Official Title:	**A Multi-center, Randomized, Phase 3 Study of Sequential Pralatrexate Versus Observation in Patients with Previously Undiagnosed Peripheral T-cell Lymphoma Who Have Achieved an Objective Response Following Initial Treatment with CHOP-based Chemotherapy**
NCT Number:	NCT01420679
Document Date:	Protocol Version 2.1: 31 October 2011

Clinical Study Protocol

Study Title:	A Multi-center, Randomized, Phase 3 Study of Sequential Pralatrexate Versus Observation in Patients with Previously Undiagnosed Peripheral T-cell Lymphoma Who Have Achieved an Objective Response Following Initial Treatment with CHOP-based Chemotherapy
Study Number:	PDX-017
Study Phase:	3
Study Drug:	Pralatrexate Injection
IND Number:	52,604
EudraCT Number:	2010-022230-81
Sponsor:	Allos Therapeutics, Inc.
Sponsor Contact:	[redacted], MD [redacted] [redacted] USA Phone: [redacted] Fax: [redacted]

Protocol Version/Date: 2.1/31 Oct 2011

This study will be conducted according to Good Clinical Practice (GCP) as described by the GCP Directive and European Union (EU) Directive (2001/20/EC) and other applicable GCP requirements of the regions where the study is conducted. All essential documents will be archived.

Confidentiality Statement

SYNOPSIS

Study Title:

A Multi-center, Randomized, Phase 3 Study of Sequential Pralatrexate Versus Observation in Patients with Previously Undiagnosed Peripheral T-cell Lymphoma Who Have Achieved an Objective Response Following Initial Treatment with CHOP-based Chemotherapy

Study Number:

PDX-017

Study Phase: 3

Study Centers Planned: This will be an international, multi-center study.

Objectives:

Primary

- Determine the efficacy of pralatrexate compared to observation when administered to patients with previously undiagnosed peripheral T-cell lymphoma (PTCL) who have achieved an objective response after completing at least 6 cycles of cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP)-based treatment.

Secondary

- Determine the safety of pralatrexate when administered following a course of CHOP-based treatment to patients with previously undiagnosed PTCL.

Efficacy Endpoints:

Primary

- Progression-free survival (PFS) and overall survival (OS)

Secondary

- Objective response (complete response [CR] or partial response [PR]) to pralatrexate versus observation

Treatment Plan:

This is an international, multi-center, randomized, Phase 3, open-label study of sequential pralatrexate versus observation in patients with previously undiagnosed PTCL who have achieved an objective response following initial treatment with CHOP-based chemotherapy. Upon documentation of completion of an objective response following at least 6 cycles of a designated CHOP-based chemotherapy confirmation of histopathology by independent review, and confirmation that all eligibility criteria are met, patients will be randomized in a 2:1 ratio to either pralatrexate or observation, according to a permuted block design with stratification factor of:

- Response per investigator at completion of CHOP-based therapy (complete response [CR] vs partial response [PR])

Patients randomized to the Pralatrexate Arm will receive pralatrexate as an intravenous (IV) push administered over a minimum of 30 seconds up to a maximum of 5 minutes via a patent free-flowing IV line containing normal saline (0.9% sodium chloride [NaCl]) weekly for

3 weeks (± 1 day at each time point) of a 4-week cycle. The initial dose of pralatrexate will be 30 mg/m^2, which based on protocol-defined criteria, may be reduced to 20 mg/m^2 with potential further reductions to 15 and 10 mg/m^2. Pralatrexate will continue to be administered until a criterion for study treatment discontinuation is met or up to a maximum of 2 years.

Patients randomized to the Observation Arm will remain under observation, attend clinic visits every 4 weeks, and be contacted by a healthcare professional during week 2 of every 4-week period until a criterion for study treatment discontinuation is met.

All patients will receive vitamin supplementation, consisting of vitamin B_{12} 1 mg intramuscular (IM) every 8-10 weeks and folic acid 1-1.25 mg by mouth (po) once a day (qd). Vitamin supplementation will begin at least 7 days prior to the projected initiation of pralatrexate/observation and continue throughout the study until the Initial Follow-up Visit.

Number of Patients Planned:

A total of 549 patients will be randomized 2:1 to pralatrexate or observation.

Target Population:

Adult patients with previously undiagnosed PTCL who have achieved an objective response after completion of initial treatment of at least 6 cycles of one of the following CHOP-based therapy regimens:

a. CHOP 21
b. CHOP 14
c. CHOEP
d. Other CHOP variants

Duration of Treatment:

Patients will receive study treatment (pralatrexate or observation) until one of the following criteria for study treatment discontinuation applies:

- Development of progressive disease (PD)
- Initiation of radiation therapy (RT) or systemic chemo/biological therapy for treatment of PTCL
- Receipt of systemic steroids > 10 days, with the exception of those as stated in exclusion criterion #5
- Development of an adverse event (AE) that interferes with the patient's participation
- Lost to follow-up
- Patient decision
- Investigator decision
- Sponsor decision

In addition, for patients randomized to the Pralatrexate Arm, the following treatment discontinuation criteria apply:

- 3 or more consecutive doses of pralatrexate omitted or more than 28 days between doses of pralatrexate

- Treatment with pralatrexate for 2 years

Study Duration:

All patients who receive at least 1 dose of pralatrexate will be followed for safety through 35 (± 5) days after their last dose of pralatrexate or until all treatment-related AEs have resolved or returned to baseline/Grade 1, whichever is longer, or until it is determined that the outcome will not change with further follow-up.

Patients who are randomized to the Observation Arm who do not discontinue the study within 3 days of randomization will be followed for safety until 35 (± 5) days after the study treatment discontinuation criteria are met.

All patients who are randomized will have follow-up until objectively documented PD; thereafter, patients are followed for survival. The timing of follow-up will be at 8 weeks (± 1 week) then every 12 weeks (± 1 week) through 3 years post-randomization, and then every 24 weeks (±4 weeks) thereafter through 7 years post-randomization. PD will be confirmed by central review until the first PFS analysis (described below), and per investigator assessment thereafter.

All subsequent therapies for PTCL will be collected for up to 7 years from randomization; the best response to the first subsequent therapy will be collected. Survival follow-up will continue for up to 7 years from randomization.

As discussed in the statistical methods section, an analysis will be performed when both 280 PFS events and 128 OS events have occurred. If the PFS analysis is not significant at the 0.05 level, the study will be stopped.

Eligibility Criteria

Inclusion Criteria

1. Patient's PTCL histology has been confirmed as one of the following by an independent pathology reviewer, using the Revised European American Lymphoma (REAL) World Health Organization (WHO) disease classification:
   a. T/natural killer (NK)-cell leukemia/lymphoma
   b. Adult T-cell lymphoma/leukemia (human T-cell leukemia virus [HTLV] 1+)
   c. Angioimmunoblastic T-cell lymphoma
   d. Anaplastic large cell lymphoma (ALCL), primary systemic type, excluding anaplastic lymphoma kinase positive (ALK+) with International Prognostic Index (IPI) score < 2 at initial diagnosis and CR after completion of CHOP-based therapy
   e. PTCL-unspecified
   f. Enteropathy-type intestinal lymphoma
   g. Hepatosplenic T-cell lymphoma
   h. Subcutaneous panniculitis T-cell lymphoma
   i. Transformed mycosis fungoides
   j. Extranodal T/NK-cell lymphoma nasal or nasal type
   k. Primary cutaneous gamma-delta T-cell lymphoma
   l. Primary cutaneous CD8+ aggressive epidermic cytotoxic T-cell lymphoma

2. Documentation that the patient has completed at least 6 cycles of CHOP-based therapy, including:
   a. CHOP 21
   b. CHOP 14
   c. CHOEP
   d. Other CHOP variants: includes all 4 components of CHOP represented, with substitution allowed for any 1 component with a drug of the same mechanism of action (eg, variant anthracyclines). Additional components to CHOP are allowed, with the exception of alemtuzumab; rituximab may be combined with CHOP provided that it is not given within 3 cycles of randomization.
3. Patient has achieved a CR or PR per investigator's assessment following completion of CHOP-based therapy and has had a radiological assessment within 21 days prior to randomization.
4. $\geq$ 18 years of age.
5. Eastern Cooperative Oncology Group (ECOG) performance status $\leq$ 2.
6. Adequate hematological, hepatic, and renal function as defined by:
   a. Absolute neutrophil count (ANC) $\geq$ 1000/µL
   b. Platelet count $\geq$ 100,000/µL
   c. Total bilirubin $\leq$ 1.5 mg/dL
   d. Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) $\leq$ 2.5 $\times$ upper limit of normal (ULN), (AST/ALT < 5 $\times$ ULN if documented hepatic involvement with lymphoma). All patients with hepatitis B virus (HBV)-positive serology must have liver function tests within the above parameters.
   e. Creatinine $\leq$ 1.5 mg/dL (if the patient's creatinine is > 1.5 mg/dL, then the calculated creatinine clearance must be $\geq$ 50 mL/min).
7. Females of childbearing potential (ie, excluding patients who are postmenopausal for at least 1 year [> 12 months since last menses] or are surgically sterilized) must:
   a. Have a negative serum pregnancy test within 14 days prior to randomization and
   b. Agree to practice a medically acceptable contraceptive regimen from study treatment initiation until at least 30 days after the last administration of pralatrexate.
8. Males who are sexually active, including those with a pregnant partner, must agree to practice a medically acceptable barrier method contraceptive regimen (eg, condoms) while receiving pralatrexate and for 90 days after the last administration of pralatrexate.
9. Patient has given written informed consent (IC).

Exclusion Criteria

1. Patient has:
   a. Precursor T/NK neoplasms
   b. ALCL (ALK+) with IPI score < 2 at initial diagnosis and CR after completion of CHOP-based therapy
   c. T-cell prolymphocytic leukemia (T-PLL)
   d. T-cell large granular lymphocytic leukemia
   e. Mycosis fungoides, other than transformed mycosis fungoides
   f. Sézary syndrome
   g. Primary cutaneous CD30+ disorders: ALCL and lymphomatoid papulosis
2. If there is a history of prior malignancies other than those exceptions listed below, the patient must be disease-free for ≥ 5 years. Patients with the following prior malignancies less than 5 years before study entry may still be enrolled if they have received treatment resulting in complete resolution of the cancer and currently have no clinical, radiologic, or laboratory evidence of active or recurrent disease.
   a. Non-melanoma skin cancer
   b. Carcinoma in situ of the cervix
   c. Localized prostate cancer
   d. Localized thyroid cancer
3. Patient has received prior treatment (chemotherapy or radiation) for PTCL, other than a single allowed CHOP regimen, with the exception of:
   a. Patients with nasal NK lymphoma are permitted to have received local radiation therapy no less than 4 weeks prior to randomization.
   b. Patients with transformed mycosis fungoides are permitted to have received 1 systemic single-agent chemotherapy (other than methotrexate) prior to transformation of their disease.
4. Prior exposure to pralatrexate.
5. Receipt of systemic corticosteroids within 3 weeks of study treatment, unless patient has been taking a continuous dose of ≤ 10 mg/day of oral prednisone or equivalent for at least 4 weeks or as part of a CHOP prednisone taper.
6. Planned use of any treatment for PTCL during the course of the study.
7. Patient has:
   a. Human immunodeficiency virus (HIV)-positive diagnosis with a CD4 count of < 100 mm^3 or detectable viral load within past 3 months and is receiving anti-retroviral therapy.
   b. HBV-positive serology and is receiving interferon therapy or has liver function test results outside the parameters of study inclusion criteria. Patients are permitted to receive other antiviral therapies if the therapy has been administered at a stable dose for ≥ 4 weeks.

c. Hepatitis C virus (HCV) with detectable viral load or immunological evidence of chronic active disease or receiving/requiring antiviral therapy.
d. Symptomatic central nervous system (CNS) metastases or lesions for which treatment is required.
e. Uncontrolled hypertension or congestive heart failure Class III/IV according to the New York Heart Association's Heart Failure Guidelines (see http://www.americanheart.org/presenter.jhtml?identifier=3065080).
f. Active uncontrolled infection, underlying medical condition including unstable cardiac disease, or other serious illness that would impair the ability of the patient to receive protocol treatment.

8. Patient has had major surgery within 2 weeks prior to study entry; other than for line placement or biopsy procedure.

Test Product, Dose, and Mode of Administration:

Pralatrexate will be administered via IV push over a minimum of 30 seconds up to a maximum of 5 minutes. One cycle is 4 weeks in duration consisting of weekly dosing at a starting dose of pralatrexate 30 mg/m^2 for 3 weeks, followed by 1 week of rest. Dose reduction to 20 mg/m^2 with further reductions to 15 and 10 mg/m^2 will be allowed for defined toxicity.

Pralatrexate will be administered into a patent free-flowing IV line containing normal saline (0.9% sodium chloride [NaCl]).

Efficacy Assessments:

The primary efficacy set, also referred to as the intent-to-treat population, includes all randomized patients. Each patient will be included in the treatment group assigned at randomization, regardless of the treatment received. This analysis set will be used for the primary analyses of all efficacy endpoints.

Tumor Response Assessments

Measured from randomization, response evaluations are to occur at 8 weeks (± 1 week) then every 12 weeks (± 1 week) through 3 years post-randomization, then every 24 weeks (± 4 weeks) through 7 years post-randomization. Tumor response will be determined by central review at least until the analysis of PFS. If PFS analysis is not significant at the 0.05 level at that analysis, the study will be stopped.

Progression-free Survival

PFS time is calculated as the number of days from randomization to the date of objective documentation of PD or death, regardless of cause (date of PD or death - date of randomization + 1). Patients who are alive without a disease response assessment of PD will be censored at their last disease assessment date or the date of randomization, whichever is later. Date of progression will not be imputed for patients with missing tumor assessment(s) before an assessment of PD. Patients who withdraw from treatment prior to PD will be followed for disease status whenever possible, even if subsequent therapy, including transplant, has been initiated prior to documented PD per central review at least until the PFS analysis. Patients who have no response assessments after baseline will be censored at randomization.

Overall Survival

Overall survival time is calculated as the number of days from randomization to the date of death, regardless of cause (date of death - date of randomization + 1). Survival follow-up will continue for up to 7 years from randomization.

Safety Assessments:

All patients who are randomized to the Pralatrexate Arm who receive at least 1 dose of pralatrexate plus all patients randomized to the Observation Arm who do not discontinue the study within 3 days of randomization will be evaluable for safety. Safety will be evaluated by assessment of physical examinations, clinical laboratory values, treatment-emergent AEs (all grades), SAEs, and discontinuations due to treatment-related AEs. Safety will be assessed according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) scale, Version 4.0.

Pharmacokinetic Assessments:

There will be sparse sampling for population pharmacokinetics (POPPK). Approximately two-thirds of the patients randomized to the Pralatrexate Arm ($n \approx 245$) who consent to plasma sampling will have sampling performed at cycle 1, dose 1 (pre-injection, end of injection, and 8 and 24 hours post-injection). Of these 245 patients, 20 patients at select sites will also have plasma sampling performed at cycle 2, dose 3 (pre-injection, end of injection, and 8 and 24 hours post-injection).

Statistical Methods:

The sample size is based on comparing the treatment groups with respect to the primary efficacy endpoints of PFS and OS. There will be 1 final analysis of PFS, and 2 interim and 1 final analysis of OS. The first interim analysis of OS will be performed at the same time as the PFS analysis. The first analysis will be performed when both 280 PFS events and 128 OS events have occurred. The only analysis for PFS will be performed at this first analysis point, and will be assessed at the 0.05 level of significance. If PFS is significant at the 0.05 level, the first interim analysis will be conducted on survival at this time. If the PFS analysis is not significant at the 0.05 level, the study will be stopped. The second interim and final analyses for OS will be performed when two-thirds (256) and all 385 OS events have occurred, respectively.

The stratified log-rank test will be the primary method used to test the hypothesis that pralatrexate extends PFS and OS relative to observation. In addition, the stratified Cox regression model will be used to calculate the PFS and survival hazard ratio (HR), along with their 95% confidence interval (CIs). Results of the unstratified Cox regression model (and log-rank test) will also be presented. The proportional hazards assumption of the Cox model will be assessed.

A DMC will periodically review safety data at regularly scheduled meetings and at the same time as each analysis of efficacy. The first formal safety review will occur when approximately 100 patients have been randomized and completed at least 8 weeks post-randomization pralatrexate/observation or have discontinued.

At each interim analysis for survival, the study may be stopped for overwhelming evidence of futility or superiority according to specified boundaries. The DMC may also make recommendations regarding adjustments to the sample size, if they are warranted.

Date of Protocol: 31 Oct 2011

TABLE OF CONTENTS

LIST OF IN-TEXT TABLES

LIST OF IN-TEXT FIGURES

LIST OF APPENDICES

LIST OF ABBREVIATIONS

AE	adverse event
AIDS	acquired immunodeficiency syndrome
ALCL	anaplastic large cell lymphoma
ALK	anaplastic lymphoma kinase
ALT	alanine aminotransferase
ANC	absolute neutrophil count
Ara-C	cytarabine or cytosine arabinoside
AST	aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
AUC	area under the curve
AUC_{∞}	area under the curve to infinity
β-hCG	β-human chorionic gonadotropin
BSA	body surface area
°C	degrees Celsius
CAS	Chemical Abstracts Service
CFR	Code of Federal Regulations
CHOP	cyclophosphamide, doxorubicin, vincristine, and prednisone
CHOP 14	CHOP given every 2 weeks or 14 days
CHOP 21	CHOP given every 3 weeks or 21 days
CI	confidence interval
cm	centimeter
C_{max}	maximum concentration
CNS	central nervous system
CR	complete response
CRA	clinical research associate
CRF	case report form
CRO	clinical research organization
CRu	unconfirmed CR
CT	computed tomography
CTA	clinical trial agreement

CTCAE	Common Terminology Criteria for Adverse Events
CTCL	cutaneous T-cell lymphoma
CTEP	Cancer Therapy Evaluation Program
DCF	Data Clarification Forms
DHFR	dihydrofolate reductase
dL	deciliter
DLBCL	diffuse large B-cell
DLT	dose-limiting toxicity
DMC	Data Monitoring Committee
EBV	Epstein Barr virus
EC	Ethics Committee
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EDC	electronic data capture
ESHAP	etoposide, methylprednisolone, cytarabine, and cisplatin
EU	European Union
°F	degrees Fahrenheit
FDA	Food and Drug Administration
FDG	fluorodeoxyglucose
FFS	failure-free survival
FPGS	folylpolyglutamyl synthetase
GCP	good clinical practice
G-CSF	granulocyte colony-stimulating factor
Gem	gemcitabine
GFR	glomerular filtration rate
GLP	good laboratory practice
GM-CSF	granulocyte-macrophage colony-stimulating factor
HBV	hepatitis B virus
Hct	hematocrit
HCV	hepatitis C virus
Hgb	hemoglobin

HIV	human immunodeficiency virus
HR	hazard ratio
HTLV	human T-cell leukemia virus
IB	Investigator's Brochure
IC	informed consent
ICH	International Conference on Harmonisation
IC_{50}	half maximum inhibitory concentration
ILSG	International Lymphoma Study Group
IM	intramuscular
IND	investigational new drug
INN	international nonproprietary name
IP	intraperitoneal
IPI	International Prognostic Index
IRB	Institutional Review Board
IRT	interactive response technology
IV	intravenous
IVRS	interactive voice response system
IWC	International Workshop Criteria
kg	kilogram
K_i	inhibition constant
K_m	binding constant
L	liter
LDH	lactic dehydrogenase
m^2	square meter
MALT	mucosa-associated lymphatic tissue lymphomas
MC	mantle cell
MedDRA®	medical dictionary for regulatory activities
mg	milligram
min	minute
mL	milliliter
mm	millimeter

mOsmol	milliosmole
MRI	magnetic resonance imaging
MSKCC	Memorial Sloan-Kettering Cancer Center
MTD	maximum tolerated dose
MTX	methotrexate
NaCl	sodium chloride
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NDA	New Drug Application
NHL	non-Hodgkin's lymphoma
NK	natural killer
N, n, or no.	number
NOD/SCID	non-obese, diabetic/severe combined immunodeficient
NOS	not otherwise specified
NSAID	non-steroidal anti-inflammatory drug
NSCLC	non-small cell lung cancer
nM	nanomolar
nmol	nanomole
ORR	overall response rate
OS	overall survival
PBSCT	peripheral blood stem cell transplant
PD	progressive disease
PDX	pralatrexate, (*RS*)-10-propargyl-10-deazaaminopterin
PET	positron emission tomography
PFS	progression-free survival
PK	pharmacokinetics
pM	picomolar
po	oral
POPPK	population PK
PR	partial response
PTCL	peripheral T-cell lymphoma

PTCL-U	PTCL-unspecified
q	every
qd	once a day
REAL	Revised European American Lymphoma
REB	Research Ethics Board
RFC-1	reduced folate carrier-1
RS	rectus sinister; a racemic mixture of a chiral compound
RT	radiation therapy
SAE	serious adverse event
SAER	serious adverse event report
SD	stable disease
SE	standard error
SN	site notification
SOC	system organ class
SPD	sum of the product of the diameters
SRI	Southern Research Institute
SRI International	Stanford Research Institute International
$t_{1/2}$	half-life
TCC	transitional cell carcinoma
TEN	toxic epidermal necrolysis
T-LB	precursor T-lymphoblastic lymphoma
T-PLL	T-cell prolymphocytic leukemia
ULN	upper limit of normal
US	United States
USAN	United States Adopted Name
USP	United States Pharmacopeia
µg	microgram
µL	microliter
µM	micromolar
µmol	micromole
V_{max}	maximum rate constant

WBC	white blood cells
WHO	World Health Organization

1 INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE

Prior to study initiation, the investigator at each site must provide to Allos Therapeutics, Inc. (Allos) a signed protocol signature page, a fully executed and signed United States (US) Form Food and Drug Administration (FDA) 1572, and a Financial Disclosure Form. Financial Disclosure Forms must also be completed for all subinvestigators listed on the US Form FDA 1572 who will be directly involved in the treatment or evaluation of research patients in this study.

The study will be administered and monitored by employees or representatives of Allos. Clinical research associates (CRAs) will monitor each site on a periodic basis and perform verification of source documentation for each patient. The Clinical Drug Safety and Pharmacovigilance Department at Allos will be responsible for ensuring timely reporting of expedited serious adverse event reports (SAERs) to regulatory agencies and investigators.

2 INTRODUCTION

2.1 Background Information on Non-Hodgkin's Lymphomas

Included under the category of lymphoma are some of the fastest growing and most aggressive cancers (Burkitt's lymphoma, lymphoblastic lymphoma/leukemia), as well as some of the most indolent (small lymphocytic lymphoma, follicular lymphoma, and marginal zone lymphoma), making lymphoma one of the most heterogeneous groups of malignancies. It is this considerable biological diversity that imposes significant challenges in understanding the cell of origin and differentiating the sometimes subtle distinctions between the related subtypes of disease, as well as in identifying the best treatments for each. T-cell lymphomas represent a heterogeneous array of aggressive non-Hodgkin's lymphoma (NHLs) and account for approximately 10-15% of all newly diagnosed cases of NHL in the US.[1-3]

While the etiology of the lymphoma diseases remains largely unknown, it is clear that beginning prior to 1950, an epidemic of NHL, but not other hematopoietic neoplasms, was documented in many populations, with an estimated 50% increase in the age-adjusted incidence from 1970-1990 in the US.[4-6] While reports suggest that the steep rise in incidence may have slowed in recent years, caution needs to be exercised in interpreting these incidence rates given the innumerable factors that can influence these statistics, like acquired immunodeficiency syndrome (AIDS), new diagnostic techniques, and other etiologic factors, such as infections. Interestingly, industrialized nations experience a higher incidence of NHL than do developing countries, with the highest incidence rate in the world occurring in the US and Canada.[7] These statistics rank NHL as the sixth most common cancer and the sixth most common cause of cancer death, accounting for 4% of all cancers and 4% of cancer deaths. While they are considered biologically diverse diseases with respect to their cell of origin, all are thought to be derived from lymphocytes.

2.2 Classification of T-cell Lymphomas

As mentioned, T-cell lymphomas account for approximately 10-15% of all newly diagnosed cases of NHL in the US. According to the World Health Organization (WHO) classification, T-cell lymphomas are divided into a variety of subtypes, as shown below in Table 2.1. According to this classification, there are considered to be at least 16 distinct subtypes of T-cell lymphoma.[8]

Table 2.1 WHO T-cell Lymphoma Classification[8]

Mature T- and NK-cell Neoplasms
T-cell prolymphocytic leukemia
T-cell large granular lymphocytic leukemia
Chronic lymphoproliferative disorder of NK-cells
Aggressive NK-cell leukemia
EBV+ T-cell lymphoproliferative disorder of childhood
Adult T-cell lymphoma/leukemia
Extranodal T-cell/NK-cell lymphoma, nasal type
Enteropathy-associated T-cell lymphoma
Hepatosplenic T-cell lymphoma
Subcutaneous panniculitis-like T-cell lymphoma
Mycosis fungoides
Sézary syndrome
Primary cutaneous CD30+ T-cell lymphoproliferative disorders
Primary cutaneous gamma-delta T-cell lymphomas
Peripheral T-cell lymphoma, NOS
Angioimmunoblastic T-cell lymphoma
Anaplastic large cell lymphoma, ALK+ type
Anaplastic large cell lymphoma, ALK- type

NK = natural killer
EBV = Epstein Barr virus
NOS = not otherwise specified
ALK = anaplastic lymphoma kinase

2.3 Prognosis of T-cell Lymphomas

Almost all T/natural killer (NK)-cell lymphomas are aggressive diseases requiring systemic chemotherapy. There are select T-cell subsets of disease that are considered more indolent, including T-cell large granular lymphocytic leukemia, primary cutaneous CD30+ disorders (including anaplastic large cell lymphoma [ALCL] and lymphomatoid papulosis), or mycosis fungoides/Sézary syndrome.

In general, T/NK-cell diseases are associated with a worse prognosis compared with their B-cell counterparts. It is not entirely clear why T-cell lymphomas have a worse prognosis; however, several theories have been advanced around the fundamental biological differences between B- and T-cell lymphomas with regard to their intrinsic chemosensitivity. The observation has also been made that patients with T-cell lymphomas generally present with

more high-risk disease, at least based on the International Prognostic Index (IPI).[9] The IPI allows for the risk stratification of patients with all types of lymphoma, and has been applied to patients with both indolent and aggressive lymphomas.[9] This index is based upon 5 important prognostic factors: age, Eastern Cooperative Oncology Group (ECOG) Performance Status, abnormal levels of lactic dehydrogenase (LDH), number of extra nodal sites, and stage, with higher scores indicating worse outcome.[9] Table 2.2 provides information on the relative risk of death associated with each of these prognostic factors.

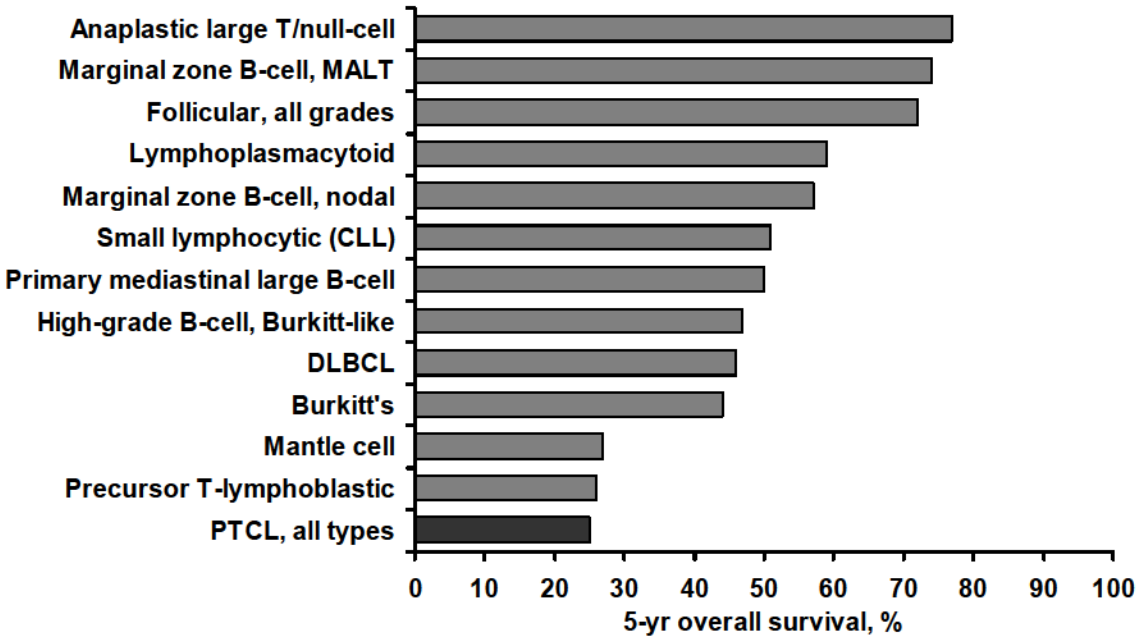
Table 2.2 Lymphoma-independent Prognostic Risk Factors per the International Prognostic Index

Factor	Relative Risk of Death
Age (≤ 60 versus > 60)	1.96
Serum LDH (≤ 1 x normal versus > 1 x normal)	1.85
ECOG Performance Status (0 or 1 versus 2-4)	1.80
Stage of Disease (I or II versus III or IV)	1.47
Extranodal Site Involvement (≤ 1 site versus > 1 site)	1.48

The IPI is calculated by adding the number of risk factors identified above, resulting in the classification of patients with low (any 1 risk factor), low-intermediate (any 2 risk factors), high-intermediate (any 3 risk factors), and high (4-5 risk factors) risk disease.

Assessment of these prognostic factors in a large cohort of B-cell and T-cell lymphomas suggested that T-cell phenotype appears to be an independent adverse prognostic factor in addition to the IPI score.[10] Of note, approximately 80% of patients with peripheral T-cell lymphoma (PTCL) have an IPI of 2 or higher at diagnosis compared with 69% of patients with diffuse large B-cell lymphoma.[1] Figure 2.1 displays the 5-year survival by histological subtype.[1]

Figure 2.1. 5-year Overall Survival by Histologic Type[1]



While never fully established in any prospective randomized clinical study, it is reasonably well accepted that T-cell lymphomas are more challenging to effectively treat than B-cell lymphomas. Table 2.3 presents some of these data.[10] For example, in the previously mentioned study, the 5-year survival rate for patients with 1, 2, or 3 risk factors with B- versus T-cell lymphoma was 63% versus 60%, 53% versus 36%, and 35% versus 23%, respectively. Similar trends were also observed for the rate of complete responses (CR).

Table 2.3 Comparison of Complete Response Rate and 5-Year Overall Survival in B- and T-cell Neoplasms[10]

IPI Factors	Lineage Assignment	Complete Remission Rate (%)	5-Year Overall Survival (%)
Overall	B- T-	63% 54%	53% 41%
0	B- T-	81% 82%	84% 77%
1	B- T-	71% 73%	63% 60%
2	B- T-	63% 58%	53% 36%
3	B- T-	52% 35%	35% 23%

These data are corroborated to some extent by the categorization of different overall survival (OS) rates by histological subtype using the International Lymphoma Study Group (ILSG) classification, which sub-divided the lymphomas into 4 broad groupings, including: (1) those with 5-year overall survival rate of greater than 70% including follicular lymphoma, marginal zone B-cell lymphoma of mucosa-associated lymphatic tissue lymphomas (MALT type), and anaplastic lymphoma kinase (ALK) positive anaplastic large T-cell lymphoma; (2) those histological subtypes with 5-year survival rates of 50%-70%, including small lymphocytic, lymphoplasmacytoid, and nodal marginal zone B-cell lymphomas; (3) those lymphomas with 5-year overall survival rates of 30%-49%, including diffuse large B-cell lymphoma, primary mediastinal large B-cell lymphoma, and the high-grade, B-cell, Burkitt-like and Burkitt lymphomas; and finally, (4) those histological subtypes with the worse overall prognosis and 5-year survival rates less than 30%, including PTCL, precursor T-lymphoblastic lymphoma, and mantle cell lymphoma.[11] These results have been more recently confirmed by others showing that patients with PTCL have an especially poor outcome with a 5-year overall survival rate of only 26% following treatment with standard doxorubicin-containing regimens.[12]

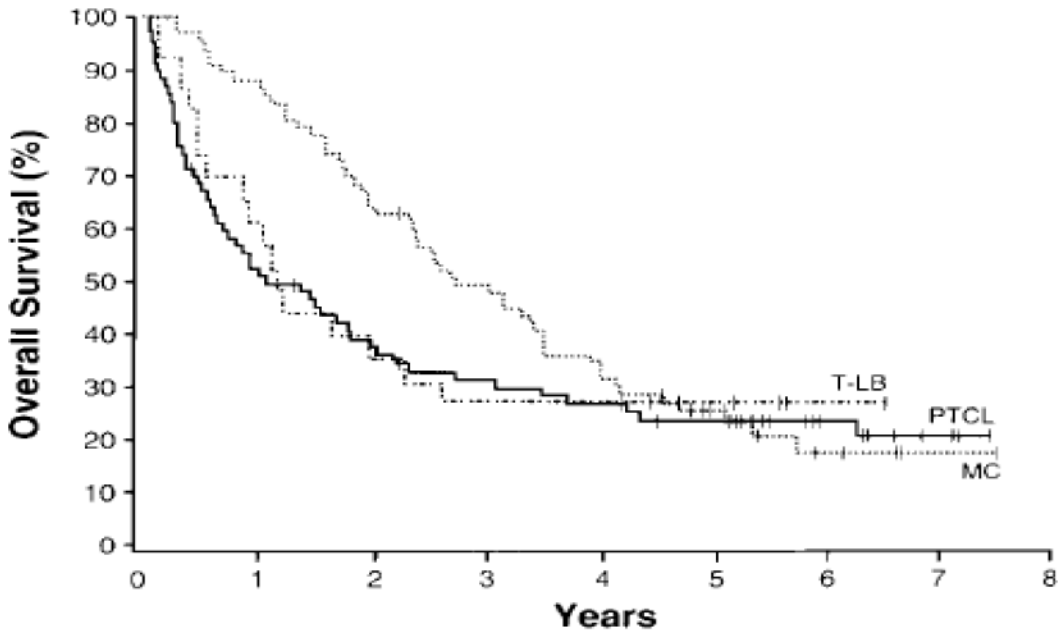
These observations strongly suggest that patients with T-cell lymphoma are in need of new treatment options.

2.3.1 Current First-line Therapy for Peripheral T-cell Lymphoma

There are currently no approved agents for first-line treatment of PTCL. Patients with the most aggressive T-cell lymphoma subtypes receive very little clinical benefit from standard therapies[13, 14, 15], and new treatment combinations are needed to improve both progression-free survival (PFS) and OS in the patient population under study in this protocol.

The diverse nature and rarity of T-cell lymphomas pose a challenge to the systematic study of these malignancies and the identification of "standard" therapeutic strategies. Recent reviews have attempted to characterize treatment approaches to PTCL, as well as to describe new agents that have potential activity against a variety of these diseases.[13, 14] First-line treatment of patients with PTCL generally consists of combination chemotherapy, primarily with cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP), but response is achieved in approximately half the patients and is generally of short duration.[12, 16] The median survival for PTCL, including all subtypes, is 1-3 years.[1, 17,15] Figure 2.2 displays the OS of PTCL, as well as that for precursor T-lymphoblastic lymphoma and the B-cell NHL with the lowest OS, mantle cell. In a study evaluating 4 different chemotherapy regimens in 288 patients with PTCL and 1595 patients with B-cell lymphoma, the 5-year event-free survival rate was 32% for PTCL patients.[10] For the most common histologic subtype of PTCL, PTCL-unspecified (PTCL-U), which comprise approximately 34% of all cases seen in North America, the 5-year failure-free survival (FFS) is 20%.[18]

Figure 2.2. Overall Survival by Histologic Type[1]



T-LB = precursor T-lymphoblastic lymphoma
PTCL = peripheral T-cell lymphoma
MC = mantle cell

Outcome data for patients with T-cell lymphoma who receive first-line CHOP are limited. A retrospective study of the International T-Cell Lymphoma Project demonstrated a 5-year OS rate of 32% and a 5-year FFS rate of 20% for patients with PTCL-U, with widely varying results for other subtypes, most of whom received an anthracycline-containing regimen.[18] In a retrospective evaluation of 96 patients diagnosed within the Non-Hodgkin's Lymphoma Classification Project, Rudiger et al report a similar finding, with 5-year OS and FFS rates of

26% and 20%, respectively, for PTCL patients treated with a doxorubicin-containing regimen.[12] The estimated median FFS in these patients is approximately 6 months.

The first-line response rates to anthracycline-containing regimens, including CHOP chemotherapy, for patients with PTCL have been reported to range between 50% and 70%, yet the long-term survival of these patients remains dismal.[18] A variety of other anthracycline-based combination therapies have also shown activity, including infusional treatment programs, such as CHOP plus etoposide.[19] Non-alkylator based treatment programs exploiting nucleoside analogs like deoxycoformycin, fludarabine, gemcitabine, and cladribine, as well as monoclonal antibodies/immunotoxins, and high-dose chemotherapy followed by peripheral blood stem cell transplant (PBSCT) have also been used in patients with T-cell lymphomas with varying degrees of success.[20] While early data suggest that these strategies may be more effective at inducing meaningful durable CRs, many patients never achieve the remissions necessary to make PBSCT feasible and there are no randomized data available that allow a determination that PBSCT is superior to other forms of up-front conventional combination chemotherapy programs.[21]

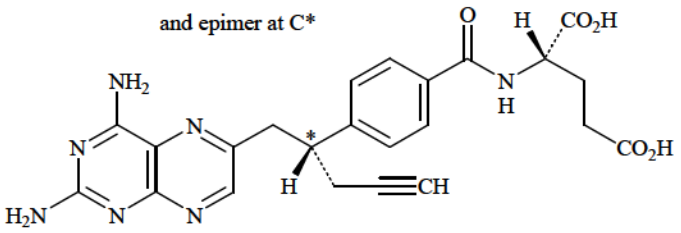
The essential therapeutic goal with this PTCL patient population is to control disease progression in order to prolong the clinical benefit achieved from intensive chemotherapy regimens such as CHOP and CHOP-based therapy and so extend survival.

3 PRALATREXATE

3.1 Physical, Chemical, Pharmaceutical Properties

Name of Drug Product	Pralatrexate Injection (Pralatrexate Solution for Infusion in the European Union [EU])
Name of Active Pharmaceutical Ingredient	Pralatrexate
United States Adopted Name (USAN) Council Chemical Name	(2*S*)-2-[[4-[(1*RS*)-1-[(2,4-diaminopteridin-6-yl) methyl]but-3-ynyl]benzoyl]amino]pentanedioic acid
Other Chemical Names	(*RS*)-10-propargyl-10-deazaaminopterin International nonproprietary name (INN) Chemical Name: *N*-{4-[1-(2,4-diaminopteridin-6-yl)pent-4-yn-2-yl]benzoyl}-*L*-glutamic acid Chemical Abstracts Service (CAS) Name: L-glutamic acid, N-[4-[1-[(2,4-diamino-6-pteridinyl)methyl]-3-butyn-1-yl]benzoyl]
USAN and INN Nonproprietary Name	Pralatrexate
Trade Name	FOLOTYN®
Pharmacological Class	Antineoplastic agent/antimetabolite/folic acid analog (Anatomical Therapeutic Chemical [ATC] code L01 BA05)
Empirical Formula	$C_{23}H_{23}N_7O_5$
Molecular Weight	477.5
Chemistry Abstract Registry Number	146464-95-1

Structural Formula



For detailed information about the general pharmacology, pharmacokinetics (PK), and nonclinical toxicology and efficacy studies of pralatrexate, refer to the current pralatrexate Investigator's Brochure (IB) supplied by Allos. This document must be reviewed prior to initiating the study.

3.2 Nonclinical Studies with Pralatrexate

3.2.1 Nonclinical Pharmacology

Pralatrexate, a methotrexate analog, was initially developed by Memorial Sloan-Kettering Cancer Center (MSKCC) in collaboration with Southern Research Institute (SRI) and Stanford Research Institute International (SRI International). Pralatrexate is a synthetic 10-deazaaminopterin antifolate. The 10-deazaaminopterins are a class of rationally designed antifolates demonstrating greater antitumor effects than methotrexate in in vitro tumor models and human tumor xenografts in mice.[22-24]

Pralatrexate is a folate analog metabolic inhibitor that competitively inhibits the enzyme dihydrofolate reductase (DHFR). In in vitro studies, pralatrexate showed improved cytotoxic activity against a panel of cancer cell lines compared with methotrexate. The improved cytotoxic activity is likely due to pralatrexate being a more efficient permeant for reduced folate transport and it being more efficiently polyglutamylated by the enzyme folylpolyglutamyl synthetase (FPGS).[23, 25] Similar to what has been reported for methotrexate, cellular uptake of pralatrexate is thought to occur via the reduced folate carrier-1 (RFC-1) membrane protein. This protein has evolved to efficiently transport reduced natural folates into highly proliferative cells, in order to meet the demands for purine and pyrimidine nucleotides during cell replication. Inside the cell, pralatrexate is polyglutamylated by FPGS, an enzyme involved in polyglutamylation of reduced natural folates. Therefore, pralatrexate may act as a competitive inhibitor for polyglutamylation of natural folates. Further, it is believed that the addition of glutamate residues to pralatrexate leads to increased intracellular half-life, thus allowing for prolonged drug action in malignant cells. The relative increase in cellular uptake and differences in polyglutamate formation in normal versus malignant cells may account for the enhanced activity of pralatrexate.

Pralatrexate demonstrated a 10-fold greater rate of polyglutamylation by FPGS than methotrexate (Table 3.1). In a cytotoxicity assay using a number of human non-small cell lung cancer (NSCLC) and breast cancer cell lines, pralatrexate was found to be superior to both methotrexate (13- to 40-fold lower IC_{50} [half maximum inhibitory concentration]) and another methotrexate analog, edatrexate (2- to 4-fold lower IC_{50}).

Table 3.1. In Vitro Comparison of Methotrexate Analogs

	Pralatrexate	Edatrexate	Methotrexate
DHFR Inhibition, K_i (pM)	13.4	5.8	4.9
FPGS Activity, V_{max}/K_m	23.2	10.3	2.2
In vitro Activity			
IC_{50} Concentration (µM):			
MDA-468 (breast)	0.11	0.39	4.5
SK-BR III (breast)	0.28	0.99	4.2
ZR-75-1 (breast)	0.26	0.86	3.5
SK-LC8 (NSCLC)	0.42	1.24	10.3
SK-LC16 (NSCLC)	0.11	0.26	2.1

DHFR = dihydrofolate reductase; K_i = inhibition constant; pM = picomolar; FPGS = folylpolyglutamyl synthetase; V_{max} = maximum rate constant; K_m = binding constant; IC_{50} = half maximum inhibitory concentration; µM = micromolar; NSCLC = non-small cell lung cancer

Screening of pralatrexate in the National Cancer Institute (NCI) 60-Cell Screen suggest potent cytotoxic activity across a broad spectrum of tumor types, including leukemia, NSCLC, colon cancer, central nervous system cancer, melanoma, ovarian cancer, renal cancer, and breast cancer.

Pralatrexate was evaluated for growth inhibitory activity against human tumor cell lines representing head and neck cancer (HLaC), breast cancer (MDA-MB-231, MDA-MB-435), and NSCLC (A549, MV522). Under the experimental conditions, pralatrexate, tested as a single agent, was most active in the MV522 lung and MDA-MB-231 breast cell lines with IC_{50} values of 12.8 nM (MV522) and 18.0 nM (MDA-MB-231). Cytotoxicity of pralatrexate was comparable in HLaC and MDA-MB-435 with IC_{50} values of 25.8 nM and 24.1 nM. The A549 lung adenocarcinoma line was least sensitive to pralatrexate (IC_{50} = 65.1 nM). In a head-to-head comparison with conventional therapeutics, pralatrexate was more cytotoxic than cisplatin in every cancer cell line tested and superior to paclitaxel in the MDA-MB-231 breast and both lung lines. Pralatrexate also demonstrated superior activity versus docetaxel in the MV522 lung line.

Overall, the NCI-60 cell line results, as well as in vitro testing in additional human tumor cell types, indicates that pralatrexate exhibits significant cytotoxic activity across a number of solid and lymphoproliferative tumor types.

3.2.1.1 Xenograft Studies in Lymphoma Models

Because methotrexate is active in the treatment of aggressive NHL, the efficacy of pralatrexate and methotrexate were comparatively evaluated against 5 lymphoma cell lines: RL (transformed follicular lymphoma), HT, SKI-DLBCL-1 (diffuse large B-cell lymphoma), Raji (Burkitt's), and Hs445 (Hodgkin's disease). After 5 days of continuous in vitro exposure, pralatrexate demonstrated 8- to 20-fold greater cytotoxicity than methotrexate in all cell lines (Table 3.2).

Table 3.2. Comparison of Growth Inhibition by Pralatrexate and Methotrexate Against Human Lymphoma Cell Lines

Cell line	Lymphoma type	IC_{50} Pralatrexate (nM)	IC_{50} Methotrexate (nM)	*P* value
Hs445	Hodgkin's disease	1.6 ± 0.8	32 ± 2.2	0.0455
HT	Diffuse large B-cell	3.0 ± 0.4	35 ± 5.0	0.0236
Raji	Burkitt's	2.0 ± 0.3	16 ± 0.8	0.0034
RL	Transformed follicular	23 ± 2.0	210 ± 40	0.0429
SKI-DLBCL-1	Diffuse large B-cell	5.1 ± 0.1	48 ± 2.5	0.0035

IC_{50} = half maximum inhibitory concentration, nM = nanomolar

Next, pralatrexate and methotrexate were evaluated in tumor xenograft models of 3 human NHL cell lines. Tumor-bearing non-obese, diabetic/severe combined immunodeficient (NOD/SCID) mice were treated with saline (control) or the maximum tolerated doses (MTDs) of methotrexate (40 mg/kg) or pralatrexate (60 mg/kg) via an intraperitoneal (IP) route twice weekly for 2 weeks. Almost 90% of HT lymphomas treated with pralatrexate completely regressed, whereas those treated with methotrexate showed only modest growth delays (Table 3.3).

Table 3.3. Treatment of Human HT (Diffuse Large B Cell) Non-Hodgkin's Lymphoma Xenografts in NOD/SCID Mice

Agent	Dose (mg/kg)	Weight change (%)	Tumor diameter (mm ± SE)	Tumor volume (mm^3 ± SE)	Average tumor regression (%)	Complete regressions (no./total)
Control	—	+13.3	11.2 ± 1.3	+641 ± 252	—	0/8
Methotrexate	40	- 9.8	8.7 ± 2.0	+300 ± 225	—	0/7
Pralatrexate	60	- 8.9	0.5 ± 0.3	-95 ± 0.8	99	8/9

NOD/SCID = non-obese, diabetic/severe combined immunodeficient; mg = milligram; kg = kilogram; mm = millimeter; no. = number; SE = standard error

In 2 other models, complete tumor regression rates of 56% (RL, Table 3.4) and 30% (SKI-DLBCL-1, Table 3.5) were observed after pralatrexate treatment. No tumor regressions and only minor growth inhibition was noted in the methotrexate-treated animals.

Table 3.4. Treatment of Human RL (Transformed Follicular) Non-Hodgkin's Lymphoma Xenografts in NOD/SCID Mice

Agent	Dose (mg/kg)	Weight change (%)	Tumor diameter (mm ± SE)	Change in tumor volume (mm^3 ± SE)	Tumor regression (%)	Complete regressions (no./total)
Control	—	+15.9	12.5 ± 1.3	+1228 ± 238	—	0/7
Methotrexate	40	-14.8	10.9 ± 0.5	+618 ± 108	—	0/12
Pralatrexate	60	-11.1	2.7 ± 1.1	-46 ± 34	57	5/9

NOD/SCID = non-obese, diabetic/severe combined immunodeficient; mg = milligram; kg = kilogram; no. = number; SE = standard error

Table 3.5. Treatment of Human SKI-DLBCL-1 (De Novo Diffuse Large B-Cell) Non-Hodgkin's Lymphoma Xenografts in NOD/SCID Mice

Agent	Dose (mg/kg)	Weight change (%)	Tumor diameter (mm ± SE)	Change in tumor volume (mm^3 ± SE)	Tumor regression (%)	Complete regressions (no./total)
Control	—	+4.9	12± 0.3	+786 ± 646	—	0/8
Methotrexate	40	+1.9	9.5± 0.4	+299 ± 58	—	0/10
Pralatrexate	60	-1.2	3.5± 0.7	-81 ± 16	54	3/10

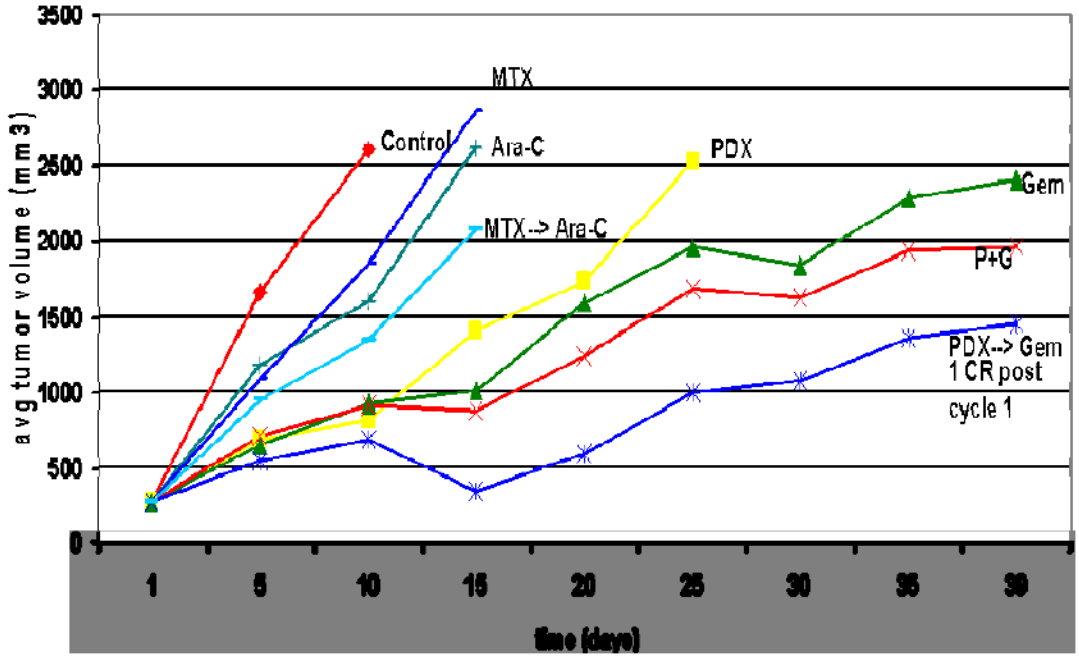
NOD/SCID = non-obese, diabetic/severe combined immunodeficient; mg = milligram; kg = kilogram; no. = number; SE = standard error

These results demonstrate that pralatrexate has the potential to exhibit greater activity against human NHL than methotrexate.

Antifolates and cytidine analogs have had a role in the treatment of many kinds of lymphoproliferative malignancies. Methotrexate is known to synergize with cytarabine in a schedule-dependent manner. The combination of pralatrexate and the cytidine analog gemcitabine (2',2'-difluorodeozycytidine) was studied. The activity of the standard combination of methotrexate/cytarabine was compared with that of pralatrexate/gemcitabine.

A xenograft experiment in the SKI-DLBCL-1 model was conducted at one-quarter of the MTD of pralatrexate and gemcitabine (15 mg/kg each). A similar dose reduction for methotrexate and cytarabine was not performed given the lack of activity seen at the MTD in an exploratory study. Control groups had to be euthanized early due to excessive tumor growth, as did animals receiving methotrexate (60 mg/kg) alone, cytarabine (300 mg/kg) alone, or both drugs in combination. In contrast, treatment with pralatrexate, gemcitabine, or combinations of these 2 at 25% of the MTD was markedly more efficacious. Complete tumor regressions were only observed in those animals receiving pralatrexate followed by gemcitabine (Figure 3.1). These in vivo experiments clearly establish a marked superiority of pralatrexate and gemcitabine when given in a sequential fashion. These results raise the possibility that pralatrexate, with or without the scheduled administration of gemcitabine, may provide a new treatment modality for select lymphoproliferative malignancies.

Figure 3.1. In Vivo SCID Beige Xenograft Model of SKI-DLBCL-1



SCID = severe combined immunodeficient; MTX = methotrexate; Ara-C = cytarabine; PDX or P = pralatrexate; Gem or G = gemcitabine; CR = complete remission/response

3.2.2 Nonclinical Toxicology

A comprehensive acute and subacute toxicology evaluation program has been performed to good laboratory practices (GLP) compliance and per International Conference on Harmonisation (ICH) guidance to emulate the route, dose, and schedule of pralatrexate administration used in clinical development, including: cardiovascular and neurological safety assessments; single and repeat-dose toxicology studies in rats and dogs; in vitro and in vivo genotoxicity studies to determine mutagenic potential of pralatrexate; embryofetal development and maternal toxicity studies in rats; and local tolerance studies in rats. Pralatrexate did not show evidence of cardiovascular or neurologic toxicity. Toxicological assessments in rats and dogs revealed the anticipated dose-limiting toxicities (DLTs) of the gastrointestinal and hematological systems. Pralatrexate was found to have low mutagenic potential in a panel of genotoxicity assays. Similar to other antifolates, pralatrexate was found to be toxic to developing embryos in embryofetal development studies in rats and rabbits. Pralatrexate was not toxic in local tolerance studies in rats. Refer to the pralatrexate IB for further information on nonclinical toxicology studies conducted with pralatrexate.

4 ONCOLOGY STUDIES WITH PRALATREXATE

Over 600 adult cancer patients have received pralatrexate in 15 ongoing or completed Phase 1 or 2 clinical oncology studies.

For detailed information about the oncology studies of pralatrexate, refer to the current pralatrexate IB.

4.1 Studies in Patients with Lymphoproliferative Malignancies

4.1.1 Single-Agent Studies

Study PDX-02-078 is a Phase 1/2 study in patients with relapsed or refractory aggressive NHL or Hodgkin's disease. After initial assessment of an every other week schedule, a weekly schedule with vitamin B_{12} and folic acid supplementation was initiated. In the initial version of the study, the starting dose of pralatrexate was 135 mg/m^2 administered every other week with intrapatient dose escalation. When DLTs occurred at the dose of 45 mg/m^2 for 6 weeks of a 7-week cycle, the MTD was determined to be 30 mg/m^2/week for 6 weeks on a 7-week cycle.

Data from PDX-02-078, were published on 48 patients evaluable for response in the study.[26] Responses were observed in 15 of 48 evaluable patients, for an overall response rate (ORR) of 31%. Fourteen of 26 (54%) evaluable patients with T-cell lymphoma responded to pralatrexate treatment (8 with CRs and 6 with partial responses [PRs]). Among the 20 evaluable patients with B-cell lymphoma, 1 patient achieved a PR.

Due in part to the responses seen in the PDX 02-078 study, it was decided to explore pralatrexate as a single agent in relapsed/refractory PTCL in study PDX-008. PDX-008 is a Phase 2, single-arm, non-randomized, open-label, international, multi-center, registration-directed study designed to evaluate the safety and efficacy of pralatrexate when administered concurrently with vitamin B_{12} and folic acid supplementation to patients with relapsed or refractory PTCL. The study completed enrollment of 115 patients in Apr 2008; 111 patients received at least 1 dose of pralatrexate and were considered evaluable for safety.

The objectives of the study were to determine the efficacy, safety, and PK profile of pralatrexate with concurrent vitamin B_{12} and folic acid supplementation when administered to patients with relapsed or refractory PTCL. The primary efficacy endpoint of the study was response rate and secondary efficacy endpoints were duration of response, PFS, and OS. Data from PDX-008 were presented in the clinical study report, which was submitted in New Drug Application (NDA) to the US FDA. In Sep 2009, the FDA granted accelerated approval for pralatrexate in the treatment of patients with relapsed or refractory PTCL. Pralatrexate is marketed in the US as FOLOTYN® (Pralatrexate Injection) at a concentration of 20 mg/mL for use in this patient population.

In PDX-008, pralatrexate was administered at a dose of 30 mg/m^2/week for 6 weeks in a 7-week cycle. The protocol allowed for dose reduction to 20 mg/m^2/week if a patient

experienced protocol-defined adverse events (AEs). A patient was considered evaluable if he/she received at least 1 dose of pralatrexate and met the major inclusion criterion # 1, ie, the diagnosis of eligible PTCL histopathological subtype confirmed by central pathology review. In the PDX-008 study, 109 patients were considered evaluable for efficacy. Twenty-nine percent (n = 32) of evaluable patients experienced either a CR, an unconfirmed CR (CRu), or a PR, as assessed by central independent oncology review. Thirty-nine percent of patients (n = 43) experienced either a CR/CRu or PR, as assessed by the study investigators.[27] The responses observed were durable as assessed by independent central review, with a median duration of 10.1 months and a Kaplan-Meier estimate of 60% for the probability of achieving a duration of response ≥ 6 months. The median PFS and OS for the 109 patients as estimated by the Kaplan-Meier method were 3.5 months (range 1 day - 23.9 months) and 14.5 months (range 1.0-24.1 months), respectively.

Study PDX-010 is a Phase 1, open-label, multi-center study designed to determine an effective and well-tolerated dose and schedule of pralatrexate as a single agent when administered concurrently with vitamin B_{12} and folic acid supplementation to patients with relapsed or refractory cutaneous T-cell lymphoma (CTCL). Following preliminary review of safety and response data from the dosing regimens explored thus far, 15 mg/m^2 for 3/4 weeks was determined to be the dose utilized in the dose expansion phase of the study, in which an additional 20 patients will be evaluated.

Interim efficacy data were presented at the 15th Congress of the European Hematology Association on the PDX-010 study in patients with CTCL.[28] Investigator-assessed responses were observed in 19 of 47 evaluable patients (40%), including 2 CRs and 17 PRs. Final efficacy data will be analyzed at the completion of the study.

Study PDX-015 is a Phase 2, single-arm, non-randomized, open-label, multi-center study designed to evaluate the efficacy and safety/tolerability of pralatrexate when administered concurrently with vitamin B_{12} and folic acid supplementation to patients with relapsed or refractory B-cell NHL. This study is ongoing and no data are currently available.

4.1.2 Combination Studies

Pralatrexate is being studied as combination treatment with gemcitabine in relapsed/refractory lymphoproliferative malignancies (PDX-009). Study PDX-009 is a Phase 1/2a, open-label, multi-center study of pralatrexate and gemcitabine administered on sequential days, or the same day depending on cohort, with vitamin B_{12} and folic acid supplementation to patients with relapsed or refractory lymphoproliferative malignancies. The Phase 1 portion of the study was nonrandomized, while the Phase 2 portion is randomized between same day dosing or sequential day dosing. The objectives of the study are: 1) to determine the MTD and recommended Phase 2 dose of the combination of pralatrexate and gemcitabine (Phase 1); 2) to evaluate the safety and tolerability of escalating doses of pralatrexate and gemcitabine (Phase 1); 3) to determine the PK profile of the combination of pralatrexate and gemcitabine (Phase 1 and 2a); and 4) to confirm tolerability and assess preliminary efficacy in patients with relapsed or refractory Hodgkin's lymphoma, PTCL, and B-cell lymphoma (Phase 2a).

Interim efficacy data were presented in a poster presentation at the 51st Annual American Society of Hematology Meeting on the 33 patients enrolled in this study who were evaluable for response.[29] Four of 7 patients with Hodgkin's lymphoma, 2 of 11 patients with PTCL, and 2 of 15 patients with diffuse large B-cell lymphoma (1 of whom also had PTCL) achieved a PR. Final efficacy data will be analyzed at the completion of the study.

4.2 Studies in Patients with Solid Tumors

4.2.1 Allos Single-agent Studies

In the Phase 1 study, PDX-007, investigating pralatrexate as a single agent with vitamin supplementation in patients with relapsed NSCLC, dosing started at 150 mg/m^2 every 2 weeks and initially escalated in 40 mg/m^2 increments to 270 mg/m^2 every (q) 2 weeks. Based on the DLTs experienced in the 325 mg/m^2 cohort of Treatment Group A, the MTD for Treatment Group A was determined to be 270 mg/m^2. Cohorts in Treatment Group B were initiated at dose levels below the MTD determined for Treatment Group A to further assess the safety and tolerability of pralatrexate. The starting dose for Treatment Group B was 230 mg/m^2. Although DLTs were observed at the 190 mg/m^2 dose given every 2 of 4 weeks, these DLTs were of lower grade (2 patients both with Grade 2 mucositis) than DLTs observed in any other cohort, and therefore, this dose is the recommended Phase 2 dose.

Study PDX-011 is a Phase 2, open-label, multi-center study of pralatrexate when administered concurrently with vitamin B_{12} and folic acid supplementation in patients with advanced or metastatic relapsed transitional cell carcinoma (TCC) of the urinary bladder. The objectives of this study are: 1) to determine the objective response rate (CR + PR); 2) to determine the duration of response, clinical benefit rate, PFS, and OS; and 3) to evaluate the safety and tolerability of pralatrexate with concurrent vitamin B_{12} and folic acid supplementation in patients with advanced or metastatic relapsed TCC of the urinary bladder.

Study PDX-012 is a randomized, open-label, multi-center Phase 2b study comparing pralatrexate and erlotinib in patients with Stage IIIB/IV NSCLC who are or have been cigarette smokers. The objectives of the study are: 1) to estimate the efficacy of pralatrexate as assessed by overall survival compared to that of erlotinib; 2) to estimate the efficacy of pralatrexate as assessed by response rate compared to that of erlotinib; 3) to estimate the efficacy of pralatrexate as assessed by PFS compared to that of erlotinib; and 4) to evaluate the safety and tolerability of q 2 weeks administration of pralatrexate in patients with Stage IIIB/IV NSCLC.

Study PDX-014 is an open label, multi-center, Phase 2 study of pralatrexate in female patients with Previously-treated advanced or metastatic breast cancer who have failed prior treatment(s).

Study PDX-016 is a Phase 1, nonrandomized, open-label, single-arm, combined clinical pharmacology and clinical study to evaluate the excretion and metabolic profile of

pralatrexate and to relate these findings to concurrent PK assessments in patients with advanced cancer.

4.2.2 MSKCC Studies in Patients with Solid Tumors

Study PDX-97-006 was a Phase 1, single-center, dose-escalation study to determine the MTD and schedule (weekly or biweekly) of single-agent pralatrexate. The study was conducted exclusively in patients with NSCLC, who had been previously treated with a median of 2 prior chemotherapy regimens.[30] Thirty-five patients were enrolled and 33 were treated. Initially, pralatrexate was administered at a dose of 30 mg/m^2 weekly for 3 of 4 weeks. The protocol was amended to a q 2 weeks treatment on a 4-week cycle, with dose escalation from 15 - 170 mg/m^2. The weekly treatment with pralatrexate for 3 weeks in a 4-week cycle was dose limiting at 30 mg/m^2. Altering the treatment schedule, however, to q 2 weeks (in a 4-week cycle) allowed much higher doses to be administered. The MTD and recommended Phase 2 dose was 150 mg/m^2. One patient in Study PDX-97-006, who received the MTD of 150 mg/m^2, achieved a PR, and 6 patients achieved stable disease (SD).

Study PDX-99-053 was a Phase 2, open-label, single-center study evaluating the efficacy of single-agent pralatrexate in patients with Stage IIIB or Stage IV NSCLC.[31] Thirty-nine patients were enrolled and treated. Patients received pralatrexate q 2 weeks on a 4-week cycle. Twenty-nine patients were treated in the 150 mg/m^2 dose group. To decrease the incidence of stomatitis, the last 10 patients enrolled were treated with 135 mg/m^2 of pralatrexate. In study PDX-99-053, the median duration of survival for all patients was 13 months (mean = 16 months), with median durations of 16 months for the 150 mg/m^2 group and 7.5 months for the 135 mg/m^2 group.

Study PDX 99-083 was a Phase 1, open-label, single-center, dose-escalation study evaluating the combination of pralatrexate with a taxane (paclitaxel or docetaxel) in adult patients with advanced solid tumors.[32] Forty-eight patients were enrolled and treated. Forty-six of those patients had NSCLC. The initial starting dose of pralatrexate was 110 mg/m^2 combined with 175 mg/m^2 of paclitaxel administered on the same day q 2 weeks in a 4-week cycle, however, DLTs prevented determination of a tolerable dose with this combination. The MTD and recommended Phase 2 dose of the pralatrexate-docetaxel combination with vitamins was 120 mg/m^2 of pralatrexate with 35 mg/m^2 docetaxel administered on the same day once q 2 weeks. One patient in PDX-99-083 treated below the MTD (treated with pralatrexate 90 mg/m^2 + paclitaxel 175 mg/m^2, without vitamin supplementation) achieved a PR and 32 patients had SD, 10 of whom were treated without vitamins and 22 of whom received vitamins.

Study PDX 01-014 was a Phase 1, open-label, single-center, dose-escalation study to determine the MTD for pralatrexate and probenecid given in combination q 2 weeks in patients with solid tumors.[13] Seventeen patients were enrolled. The pralatrexate dose was kept at 40 mg/m^2; the dose escalation of probenecid proceeded from 70 to 233 mg/m^2. Treatment with pralatrexate in combination with probenecid q 2 weeks on a 4-week cycle exceeded the MTD at 40 mg/m^2 pralatrexate and 233 mg/m^2 probenecid due to stomatitis. The MTD and recommended Phase 2 dose of the pralatrexate and probenecid combination

was 40 mg/m^2 of pralatrexate administered with 140 mg/m^2 probenecid q 2 weeks. No patient achieved a CR or PR, but 5 patients experienced SD. The combination of pralatrexate with probenecid did not demonstrate enhanced therapeutic activity and the dose levels that were tolerated were limited.

Study PDX 01-076 was a Phase 2, open-label, single-center study in patients with unresectable malignant pleural mesothelioma.[33] Seventeen patients were enrolled and 16 patients were treated. The dose of pralatrexate was 135 mg/m^2 intravenous (IV) q 2 weeks on a 4-week cycle. No patient in the study achieved a CR or a PR; however, 10 patients had SD (duration range: 2+ to 47 months). The median time to progressive disease (PD) for all 16 patients treated in the study was 3 months. The median duration of survival for all 16 patients was 5.5 months.

4.3 Safety Overview of Oncology Patients Receiving Pralatrexate

4.3.1 Precautions

Bone marrow suppression: Pralatrexate may suppress bone marrow function, manifested by neutropenia, thrombocytopenia, and anemia. Dose modifications are described in Section 7.4 (Table 7.1) based on absolute neutrophil count (ANC) and platelet counts prior to each dose.

Mucositis: Treatment with pralatrexate may cause mucositis. If ≥ Grade 2 mucositis is observed, the dose should be modified according to Section 7.4, Table 7.2.

Dermatologic reactions: Pralatrexate has been associated with severe dermatologic reactions, which may result in death. These dermatologic reactions have been reported in clinical studies (14/663 patients [2.1%]) and post marketing experience, and have included skin exfoliation, ulceration, and toxic epidermal necrolysis (TEN). These reactions may be progressive and increase in severity with further treatment, and may involve skin and subcutaneous sites of known lymphoma. Patients with skin reactions must be monitored closely, and if skin reactions are severe, study treatment may be modified or discontinued (see Section 7.4, Table 7.3).

Tumor lysis syndrome: Tumor lysis syndrome has been reported in patients with lymphoma receiving pralatrexate. Patients receiving pralatrexate should be monitored closely and treated for complications.

Folic acid and vitamin B_{12} supplementation: Patients must be instructed to take folic acid and vitamin B_{12} to potentially reduce treatment-related hematological toxicity and mucositis (see Section 7.1).

Pregnancy and breastfeeding: Pralatrexate may cause fetal harm when administered to a pregnant woman. Pralatrexate was embryotoxic and fetotoxic in rats and rabbits. It is not known whether pralatrexate is excreted in human milk. Many drugs are excreted in human milk and there is the potential for serious adverse reactions in nursing infants from this drug.

Study treatment must not be administered during pregnancy or when breastfeeding (see Section 14.7).

Renal impairment: Pralatrexate has not been formally tested in patients with moderate and severe renal impairment. Patients must have adequate renal function to be eligible for inclusion in this study, as defined in Section 8.3.

Hepatic impairment: Pralatrexate has not been formally tested in patients with hepatic impairment. Patients must have adequate hepatic function to be eligible for inclusion in this study, as defined in Section 8.3. Liver function test abnormalities have been observed after pralatrexate administration, but are usually not cause for modification of pralatrexate treatment. However, persistent liver function test abnormalities may be indicators of liver toxicity and may require dose modification (see Table 7.3).

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

4.4 Clinical Pharmacology

4.4.1 Pharmacokinetics

Pralatrexate *R* and *S* diastereomers follow apparent first-order PK with the area under the curve to infinity (AUC_{∞}) increasing in a near linear manner with dose. Total, renal, and non-renal clearances as well as volume of distribution were constant within (nominal) doses ranging from 30 mg/m^2 to 325 mg/m^2. Comparing the 2 diastereomers, plasma exposures of the *R* diastereomer exceed those of the *S* diastereomer by approximately 2-fold; the reason for this is unclear at this point. For a more detailed description of pralatrexate PK and population PK (POPPK), see the pralatrexate IB.

5 RATIONALE FOR THE CURRENT STUDY

Patients with PTCL are in need of additional treatment options. Pralatrexate exhibited encouraging activity in nonclinical in vitro and in vivo models of lymphoma. This activity was evaluated clinically in a Phase 1/2 study (PDX-02-078) in patients with lymphoma in which a response rate of 54% was observed in patients with T-cell lymphoma.[26] Efficacy analyses from the Phase 2 study PDX-008, which was conducted in patients with relapsed or refractory PTCL, indicates that pralatrexate exhibited clinically significant activity in the patients under study, demonstrating an overall response rate of 29% and median duration of response of 10.1 months.

CHOP and CHOP-based treatments are the most commonly used therapeutic regimens for patients with newly diagnosed PTCL. However, as a majority of these patients progress or relapse following CHOP, the PFS outcome for patients responding to CHOP remains dismal. In the PDX-008 study, 15 evaluable patients received pralatrexate as their second-line treatment after CHOP, 7 of whom (47%) responded to pralatrexate by central review. Based on the responses observed in the PDX-008 study, the current protocol will determine for those patients who respond to CHOP therapy whether pralatrexate administered directly after completion of a CHOP regimen can improve PFS and OS relative to observation directly after completion of a CHOP regimen.

As described in Section 4.1.1, pralatrexate administered at 30 mg/m^2 has been tolerated and demonstrated to have a therapeutic effect in patients with lymphoma in studies PDX-02-078 and PDX-008. The proposed dosing regimen for this study includes weekly dosing for 3 weeks followed by 1 week of rest. This differs slightly from PDX-008, which utilized a dosing regimen of weekly administration for 6 weeks followed by 1 week of rest. An analysis of the PDX-008 results revealed that of the 57 treated patients who received the first 3 doses without a dose modification, 24 patients (42%) required a dose modification, including possibly treatment discontinuation, prior to the rest week, ie, at either doses 4, 5, or 6. Thus, allowing a break after 3 doses may increase the long-term tolerability to full-dose pralatrexate. Therefore, the initial dose and frequency of pralatrexate in PDX-017 will be 30 mg/m^2 administered IV weekly for 3 weeks, with 1 week rest (4-week cycle), with subsequent dose reduction(s) based on toxicity. All patients will receive vitamin supplementation consisting of vitamin B_{12} and folic acid.

6 STUDY OBJECTIVES

The primary objective of this study is:

- Determine the efficacy of pralatrexate compared to observation when administered to patients with previously undiagnosed PTCL who have achieved an objective response after completing at least 6 cycles of CHOP-based treatment.

The secondary objective of this study is:

- Determine the safety of pralatrexate when administered following a course of CHOP-based treatment to patients with previously undiagnosed PTCL.

7 INVESTIGATIONAL PLAN

This is an international, multi-center, randomized, Phase 3, open-label study of sequential pralatrexate versus observation in patients who have achieved an objective response following initial treatment with CHOP-based chemotherapy in patients with previously undiagnosed PTCL. Patients will be randomized 2:1 to either pralatrexate or observation. Patients will be stratified by:

- Response per investigator at completion of CHOP-based therapy (CR vs PR)

7.1 Vitamin Administration

Vitamin supplementation for patients in both arms of the study will consist of vitamin B_{12} 1 mg intramuscular (IM) every 8-10 weeks and folic acid 1-1.25 mg orally (po) once a day (qd). Vitamin supplementation will begin at least 7 days prior to the projected initiation of pralatrexate/observation and continue throughout the study until the Initial Follow-up Visit (Section 10.7).

7.2 Pralatrexate Administration

One cycle of pralatrexate therapy is 4 weeks in duration and consists of 3 weekly doses of pralatrexate IV push over 30 seconds and up to 5 minutes, with 1 week of rest. The initial dose of pralatrexate will be 30 mg/m^2/week. For patients with a body surface area (BSA) > 2 m^2, the administered dose will be calculated using a capped BSA value of 2 m^2. Pralatrexate dose reduction to 20 mg/m^2 with further reduction to 15 and 10 mg/m^2 will be allowed for defined toxicities (see Section 7.4). Pralatrexate will continue to be administered until a criterion for study treatment discontinuation is met (Section 7.3) or up to a maximum of 2 years.

7.3 Study Duration

Patients will receive study treatment (pralatrexate or observation) until one of the criteria listed below for study treatment discontinuation applies:

- Development of PD
- Initiation of radiation therapy (RT) or systemic chemo/biological therapy for treatment of PTCL
- Receipt of systemic steroids for > 10 days, with the exception of those as stated in exclusion criterion #5 (see Section 8.4)
- Development of an AE that interferes with the patient's participation
- Lost to follow-up
- Patient decision
- Investigator decision
- Sponsor decision

In addition, for those patients randomized to the Pralatrexate Arm, additional pralatrexate treatment discontinuation criteria are:

- 3 or more consecutive doses of pralatrexate omitted or more than 28 days between doses of pralatrexate
- Treatment with pralatrexate for 2 years

All patients who receive at least 1 dose of pralatrexate will be followed for safety through 35 (± 5) days after their last dose of pralatrexate or until all treatment-related AEs have resolved or returned to baseline/Grade 1, whichever is longer, or until it is determined that the outcome will not change with further follow-up.

Patients who are randomized to the Observation Arm who do not discontinue the study within 3 days of randomization will be followed for safety until 35 (± 5) days after study treatment discontinuation criteria are met.

All patients who are randomized will be followed until objectively documented PD for up to 7 years from randomization. The details of response follow-up are provided in Section 10.8. PD will be confirmed by central review until the first PFS analysis, see Section 15.6.1, and per investigator assessment thereafter. Subsequent therapies for PTCL will be collected for up to 7 years from randomization; the best response to the first subsequent therapy will be collected. Survival follow-up will continue for up to 7 years from randomization.

As discussed in Section 15.6.1, an analysis will be performed when both 280 PFS events and 128 OS events have occurred. If the PFS analysis is not significant at the 0.05 level, the study will be stopped.

7.4 Treatment Modifications of Pralatrexate

Pralatrexate dose modifications will be allowed according to the criteria outlined below in Table 7.1, Table 7.2, and Table 7.3. Dose reduction to 20 mg/m^2 with further reductions to 15 mg/m^2 and 10 mg/m^2 will be allowed for the toxicities defined in the tables below. If an AE occurs that prevents the administration of pralatrexate on the scheduled dosing day (± 1 day), the dose will be omitted that week and the patient will be reassessed the following week to proceed to the next dose of the cycle.

7.4.1 Hematological Adverse Events

Treatment modification for **hematological** AEs occurring on the planned dosing day will be made as outlined in Table 7.1.

Table 7.1. Pralatrexate Treatment Modifications for Hematological AEs

Hematological Parameter on Planned Dosing Day	Action
ANC ≥ 1000/µL (≤ Grade 2) or platelets ≥ 50,000/µL (≤ Grade 2)	• No change in pralatrexate dose.
ANC ≥ 500/µL and < 1,000/µL (Grade 3) without fever	• Administer cytokine prophylaxis and/or treatment per ASCO guidelines.34. • Do not administer pralatrexate until recovery to ≤ Grade 2 (≥ 1000/µL). Upon recovery to ≤ Grade 2, administer pralatrexate without a change in dose.
ANC ≥ 500/µL and < 1,000/µL (Grade 3) associated with single oral temperature ≥ 38.1°C requiring parenteral antibiotics or ANC < 500/µL (Grade 4)	• Administer cytokine prophylaxis and/or treatment per ASCO guidelines.34 • Do not administer pralatrexate until recovery to ≤ Grade 2 (≥ 1000/µL). Upon recovery to ≤ Grade 2, administer pralatrexate without a change in dose. • If reoccurrence within 28 days, reduce the pralatrexate dose to the next lower dose level. • Discontinue pralatrexate if event reoccurs at 10 mg/m^2 despite cytokine support.
Platelets < 50,000/µL (≥ Grade 3)	• Do not administer pralatrexate until recovery to ≤ Grade 2 (≥ 50,000/µL). Upon recovery to ≤ Grade 2, administer pralatrexate without a change in dose. • If a platelet count of Grade 4 (< 25,000/µL) reoccurs within 28 days, reduce the pralatrexate dose to the next lower dose level. • Discontinue pralatrexate if a platelet count of Grade 4 (< 25,000/µL) occurs twice within 28 days at 10 mg/m^2.

ANC – absolute neutrophil count
°C – degrees Celsius

7.4.2 Non-hematological Adverse Events

For all instances of **mucositis** occurring on the planned dosing day, treatment modifications will be made as outlined in Table 7.2. For **treatment-related cardiovascular, dermatological, hepatic, neurologic, renal, or respiratory** AEs, treatment modifications will be made as outlined in Table 7.3. For all other non-hematological treatment-related AEs, treatment modifications should be made at the investigator's discretion.

Table 7.2. Pralatrexate Treatment Modifications for Mucositis

Mucositis Grade on Planned Dosing Day	Action
0 or 1	• No change in pralatrexate dose.
2	• Omit this week's dose of pralatrexate. Administer with no change in pralatrexate dose if resolution to Grade 0-1. • If reoccurrence, omit this week's dose, upon resolution to Grade 0-1, reduce the dose to next lower dose level..
3	Do not administer pralatrexate until recovery to Grade 0-1. • Upon recovery to Grade 0-1, reduce to next lower dose level • Discontinue pralatrexate if ≥ Grade 3 mucositis persists for ≥ 2 consecutive weeks or reoccurs within 28 days if on 10 mg/m^2
4	• Discontinue pralatrexate.

Table 7.3. Pralatrexate Treatment Modifications for Treatment-related Cardiovascular, Dermatological, Hepatic, Neurologic, Renal, or Respiratory AEs

Event Grade	Action
0-2	• No change in pralatrexate dose.
3	Do not administer pralatrexate until recovery to ≤ Grade 2. • Upon recovery to ≤ Grade 2 administer pralatrexate without a change in dose. • If the patient experiences the same Grade 3 treatment-related AE do not administer until recovery to ≤ Grade 2 and administer with a reduction to the next lower dose level. • Discontinue pralatrexate if the same Grade 3 treatment-related AE recurs within 28 days at 10 mg/m^2.
4	• Discontinue pralatrexate.

8 PATIENT POPULATION

8.1 Number of Patients and Patient Selection

The target patient population is adult patients with previously undiagnosed PTCL who have achieved an objective response after pre-study first-line treatment with at least 6 cycles of one of the following CHOP-based treatments:

a. CHOP 21
b. CHOP 14
c. CHOEP
d. Other CHOP variants

A total of 549 patients will be randomized 2:1 to pralatrexate or observation.

8.2 Inclusion of Females and Minorities

Entry into this study is open to males and females of any ethnic origin. Race and gender are not known to affect survival outcome in this disease, nor are they known to be associated with differential survival by treatment. Females and minorities will be actively recruited for this protocol.

8.3 Inclusion Criteria

A patient will be eligible for inclusion only if all of the following criteria apply:

1. Patient's PTCL histology has been confirmed as one of the following by an independent pathology reviewer, using the Revised European American Lymphoma (REAL) WHO disease classification
   a. T/ NK-cell leukemia/lymphoma
   b. Adult T-cell lymphoma/leukemia (human T-cell leukemia virus [HTLV] 1+)
   c. Angioimmunoblastic T-cell lymphoma
   d. ALCL, primary systemic type, excluding ALK+ with IPI score < 2 at initial diagnosis and CR after completion of CHOP-based therapy
   e. PTCL- unspecified
   f. Enteropathy-type intestinal lymphoma
   g. Hepatosplenic T-cell lymphoma
   h. Subcutaneous panniculitis T-cell lymphoma
   i. Transformed mycosis fungoides
   j. Extranodal T/NK-cell lymphoma nasal or nasal type
   k. Primary cutaneous gamma-delta T-cell lymphoma
   l. Primary cutaneous CD8+ aggressive epidermic cytotoxic T-cell lymphoma
2. Documentation that the patient has completed at least 6 cycles of CHOP-based therapy, including:
   - CHOP 21

- CHOP 14
- CHOEP
- Other CHOP variants: includes all 4 components of CHOP represented, with substitution allowed for any 1 component with a drug of the same mechanism of action (eg, variant anthracyclines). Additional components to CHOP are allowed, with the exception of alemtuzumab; rituximab may be combined with CHOP provided that it is not given within 3 cycles of randomization.

3. Patient has achieved a CR or PR per investigator's assessment following completion of CHOP-based therapy and has had a radiological assessment within 21 days prior to randomization.
4. ≥ 18 years of age.
5. ECOG performance status ≤ 2.
6. Adequate hematological, hepatic, and renal function as defined by:
   a. Absolute neutrophil count (ANC) ≥ 1000/μL
   b. Platelet count ≥ 100,000/μL
   c. Total bilirubin ≤ 1.5 mg/dL
   d. Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤ 2.5 × upper limit of normal (ULN), (AST/ALT < 5 × ULN if documented hepatic involvement with lymphoma). All patients with hepatitis B virus (HBV)-positive serology must have liver function tests within the above parameters.
   e. Creatinine ≤ 1.5 mg/dL (if the patient's creatinine is > 1.5 mg/dL, then the calculated creatinine clearance must be ≥ 50 mL/min).
7. Females of childbearing potential (ie, excluding patients who are postmenopausal for at least 1 year [> 12 months since last menses] or are surgically sterilized) must:
   a. Have a negative serum pregnancy test within 14 days prior to randomization and
   b. Agree to practice a medically acceptable contraceptive regimen from study treatment initiation until at least 30 days after the last administration of pralatrexate.
8. Males who are sexually active, including those with a pregnant partner, must agree to practice a medically acceptable barrier method contraceptive regimen (eg, condoms) while receiving pralatrexate and for 90 days after the last administration of pralatrexate.
9. Patient has given written informed consent (IC).

8.4 Exclusion Criteria

A patient will not be eligible for inclusion if any of the following criteria apply:

1. Patient has:
   a. Precursor T/NK neoplasms
   b. ALCL (ALK+) with IPI score < 2 at initial diagnosis and CR after completion of CHOP-based therapy
   c. T-cell prolymphocytic leukemia (T-PLL)

d. T-cell large granular lymphocytic leukemia
e. Mycosis fungoides, other than transformed mycosis fungoides
f. Sézary syndrome
g. Primary cutaneous CD30+ disorders: ALCL and lymphomatoid papulosis

2. If there is a history of prior malignancies other than those exceptions listed below, the patient must be disease-free for ≥ 5 years. Patients with the following prior malignancies less than 5 years before study entry may still be enrolled if they have received treatment resulting in complete resolution of the cancer and currently have no clinical, radiologic, or laboratory evidence of active or recurrent disease.
   a. Non-melanoma skin cancer
   b. Carcinoma in situ of the cervix
   c. Localized prostate cancer
   d. Localized thyroid cancer
3. Patient has received prior treatment (chemotherapy or radiation) for PTCL, other than a single allowed CHOP regimen, with the exception of:
   a. Patients with nasal NK lymphoma are permitted to have received local radiation therapy no less than 4 weeks prior to randomization.
   b. Patients with transformed mycosis fungoides are permitted to have received 1 systemic single-agent chemotherapy (other than methotrexate) prior to transformation of their disease.
4. Prior exposure to pralatrexate.
5. Receipt of systemic corticosteroids within 3 weeks of study treatment, unless patient has been taking a continuous dose of ≤ 10 mg/day of oral prednisone or equivalent for at least 4 weeks or as part of a CHOP prednisone taper.
6. Planned use of any treatment for PTCL during the course of the study.
7. Patient has:
   a. Human immunodeficiency virus (HIV)-positive diagnosis with a CD4 count of $< 100\ mm^3$ or detectable viral load within past 3 months and is receiving anti-retroviral therapy.
   b. HBV-positive serology and is receiving interferon therapy or has liver function test results outside the parameters of study inclusion criteria. Patients are permitted to receive other antiviral therapies if the therapy has been administered at a stable dose for ≥ 4 weeks.
   c. Hepatitis C virus (HCV) with detectable viral load or immunological evidence of chronic active disease or receiving/requiring antiviral therapy.
   d. Symptomatic central nervous system (CNS) metastases or lesions for which treatment is required.
   e. Uncontrolled hypertension or congestive heart failure Class III/IV according to the New York Heart Association's Heart Failure Guidelines (see http://www.americanheart.org/presenter.jhtml?identifier=3065080).

f. Active uncontrolled infection, underlying medical condition including unstable cardiac disease, or other serious illness that would impair the ability of the patient to receive protocol treatment.

8. Patient has had major surgery within 2 weeks prior to study entry; other than for line placement or biopsy procedure.

9 STUDY DRUG AND PHARMACEUTICAL INFORMATION

9.1 Pralatrexate Injection

9.1.1 Pralatrexate Injection Formulation

Pralatrexate Injection (Pralatrexate Solution for Infusion in the EU) will be supplied by Allos and will have been tested and released according to established specifications. Pralatrexate Injection is formulated as a sterile solution for injection and will be supplied in single-use glass vials containing an isotonic parenteral solution at a concentration of 20 mg/mL of pralatrexate. The osmolality of Pralatrexate Injection is ~300 mOsmol/kg. The formulation is a clear yellow solution.

9.1.2 Pralatrexate Injection Storage and Handling

Pralatrexate Injection is a cytotoxic anticancer agent. Caution should be exercised in handling, preparing, and administering of the solution. The use of gloves and other protective clothing is recommended. If Pralatrexate Injection comes in contact with the skin, immediately and thoroughly wash with soap and water. If Pralatrexate Injection comes in contact with mucous membranes, flush thoroughly with water.

The institutional, local, and all applicable policies and procedures must be followed for proper handling and disposal of chemotherapy drugs.

Pralatrexate Injection must be stored refrigerated at 2-8°C (36-46°F) (see United States Pharmacopeia [USP] Controlled Cold Temperature) until use. Pralatrexate Injection vials should be stored in original carton to protect from light until use. Pralatrexate Injection vials contain no preservatives and are intended for single use only. Vials of Pralatrexate Injection must be stored under secured conditions with access limited to authorized study personnel only. After withdrawal of dose, discard vial including any unused portion.

9.1.3 Packaging/Labeling

The contents of the label will be in accordance with all applicable regulatory requirements.

9.1.4 Pralatrexate Injection Dosage and Administration

9.1.4.1 Preparation and Pralatrexate Injection Dose Calculation

Appropriate mask, protective clothing, eye protection, gloves, and Class II vertical laminar-airflow safety cabinets are required during preparation and handling. Please refer to the Study Instructions provided by Allos/designee for detailed guidance regarding dispensing, disposal, and accountability of Pralatrexate Injection.

Pralatrexate Injection must be infused as the volume of administration based on the original concentration of 20 mg/mL.

The BSA will be calculated based on the patient's actual weight obtained within 2 days prior to the first Pralatrexate Injection dose of each cycle, unless otherwise noted in Section 10.4. The patient will receive the same Pralatrexate Injection dose (based on the BSA calculated at cycle 1) throughout treatment unless the patient's actual weight changes by ≥ 10%. The volume to be infused will be based on the following calculation:

$$\frac{\text{Volume (mL)} = (\text{Patient BSA } [m^2]) \times (\text{pralatrexate dose } [mg/m^2])}{20 \text{ mg/mL (pralatrexate concentration)}}$$

Patients with a BSA > 2 m^2 will be capped at 2 m^2.

9.1.5 Administration of Pralatrexate Injection

Pralatrexate Injection is a clear, yellow solution. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Do not use any vials exhibiting particulate matter or discoloration.

The calculated dose of Pralatrexate Injection should be aseptically withdrawn into a syringe for immediate use. Do not dilute Pralatrexate Injection.

Appropriate procedures for cytotoxic agents must be followed for administration of Pralatrexate Injection.

Pralatrexate Injection will be administered as an IV push over a minimum of 30 seconds up to a maximum of 5 minutes into a patent IV line containing normal saline (0.9% sodium chloride [NaCl] at an initial dose of 30 mg/m^2. If the IV push of pralatrexate is interrupted or delayed, the administration should be restarted as soon as possible.

The pharmacist/designee may dispense Pralatrexate Injection to the research team in the vial or in a pre-filled syringe according to the institutional practice. Pralatrexate Injection vials will be disposed of immediately after use. The vial and remaining volume of Pralatrexate Injection should be discarded according to the institution's policy for disposal of cytotoxic agents.

9.2 Drug Accountability

Allos requires that drug accountability logs be maintained. These logs must record quantities of Pralatrexate Injection received from Allos and quantities dispensed to patients, including lot/batch number, date dispensed, patient identifier number, patient initials, protocol number, dose, balance forward, and the initials of the person dispensing the medication.

10 STUDY PROCEDURES

Study procedures are summarized in Appendix 1 and Appendix 2, Schedule of Study Procedures/Evaluations Tables.

10.1 Screening

The procedures and evaluations required for randomization are summarized below. Randomization of eligible patients must occur within 6 weeks of day 1 of the last planned cycle of CHOP-based chemotherapy.

1. Review eligibility criteria.
2. Obtain written IC for pathology review prior to sending pathology specimen(s) to independent pathology reviewer.
3. Send the pathology specimen(s) to independent pathology reviewer (see Section 12.2.2). Independent pathology review of tumor tissue specimens and confirmation of diagnosis must occur prior to randomization and can occur any time after the initial PTCL diagnosis, provided that the patient has consented to the pathology review.

Unless otherwise specified, the following procedures and evaluations will be performed within 21 days prior to randomization:

1. Obtain written IC for participation in this study prior to initiating any study procedure that is not considered standard of care.
2. Review eligibility criteria.
3. Review medical chart and record medical/surgical history.
4. Document histopathology from local pathology report.
5. Document IPI score at initial diagnosis.
6. Record baseline/current medical status, including B symptoms related to PTCL.
7. Document dates of CHOP-based chemotherapy.
8. Document the investigator's assessment of response after receipt of CHOP-based chemotherapy.
9. Document known measurable disease parameters by obtaining the following radiographic imaging:
   - Computed tomography (CT) of chest, neck, abdomen, and pelvis (magnetic resonance imaging [MRI] allowed if the patient cannot tolerate the IV contrast).
   - Other imaging techniques documenting disease site other than chest, neck, abdomen, and pelvis, if applicable.
10. Perform whole body positron emission tomography (PET) (base of skull to mid-thigh) if local standard of care.
11. Document cutaneous disease with medical photography of up to 5 target lesions, which will be chosen by the investigator (refer to Study Instructions).

12. Obtain a unilateral bone marrow biopsy/aspirate unless the patient's most recent bone marrow biopsy is negative for lymphoma involvement.
13. Obtain a 12-lead electrocardiogram (ECG). Repeat ECG during study only if clinically indicated.
14. Perform a comprehensive physical examination.
15. Assess and record ECOG Performance Status.
16. Vitamin supplementation will consist of vitamin B_{12} 1 mg IM every 8-10 weeks and folic acid 1-1.25 mg po qd. Begin vitamin supplementation at least 7 days prior to the projected initiation of pralatrexate/observation and continue throughout the study until the Initial Follow-up Visit (Section 10.7).
17. Local laboratory: Collect blood for hematology, chemistry (including serum β-human chorionic gonadotropin [β-hCG] pregnancy test for females who are not postmenopausal or surgically sterile [within 14 days prior to randomization]).
18. If screening serum creatinine is > 1.5 mg/dL, calculate creatinine clearance using the glomerular filtration rate (GFR) according to the Cockcroft and Gault Equation:

$$GFR^* = \frac{(140 - \text{age [years]}) \times \text{actual body weight (kg)}}{72 \times \text{serum creatinine}}$$

*For female patients, multiply by 0.85

10.2 Patient Randomization

Each patient who signs an IC document for participation in this study will be assigned a unique screening number. The screening number consists of 7 digits; the first 4 digits will be the site number used for all study activities, and the final 3 digits will be a consecutive number starting with [redacted] (eg, the screening number for the fourth patient screened at site number [redacted] would be [redacted]).

Once it has been determined that a patient meets eligibility criteria as outlined in Section 8.2, the site must randomize via interactive response technology (IRT), formally referred to as interactive voice response system (IVRS). The randomization treatment group and patient randomization number will be assigned at this time. Randomization of patients to either pralatrexate or observation must occur within 6 weeks following day 1 of the last planned cycle of CHOP-based chemotherapy. Please refer to the study binder for detailed instructions regarding randomization.

10.3 Pralatrexate Treatment/Observation Initiation

10.3.1 Pralatrexate Administration

Pralatrexate Injection will be administered as an IV push over a minimum of 30 seconds up to a maximum of 5 minutes into a patent IV line containing normal saline.

10.4 Pralatrexate Arm Procedures

10.4.1 Pralatrexate Cycle 1, Dose 1

The following evaluations and procedures must take place within 3 days following randomization and prior to treatment initiation (pralatrexate cycle 1, dose 1), unless otherwise noted below:

1. Record current medications including compliance with vitamin supplementation administered from 7 days prior to randomization (see Section 13).
2. Assess and record B symptoms .
3. Record study-procedure-related AEs and attribution (see http://ctep.cancer.gov/reporting/ctc.html).
4. Record weight in kilograms (kg), height in centimeters (cm) and calculate BSA. The patient's weight and BSA, to calculate the volume of the pralatrexate dose may be assessed up to 7 days prior to cycle 1, dose 1.
5. Local laboratory: Collect pre-injection blood for hematology and chemistry (including baseline LDH) (see Section 12.1). If any of the laboratory eligibility criteria are no longer met at this time, delay treatment for up to 1 week until these values return to the specified parameters, as follows: ANC ≥ 1000/μL, platelet count ≥ 100,000/μL, total bilirubin ≤ 1.5 mg/dL, AST and ALT ≤ 2.5 × ULN (AST/ALT < 5 × ULN if documented hepatic involvement with lymphoma), creatinine ≤ 1.5 mg/dL or calculated creatinine clearance ≥ 50 mL/min.
6. Collect pre-injection blood sample for PK (see Section 12.2.1). PK sampling will be performed at cycle 1, dose 1 until samples have been obtained on 245 patients. Obtain samples until notified by Allos or designee.
7. Administer pralatrexate IV push over a minimum of 30 seconds up to a maximum of 5 minutes.
8. Collect blood samples for PK at the end of injection and at 8 and 24 hours post-injection (see Section 12.2.1). PK sampling will be performed at cycle 1, dose 1 until samples have been obtained on 245 patients. Obtain samples until notified by Allos or designee.

10.4.2 Pralatrexate Arm: Cycle 1, Doses 2-3

1. Record AEs and attribution (see http://ctep.cancer.gov/reporting/ctc.html). Refer to Section 7.4 for the pralatrexate dose modification criteria.
2. Record current medications including compliance with vitamin supplementation.
3. Review date of previous vitamin B_{12} injection. Administer vitamin B_{12} 1 mg IM q 8-10 weeks.
4. Local laboratory: Collect blood for hematology and chemistries within 1 day prior to each pralatrexate dose.
5. If the patient is not experiencing any AEs that warrant treatment modification or discontinuation, administer pralatrexate IV push over a minimum of 30 seconds up to a maximum of 5 minutes.

10.4.3 Procedures for Subsequent Cycles, Doses 1-3 for a Maximum of 2 Years

Patients may continue to receive pralatrexate unless the patient experiences any of the criteria noted in protocol Section 11.1.

1. Prior to each new cycle: record weight in kg and calculate BSA. The patient's weight and BSA may be assessed up to 2 days prior to the start of each cycle.
2. Prior to each new cycle: Assess and record B symptoms up to 2 days prior to the start of each cycle.
3. Record AEs and attribution (see http://ctep.cancer.gov/reporting/ctc.html). Refer to Section 7.4 for the pralatrexate dose modification criteria.
4. Record current medications including compliance with vitamin supplementation.
5. Review date of previous vitamin B_{12} injection. Administer vitamin B_{12} 1 mg IM q 8-10 weeks.
6. Local laboratory: Collect blood for hematology and chemistries (including LDH during week 1) within 1 day prior to each pralatrexate dose (see Section 12.1).
7. At cycle 2, dose 3, collect pre-injection blood sample for PK in 20 patients at select sites (see Section 12.2.1).
8. If the patient is not experiencing any AEs that warrant treatment modification or discontinuation, administer pralatrexate IV push over a minimum of 30 seconds up to a maximum of 5 minutes.
9. At cycle 2, dose 3, collect blood samples for PK in 20 patients at select sites pre-injection, end of injection, and 8 and 24 hours post-injection (see Section 12.2.1).

10.5 Observation Arm Procedures

10.5.1 Observation Arm: Baseline Visit

The following evaluations and procedures must take place within 3 days following randomization, unless otherwise noted below:

1. Record current medications including compliance with vitamin supplementation administered from 7 days prior to randomization (see Section 13).
2. Assess and record B symptoms.
3. Record study-procedure-related AEs and attribution (see http://ctep.cancer.gov/reporting/ctc.html).
4. Record weight in kg and height in cm up to 7 days prior to baseline visit.
5. Local laboratory: Collect blood for hematology and chemistry (including baseline LDH) (see Section 12.1).

10.5.2 Observation Arm: Week 2 of Every 4-week Period for a Maximum of 2 Years

The patient will be contacted (eg, phone call or clinic visit) week 2 of every 4-week period.

1. Record AEs and attribution (see http://ctep.cancer.gov/reporting/ctc.html).

10.5.3 Observation Arm: Every 28 days (± 3 days) for a Maximum of 2 Years

1. Record AEs and attribution (see http://ctep.cancer.gov/reporting/ctc.html).
2. Assess and record B symptoms.
3. Record current medications including compliance with vitamin supplementation.
4. Review date of previous vitamin B_{12} injection. Administer vitamin B_{12} 1 mg IM q 8-10 weeks.
5. Local laboratory: Collect blood for hematology and chemistries (including LDH) (see Section 12.1).

10.6 Response Evaluation

Response and progression of disease will be evaluated by using the International Workshop Criteria (IWC, Appendix 4). All responses will be evaluated by a designated, independent central review at least until the PFS analysis (see Section 15.6.1). The investigator's assessment of response will also be collected. All necessary documentation to determine response will be collected at the investigational sites and sent to the central reviewer. The first response evaluation is to occur 8 weeks (± 1 week) after randomization. Subsequent response evaluations are to occur every 12 weeks (± 1 week) timed from randomization through 3 years post-randomization, then every 24 weeks (± 4 weeks) through 7 years post-randomization. Unscheduled response assessments will also be sent to the central reviewer for evaluation. Response assessments will occur until PD per central review, at least until the PFS analysis.

The following procedures/tests are to be performed for each response evaluation:

1. Radiographic imaging (use same imaging technique as pre-pralatrexate/observation screening):
   - CT of chest, neck, abdomen, and pelvis (MRI allowed if the patient cannot tolerate the IV contrast)
   - Whole body PET (base of skull to mid-thigh) if performed as per local standard of care
   - Other imaging techniques documenting disease site(s) other than chest, neck, abdomen, and pelvis, if applicable.
2. If applicable, assess cutaneous disease using medical photography (refer to Study Instructions).
3. Document disease-related findings per physical examination.
4. If the patient has a CR by imaging, a bone marrow biopsy/aspirate assessment (including immunohistochemistry) must be performed to confirm CR if bone marrow biopsy/aspirate results were positive or indeterminate prior to randomization to pralatrexate/observation. Once a patient's bone marrow is negative for lymphoma, the bone marrow biopsy/aspirate will be repeated only when clinically indicated unless it is the patient's only site of disease.

5. A tumor biopsy may be performed if needed to confirm a response evaluation as per investigator discretion.
6. Document investigator's assessment of response.

10.7 Initial Follow-up Visit

10.7.1 Pralatrexate Arm

All patients who receive at least 1 dose of pralatrexate will attend the Initial Follow-up Visit 35 (± 5) days after the last dose of pralatrexate.

In the event the patient withdraws consent to any further study participation and refuses to attend the Initial Follow-up Visit, the following procedures and evaluations must be performed at the time the patient withdraws consent.

1. Record concomitant medications through 30 days after the last pralatrexate dose.
2. Record all AEs and attribution through 30 days after the last pralatrexate dose. From 31 days after the last pralatrexate dose, only record pralatrexate-related AEs and attribution (see http://ctep.cancer.gov/reporting/ctc.html).
3. Assess and record B symptoms.
4. Perform physical examination. Document any new or worsened findings as AEs.
5. Assess and record ECOG performance status (see Appendix 3).
6. Local laboratory: collect blood for hematology and serum chemistry (including LDH, see Section 12.1).
7. Review dosing of folic acid and document compliance.
8. Instruct patient to discontinue folic acid and vitamin B_{12}.
9. Record reason for discontinuation of pralatrexate (Section 11.1).
10. Record first subsequent therapy for PTCL, if applicable.

10.7.2 Observation Arm

Patients who are randomized to the Observation Arm will attend the Initial Follow-up Visit 35 days (± 5 days) after study treatment discontinuation criteria are met.

In the event the patient withdraws consent to any further study participation and refuses to attend the Initial Follow-up Visit, the following procedures and evaluations must be performed at the time the patient withdraws consent.

1. Record concomitant medications through 30 days after study treatment discontinuation criteria (Section 11.1) are met.
2. Record all AEs and attribution (see http://ctep.cancer.gov/reporting/ctc.html) through 30 days after study treatment discontinuation criteria (Section 11.1) are met.
3. Assess and record B symptoms.

4. Perform physical examination. Document any new or worsened findings as AEs.
5. Assess and record ECOG performance status (see Appendix 3).
6. Local laboratory: collect blood for hematology and serum chemistry (including LDH, see Section 12.1)
7. Review dosing of folic acid and document compliance.
8. Instruct patient to discontinue folic acid and vitamin B_{12}.
9. Record reason for discontinuation of observation (Section 11.1).
10. Record first subsequent therapy for PTCL, if applicable. First subsequent therapy for PTCL is at the investigator's discretion and can include pralatrexate.

10.8 Follow-up Visits

All patients who are randomized are to have follow-up as outlined below until objectively documented PD; thereafter, patients are followed for survival. The timing of follow-up will be at 8 weeks (± 1 week), then every 12 weeks (± 1 week) through 3 years post-randomization, and then every 24 weeks (±4 weeks) thereafter through 7 years post-randomization. PD will be confirmed by central review until the first PFS analysis, see Section 15.6.1, and per investigator assessment thereafter.

The following procedures/evaluations must be performed at each follow-up time point.

1. Record study-treatment-related AEs (see http://ctep.cancer.gov/reporting/ctc.html).
2. Evaluation of response (see Section 10.6 for tests and procedures).
3. Record subsequent therapies for PTCL and document the best response to the first subsequent therapy.

10.9 Long-term Follow-up

All subsequent therapies for PTCL will be collected for up to 7 years from randomization and the best response to the first subsequent therapy will be documented. Once patients have documented PD, survival status and subsequent therapies will be collected on all patients approximately every 6 months through 7 years from randomization.

11 DURATION OF TREATMENT

All patients are free to withdraw from participation in this study at any time, for any reasons, specified or unspecified, and without prejudice. The reason for the patient discontinuing pralatrexate/observation or terminating from the study must be recorded on the case report form (CRF). Pralatrexate will continue to be administered until a criterion for study treatment discontinuation is met (Section 7.3) or up to a maximum of 2 years.

11.1 Criteria for Study Treatment Discontinuation

Patients will receive study treatment (pralatrexate or observation) until one of the following criteria for study treatment discontinuation applies:

- Development of PD
- Initiation of RT or systemic chemo/biological therapy for treatment of PTCL
- Receipt of systemic steroids > 10 days, with the exception of those as stated in exclusion criterion #5 (see Section 8.4)
- Development of an AE that interferes with the patient's participation
- Lost to follow-up
- Patient decision
- Investigator decision
- Sponsor decision

In addition, for those patients randomized to the Pralatrexate Arm, additional pralatrexate treatment discontinuation criteria are:

- 3 or more consecutive doses of pralatrexate omitted or more than 28 days between doses of pralatrexate
- Treatment with pralatrexate for 2 years

Patients will be seen for the Initial Follow-up Visits as outlined in Section 10.7.

If an investigator feels that a patient would continue to benefit from pralatrexate therapy after completion of 2 years' therapy, they should discuss with the sponsor's medical contact and agree whether or not it is appropriate to continue treatment.

12 LABORATORY TESTS

12.1 Local Laboratory Tests

The following panels will be done locally with the designated tests. Copies of current laboratory certifications and normal ranges will be provided to Allos at study start and upon every renewal throughout the duration of pralatrexate or observation for the longest participating patient at the site.

12.1.1 Hematology

Tests to be conducted are white blood cell (WBC) count, hemoglobin (Hgb) concentration, hematocrit (Hct), platelet count, and ANC.

12.1.2 Chemistry

Tests to be conducted are creatinine, total bilirubin, AST, ALT, LDH, total protein, albumin, and β-hCG pregnancy test at screening (if applicable).

12.2 Central Laboratory

12.2.1 Plasma Pharmacokinetics

At sites participating in plasma sampling for PK analysis, approximately 245 patients randomized to the Pralatrexate Arm (two-thirds of the planned total) who consent to plasma sampling will have sampling performed at cycle 1, dose 1 (pre-injection, end of injection, and 8 and 24 hours post-injection). Of these 245 patients, 20 patients at select sites will also have plasma sampling performed at cycle 2, dose 3 (pre-injection, end of injection, and 8 and 24 hours post- injection).

Plasma samples will be split in 2 equal aliquots and frozen in separate tubes for analysis of pralatrexate concentration. The concentrations of pralatrexate at each time-point will be determined using validated bioanalytical methods at MPI Research. See Study Instructions provided by Allos/designee for detailed guidance regarding the collection, processing, and shipment of samples.

Standard PK parameters will be estimated from the limited plasma sampling (eg, area under the curve [AUC], maximum concentration [C_{max}], and half-life [$t_{1/2}$]), and POPPK analyses will be conducted via nonlinear mixed-effects modeling to estimate POPPK parameters for pralatrexate.

12.2.2 Independent Pathology Review

Confirmation of PTCL histopathology subtype will be performed by an independent pathology reviewer. Pathology specimens from the patient's initial diagnosis will be sent to independent pathology review. Confirmation of an eligible PTCL histopathology subtype must be documented by the independent pathology reviewer prior to randomization. See Study Instructions provided by Allos/designee for detailed guidance regarding sample requirements and the preparation and shipment of slides.

12.2.3 Medical Photography

Documentation of cutaneous disease with medical photography will be performed by the site at screening and at each response assessment, if applicable. Up to 5 target lesions will be chosen by the investigator and photographed. See Study Instructions provided by the central medical photography laboratory (Canfield Scientific, Inc.) for detailed guidance regarding photograph requirements and transfer.

12.2.4 Central Radiology Imaging

Radiologic imaging of each patient will be completed at screening and at each response assessment as described in Sections 10.1 and 10.6. All scans will be sent to a designated, independent central reviewer until at least the first interim analysis. See Study Instructions provided by the central reviewer (CoreLab Partners) for detailed guidance regarding imaging requirements and transfer.

13 CONCOMITANT MEDICATIONS

All medications administered from 7 days prior to randomization through 30 days after the last pralatrexate administration, or through 30 days after treatment discontinuation criteria are met for patients in the Observation Arm, will be recorded on the CRF. Additions, deletions, or changes of dosage of medications will also be noted.

13.1 Antiemetic Therapy

There is no evidence to expect drug-drug interactions between pralatrexate and standard antiemetic therapy and no specific antiemetic therapy has yet been proven to be superior over others in the setting of pralatrexate administration. Therefore, prophylaxis and treatment of nausea and vomiting can be administered according to the standard of care within the institution; however, administration is not recommended prior to the first dose because of the low emetogenicity of pralatrexate.

Steroids are not allowed for prophylaxis or treatment of nausea/vomiting.

13.2 Hematopoietic Growth Factors

Hematopoietic growth factors may be administered in accordance with the instructions for treatment modification for hematological events in Table 7.1. Erythropoietin will be allowed if it is judged by the investigator to be in the best interest of the patient (eg, for patients with underlying anemia or unacceptable hematologic toxicity). Other hematopoietic growth factors (eg, granulocyte colony-stimulating factor [G-CSF], granulocyte-macrophage colony-stimulating factor [GM-CSF]), with the exception of pegfilgrastim (Neulasta®, Amgen), are to be administered per package insert.

13.3 Mucositis Management

Patients receiving pralatrexate should be assessed for risk of mucositis prior to start of treatment with continued assessment for symptoms prior to each dose. Medications and mouthwashes, including salt and soda mouthwashes, used for prophylaxis and/or treatment of mucositis must be recorded as concomitant medications. Dose modifications for mucositis are found in Table 7.2; however, investigators should refer to the National Comprehensive Cancer Network (NCCN) Task Force Report for the Prevention and Management of Mucositis in Cancer Care for assistance with risk assessment and grading of mucositis, guidance on symptom management, and patient education tools on effective oral care regimens and reporting of mucositis symptoms.[35]

13.4 Corticosteroid Use

Patients are allowed to begin study treatment while receiving systemic corticosteroids provided the patient has been taking a continuous dose of $\leq$ 10 mg/day of oral prednisone or equivalent for at least 4 weeks or as part of a CHOP prednisone taper. Other concomitant systemic corticosteroid therapy during the pralatrexate treatment/observation phase of this

study is prohibited (with exception of corticosteroids administered for a non-lymphoma condition, eg, bronchitis, for ≤ 10 days). Inhaled or topical steroids (administered for reasons other than to treat cutaneous disease) are allowed.

13.5 Prophylactic Anti-infective Agents

Use of prophylactic antibiotics/antivirals/antifungals is allowed and may be administered at the discretion of the investigator. If antibiotic prophylaxis is indicated, alternatives to sulfamethoxazole/trimethoprim must be considered as it has antifolate activity. Due to the possibility of additive toxicity (including myelosuppression) when used in combination with pralatrexate, concurrent use of the 2 drugs should be avoided.

13.6 Pain Management

Pain management should be addressed promptly by the attending physician managing the patient. Due to the contribution of renal excretion (approximately 34%) to the overall clearance of pralatrexate, concomitant administration of non-steroidal anti-inflammatory drugs (NSAIDs) and probenecid may result in delayed clearance of pralatrexate. These drugs should be used with caution while patients are enrolled in this study; alternatives to NSAIDs and probenecid should be considered when possible.

13.7 Blood Products

Blood product transfusions are allowed per the discretion of the investigator.

13.8 Other Supportive Care Medications

The administration of appetite-stimulating hormones (eg, megestrol acetate) is allowed to control anorexia and cachexia.

13.9 Radiotherapy, Cytotoxic Therapy, Biologic Therapy, or Immune Response Modifiers

No RT, other cytotoxic agents, biologic therapy, immune response modifiers, or stem cell transplant are to be administered to patients until pralatrexate/observation has been discontinued.

14 ADVERSE EVENTS

14.1 Definition

An AE is defined as any untoward medical occurrence in a patient or clinical investigation patient, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. Therefore, an AE can be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal product. This definition of an AE will be extended in this study to include any untoward medical occurrence in patients participating in the Observation Arm of the study, as well.

The term "toxicity" is not clearly defined by regulatory organizations and is currently used only for historical reasons by the NCI. Therefore, the term "adverse event" is used throughout this document to refer to any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the study drug, as well as any other study-treatment-related toxicities. However, since this is an investigational study, all toxicities are considered AEs and must be reported.

Examples of an AE **include**:

- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after investigational product administration, even though it may have been present prior to the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected drug interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either investigational product or a concurrent medication.
- AEs may include pre-treatment or post-treatment events that occur as a result of protocol-mandated procedures (ie, invasive procedures, modification of patient's previous therapeutic regimen).

Examples of an AE **do not include** a/an:

- Medical or surgical procedures (eg, endoscopy, appendectomy); the condition that leads to the procedure is an AE.
- Situations where an untoward medical occurrence does not occur (eg, social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

14.2 Guidelines for Recording and Attribution Scoring of Adverse Events

Timely and complete reporting of AEs is essential. Monitoring and documentation of all AEs allows for identification of potential study-drug or dose-related AEs, and for adherence to regulatory requirements. Please refer to the CRF Completion Guidelines located in the study binder for detailed instructions.

14.3 Recording of Adverse Events

14.3.1 Recording of Adverse Events

Any AE that occurs from the time the study IC is obtained until randomization needs to be recorded on the AE CRF page(s), **only** if the event was related to a study procedure. All other AEs/findings prior to randomization must be recorded as baseline findings on the applicable CRF page(s).

Any AE that occurs from randomization through 30 days after the last dose of pralatrexate or through 30 days after treatment discontinuation criteria are met for the Observation Arm must be recorded on the AE CRF. From 31 days after the last dose of pralatrexate, only AEs that are related to pralatrexate need to be captured on the AE CRF.

14.3.2 Grading of Adverse Events

This study will utilize the NCI Common Terminology Criteria for Adverse Events (CTCAE) Scale, Version 4.0 for AE grading (http://ctep.cancer.gov/reporting/ctc.html).

14.4 Follow-up of Adverse Events

All AEs and significant abnormal laboratory values must be followed up in accordance with the ICH Good Clinical Practice (GCP) guidelines, and other applicable regulatory requirements (eg, US Code of Federal Regulations [CFR]).

14.5 Relationship

The relationship of the event to pralatrexate will be assessed using the following definitions:

Not Related:
Evidence exists that the AE has an etiology other than pralatrexate (such as, pre-existing condition, underlying disease, intercurrent illness, or concomitant medications).

Related:
A temporal relationship exists between the event onset (or worsening) and the administration of pralatrexate. It cannot be readily explained by the patient's clinical state, intercurrent illness, or concomitant medications. In case of cessation or reduction of the dose, the event abates or resolves, and it reappears upon challenge.

It should be emphasized that ineffective treatment should not be considered as causally related in the context of AE reporting.

These criteria, in addition to good clinical judgment, should be used as a guide for determining the causal assessment.

14.6 Serious Adverse Events

In the interest of patient care and to allow Allos to fulfill all regulatory requirements, any serious adverse event (SAE), regardless of causal relationship to pralatrexate, must be reported to Allos within 24 hours of knowledge of the event.

14.6.1 Definition

SAEs are defined (CFR 312.32, ICH of Technical Requirements for Registration of Pharmaceuticals for Human Use E2A Guideline) as those AEs that meet any of the following criteria:

- Results in death.
- Is life-threatening: ie, any event that, in the opinion of the investigator, poses an immediate risk of death from that event.
- Requires inpatient hospitalization or prolongation of existing hospitalization (excluding hospitalizations for study therapy, disease-related procedures, or placement of an indwelling catheter, unless associated with other SAEs).
- Results in a persistent or significant disability/incapacity.
- Results in a congenital anomaly/birth defect.
- Includes important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent 1 of the outcomes listed in this definition.

14.6.2 Serious Adverse Event Reporting

- Any SAE that occurs from the time the study IC is obtained until randomization needs to be reported only if the event was related to a study procedure.
- Any SAE that occurs from randomization through 30 days after the last dose of pralatrexate or through 30 days after treatment discontinuation criteria are met for the Observation Arm must be reported to Allos within 24 hours of knowledge of the event. From 31 days after the last dose of pralatrexate, patients will continue to be assessed for SAEs that are related to pralatrexate.

- SAEs (regardless of causality) must be reported and the SAER faxed **within 24 hours of knowledge of the event to**:

Allos Therapeutics, Inc.
Primary Contact: Clinical Drug Safety and Pharmacovigilance Department
Phone: [redacted]
Fax: [redacted] or [redacted]
Email: allosdrugsafety@allos.com

Allos may request additional information from the investigator to ensure the timely completion of accurate safety reports. Safety data that are critical to the reportability of an SAE, such as causality assessment and serious criteria, should be included in the initial fax for SAER. If omitted, a timely response to drug safety data queries received from Allos or an Allos designee is expected.

The investigator must take all therapeutic measures necessary for resolution of the SAE. Any medications necessary for treatment of the SAE must be recorded onto the concomitant medication section of the patient's CRF.

SAEs that are pralatrexate-related will be followed until resolution or returned to baseline/Grade 1, whichever is longer, or until it is determined that the outcome will not change with further follow-up.

Additionally, the SAE must be entered on the AE page(s) of the CRF. Follow-up SAERs need to be submitted to Allos as soon as additional information regarding the event becomes available (eg, diagnosis is made, laboratory or test results, event course, outcome, etc). The Allos CRA or designee will collect the original SAER from the site.

Allos/designee will be responsible for reporting SAEs to the regulatory authorities in accordance with applicable expedited reporting regulatory guidelines. The investigator is responsible for submitting SAEs to his/her Institutional Review Board (IRB)/Ethics Committee (EC)/Research Ethics Board (REB).

14.6.3 Exclusions to Serious Adverse Event Reporting Requirements

The following are not considered SAEs:

- Situations where an untoward medical occurrence did not occur (eg, social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected prior to randomization that do not worsen.
- Elective hospitalizations solely for the initiation of subsequent therapy for the disease being studied.

14.7 Reproductive Risks

Pralatrexate must not be used during pregnancy or breastfeeding. Pre-menopausal females of childbearing potential will follow an approved, medically accepted birth control regimen (eg, birth control pills, intrauterine device, condoms, implants) or agree to abstain from heterosexual intercourse while participating in the study and for 30 days following the last dose of pralatrexate.

Males who are sexually active must agree to practice a medically acceptable barrier method contraceptive regimen (eg, condoms) or agree to abstain from heterosexual intercourse while receiving pralatrexate and for 90 days after the last administration of pralatrexate.

14.7.1 Pregnancy Notification

Pregnancies involving a study patient or a patient's partner that occur from the first dose of pralatrexate through 30 days after the last dose of pralatrexate must be brought to the attention of the treating physician immediately and reported to Allos within 24 hours after the investigator has gained knowledge of the event, using the Pregnancy Notification Form. The investigator must report any such event to Allos within 24 hours via telephone and via fax (see contact information in Section 14.6.2). Follow-up information regarding the outcome of the pregnancy will be requested by the Allos Clinical Drug Safety and Pharmacovigilance Department.

Treatment will be discontinued for all patients who become pregnant during participation in this study.

15 STATISTICAL PLAN

15.1 Objectives

Primary

- Determine the efficacy of pralatrexate compared to observation when administered to patients with previously undiagnosed PTCL who have achieved an objective response after completing at least 6 cycles of CHOP-based treatment.

Secondary

- Determine the safety of pralatrexate when administered following a course of CHOP-based treatment to patients with previously undiagnosed PTCL.

15.2 Endpoints

15.2.1 Efficacy Endpoints

Primary

- PFS and OS.

Secondary

- Objective response (CR or PR) to pralatrexate versus observation.

The primary analyses of PFS and response will use the central review tumor assessments per IWC without using PET. Additional analyses of PFS and response will use IWC, including PET, and investigators' assessment of response.

15.2.2 Safety Endpoints

The safety endpoints include:

- Incidence and severity of treatment-emergent AEs.
- Changes in laboratory values.

15.3 Analysis Population

15.3.1 Primary Analysis Set/Intent-to-treat Analysis Set

The primary efficacy set, also referred to as the intent-to-treat population, includes all randomized patients. Each patient will be included in the treatment group assigned at randomization, regardless of the treatment received. This analysis set will be used for the primary analyses of all efficacy endpoints.

15.3.2 Safety Analysis Set

The safety analysis set consists of all patients randomized to the Pralatrexate Arm who receive at least 1 dose of pralatrexate plus all patients randomized to the Observation Arm who do not discontinue the study within 3 days of randomization. This analysis set will be used for the primary analyses of all safety endpoints.

15.3.3 Interim Analyses Sets

One analysis of PFS, and 2 formal interim analyses and a final analysis of OS will be performed. The first analysis will be performed when both 280 PFS events and 128 OS events have occurred. The only analysis for PFS will be performed at this first analysis, and will be assessed at the 0.05 level of significance. If PFS is significant at the 0.05 level, an analysis will be conducted on OS at this time. If PFS is not significant at the 0.05 level, the study will be stopped. Two additional analyses of survival will be performed when approximately two-thirds of 385 deaths, and all 385 deaths have occurred, respectively.

15.4 Sample Size

A total of 549 randomized patients are planned for this study.

Outcome data for patients with T-cell lymphoma who receive first-line CHOP is limited. A retrospective study of the International T-Cell Lymphoma Project demonstrated a 5-year OS rate of 32% and a 5-year FFS rate of 20% for patients with PTCL-NOS, with widely varying results for other subtypes.[18] Median OS for these patients did not seem to be a function of whether the patient received an anthracycline-based induction therapy. In a retrospective evaluation of 96 patients diagnosed within the Non-Hodgkin's Lymphoma Classification Project, Rudiger et al report a similar finding, with 5-year OS and FFS rates of 26% and 20%, respectively, for PTCL patients treated with a doxorubicin-containing regimen.[12] Per Figure 1 of the Rudiger publication, the estimated median FFS in these patients is approximately 6 months.

Reports of response rate to first-line CHOP-based regimens in patients with PTCL are also available. Gallamini, et al (2007) conducted a small study (n = 24 evaluable) evaluating CHOP plus alemtuzumab administered every 4 weeks for a total of 28 weeks.[16] They observed an overall response rate of 75% (71% CR, 4% PR). In a separate report, Gallamini, et al performed a retrospective analysis of 385 patients with PTCL-U, with the majority (78%) receiving chemotherapy containing anthracycline.[36] They reported an overall response rate of 74% (53% CR, 21% PR) in the 372 evaluable patients. Mercadal and colleagues reported on a series of 41 patients ≤ 65 years old who were planned to receive 6 cycles of intensive chemotherapy (high-dose CHOP alternating with etoposide, methylprednisolone, cytarabine, and cisplatin [ESHAP]) followed by autologous stem cell transplantation, if in response.[37] Twenty-eight patients (68%) received the planned 6 courses of therapy, 6 (15%) patients received 5 courses of therapy, and 7 (17%) received less than 5 courses. Following the chemotherapy phase, the CR rate was 49% and the PR rate was 10%. Kim and collaborators administered CHOP plus etoposide and gemcitabine to a cohort

of 26 first-line PTCL patients.[38] The median number of cycles administered was 4, and the overall response rate was 77% (62% CR, 15% PR). Abouyabis and colleagues performed a meta-analysis of non-ALCL PTCL patients receiving anthracycline-based chemotherapy in the first-line setting.[39] A total of 31 studies were identified involving a total of 1996 patients. The overall CR rate was 55% and the 5-year OS rate was 37%.

Across all of these reported studies, approximately 50% of patients achieve a CR to first-line CHOP, with an additional 10-20% achieving a PR. Furthermore, the 5-year PFS is approximately 20%, with a median PFS of approximately 9 months in all patients. For the PDX-017 study, we assume one-third of patients will have disease refractory to CHOP, and that the median PFS in these patients will be 3 months. Coupled with an overall median PFS of 9 months, and assuming exponentially distributed PFS, this implies the median PFS in patients who respond to CHOP is approximately 16 months. Subtracting out 6 months for CHOP administration and washout prior to randomization results in an estimated 10 month median PFS for the Observation Arm patients in this study.

The sample size is based on comparing the treatment groups with respect to the primary efficacy endpoints of PFS and OS. Assuming proportional hazards, a true hazard ratio (HR) on OS of 0.73, and a 2:1 randomization (treatment:observation) with a total of 549 patients (366 in the treatment group vs 183 in the observation group), a total of 385 OS events (deaths) will provide at least 80% power to show HR < 1.00 using a 2-sided stratified log-rank test at a 0.05 significance level (alpha = 0.05), assuming an accrual period of 54 months and a follow up period of 30 months. For a HR on PFS of 0.67, and a 2:1 randomization (treatment:observation), a total of 280 PFS events (PD + deaths) will provide at least 80% power to show HR < 1.00 using a 2-sided stratified log-rank test at a 0.05 significance level (alpha = 0.05).

15.5 Stratification

Patients meeting randomization eligibility criteria will be randomized 2:1 to the Pralatrexate Arm or the Observation Arm according to a permuted block design, balancing within the following stratum.

- Response per investigator at completion of CHOP-based therapy (CR vs PR)

15.6 Analysis Plans

15.6.1 Interim Analyses of OS

Two formal interim analyses and a final analysis of OS will be performed. The first interim analysis will be performed when both 280 PFS events and 128 OS events have occurred. The only analysis for PFS will be performed at this time, and will be assessed at the 0.05 level of significance. If PFS is significant at the 0.05 level, an interim analysis will be conducted on survival at this time. If there are 128 OS events, or 1/3 of the information of 385 deaths, included in the first interim analysis of OS, the level of significance (alpha) would be 0.0002, according to O'Brien and Fleming.[40] If PFS is significant, a test for futility

of OS will not be conducted at the first interim analysis since such a result could not occur. The second interim analysis for OS will be performed when two-thirds (256) of the survival events have occurred, at the 0.013 level of significance. The HR stopping bound for futility at this interim analysis will be 1.05 (95% confidence interval [CI]: 0.80, 1.29). If the HR for OS is greater than 1.05, the study will be stopped. The final analysis for survival will be performed when 385 OS events have occurred, at the 0.046 level of significance.

A DMC will periodically review safety data at regularly scheduled meetings and at the same time as each interim analysis of efficacy. The first formal safety review will occur when approximately 100 patients have been randomized and completed at least 8 weeks post-randomization pralatrexate/observation or have discontinued.

At each interim analysis for survival, the study may be stopped for overwhelming evidence of futility or superiority according to specified boundaries. The DMC may also make recommendations regarding adjustments to the sample size, if they are warranted.

15.6.2 Final Analyses of Efficacy Endpoints

The primary efficacy analysis on PFS will be performed when approximately 280 PFS events and 128 OS events have occurred. This is estimated to occur approximately 48 months after the first patient is randomized. Allos will set a data cut-off date for the primary efficacy analyses in anticipation of 280th PFS event and 128th OS event. The primary efficacy analysis on OS will be performed when approximately 385 OS events have occurred.

A step-down procedure will be used for analyzing the co-primary endpoints of PFS and OS. If the PFS endpoint is significant at the 0.05 level the OS endpoint will be tested at an overall significance level of 0.05. However, if the PFS endpoint fails to show significance, the study will be stopped and OS will not be tested. The study will meet its primary objective if both the PFS and OS endpoints are significant. The interim analysis for OS will be implemented using the error-spending approach of Lan and DeMets according to the unified family approach with boundary relationships of O'Brien and Fleming for early stopping to reject the null hypothesis (superiority).[41] The boundaries for early stopping due to failure to reject the null hypothesis (futility) will be determined according to the unified family approach with boundary shape parameters on the sample mean scale that result from choosing $P = 2.0$ (all R and A parameters in the unified family approach set equal to zero)[42].

The primary analyses of PFS and objective response will use the central review tumor assessments per IWC without using PET. Additional analyses of PFS and response will use IWC, including PET, and investigators' assessment of response. Additional details regarding central review will be provided in the reviewer's charter.

15.7 Efficacy Endpoints

15.7.1 Progression-free Survival

PFS time is calculated as the number of days from randomization to the date of objective documentation of PD or death, regardless of cause (date of PD or death - date of randomization + 1). Patients who are alive without a disease response assessment of PD will be censored at their last disease assessment date or the date of randomization whichever is later. Date of progression will not be imputed for patients with missing tumor assessment(s) before an assessment of PD. Patients who withdraw from treatment prior to PD without withdrawing consent will be followed for disease status whenever possible, even if subsequent therapy, including transplant, has been initiated prior to documented PD per central review at least until the PFS analysis. Patients who have no response assessments after baseline will be censored at randomization.

Strata used in the analyses will be those used for study randomization (as recorded on the IRT). With this technique, the HR can be consistently estimated (assuming the proportional hazards model is correct), as the potential bias due to the asymmetric visits is removed. It also corrects for the Type I error inflation and retains the nominal study power.

The primary analysis of PFS will be based on PD as determined by independent central review blinded to treatment group assignment. A separate charter will detail specifics about central review operation and response/PD definition details. Additional analyses will use the investigators' assessment of response.

The stratified log-rank test will be the primary method used to test the hypothesis that pralatrexate extends PFS relative to observation. In addition, the stratified Cox regression model will be used to calculate the PFS (HR), along with the 95% confidence interval (CI). Results of the unstratified Cox regression model (and log-rank test) will also be presented. The proportional hazards assumption of the Cox model will be assessed.

15.7.2 Overall Survival

OS time is calculated as the number of days from randomization to the date of death, regardless of cause (date of death - date of randomization + 1). Survival follow-up will continue for up to 7 years from randomization.

The stratified log-rank test will be the primary method used to test the hypothesis that pralatrexate extends OS relative to observation. In addition, the OS HR, along with 95% CIs, will be estimated via the stratified Cox model. Strata used in these analyses will be those used for study randomization (as recorded using the IRT). Results of the unstratified Cox regression model (and log-rank test) will also be presented. The proportional hazards assumption of the Cox model will be assessed.

15.7.3 Objective Response Rate

The number and percentage of patients with an objective response of CR or PR will be summarized. The percentage will be calculated by dividing the number of patients within each category of response by the number of patients with measurable disease at baseline. Each patient will be counted within only 1 response group, with the overall best response during the study as the classification group. The treatment groups will be compared with respect to objective response rate (CR + PR) using the stratified Cochran-Mantel-Haenszel test. A 2-sided 95% exact CI will be calculated for the difference in objective response rates between the 2 treatment groups. Descriptive statistics will be provided for best tumor response for each treatment group.

15.8 Safety Analysis

Analysis of safety will be performed on the safety analysis set. Study data will be monitored on an ongoing basis by the clinical study team to ensure patients' safety.

15.8.1 Adverse Events

The Medical Dictionary for Regulatory Activities (MedDRA) will be used to code all AEs to a system organ class (SOC) and a preferred term. Patient incidence of AEs will be tabulated by SOC, preferred term, and severity grade for all AEs, SAEs, treatment-related AEs, and treatment-related SAEs. Each of these outputs will include tabulation by maximum severity for each SOC and preferred term as reported by the investigator based on CTCAE, Version 4.0. If an AE cannot be graded based on CTCAE, the investigator will assign a severity based on 1 = mild, 2 = moderate, 3 = severe, 4 = life threatening, and 5 = death related to AE. Summaries of AEs, SAEs, treatment-related AEs, and treatment-related SAEs occurring in at least 5% of the patients will be provided in descending order of frequency by SOC and preferred term.

Additional tables summarizing patient incidence (by preferred term) of the following will be generated:

- All AEs
- SAEs
- Treatment-related AEs
- Treatment-related SAEs
- Grade 3 or higher AEs
- AEs leading to the discontinuation of pralatrexate or observation or removal from study
- AEs leading to dose reductions of the study drug
- AEs with incidence $\geq 5\%$
- Deaths

15.8.2 Adverse Events Grouped by Similar Preferred Term

Summary tables of treatment emergent, treatment-related, serious, and serious treatment-related AEs grouped by similar preferred term will be presented. For this presentation, certain similar preferred terms have been identified and will be coded to the same preferred term in order to present the event in a uniform manner. These terms are presented in the statistical analysis plan (additional preferred terms may be identified within each category during data review and added to this list).

Separate outputs will be provided for subgroups defined by age group (< 65, ≥ 65), gender, and race (if feasible).

Detailed listings for all AEs and listings and/or narratives will be provided for serious and significant AEs, and deaths (with 'on study' deaths [deaths that occur before the end of safety follow up period] identified).

15.8.3 Laboratory Parameters

Laboratory parameters for hematology and blood chemistry will be summarized at baseline and last observed value. Additionally, the maximum and minimum observed post baseline values will be summarized along with the change from baseline to the maximum observed value, minimum observed value, and last observed value. Tables of shifts in severity (CTCAE Version 4.0) from baseline for selected laboratory parameters and selected time-points may also be provided. A listing of all laboratory assessments may be provided.

Incidence of laboratory abnormalities and subject incidence of Grade 3 or 4 laboratory toxicities will be presented. Summaries of hematology and serum chemistry parameters along with grade shifts from baseline will be presented.

Standard PK parameters will be estimated from the limited plasma sampling (eg, AUC, C_{max}, and $t_{1/2}$).

POPPK analyses will be conducted via nonlinear mixed-effects modeling to estimate POPPK parameters for pralatrexate, including typical values, inter-individual variation, and residual variability after administration of pralatrexate in the patient population, and to estimate the effects of individual-specific covariate factors (eg, demographics, disease state, etc) that may be predictive of the unexplained random variability in pralatrexate PK. In addition, the relationship between the PK of pralatrexate and response (safety and efficacy) will be explored.

16 STUDY MANAGEMENT

16.1 Investigator Responsibilities

16.1.1 Good Clinical Practice

The investigator will ensure that this study is conducted in full compliance with the principles of the "Declaration of Helsinki" (as amended in Tokyo, Venice, Hong Kong, and South Africa), ICH guidelines, or with the laws and regulations of the country in which the research is conducted. By signing the US Form FDA 1572, "Statement of Investigator", the investigator commits to adhere to applicable sections of the US CFR parts 50 "Protection of Human Subjects", 54 "Financial Disclosure by Clinical Investigators", 56 "Institutional Review Boards", and 312 subpart D "Responsibilities of Sponsors and Investigators". All investigators will ensure adherence to ICH guidelines for GCP and Clinical Safety Data Management.

16.1.2 IRB/EC/REB Approval

The institution's IRB/EC/REB, or other committee functioning in a similar capacity, will review and approve the protocol, initial and revised IC documents, protocol amendments, and safety items. After approval by the IRB/EC/REB, documentation of approval and the approved IC document will be sent to Allos/designee before any patient is enrolled into this study.

16.1.3 Informed Consent

The investigator is responsible for preparing the written IC document for this study. Allos or its designee will provide the investigator with templates for an IC document. The investigator may rearrange or reword the contents of these templates, or may add other elements or language, provided the meaning and content are not changed or deleted. Allos or designee must review and approve the IC document that is used by the investigator for this study prior to IRB/EC/REB submission.

Written IC will be obtained from all patients participating in this study, in accordance with ICH GCP and current regulatory requirements. The case history for each patient must document that the IC process was obtained prior to participation in the study. The original IC document will be kept in the patient's record, and a copy will be provided to the patient.

16.1.4 Study Files and Retention of Records

The investigator must retain all study records until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product as per 21 CFR 312.62 and ICH GCP E6 4.9.5 and 5.5.12. These documents must be retained for a longer period, however, if required by the applicable regulatory requirements or by an agreement with

Allos. It is the responsibility of the sponsor to inform the investigator as to when these documents no longer need to be retained. If the investigator relocates, or for any reason desires to dispose of the records, the study records may be transferred to another institution, another investigator, or to the sponsor upon written agreement between the investigator and the sponsor.

16.2 Recording and Collecting of Data

In accordance with ICH and GCP guidelines, the investigator will maintain complete, accurate, legible, and easily retrievable data, and will allow personnel authorized by Allos access to all study data at any time. Such data shall also be secured in order to prevent loss of data.

16.2.1 Case Report Forms

Allos may make use of electronic data capture (EDC) or paper CRFs.

When using paper, Allos' CRFs are printed on no carbon-required paper to permit multiple copies. The investigator will retain the bottom copy for his/her study files. Data collected for each patient will be recorded on the CRFs. The investigator is responsible for ensuring that all data submitted are true, accurate, and ultimately complete.

Completed CRFs will be reviewed and signed by an investigator listed on the US Form FDA 1572 or equivalent. The CRA will verify the CRF data with the patient's source data, evaluate the data for accuracy, consistency, and completeness, and will ensure that all forms with missing data and/or errors are ultimately addressed.

When using EDC, data collected for each patient will be entered by site staff into an EDC database. The investigator is responsible for ensuring that all data submitted are true, accurate, and ultimately complete.

Completed, EDC data will be reviewed by an investigator listed on the US Form FDA 1572 or equivalent. This review will be documented by the investigator or equivalent logging into the EDC database and providing sign off using his/her 21 CFR Part 11compliant electronic signature. The CRA will verify the CRF data with the patient's source data, evaluate the data for accuracy, consistency, and completeness, and will ensure that all screens with missing data and/or errors are ultimately addressed.

Accurate and complete CRFs for a patient, either via paper or EDC, must be submitted to Allos in a timely manner.

16.2.2 Data Clarification Forms

Data Clarification Forms (DCFs), such as Queries, Site Notifications, and CRA Addenda, will be used by Allos staff or designee to attempt to correct or clarify missing, incomplete, or illogical data. Queries and Site Notification may be completed individually by an appropriate person on the Delegation of Authority form, but must be reviewed, and the

tracking coversheet signed by, an investigator listed on the US Form FDA 1572 or equivalent. CRA Addenda may be completed by the CRA but must be reviewed and signed by an investigator listed on the US Form FDA 1572 or equivalent.

For EDC studies, this process is performed electronically.

16.2.3 Self-evident Corrections

CRF data are expected to be accurate, consistent, and complete. Allos Clinical Data Management department or designee (eg, a clinical research organization [CRO]) may apply the following conventions to correct the Allos database without issuing a DCF to site staff. However, a DCF may still be generated as needed for clarification/confirmation.

- Header data will be corrected if the error is obvious and a correction is supported by the remainder of the CRFs.
- Duplicate data will be deleted unless the CRF specifically allows for repeat values. For example, if identical lab values (including date and time, if applicable) are recorded for a protocol-specified visit and for a miscellaneous/unscheduled visit, only the protocol specified visit data will be entered in the database.
- Data recorded within the casebook can be moved to the appropriate CRF field if no data are changed.
- Relevant comments or marginalia will be added to the Comments section.
- Misspellings may be corrected only if the correction clarifies (eg, enables coding), but does not change, the meaning or contextual use of the word.
- Long text fields will be shortened, if needed, using generally accepted abbreviations that do not change the clinical meaning of the text.
- Dates (eg, year boundary, day/month inversion) will be corrected if the change is supported by the remainder of the CRFs.
- Only the Stop Date will be recorded if a Stop Date and “Continuing" (or similar) are provided.
- An indicator field left blank or marked “no” (eg, AEs present?) will be updated to “yes” if data are present.
- If a field where “If Other, specify” (or similar situation) includes data but the box is blank (or similar), the box will be checked for the database.
- If the resolution area of a Site Notification (SN) is blank but the SN is signed, the response from the site will be interpreted as “Agree”.

16.2.4 Drug Accountability

In accordance with all applicable regulatory requirements, the investigator or designated site staff must maintain pralatrexate accountability records throughout the course of the study. This person(s) will document the amount of pralatrexate administered to patients. The CRA will review inventory and accountability documentation during monitoring visits.

The investigator will not supply investigational study drug to other investigators not listed on the US Form FDA 1572 or equivalent. Investigational study drug use, other than as directed by this protocol, is not allowed without prior authorization from Allos.

All unused vials of pralatrexate must be accounted for at the site and maintained in a secured, locked storage area with access limited to authorized study personnel only. Since pralatrexate is cytotoxic, used vials will be destroyed per institution, local, and all applicable policies and procedures. After study conclusion, all unused vials of pralatrexate may be destroyed at the site, following verification of accountability by an Allos representative.

16.3 Protocol Compliance

The investigator is responsible for ensuring the study is conducted in accordance with the procedures and evaluations described in this protocol.

16.4 Sponsor Responsibilities

16.4.1 Amendments to the Protocol

Any amendment to the protocol, as deemed appropriate by Allos, will be implemented as the study progresses. Allos may also make such changes to the protocol, as it deems necessary for safety reasons, or as may be required by the regulatory authorities. Amendments will be submitted to the IRB/EC/REB for written approval, before implementation. The expedited review procedure for an amendment is appropriate only if minor changes are made in the protocol.

16.4.2 Safety Monitoring

The clinical drug safety of pralatrexate will be continuously evaluated by the Study Medical Monitor on an ongoing basis during the course of this clinical study. All SAEs for pralatrexate in this study and all other ongoing clinical studies with pralatrexate will be processed in compliance with current regulatory guidelines by the Allos Clinical Drug Safety and Pharmacovigilance group. This processing will include a formal assessment of each SAE by the physician medical monitor for clinical drug safety. In addition, a cumulative review of all SAEs from all sources will be assessed on a bimonthly basis for change in frequency and severity of the SAEs by the physician medical monitor for clinical drug safety as a signal detection/trend evaluation.

16.5 Joint Investigator/Sponsor Responsibilities

16.5.1 Access to Information for Monitoring and Auditing

In accordance with ICH GCP guidelines and 21 CFR 312, the CRA/auditor must have direct access to the patient's source documentation in order to verify the data recorded in the CRFs. The CRA is responsible for routine review of the CRFs at regular intervals throughout the study and to verify adherence to the protocol, as well as the completeness, consistency, and accuracy of the data being recorded. The CRA/auditor must have access to any patient records needed to verify the entries on the CRFs. The investigator agrees to cooperate with the monitor to ensure that any problems detected in the course of these monitoring/auditing visits are resolved.

16.5.2 Termination of the Study

For reasonable cause, either the investigator or the sponsor, Allos, may terminate the investigator's participation in this study, provided a written notice is submitted within the time period provided for in the Clinical Trial Agreement (CTA). In addition, Allos may terminate the study at any time upon immediate notice for any reason, including but not limited to, Allos' belief that termination is necessary for the safety of patients.

16.5.3 Publication Policy

Allos recognizes the importance of communication of medical study data, and encourages the publication of such data in reputable scientific journals and the presentation of such data at scientific seminars and conferences. Any proposed publication or presentation of the data generated from the study must be provided to Allos for timely review in accordance with the terms of the CTA between the investigator, the institution, and Allos. Allos shall not, in its scientific publications or promotional material, quote from publications by investigators without full acknowledgment of the source. Criteria for inclusion in authorship in any publications resulting from the study will be determined and communicated in writing to all participating principal investigators.

16.6 Confidentiality

All information provided to the investigator by Allos, including nonclinical data, protocols, CRFs, and verbal and written information, will be kept strictly confidential and confined to the clinical personnel involved in conducting this study, and no disclosure shall be made except in accordance with any right of publication granted to the investigator. All personnel will handle patient data in a confidential manner in accordance with applicable regulations governing clinical research. Upon request by a regulatory authority such as the US FDA and other regulatory authorities worldwide, the investigator/institution must make available for direct access all requested study-related records or reports generated as a result of a patient's participation in this study. This information may be related in confidence to the IRB/EC/REB or other committee functioning in a similar capacity. In addition, no reports or information about the study or its progress will be provided to anyone not involved in the study other than to Allos, or in confidence to the IRB/EC/REB or similar committee, except if required by law.

17 REFERENCES

1. The Non-Hodgkin's Lymphoma Classification Project. A clinical evaluation of the International Lymphoma Study Group classification of non-Hodgkin's lymphoma. . Blood 1997;89(11):3909-18.

2. Hennessy BT, Hanrahan EO, Daly PA. Non-Hodgkin lymphoma: an update. Lancet Oncol 2004;5(6):341-53.

3. Dearden CE, Foss FM. Peripheral T-cell lymphomas: diagnosis and management. Hematol Oncol Clin North Am 2003;17(6):1351-66.

4. Zheng T, Mayne ST, Boyle P, et al. Epidemiology of non-Hodgkin lymphoma in Connecticut. 1935-1988. Cancer 1992;70(4):840-9.

5. Cartwright RA, Gilman EA, Gurney KA. Time trends in incidence of haematological malignancies and related conditions. Br J Haematol 1999;106(2):281-95.

6. Surveillance, epidemilogy, and end results (SEER) Program (www.seer.cancer.gov/publicdata) SEER Stat Database: Incidence-SEER 9 Regs Public Use. Nov. 2003 Sub (1973-2001), National Cancer Institute, DCCPS, Surveillance Research Program, Cancer Statistics Branch, released April 2004, based on the November 2003 submission.

7. Devesa SS, Fears T. Non-Hodgkin's lymphoma time trends: United States and international data. Cancer Res 1992;52(19 Suppl):5432s-5440s.

8. Swerdlow SH, International Agency for Research on Cancer., World Health Organization. WHO classification of tumours of haematopoietic and lymphoid tissues. 4th ed. Lyon, France: International Agency for Research on Cancer; 2008.

9. Shipp MA. Prognostic factors in aggressive non-Hodgkin's lymphoma: who has "high-risk" disease? Blood 1994;83(5):1165-73.

10. Gisselbrecht C, Gaulard P, Lepage E, et al. Prognostic significance of T-cell phenotype in aggressive non-Hodgkin's lymphomas. Groupe d'Etudes des Lymphomes de l'Adulte (GELA). Blood 1998;92(1):76-82.

11. Harris NL, Jaffe ES, Stein H, et al. A revised European-American classification of lymphoid neoplasms: a proposal from the International Lymphoma Study Group. Blood 1994;84(5):1361-1392.

12. Rudiger T, Weisenburger DD, Anderson JR, et al. Peripheral T-cell lymphoma (excluding anaplastic large-cell lymphoma): results from the Non-Hodgkin's Lymphoma Classification Project. Ann Oncol 2002;13(1):140-9.

13. Fury MG, Krug LM, Azzoli CG, et al. A phase I clinical pharmacologic study of pralatrexate in combination with probenecid in adults with advanced solid tumors. Cancer Chemother Pharmacol 2005:1-7.

14. O'Connor OA. Developing new drugs for the treatment of lymphoma. Eur J Haematol Suppl 2005(66):150-8.

15. Savage KJ. Peripheral T-cell lymphomas. Blood Rev 2007;21(4):201-16.

16. Gallamini A, Zaja F, Patti C, et al. Alemtuzumab (Campath-1H) and CHOP chemotherapy as first-line treatment of peripheral T-cell lymphoma: results of a GITIL (Gruppo Italiano Terapie Innovative nei Linfomi) prospective multicenter trial. Blood 2007;110(7):2316-2323.

17. Armitage JO, Vose JM, Weisenburger DD. Towards understanding the peripheral T-cell lymphomas. Ann Oncol 2004;15(10):1447-9.

18. Vose J, Armitage J, Weisenburger D. International peripheral T-cell and natural killer/T-cell lymphoma study: pathology findings and clinical outcomes. J Clin Oncol 2008;26(25):4124-30.

19. Wilson WH, Grossbard ML, Pittaluga S, et al. Dose-adjusted EPOCH chemotherapy for untreated large B-cell lymphomas: a pharmacodynamic approach with high efficacy. Blood 2002;99(8):2685-93.

20. Rizvi MA, Evens AM, Tallman MS, et al. T-cell non-Hodgkin lymphoma. Blood 2006;107(4):1255-64.

21. Mounier N, Gisselbrecht C, Briere J, et al. Prognostic factors in patients with aggressive non-Hodgkin's lymphoma treated by front-line autotransplantation after complete remission: a cohort study by the Groupe d'Etude des Lymphomes de l'Adulte. J Clin Oncol 2004;22(14):2826-34.

22. Schmid FA, Sirotnak FM, Otter GM, et al. New folate analogs of the 10-deaza-aminopterin series: markedly increased antitumor activity of the 10-ethyl analog compared to the parent compound and methotrexate against some human tumor xenografts in nude mice. Cancer Treat Rep 1985;69(5):551-3.

23. Sirotnak FM, DeGraw JI, Moccio DM, et al. New folate analogs of the 10-deaza-aminopterin series. Basis for structural design and biochemical and pharmacologic properties. Cancer Chemother Pharmacol 1984;12(1):18-25.

24. Sirotnak FM, DeGraw JI, Schmid FA, et al. New folate analogs of the 10-deaza-aminopterin series. Further evidence for markedly increased antitumor efficacy compared with methotrexate in ascitic and solid murine tumor models. Cancer Chemother Pharmacol 1984;12(1):26-30.

25. Sirotnak FM, Schmid FA, Samuels LL, et al. 10-Ethyl-10-deaza-aminopterin: structural design and biochemical, pharmacologic, and antitumor properties. NCI Monogr 1987;5:127-31.

26. O'Connor OA, Horwitz S, Hamlin P, et al. Phase II-I-II study of two different doses and schedules of pralatrexate, a high-affinity substrate for the reduced folate carrier, in patients with relapsed or refractory lymphoma reveals marked activity in T-cell malignancies. J Clin Oncol 2009;27(26):4357-64.

27. Shustov AR, Pro B, Horwitz SM, et al. Pralatrexate in patients with relapsed/refractory peripheral T-cell lymphoma (PTCL): Relationship between response and survival (abstract 8054). . Amer Soc of Clinical Oncol; 2010. Accessed: (28Jun2010). http://www.asco.org/ASCOv2/Meetings/Abstracts?&vmview=abst_detail_view&confID=74&abstractID=54218.

28. Horwitz M, Duvic M, Kim Y, et al. Pralatrexate efficacy and tolerability in patients with relapsed or refractory cutaneous T-cell lymphoma (CTCL) (abstract 0300). Haematologica 2010;95(Suppl 2):120.

29. Horwitz SM, Vose JM, Advani R, et al. Pralatrexate and gemcitabine in patients with relapsed or refractory lymphoproliferative malignancies: phase 1 results. (poster presentation). Presented at American Society of Hematology (ASH) 51st Annual Meeting, Dec 5-8; New Orleans, LA. 2009.

30. Krug LM, Ng KK, Kris MG, et al. Phase I and pharmacokinetic study of 10-propargyl-10-deazaaminopterin, a new antifolate. Clin Cancer Res 2000;6(9):3493-8.

31. Krug LM, Azzoli CG, Kris MG, et al. 10-propargyl-10-deazaaminopterin: an antifolate with activity in patients with previously treated non-small cell lung cancer. Clin Cancer Res 2003;9(6):2072-8.

32. Azzoli CG, Krug LM, Gomez J, et al. A phase 1 study of pralatrexate in combination with paclitaxel or docetaxel in patients with advanced solid tumors. Clin Cancer Res 2007;13(9):2692-8.

33. Krug LM, Heelan RT, Kris MG, et al. Phase II Trial of Pralatrexate (10-Propargyl-10-deazaaminopterin, PDX) in Patients with Unresectable Malignant Pleural Mesothelioma. J Thorac Oncol 2007;2(4):317-320.

34. Smith TJ, Khatcheressian J, Lyman GH, et al. 2006 update of recommendations for the use of white blood cell growth factors: an evidence-based clinical practice guideline. J Clin Oncol 2006;24(19):3187-205.

35. Bensinger W, Schubert M, Ang KK, et al. NCCN Task Force Report. prevention and management of mucositis in cancer care. J Natl Compr Canc Netw 2008;6 Suppl 1:S1-21; quiz S22-4.

36. Gallamini A, Stelitano C, Calvi R, et al. Peripheral T-cell lymphoma unspecified (PTCL-U): a new prognostic model from a retrospective multicentric clinical study. Blood 2004;103(7):2474-9.

37. 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.

38. Kim JG, Sohn SK, Chae YS, et al. CHOP plus etoposide and gemcitabine (CHOP-EG) as front-line chemotherapy for patients with peripheral T cell lymphomas. Cancer Chemother Pharmacol 2006;58(1):35-9.

39. Abouyabis AN, Shenoy PJ, Lechowicz MJ, et al. Incidence and outcomes of the peripheral T-cell lymphoma subtypes in the United States. Leuk Lymphoma 2008;49(11):2099-107.

40. O'Brien PC, Fleming TR. A multiple testing procedure for clinical trials. Biometrics 1979;35:549-56.

41. Lan KKG, DeMets DL. Discrete sequential boundaries for clinical trials. Biometrika 1983;70(3):659-63.

42. Kittelson JM, Emerson SS. A unifying family of group sequential test designs. Biometrics 1999;55(3):874-82.

43. Cheson BD, Pfistner B, Juweid ME, et al. Revised response criteria for malignant lymphoma. J Clin Oncol 2007;25(5):579-86.

Appendix 1 Schedule of Study Procedures/Evaluations Table for Pralatrexate Treatment

	SCREENING	CYCLE 1		SUBSEQUENT CYCLES	RESPONSE	FOLLOW-UP		
Visit	**Within 21 Days Prior to Randomization**	**Dose 1**	**Doses 2-3**	**Cycle X, Dose X**	**At 8 (± 1) Weeks Post Randomization, Every 12 (± 1) Weeks Thereafter[1]**	**Initial Follow-up**	**Post-treatment Follow-up**	**Long-term FU**
Informed consent[2], Eligibility[2], Medical/surgical history	X							
Confirmation of diagnosis by independent pathology review	X[2]							
B symptoms (> 38°C, night sweats, loss > 10% of body weight)	X	X		X[3]				
IPI score	X[4]							
CHOP-based chemotherapy	X[5]							
CT scan (chest, neck, abdomen, pelvis)[6]; Whole-body PET[6]; Medical photography[6]	X				X		X	
Bone marrow biopsy/aspirate	X[7]				X[8]		X[8]	
ECG	X							
Physical examination	X				X	X	X	
ECOG Performance Status (see Appendix 3)	X					X		
Hematology[9]/Chemistry[9]/Serum β-hCG pregnancy test[10]	X	X[11]	X[11]	X[11]		X		
Vitamin B_{12}[12]	X	X	X	X				
Folic acid[12]	X	X	X	X		X		
Concomitant medications		X	X	X		X[13]		
Adverse events	X	X	X	X		X[13, 14]	X[13, 14]	
Height, weight, BSA		X[11]		X[11]				
Pralatrexate Injection[15] and pharmacokinetics[16]		X[16]	X	X[16]				
Response assessment					X[17, 18]		X[17, 18]	
Reason for discontinuation of pralatrexate						X		
Subsequent therapy						X	X	X
Survival status								X

[1]First response evaluation is 8 weeks (± 1 week) after randomization; see Section 10.6 for timing of response.[2]Can be obtained prior to the screening period in order for confirmation of pathology prior to randomization. [3]Prior to start of each new cycle. [4]Document IPI score at initial diagnosis. [5]Document dates, best response and post-CHOP response. [6]Sections 10.1 and 10.6. [7]Section 10.1. [8]Section 10.6. [9]Section 12.1.[10]For females who are not postmenopausal or surgically sterile; perform within 14 days prior to randomization.[11]Section 10.4.[12]Section 7.1. [13]Through 30 days after the last pralatrexate dose.[14]From 31 days after the last dose of pralatrexate, only record pralatrexate-related AEs and attribution. [15]Section 10.3.1.[16]Collect sample for PK (Section 12.2.1). [17]Tumor biopsy may be performed if needed to confirm response, per investigator decision. [18]Document investigator's assessment of response.

Appendix 2 Schedule of Study Procedures/Evaluations Table for Observation

	SCREENING	BASELINE VISIT	SUBSEQUENT ASSESSMENTS		RESPONSE	FOLLOW-UP		
Visit	**Within 21 Days Prior to Randomization**	**Within 3 Days Following Randomization**	**Patient Contact Week 2 of 4-week Period**	**Clinic Visit Every 28 (± 3) Days**	**At 8 (± 1) Weeks Post Randomization, Every 12 (± 1) Weeks Thereafter[1]**	**Initial FU**	**Post-treatment FU/ Response Evaluation**	**Long-term FU**
Informed consent[2], Eligibility[2], Medical/surgical history	X							
Confirmation of diagnosis by independent pathology review	X[2]							
B symptoms (> 38°C, night sweats, loss > 10% of body weight)	X	X		X				
IPI score	X[3]							
CHOP-based chemotherapy	X[4]							
CT scan (chest, neck, abdomen, pelvis)[5]; Whole-body PET[5]; Medical photography[5]	X				X		X	
Bone marrow biopsy/aspirate	X[6]				X[7]		X[7]	
ECG	X							
Physical examination	X				X	X	X	
ECOG Performance Status (see Appendix 3)	X					X		
Hematology[8]/Chemistry[8]/Serum β-hCG Pregnancy Test[9]	X	X[10]		X[10]		X		
Vitamin B_{12}[11]	X	X		X				
Folic acid[11]	X	X		X		X[12]		
Concomitant medications		X		X		X[12]		
Adverse events	X	X	X	X		X[12]		
Height and weight		X[10]						
Response assessment					X[13]		X[13]	
Reason for discontinuation of observation						X		
Subsequent therapy						X	X	X
Survival status								X

[1]First response evaluation is 8 weeks (± 1 week) after randomization; see Section 10.6 for timing of response. [2]Can be obtained prior to the screening period in order for confirmation of pathology prior to randomization. [3]Document IPI score at initial diagnosis. [4]Document dates, best response and post-CHOP response. [5]Sections 10.1 and 10.6. [6]Section 10.1. [7]Section 10.6. [8]Section 12.1. [9]For females who are not postmenopausal or surgically sterile; perform within 14 days prior to randomization. [10]Section 10.5. [11]Section 7.1. [12]Until treatment discontinuation criteria are met for patients in the Observation Arm. [13]Tumor biopsy may be performed, if needed to confirm response, per investigator decision.

Appendix 3 ECOG Performance Scale

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

Appendix 4 The International Workshop Criteria[43]

The designation of complete response (CR) requires the following (Table 1):

1. Complete disappearance of all detectable clinical evidence of disease and disease-related symptoms if present before therapy.

2a. Typically (^{18}F)fluorodeoxyglucose (FDG)-avid lymphoma: in patients with no pretreatment positron emission tomography (PET) scan or when the PET scan was positive before therapy, a post-treatment residual mass of any size is permitted as long as it is PET negative.

2b. Variably FDG-avid lymphomas/FDG avidity unknown: in patients without a pretreatment PET scan, or if a pretreatment PET scan was negative, all lymph nodes and nodal masses must have regressed on computed tomography (CT) to normal size ($\leq$ 1.5 cm in their greatest transverse diameter for nodes > 1.5 cm before therapy). Previously involved nodes that were 1.1 to 1.5 cm in their long axis and more than 1.0 cm in their short axis before treatment must have decreased to $\leq$ 1.0 cm in their short axis after treatment.

3. The spleen and/or liver, if considered enlarged before therapy on the basis of a physical examination or CT scan, should not be palpable on physical examination and should be considered normal size by imaging studies, and nodules related to lymphoma should disappear. However, determination of splenic involvement is not always reliable because a spleen considered normal in size may still contain lymphoma, whereas an enlarged spleen may reflect variations in anatomy, blood volume, the use of hematopoietic growth factors, or causes other than lymphoma.

4. If the bone marrow was involved by lymphoma before treatment, the infiltrate must have cleared on repeat bone marrow biopsy. The biopsy sample on which this determination is made must be adequate (with a goal of > 20 mm unilateral core). If the sample is indeterminate by morphology, it should be negative by immunohistochemistry. A sample that is negative by immunohistochemistry but that demonstrates a small population of clonal lymphocytes by flow cytometry will be considered a CR until data become available demonstrating a clear difference in patient outcome.

Table 1: Response Definitions for Clinical Trials

Response	Definition	Nodal Masses	Spleen, Liver	Bone Marrow
CR	Disappearance of all evidence of disease	(a) FDG-avid or PET positive prior to therapy; mass of any size permitted if PET negative (b) Variably FDG-avid or PET negative; regression to normal size on CT	Not palpable, nodules disappeared	Infiltrate cleared on repeat biopsy; if indeterminate by morphology, immunohistochemistry should be negative
PR	Regression of measurable disease and no new sites	≥ 50% decrease in SPD of up to 6 largest dominant masses; no increase in size of other nodes (a) FDG-avid or PET positive prior to therapy; 1 or more PET positive at previously involved site (b) Variably FDG-avid or PET negative; regression on CT	≥ 50% decrease in SPD of nodules (for single nodule in greatest transverse diameter); no increase in size of liver or spleen	Irrelevant if positive prior to therapy; cell type should be specified
SD	Failure to attain CR/PR or PD	(a) FDG-avid or PET positive prior to therapy; PET positive at prior sites of disease and no new sites on CT or PET (b) Variably FDG-avid or PET negative; no change in size of previous lesions on CT		
Relapsed disease or PD	Any new lesion or increase by ≥ 50% of previously involved sites from nadir	Appearance of a new lesion(s) > 1.5 cm in any axis, ≥ 50% increase in SPD of more than 1 node, or ≥ 50% increase in longest diameter of a previously identified node > 1 cm in short axis Lesions PET positive if FDG-avid lymphoma or PET positive prior to therapy	> 50% increase from nadir in the SPD of any previous lesions	New or recurrent involvement

CR = complete remission
FDG = (^{18}F)fluorodeoxyglucose
PET = positron emission tomography
CT = computed tomography
PR = partial remission
SPD = sum of the product of the diameters
SD = stable disease
PD = progressive disease

The use of the above definition for CR and that below for partial response (PR) eliminates the category of complete response unconfirmed (CRu).

The designation of PR requires all of the following (Table 1):

1. At least a 50% decrease in the sum of the product of the diameters (SPD) of up to 6 of the largest dominant nodes or nodal masses. These nodes or masses should be selected according to all of the following: they should be clearly measurable in at least 2 perpendicular dimensions; if possible they should be from disparate regions of the body; and they should include mediastinal and retroperitoneal areas of disease whenever these sites are involved.

2. No increase should be observed in the size of the other nodes, liver, or spleen.

3. Splenic and hepatic nodules must regress by ≥ 50% in their SPD or, for single nodules, in the greatest transverse diameter.

4. With the exception of splenic and hepatic nodules, involvement of other organs is usually assessable and no measurable disease should be present.

5. Bone marrow assessment is irrelevant for determination of a PR if the sample was positive before treatment. However, if positive, the cell type should be specified (eg, large-cell lymphoma or small neoplastic B cells). Patients who achieve a CR by the above criteria, but who have persistent morphologic bone marrow involvement will be considered partial responders.
   When the bone marrow was involved before therapy and a clinical CR was achieved, but with no bone marrow assessment after treatment, patients should be considered partial responders.

6. No new sites of disease should be observed.

7. Typically FDG-avid lymphoma: for patients with no pretreatment PET scan or if the PET scan was positive before therapy, the post-treatment PET should be positive in at least 1 previously involved site.

8. Variably FDG-avid lymphomas/FDG-avidity unknown: for patients without a pretreatment PET scan, or if a pretreatment PET scan was negative, CT criteria should be used.
   In patients with follicular lymphoma or mantle-cell lymphoma, a PET scan is only indicated with 1 or at most 2 residual masses that have regressed by more than 50% on CT; those with more than 2 residual lesions are unlikely to be PET negative and should be considered partial responders.

Stable disease (SD) is defined as the following (Table 1):

1. A patient is considered to have SD when he or she fails to attain the criteria needed for a CR or PR, but does not fulfill those for progressive disease (see Relapsed Disease [after CR]/Progressive Disease [after PR, SD]).

2. Typically FDG-avid lymphomas: the PET should be positive at prior sites of disease with no new areas of involvement on the post-treatment CT or PET.

3. Variably FDG-avid lymphomas/FDG-avidity unknown: for patients without a pretreatment PET scan or if the pretreatment PET was negative, there must be no change in the size of the previous lesions on the post-treatment CT scan.

Relapsed Disease (after CR)/Progressive Disease (after PR, SD) (Table 1)

Lymph nodes should be considered abnormal if the long axis is more than 1.5 cm regardless of the short axis. If a lymph node has a long axis of 1.1 to 1.5 cm, it should only be considered abnormal if its short axis is more than 1.0. Lymph nodes ≤ 1.0 x ≤ 1.0 cm will not be considered as abnormal for relapse or progressive disease.

1. Appearance of any new lesion more than 1.5 cm in any axis during or at the end of therapy, even if other lesions are decreasing in size. Increased FDG uptake in a previously unaffected site should only be considered relapsed or progressive disease after confirmation with other modalities. In patients with no prior history of pulmonary lymphoma, new lung nodules identified by CT are mostly benign. Thus, a therapeutic decision should not be made solely on the basis of the PET without histologic confirmation.

2. At least a 50% increase from nadir in the SPD of any previously involved nodes, or in a single involved node, or the size of other lesions (eg, splenic or hepatic nodules). To be considered progressive disease, a lymph node with a diameter of the short axis of less than 1.0 cm must increase by ≥ 50% and to a size of 1.5 x 1.5 cm or more than 1.5 cm in the long axis.

3. At least a 50% increase in the longest diameter of any single previously identified node more than 1 cm in its short axis.

4. Lesions should be PET positive if observed in a typical FDG-avid lymphoma or the lesion was PET positive before therapy unless the lesion is too small to be detected with current PET systems (< 1.5 cm in its long axis by CT).
   Measurable extranodal disease should be assessed in a manner similar to that for nodal disease. For these recommendations, the spleen is considered nodal disease. Disease that is only assessable (eg, pleural effusions, bone lesions) will be recorded as present or absent only, unless, while an abnormality is still noted by imaging studies or physical examination, it is found to be histologically negative.

In clinical trials where PET is unavailable to the vast majority of participants, or where PET is not deemed necessary or appropriate for use (eg, a trial in patients with MALT lymphoma), response should be assessed as above, but only using CT scans. However, residual masses should not be assigned CRu status, but should be considered partial responses.

Appendix 5 Sponsor Signature

Study Title:	A Multi-center, Randomized, Phase 3 Study of Sequential Pralatrexate Versus Observation in Patients with Previously Undiagnosed Peripheral T-cell Lymphoma Who Have Achieved an Objective Response Following Initial Treatment with CHOP-based Chemotherapy
Study Number:	PDX-017
Version Number/ Final Date:	2.1/31 Oct 2011

This clinical study protocol was subject to critical review and has been approved by Allos Therapeutics, Inc. The following signature documents this approval.

[redacted], MD

Sponsor Signatory Name (Printed)

[redacted]

Signat[redacted]

03 Nov 2011

Date

Appendix 6 Investigator Signature

Study Title:	A Multi-center, Randomized, Phase 3 Study of Sequential Pralatrexate Versus Observation in Patients with Previously Undiagnosed Peripheral T-cell Lymphoma Who Have Achieved an Objective Response Following Initial Treatment with CHOP-based Chemotherapy
Study Number:	PDX-017
Version Number/ Final Date:	2.1/31 Oct 2011

I have read the protocol, including all appendices, and I agree that it contains all necessary details for me and my staff to conduct this study as described. I will conduct this study in compliance with all applicable regulations and guidelines as stated in the protocol and other information supplied to me. I will make a reasonable effort to complete the study within the time designated.

I will provide all study personnel under my supervision with copies of the protocol and access to all information provided by Allos Therapeutics, Inc. or designees. I will discuss this material with them to ensure that they are fully informed about the drug(s) and the study.

Principal Investigator Name (Printed)	Signature
Date	Site Number