CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-468

STATISTICAL REVIEW(S)

NDA 22-468 Folotyn

Stats Division Director Memo

Concurred with primary review dated 9-3-09.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Science
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES – TEAM LEADER'S MEMO

NDA/Serial Number:	22-468/0000
Drug Name:	Folotyn™ (pralatrexate)
Indication(s):	Refractory or Relapsed Peripheral T-Cell Lymphoma (PTCL)
Applicant:	Allos
Date(s):	Submission date: 3/24/2009
	PDUFA date: 9/23/2009
	Review finish date: 9/03/2009
Review Priority:	Priority
Biometrics Division:	DBV
Primary Statistical Reviewer:	Qiang (Casey) Xu
Secondary Reviewer:	Shenghui Tang, Ph.D., Acting Team Leader
Concurring Reviewer:	Rajeshwari Sridhara, Ph.D., Deputy Director
Medical Division:	Oncology Drug Products (HFD 150)
Clinical Team:	Shakun Malik, M.D., Clinical Reviewer
	Ke Liu, M.D., Team Leader
Project Manager:	Milinda Vialpando

Keywords: PTCL, Response Rate, Progression-Free Survival, Overall Survival, Kaplan-Meier product limit

The applicant has submitted results from a Phase 2, single arm, non-randomized, open-label, multi-center, international 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 peripheral T-cell lymphoma (PTCL). There are no approved agents for treatment of relapsed or refractory PTCL, thus there is an unmet medical need for new agents in the treatment of patients with refractory or relapsed PTCL.

The primary efficacy endpoint was response rate defined as complete response (CR), complete response unconfirmed (CRu), or partial response (PR). The response was assessed based on central review of imaging and clinical data according to the International Workshop Criteria (IWC) developed by the National Cancer Institute (NCI) sponsored by International Working Group.

Enrollment of a minimum of 100 evaluable patients was planned; 115 patients were enrolled across 25 study sites in 6 countries. A total of 111 patients who had received at lease one dose of pralatrexate were analyzed for safety; and 109 treated patients whose diagnosis of PTCL was confirmed by central pathology review were included in efficacy analysis.

For further details regarding the design, data analyses, and results of this phase 2 study, please refer to the statistical review by Dr. Qiang Xu (September 3, 2009).

The response rate reported by the sponsor was 27% (95% CI: 19-36%). However, due to **the major concerns elaborated in Dr. Xu's** review, the duration of response cannot be accurately estimated by Kaplan-Meier method. Instead, the FDA proposed a response rate which included only those responses that were confirmed on a subsequent scan lasting for at least 14 weeks, and such a durable response rate was 12% (95% CI: 17-20%). An ODAC meeting was held on Sep 2, 2009 to discuss whether or not the results of this single arm trial demonstrate a favorable benefit-risk profile for pralatrexate in the treatment of patients with refractory or relapsed PTCL. The ODAC voted in favor of the accelerated approval of pralatrexate (10 vs 4) as there is an unmet need in this population, and believed that pralatrexate may produce durable response in a small subpopulation of PTCL patients.

This Team Leader concurs with the recommendations and conclusions of the statistical reviewer (Dr. Qiang Xu) of this application. The inference regarding favorable benefit-risk profile for pralatrexate in the treatment of patients with refractory or relapsed PTCL based on one single arm trial is deferred to the clinical review team.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22468	ORIG-1	ALLOS THERAPEUTICS INC	FOLOTYN

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/s/

SHENGHUI TANG
09/04/2009

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09/04/2009

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Science
Office of Biostatistics

STATISTICAL REVIEW ADDENDUM #1

NDA/Serial Number:	22-468/0000
Drug Name:	Folotyn™ (pralatrexate)
Indication(s):	Refractory or Relapsed Peripheral T-Cell Lymphoma (PTCL)
Applicant:	Allos
Date(s):	Submission date: 3/24/2009
	PDUFA date: 9/23/2009
	Review finish date: 9/03/2009
Review Priority:	Priority
Biometrics Division:	DBV
Statistical Reviewer:	Qiang (Casey) Xu
Concurring Reviewers:	Shenghui Tang, Ph.D., Acting Team Leader
	Rajeshwari Sridhara, Ph.D., Deputy Director
Medical Division:	Oncology Drug Products (HFD 150)
Clinical Team:	Shakun Malik, M.D., Clinical Reviewer
	Ke Liu, M.D., Team Leader
Project Manager:	Milinda Vialpando

Keywords: PTCL, Response Rate, Progression-Free Survival, Overall Survival, Kaplan-Meier product limit

This is a correction to typographical errors in the earlier Statistical Review and Evaluation (September 03, 2009) in Sections 1.1 and 5.2. The correct confidence interval of the response rate for those responses being confirmed to last at least 14 weeks is 7-20% (instead of 17-20% as reported earlier).

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22468	ORIG-1	ALLOS THERAPEUTICS INC	FOLOTYN

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/s/

QIANG XU
09/22/2009

SHENGHUI TANG
09/22/2009

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Science
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/Serial Number:	22-468/0000
Drug Name:	Folotyn™ (pralatrexate)
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Table of Contents

1. EXECUTIVE SUMMARY

1.1 Conclusions and Recommendations

There are no approved agents for treatment of relapsed or refractory PTCL, thus there is an unmet medical need for new agents. The response rate reported by the sponsor was 27% (95% CI: 19-36%). However, due to the major concerns elaborated in Section 3.1.5, the duration of response cannot be accurately estimated by Kaplan-Meier method. Instead, the FDA proposed a response rate for those responses being confirmed to last at least 14 weeks, and such durable response rate was 12% (95% CI: 17-20%). An ODAC meeting was held on Sep 2, 2009 to discuss whether or not the results of this single arm trial demonstrate a favorable benefit-risk profile for pralatrexate in the treatment of patients with refractory or relapsed PTCL. The ODAC voted in favor of the approval of pralatrexate (10 vs 4) as there is an unmet need in this population, and believed that pralatrexate may produce durable response in a small subpopulation of PTCL patients.

1.2 Brief Overview of Clinical Studies

This was a Phase 2, single arm, non-randomized, open-label, multi-center, international 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 peripheral T-cell lymphoma (PTCL).

The primary efficacy endpoint was response rate defined as complete response (CR), complete response unconfirmed (CRu), or partial response (PR). The response was assessed based on central review of imaging and clinical data according to the International Workshop Criteria (IWC) developed by the National Cancer Institute (NCI) sponsored by International Working Group.

Enrollment of a minimum of 100 evaluable patients was planned; 115 patients were enrolled across 25 study sites in 6 countries. A total of 111 patients who had received at lease one dose of pralatrexate were analyzed for safety; and 109 treated patients whose diagnosis of PTCL was confirmed by central pathology review were included in efficacy analysis.

1.3 Statistical Issues and Findings

The response rate according to IWC per independent central review was 27% (n = 29, 95%CI: 19-36%). Nine patients (8%) achieved a CR/CRu and 20 patients (18%) achieved a PR. Most patients (n = 20, 69% of responders) responded by the first scheduled scan. The Kaplan-Meier estimate for the median duration of response assessed by IWC for the 29 responding patients was 287 days (95% CI, **99 – not estimable), with a range of 1 –** 503 days. The Kaplan-Meier median progression-free survival (PFS) based on response **assessed by IWC was 106 days (95% CI, 51 – 143), with a range of 1 – 547 days. The** median overall survival (OS) for the efficacy analysis set was 14.5 months (95% CI, 10.6

– not estimable), with a range of 1.0 – 22.9 months. The PFS and OS results from this single arm study without comparators are considered as exploratory.

2. INTRODUCTION

2.1 Overview

Pralatrexate is a New Molecular Entity (NME) and is an analog of the widely used anti-folate, methotrexate, which has been in the market for over 40 years. The sponsor claimed in their clinical study report that compared to methotrexate, pralatrexate is more effectively taken up by cancer cells through increased affinity for the 1-carbon reduced folate carrier and more efficiently polyglutamylated by folylpolyglutamyl synthetase (FPGS).

Pralatrexate is being developed for the treatment of patients with relapsed or refractory peripheral T-cell lymphoma (PTCL). This application is based on Study PDX-008, a phase 2, single arm, non-randomized, open-label, multi-center, international 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.

There are no approved drugs and standard therapies in this proposed population. As T-cell malignancies are very uncommon and are made up of multiple varied sub-types, randomized trials in patients with relapsed or refractory disease are lacking. Therefore, for this application, in the Special Protocol Assessment (SPA) agreement, which was reached on July 28th, 2006, FDA agreed that the primary endpoint of response rate (RR) is acceptable; however, the magnitude and duration of response for approval would be a review issue.

2.2 Data Sources

The path to the CDER Electronic Document Room (EDR) is:

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3. STATISTICAL EVALUATION

3.1 Evaluation of Efficacy

3.1.1 Objectives of Study PDX-008

The primary objective of Study PDX-008 (PROPEL) was to determine the efficacy of pralatrexate with concurrent vitamin B_{12} and folic acid supplementation to patients with relapsed or refractory PTCL. Secondary objectives included safety determination and PK profile determination.

3.1.2 Study Design

This was a Phase 2, single arm, non-randomized, open-label, multi-center study designed to determine the safety and efficacy of pralatrexate when administered concurrently with vitamin B_{12} and folic acid supplementation to patients with relapsed or refractory PTCL

A 2-stage Simon design was employed for this study. The null and alternative response rates were chosen to be 15% and 27%, respectively. With type I error of 2.2% and power of 84.3%, at least 4 out of 35 evaluable patients had to experience a response (defined as complete response [CR], complete response unconfirmed [CRu], or partial response [PR]) in Stage 1 for the study to proceed to Stage 2. In Stage 2, 65 additional evaluable patients were to be enrolled. At least 23 out of the total evaluable 100 patients were to have experienced a response to determine that pralatrexate had true activity in this patient population.

Patients received pralatrexate (30 mg/m^2) with concurrent vitamin B_{12} and folic acid supplementation. One cycle of pralatrexate therapy was 7 weeks in duration and consists of 6 weekly doses of pralatrexate IV push over 3-5 minutes, followed by 1 week of rest.

The primary efficacy endpoint was response rate (CR+CRu+PR), which was assessed based on central review of imaging and clinical data according to the International Workshop Criteria (IWC) developed by the National Cancer Institute (NCI) sponsored International Working Group. Evaluation of response was to be performed within 7 days prior to the projected first dose of the second cycle and then within 7 days prior to the projected first dose of every even-numbered subsequent cycle (ie, prior to cycles 4, 6, 8, etc). Patients were also to have response assessed by PET imaging.

Secondary efficacy endpoints included duration of response (DOR), progression-free survival (PFS), and overall survival (OS). Duration of response was defined as the number of days between the date of first tumor response assessment of objective response to the time of the first tumor response assessment of PD or death due to any cause (date of first PD assessment or death - date of first objective response assessment + 1). This was calculated only for those patients who had an objective response. PFS was calculated as the number of days from study day 1 to the date of PD per central radiology review or death, regardless of cause (date of PD or death - study day 1 + 1) and was estimated using

the product-limit estimator. OS time was calculated as the number of days from study day 1 to death (date of death - date of enrollment + 1) and was estimated using the product-limit estimator. Details of the analyses for all efficacy variables are provided in Sections 3.1.4 and 3.1.5.

Safety was assessed at every study visit by evaluating changes in hematology and biochemistry parameters, and by monitoring the incidence, severity, and relationship of adverse events (AEs) to pralatrexate. AEs were graded using the NCI Common Toxicity Criteria for Adverse Events (CTCAE), Version 3.0. Physical examinations were performed and changes recorded on week 3 of cycle 1, within 7 days of the first dose of each subsequent cycle, and at the safety follow-up visit.

After discontinuing protocol treatment, patients were to attend the safety follow-up visit 35 (± 5) days after the last dose of pralatrexate. Patients were also to attend routine follow-up visits, which occurred every 3 months (± 2 weeks) after the safety follow-up visit until progressive disease (PD) was determined or subsequent treatment for T-cell lymphoma had been initiated. Once PD had been documented or subsequent treatment for T-cell lymphoma was initiated, routine follow-up visits were no longer required and patients were to be followed for survival and subsequent treatment for T-cell lymphoma every 6 months for a total duration of 2 years after the first dose of pralatrexate. Table 3.1.2 presents the schedule of events for study and follow-up visits.

Table 3.1.2 Schedule of Visits

		CYCLE 1				SUBSEQUENT CYCLES			FOLLOW-UP			
Visit	21 Days Prior to Pralatrexate Dose 1	10 Days Prior to Pralatrexate Dose 1 through Cycle 1, Dose 1	24, 48, 72 hours post-end pralatrexate Dose 1	Weeks 2-6	Additional Procedures Weeks 3 & 6	Within 7 Days Prior to Projected Dose Day 1	Dose 1	Weeks 2-6	Early Study Termination Visit	Safety FU Visit	Routine FU	Survival & Subsequent Treatment FU
Eligibility Criteria/Informed Consent/Privacy Authorization	X											
Medical/Surgical History	X											
Document Histopathology[1]	X[1]											
Unilateral bone marrow biopsy and aspirate	X[2]					X[4]			X[4,5]	X[6]	X[4]	
CT of Chest, Neck, Abdomen, Pelvis (CNAP)	X					X[4]			X[4,5]	X[6]	X[4]	
Other imaging of disease site other than CNAP[3]	X[3]					X[3,4]			X[3,4,5]	X[3,6]	X[3,4]	
PET (base of skull to mid-thigh)	X[2]					X[4]			X[4,5]	X[6]	X[4]	
Medical photography with ruler measurement of cutaneous lesions[3]	X[3]					X[3,4]			X[3,4,5]	X[3,6]	X[3,4]	
Record Prior Treatment and Response for T-cell Lymphoma	X											
Record Medications		X		X			X	X	X	X		
Record Baseline Symptoms		X										
Record AEs/Attribution		X		X			X	X	X	X[7]	X[7]	X[7]
Record ECOG Performance Status	X				X[8]	X			X	X		
Physical Examination	X				X[8]	X			X	X		
Record Height in cm		X[9]										
Record Weight in kg		X[9]				X						

*From Table 9.4 in the sponsor's clinical study report

3.1.3 Patient Disposition

3.1.3.1 Patient Enrollment

A total of 130 patients were screened and 115 patients were enrolled in this study. Patients were enrolled between 24 Aug 2006 and 14 Apr 2008 across 25 study sites, 15 sites in the US (80 patients), 8 in Europe (26 patients), and 2 in Canada (9 patients). A patient was considered evaluable if he/she received at least one dose of pralatrexate and met the major inclusion criterion that the diagnosis of eligible PTCL histopathological subtype needed to be confirmed by central pathology review.

Four out of 115 enrolled patients were never treated with pralatrexate, and the safety population was constituted by 111 patients who received at least one dose of pralatrexate. An additional 2 patients were treated in the study but excluded from the efficacy analysis set as they were considered not evaluable due to their histopathology assessment by central pathology review. Therefore, the efficacy analysis set consists of all evaluable 109 patients. Table 3.1.3.1 presents patient populations by country.

Table 3.1.3.1 Patients Enrolled by Country

	Enrolled Patients (N=115)	Safety Patients (N=111)	Efficacy Patients (N=109)
USA	80 (70%)	76 (68%)	76 (70%)
France	17 (15%)	17 (15%)	15 (14%)
Canada	9 (8%)	9 (8%)	9 (8%)
Italy	5 (4%)	5 (5%)	5 (5%)
Belgium	3 (3%)	3 (3%)	3 (3%)
UK	1 (1%)	1 (1%)	1 (1%)

3.1.3.2 Treatment Discontinuation and Study Termination

The date of the database cut-off (no further CRF or query data entry) for all analyses was 19 Jan 2009. As of the data cut-off date, 9 patients remained on therapy. The reasons for discontinuing study treatment and for terminating the study are displayed in Table 3.1.3.2. Most patients (n = 64 in safety analysis set / 63 in efficacy analysis set, 58% each) discontinued study treatment due to the development of PD. Twenty-five patients (23%) in the safety analysis population discontinued treatment due to AEs. One patient (Patient 084) was lost to follow-up, for whom the last contact date was 19 May 2008, approximately 1 month after discontinuation of study treatment due to PD.

Table 3.1.3.2 Reasons for Treatment and Study Discontinuation

	Safety Analysis Set (N = 111) n (%)	Efficacy Analysis Set (N = 109) n (%)
Number of patients discontinuing study treatment	102 (92)	100 (92)
Reason for discontinuing study treatment		
Disease progression	64 (58)	63 (58)
Adverse event	25 (23)	24 (22)
Investigator decision	7 (6)	7 (6)
Patient decision	5 (5)	5 (5)
Other	1 (< 1)	1 (< 1)
Number of patients terminating study	52 (47)	51 (47)
Reason for terminating study		
Death	48 (43)	47 (43)
Other	2 (2)	2 (2)
Patient withdrew consent	1 (< 1)	1 (< 1)
Lost to follow-up	1 (< 1)	1 (< 1)

*From Table 10.1 in the sponsor's clinical study report

3.1.3.3 Patient Demographics

Table 3.1.3.3 summarizes patient demographics for the 111 treated patients. There were 76 males (68%) and 35 (32%) females treated, with a mean age of 57.7 years (range 21-85). The majority of patients were White (n = 80, 72%).

Table 3.1.3.3 Patient Demographics

	Value	Safety Analysis Set (N = 111)
Gender n (%)	Male	76 (68)
	Female	35 (32)
Race n (%)	White	80 (72)
	Black	14 (13)
	Asian	6 (5)
	Hispanic	9 (8)
	Other	1 (< 1)
	Unknown	1 (< 1)
Age (years) n (%)	< 65	71 (64)
	≥ 65	40 (36)
	Median	59.0
	Mean	57.7
	Std Dev	15
	Min-Max	21-85
	N Missing	0
Weight (kg)	Mean	77.3
	Std Dev	18.0
	Min-Max	48.7-158.0
	N Missing	0
Height (cm)	Mean	169.2
	Std Dev	10.4
	Min-Max	132.1-203.2
	N Missing	1

* From Table 11.1 in the sponsor's clinical study report

Forty-three patients (39%) entered with an ECOG performance status of 0, 49 patients (44%) had an ECOG performance status of 1, and the remaining 19 patients (17%) had an ECOG performance status of 2.

3.1.3.4 Patient Histopathology

Patient histopathology is summarized by central review for all treated Patients in Table 3.1.3.4. The majority in the full analysis population (n = 59, 53%) had PTCL-unspecified (PTCL-U, also referred to as PTCL not-otherwise specified [PTCL-NOS]) according to central review assessment. Seventeen (15%) patients had ALCL, primary systemic type, 13 (12%) had angioimmunoblastic T-cell lymphoma, and 12 (11%) had transformed mycosis fungoides. Two treated patients (Patients 042, 063) were determined to be ineligible due to incorrect histopathology per central review, and are excluded from the efficacy analysis set.

Table 3.1.3.4 Histopathology per Central Review

		Safety Analysis Set (N = 111) n (%)
Histopathology per Central Review	PTCL-unspecified	59 (53)
	Anaplastic large cell lymphoma, primary systemic type	17 (15)
	Angioimmunoblastic T-cell lymphoma	13 (12)
	Transformed mycosis fungoides	12 (11)
	Blastic NK lymphoma (with skin, lymph node, or visceral involvement)	4 (4)
	Other	2 (2)
	T/NK-cell lymphoma-nasal	2 (2)
	Extranodal peripheral T/NK-cell lymphoma unspecified	1 (<1)
	Adult T-cell leukemia/lymphoma (HTLV 1+)	1 (<1)

*From Table 11.2 in the sponsor's clinical study report

Previous tissue blocks were reviewed by the central pathologists in 86 patients, some of which were more than 3 years old. Only 25 patients had tumor re-biopsy after last treatment to confirm progression prior to study enrollment.

3.1.3.5 Prior Treatment

Patients were heavily pretreated prior to entering this study. The median number of prior therapies was 3 (range 1-13). Most prior therapies were systemic treatments (median = 3, range 1 – 12). Twenty-one patients (19%) had received ≥5 prior systemic therapies before entering this study. The most common prior therapy was CHOP, which 78 patients (70%) had received. Eighteen patients (16%) had undergone a transplant prior to study entry.

Table 3.1.3.5 Prior Systemic Therapy

	n (N=111)	Percent
1	23	21
2	30	27
3	23	21
4	14	13
≥5	21	19
Median (range)	3.0 (1 -12)	

The response rate of the most recent prior therapy in 91 evaluable patients who had at least two prior therapies (including the most recent one) was 30% (11 CRs + 16 PRs).

3.1.4 Applicant's Efficacy Results

The primary efficacy endpoint was response rate, and secondary efficacy endpoints were duration of response, PFS, and OS. All efficacy endpoints were analyzed using the evaluable patient population (N=109).

3.1.4.1 Response Rate

The response rate per central review was 27% (n = 29), as presented in Table 3.1.4.1. Response rate was defined as number of responding patients divided by number of 109 evaluable patients, where a patient was considered a responder if she/he had obtained either a CR, a CRu, or a PR. Response was assessed on the basis of clinical, radiological, and pathological criteria. In addition to the primary analysis of response by IWC, response was also analyzed by combining IWC and results from a whole-body PET scans (from the base of the skull to mid-thigh). Assessment of response was also collected from the local investigators. Table 3.1.4.1 provides a summary of best overall response for all 3 methods of assessment, IWC, IWC plus PET scans, and investigator.

According to IWC, 9 patients (8%) achieved a CR/CRu and 20 patients (18%) achieved a PR. Twenty-four patients (22%) had SD. Eight (7%) patients with SD had a time to progression of ≥21 weeks (which coincides with the cycle 3 response assessment). Imaging for assessment of response was not required to be performed until the completion of cycle 1; 14 patients (13%) did not have a response assessment as they stopped treatment with pralatrexate prior to completion of cycle 1 and had no response assessment. Two (2%) other patients with their only response assessments in cycle 1 were not evaluable for response by IWC due to insufficient materials provided to central review. Five of the patients who responded (17% of all responders) to pralatrexate per IWC did not have evidence of response to any prior therapy. For the overall efficacy analysis set, 26 patients (24%) did not have evidence of response to any prior therapy.

Fourteen responders (48% of all responders) per IWC did not have evidence of response to their most recent prior therapy. Sixty-nine (63%) patients in the overall efficacy analysis set did not have evidence of response to their most recent prior therapy.

All but 2 patients who were deemed responders by IWC or IWC plus PET were also considered responders by investigator assessment. There were 15 patients for whom the investigator considered the patient to have a CR or PR but central review deemed as not having a response and listed 8 of those patients as PD and 7 as SD.

Table 3.1.4.1 Summary of Best Response

		Efficacy Analysis Set (N=109)		
		n	(%)	(95% CI)
Best Response per Central Review - IWC	CR+CRu+PR	29	(27)	(19, 36)
	CR	7	(6)	
	CRu	2	(2)	
	PR	20	(18)	
	SD	24	(22)	
	PD	40	(37)	
	UE	2	(2)	
	Missing: off-treatment in cycle 1	14	(13)	
Best Response per Central Review - IWC+PET	CR+CRu+PR	26	(24)	(16, 33)
	CR	14	(13)	
	PR	12	(11)	
	SD	20	(18)	
	PD	31	(28)	
	UE	18	(17)	
	Missing: off-treatment in cycle 1	14	(13)	
Best Response per Local Investigator	CR+CRu+PR	42	(39)	(29, 48)
	CR	15	(14)	
	CRu	4	(4)	
	PR	23	(21)	
	SD	22	(20)	
	PD	40	(37)	
	UE: off-treatment in cycle 1	5	(5)	

CI = confidence interval
IWC = International Workshop Criteria
CR = complete response
CRu = complete response unconfirmed
PR = partial response
SD = stable disease
PD = progressive disease
UE = unevaluable
PET = positron emission tomography

* From Table 11.5 in the sponsor's clinical study report

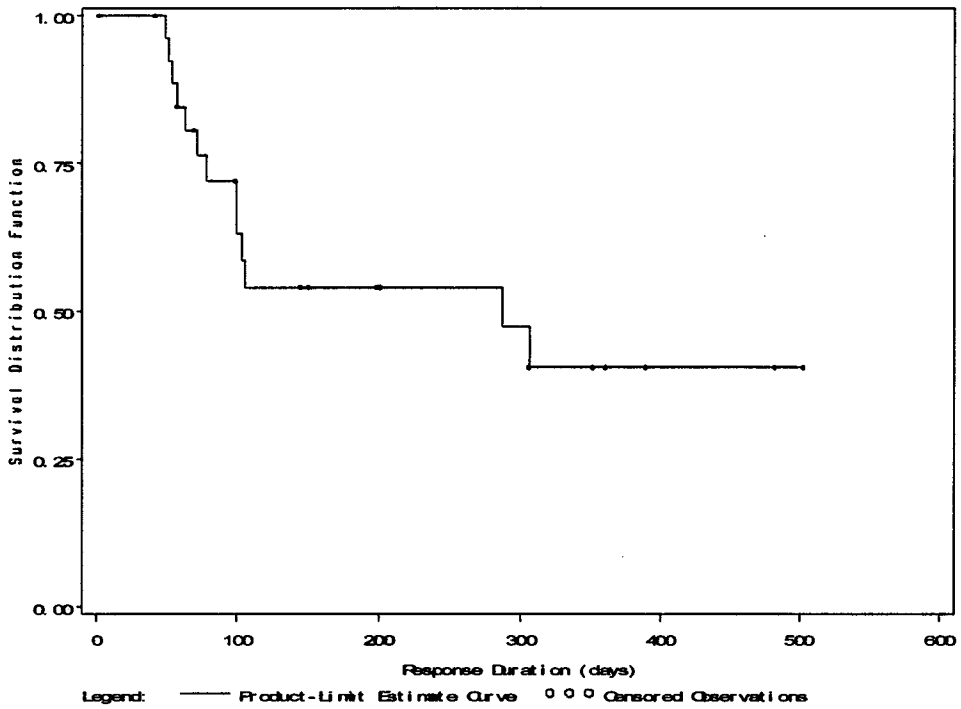
3.1.4.2 Duration of Response

The duration of response based on response assessed by IWC, estimated by the Kaplan-Meier method, is presented in Figure 3.1.4.2. The median duration of response assessed by IWC based on 29 responding patients, was **287 days (95% CI, 99 – not estimable),** with a range of 1-503 days. The median duration of response assessed by IWC plus PET based on 26 responding patients, was 311 days **(95% CI, 106 – not estimable), with a** range of 1-482 days. The median duration of response assessed by local investigator based on 42 responding patients was 246 days (95% CI, 135-372), with a range of 1-500 days. Summary of median duration of response by three assessment methods is presented in Table 3.1.4.2.

Table 3.1.4.2 Summary of Median Duration of Response

	# of Responders	KM Estimates (days)	95% CI (days)	Range (days)
IWC	29	287	99, NE	1-503
IWC+PET	26	311	106, NE	1-482
Investigator	42	246	135, 372	1-500

Figure 3.1.4.2 Kaplan-Meier Estimate of Duration of Response per IWC

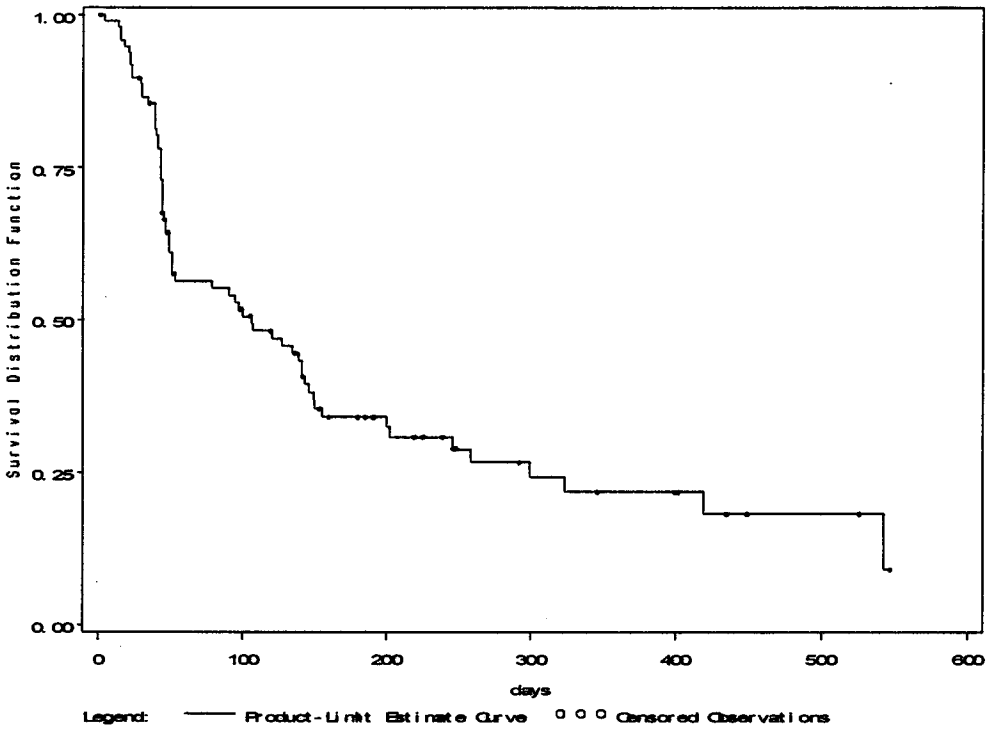


Sixteen (55%) of the responders were censored because they had not yet progressed at the time of the data cut-off date (n = 8, 28%) or they received anti-cancer therapy before PD was assessed (n = 7, 24%), and 1 patient (3%) terminated study follow-up for response. Four patients (14%) were censored due to transplant. Thirteen (45%) patients had an event of either PD (n = 12, 41%) or death (n = 1, 3%).

3.1.4.3 Progression-Free Survival

PFS based on response assessed by central review using IWC, estimated by the Kaplan-Meier method, is presented in Figure 3.1.4.3. Forty-two (39%) of the efficacy analysis set were censored for PFS (based on response assessed by central review using IWC) because they had not yet progressed at the time of the data cut-off date (n = 13, 12%) or they received anti-cancer therapy before PD was assessed (n = 28, 26%), and 1 patient (1%) terminated study follow-up for response. Four patients (4%) were censored due to transplant. Sixty-seven (61%) patients had an event of either PD (n = 62, 57%) or death (n = 5, 5%).

Figure 3.1.4.3 Progression-Free Survival per IWC

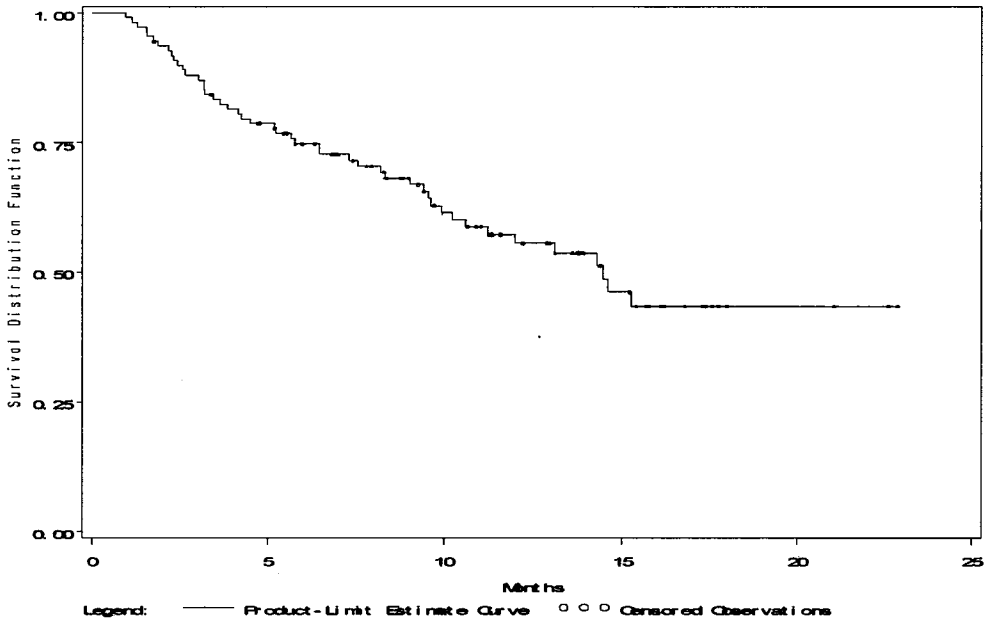


The median PFS based on response assessed by IWC, estimated by the Kaplan-Meier **method, was 106 days (95% CI, 51 – 143), with a range of 1 – 547 days.**

3.1.4.5 Overall Survival

The Kaplan-Meier estimate on overall survival is presented in Figure 3.1.4.5. The median OS for the efficacy analysis set was 14.5 **months (95% CI, 10.6 – not estimable), with a** range of 1.0-22.9 months. Sixty-two patients (57%) were censored for OS because they were still alive at the time of the data cut-off date. Forty-seven (43%) of patients had died, most (n = 42, 89%) due to progression of their PTCL.

Figure 3.1.4.5 Kaplan-Meier Estimate of Overall Survival



3.1.4.6 Time to Response

Most patients (n = 19, 66% of responders) responded within cycle 1 based on assessment by IWC. Table 3.1.4.6 presents the time to first and best response.

Table 3.1.4.6 Time to Response

		Efficacy Analysis Set (N = 109)
Central Review - IWC (Number of Responders = 29)		
Time to First Response (days)	Median	45
	Min-Max	37-349
Time to Best Response (days)	Median	51
	Min-Max	37-399
Central Review - IWC+PET (Number of Responders = 26)		
Time to First Response (days)	Median	48
	Min-Max	37-249
Time to Best Response (days)	Median	117
	Min-Max	37-254
Local Investigator (Number of Responders = 42)		
Time to First Response (days)	Median	50
	Min-Max	38-154
Time to Best Response (days)	Median	51
	Min-Max	38-338

*From Table 11.6 in the sponsor's clinical study report

3.1.4.7 Subsequent Therapy

Seventy-five (69%) patients went on to treatment with a subsequent therapy after discontinuing treatment with pralatrexate. Table 3.1.4.7 summarizes the types of subsequently therapy patients received as their first therapy after discontinuing pralatrexate treatment. Combination chemotherapy (with or without a platinum agent) was the treatment regimen selected most (n = 33, 30%), followed by single-agent chemotherapy (n = 14, 13%).

Table 3.1.4.7 Type of Subsequent Therapy

	Subsequent Therapy for PTCL	Efficacy Analysis Set (N=109) n (%)
Initial Subsequent Treatment for PTCL	Non platinum-containing multi-agent chemotherapy	19 (17)
	Platinum-containing multi-agent chemotherapy	14 (13)
	Single-agent chemotherapy	14 (13)
	Systemic investigational agents	8 (7)
	Stem cell transplant	6 (6)
	Radiation therapy with or without systemic treatment	4 (4)
	Steroids alone	4 (4)
	CHOP	2 (2)
	Other	2 (2)
	Bexarotene	1 (<1)
	Denileukin diftitox	1 (<1)
Subsequent Stem Cell Transplant at Any Time		13 (12)

CHOP = cyclophosphamide, doxorubicin, vincristine, prednisone
* From Table 11.8 in the sponsor's clinical study report

3.1.5 The Reviewer's Efficacy Analysis

This reviewer confirmed the applicant's analyses in this clinical report based on the datasets submitted by the applicant. After reviewing this application, the reviewer has the following major concerns: (1) uncertainty in duration of response, (2) uncertainty regarding response determination, and (3) limited exposure to pralatrexate.

3.1.5.1 Duration of Response

Tumor status in 99% of patients enrolled was evaluated by the imaging scans. The study design dictated that the tumor responses were evaluated by imaging scans at the end of cycle 1 and every 14 weeks subsequently. Patients were designated as responders if their tumor shrinkage met the IWC criteria seen from a given scan. Note that there were no confirmatory scans after the initial response designation according to IWC.

Figure 3.1.5.1 demonstrates individual duration of response in 29 responders with one line representing each responder. The solid lines represent those responders who had progressed or died, and the dashed lines stand for responders who were censored due to subsequent therapies, study termination or at the time of data cut-off. From the plot, it can be seen that most responses occurred at or before first scan (20 of 29 patients, 69%). Responses were identified based on scheduled or unscheduled scans.

The censored responders (4 transplants, 3 on other drugs, 1 study termination, and 8 on-goings) may have different health status from those who have already progressed or died, creating informative censoring in this study. Furthermore, the large assessment interval (14 weeks) made it difficult to determine the true time when a response or a progression occurred. Therefore, the Kaplan-Meier estimate for median duration of response may be biased and give prolonged response duration.

The FDA preferred using durable response rate, defined as the proportion of those responses last at least 14 weeks and confirmed by subsequent scans, to predict the clinical benefit of pralatrexate in this population. The 13 solid lines represent 12 PDs and 1 death. Only 2 patients had more than 2 scans before disease progression, represented by the two long solid lines. In other words, 11 responses had a duration of response less than 14 weeks, and were not able to be confirmed by subsequent scans. In addition, 5 responders were censored within 14 weeks represented by short dashed lines. Out of these 5 censored responders, 2 responders with duration of response of 1 day had no subsequent imaging scans due to off-study treatment. Therefore, only 13 (6 CRs, 1 CRu, and 6 PRs) of 29 responders (45%) were confirmed by the subsequent scans and sustained till 14 weeks. The resulting durable response rate is presented in Table 3.1.5.1.

Figure 3.1.5.1 Individual Duration of Response

Table 3.1.5.1 FDA Analysis of PDX-008

	N = 109
Responses ≥ 14 weeks CR+CRu+PR 95% CI	 13 (12%) 7-20%
CR	6 (6%)
CRu	1 (1%)
PR	6 (6%)

3.1.5.2 Response Determination

Response in this trial was assessed on the basis of clinical and radiological evaluation and pathological review of bone marrow. The imaging modalities used were CT or MRI scans, and medical photography was used for cutaneous lesions. PET scans were used for exploratory analysis only. Two radiologists reviewed all images for a subject during this study. If there was a disagreement between central readers 1 and 2 of the independent imaging review committee, responders needed adjudication of their responses by a third reviewer. The uncertainty of response determination in this study was reflected in high adjudication rate (52%) in responders, presented in Table 3.1.5.2.

Table 3.1.5.2 Adjudication Rate in Response Determination

	# of Adjudicated Patients	Percent (%)
Efficacy Set (N=109)	37	34
Responders (N=29)	15	52

3.1.5.3 Treatment Exposure

Limited treatment exposure is another concern of this study. Table 3.1.5.3 demonstrates the number of non-zero doses administrated by the time of responding in 29 responders. Four out of 29 responders (14%) received no more than 3 doses before responding. It is difficult to attribute the causal effect of pralatrexate to disease response in these cases.

Table 3.1.5.3 Number of Doses before Response

# of Non-Zero Doses	Patients (N=29)	Percent	Cumulative Percent
1	1	3	3
2	1	3	7
3	2	7	14
4	4	14	28
≥5	21	73	100

Table 3.1.5.4 demonstrates the total number of treatment cycles in 109 evaluable patients. Forty-five patients (41%) were off the treatment before cycle 2; and 85 patients (78%) were off the treatment before cycle 4.

Table 3.1.5.4 Treatment Cycles in Efficacy Set

# of Cycles	Patients	Percent	Cumulative Percent
1	45	41	41
2	21	19	61
3	19	17	78
4	7	6	84
≥5	17	17	100

3.2 Evaluation of Safety

Please refer to Clinical Review.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race and Age

Table 4.1.1 presents response rate by gender, age and race, respectively, showing that the efficacy of pralatrexate was consistent in different gender, age and race groups. The response rate varied from 24% to 31%. The results in Table 4.1 were not controlled for multiple comparisons and thus only served for exploratory presentation.

Table 4.1.1 Response Rate by Gender, Age and Race per IWC

Subgroup	Characteristics	N	CR+CRu+PR	RR % (95% CI)
Gender	Male	74	20	27 (17-39)
	Female	35	9	26 (12-43)
Age*	< 65	70	17	24 (15-36)
	≥ 65	39	12	31 (17-48)
Race	White	79	21	27 (17-38)
	Non-White	30	8	27 (12-46)

Table 4.1.2 presents the durable confirmed response rate (≥14 weeks) by gender, age and race, respectively. The resulting response rates varied from 9% to 20%. Due to the limited number of durable responses and multiple comparisons, these results thus only served for exploratory presentation.

Table 4.1.2 Durable Response Rate by Gender, Age and Race per IWC

Subgroup	Characteristics	N	CR+CRu+PR (≥14 weeks)	RR % (95% CI)
Gender	Male	74	8	11 (5-20)
	Female	35	5	14 (5-30)
Age*	< 65	70	6	9 (3-18)
	≥ 65	39	7	18 (8-34)
Race	White	79	7	9 (4-17)
	Non-White	30	6	20 (8-39)

4.2 Other Special/Subgroup Populations

Table 4.2.1 presents response rate by country, number of prior treatments and prior methotrexate use, with estimates from 24% to 30%, suggesting consistent effect of pralatrexate across these subgroups.

Table 4.2.1 Response Rate by Country and Prior Treatment per IWC

Subgroup	Characteristics	N	CR+CRu+PR	RR % (95% CI)
Country	USA	76	19	25 (16-36)
	Non-USA	33	10	30 (16-49)
Prior Treatment	≤ 3	67	19	28 (18-41)
	> 3	42	10	24 (12-39)
Prior Methotrexate	Yes	21	5	24 (8-47)
	No	88	24	27 (18-38)

Table 4.2.2 presents confirmed durable response rate by country and number of prior treatments, with estimates from 9% to 18%.

Table 4.2.2 Durable Response Rate by Country and Prior Treatment per IWC

Subgroup	Characteristics	N	CR+CRu+PR (≥14 weeks)	RR % (95% CI)
Country	USA	76	7	9 (4-18)
	Non-USA	33	6	18 (7-35)
Prior Treatment	≤ 3	67	9	13 (6-24)
	> 3	42	4	10 (3-23)

5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

This was a Phase 2, single arm, non-randomized, open-label, multi-center, international study with response rate as the primary endpoint and duration of response, progression-free survival and overall survival as the secondary endpoints 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. One cycle of pralatrexate therapy was 7 weeks in duration and consisted of 6 weekly doses of pralatrexate administered via intravenous (IV) push over 3-5 minutes, followed by 1 week of rest.

Enrollment of a minimum of 100 evaluable patients was planned; 115 patients were enrolled. A total of 111 patients who had received at lease one dose of pralatrexate were analyzed for safety; and 109 treated patients whose diagnosis of PTCL was confirmed by central pathology review were included in efficacy analysis.

There were 76 males (68%) and 35 (32%) females treated, with a mean age of 57.7 years (range 21 - 85). The majority of patients were white (n = 80, 72%). The majority of

patients (n = 59, 53%) had PTCL-unspecified according to central review assessment. Seventeen (15%) patients had ALCL, primary systemic type; 13 (12%) had angioimmunoblastic T-cell lymphoma; and 12 (11%) had transformed mycosis fungoides.

The response rate according to IWC per independent central review was 27% (n = 29, 95%CI: 19-36%). Nine patients (8%) achieved a CR/CRu and 20 patients (18%) achieved a PR. Most patients (n = 20, 69% of responders) responded by the first scheduled scan. When IWC was supplemented with PET scans for assessment of response, the response rate was 24% (n = 26, 95%CI: 16-33%) with 14 CRs (13%) and 12 PRs (11%). The response rate based on the assessments of the local investigators was 39% (n = 42, 95%CI: 29-48%), with 19 CRs/CRu's **(17%) and 23 PRs (21%).**

The Kaplan-Meier estimate for the median duration of response assessed by IWC for the 29 responding patients was 287 days (95% CI, **99 – not estimable), with a range of 1 –** 503 days. However, the Kaplan-Meier estimate in this scenario was not representative due to the informative censoring and large assessment interval as discussed in Section 3.1.5.1. The median duration of response based on response assessed by IWC plus PET for the 26 responding patients was 311 days **(95% CI, 106 – not estimable), with a range of 1 – 482 days. The median duration of** response based on response assessed by local investigator for the 42 responding patients **was 246 days (95% CI, 135 – 372), with a range of 1 – 500 days.**

The Kaplan-Meier median PFS based on response assessed by IWC was 106 days (95% **CI, 51 – 143), with a range of 1 – 547 days.** The median PFS based on response assessed **by IWC plus PET was 141 days (95% CI, 79 – 246), with a range of 1 – 542 days. The** median PFS based on response assessed by local investigator **was 121 days (95% CI, 77 – 148 days), with a range of 1 – 549 days.**

The median OS for the efficacy analysis **set was 14.5 months (95% CI, 10.6 – not estimable), with a range of 1.0 – 22.9 months.** Over half of the patients (n = 62, 57%) were censored for OS because they were still alive at the time of the data cut-off date.

The PFS and OS results from this single arm study without comparators are considered as exploratory.

5.2 Conclusions and Recommendations

There are no approved agents for treatment of relapsed or refractory PTCL, thus there is an unmet medical need for new agents. The response rate reported by the sponsor was 27% (95% CI: 19-36%). However, due to the major concerns elaborated in Section 3.1.5, the duration of response cannot be accurately estimated by Kaplan-Meier method. Instead, the FDA proposed a response rate for those responses being confirmed to last at least 14 weeks, and such durable response rate was 12% (95% CI: 17-20%). An ODAC meeting was held on Sep 2, 2009 to discuss whether or not the results of this single arm trial demonstrate a favorable benefit-risk profile for pralatrexate in the treatment of

patients with refractory or relapsed PTCL. The ODAC voted in favor of the approval of pralatrexate (10 vs 4) as there is an unmet need in this population, and believed that pralatrexate may produce durable response in a small subpopulation of PTCL patients.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22468	ORIG-1	ALLOS THERAPEUTICS INC	FOLOTYN

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