders.
	Grade 3 or 4	Withhold or permanently discontinue pembrolizumab[1]		
Hypothyroidism	Grade 2, 3, or 4	Continue pembrolizumab	• Initiate thyroid replacement hormones (eg, levothyroxine or liothyroinine) per standard of care	• Monitor for signs and symptoms of thyroid disorders.
Nephritis and Renal dysfunction	Grade 2	• Withhold pembrolizumab • Hold pralatrexate	• Administer corticosteroids (prednisone 1-2 mg/kg or equivalent) followed by taper.	• Monitor changes of renal function
	Grade 3	• Permanently discontinue pembrolizumab • Hold pralatrexate		
	Grade 4	• Permanently discontinue pembrolizumab and pralatrexate		
Neurological Toxicities	Grade 2	• Withhold pembrolizumab • Hold pralatrexate	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 3 or 4	• Permanently discontinue pembrolizumab • Hold pralatrexate		

		If the neurological toxicity is felt to be due to pembrolizumab and not pralatrexate, resumption of pralatrexate may be considered in consultation with the study PI.		
Myocarditis	Grade 1	• Withhold pembrolizumab • Hold pralatrexate	• 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 pembrolizumab • Hold pralatrexate		
Exfoliative Dermatologic Conditions	Suspected SJS, TEN, or DRESS	• Withhold pembrolizumab • Hold pralatrexate	• 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 pembrolizumab and pralatrexate		
All other immune-related AEs	Intolerable/ persistent Grade 2	Withhold pembrolizumab	• 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 pembrolizumab based on the type of event. Events that require discontinuation include, but are not limited to: encephalitis and other clinically important irAEs		
	Grade 4 or recurrent Grade 3	Permanently discontinue pembrolizumab		

1. Withhold or permanently discontinue pembrolizumab is at the discretion of the investigator or treating physician.

NOTE:

For participants with Grade 3 or 4 immune-related endocrinopathy where withhold of pembrolizumab is required, pembrolizumab may be resumed when AE resolves to ≤ Grade 2 and is controlled with hormonal replacement therapy or achieved metabolic control (in case of T1DM).

6.4 Dose Delay/Modifications Guidelines for Pralatrexate-Associated Adverse Events

Pralatrexate dose modifications will be allowed according to the criteria outlined in Table 6.4.1, Table 6.4.2, and Table 6.4.3.

Exceptions:

- For patients who develop severe renal impairment (eGFR or CrCl 15 to < 30 mL/min/1.73m^2) while on treatment with pralatrexate at the 30 mg/m^2 dose level, the dose of pralatrexate upon recovery will be reduced to 15 mg/m^2.
- For patients who develop severe renal impairment (eGFR or CrCl 15 to < 30 mL/min/1.73m^2) while on treatment with pralatrexate at the 20 mg/m^2 dose level or lower, pralatrexate will be permanently discontinued.

Treatment may be delayed to allow sufficient time for recovery. Patients whose treatment is delayed because of pralatrexate-related toxicity should be evaluated at weekly intervals (or less) until adequate recovery has occurred. A patient who has not received pralatrexate for more than 28 days since last study drug administration should be discontinued from further pralatrexate treatment. Any patient who requires a pralatrexate dose modification due to toxicity should continue to receive the modified regimen for the remainder of the study unless agreed otherwise with the overall study PI or their designee. For patients who require a pralatrexate dose reduction, for any reason, leucovorin should continue to be administered at the specified dose and schedule. For patients who require doses of pralatexate to be omitted due to mucositis (Table 6.4.1), leucovorin dosing should continue per protocol. For patients who require doses of pralatrexate be omitted for an adverse event other than mucositis or stomatitis (Table 6.4.2 and Table 6.4.3), leucovorin treatment should be stopped until the patient resumes pralatrexate treatment. Safety assessment and routine clinical care should be followed at all times.

Table 6.4.1 Dose Modifications for Mucositis, based on NCI CTCAE Version 5.0

Mucositis Grade on Day of Treatment	Action	Dose Upon Recovery to ≤Grade 1
Grade 2	Omit pralatrexate dose	Continue prior pralatrexate dose
Grade 2 recurrence	Omit pralatrexate dose	Reduce pralatrexate by one dose level (e.g. should be lowered to 20 mg/m^2 if receiving 30 mg/m^2, 15 mg/m^2 if receiving 20 mg/m^2)
Grade 3	Omit pralatrexate dose Hold pembrolizumab	Reduce pralatrexate by one dose level Resume pembrolizumab
Grade 4	Permanently discontinue pralatrexate Hold pembrolizumab	If not probably or definitely related to pembrolizumab, pembrolizumab resumption can be considered in discussion with Study PI

Table 6.4.2 Dose Modifications for Hematologic Toxicities

Blood Count on Day of Treatment	Duration of Toxicity	Action	Dose Upon Restart
Platelet ≤25,000/μL	1 week	Omit pralatrexate dose Hold pembrolizumab	Continue prior pralatrexate dose Resume pembrolizumab
	2 weeks	Omit pralatrexate dose Hold pembrolizumab	reduce pralatrexate by one dose level Resume pembrolizumab
	3 weeks	Permanently stop pralatrexate Hold pembrolizumab	Pembrolizumab resumption can be considered in discussion with Study PI
ANC 500-1,000/μL with fever OR ANC <500/μL	1 week	Omit pralatrexate dose, give GCSF support Hold pembrolizumab	Continue prior pralatrexate dose with GCSF support Resume pembrolizumab
	2 weeks or recurrence	Omit pralatrexate dose, give GCSF support Hold pembrolizumab	reduce pralatrexate by one dose level with GCSF support Resume pembrolizumab
	3 weeks or 2nd recurrence	Permanently stop pralatrexate Hold pembrolizumab	Pembrolizumab resumption can be considered in discussion with Study PI

ANC= absolute neutrophil count, GCSF=granulocyte colony stimulating factor, GMCSF= granulocyte macrophage colony stimulating factor.

Table 6.4.3 Dose Modifications for all Other Pralatrexate-Related Toxicities

Toxicity Grade On Day of Treatment	Action	Dose Upon Recovery to ≤Grade 1
Grade 3	Omit pralatrexate dose	reduce pralatrexate by one dose level
Grade 4	Permanently stop pralatrexate therapy	---

7.0 REPORTING OF ADVERSE EVENTS, UNANTICIPATED PROBLEMS & OTHER EVENTS OF INTEREST

The research team is responsible for classifying adverse events (AEs) and unanticipated problems (UPs) as defined in the relevant regulations and reporting to all applicable parties, including but not limited to the COH IRB, DSMC, Food and Drug Administration (FDA), National Institutes of Health (NIH) and other collaborators, e.g., pharmaceutical companies. The research team is responsible for the continued monitoring and tracking of all AEs in order to ensure non-reportable events are reviewed and monitored and do not rise to a reporting level.

7.1 Assessment of Adverse Events

The site Investigator will be responsible for determining the event name, and assessing the severity (i.e., grade), expectedness, and attribution of all adverse events as applicable per the City of Hope Clinical Research Adverse Event and Unanticipated Problem policy (available from the DCC). Adverse events will be characterized using the descriptions and grading scales found in NCI CTCAE v5.0. A copy of the scale can be found at:

https://ctep.cancer.gov/protocoldevelopment/electronic_applications/ctc.htm.

The following definitions will be used to determine the causality (attribution) of the event to the study agent or study procedure.

- **Unrelated –** The event is clearly NOT related to study treatment, and is clearly related to other factors such as the participant's clinical state, other therapeutic interventions, or concomitant medications administered to the participant.
- **Unlikely –** The event is unlikely related to the study treatment, and is most likely related to other factors such as the participant's clinical state, other therapeutic interventions, or concomitant drugs.
- **Possible –** The event may be related to study treatment, as it follows a reasonable temporal sequence from the time of drug administration, but could have been produced by other factors such as the participant's clinical state, other therapeutic interventions, or concomitant drugs.
- **Probable –** The event is most likely related to the study treatment, as it follows a reasonable temporal sequence from the time of drug administration and a known response pattern to the study drug, and is unlikely related to the participant's clinical state, other therapeutic interventions, or concomitant drugs.

Definite – The event is clearly related to the study treatment, as it follows a reasonable temporal sequence from the time of drug administration and a known response pattern to the study drug, and is not reasonably explained by other factors such as the participant's condition, therapeutic interventions, or concomitant drugs.

7.2 Secondary Malignancy

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

The investigator must immediately notify the Study PI/ DCC via an expedited report.

7.3 Adverse Events of Special Interest (AESI) Requiring Expedited Reporting

7.3.1 Immune-related AEs

An immune-related adverse event (irAE) is defined as an adverse event that is associated with drug exposure and is consistent with an immune-mediated mechanism of action and where there is no clear alternate etiology. Serologic, immunologic, and histologic (biopsy) data, as appropriate, should be used to support an irAE diagnosis. Appropriate efforts should be made to rule out neoplastic, infectious, metabolic, toxin, or other etiologic causes of the irAE.

7.3.2 Overdose

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

No specific information is available on the treatment of pralatrexate overdosage. If an overdose occurs, general supportive measures should be instituted as deemed necessary by the treating physician. Although there has been no formal or definitive evaluation of the effect of leucovorin following an overdose of pralatrexate, it has been established in clinical studies that leucovorin reduces pralatrexate toxicity, and based on the mechanism of action of pralatrexate, the prompt administration of leucovorin should be considered.

7.3.3 Abnormal Liver Function Tests

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.

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

7.4 Pregnancies

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

Efforts must be made by the investigator to follow the outcome of pregnancy outcome per institutional policies.

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. If the newborn is healthy additional follow-up is not necessary.

Any pregnancy related event described above must be reported to the Study PI/ DCC immediately within 24 hours of awareness. Protocol therapy is to be discontinued immediately.

7.5 Adverse Event (AE) collection guidelines

- During Cycles 1 & 2, all grade toxicities with start and stop dates will be reported in the eCRFs.
- After Cycle 2 until the end of the safety follow-up period (30-days post-last dose for AE or 90 days post-last dose for SAE), the highest grade AND all Grade 3+ toxicities (regardless of whether highest grade or not) per cycle and all SAEs with start/stop dates will be reported in the eCRFs.

7.6 Routine AE Collection and Reporting Guidelines

AEs will be collected from the signing of informed consent until ending study participation. Routine AE reporting will occur via data entry into the study eCRF. AEs will be monitored by the Protocol Management Team (PMT). AEs reported through expedited processes (e.g., reported to the IRB, FDA, etc.) must also be reported in routine study data submissions.

AEs recorded in the CRF include:

- All events considered unrelated, unlikely, possibly, probably or definitely related to protocol therapy.
- Any Grade 1-5 during the DLT period (cycles 1 and 2), the highest grade AND all Grade 3+ toxicities (regardless of whether the highest grade or not) after cycle 2 during each cycle and during the safety follow-up period.
- All SAEs.

7.7 Expedited Reporting

Table 7.7 indicates what events must be reported expeditiously.

Table 7.7 Criteria for Expedited Reporting

Time point	What to report expeditiously
From the signing of the consent to study completion	All unanticipated problems
From Screening until Day 1 of protocol therapy	• All SAEs related to protocol procedures • Pregnancy and lactation • Any reason for not starting Day 1 of protocol therapy
For the time period beginning at treatment through 90 days following cessation of treatment, or 30 days following cessation of treatment if the subject initiates new anticancer therapy, whichever is earlier	• All SAEs regardless of relationship to protocol therapy, study procedure, underlying disease or concomitant treatment. • Death due to any cause other than progression of the cancer under study. • All AEs that meet the definition of an unanticipated problem. • Overdose of either agent. • Pregnancies and lactation. • Abnormal liver function tests • Discontinuation of protocol therapy due to unusual or unusually severe AE considered related to protocol therapy
For participants yet to initiate anti-cancer therapy: From Day 1 of therapy up to 120 days post-last pembrolizumab dose	• Pregnancies and lactation.
Post Safety follow-up to removal from study	• All SAEs that are considered possibly, probably, or definitely related to pembrolizumab
NOTE: All events reported expeditiously require follow-up reporting until the event is resolved, stabilized, or	

determined to be irreversible by the investigator.

The DCC should be consulted prior to ending the follow-up of events that have stabilized.

7.7.1 Expedited reporting guidelines **(COH only)**

7.7.1.1 To the COH DSMC/IRB

Serious Adverse Events that require expedited reporting and unanticipated problems will be reported according to the approved City of Hope Clinical Research Adverse Event and Unanticipated Problem policy. This includes all SAEs and UPs that meet COH DSMC/IRB expedited reporting criteria that occurred at COH and non-COH sites. For non-COH sites, the DCC will be responsible for reporting (see section 7.7.2)

7.7.1.2 To Participating Investigators

- Report all expedited reportable AEs to participating investigators as an IND Safety Report occurring within 30 calendar days of receipt of sponsor (lead site) notification, and indicate whether or not a protocol and/or consent form change is required. A cover letter will indicate the protocol title, the IND#, whether the FDA was informed (if applicable), and, for non-COH sites, a statement that the report should be submitted to their local IRB for review if applicable per local IRB policy.

- Forward to participating sites all IND safety reports received from Merck and Acrotech Biopharma, LLC, indicating whether a consent form or protocol change is required within 30 days of notification to Study PI.

7.7.2 Expedited reporting guidelines **(non-COH sites only)**

7.7.2.1 To the DCC/Study PI

All events that meet the criteria specified in Table 7.7 will be reported to the DCC and Study PI within 24 hours of notification that the event met the expedited reporting criteria.

1. Sites are to report to their local IRB per their site's specific institutional and IRB guidelines. As soon as possible, non-COH sites will provide to the COH DCC copies of the IRB submission and corresponding IRB response.
2. Document/describe the AE/UP on each of the following:
    a. MedWatch 3500A or local IRB submission document*
    MedWatch 3500A is downloadable form at http://www.fda.gov/medwatch/getforms.htm
    *The local IRB submission document may be used if the document template is approved by the DCC
    b. Expedited Reporting Coversheet. A modifiable Microsoft Word document is available from the DCC. An electronic signature on the document will be accepted.
3. Scan and email above documents to the Study PI (aherrera@coh.org) and DCC@coh.org with the subject title as "Herrera Pembro-PDX SAE COH IRB #17501".
    a. If available, sites may include the local IRB submission for this event in the submission.
4. If an email receipt from DCC personnel is not received within one working day, please email DCC@coh.org.

7.8 Reporting to the FDA

The PI or designee will be responsible for contacting the Office of IND Development and Regulatory Affairs (OIDRA) at COH to ensure prompt reporting of safety reports to the FDA. OIDRA will assist the PI with the preparation of the report and submit the report to the FDA in accordance with the approved City of Hope Clinical Research Adverse Event and Unanticipated Problem policy.

Serious Adverse Events meeting the requirements for expedited reporting to the Food and Drug Administration (FDA), as defined in 21 CFR 312.32, regardless of the site of occurrence, will be reported as an IND safety report using the MedWatch Form FDA 3500A for Mandatory Reporting.

The criteria that require reporting using the MedWatch 3500A are:

- Any unexpected fatal or life threatening adverse experience associated with use of the drug must be reported to the FDA no later than 7 calendar days after initial receipt of the information [21 CFR 312.32(c)(2)]
- Any adverse experience associated with use of the drug that is both serious and unexpected must be submitted no later than 15 calendar days after initial receipt of the information [21 CFR 312.32(c)(1)]
- Any follow-up information to a study report shall be reported as soon as the relevant information becomes available. [21 CFR 312.32(d)(3)]

The final IND report will be distributed to the Study PI and DCC. If it is determined that the IND safety report requires a change to the protocol or the consent form, the DCC will include instructions to participating sites for local IRB reporting.

In addition, on behalf of the study PI, OIDRA will submit annually within 60 days of the anniversary date of when the IND went into effect, an annual report to the FDA which is to include a narrative summary and analysis of the information of all FDA reports within the reporting interval, a summary report of adverse drug experiences, and history of actions taken since the last report because of adverse drug experiences.

7.9 Reporting to Industry Partners

- **Report to Merck using a MedWatch form, regardless of the site of occurrence, any expedited AEs within 2 working days of being aware of the event.** The initial report will be as complete as possible and include an assessment of the causal relationship between the event and the study agent(s). Information not available at the time of the initial report will be documented on a follow-up report and submitted to Merck.

  The Merck protocol number will be included on expedited reports (or on the fax cover letter). A copy of the fax transmission confirmation of the expedited report to Merck will be retained with the patient records.

  Merck Global Safety
  Attn: Worldwide Product Safety
  Fax: (215) 993-1220

- **Notify and forward information related to Serious Adverse Events (SAEs) to Acrotech Biopharma, LLC** via facsimile or e-mail **using the MedWatch form**, whether the SAE is unexpected or not based on the product investigator's brochure, and whether drug-related or not based on

clinical investigator's assessment, **within 24 hours of becoming aware of the event**. Every effort should be made to provide complete and accurate information on the MedWatch form.

Forms should be e-mailed to:

E-mail: DrugSafety@acrotechbiopharma.com

Please cc: NKapoor@acrotechbiopharma.com for all correspondence

- Report to Merck aggregate safety at time of COH PMT report.
- Forward to Merck and Acrotech Biopharma, LLC copies of initial/annual/final FDA IND submissions.

8.0 AGENT INFORMATION

8.1 Pembrolizumab

Please refer to the IB for a detailed description.
As of September 2017, pembrolizumab is FDA approved for advanced melanoma, metastatic non-small cell lung cancer, recurrent or metastatic head and neck cancer, relapsed/refractory classical Hodgkin lymphoma, advanced/metastatic urothelial carcinoma, unresectable or metastatic microsatellite instability-high cancer or mismatch repair deficient solid tumors, and advanced/metastatic gastric cancer. Refer to the package insert for a detailed description of the indications. Pembrolizumab is not approved for PTCL.

8.1.1 Other Names

KEYTRUDA®, MK-3475.

8.1.2 Description and Molecular Weight

Type	IgG4 kappa monoclonal
Source:	Humanized (from mouse)
Target:	PD-1 receptor
Molecular weight:	147 kDa

8.1.3 Mechanism of Action

Binding of the PD-1 ligands, PD-L1 and PD-L2, to the PD-1 receptor found on T cells, inhibits T cell proliferation and cytokine production. Upregulation of PD-1 ligands occurs in some tumors and signaling through this pathway can contribute to inhibition of active T-cell immune surveillance of tumors. Pembrolizumab is a monoclonal antibody that binds to the PD-1 receptor and blocks its interaction with PD-L1 and PD-L2, releasing PD-1 pathway-mediated inhibition of the immune response, including the anti-tumor immune response. In syngeneic mouse tumor models, blocking PD-1 activity resulted in decreased tumor growth.

8.1.4 Pharmacokinetics

Half-life elimination: 22 days (per package insert).

8.1.5 Human Toxicity

See Section 6.1.1.

8.1.6 Formulation

Pembrolizumab Solution for Infusion is a sterile, non-pyrogenic aqueous solution supplied in single-use Type I glass vial containing 100 mg/4 mL of pembrolizumab. The product is preservative-free, latex free solution which is essentially free of extraneous particulates.

Pembrolizumab Solution for Infusion vials are filled to a target of 4.25mL (106.25mg) to ensure recovery of 4.0mL (100mg).

8.1.7 Storage and Stability

8.1.7.1 Non-diluted product

Pembrolizumab Solution for Infusion, 100 mg/ 4 mL vial: pembrolizumab Solution for Infusion vials should be stored at refrigerated conditions 2 - 8 °C (36 - 46 °F) and protected from light. Do not shake and do not freeze. Vials should be stored in the original box to ensure the drug product is protected from light.

8.1.7.2 Reconstituted and diluted solutions

Pembrolizumab should not be mixed with other diluents.

From a microbiological point of view, diluted solution should be used as soon as possible after preparation.
Pembrolizumab solutions (which contain no preservative) may be stored at room temperature for a cumulative time of up to 6 hours. The 6-hour countdown begins when the vial is pierced and includes room temperature storage of admixture solutions in the IV bags and the duration of infusion. (Please note this 6-hour timeframe is to provide a microbial control strategy. The microbial clock only starts when the product stopper is pierced and not when the vial is removed from the refrigerator).
In addition, IV bags may be stored under refrigeration at 2°C to 8°C (36 °F to 46 °F), total cumulative storage time at room temperature and refrigeration should not exceed 24 hours.

Temperature monitoring records are required when pembrolizumab admixture solution is refrigerated during storage or transfer. Only a period with recorded 2-8 °C can be accounted for refrigerated time. Time when temperature is above 8 °C and below 25°C should be deducted from a 6-hour room temperature storage time bucket.

If refrigerated, allow the IV bags to come to room temperature prior to use.

8.1.8 Handling

Qualified personnel, familiar with procedures that minimize undue exposure to themselves and the environment, should undertake the preparation, handling, and safe disposal of the agent.

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

8.1.9 Preparation

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

Pembrolizumab infusion solutions should be prepared in **0.9% Sodium Chloride Injection, USP** (normal saline) or regional equivalent or 5% Dextrose Injection, USP (5% dextrose) or regional equivalent and the final concentration of pembrolizumab in the infusion solutions should be between 1 mg/mL and 10 mg/ml.

8.1.10 Administration

Refer to Section 5.8.1.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration. Discard the drug product vial if visible particles are observed. In addition, the following precautions should be observed:

- **Do not use pembrolizumab if discoloration is observed.**
- **Do not shake or freeze the vial(s).**

- **Do not administer the product as an intravenous (iv) push or bolus.**
- **Do not combine, dilute or administer it as an infusion with other medicinal products.**

8.1.11 Supplier

The agent will be supplied free of charge by Merck.

8.1.12 Ordering

Sites will be provided with an ordering form.

8.1.13 Accountability

The investigator, or a responsible party designated by the investigator, must maintain a careful record of the inventory and disposition of the agent (investigational or free of charge) using a drug accountability log.

8.1.14 Destruction and Return

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

Any unused agent at the end of the study, expired agent, and damaged agent will be destroyed according to applicable federal, state, local and institutional guidelines and procedures. Destruction will be documented in a drug accountability log.

8.2 Pralatrexate

Please refer to the IB for a detailed description. Pralatrexate is indicated for the treatment of patients with relapsed/refractory (R/R) peripheral T-cell lymphoma (PTCL) with an Objective Response Rate (ORR) of 27%.[57]

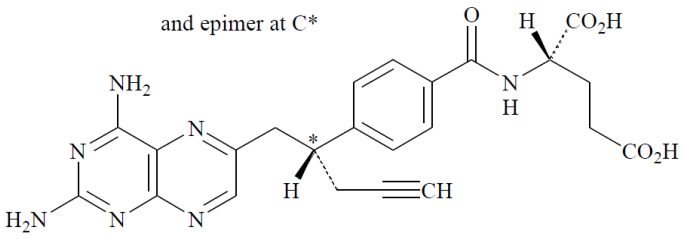
8.2.1 Other Names

FOLOTYN®, DIFOLTA.

8.2.2 Description and Molecular Weight

Pralatrexate is a 10-deazaaminopterin analog of the DHFR inhibitor methotrexate, with a propargyl substitution at the carbon-10 (C-10) position. The molecular weight of pralatrexate is 477.5 g/mol.

The structural formula of pralatrexate is shown below:



Pralatrexate is a 1:1 racemic mixture of S- and R- diastereomers at the C10 position (indicated with *).

The molecular formula of pralatrexate is: $C_{23}H_{23}N_7O_5$

8.2.3 Mechanism of Action

Pralatrexate is a folic acid analog metabolic inhibitor that competitively inhibits dihydrofolate reductase. Similar to what has been reported for methotrexate, cellular uptake of pralatrexate is thought to occur via the RFC-1 protein. Inside the cell, pralatrexate is polyglutamated by folylpolyglutamyl synthase (FPGS), an enzyme involved in polyglutamation of reduced natural folates. Therefore, pralatrexate may also act as a competitive inhibitor for polyglutamation of natural folates. Further, it is believed that the addition of glutamate residues to pralatrexate leads to increased intracellular half-life (t1/2), thus allowing for prolonged drug action in malignant cells.[56]

Treatment with pralatrexate leads to depletion of thymidine and other biological molecules, the synthesis of which depends on 1-carbon transfer. Depletion of thymidine results in inhibition of DNA replication and thus interference with cell proliferation.

8.2.4 Pharmacokinetics

Refer to package insert.[57]

8.2.5 Human Toxicity

See Section 6.1.2.

8.2.6 Formulation

Refer to package insert.

8.2.7 Storage and Stability

Pralatrexate Injection should be stored refrigerated (2-8ºC) and protected from light. Refer to package insert.

8.2.8 Handling

Qualified personnel, familiar with procedures that minimize undue exposure to themselves and the environment, should undertake the preparation, handling, and safe disposal of the agent.

Appropriate mask, protective clothing, eye protection, gloves, and Class II vertical-laminar-airflow safety cabinets are recommended during preparation and handling.

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

8.2.9 Preparation

Follow package label instructions.

8.2.10 Administration

Refer to Section 5.8.2.

8.2.11 Supplier

Pralatrexate is commercially available and will be sourced locally as per standard of care.

9.0 CENTRAL REVIEW & CORRELATIVE/ SPECIAL STUDIES

9.1 Biomarker Research

Immunologic and genomic biomarkers have been associated with tumor response to immunotherapy, including checkpoint inhibitors like pembrolizumab. We propose to evaluate a series of exploratory immunologic and genomic correlatives to explore the association between each biomarker and response or resistance to combined pembrolizumab and pralatrexate therapy. The correlative studies described below are exploratory in nature, and meant to be hypothesis-generating -they will not be powered for statistical significance. The below description is an anticipated rather than an exact list of studies that will be performed, as the investigators reserve the right to adjust the studies to be performed as techniques evolve and new data may become available that is relevant to the study agent and/or study population.

Correlative studies will mainly be performed in the laboratories of Peter Lee, MD, Chair of the City of Hope Beckman Research Institute Division of Cancer Immunotherapeutics and Tumor Immunology, and John Chan, MD, Professor of Pathology at City of Hope Medical Center.

・Immunologic Biomarkers:

PD-L1 expression in tumor cells is a biomarker for response to anti-PD1 therapy in solid tumors.[61] PD-L1 expression has also been demonstrated in all HL patients tested who responded to PD-1 inhibition with pembrolizumab or nivolumab.[43,62] Furthermore, the pattern and spatial relationship between PD-1 and PD-L1-expressing cells are associated with response in patients with melanoma treated with pembrolizumab.[63]

The presence, abundance, and composition of tumor infiltrating lymphocyte (TIL) populations in various tumor types are associated with clinical outcome.[64-66] In addition, the presence of certain TIL populations, particularly CD8+ T-cells, and their spatial orientation in tumors is associated with outcome after immunotherapy, including PD-1 blockade with pembrolizumab.[63,67] Using high-resolution spectral analysis and automated scanning of tissue sections, the Lee laboratory at City of Hope has developed a technique for quantitative, spatial IHC analysis of TIL and other immune cell subsets in a tumor. The Lee lab has demonstrated that spatial grouping patterns of TILs and dendritic cells differ between tumor-draining lymph nodes and normal lymph nodes and are associated with outcome in patients with breast cancer.[68,69]

We will evaluate the relationship between PD-1, PD-L1, and PD-L2 expression, and potentially other checkpoint receptors/ligands by immunohistochemistry (IHC) in pre-treatment tumor samples and response to study therapy. We will perform quantitative, spatial IHC analysis using the Vectra system in the Lee laboratory, including PD-1, PD-L1, PD-L2, other checkpoint receptors/ligands, dendritic cells, tumor associated macrophages,[70] TILs including regulatory T-cells, and possibly other immune cell subsets and explore the association with response to study therapy. We will also analyze changes in immune cell subsets by flow cytometry on peripheral blood mononuclear cells (PBMCs) at baseline and during treatment and explore the association with response to study therapy. Cytokine analyses may be performed on the plasma portion of these samples.

・Genomic Biomarkers:

Genomic signatures define distinct subsets of T-cell lymphomas and are associated with outcome after standard therapy.[71-73] Molecularly distinct subgroups exist even within PTCL histologic subtypes that are biomarkers of outcome and enhance prognostication over simple morphologic classification. Genomic

studies have elucidated tumor target-specific and microenvironmental characteristics that predict response to novel immunotherapies, including checkpoint inhibitors. One key target-specific genomic biomarker of response to immunotherapy is a tumor's mutational burden. In clinical trials of melanoma patients treated with the anti-CTLA-4 antibody, ipilimumab, and non-small cell lung cancer (NSCLC) patients treated with pembrolizumab, patients with a higher mutational load in pre-treatment tumor samples have a higher rate of durable clinical benefit, objective response rate, and improved survival compared to patients with fewer mutations.[74,75] Nonsynonymous genetic mutations result in the formation of neoantigens that improve recognition of the tumor by the host immune system, which appears to drive anti-tumor responses in the enhanced effector cell milieu created by checkpoint blockade. Similarly, in melanoma patients who have durable, complete responses after adoptive TIL therapy, specific neoantigens resulting from nonsynonymous mutations can be identified that are responsible for the robust anti-tumor responses observed.[76,77]

In addition to a tumor's mutational profile, tumor gene expression patterns impact response to novel immunotherapies. Increased expression of genes that encode for immune-related targets, such as T-cell surface markers, immune receptors, and cytokines/chemokines, in pre-treatment melanoma tumor samples are associated with response to ipilimumab.[78] Similarly, overexpression of immune-related genes in pretreatment tumors of patients with melanoma and NSCLC is associated with outcome after treatment with an antigen-specific tumor vaccine and immunostimulant.[79]

We will explore whether genomic signatures as determined for example by mutational or gene expression profiles in pre- and post-treatment tumor samples are associated with response and outcome after pralatrexate plus pembrolizumab therapy.

・Circulating tumor DNA:

The detection of circulating tumor DNA (ctDNA) has been studied in lymphoma. Next-generation sequencing (NGS)-based ctDNA detection performed by NGS of the immunoglobulin (Ig) or T-cell receptor (TCR) genes can identify ctDNA in the peripheral blood mononuclear cells (PBMC) and plasma (cell-free DNA) at diagnosis in a range of lymphomas, including classical Hodgkin lymphoma and diffuse large B-cell lymphoma (DLBCL).[80-83] In addition, ctDNA levels correlate with treatment response in DLBCL, and the persistence or recurrence of ctDNA during and after upfront therapy is associated with subsequent DLBCL relapse.[82,83] Ig/TCR-NGS assessment of can detect ctDNA in patients with PTCL prior to and after allogeneic stem cell transplantation.[84] While the Ig-NGS method is powerful, the investigation of only *Ig* and *TCR* genes limits its sensitivity, resulting in a sizable minority of patients in whom the assay is not applicable. Meanwhile, ctDNA assessment using NGS for recurrent mutations and rearrangements has been explored in DLBCL, and the method appears feasible and highly sensitive.[85,86].

We will explore the performance of ctDNA assessment in the peripheral blood by capture-based NGS for recurrent somatic mutations in PTCL and explore the value of ctDNA as a biomarker of response to study therapy.

9.2 Tumor tissue

Each subject will have available archival tissue from a biopsy that was performed after the most recent systemic therapy or a fresh core or excisional biopsy of a tumor lesion (performed as standard of care) prior to starting study therapy. Exception can be granted by the PI if a biopsy is not feasible and/or safe. If feasible and safe, all subjects will also undergo biopsy of a tumor lesion at the time of disease progression (as part of standard of care).

9.2.1 Tumor tissue handling guidelines

9.2.1.1 Guidelines for paraffin-embedded specimens

Using the formalin-fixed paraffin embedded (FFPE) tissue block, the following samples will be processed for correlative studies:

- If tissue block is available submit (e.g. archived at participating study site):
  - 6 paraffin scrolls measuring 10 µm thick placed into a Nunc tube and frozen at -80° C AND
  - 10 x 5 micron unstained slides
- If tissue block is unavailable (e.g. archived at external site):
  - submit 20 x 5 µm unstained slides
  - 5 of these unstained slides will be processed according to the QualTek Sample Handling Manual.

9.2.1.2 Guidelines for fresh tumor tissue processing

Non-COH sites:

After core biopsies are obtained for standard of care diagnostic purposes, 3 core biopsies (or fewer if it is not feasible to take 3 biopsies for research purposes) or 3 portions (1cm x 1cm) of excisional biopsy tumor specimens should be flash frozen and kept at -80^{o}C until batch shipment.

COH only:

Three core biopsies OR 3 separate tissue sections from excisional biopsies should be submitted. If fewer than 3 core biopsies are available because of safety, then 1 or 2 cores may be submitted.

Core biopsies:

Three core biopsies will be obtained for diagnostic purposes and 3 (if feasible) similar additional cores will be obtained for research.

The research portion of the specimen (banking):

- One core biopsy will be snap frozen in OCT fixative, and an additional half of a core will be snap frozen without OCT fixative.
- Half of a core will be finely minced in a 10cm petri dish and frozen at -80° C in a Nunc tube in 1 ml of RPMI-1640 medium containing 20% fetal calf serum and 10% DMSO, then will be transferred to liquid nitrogen.
- Half of a core will be processed for DNA and RNA extraction according to the manufacturer's recommendation.
- The final half of a core biopsy will be processed to dissociate the cells, with the cell suspension cryopreserved in liquid nitrogen.

Excisional biopsies:

- An approximately 1cm x 1cm tumor sample will be divided into 5 equal portions and processed as described for core biopsies.

The diagnostic portion of the specimen:

- Process in a routine fashion by hematopathology. Using the formalin-fixed paraffin embedded (FFPE) tissue block, 15 x 5 micron unstained slides will be obtained
  - 5 of these unstained slides will be processed according to the QualTek Sample Handling Manual.

9.2.1.3 Labeling of samples

Samples will be labeled with the study number, institution, subject ID (issued by DCC), date, time point of collection (i.e. baseline or progression), and if applicable patient initials.

9.2.1.4 Sample shipment and receiving lab

Tissue specimens collected at the above indicated time points will either be taken to (COH only) or batch-shipped (non-COH sites) to COH Pathology Core. For all sites, please include the **Correlative Tissue form (Appendix G)** with your shipment.

Please note that samples should be **batch shipped from non-COH sites on Monday to Wednesday** in time for receipt Tuesday to Friday. **Refer to** Appendix H **for tissue shipping details.**

9.3 Correlative blood collection

9.3.1 Overview and Time points

Peripheral blood (PB) will be collected prior to study treatment/procedures on C1D1, C2D1, C4D1, C5D1, and at EOT*. Refer to Table 9.3.1 for details.Table 9.3.1 Overview of correlative blood studies

Time points of collection	Total volume collected	Tube type	Receiving laboratory	Type of analysis (non-exhaustive)
C1D1, C2D1, C4D1	20 ml	Green-top (sodium or lithium heparin)	APCF	FACS/Cytokine
C1D1, C2D1, C5D1, and at EOT*	20 ml	Purple-top (K+EDTA) **(For all COH patients)** **OR** Cell-free DNA BCT® (Streck) **(For all non-COH patients)**	APCF	ctDNA/MRD

***EOT time point:** correlative blood will not be collected if a correlative blood sample for ctDNA/MRD (purple-top/cell-free DNA BCT® tube) was collected within the prior 8 weeks.

APCF = Analytical Pharmacology Core Facility (COH).

9.3.2 Labeling of blood samples

Label tubes with COH protocol #, subject ID (issued by DCC), institution (for non-COH sites), date and actual timepoint of collection (e.g. D1C1 for Day1 of Cycle 1), and if applicable patient initials.

9.3.3 Blood collection

9.3.3.1 Notifying the receiving laboratory

Before a scheduled blood collection (at least one day in advance) e-mail Leslie Smith-Powell (LSmith-Powell@coh.org) or Stephanie Lee (stlee@coh.org) at the Analytical Pharmacology Core Facility (APCF) to inform them of a pending collection.

9.3.3.2 Order of draw for the research blood samples

Please draw purple-top/ Cell-free DNA BCT® (Streck) tubes **before** the green-top tubes.

Any heparin in the collection tube of the line used to draw the blood in a purple tube/ Cell-free DNA BCT® tube will make it unusable.

If a purple tube/ Cell-Free DNA BCT tube immediately follows a heparin (green-top) tube in the draw order (for example if the last clinical/non-research sample was collected in a green-top tube), please collect a non-additive or EDTA tube as a waste tube prior to collection in the purple tube/ Cell-Free DNA BCT tube.

If applicable, Cell-Free DNA BCT tubes can also be drawn after the EDTA tube and before the fluoride oxalate (glycolytic inhibitor) tube.

9.3.3.3 Collection and post-collection guidelines

Refer to Table 9.3.3 for collection and post-collection instructions.

Refer to **Appendix I** and **Appendix J** for blood collection form and blood shipping guidelines, respectively.

Table 9.3.3. Blood sample collection and post-collection instructions.

Tube Type	Collection details	Site of collection	Post-collection instructions
Green-top	1- Blood samples will be collected from an indwelling venous catheter or by venipuncture. 2- Invert tubes eight times after collection. 3- **Immediately** place the tubes on **ice**.	COH	**Promptly** deliver the blood samples on ice to the APCF, Shapiro room 1042 for processing **within 4 hours**.
		Non-COH	**Ship overnight** at **~+4°C** to APCF laboratory. See Appendix J. Include with shipment: - Blood sample collection form (Appendix I). - Copy of latest CBC results (with differential) and date of test.
Purple-top	Same as for green-top.	COH Only	**Promptly** deliver the blood samples on ice to the APCF, Shapiro room 1042 for processing **within 4 hours**.
Cell-free DNA BCT® (Streck)*	1- Blood samples will be collected from an indwelling venous catheter or by venipuncture. **Prevention of backflow:** *(Because cell-free DNA BCT® contain chemical additives)* a. Keep patient's arm in the downward position during the collection procedure. b. Hold the tube with the stopper in the uppermost position so that the tube contents do not touch the stopper or the end of the needle during sample collection. c. Release tourniquet once blood starts to flow in the tube, or within 2 minutes of application. 2- Fill tube completely. 3- Remove tube from adapter and immediately mix by gentle inversion 8 to 10 times. 4- **Do not freeze** samples. Store samples at 18-25°C until shipment.	Non-COH Sites only	Ship to APCF laboratory. See Appendix J. Include with shipment: - Blood sample collection form (Appendix I). - Copy of latest CBC results (with differential) and date of test.

* Tubes are stable when stored at 2-30°C through expiration date. Do not use expired tubes. If there is any indication of cloudiness or visible precipitate immediately contact the the COH Data Coordinating Center (DCC). Contact information: E-mail: DCC@coh.org.

9.3.4 Sample Processing by APCF (COH)

All blood samples will be processed at COH APCF. External (non-COH) sites will only be expected to collect and ship whole blood to COH APCF.

Blood samples will be kept on a rocker set at low speed to mimic circulation and avoid clot formation until processing.

Green-top tubes (PBMCs AND plasma), for FACS/Cytokine assays:

(Process within 4h of collection for COH samples OR upon receipt of non-COH samples).

・Centrifuge for 10 min at 1800g at 4°C. Both supernatant and pellet will be used.

・Plasma:

- The resulting upper plasma layer from each tube will be drawn up sequentially into a sterile 5 mL syringe and pushed through a sterile 0.2/0.8 micron disposable filter.
- The filtered plasma will then be transferred in 500 µL aliquots into multiple appropriately-labeled Starstedt microfuge tubes.
- To one aliquot, add 0.5 mL glycerol/0.02% sodium azide solution to dilute the plasma 50/50 v/v. Keep the diluted plasma sample at -20˚C and do not freeze.
- All the remaining plasma aliquots will be stored frozen at -80˚C until ready for testing.

・PBMCs:

- Dilute the blood remaining in the green-top tubes used to prepare plasma above 1:1 with Hank's Balanced Salt Solution (or equivalent) in a sterile conical centrifuge tube.
- Isolate PBMCs by Ficoll-gradient separation per COH APCF procedures.
- PBMCs samples will be stored in liquid nitrogen until use.

Purple-top and Cell-free BCT tubes (Plasma and PDWB), for sequencing assays:

Purple-top (~20 mL) **(Collected from COH patients only)**	Plasma and Plasma depleted whole blood cells (PDWB)	1. Centrifuge for 10 minutes at 1800 x g at 4°C. 2. Remove the tubes from the centrifuge. Do not disturb the cellular layer. 3. Extract plasma carefully. a. **Do not disturb** the **buffy coat** while pipetting plasma; leave ~3-4mm of plasma behind to ensure the buffy coat is undisturbed. b. **Save** the PDWB portion (see below). 4. Freeze plasma at -80°C in 1-2mL aliquots. Do not fill tubes beyond 70% capacity.
		5. Mix the remaining PDWB. *6.* Freeze at -80°C in 1-2mL aliquots.

Cell-free DNA BCT (~20 mL) **(Collected from non-COH patients only)**	Plasma and Plasma depleted whole blood cells (PDWB)	*1.* Centrifuge for 10 minutes at 1600 x g at **room temperature.** *2.* Remove the upper plasma layer and transfer to a new conical tube. **Save** the PDWB portion (see below). *3.* Centrifuge the plasma at 16000 x g for 10 minutes. *4.* Collect the plasma. *5.* Freeze plasma at -80°C in 1-2mL aliquots. Do not fill tubes beyond 70% capacity.
		6. Mix the remaining PDWB. *7.* Freeze at -80°C in 1-2mL aliquots.

10.0 STUDY CALENDAR

All procedures may increase in frequency if clinically indicated.

Table 10 Study Activity Calendar

Protocol Activity	Screening (Days -28 to D1)	Protocol Therapy (Cycles)[a, c, m] (± 3 Days for all time points except [g])															EOT[p]	Follow-up[w]		
		To be repeated (except [e and l])																		
		1		2		3		4			5		6		7			Safety post[b]	Response[q] (Every 12 weeks)	Survival[z] (Every 12 weeks)
		D1	D8	D1	D8	D1	D8	D1	D8	D15[g]	D1	D8	D1	D8	D1	D8				
Informed Consent	X																			
Eligibility Criteria	X																			
Registration	X																			
Medical History	X																			
Prior and Con. Med. review	X	X	X	X	X	X	X	X			X	X	X	X	X	X		X		
Post-study anti-cancer ther. status																		X	X	X
Survival status		X	X	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X
Pembrolizumab		X		X		X		X			X		X		X					
Pralatrexate		X	X	X	X	X	X	X	X		X	X	X	X	X	X				
Leucovorin[d]		X	X	X	X	X	X	X	X		X	X	X	X	X	X				
Vitamin B12[e]	X							X												
Folic acid[n]	X	X																		
AE review		X	X	X	X	X	X	X	X		X	X	X	X	X	X	X	X		
Physical Exam.	X	X	X	X	X	X	X	X	X		X	X	X	X	X	X	X	X		
Vital signs[f]	X	X	X	X	X	X	X	X	X		X	X	X	X	X	X	X	X		
ECOG status	X	X	X	X	X	X	X	X	X		X	X	X	X	X	X	X	X		
Pregnancy Test [o]	X[k]	X		X		X		X			X		X		X		X	X[s]		
PT/INR and aPPT	X[*]																			
CBC w/diff, Plt	X[*]	X	X	X	X	X	X	X	X		X	X	X	X	X	X	X	X		
Serum Chemistry[u]	X[*]	X	X	X	X	X	X	X	X		X	X	X	X	X	X	X	X		

Protocol Activity	Screening (Days -28 to D1)	Protocol Therapy (Cycles)[a, m] (± 3 Days for all time points except [g])															EOT[p]	Follow-up[w]		
								To be repeated (except [e] and [l])												
		1		2		3		4			5		6		7			Safety post[b]	Response[q] (Every 12 weeks)	Survival[z] (Every 12 weeks)
		D1	D8	D1	D8	D1	D8	D1	D8	D15[g]	D1	D8	D1	D8	D1	D8				
Urinalysis[x]	x*																			
Thyroid Test[v]		x				x					x						x			
PET-CT or CT N/C/A/P[h]	x									x							x[r]		x	
Archival or Newly Obtained Tumor Tissue Collection	x[i]																x[i]			
Bone Marrow Aspirate and Biopsy [j]	x[y]																			
Correlative Blood Collection		x		x				x[l]			x[l]						x[t]			

* Tests to be performed within 28 days of treatment initiation.

a. In the absence of a delay due to toxicity, each treatment cycle lasts 21 days ± 3 days.

b. Safety visit to occur 30 (-2/+7) days post-last dose of protocol therapy. At the end of the treatment, each subject will be followed for 30 days for adverse event monitoring, and 90 days for severe adverse events and events of clinical interest. Safety follow up may be extended until resolution/stabilization of reportable AEs.

c. Protocol therapy will continue for a maximum of 24 months until progressive disease, unacceptable toxicity, withdrawal of consent, pregnancy of the subject, non-compliance, or administrative reasons.

d. Leucovorin will be administered orally three times daily (every 8 hours) for 2 days for a total of 6 doses **beginning 24h (+/- 2h) after each dose of pralatrexate** is administered. Refer to Section 5.13.2.

e. Vitamin B12 (1 mg IM) will be administered anytime within 10 weeks prior to initiation of pralatrexate (per pralatrexate product insert) and can be administered during screening, and will be administered every 3 cycles. Administration should continue during the full course of pralatrexate therapy and for 30 days after the last dose of pralatrexate. Refer to Section 5.13.2.

f. Vital signs: Weight, heart rate, blood pressure, respiration rate, and temperature. Height required only at baseline.

g. To be done between D15 and D21 (-3 days).

h. Disease staging is performed at screening and every 4 cycles until disease progression or off study therapy. Disease staging will be by either PET/CT (preferred) or CT scan, but, in patients with FDG-avid disease, it will be preferred (but not mandatory) to have PET/CT at baseline, Cycle 4 and every 8 cycles thereafter. Note: if there is no evidence of neck involvement by lymphoma at baseline, CT of chest, abdomen and pelvis (C/A/P) can be performed instead of N/C/A/P at subsequent re-staging.

i. Tumor biopsy tissue will be obtained after routine diagnostic biopsy is done with the patient's consent. Exception can be granted by the PI if a biopsy is not feasible and/or safe. For the EOT time point, tumor tissue will be collected from a standard of care tumor biopsy performed at the time of lymphoma relapse/progression (if such a biopsy is performed), unless the tumor is inaccessible or there is a safety concern.

j. Following initial screening, and unless clinically indicated, bone marrow specimens will be collected only to confirm CR.

k. 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.

l. Do not repeat this time point for correlative blood collection: peripheral blood is collected prior to study treatment/procedures on C1D1, C2D1, C4D1, C5D1, and at EOT (see also footnote t).

m. Day 8 labs/visits are set up because of pralatrexate administration on these days. If a patient discontinues pralatrexate (and continues with pembrolizumab alone), these Day 8 labs/visits can be omitted.

n. Folic acid supplementation is to begin within 10 days (as early as possible) prior to the first dose of pralatrexate administration (per pralatrexate product insert). However, if folic acid was not taken but MMA (methylmalonic acid) and HCY (homocysteine) levels were checked and are in normal range at screening, the investigator can decide to start study therapy immediately. Administration should continue during the full course of pralatrexate therapy and for 30 days after the last dose of pralatrexate. Refer to Section 5.13.2.

o. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required. Pregnancy testing will also be performed whenever an expected menstrual cycle is missed or when pregnancy is otherwise suspected.

p. Assessments to be performed within 10 days of treatment discontinuation (except tumor imaging, see footnote r). Assessments performed after last dose of study agent and within 7 days of the decision to end treatment may serve as EOT assessments.

q. For participants yet to progress. Follow-up will occur every 12 weeks (-/+ 7 days) starting from last on-treatment scan. After one year, the imaging time point will occur every 18 weeks (+/- 7 days). Response Follow-up will be performed until progression or off study, and for at least one year in each patient who did not progress yet.

r. PET-CT (or CT) at time of discontinuation (EOT) will **only** be performed in patients who discontinue treatment for disease progression. Note: if a previous scan was obtained within 4 weeks prior to the date of discontinuation, then repeating the scan at treatment discontinuation is not mandatory. For patients who discontinue treatment for other reasons than disease progression (e.g. for toxicity, CR): PET-CT (or CT) will not be performed at EOT and will be performed 12 weeks

after their last scan, and according to the follow-up schedule thereafter (refer to footnote q for the frequency of scans during the follow-up period).

s. Pregnancy test will be performed at the safety visit (30 days post last dose of protocol therapy).

t. EOT time point: correlative blood will not be collected if a correlative blood sample for ctDNA/MRD (purple-top/cell-free DNA BCT® tube) was collected within the prior 8 weeks.

u. Serum chemistry panel to include: glucose, Blood Urea Nitrogen (BUN), creatinine, uric acid, total protein, albumin, magnesium, calcium, inorganic phosphorus, sodium, potassium, chloride, total CO_2 or bicarbonate, total bilirubin, direct bilirubin (if total bilirubin is elevated above the upper limit of normal), alkaline phosphatase, ALT, AST, and LDH.

v. Thyroid test includes TSH only.

w. Please refer to Section 5.11 for details about the Follow-up period.

x. Urinalysis to include blood, glucose, protein, specific gravity, and microscopic exam (if abnormal).

y. Bone marrow biopsy at screening is not mandatory, and should only be performed if clinically indicated (e.g. for cytopenias).

z. Participants who end Response Follow-up will enter Survival Follow-up. Survival assessment to occur bi-annually or as requested by the Study PI via medical record review, review of social security registry, or telephone call.

11.0 ENDPOINT EVALUATION CRITERIA/MEASUREMENT OF EFFECT

11.1 Response/Progression

Disease response/progression will be evaluated using 2014 Lugano Classification (see Appendix B) [8,11]. Participants who meet the definition of progressive disease per Lugano Classification should be evaluated using the LYRIC criteria[10] (see Appendix C). The ORR and CR rate will also be estimated according to the International Harmonization Project response criteria (Cheson 2007).[9]

PET-CT or diagnostic quality CT of the neck, chest, abdomen, and pelvis (N/C/A/P) with IV contrast will be performed at baseline (within the screening window, 28 days) prior to initiation of study therapy, and then after initiation of study therapy during cycle 4 and every 4 cycles thereafter until disease progression or off study therapy. Refer to study calendar (footnote r) for disease staging at EOT. Disease staging will be by either PET/CT (preferred) or CT scan, but, in patients with FDG-avid disease, it will be preferred (but not mandatory) to have PET/CT at baseline, Cycle 4 and at least every 8 cycles thereafter. In patients with FDG-avid disease, CR must be confirmed with PET/CT. Patients who enter CR with study therapy can be monitored with diagnostic quality CT scans thereafter until disease progression. MRI may be performed at the investigator's discretion for lesions not well-visualized by CT, or if CT with intravenous contrast is contraindicated. PET-CT and CT results will be read by radiology at each study site and investigator response based on radiology reading will be performed. Lymphoma response assessment based on PET-CT/CT will be based on the 2014 Lugano Classification (Appendix B).[8,11]

Note: if there is no evidence of neck involvement by lymphoma at baseline, CT of chest, abdomen and pelvis (C/A/P) can be performed instead of N/C/A/P at subsequent re-staging.

Following initial screening, and unless clinically indicated, bone marrow specimens will be collected only to confirm CR.

For patients with progression of disease on imaging, it is strongly recommended that a confirmatory biopsy (performed as standard of care) be obtained whenever possible. Note that only an FDG-negative PET scan will be considered complete remission in patients whose tumor was FDG-avid at baseline.

11.2 Clinical Endpoint Definitions

Overall Response Rate (ORR): Defined as the proportion of patients that have a documented CR or PR at any time during study treatment.

Complete Response (CR) rate: Defined as the proportion of patients that have a documented CR at any time during study treatment.

Duration of Response (DOR): Defined as the time from the first achievement of PR or CR to time of PD. Patients who never achieve PR or CR are excluded. Patient who has not had disease progression/relapse at last follow-up is censored at the time of last follow-up.

Overall Survival (OS): Defined as time from initiation of study therapy to death from any cause. If a patient is alive at the last evaluation time period, survival time is censored at the time of last follow-up.

Progression-Free Survival (PFS): Defined as the time from initiation of study therapy to the first observation of disease relapse/progression or death from any cause, whichever occurs first. If the patient has not progressed relapsed or died, the patient is censored at the time of last follow-up.

Toxicity: Toxicity and adverse events will be recorded using the NCI CTCAE 5.0 scale. Observed toxicities will be summarized by type (organ affected or laboratory determination such as absolute neutrophil

count), severity (by NCI CTCAE v5.0 and nadir or maximum values for lab measures), date of onset, duration, reversibility, and attribution.

Unacceptable Toxicity: defined as one of the following AEs that is at least possibly related to study treatment:

- Any ≥ **grade 3 immune-related AE** (IrAE) that does not resolve to grade ≤ 1 within 7 days with the exception of:
  - Grade 3 immune-related hepatitis if ALT or AST < 8 x ULN or total bilirubin < 5 x ULN.
  - Grade 3 asymptomatic endocrinopathy.
  - Inflammatory response attributed to local antitumor response.
  - Vitiligo or alopecia of any grade.

- Any non-hematologic **grade 4 AE** that does not resolve to grade ≤ 1 within 7 days with the exception of:
  - Grade 4 asymptomatic lipase or amylase without evidence of pancreatitis
  - Grade 4 asymptomatic laboratory abnormalities including, but not limited to, hypo- or hyperglycemia, hypo- or hypernatremia, hypo- or hyperkalemia, hypo- or hypermagnesemia, hypo- or hyperphosphatemia, or hyperuricemia that do improve within 48 hours to Grade ≤ 2 with supportive measures.
  - Inflammatory response attributed to local antitumor response.

- Any Grade 5 AE.

12.0 STATISTICAL CONSIDERATIONS

12.1 Study design overview

This is a multi-center, single arm phase 1/2 study of pembrolizumab plus pralatrexate for patients with relapsed/refractory PTCL. Patients will receive 21-day cycles of the combination therapy up to 2 years until disease progression, unacceptable toxicity, or until the patient meets any criteria for removal from protocol therapy in Section 5.10, whichever is earlier. Response will be assessed every 4 cycles. The phase 1 dose-escalation portion of the study, with 2 dose levels and 1 possible de-escalation dose level (Table 5.3), will determine the MTD and the RP2D of the combination therapy. After the completion of the phase 1 portion, additional patients will be enrolled and treated at the RP2D in the Phase 2 portion. Another primary endpoint is overall response rate per the Lugano classification.[8] Secondary endpoints include CR rate, duration of response, overall survival, progression-free survival, ORR and CR rate per the International Harmonization Project response criteria (Cheson 2007)[9] and response status based on LYRIC criteria[10].

12.1.1 Phase 1 design

During the Phase 1 portion of the study, a modified, more conservative version of the Rolling 6 design of Skolnik et al will be employed.[87] In this design, at most, 3 patients will be under observation for DLT on the current test dose level at any time. DLT observation period is 2 cycles (defined in Section 5.5). DLTs are defined in Section 5.5. Patients who are not evaluable for DLT (defined in Section 5.7), i.e., those who did not receive the doses of pembrolizumab during DLT period (not due to DLT) or those who missed any doses of pralatrexate during DLT period (not due to DLT), will be replaced. Once 3 patients are evaluable

with no patient at that dose level experiencing a DLT, the dose can be escalated, or up to 3 additional patients may be treated at the current dose level. No more than 6 evaluable patients will be accrued to any dose level. Escalation will terminate as soon as ≥ 2 patients experience DLT at a given dose level. If 1/6 patients experience DLT at the current dose level, the dose will be escalated to the next higher level. If more than 1/6 patients experiences DLT, then the next lower dose will be expanded. MTD will be declared the highest dose level at which 6 evaluable patients have been treated and, at most, 1/6 patients experiences DLT. The MTD will be considered the RP2D, unless the PI chooses a lower dose level, based on toxicity in subsequent cycles.

These rules are outlined in the Table below.

Table 12.1.1. Dose Escalation Rules

# Patients on Current Level			Action
With DLT^	**Evaluable**	**Evaluable + At Risk^**	
0	0	1-2	Accrue next patient at this level*
0	0	3	Hold accrual
0	1	1-3	Accrue next patient at this level
0	1	4	Hold accrual
0	2	2-4	Accrue next patient at this level
0	2	5	Hold accrual
0	3-6	3-6	Accrue next patient at the next higher level*,+
1	1	1-2	Accrue next patient at this level
1	1	3	Hold Accrual
1	2	2	Accrue next patient at this level
1	2	3-4	Hold accrual
1	3-5	3-5	Accrue next patient at this level
1	3-5	6	Hold accrual
1	6	6	Accrue next patient at the next higher level*
2**	any	any	Accrue next patient at next lower level (max 6)

^: DLT: a patient with a documented DLT

Evaluable: a patient who is either fully evaluable for toxicity for the purpose of dose escalations or has a DLT

At Risk: a patient who is on treatment and has not yet passed the evaluation period nor had a DLT

*: During the dose-escalation portion, if higher dose level is already closed, the next lower dose will accrue to a total of 6 patients, with 2 or higher DLTs requiring further dose de-escalation.

+: Although under this scenario escalating to the next higher dose level is suggested, additional patients can be accrued to the current level -up to n=6 patients.

**: Patients treated on a higher dose will have their treatment modified to the dose below the dose level with 2 DLTs, if pending patients have DLT.

12.1.2 Phase 2 Design

In the phase 2 portion, patients will be treated at the RP2D. The phase 2 portion of this study will implement a Gehan two-stage design[88] to estimate the ORR and to evaluate the activity of the combination therapy. Patients treated during the Phase 1 portion at the RP2D will be included in the Phase 2 evaluations if they are evaluable for response, defined as patients who received at least 1 dose of pembrolizumab and at least 1 dose of pralatrexate and had at least 1 disease assessment (Section 5.7). The sample size is based on the desire to estimate the response rate with approximately 10% standard error, and early stopping if the combination is unexpectedly ineffective. In the pivotal PROPEL trial, the overall response rate (ORR) in 109 evaluable patients who received pralatrexate as a single agent was 29%, including 12 (11%) complete responses (CR) and 20 (18%) partial responses (PR).[5]

The phase 2 portion of the study is expected to evaluate a minimum of 7 and a maximum of 24 patients, including the patients treated at RP2D during the Phase 1 portion that are evaluable for response. At stage 1, if 0 responses are seen in the first 7 evaluable patients (including up to 6 patients enrolled during the Phase 1 portion that are evaluable for response), the study will be terminated and the true ORR will be declared ≤35%. If at least 1 patient responds, the trial will continue to the second stage. At stage 2, a total of 24 patients will be evaluated (including up to 6 patients enrolled during the Phase 1 portion that are evaluable for response).

This design provides for estimation of the response rate with approximately 10% standard error. The standard error will be 9.4%-10.2% after 24 patients if the ORR rate is 30%-70%. The maximum width of the 95% exact binomial confidence interval for ORR will be 42% after 24 patients. Under this design if the ORR is >35%, there would be ≥95% chance of at least one response among the first 7 patients.

12.2 Sample size accrual rate

The expected sample size is 30 evaluable patients: 12 during the Phase 1, and 18 additional patients in the Phase 2, assuming 6 patients treated at RP2D during the Phase 1 are also evaluable for response. Between 3-4 high-volume PTCL centers, we expect to accrue 12 patients at COH and 30-36 total in 48 months. The expected sample size may go up to 36 evaluable patients if the higher 2 dose levels are not safe and the lowest dose level is safe (18 in the Phase 1 and 18 in the Phase 2). Patients evaluable/inevaluable for Phase 1/2 portions are described in Section 5.7. Considering replacement of inevaluable patients, the maximum study accrual is set at 40 patients.

12.3 Statistical analysis plan

12.3.1 Demographic and Baseline Characteristics

Patient demographic and baseline characteristics, including age, gender, medical history, and prior therapy, will be summarized using descriptive statistics. For continuous variables, descriptive statistics (number [n], mean, standard deviation, standard error, median (range) will be provided. For categorical variables, patient counts and percentages will be provided.

12.3.2 Toxicity Analysis

Observed toxicities will be summarized by type (organ affected or laboratory determination such as absolute neutrophil count), severity (by NCI CTCAE v5.0 and nadir or maximum values for lab measures), date of onset, duration, reversibility, and attribution.

12.3.3 Analysis of Anti-tumor Activity

This study will aim to obtain an estimate of the anti-tumor activity of the study combination. ORR will be calculated as the proportion of evaluable patients that have confirmed CR or PR, as defined according to the 2014 Lugano Classification, exact 95% confidence intervals will be calculated for these estimates. Response rates will also be evaluated based on number and type of prior therapy(ies). Duration of response, as well as progression-free survival and overall survival will be estimated using the product-limit method of Kaplan and Meier. As secondary endpoints, the ORR and CR rate will also be estimated according to the International Harmonization Project response criteria (Cheson 2007).[9]

Any patient treated at the RP2D, including those from the Phase 1 portion, will be included in efficacy analyses. Patients will be evaluable for efficacy assessment if they received at least one dose of pralatrexate and at least one dose of pembrolizumab and underwent at least one response assessment. As discussed in Section 5.7, patients will be evaluable for efficacy if they discontinued study therapy prior to the first response assessment because of progression of disease rather than solely because of unacceptable toxicity, withdrawal of consent, or investigator's decision.

12.3.4 Safety Analysis and Stopping Rules for Excessive Toxicity or for Rapid Disease Progression

Because of the unique immune-related adverse events (IrAEs) observed with checkpoint inhibitors, we will monitor for "unacceptable toxicity" (defined in Section 11.2) and treatment-related mortality at any time during study treatment with this new combination of drugs. This monitoring will include all patients treated on the study regardless of the dose levels they were on. The expected rate of "unacceptable toxicity" should not be >33%. If the rate of "unacceptable toxicity" is >33% after at least 6 patients are treated on study at any bi-annual safety review, or if a 2nd death that is at least possibly related to study treatment occurs regardless of the number of patients on study, accrual will be halted and a full review of these events will be performed by the City of Hope Data Safety Monitoring Committee (DSMC). Patient accrual will not resume until approved by the DSMC to do so. These rules are in addition to the bi-annual review of all toxicities submitted to the City of Hope Data Safety Monitoring Committee (DSMC). Patients with ongoing toxicity will be followed until resolution or stability.

In addition, because of the evidence that PD-1 may act as a tumor suppressor in preclinical T-cell lymphoma models and the recent reports of rapid disease progression in patients with ATLL, a subtype of PTCL, we will also monitor for rapid progression of disease. If at any bi-annual safety review during the conduct of the study, and after at least 3 patients are treated on study, > 33% of patients who received at least one dose each of pembrolizumab and pralatrexate (regardless of the dose level or if during the phase 1 or phase 2 portion of the study) experience rapid progression (i.e. an acceleration of disease activity with disease progression according to the 2014 Lugano classification prior to completion of 3 cycles of study therapy), the study accrual will be halted and a full review of these events will be performed by the City of Hope Data Safety Monitoring Committee (DSMC). Patient accrual will not resume until approved by the DSMC to do so.

13.0 DATA HANDLING, DATA MANAGEMENT, RECORD KEEPING

13.1 Source Documents

Source documents are original documents, data, and records (e.g., medical records, pharmacy dispensing records, recorded data from automated instruments, laboratory data) that are relevant to the clinical trial. The investigator or their designee will prepare and maintain adequate and accurate source documents. These documents are designed to record all observations and other pertinent data for each patient enrolled in this clinical trial. Source documents must be adequate to reconstruct all data transcribed onto the case report forms.

13.2 Data Capture Methods and Management

Data for this trial will be collected using City of Hope's electronic capture system (EDC) that is compliant with 21 CFR Part 11.

Study personnel will enter data from source documents corresponding to a subject's visit into the protocol-specific electronic Case Report Form (eCRF).

13.3 Case Report Forms/Data Submission Schedule

The investigator is responsible for all information collected on participants enrolled in this study. All data collected during the course of this study must be reviewed and verified for completeness and accuracy by the investigator. All case report forms must be completed by designated study personnel. The completed case report forms must be reviewed, signed and dated by the Investigator or designee in a timely fashion.

All data will be collected using electronic data collection, stored as indicated in Section 13.2, and will be submitted according to the timelines indicated in Table 13.3.

Table 13.3 Data Submission Schedule

Form	Submission Timeline
Eligibility Checklist	Complete prior to registration
On Study Forms	Within 14 calendar days of registration
Baseline Assessment Forms	Within 14 calendar days of registration
Treatment Forms	Within 14 calendar days of treatment administration
Adverse Event Report Forms	**Phase 1/ Safety Lead-in**: Within 7 calendar days of the assessment/notification **Phase 2**: Within 10 calendar days of the assessment/notification
Response Assessment Forms	Within 10 calendar days of the response assessment
Other Assessment Forms	Within 10 calendar days of the assessment
Off Treatment/Off Study Forms	Within 10 calendar days of completing treatment or being taken off study for any reason
Follow up/ Survival Forms	Within 14 calendar days of the protocol defined follow up visit date or call

13.4 Regulatory Records

The investigator will maintain regulatory records, including updating records in accordance with Good Clinical Practice guidelines and FDA regulations.

14.0 ADHERENCE TO THE PROTOCOL

Deviations from the protocol should be avoided, except when necessary to eliminate immediate hazard(s) for the protection, safety, and well-being of a research participant. As a result of deviations, corrective actions are to be developed by the study staff and implemented promptly. All protocol deviations and planned protocol deviations will be reported in accordance with the City of Hope Clinical Research Protocol Deviation policy.

Non-COH Sites:

Deviations meeting the criteria specified in the City of Hope Clinical Research Protocol Deviation policy (available from the DCC) will be reported to the DCC and Study PI within **24 hours** of notification that the event occurred.

Procedure for reporting deviations to the COH DCC:

1. Document the deviation on the Deviation Reporting Coversheet or submit your site-specific protocol deviation log if the log format has been approved for use by the DCC. This modifiable Microsoft Word document is available from the DCC. An electronic signature on this document will be accepted.
2. Scan and email the Deviation Reporting Coversheet or protocol deviation log to the Study PI (aherrera@coh.org) and DCC@coh.org **within 24 hours** of notification of the deviation with the email subject title of "Herrera Pembro-PDX Deviation COH IRB #17501". If an email receipt from the DCC is not received within one working day, please email DCC@coh.org.

Sites are to report to their local IRB and DSMC per their site's specific institutional and IRB guidelines. As soon as possible, non-COH sites will provide to the COH DCC copies of the IRB and/or DSMC submission and corresponding response(s).

15.0 STUDY OVERSIGHT, QUALITY ASSURANCE, AND DATA & SAFETY MONITORING

15.1 All Investigator Responsibilities

An investigator is responsible for ensuring that an investigation is conducted according to the signed investigator statement, the investigational plan, and applicable regulations; for protecting the rights, safety, and welfare of subjects under the investigator's care; and for the control of drugs under investigation.

15.2 Study Principal Investigator Responsibilities

The Study Principal Investigator is responsible for the conduct of the clinical trial, including overseeing that sponsor responsibilities are executed in accordance with federal regulations.

15.3 Protocol Management Team (PMT)

The Protocol Management Team (PMT), minimally consisting of the study PI, collaborating investigators, site investigators, research nurse, clinical research associate/coordinator, and the study biostatistician, is responsible for ongoing monitoring of the data and safety of this study, including implementation of the stopping rules for safety/toxicity.

The PMT is recommended to meet (in person or via teleconference) to review study status. The meeting is a forum to discuss study related issues including accrual, SAE/AE/UPs experienced, study response, deviations/violations, and study management issues. The appropriateness of further subject enrollment and the specific intervention for subsequent subject enrollment are addressed.

15.4 Quality Assurance

Clinical site monitoring is conducted to ensure that the rights of human subjects are protected, that the study is implemented in accordance with the protocol and regulatory requirements, and that the quality and integrity of study data and data collection methods are maintained. Monitoring for this study will be performed by the City of Hope Office of Clinical Trials Monitoring (OCTM), within City of Hope's Office for Safety and Data Quality.

Details of clinical site monitoring are documented in the OCTM SOP and the Risk Based Monitoring (RBM) plan. These documents specify the frequency of monitoring, monitoring procedures, the amount of subject data to be reviewed, and the distribution of monitoring reports to the study team and the COH DSMC.

15.5 Risk Determination

This is a high risk study, as defined in the City of Hope Institutional DSMP. This determination was made because this study involves a COH IND.

15.6 City of Hope Data and Safety Monitoring Committee

The COH Data and Safety Monitoring Committee (DSMC) will review and monitor study progress, compliance, toxicity, safety, and accrual data from this trial via the PMT Progress Report (submitted by the Study Principal Investigator according to the frequency outlined in the City of Hope Institutional DSMP). The DSMC is composed of clinical specialists who have no direct relationship with the study. Information that raises any questions about participant safety will be addressed with the Protocol Management Team.

16.0 ETHICAL AND REGULATORY CONSIDERATIONS

16.1 Ethical Standard

This study will be conducted in conformance with the principles set forth in The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research (US National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, April 18, 1979) and the Declaration of Helsinki.

16.2 Regulatory Compliance

This study is to be conducted in compliance with the IRB approved protocol and according to the following considerations:

- US Code of Federal Regulations (CFR) governing clinical study conduct
  - Title 21 Part 11 – Electronic Records; Electronic Signatures
  - Title 21 Part 50 – Protection of Human Subjects
  - Title 21 Part 54 – Financial Disclosure by Clinical Investigators
  - Title 21 Part 56 – Institutional Review Boards
  - Title 21 Part 58 – Good Laboratory Practice for Nonclinical Laboratory Studies

- Title 21 Part 312 – Investigational New Drug Application
- Title 45 Part 46 – Protection of Human Subjects

- US Federal legislation, including but not limited to
  - Health Insurance Portability and Accountability Act of 1996
  - Section 801 of the Food and Drug Administration Amendments Act
- Applicable state and local laws. For research occurring in California, this includes but is not limited to State of California Health and Safety Code, Title 17
- Applicable institutional research policies and procedures

16.3 Institutional Review Board

An Institutional Review Board (IRB) that complies with the federal regulations at 45 CFR 46 and 21 CFR 50, 56 and State of California Health and Safety code, Title 17, must review and approve this protocol, informed consent form and any additional documents that the IRB may need to fulfill its responsibilities (Investigator's Brochure, information concerning patient recruitment, payment or compensation procedures, or other pertinent information) prior to initiation of the study. Revisions to approved documents will require review and approval by the IRB before the changes are implemented in the study. All institutional, NCI, Federal, and State of California regulations must be fulfilled.

Each participating non-COH institution must provide for the review and approval of this protocol and the associated informed consent documents by an appropriate IRB holding a current US Federal wide Assurance issued by and registered with the Office for Human Research Protections (OHRP). The protocol and consent will be reviewed and approved by the COH IRB before submission to a participating site IRB.

The IRB's written unconditional approval of the study protocol and the informed consent document must be in the possession of the investigator, and, for external sites, the possession of the DCC, before the study is initiated.

The IRB will be informed of serious unexpected, unanticipated adverse experiences, and unanticipated problems occurring during the study, and any additional adverse experiences in accordance with the standard operating procedures and policies of the IRB; new information that may affect adversely the safety of the patients of the conduct of the study; an annual update and/or request for re-approval; and when the study has been completed.

All participating sites must follow the lead institution's IRB-approved protocol.

16.4 Informed Consent

Each participating non-COH institution will be provided with a model informed consent form. Each institution may revise or add information to comply with local and/or institutional requirements, but may not remove procedural or risk content from the model consent form. Furthermore, prior to submission to the site's IRB (initial submission and amendments), the consent and accompanying HIPAA form, if separate to the consent, must be reviewed and approved by the DCC.

The Principal Investigator or IRB approved named designee will explain the nature, duration, purpose of the study, potential risks, alternatives and potential benefits, and all other information contained in the informed consent document. In addition, they will review the experimental subject's bill of rights if applicable, and the HIPAA research authorization form. Prospective participants will be informed that they may withdraw from the study at any time and for any reason without prejudice, including as applicable, their current or future care or employment at City of Hope or participating institution or any relationship

they have with City of Hope or participating institution. Prospective participants will be afforded sufficient time to consider whether or not to participate in the research.

After the study has been fully explained, written informed consent will be obtained from either the prospective participant or his/her guardian or legal representative before study participation. The method of obtaining and documenting the informed consent and the contents of the consent must comply with the ICH-GCP and all applicable regulatory requirements.

A copy of the signed informed consent will be given to the participant or his/her legally authorized representative. The original signed consent must be maintained by the site investigator and available for inspection by sponsor designated representatives, or regulatory authority at any time.

Informed consent is a process that is initiated prior to the individual agreeing to participate in the study and continues throughout study participation.

16.5 Participant Withdrawal

Participants may withdraw from the study at any time and for any reason without prejudice. The withdrawal must be documented per institutional policies. The COH DCC should be promptly notified of the change in participant status.

Participant withdrawal may consist of any of the following with regard to study procedures and data collection:

- Withdrawal from study treatment, but agreement to continue with active study procedures and chart review and survival follow-up.
- Withdrawal from study treatment and all active procedures, but agreement for chart review and survival follow-up.
- Withdrawal from study treatment, all active procedures, and any future data collection.

Participants who agreed to the collection of research blood samples may withdraw consent to use their specimens, if they are not yet processed as detailed in the consent form. Once the PI and site PI is notified of this withdrawal of informed consent, the research specimens will not be used in any research. At that time, any of the existing specimens will be destroyed.

16.6 Special and Vulnerable Populations

16.6.1 Inclusion of Women and Minorities

The study is open anyone regardless of gender, race or ethnicity. Efforts will be made to extend the accrual to a representative population. If differences in outcome that correlate to gender, racial, or ethnic identity are noted, accrual may be expanded or additional studies may be performed to investigate those differences more fully.

Pregnant women are excluded because the effects of study agent(s) on embryogenesis, reproduction, and spermatogenesis in humans are unknown.

16.6.2 Exclusion of Pediatric Population

Pediatric participants (< 18 years old of age) are excluded from this study since safety and effectiveness of protocol therapy has not been defined for the study population.

Participants with a history of HIV are excluded due to concerns about inadvertent augmentation of infectious and/or inflammatory activity.

16.6.3 Vulnerable Populations

45 CFR §46.111 (a)(3) and 45 CFR §46, Subparts B-D identifies children, prisoners, pregnant women, mentally incapacitated persons, or economically or educationally disadvantaged persons as vulnerable populations.

Adults lacking capacity to consent are not excluded from participation. This study does not pose additional risks for adults lacking capacity than for the general population. In such instances, informed consent will be sought and documented from the prospective participant's legally authorized representative in agreement with institutional policies and local IRB approval.

16.7 Participant Confidentiality

Participant confidentiality is strictly held in trust by the investigators, study staff, and the sponsor(s) and their agents. This confidentiality is extended to cover testing of biological samples in addition to any study information relating to participants.

This research will be conducted in compliance with federal and state requirements relating to protected health information (PHI), including the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). HIPAA regulations require a signed subject authorization informing the subject of the nature of the PHI to be collected, who will have access to that information and why, who will use or disclose that information, ant the rights of a research participant to revoke their authorization for use of their PHI. In the event that a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For subjects that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (i.e. that the subject is alive) at the end of their scheduled study period.

Release of research results should preserve the privacy of medical information and must be carried out in accordance with Department of Health and Human Services Standards for Privacy of Individually Identifiable Health Information, 45 CFR 164.508. When results of this study are reported in medical journals or at meetings, identification of those taking part will not be disclosed and no identifiers will be used.

Medical records of subjects will be securely maintained in the strictest confidence, according to current legal requirements. Data will be entered, analyzed and stored in encrypted, password protected, secure computers that meet all HIPAA requirements. All data capture records, drug accountability records, study reports and communications will identify the patient by initials and the assigned patient number.

Source documents provided to the DCC for the purpose of auditing or monitoring will be de-identified and labeled with the study number, subject ID, and if applicable patient initials.

The investigator/institution will permit direct access to source data and documents by sponsor representatives, the FDA, and other applicable regulatory authorities. The access may consist of trial-related monitoring, including remote monitoring, audits, IRB/IEC reviews, and FDA/regulatory authority inspections. The patient's confidentiality will be maintained and will not be made publicly available to the extent permitted by the applicable laws and regulations.

Participant specimens will be de-identified (coded) prior to submission to research laboratories. The specimens will be labeled with the study number, subject (accession) ID, date and timepoint of collection. The key to the code will be maintained in the COH clinical trials management system which is a secure environment.

16.8 Use of Unused (Leftover) Specimens Collected for this Trial

Unused samples in existence at study completion (i.e. completion of all research activities under this study) will be either: (a) discarded or (b) placed in a COH IRB approved biorepository with clinical information and potentially PHI attached.

With regard to which option will apply, each site IRB may choose to either: (a) leave the determination to the participant via a question in the informed consent document, which would communicated to the study registrar (DCC) at the time of participant registration, OR b) may choose to make a single determination on behalf of their respective participants, and communicate that determination to their respective participants via the informed consent.

16.9 Conflict of Interest

Any investigator who has a conflict of interest with this study (patent ownership, royalties, or financial gain greater than the minimum allowable by their institution, etc.) must have the conflict reviewed by a properly constituted Conflict of Interest Committee with a Committee-sanctioned conflict management plan that has been reviewed and approved by the study Sponsor (City of Hope) prior to participation in this study. All City of Hope investigators will follow the City of Hope conflict of interest policy.

16.10 Financial Obligations, Compensation, and Reimbursement of Participants

Pembrolizumab will be provided free of charge to participants.

Neither the research participant nor the insurance carrier will be responsible for the research procedures related to this study.

Standard of care drugs or procedures provided during the course of study participation will be the responsibility of the research participant and/or the insurance carrier. The participant will be responsible for all copayments, deductibles, and other costs of treatment and diagnostic procedures as set forth by the insurance carrier. The participant and/or the insurance carrier will be billed for the costs of treatment and diagnostic procedures in the same way as if the participant were not in a research study.

In the event of physical injury to a participant resulting from research procedures, appropriate medical treatment will be available at City of Hope or at the non-COH site to the injured participant. There are no plans for City of Hope to provide financial compensation in the event of physical injury to a participant.

The research participant will not receive reimbursement or payment for taking part in this study.

16.11 Publication/ Data Sharing

Neither the complete nor any part of the results of the study carried out under this protocol, nor any of the information provided by City of Hope for the purposes of performing the study, will be published or passed on to any third party without the written approval of the Study PI. Any investigator involved with this study is obligated to provide City of Hope with complete test results and all data derived from the study.

The preparation and submittal for publication of manuscripts containing the study results shall be in accordance with a process determined by mutual written agreement between City of Hope, Merck, Acrotech Biopharma, LLC, and participating non-COH institutions. The publication or presentation of any study results shall comply with all applicable privacy laws, including, but not limited to, the Health Insurance Portability and Accountability Act of 1996.

In accordance with the U.S. Public Law 110-85 (Food and Drug Administration Amendments Act of 2007 or FDAAA), Title VIII, Section 801, this trial will be registered onto ClinicalTrials.gov and results will be reported on ClinicalTrials.gov within 12 months of the estimated or actual completion date of the trial, whichever date is earlier.

REFERENCES

1. Nademanee A, Palmer JM, Popplewell L, et al. High-dose therapy and autologous hematopoietic cell transplantation in peripheral T cell lymphoma (PTCL): analysis of prognostic factors. *Biol Blood Marrow Transplant*. 2011;17(10):1481-1489.

2. Smith SM, Burns LJ, van Besien K, et al. Hematopoietic cell transplantation for systemic mature T-cell non-Hodgkin lymphoma. *J Clin Oncol*. 2013;31(25):3100-3109.

3. Coiffier B, Pro B, Prince HM, et al. Results from a pivotal, open-label, phase II study of romidepsin in relapsed or refractory peripheral T-cell lymphoma after prior systemic therapy. *J Clin Oncol*. 2012;30(6):631-636.

4. Foss F, Advani R, Duvic M, et al. A Phase II trial of Belinostat (PXD101) in patients with relapsed or refractory peripheral or cutaneous T-cell lymphoma. *Br J Haematol*. 2014.

5. O'Connor OA, Pro B, Pinter-Brown L, et al. Pralatrexate in patients with relapsed or refractory peripheral T-cell lymphoma: results from the pivotal PROPEL study. *J Clin Oncol*. 2011;29(9):1182-1189.

6. Anraku M, Tagawa T, Wu L, et al. Synergistic antitumor effects of regulatory T cell blockade combined with pemetrexed in murine malignant mesothelioma. *J Immunol*. 2010;185(2):956-966.

7. Davis M, Conlon K, Bohac GC, et al. Effect of pemetrexed on innate immune killer cells and adaptive immune T cells in subjects with adenocarcinoma of the pancreas. *J Immunother*. 2012;35(8):629-640.

8. Cheson BD, Fisher RI, Barrington SF, et al. Recommendations for Initial Evaluation, Staging, and Response Assessment of Hodgkin and Non-Hodgkin Lymphoma: The Lugano Classification. *Journal of Clinical Oncology*. 2014.

9. Cheson BD, Pfistner B, Juweid ME, et al. Revised response criteria for malignant lymphoma. *J Clin Oncol*. 2007;25(5):579-586.

10. Cheson BD, Ansell S, Schwartz L, et al. Refinement of the Lugano classification response criteria for lymphoma in the era of immunomodulatory therapy. *Blood*. 2016.

11. Barrington SF, Mikhaeel NG, Kostakoglu L, et al. Role of imaging in the staging and response assessment of lymphoma: consensus of the International Conference on Malignant Lymphomas Imaging Working Group. *J Clin Oncol*. 2014;32(27):3048-3058.

12. Vose J, Armitage J, Weisenburger D, International TCLP. International peripheral T-cell and natural killer/T-cell lymphoma study: pathology findings and clinical outcomes. *J Clin Oncol*. 2008;26(25):4124-4130.

13. Weisenburger DD, Anderson JR, Diebold J, et al. Systemic anaplastic large-cell lymphoma: results from the non-Hodgkin's lymphoma classification project. *Am J Hematol*. 2001;67(3):172-178.

14. Sibon D, Fournier M, Briere J, et al. Long-term outcome of adults with systemic anaplastic large-cell lymphoma treated within the Groupe d'Etude des Lymphomes de l'Adulte trials. *J Clin Oncol*. 2012;30(32):3939-3946.

15. Mercadal S, Briones J, Xicoy B, et al. Intensive chemotherapy (high-dose CHOP/ESHAP regimen) followed by autologous stem-cell transplantation in previously untreated patients with peripheral T-cell lymphoma. *Ann Oncol*. 2008;19(5):958-963.

16. Simon A, Peoch M, Casassus P, et al. Upfront VIP-reinforced-ABVD (VIP-rABVD) is not superior to CHOP/21 in newly diagnosed peripheral T cell lymphoma. Results of the randomized phase III trial GOELAMS-LTP95. *Br J Haematol*. 2010;151(2):159-166.

17. Weisenburger DD, Savage KJ, Harris NL, et al. Peripheral T-cell lymphoma, not otherwise specified: a report of 340 cases from the International Peripheral T-cell Lymphoma Project. *Blood*. 2011;117(12):3402-3408.

18. Rodriguez J, Conde E, Gutierrez A, et al. Prolonged survival of patients with angioimmunoblastic T-cell lymphoma after high-dose chemotherapy and autologous stem cell transplantation: the GELTAMO experience. *Eur J Haematol*. 2007;78(4):290-296.

19. Rodriguez J, Conde E, Gutierrez A, et al. Frontline autologous stem cell transplantation in high-risk peripheral T-cell lymphoma: a prospective study from The Gel-Tamo Study Group. *Eur J Haematol*. 2007;79(1):32-38.

20. Schetelig J, Fetscher S, Reichle A, et al. Long-term disease-free survival in patients with angioimmunoblastic T-cell lymphoma after high-dose chemotherapy and autologous stem cell transplantation. *Haematologica*. 2003;88(11):1272-1278.

21. d'Amore F, Relander T, Lauritzsen GF, et al. Up-front autologous stem-cell transplantation in peripheral T-cell lymphoma: NLG-T-01. *J Clin Oncol*. 2012;30(25):3093-3099.

22. Thompson CA. Belinostat approved for use in treating rare lymphoma. *Am J Health Syst Pharm*. 2014;71(16):1328.

23. Pro B, Advani R, Brice P, et al. Brentuximab vedotin (SGN-35) in patients with relapsed or refractory systemic anaplastic large-cell lymphoma: results of a phase II study. *J Clin Oncol*. 2012;30(18):2190-2196.

24. Pardoll DM. The blockade of immune checkpoints in cancer immunotherapy. *Nat Rev Cancer*. 2012;12(4):252-264.

25. Green MR, Monti S, Rodig SJ, et al. Integrative analysis reveals selective 9p24.1 amplification, increased PD-1 ligand expression, and further induction via JAK2 in nodular sclerosing Hodgkin lymphoma and primary mediastinal large B-cell lymphoma. *Blood*. 2010;116(17):3268-3277.

26. Chen BJ, Chapuy B, Ouyang J, et al. PD-L1 expression is characteristic of a subset of aggressive B-cell lymphomas and virus-associated malignancies. *Clin Cancer Res*. 2013;19(13):3462-3473.

27. Shi M, Roemer MG, Chapuy B, et al. Expression of Programmed Cell Death 1 Ligand 2 (PD-L2) Is a Distinguishing Feature of Primary Mediastinal (Thymic) Large B-cell Lymphoma and Associated With PDCD1LG2 Copy Gain. *Am J Surg Pathol*. 2014;38(12):1715-1723.

28. Carreras J, Lopez-Guillermo A, Roncador G, et al. High numbers of tumor-infiltrating programmed cell death 1-positive regulatory lymphocytes are associated with improved overall survival in follicular lymphoma. *J Clin Oncol*. 2009;27(9):1470-1476.

29. Xerri L, Chetaille B, Serriari N, et al. Programmed death 1 is a marker of angioimmunoblastic T-cell lymphoma and B-cell small lymphocytic lymphoma/chronic lymphocytic leukemia. *Hum Pathol*. 2008;39(7):1050-1058.

30. Dorfman DM, Brown JA, Shahsafaei A, Freeman GJ. Programmed death-1 (PD-1) is a marker of germinal center-associated T cells and angioimmunoblastic T-cell lymphoma. *Am J Surg Pathol*. 2006;30(7):802-810.

31. Krishnan C, Warnke RA, Arber DA, Natkunam Y. PD-1 expression in T-cell lymphomas and reactive lymphoid entities: potential overlap in staining patterns between lymphoma and viral lymphadenitis. *Am J Surg Pathol*. 2010;34(2):178-189.

32. Zhan HQ, Li XQ, Zhu XZ, Lu HF, Zhou XY, Chen Y. Expression of follicular helper T cell markers in nodal peripheral T cell lymphomas: a tissue microarray analysis of 162 cases. *J Clin Pathol*. 2011;64(4):319-324.

33. Han L, Liu F, Li R, et al. Role of programmed death ligands in effective T-cell interactions in extranodal natural killer/T-cell lymphoma. *Oncol Lett*. 2014;8(4):1461-1469.

34. Shimauchi T, Kabashima K, Nakashima D, et al. Augmented expression of programmed death-1 in both neoplastic and non-neoplastic CD4+ T-cells in adult T-cell leukemia/lymphoma. *Int J Cancer*. 2007;121(12):2585-2590.

35. Liu J, Hamrouni A, Wolowiec D, et al. Plasma cells from multiple myeloma patients express B7-H1 (PD-L1) and increase expression after stimulation with IFN-{gamma} and TLR ligands via a MyD88-, TRAF6-, and MEK-dependent pathway. *Blood*. 2007;110(1):296-304.

36. Kronig H, Kremmler L, Haller B, et al. Interferon-induced programmed death-ligand 1 (PD-L1/B7-H1) expression increases on human acute myeloid leukemia blast cells during treatment. *Eur J Haematol*. 2014;92(3):195-203.

37. Tamura H, Dan K, Tamada K, et al. Expression of functional B7-H2 and B7.2 costimulatory molecules and their prognostic implications in de novo acute myeloid leukemia. *Clin Cancer Res*. 2005;11(16):5708-5717.

38. Kondo A, Yamashita T, Tamura H, et al. Interferon-gamma and tumor necrosis factor-alpha induce an immunoinhibitory molecule, B7-H1, via nuclear factor-kappaB activation in blasts in myelodysplastic syndromes. *Blood*. 2010;116(7):1124-1131.

39. Yang H, Bueso-Ramos C, DiNardo C, et al. Expression of PD-L1, PD-L2, PD-1 and CTLA4 in myelodysplastic syndromes is enhanced by treatment with hypomethylating agents. *Leukemia*. 2014;28(6):1280-1288.

40. Green MR, Rodig S, Juszczynski P, et al. Constitutive AP-1 activity and EBV infection induce PD-L1 in Hodgkin lymphomas and posttransplant lymphoproliferative disorders: implications for targeted therapy. *Clin Cancer Res*. 2012;18(6):1611-1618.

41. Berger R, Rotem-Yehudar R, Slama G, et al. Phase I safety and pharmacokinetic study of CT-011, a humanized antibody interacting with PD-1, in patients with advanced hematologic malignancies. *Clin Cancer Res*. 2008;14(10):3044-3051.

42. Westin JR, Chu F, Zhang M, et al. Safety and activity of PD1 blockade by pidilizumab in combination with rituximab in patients with relapsed follicular lymphoma: a single group, open-label, phase 2 trial. *Lancet Oncol*. 2014;15(1):69-77.

43. Ansell SM, Lesokhin AM, Borrello I, et al. PD-1 blockade with nivolumab in relapsed or refractory Hodgkin's lymphoma. *N Engl J Med*. 2015;372(4):311-319.

44. Younes A, Santoro A, Shipp M, et al. Nivolumab for classical Hodgkin's lymphoma after failure of both autologous stem-cell transplantation and brentuximab vedotin: a multicentre, multicohort, single-arm phase 2 trial. *Lancet Oncol*. 2016.

45. Armand P, Shipp MA, Ribrag V, et al. Programmed Death-1 Blockade With Pembrolizumab in Patients With Classical Hodgkin Lymphoma After Brentuximab Vedotin Failure. *J Clin Oncol*. 2016.

46. Moskowitz CH, Zinzani, P. L., Fanale, M. A., et al. MULTICOHORT PHASE 2 STUDY OF PEMBROLIZUMAB FOR RELAPSED/REFRACTORY CLASSICAL HODGKIN LYMPHOMA (R/R CHL): KEYNOTE-087. European Hematology Association Annual Congress. Copenhagen, Denmark; 2016.

47. Lesokhin AM, Ansell SM, Armand P, et al. Nivolumab in Patients With Relapsed or Refractory Hematologic Malignancy: Preliminary Results of a Phase Ib Study. *J Clin Oncol*. 2016;34(23):2698-2704.

48. Armand P, Nagler A, Weller EA, et al. Disabling immune tolerance by programmed death-1 blockade with pidilizumab after autologous hematopoietic stem-cell transplantation for diffuse large B-cell lymphoma: results of an international phase II trial. *J Clin Oncol*. 2013;31(33):4199-4206.

49. Kwong YL, Chan TSY, Tan D, et al. PD1 blockade with pembrolizumab is highly effective in relapsed or refractory NK/T-cell lymphoma failing l-asparaginase. *Blood*. 2017;129(17):2437-2442.

50. Li X, Cheng Y, Zhang M, et al. Activity of pembrolizumab in relapsed/refractory NK/T-cell lymphoma. *J Hematol Oncol*. 2018;11(1):15.

51. Ratner L, Waldmann TA, Janakiram M, Brammer JE. Rapid Progression of Adult T-Cell Leukemia-Lymphoma after PD-1 Inhibitor Therapy. *N Engl J Med*. 2018;378(20):1947-1948.

52. Wartewig T, Kurgyis Z, Keppler S, et al. PD-1 is a haploinsufficient suppressor of T cell lymphomagenesis. *Nature*. 2017;552(7683):121-125.

53. Allos Therapeutics I. PDX-008: A Multi-center, Phase 2, Open-label Study of (RS)-10-Propargyl-10-Deazaaminopterin (Pralatrexate) with Vitamin B12 and Folic Acid Supplementation in Patients with Relapsed or Refractory Peripheral T-cell Lymphoma. 2009.

54. PDX-010: A Phase 1, Open-label Study of Pralatrexate with Vitamin B12 and Folic Acid Supplementation in Patients with Relapsed or Refractory Cutaneous T-cell Lymphoma. 2012.

55. Mould DR, Sweeney K, Duffull SB, et al. A population pharmacokinetic and pharmacodynamic evaluation of pralatrexate in patients with relapsed or refractory non-Hodgkin's or Hodgkin's lymphoma. *Clin Pharmacol Ther*. 2009;86(2):190-196.

56. Folotyn [Investigator's Brochure]. *Allos Therapeutics I, editor Westminster, CO*. 2013.

57. Folotyn [Package Insert]. *Allos Therapeutics Inc Westminster, CO*. Nov 2016.

58. Leucovorin [Package Insert]. *Roxane Laboratories I, editor Columbus, OH*. 2012.

59. PA H. Efficacy of Short Oral Leucovorin Rescue (SOLR) In Managing Recurrent Pralatrexate (Folotyn) Induced Mucositis (RPIM) Despite Dose Reduction. *ASH Annual Meeting Abstracts*. 2011.

60. Koch E, Story SK, Geskin LJ. Preemptive leucovorin administration minimizes pralatrexate toxicity without sacrificing efficacy. *Leuk Lymphoma*. 2013;54(11):2448-2451.

61. Topalian SL, Hodi FS, Brahmer JR, et al. Safety, activity, and immune correlates of anti-PD-1 antibody in cancer. *N Engl J Med*. 2012;366(26):2443-2454.

62. Moskowitz CH, Ribrag, V., Michot, J. M., et al. PD-1 Blockade with the Monoclonal Antibody Pembrolizumab (MK-3475) in Patients with Classical Hodgkin Lymphoma after Brentuximab Vedotin Failure: Preliminary Results from a Phase 1b Study (KEYNOTE-013). Vol. Blood (ASH Annual Meeting Abstracts) 2014 124: 290.

63. Tumeh PC, Harview CL, Yearley JH, et al. PD-1 blockade induces responses by inhibiting adaptive immune resistance. *Nature*. 2014;515(7528):568-571.

64. Curiel TJ, Coukos G, Zou L, et al. Specific recruitment of regulatory T cells in ovarian carcinoma fosters immune privilege and predicts reduced survival. *Nat Med*. 2004;10(9):942-949.

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

66. Pages F, Berger A, Camus M, et al. Effector memory T cells, early metastasis, and survival in colorectal cancer. *N Engl J Med*. 2005;353(25):2654-2666.

67. Bachireddy P, Hainz U, Rooney M, et al. Reversal of in situ T-cell exhaustion during effective human antileukemia responses to donor lymphocyte infusion. *Blood*. 2014;123(9):1412-1421.

68. Chang AY, Bhattacharya N, Mu J, et al. Spatial organization of dendritic cells within tumor draining lymph nodes impacts clinical outcome in breast cancer patients. *J Transl Med*. 2013;11:242.

69. Setiadi AF, Ray NC, Kohrt HE, et al. Quantitative, architectural analysis of immune cell subsets in tumor-draining lymph nodes from breast cancer patients and healthy lymph nodes. *PLoS One*. 2010;5(8):e12420.

70. Reichel J, Chadburn A, Rubinstein PG, et al. Flow sorting and exome sequencing reveal the oncogenome of primary Hodgkin and Reed-Sternberg cells. *Blood*. 2015;125(7):1061-1072.

71. Iqbal J, Weisenburger DD, Greiner TC, et al. Molecular signatures to improve diagnosis in peripheral T-cell lymphoma and prognostication in angioimmunoblastic T-cell lymphoma. *Blood*. 2010;115(5):1026-1036.

72. Iqbal J, Wright G, Wang C, et al. Gene expression signatures delineate biological and prognostic subgroups in peripheral T-cell lymphoma. *Blood*. 2014;123(19):2915-2923.

73. Piccaluga PP, Fuligni F, De Leo A, et al. Molecular profiling improves classification and prognostication of nodal peripheral T-cell lymphomas: results of a phase III diagnostic accuracy study. *J Clin Oncol*. 2013;31(24):3019-3025.

74. Rizvi NA, Hellmann MD, Snyder A, et al. Cancer immunology. Mutational landscape determines sensitivity to PD-1 blockade in non-small cell lung cancer. *Science*. 2015;348(6230):124-128.

75. Snyder A, Makarov V, Merghoub T, et al. Genetic basis for clinical response to CTLA-4 blockade in melanoma. *N Engl J Med*. 2014;371(23):2189-2199.

76. Lu YC, Yao X, Crystal JS, et al. Efficient identification of mutated cancer antigens recognized by T cells associated with durable tumor regressions. *Clin Cancer Res*. 2014;20(13):3401-3410.

77. Robbins PF, Lu YC, El-Gamil M, et al. Mining exomic sequencing data to identify mutated antigens recognized by adoptively transferred tumor-reactive T cells. *Nat Med*. 2013;19(6):747-752.

78. Ji RR, Chasalow SD, Wang L, et al. An immune-active tumor microenvironment favors clinical response to ipilimumab. *Cancer Immunol Immunother*. 2012;61(7):1019-1031.

79. Ulloa-Montoya F, Louahed J, Dizier B, et al. Predictive gene signature in MAGE-A3 antigen-specific cancer immunotherapy. *J Clin Oncol*. 2013;31(19):2388-2395.

80. Armand P, Oki Y, Neuberg DS, et al. Detection of circulating tumour DNA in patients with aggressive B-cell non-Hodgkin lymphoma. *Br J Haematol*. 2013;163(1):123-126.

81. Oki Y, Neelapu SS, Fanale M, et al. Detection of classical Hodgkin lymphoma specific sequence in peripheral blood using a next-generation sequencing approach. *Br J Haematol*. 2015;169(5):689-693.

82. Roschewski M, Dunleavy K, Pittaluga S, et al. Circulating tumour DNA and CT monitoring in patients with untreated diffuse large B-cell lymphoma: a correlative biomarker study. *Lancet Oncol*. 2015;16(5):541-549.

83. Kurtz DM, Green MR, Bratman SV, et al. Noninvasive monitoring of diffuse large B-cell lymphoma by immunoglobulin high-throughput sequencing. *Blood*. 2015;125(24):3679-3687.

84. Herrera AF, Kim HT, Kong KA, et al. Next-generation sequencing-based detection of circulating tumour DNA After allogeneic stem cell transplantation for lymphoma. *Br J Haematol*. 2016.

85. Scherer F KD, Newman AM, et al. Noninvasive Genotyping And Assessment of Treatment Response in Diffuse Large B-Cell Lymphoma. ASH 2015, abstract #126.

86. Kurtz DM SF, Newman AM, et al. Dynamic Noninvasive Genome Monitoring for Outcome Prediction in Diffuse Large B-Cell Lymphoma. ASH 2015, abstract #130.

87. Skolnik JM, Barrett JS, Jayaraman B, Patel D, Adamson PC. Shortening the timeline of pediatric phase I trials: the rolling six design. *J Clin Oncol*. 2008;26(2):190-195.

88. Gehan EA. The determination of the number of patients required in a preliminary and a follow-up trial of a new chemotherapeutic agent. *J Chronic Dis*. 1961;13:346-353.

89. Oken MM, Creech RH, Tormey DC, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. *Am J Clin Oncol*. 1982;5(6):649-655.

90. Dolgin M, Fox AC, Gorlin R, Levin RI. Nomenclature and Criteria for Diagnosis of Diseases of the Heart and Great Vessels. *9 edn (Boston, Little, Brown and Company)*. 1994.

APPENDIX A: PERFORMANCE STATUS

ECOG Performance Scale [89]	
Grade	**Descriptions**
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.

APPENDIX B: 2014 LUGANO RESPONSE CRITERIA

Response	Site	CT-Based Response	PET-CT Based Response
Complete Response		Complete radiologic response (all of the following)	Complete metabolic response (even with a persistent mass)
	Lymph nodes and extralymphatic sites	Target nodes/nodal masses must regress to ≤1.5 cm in longest diameter (LDi). No extralymphatic sites of disease.	Score ≤ 3* with or without a residual mass on 5-point scale†. It is recognized that in Waldeyer's ring or extranodal sites with high physiologic uptake or with activation within spleen or marrow (e.g., with chemotherapy or myeloid colony-stimulating factors), uptake may be greater than normal mediastinum and/or liver. In this circumstance, complete metabolic response may be inferred if uptake at sites of initial involvement is no greater than surrounding normal tissue even if the tissue has high physiologic uptake.
	Nonmeasured lesion	Absent	Not applicable
	Organ enlargement	Regress to normal	Not applicable
	New lesions	None	None
	Bone marrow	Normal by morphology; if indeterminate, IHC negative	No evidence of FDG-avid disease in marrow
Partial Response		Partial remission (all of the following)	Partial metabolic response
	Lymph nodes and extralymphatic sites	≥ 50% decrease in SPD of up to 6 target measurable nodes and extranodal sites When a lesion is too small to measure on CT, assign 5 mm X 5 mm as the default value When no longer visible, 0 X 0 mm For a node > 5 mm X 5 mm, but smaller than normal, use actual measurement for calculation	Score 4 or 5† with reduced uptake compared with baseline and residual mass(es) of any size At interim, these findings suggest responding disease At end of treatment, these findings indicate residual disease

Response	Site	CT-Based Response	PET-CT Based Response
	Nonmeasured lesion	Absent/normal, regressed, but no increase	Not applicable
	Organ enlargement	Spleen must have regressed by > 50% in length beyond normal	Not applicable
	New lesions	None	None
	Bone marrow	Not applicable	Residual uptake higher than uptake in normal marrow but reduced compared with baseline (diffuse uptake compatible with reactive changes from chemotherapy allowed). If there are persistent focal changes in the marrow in the context of a nodal response, consideration should be given to further evaluation with MRI or biopsy or an interval scan
No response or stable disease		Stable disease	No metabolic response
	Target nodes/nodal masses, extranodal lesions	< 50% decrease from baseline in SPD of up to 6 dominant, measurable nodes and extranodal sites; no criteria for progressive disease are met	Score 4 or 5† with no significant change in FDG uptake from baseline at interim or end of treatment
	Nonmeasured lesion	No increase consistent with progression	Not applicable
	Organ enlargement	No increase consistent with progression	Not applicable
	New lesions	None	None
	Bone marrow	Not applicable	No change from baseline
Progressive disease		Progressive disease requires at least 1 of the following	Progressive metabolic disease
	Individual target nodes/nodal masses	PPD progression:	Score 4 or 5† with an increase in intensity of uptake from baseline and/or
	Extranodal lesions	An individual node/lesion must be abnormal with: Longest diameter (LDi) > 1.5 cm and Increase by ≥ 50% from PPD nadir and	New FDG-avid foci consistent with lymphoma at interim OR end-of-treatment assessment

Response	Site	CT-Based Response	PET-CT Based Response
		An increase in LDi or shortest diameter (SDi) from nadir 0.5 cm for lesions ≤ 2 cm 1.0 cm for lesions > 2 cm In the setting of splenomegaly, the splenic length must increase by > 50% of the extent of its prior increase beyond baseline (e.g., a 15-cm spleen must increase to >16 cm). If no prior splenomegaly, must increase by at least 2 cm from baseline New or recurrent splenomegaly	
	Nonmeasured lesion	New or clear progression of preexisting nonmeasured lesions	None
	New lesions	Regrowth of previously resolved lesions A new node > 1.5 cm in any axis A new extranodal site > 1.0 cm in any axis; if < 1.0 cm in any axis, its presence must be unequivocal and must be attributable to lymphoma Assessable disease of any size unequivocally attributable to lymphoma	New FDG-avid foci consistent with lymphoma rather than another etiology (eg, infection, inflammation). If uncertain regarding etiology of new lesions, biopsy or interval scan may be considered.
	Bone marrow	New or recurrent involvement	New or recurrent FDG-avid foci

Measured dominant lesions:

Up to six of the largest dominant nodes, nodal masses, and extranodal lesions selected to be clearly measurable in two diameters. Nodes should preferably be from disparate regions of the body and should include, where applicable, mediastinal and retroperitoneal areas.

Non-nodal lesions include those in solid organs (e.g., liver, spleen, kidneys, lungs), GI involvement, cutaneous lesions, or those noted on palpation.

Nonmeasured lesions:

Any disease not selected as measured, dominant disease and truly assessable disease should be considered not measured. These sites include any nodes, nodal masses, and extranodal sites not selected as dominant or measurable or that do not meet the requirements for measurability but are still considered abnormal, as well as truly assessable disease, which is any site of suspected disease that would be difficult to follow quantitatively with measurement, including pleural effusions, ascites, bone lesions, leptomeningeal disease, abdominal masses, and other lesions that cannot be confirmed and followed by imaging. In Waldeyer's ring or in extranodal sites (e.g., GI tract, liver, bone marrow), FDG uptake may be greater than in the mediastinum with complete

metabolic response, but should be no higher than surrounding normal physiologic uptake (eg, with marrow activation as a result of chemotherapy or myeloid growth factors).

*A score of 3 in many patients indicates a good prognosis with standard treatment, especially if at the time of an interim scan. However, in trials involving PET where de-escalation is investigated, it may be preferable to consider a score of 3 as inadequate response (to avoid undertreatment).

†PET 5-point scale:

1, no uptake above background; 2, uptake ≤ mediastinum; 3, uptake > mediastinum but ≤ liver; 4, uptake moderately > liver; 5, uptake markedly higher than liver and/or new lesions; X, new areas of uptake unlikely to be related to lymphoma.

Abbreviations:

CT, computed tomography; FDG, fluorodeoxyglucose; IHC, immunohistochemistry; LDi, longest transverse diameter of a lesion; MRI, magnetic resonance imaging; PET, positron emission tomography; PPD, cross product of the LDi and perpendicular diameter; SDi, shortest axis perpendicular to the LDi; SPD, sum of the product of the perpendicular diameters for multiple lesions.

APPENDIX C: LYRIC CRITERIA

Lugano Classification was developed based on treatment with cytotoxic agents [8]. Immunotherapeutic drugs, may produce antitumor effects by potentiating endogenous cancer-specific immune responses. The response patterns seen with such an approach may extend beyond the typical time course of responses seen with cytotoxic agents, and can manifest as clinical responses after initial increases in tumor burden or even the appearance of new lesions. Thus, the 2014 Lugano Classification may not provide an accurate assessment of response to immunotherapeutic agents. Provisional modification of the Lugano criteria (LYRIC Criteria) may be used to assess participants who meet progressive disease per Lugano Classification [8,10].

Complete Response	Partial Response	Progressive Disease
Same as Lugano	Same as Lugano	As with Lugano with the following **exceptions**: **Indeterminate response (IR)** • IR1: ≥50% increase in SPD of up to 6 measurable lesions in first 12 weeks of therapy without clinical deterioration • IR2: <50% increase in the overall SPD with a. Appearance of a new lesion(s), or b. ≥50% increase in PPD of a lesion or set of lesions at any time during treatment • IR(3): Increase in FDG uptake without a concomitant increase in lesion size or number Patients with IR should continue on therapy and have repeat imaging after an additional 12 weeks (or sooner if clinically indicated). Progressive disease criteria in these patients will be met if: • IR1: An additional increase in the target SPD of ≥ 10% between the first IR1 timepoint and the SPD being assessed; or an increase in ≥ 5mm in either dimension of at least one lesion for lesions ≤ 2cm and 10mm for lesions > 2cm. • IR2: the new or growing lesion(s) should be added to the target lesions (total of no more than 6) and there is PD if the SPD if the newly defined set of target lesions has increased ≥50% from their nadir value (which may precede the IR time point). • IR3: There is evidence of PD by an increase in lesion size or the development of new lesions.
Abbreviations: SPD, sum of the product of the diameters; PPD, product of the perpendicular diameters.		

APPENDIX D: NYHA CARDIAC GRADING CRITERIA

Modified from Dolgin et al., 1994 [90]

New York Heart Association Classification of Heart Failure	
Class I	No symptoms. Ordinary physical activity such as walking and climbing stairs does not cause fatigue or dyspnea.
Class II	Symptoms with ordinary physical activity. Walking or climbing stairs rapidly, walking uphill, walking or stair climbing after meals, in cold weather, in wind or when under emotional stress causes undue fatigue or dyspnea.
Class III	Symptoms with less than ordinary physical activity. Walking one to two blocks on the level and climbing more than one flight of stairs in normal conditions causes undue fatigue or dyspnea.
Class IV	Symptoms at rest. Inability to carry on any physical activity without fatigue or dyspnea.

APPENDIX E: CONTRACEPTION GUIDELINES

Pembrolizumab may have adverse effects on a fetus in uterus. Furthermore, it is not known if pembrolizumab has transient adverse effects on the composition of sperm.
For this trial, male subjects will be considered to be of non-reproductive potential if they have azoospermia (whether due to having had a vasectomy or due to an underlying medical condition).

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

- (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**
- have had a hysterectomy and/or bilateral oophorectomy, bilateral salpingectomy or bilateral tubal ligation/occlusion, at least 6 weeks prior to screening; **OR**
- 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.

Single method (one of the following is acceptable):

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

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

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

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

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

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

APPENDIX F: REGISTRATION COVERSHEET

COH IRB#: **A Phase 1/2 Study of Pembrolizumab plus Pralatrexate for Treatment of Relapsed or Refractory Peripheral T-cell Lymphomas**

Data Coordinating Center:
City of Hope
1500 Duarte Road
Duarte, CA 91010
Tel: 626-218-7904
Email: DCC@coh.org (use #secure# in subject line)

Site Principal Investigator
Name:
Address:

Phone:
Fax:
e-mail:

CRA/Study Coordinator:	Contact Number:
Patient's Initials: (F M L):	Institution:
Medical Record No:	Investigator/Treating Physician:
Patient's DOB:	IRB approval valid until (date):
Sex: _____Male _____Female	Date Informed Consent Signed:
	Projected start date of treatment:

Race		Ethnicity		Method of Payment:_____	
☐	Black	☐	Hispanic	Codes:	
☐	Caucasian	☐	Non-Hispanic	**01** Private	**06** Military or Veterans Adm. sponsored
☐	Asian	☐	Other_____	**02** Medicare	**07** Self-pay (no insurance)
☐	American Indian			**03** Medicare & private ins.	**08** No means of payment (no insurance)
☐	Native Hawaiian/Pacific Islander			**04** Medicaid	**09** Unknown
☐	Other_____ _____			**05** Medicaid & Medicare	

Reason for Screen Failure:

Reason for Failing to Initiate Protocol Therapy:

APPENDIX G: CORRELATIVE TISSUE FORM (FOR ALL SITES)

A copy of this form should accompany the sample shipments to COH Pathology Core.

Non-COH sites: refer to Appendix H for shipping instructions to COH Pathology Core.

COH IRB number: 17501	Shipping date (MM-DD-YYYY): _____/_____/_____
Subject ID (issued by DCC):	Participant Initials (F, M, L) (if applicable):
Institution:	
Date of collection/ biopsy (MM-DD-YYYY): _____/_____/_____	
Time point: ☐ Baseline ☐ Progression	
Diagnosis:	
Tissue type (FFPE scrolls, slides, biopsies):	
Number of scrolls:	Number of slides:

CRA/Study Coordinator/Nurse Printed Name:
CRA/Study Coordinator/Nurse Signature:
Contact Number:

APPENDIX H: TISSUE SHIPPING GUIDELINES TO CITY OF HOPE PATHOLOGY CORE

*These guidelines apply to **non-COH sites** only.*

All biological material must be shipped according to applicable government and International Air Transport Association (IATA) regulations.

Shipping guidelines can also be found on the FedEx website.

1. Aim to ship samples on a **Monday through Wednesday**. If this is not feasible, advance arrangements should be made with City of Hope Pathology Core (DL-PATHCORE-BiospecimenSupport@COH.org).

2. Notify City of Hope Pathology Core (DL-PATHCORE-BiospecimenSupport@COH.org) of impending shipment. To request a FedEx shipping label, email DCC@coh.org and indicate the planned shipment date.

3. **Slides/ Blocks:** Batch ship at room temperature via FedEx. During extreme heat, include refrigerated (not frozen) gel packs or gel insulators.

   It is recommended to ship samples via FedEx overnight (for a delivery by 3 pm or earlier the next day) or FedEx 2-day (with a morning delivery). During extreme heat, ship via FedEx overnight (for a delivery ideally by 10.30 am, or 3 pm the next day).

4. **Frozen samples** should be batch shipped on dry ice via FedEx overnight (for a delivery by 10.30 am the next day). The shipment should contain enough dry ice to last at least 72 hours.

5. On the day of shipment, email the sample shipment information to City of Hope Pathology Core (DL-PATHCORE-BiospecimenSupport@COH.org).

6. Ship samples with a **copy of the correlative tissue form (Appendix G)** and a **copy of the pathology report** to:

   Karen Miller
   COH Pathology Core
   City of Hope National Medical Center
   1500 E. Duarte Road
   Familian Science (Building 084), Room 1207
   Duarte, CA 91010
   Telephone: 626-218-8408
   Email: DL-PATHCORE-BiospecimenSupport@COH.org

APPENDIX I: CORRELATIVE BLOOD COLLECTION FORM FOR NON-COH SITES ONLY

Subject ID (issued by DCC):	Participant Initials (F, M, L) (if applicable):
Institution:	

To be used by **non-COH sites** for the following blood samples being sent to **COH APCF**:

Sample #	Timepoint of Collection *	Expected Volume	Tube Type Used (Select One)	Collected Volume	Time of Collection	Date of Collection	Indicate which sample was collected
1.	Cycle 1, Day 1	20 mL	Green-top	_____ mL	____:____ AM/ PM	____/____/____	☐
		20 mL	Cell-free DNA BCT	_____ mL	____:____ AM/ PM	____/____/____	☐
2.	Cycle 2, Day 1	20 mL	Green-top	_____ mL	____:____ AM/ PM	____/____/____	☐
		20 mL	Cell-free DNA BCT	_____ mL	____:____ AM/ PM	____/____/____	☐
3.	Cycle 4, Day 1	20 mL	Green-top	_____ mL	____:____ AM/ PM	____/____/____	☐
4.	Cycle 5, Day 1	20 mL	Cell-free DNA BCT	_____ mL	____:____ AM/ PM	____/____/____	☐
5.	EOT**	20 mL	Cell-free DNA BCT	_____ mL	____:____ AM/ PM	____/____/____	☐

* Peripheral blood is collected prior to study treatment on Day 1 of each indicated cycle.

**EOT time point: correlative blood will not be collected if a correlative blood sample for ctDNA/MRD (purple-top/cell-free DNA BCT® tube) was collected within the prior 8 weeks.

A copy of this form should accompany the sample shipments to COH APCF. **Refer to the blood shipping guidelines for shipping instructions to COH APCF (Appendix J).**

CRA/Study Coordinator/ Nurse Printed Name:	Contact Number:
CRA/Study Coordinator/ Nurse Signature:	Date:

APPENDIX J: BLOOD SHIPPING GUIDELINES TO CITY OF HOPE APCF

*These guidelines apply to **non-COH sites** only, for the shipping of all green-top tubes and cell-free DNA BCT® (Streck) tubes.*

Follow the requirements for the proper packaging and shipping of biomedical material found in 42 CFR Part 72 - Interstate Shipment of Etiologic Agents Centers for Disease Control and Prevention, Office of Health and Safety Biosafety Branch.

1. Aim to ship samples on a **Monday through Wednesday**. If this is not feasible, advance arrangements should be made with Leslie Smith-Powell (LSmith-Powell@coh.org) or Stephanie Lee (stlee@coh.org) or their representative.

1. Blood samples in **green-top tubes** will be sent **overnight at around +4°C** with a refrigerated cool pack in an appropriate container via FedEx. Cell-free BCT tubes will be shipped together with green tubes for the first 2 time points. For the C5D1 and EOT time points, cell-free BCT tubes should be shipped as soon as possible but no more than 3 days after being drawn via overnight courier at ambient temperature.

2. **On the day of shipment**, email Leslie Smith-Powell (LSmith-Powell@coh.org) or Stephanie Lee (stlee@coh.org) or their representative the FedEx shipment #.

3. Ship samples with a **copy of the correlative blood collection form** (Appendix I) and a **copy of the latest CBC results (with differential)** and the **date of the test** to:

Dr. Tim Synold
Analytical Pharmacology Core Facility
Shapiro 1042
City of Hope National Medical Center
1500 E. Duarte Road
Duarte, CA 91010