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**
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STATISTICAL ANALYSIS PLAN

PROTOCOL PDX-017

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

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1 INTRODUCTION

The purpose of this statistical analysis plan is to provide details of the statistical analyses that have been outlined within version 2.1 of the protocol for pralatrexate study PDX-017 dated 31 Oct 2011. The scope of this plan includes the interim and final analyses. The analyses detailed within this plan will help to evaluate the efficacy and safety of pralatrexate as sequential therapy in patients with peripheral T-cell lymphoma (PTCL) who have achieved an objective response following initial treatment of first-line cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP)-based regimen.

2 OBJECTIVES

2.1 Primary Objective

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.

2.2 Secondary Objective

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

3 STUDY DESIGN

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 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 (block sizes of 3) stratified by 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 administration 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 reduction to 15 mg/m^2 and 10 mg/m^2. There will be sparse sampling for pharmacokinetics (PK). 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 receive a follow-up phone call from a healthcare professional during each week 2 of 4 until a criterion for study treatment discontinuation is met for a maximum of 2 years.

All patients will receive vitamin supplementation, consisting of vitamin B_{12} 1 mg intramuscularly (IM) every (q) 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.

Patients will be followed for safety until 35 (± 5) days after the study treatment discontinuation criteria are met. Patients will be followed to determine time to progressive disease (PD) and survival for up to 7 years from randomization or until 35 (± 5) days after the last dose of pralatrexate, whichever is longer. 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 first interim analysis.

3.1 Stratification Factors

The randomization will be stratified by response per investigator at completion of CHOP-based therapy (CR vs PR).

3.2 Sample Size Considerations

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

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 overall survival (OS) rate of 32% and a 5-year failure-free survival (FFS) rate of 20% for patients with peripheral T-cell lymphoma unspecified (PTCL-U), with widely varying results for other subtypes.[1] 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.[2] 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, conducted a small study (n = 24 evaluable) evaluating CHOP plus alemtuzumab administered every 4 weeks for a total of 28 weeks.[3] 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.[4] 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.[5] Twenty-eight patients (68%) received the planned 6 courses of therapy, 6 patients (15%) 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.[6] 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-anaplastic large cell lymphoma (ALCL) PTCL patients receiving anthracycline-based chemotherapy in the first-line setting.[7] 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 progression-free survival (PFS) is approximately 20%, with a median PFS of approximately 9 months in all patients. For sample size calculations for the PDX-017 study, we assume that one-third of these 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 Observation Arm patients in PDX-017.

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, 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.

Further assuming that PFS is exponentially distributed, that the median PFS in the control group is 10 months, and that uniform enrollment will occur over 54 months, under the alternative hypothesis that HR = 0.67, the 280th event will occur approximately 48 months after the first patient is randomized. Allos will set a data cut-off date for the primary efficacy analysis in anticipation of the 280th PFS event and 128th OS event.

3.3 Interim Analyses

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 analyses 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).[8, 9] 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).[10]

There will be 1 final analysis of PFS, and 2 interim and 1 final analyses of OS. The first interim analysis of OS will be performed at the same time as the PFS analysis. 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 first analysis point, 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. If there are 128 OS events, or one-third 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.[8, 9] 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.

The stratified log-rank test (stratified by response to prior CHOP-based therapy) 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% 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.

Data Monitoring Committee

A Data Monitoring Committee (DMC) will evaluate safety after approximately 100 patients have been randomized and have completed at least 8 weeks post-randomization pralatrexate/observation or have discontinued. Safety evaluations will also be performed at the same time of each interim analysis of efficacy. All interim analyses will be performed by the DMC.

At each interim analysis for survival, the DMC will make a recommendation to Allos to either stop or continue the study. The study could be stopped for overwhelming evidence of superiority or futility according to specified boundaries. At the first interim analysis for survival, the DMC could also make the recommendation to Allos to submit a regulatory filing based on positive results of the PFS endpoint plus a trend of survival in favor of the pralatrexate treatment group. Allos may discuss the DMC's recommendations with

regulatory authorities before any such action is taken. The DMC may also make recommendations regarding adjustments to the sample size, if they are warranted.

4 STUDY ENDPOINTS AND COVARIATES

4.1 Primary Efficacy Endpoints

The co-primary efficacy endpoints are PFS and OS.

4.2 Secondary Efficacy Endpoint

The secondary efficacy endpoint is objective response (CR or PR) to pralatrexate versus observation.

The primary analyses of PFS and objective response at the first interim analysis will use the central review of tumor assessments per International Workshop Criteria (IWC) without positron emission tomography (PET). Additional analyses of PFS and objective response will use IWC, including PET, and investigators' assessment of response. Additional details regarding central review will be provided in the reviewer's charter.

4.3 Safety Endpoints

Safety endpoints include:

- Incidence and severity of treatment-emergent adverse events (AEs).
- Changes in laboratory values.

4.4 Potential Covariates

The following covariates will be considered in covariate-adjusted and other exploratory analyses:

- Stratification factor (CR vs PR to prior CHOP-based therapy);
- The International Prognostic Index (IPI) score at initial diagnosis (plus individual components as collected);
- Histology (PTCL-U vs transformed mycosis fungoides vs ALCL vs other); and
- Region.

5 ABBREVIATIONS AND DEFINITIONS

5.1 Abbreviations

AE	adverse event
ALCL	anaplastic large cell lymphoma
ATC	Anatomical Therapeutic Chemical
AUC	area under the curve
CHOP	cyclophosphamide, doxorubicin, vincristine, and prednisone
CI	confidence interval
CM	concomitant medication
C_{max}	maximum concentration
CR	complete response
CRT	case report tabulations
CTCAE	Common Terminology Criteria for Adverse Events
DMC	Data Monitoring Committee
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
ESHAP	etoposide, methylprednisolone, cytarabine, and cisplatin
FAS	full analysis set
FFS	failure-free survival
HR	hazard ratio
IM	intramuscularly
IPD	important protocol deviation
IPI	International Prognostic Index
IRT	interactive response technology
IV	intravenous
IWC	International Workshop Criteria
K-M	Kaplan-Meier
m^2	square meter
MedDRA	Medical Dictionary for Regulatory Activities
mg	milligram
NaCl	sodium chloride
ORR	objective response rate
OS	overall survival
PD	progressive disease

PDX	(RS)-10-propargyl-10-deazaaminopterin (pralatrexate)
PET	positron emission tomography
PFS	progression-free survival
PK	pharmacokinetic(s)
po	by mouth
POPPK	population PK
PR	partial response
PTCL	peripheral T-cell lymphoma
PTCL-U	peripheral T-cell lymphoma unspecified
q	every
qd	once a day
SAE	serious adverse event
SD	stable disease
SOC	system organ class
$t_{1/2}$	half-life
TLGs	tables, listings, and graphs
WHODRUG	World Health Organization Drug

5.2 Definitions

Screening Phase

The screening phase is the period between signing of informed consent and randomization.

Baseline

For efficacy assessments, baseline is defined as the last assessment prior to randomization. For safety assessments, baseline is defined as the last assessment prior to study day 1.

Study Day 1

Study day 1 is defined as the treatment start date. By convention, when known, assessments that occur on the same date as the treatment start date but that occur before treatment will be assigned as study day 0; those occurring in the same day but after treatment start will be assigned as study day 1. For patients randomized to the Observation Arm, study day 1 will be assigned to all patients who do not withdraw from the study prior to 3 days post-randomization, and will be equal to the randomization date plus 3 days.

Cycle

For patients randomized to the Pralatrexate Arm, a cycle will be calculated as the time from the first administration of pralatrexate for the given cycle to the day before the first administration of the subsequent cycle. The last cycle for a patient will be calculated as the time from the first administration of protocol-specified treatment for the given cycle plus 4 weeks or to the last dose administered within the cycle, whichever is longer.

Complete Response

CR is defined based on the IWC.[11] The same imaging method(s) used to document disease pre-randomization are to be used for post-randomization response assessments.

Partial Response

PR is defined based on the IWC.[11] The same imaging method(s) used to document disease pre-randomization are to be used for post-randomization response assessments.

Objective Response

Objective response is defined as a tumor response assessment of either CR or PR based on IWC.[11] The same imaging method(s) used to document disease during screening are to be used for subsequent response assessments.

Stable Disease

SD is defined using IWC.[11]

Progressive Disease

PD is defined using IWC.[11]

Progression-free Survival Time

PFS time is calculated as the number of days from randomization to the date of objective documentation of PD or death, regardless of cause (PD date/death date - 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 first interim analysis. Patients who have not died and who have no response assessments after baseline will be censored at randomization.

Overall Survival Time

OS time is calculated as the number of days from randomization to death (date of death - date of randomization + 1). Patients who have not died (no record of death) or are lost to follow-up will be censored at the date of last contact. Patients who withdraw from study visit participation will be followed for survival status. OS will be reported in months.

Treatment-emergent Adverse Event

A treatment-emergent AE is defined as an AE that occurs on or after study day 1 and that is a higher grade than was present just prior to study day 1.

6 ANALYSIS SUBSETS

6.1 Primary Analysis Set

The primary efficacy set, also referred to as the intent-to-treat population or full analysis set (FAS), will include 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.

6.2 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 study within 3 days of randomization. This analysis set will be used for the primary analyses of all safety endpoints.

6.3 Interim Analysis Set

There are 2 formal interim analyses planned for this study: 1 after both 280 PFS events and 128 OS events have occurred and 1 after 256 OS events have occurred. The interim analysis set will include all randomized patients who have at least 8 weeks of follow-up (ie, those who have reached the first scheduled response assessment) or who have discontinued the study prior to the first scheduled response assessment. This analysis set will only be used in the analysis of objective response rate (ORR).

6.4 Subgroup Analyses

The summaries of the primary and secondary efficacy variables and the comparisons of the treatment groups will be performed for subgroups defined by the covariates identified in Section 4.4.

Summaries of treatment-emergent AEs will be provided for subgroups defined by age (< 65 vs ≥ 65), gender, and race (if feasible).

7 DATA SCREENING AND ACCEPTANCE

7.1 General Principles

The case report tabulations (CRTs) will be built for this study. Data will be reviewed and cleaned prior to the creation of the final CRTs for this study.

7.2 Handling of Missing and Incomplete Data

Missing and incomplete data will be identified through a review of tables and listings for this study. Missing and incomplete data will be identified for investigation, and possible resolution, by Allos Data Management prior to the study database lock.

In general, missing data will be treated as missing, unless otherwise specified. Missing and incomplete dates for AEs, concomitant medications, and historical data will be imputed within this study based on the conventions described in Section 11.3. Any AE with no stop date will be considered ongoing.

7.3 Testing/Validation Plan

SAS® Version 8.2 or higher on the Windows system will be used for all CRT and tables, listings, and graphs (TLGs) creation.[12] Departmental standard macros will be used whenever appropriate for the creation of these items. These macros, as well as SAS®, have already passed a rigorous validation process and further validation will not take place, although outputs will be verified. The verification of all outputs, as well as the review of all programs and macros created specifically for this study, will be conducted as outlined in Allos Standard Operating Procedures.

8 STATISTICAL METHODS OF ANALYSIS

8.1 General Principles

Unless otherwise indicated, analyses will be performed on the FAS.

8.2 Patient Accountability

The number of patients randomized (FAS) and in the safety analysis set will be summarized by treatment group and stratum. The reason for treatment discontinuation and study discontinuation will be summarized.

The number of patients included in each analysis set will be presented.

8.3 Important Protocol Deviations

The incidence of important protocol deviations (IPDs) will be summarized for each treatment group based on the IPDs identified within the database by the clinical study team. These specific IPDs will be detailed in a separate document.

8.4 Demographic and Baseline Characteristics

Demographics (age, gender, race, geriatric age group [< 65 years old vs ≥ 65 years old]) and other baseline disease characteristics including Eastern Cooperative Oncology Group (ECOG) performance status, IPI, and histopathology will be summarized using descriptive statistics for the FAS.

8.5 Efficacy Endpoints

8.5.1 Progression-free Survival

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% CI. Strata used in these analyses will be those used for study randomization (as recorded using the interactive response technology [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.

8.5.2 Overall Survival

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 stratified Cox regression model will be used to calculate the OS HR, along with the 95% CI. 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.

It is recognized a priori that pralatrexate may be administered to Observation Arm patients subsequent to meeting treatment discontinuation criteria and thus, interpretability of the effect on OS may be confounded by crossover.

8.5.3 Objective Response Rate

The number and percentage of patients with an objective response of CR or PR, relative to disease status at the time of study entry, will be summarized by treatment group. 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 (PR + CR) 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 overall best tumor response for each treatment group.

8.5.4 Additional Analysis

The relationship of the covariates listed in Section 4.4 to PFS time, OS time, and tumor response rate will be explored using a logistic regression model for tumor response rate and Cox proportional hazards regression models (univariate and multivariate) for the time-to-event endpoints.

8.5.5 Sensitivity Analyses

A sensitivity analysis using the grouped survival methods of Prentice and Gloeckler may be performed on PFS time to assess the robustness of the results if there appears to be large differences in PD assessment patterns between the treatment groups.[13]

If there is substantial crossover of observation patients to pralatrexate use, a sensitivity analysis for OS may be conducted censoring such patients at the date of first pralatrexate use.

8.6 Safety Analyses

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 including the medical monitor and the clinical drug safety team's routine activities to ensure patients' safety.

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 treatment-emergent AEs, serious adverse events (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 Common Terminology Criteria for Adverse Events (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 that are treatment-emergent, 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 removal from study;
- AEs leading to dose reductions of the study drug;
- AEs with incidence ≥ 5%; and
- Deaths.

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 were identified and coded to the same preferred term in order to present the event in a uniform manner. Terms are presented in Table 11.1 of Appendix 11.4 (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 and ≥ 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).

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. 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 shifts in severity (CTCAE Version 4.0) from baseline for selected laboratory parameters will be presented.

Plasma Pharmacokinetics

Standard PK parameters will be estimated from the limited plasma sampling (eg, area under the curve [AUC], maximum concentration [C_{max}], and half-life [$t_{1/2}$]).

Population PK (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.

Eastern Cooperative Oncology Group Performance Status

ECOG performance status scores will be summarized for each treatment group at each assessed time-point (ie, baseline and initial follow-up). The change in scores from baseline to the initial follow-up visit will also be summarized. A listing of ECOG scores will also be provided.

Protocol-specified Treatment Administration

For the Pralatrexate Arm, descriptive statistics will be calculated for total number of cycles started, the number of doses of each protocol-specified treatment, and the cumulative dose of each protocol-specified treatment. A cycle will be considered "started" if a patient receives any protocol-specified treatment during that cycle. The number and percentage of patients with modifications (including dose reductions, dose delays, or doses withheld) from the prescribed dosing of each of the protocol-specified treatments will be summarized by type of dose modification and reason for the dose modification. The overall number of dose reductions/omissions/delays per patient will also be summarized.

Electrocardiogram

A listing of all observed electrocardiogram (ECG) results will be provided.

Concomitant Medications

The number and proportion of patients receiving each reported medication will be summarized by Anatomical Therapeutic Chemical (ATC) code and preferred term for each treatment group as coded by the World Health Organization Drug (WHODRUG) dictionary. A listing of all concomitant medications by patient will also be provided.

B-symptoms and Pruritus

Presence of B-symptoms (fever, night sweats, and weight loss), along with pruritus, will be captured at baseline and will also be collected post-randomization to determine if pralatrexate has an effect on these symptoms relative to observation. Time to onset (worsening) of any,

along with time to onset of each, will be analyzed using the Cox model for the safety analysis set. Similarly, improvement in these symptoms may also be analyzed.

9 LIST OF PLANNED TABLES, FIGURES, LISTINGS, AND APPENDICES

Table, listing, and figure shells will be created prior to the final analysis and will include information regarding the structure of each output. The following tables (Table 9.1), listings (Table 9.2), and figures (Table 9.3) could be provided.

Table 9.1. Planned Tables

Title	Description
Patient Disposition – FAS	Tabulates the disposition of all patients, including the number of patients randomized, the number of patients who receive protocol-specified treatment, the number of patients who were randomized and never received protocol-specified treatment. The reason for protocol-specified treatment discontinuation and the reason for study discontinuation will also be summarized. Long-term follow-up will be summarized based on the most recent assessment (alive, dead, lost to follow-up, consent withdrawn).
Baseline Demographics – FAS	Tabulates summary statistics of the demographics (gender, race, age, geriatric age group < 65, ≥ 65).
Baseline Characteristics – FAS	Tabulates baseline disease characteristics.
Patient Accountability – FAS	Tabulates the number of patients within each analysis set and the reason for exclusion from each analysis set.
Pralatrexate Administration – FAS (Pralatrexate Arm)	Summarizes the total number of cycles started, the number of doses received, duration of treatment, the cumulative dose of treatment, the number and percentage of patients with modifications by type of dose modification and reason for the dose modification. The number of dose reductions/ omissions/delays per patient will also be summarized.
PFS – FAS	Summary of PFS results including median (95% CI) PFS time by treatment arm, HR (95% CI), and log-rank *P* value. PFS estimates (95% CIs) from K-M curves at specific time points (eg, 6-month intervals).
OS – FAS	Summary of OS results including median (95% CI) survival time by treatment arm, HR (95% CI), and log-rank *P* value. Survival estimates (95% CIs) from K-M curves at specific time points (eg, 6-month intervals).

Title	Description
Objective Response Rate – FAS	Summary of ORR results
Subsequent Therapy – FAS	Summary of number of patients receiving subsequent therapy, including stem-cell transplant, and timing of subsequent therapy. Also includes response status when subsequent therapy was received.
Overall Summary of Treatment Emergent AEs – Safety Analysis Set	High-level summary of treatment-emergent, serious, treatment-related, and serious treatment-related AEs. Only include treatment-emergent AEs (this applies to all AE tables).
Treatment-emergent AEs – Safety Analysis Set	Summary by SOC and preferred term for each treatment group.
Treatment-emergent AEs Grouped by Similar Preferred Term – Safety Analysis Set	Summary by preferred term for each treatment group, where selected AEs are grouped by similar preferred term as indicated in the appendix.
Treatment-emergent SAEs – Safety Analysis Set	Summary by SOC and preferred term for each treatment group.
Treatment-emergent SAEs Grouped by Similar Preferred Term – Safety Analysis Set	Summary by preferred term for each treatment group, where selected AEs are grouped by similar preferred term as indicated in the appendix.
Treatment-emergent AEs Grouped by Similar Preferred Term Leading to Treatment Discontinuation – Safety Analysis Set – Pralatrexate Arm	Summary by preferred term.
Treatment-emergent AEs by Age Group – Safety Analysis Set	Summary by SOC and preferred term for each age group (< 65, ≥ 65).
Treatment-emergent AEs by Gender – Safety Analysis Set	Summary by SOC and preferred term for each gender.
Treatment-emergent AEs by Race – Safety Analysis Set	Summary by SOC and preferred term for each race (if feasible).
Time to worsening of B-symptoms/Pruritus – Safety Analysis Set	Analysis using the Cox model of time to worsening of B-symptoms/pruritus.
Hematology – Safety Analysis Set	Summary of hematology parameters at baseline, last observed value, maximum observed value, and minimum observed value. Include change from baseline to maximum observed value, minimum observed value and last observed value.
Hematology Shift in Severity – Safety Analysis Set	Tables of shifts in severity from baseline for selected laboratory parameters and selected time points.
Serum Chemistry – Safety Analysis Set	Summary of serum chemistry parameters at baseline, last observed value, maximum observed value, and minimum observed value. Include change from baseline to maximum observed value, minimum observed value, and last observed value.

Title	Description
Chemistry Shift in Severity – Safety Analysis Set	Tables of shifts in severity from baseline for selected laboratory parameters and selected time points.
ECOG Performance Status – Safety Analysis Set	Summary of ECOG performance status results at each scheduled time-point and the change from baseline.
Concomitant Medications – Safety Analysis Set	Summary of administered concomitant medications by ATC code and preferred term.

FAS = full analysis set
PFS = progression-free survival
OS = overall survival
CI = confidence interval
HR = hazard ratio
K-M = Kaplan Meier
ORR = objective response rate
AE = adverse event
SOC = system organ class
SAE = serious adverse event
ATC = Anatomical Therapeutic Chemical
ECOG = Eastern Cooperative Oncology Group

Table 9.2. Planned Listings

Title	Description
Patient Accountability	Listing of all patients and the analysis set inclusion information.
Patient Withdrawal	Listing of all patients who withdraw from the study, including the reason for withdrawal and the time of withdrawal.
Protocol-specified Treatment Administration	Listing of all patient protocol-specified treatment administration information.
Adverse Events	Listing of all reported AEs by patient.
Serious Adverse Events	Listing of all patients with at least 1 reported SAE. Only the AEs identified as serious will be included. Listing will include patient number, SOC, and preferred term of AE, date of onset, date of resolution, CTCAE Grade, action taken, and outcome.
Deaths – Safety Analysis Set	Listing of deaths that occur within 30 days of the last dose of protocol specified treatment, including cause of death.
Adverse Events Leading to Protocol-specified Treatment Discontinuation	Listing of all patients who discontinue protocol-specified treatment due to an AE. The listing will include the AE, date of onset of the AE, date of resolution of the AE, severity of AE, and the CTCAE severity grade of the AE.
Hematology	Listing of all hematology parameters.
Serum Chemistry	Listing of all serum chemistry parameters.
Electrocardiograms	Listing of all ECG results, including heart rate, QRS, PR, QT, and QT_c intervals.
Concomitant Medications	Listing of all concomitant medications including the ATC code and preferred term.
ECOG Performance Status	Listing of ECOG performance status at each assessment.
Lesion Measurements	Listing of all lesions at each time-point, including the sum of all target lesions and change from baseline and percent change from baseline.
Efficacy Parameters	Listing of all efficacy parameters for each patient, including survival time, objective response, and PFS time.

AE = adverse event
SAE = serious adverse event
QT_c = QT interval corrected for heart rate
CTCAE = Common Terminology Criteria for Adverse Events
ECG = electrocardiogram
SOC = system organ class
PFS = progression-free survival
ATC = Anatomical Therapeutic Chemical
ECOG = Eastern Cooperative Oncology Group

Table 9.3. Planned Figures

Title	Description
Progression Free Survival – FAS	Kaplan-Meier plot of PFS.
Overall Survival – FAS	Kaplan-Meier plot of OS.

FAS = full analysis set
PFS = progression-free survival
OS = overall survival

10 REFERENCES

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11 APPENDICES

11.1 Table/Figure/Listing Shells

Table, listing, and figure shells will be provided in a separate document prior to final analysis of study data.

11.2 Reference Values/Severity Grades

Severity grades for AEs are provided by the investigator. Severity grades for laboratory values will be derived programmatically based on the CTCAE grading scale – Version 4.0. For laboratory values requiring a clinical assessment for determination of severity, severity will not be derived programmatically.

11.3 Handling of Dates, Incomplete Dates, and Missing Dates for Adverse Events and Concomitant Medications

Imputation Rules for Partial or Missing Stop Dates

If a partial or complete stop date is present and the "ongoing" or "continuing" box is checked, then it will be assumed that the AE or concomitant medication stopped and the stop date will be imputed if partial.

Imputation Rules for Partial or Missing Start Dates for AEs and Concomitant Medications

Several different date variables are kept in the standard analysis datasets for AEs and concomitant medications because the start and stop dates may be incomplete and data processing requires different assumptions about incomplete dates for different purposes.

The standard AE analysis datasets have the following date variables:

aestdc – character variable for AE start date. It may be partial date (eg, 20MAY07, MAY07, 07)

aestdt – numeric date variable for AE start date. Missing for partial date.

aefstdt – first possible AE start date. For missing day of month, set to first day of month. For missing month, set to first day of year. For missing year, set to missing value.

aespdc – character variable for AE stop date. May be partial date. (See aestdc above.)

aespdt – numeric date variable for AE stop date. Missing if partial date.

aelspdt – last possible AE stop date. For missing day of month, set to last day of month. For missing month, set to last day of year. For missing year, set to missing value.

Aestrsp - first possible AE start date minus the treatment stop day. Positive values are the number of days the AE started after treatment stopped and are used to set post-treatment cutoffs.

Aestdc and aespdc are used for the main AE listings. Aefstdt and aelspdt are used for ordering records in chronological order.

The standard concomitant medication analysis datasets have the following date variables:

cmstdc – character variable for concomitant medication (CM) start date. May be partial date (eg, 20MAY07, MAY07, 07)

cmstdt – numeric date variable for CM start date. Missing for partial date.

cmfstdt – first possible CM start date. For missing day of month, set to first day of month. For missing month, set to first day of year. For missing year, set to missing value.

cmlstdt – last possible CM start date. For missing day of month, set to last day of month. For missing month, set to last day of year. For missing year, set to missing value.

cmspdc – character variable for CM stop date. May be partial date. (See cmstdc above.)

cmspdt – numeric date variable for CM stop date. Missing for partial date.

cmfspdt – first possible CM stop date. (See cmfstdt above.)

cmlspdt – last possible CM stop date. (See cmlstdt above.)

cmstrsp – first possible CM start date minus the treatment stop day. Positive values are the number of days the CM started after treatment stopped and are used to set post treatment cutoffs.

Cmstdc and cmspdc are used for the main CM listings. Cmfstdt and cmlspdt are used for ordering records in chronological order.

11.4 Preferred Terms for Adverse Events Grouped by Similar Preferred Term

Listed in Table 11.1 below are the AEs identified for the pralatrexate program. The AEs grouped by similar preferred term are evolving over time as the coding dictionary is updated (there could be changes to the already identified events) and as the pralatrexate program expands (additional AEs may be added and others may be removed). AEs included in the data summary will be based on the current list identified by the clinical study team at the time of the analysis.

Table 11.1. Adverse Events Grouped by Similar Preferred Term

Category	Preferred Term
Mucosal Inflammation	Mucosal inflammation Stomatitis Anal Inflammation Mucositis Anal Vaginal Inflammation Rectal Mucositis Esophagitis Mouth Ulceration Oral Mucosal Erythema Oesophagitis Gingivitis Balanoposthitis Pharyngeal Inflammation Pharyngitis Stomatitis Haemorrhagic
Thrombocytopenia	Thrombocytopenia Platelet Count Decreased
Anemia	Anemia Hemoglobin Decreased
Hypokalemia	Hypokalemia Blood Potassium Decreased
Neutropenia	Neutropenia Neutrophil Count Decreased
Dermatitis Exfoliative	Dermatitis Exfoliative Exfoliative Rash
Rash	Rash Dermatitis Acneiform Rash Maculo-papular Rash Macular Rash Papular Dermatitis

Category	Preferred Term
	Dry Skin Rash Erythematous Skin Disorder
Liver Function Test Abnormal	Liver Function Test Abnormal Alanine Aminotransferase Increased Alanine Aminotransferase Aspartate Aminotransferase Aspartate Aminotransferase Increased Transaminases Increased
Oedema	Oedema Oedema Peripheral Pitting Oedema
Dry Mouth	Dry Mouth Lip Dry Dry Throat
Dyspepsia	Dyspepsia Gastritis Gastrooesophageal Reflux Disease
Odynophagia	Odynophagia Oesophageal Pain
Pruritus	Pruritus Pruritus Generalized
Anorexia	Anorexia Decreased Appetite
Leukopenia	Leukopenia White Blood Cell Count Decreased