

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
22-468

MEDICAL REVIEW(S)

NDA 22-468 Folutyn

MOTL memo

Concurred with MOR dated 9-17-09

Addendum to Clinical and Statistical Reviews for NDA 022468

Clinical Reviewer: Shakun Malik

Statistical Reviewer: Casey Xu

Date: September 22, 2009

1) Review of 120-day Safety Update

AMENDMENT NO: 12 submitted on July 14, 2009

This update was submitted by the applicant (Allos) and included new events reported from 20 Jan 2009 through 01 Apr 2009 (data cut-off for the 120-day safety update) of the clinical study report for PDX-008.

During this time period, no patient deaths occurred while on treatment with pralatrexate or within 30 days of the last dose and no patients experienced serious adverse events (SAEs).

Adverse Events (AEs) regardless of causality were collected for all patients on-study and events considered possibly, probably, or definitely related to pralatrexate therapy were collected during the post-treatment period. Nine patients remained on treatment between the data cut-off of the original NDA and this update. However, the safety profile remains unchanged with very few added events. Under the grouped term of mucosal inflammation, 79 patients (71%) had an event, which was the most frequently occurring AE when analyzed by grouping similar preferred terms. The severity was Grade 1-2 (n = 55, 50%), Grade 3 (n = 20, 18%), and Grade 4 (n = 4, 4%). Nausea occurred in 46 patients (41%), and the severity was Grade 1-2 (n = 42, 38%) or Grade 3 (n = 4, 4%), with no Grade 4 events. Thrombocytopenia occurred in 45 patients (41%), and the severity was Grade 1-2 (n = 9, 8%), Grade 3 (n = 15, 14%), and Grade 4 (n = 21, 19%). None of the thrombocytopenic events were associated with Grade 3 or 4 bleeding events. Fatigue occurred in 40 patients (36%), and the severity was Grade 1-2 (n = 33, 30%), Grade 3 (n = 5, 5%), and Grade 4 (n = 2, 2%). Under the grouped term of anemia, 38 patients (34%) had an event; 19 patients (17%) had Grade 1-2, 17 patients (15%) had Grade 3, and 2 patients (2%) had Grade 4.

**Table 1 Adverse Events --- 120-Day Safety Update
Adverse Events in PDX-008 Occurring in ≥ 10% of Patients**

Preferred Term	PDX-008 (N=111)									
	Grade 1		Grade 2		Grade 3		Grade 4		Total	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Any AE	6	(5)	23	(21)	48	(43)	34	(31)	111	(100)
Mucosal inflammation (grouped)	23	(21)	32	(29)	20	(18)	4	(4)	79	(71)
Nausea	29	(26)	13	(12)	4	(4)	0	(0)	46	(41)
Thrombocytopenia (grouped)	1	(1)	8	(7)	15	(14)	21	(19)	45	(41)
Fatigue	21	(19)	12	(11)	5	(5)	2	(2)	40	(36)
Anaemia (grouped)	4	(4)	15	(14)	17	(15)	2	(2)	38	(34)
Constipation	27	(24)	10	(9)	0	(0)	0	(0)	37	(33)
Pyrexia	25	(23)	9	(8)	1	(1)	1	(1)	36	(32)
Oedema (grouped)	20	(18)	12	(11)	1	(1)	0	(0)	33	(30)
Cough	27	(24)	4	(4)	1	(1)	0	(0)	32	(29)
Epistaxis	27	(24)	2	(2)	0	(0)	0	(0)	29	(26)
Vomiting	18	(16)	8	(7)	2	(2)	0	(0)	28	(25)
Neutropenia (grouped)	0	(0)	5	(5)	14	(13)	8	(7)	27	(24)
Diarrhoea	14	(13)	8	(7)	2	(2)	0	(0)	24	(22)
Dyspnoea	10	(9)	3	(3)	8	(7)	0	(0)	21	(19)
Hypokalaemia (grouped)	10	(9)	3	(3)	4	(4)	1	(1)	18	(16)
Anorexia (grouped)	13	(12)	1	(1)	3	(3)	0	(0)	17	(15)
Rash	11	(10)	6	(5)	0	(0)	0	(0)	17	(15)
Pruritus (grouped)	7	(6)	7	(6)	2	(2)	0	(0)	16	(14)

8 deaths were reported in PDX-008 trial.

7 were attributed to PD and 1 death was related to neutropenia.

Reviewer's comments:

- *No additional deaths were reported from this 120-day safety update.*
- *Other toxicity profiles were found to be similar to the original NDA submission.*
- *The most frequently occurring treatment-emergent AEs regardless of causality that occurred in all patients treated with pralatrexate were mucosal inflammation, fatigue, nausea, and epistaxis.*

2) Review of deaths reported in other PDX clinical trials:

There were a total of 29 deaths reported in other pralatrexate clinical trials. These include: **progressive disease (18)**, neutropenia with sepsis (5) stomatitis and mucositis (2), cardiopulmonary arrest (2), respiratory failure and failure to thrive 1 each.

3) Review of Updated Duration of Response

The applicant submitted AMENDMENT NO: 29 on September 21,2009 updating the duration of responses for 7 responders (Table 2).

Table 2 Updated Response Duration

Patient No.	NDA DOR (days)	Updated DOR (days)
036	482	535
041	351	519
052	360	464
057	389	487
086	98	196
105	198	299
113	200	267

The median duration of responses were not changed by this update. The range of the response duration was updated to 1-535 days (1-503 days in the original submission).

The updated response rate according to IWC per independent central review was 28% (n = 30, 95%CI: 19-37%). Ten patients (9%) achieved a CR/CRu and 20 patients (18%) achieved a PR. The Kaplan-Meier estimate for the median duration of response assessed by IWC for the 30 responding patients was 287 days (95% CI, 99 – 535), with a range of 1 – 535 days. The FDA proposed response rate for those responses being confirmed to last at least 14 weeks was 13% (95% CI: 7-21%) with 6 patients (6%) achieving a CR/CRu and 8 patients (7%) achieving a PR. The Kaplan-Meier estimate for the median duration of durable response assessed by IWC for the 14 patients was 535 days (95% CI, 306– 535), with a range of 100 – 535 days. The updated response rate and duration of response was consistent with the initial results.

Table 3 Updated Response Analysis per Independent Central Review (IWC)

	Evaluable Patients (N=109)		Median Duration of Response	Range of Duration of Response
	N (%)	95% CI		
Overall Response				
CR+CRu+PR	30 (28)	19, 37	287 days (9.4 months)	1-535 days
CR/CRu	10 (9)			
PR	20 (18)			
Responses ≥ 14 weeks				
CR+CRu+PR	14 (13)	7, 21	535	100-535 days
CR/CRu	6 (6)			
PR	8 (7)			

This update showed that the responses in these 7 patients were durable. The applicant did not update the duration of response for patient 35 (CRu).

Due to the late submission and the impending action date in two days, this updated response duration was not included in the package insert labeling.

Application
Type/Number

Submission
Type/Number

Submitter Name

Product Name

NDA-22468

ORIG-1

ALLOS
THERAPEUTICS
INC

FOLOTYN

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

SHAKUNTALA M MALIK
09/24/2009

KE LIU
09/24/2009

CLINICAL REVIEW

Application Type	NDA
Application Number(s)	022468
Priority or Standard	Priority
Submit Date	March 23, 2009
Received Date	March 23, 2009
PDUFA Goal Date	September 23, 2009
Division / Office	DDOP/OODP/CDER
Reviewer Name	Shakun Malik, MD
Review Completion Date	September 16, 2009
Established Name	Pralatrexate
(Proposed) Trade Name	FOLOTYN
Therapeutic Class	NME
Applicant	Allos Therapeutics, Inc.
Formulation	Intravenous
Dosing Regimen	30 mg/m ² intravenous push weekly for 6 weeks followed by 1 week rest
Indication	Single agent for the treatment of patients with relapsed or refractory peripheral T-cell lymphoma
Intended Population	Adults US patients with relapsed or refractory PTCL

Table of Contents

1	RECOMMENDATIONS/RISK BENEFIT ASSESSMENT	6
1.1	Recommendation on Regulatory Action	6
1.2	Risk Benefit Assessment.....	6
1.3	Recommendations for Postmarket Risk Evaluation and Mitigation Strategies ...	6
1.4	Recommendations for Postmarket Requirements and Commitments	7
2	INTRODUCTION AND REGULATORY BACKGROUND	7
2.1	Peripheral T-cell lymphoma (PTCL)	7
2.2	Product Information	9
2.3	Currently available treatment for PTCL	10
2.4	Availability of Proposed Active Ingredient in the United States	11
2.5	Important Safety Issues with Consideration to Related Drugs.....	11
2.6	Summary of Presubmission Regulatory Activity Related to Submission	12
2.6	Other Relevant Background Information	14
3	ETHICS AND GOOD CLINICAL PRACTICES.....	18
3.1	Submission Quality and Integrity	18
3.2	Compliance with Good Clinical Practices	18
3.3	Financial Disclosures.....	18
4	SIGNIFICANT EFFICACY/SAFETY ISSUES RELATED TO OTHER REVIEW DISCIPLINES	19
4.1	Chemistry Manufacturing and Controls	19
4.2	Clinical Microbiology.....	19
4.3	Preclinical Pharmacology/Toxicology	19
4.4	Clinical Pharmacology	19
4.4.1	Mechanism of Action:.....	20
4.4.2	Pharmacodynamics.....	21
4.4.3	Pharmacokinetics.....	21
5	SOURCES OF CLINICAL DATA.....	21
5.1	Tables of Studies/Clinical Trials	21
5.1.1	Study PDX-02-078	28
5.1.2	Study PDX-008	29
5.1.4	Study PDX-009	29
5.2	Review Strategy	29
5.3	Discussion of Individual Studies/Clinical Trials.....	30
5.3.1	Study Design.....	30
5.3.2	Study Drug administration and schedule.....	31
5.3.3	Study Endpoints.....	31
5.3.4	Eligibility criteria	31
5.3.5	Duration of treatment	34
5.3.6	Primary endpoint evaluation.....	35

5.3.7	Criteria for Primary Endpoint.....	36
5.3.8	Evaluations for Secondary Endpoints(s).....	38
5.3.9	Major protocol amendments.....	38
6	REVIEW OF EFFICACY.....	39
6.1	Indication.....	39
6.2	Methods.....	40
6.3	Demographics and baseline characteristics.....	40
6.3.1	Demographics.....	40
6.3.2	Histology.....	40
6.3.3	Source of tumor specimen used for histologic diagnosis.....	42
6.3.4	Prior PTCL therapies.....	42
6.4	Subject disposition.....	43
6.5	Primary endpoint results.....	43
6.5.1	Issues with the primary endpoint results.....	44
6.5.2	Clinical reviewer's analysis of complete responders (CRs).....	46
6.5.3	Clinical Reviewer's conclusion on the primary endpoint of ORR.....	47
6.5.4	Exploratory analyses for the primary endpoint.....	47
6.6	Analysis of Secondary Endpoints.....	48
6.6.1	Duration of response.....	48
6.6.2	PFS and OS.....	49
6.6.3	Subsequent therapies.....	51
6.6.4	Analysis of Clinical Information Relevant to Dosing Recommendations.....	51
7	REVIEW OF SAFETY.....	52
7.1	Methods.....	52
7.1.1	Studies/Clinical Trials Used to Evaluate Safety.....	52
7.1.2	Categorization of Adverse Events.....	52
7.2	Adequacy of Safety Assessments.....	52
7.2.1	Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations.....	52
7.2.2	Explorations for Dose Response.....	53
7.3	Major Safety Results.....	53
7.3.1	Deaths.....	53
7.3.2	Nonfatal Serious Adverse Events.....	56
7.3.3	Dropouts and/or Discontinuations.....	56
7.3.4	Significant Adverse Events.....	56
7.3.5	Electrocardiograms (ECGs).....	57
7.5	Other Safety Explorations.....	58
7.5.1	Dose Dependency for Adverse Events.....	58
7.5.2	Drug-Demographic Interactions.....	59
7.5.4	Drug-Disease Interactions.....	60
7.5.5	Drug-Drug Interactions.....	60
7.6	Additional Safety Evaluations.....	61
7.6.1	Human Reproduction and Pregnancy Data.....	61

Clinical Review
Shakun Malik, MD
NDA 022468
Folotyn (Pralatrexate)

7.6.2 Pediatrics and Assessment of Effects on Growth	61
8 APPENDICES	61
8.1 Literature Review/References.....	61
8.2 Labeling Recommendations	62
8.3 Advisory Committee Meeting.....	62

Table of Tables

Table 1 Disclosable Financial Arrangements	20
Table 2 Tables of Studies/Clinical Trials	21
Table 3 Schedule of Events	34
Table 4 The International Workshop Response Criteria (IWC).....	36
Table 5 Major Protocol Amendments	38
Table 6 Patient Characteristics	40
Table 7 Histology.....	41
Table 8 Prior Therapies.....	42
Table 9 Reasons for Discontinuing Study Treatment	43
Table 10 Applicant-reported ORR	44
Table 11 FDA Analysis of PDX-008 Response Results	45
Table 12 Clinical Reviewer’s Analysis of Complete Responders (CRs)	46
Table 13 Response analysis according to tumor histology type	47
Table 14 Response analysis according to prior therapy	48
Table 15 Clinical Reviewer’s Analysis of Duration of Response	50
Table 16 Subsequent therapies after pralatrexate treatment	51
Table 17 Reasons for Treatment Discontinuation	56
Table 18 AEs Occurring in \geq 20% of Patients (N = 111)	57

Table of Figures

Figure 1 Overall Survival by PTCL Subtypes.....	9
Figure 2 Overall Survival of Patients with PTCL according to IPI Scores	9
Figure 3 Structural Formula of Pralatrexate	10
Figure 4 Other Therapies for Patients with Relapsed or Refractory PTCL	11
Figure 5 Study design schema	30
Figure 6 Imaging Scheduling Evaluation Schema.....	35
Figure 7 Applicant’s Kaplan-Meier Estimate of Duration of Response	49

1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

I recommend an accelerate approval for pralatrexate as a single agent in the treatment of patients with relapsed or refractory peripheral T-cell lymphoma (PTCL).

My recommendation is based on the following:

- There is no therapy approved or standard of care for patients with relapsed or refractory PTCL.
- The trial showed a response rate (RR) of 27% in 109 evaluable patients. Twelve percent (12%) of responses lasted \geq 14 weeks with 6% complete responses (CRs).
- These patients were previously heavily pretreated with 16% of patients who had received peripheral stem cell transplant prior to the pralatrexate treatment.
- This application was discussed in the Oncology Drug Advisory Committee (ODAC) September 2009 meeting. The committee members voted 10 Yes to 4 No to the question "Are the response rate and duration of response results were "reasonably likely" to predict for clinical benefit?"

1.2 Risk Benefit Assessment

Although the trial supporting this application was a single arm, non-randomized trial, the magnitude of pralatrexate treatment, i.e., 27% response rate with 12% of responses lasting 14 weeks or more, most likely predicts clinical benefit in patients with PTCL.

The most common grade 3 and 4 toxicities were thrombocytopenia, mucositis and neutropenia. The toxicity profile of pralatrexate treatment was found to be acceptable, not different from that of methotrexate, a similar drug of the class of folate analogue metabolic inhibitor.

Taken together, the data submitted in this application demonstrated a favorable benefit:risk profile for pralatrexate treatment in patients with relapsed or refractory PTCL.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

Not applicable

1.4 Recommendations for Postmarket Requirements and Commitments

To confirm the clinical benefits of pralatrexate treatment and to fulfill the requirement for the recommended accelerated approval, the following postmarket requirement are recommended:

Submit clinical protocols for at least two trials to confirm the clinical benefit of pralatrexate treatment in patients with peripheral T-cell lymphoma (PTCL) with trial end dates and projected dates for the submission of final study reports.

1. One trial can be the proposed randomized trial of maintenance treatment with pralatrexate in previously untreated patients with PTCL who have demonstrated a response to CHOP or a CHOP-like regimen.
2. Another trial could be a randomized controlled trial of single agent pralatrexate vs. an appropriate control in patients with relapsed or refractory PTCL.

2 Introduction and Regulatory Background

2.1 Peripheral T-cell lymphoma (PTCL)

Peripheral T-cell lymphoma (PTCL) is a heterogeneous array of aggressive non-Hodgkin's lymphomas (NHLs), accounting for approximately 10-15% of all newly diagnosed NHL (1, 2). There are significant geographical and racial differences in incidence. The incidence is higher in the Caribbean and East Asia and has been attributed to viral etiology. Human T-cell leukemia virus (HTLV-1) infection has been implicated in the pathogenesis of adult T-cell leukemia/lymphoma in Japan and in the Caribbean basin (2, 3). The current annual prevalence of PTCL in the U.S. is estimated to be approximately 9,500 patients. The World Health Organization classification recognizes 13 different types of mature T-cell neoplasms, grouped into leukemic, extranodal, and nodal types (5).

WHO classification of mature T-cell and NK-cell neoplasms

Cutaneous

- Mycosis fungoides
- Sezary syndrome
- Primary cutaneous CD30+ T-cell LPDs
- Primary cutaneous anaplastic LC lymphoma
- Primary cutaneous $\gamma\delta$ T-cell lymphoma
- Primary cutaneous CD8+ aggressive epidermotropic lymphoma
- Primary cutaneous CD4+ small/med T-cell lymphoma

Leukemic

- T-cell prolymphocytic leukemia

- T-cell large granular lymphocytic leukemia
- Adult T-cell leukemia/lymphoma

Nodal

- Angioimmunoblastic T-cell lymphoma
- Anaplastic large-cell lymphoma, ALK pos
- Anaplastic large-cell lymphoma, ALK neg
- Peripheral T-cell lymphoma, NOS

Extranodal

- Systemic EBV+ T-cell childhood LPD
- Hydroa vaccineforme-like lymphoma
- Extranodal NK/T-cell lymphoma, nasal type
- Enteropathy-associated T-cell lymphoma
- Hepatosplenic T-cell lymphoma
- Subcutaneous panniculitis-like T-cell lymphoma

Subsets of cutaneous T cell lymphoma and mycosis fungoides with a long natural history and T-cell leukemia (that are highly aggressive) are not usually included in the classification of PTCL. Similarly, NK-cell malignancies are considered separate from PTCL. PTCL Not Otherwise specified or (NOS) nodal subtype is the most common subtype of peripheral T cell lymphoma in the US and Europe (5)

In general, PTCL has worse prognosis compared to their B-cell counterparts. In addition, the natural history and outcome of PTCL patients varies widely with the histological subtypes. Patients with anaplastic large cell ALK⁺ has better survival than those with any other subtypes (4, 6). The international T-cell lymphoma project, the largest lymphoma study conducted so far, indicated that 5-year overall survival in patients with PTCL-NOS is approximately 34%, whereas patients with anaplastic large cell Alk⁺ subtype is reported to be approximately 70% as seen in Figure 1(4).

International prognostic index (IPI) scores also predict patient survival: Patients with a higher International prognostic Index (IPI) score have a shorter survival (Figure 2). The IPI is calculated by adding the number of risk factors including age, serum lactate dehydrogenase (LDH), Eastern Group Cooperative Oncology Group (ECOG) performance status, disease stage, and extra-nodal involvement (7, 8).

Figure 1 Overall Survival by PTCL Subtypes

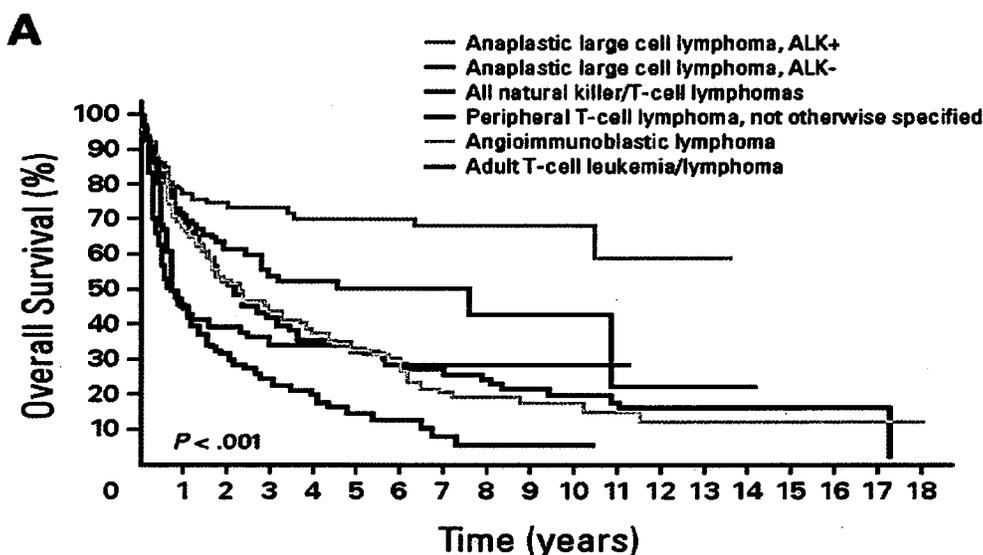
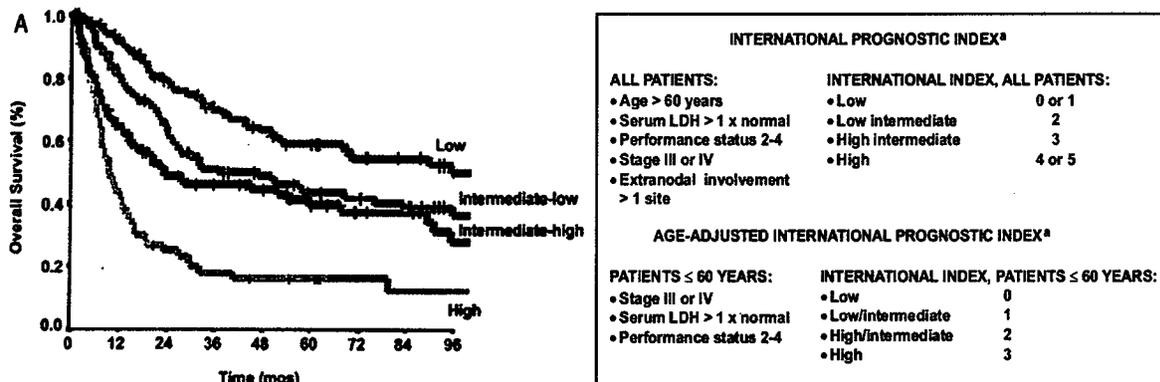


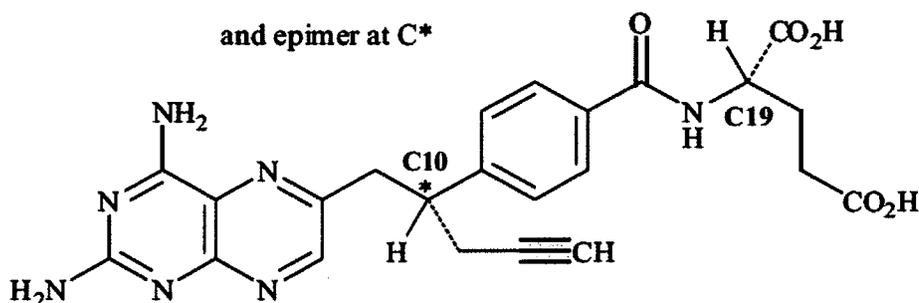
Figure 2 Overall Survival of Patients with PTCL according to IPI Scores



2.2 Product Information

Pralatrexate is a New Molecular Entity (NME) and is structural analogue of the antifolate methotrexate. It contains 2 asymmetric carbon centers at C10 and C19. Pralatrexate is an approximately 1:1 racemic mixture of the R and S configurations at the C10 chiral center and > 98.0% of the S-isomer at the C19 chiral center. The 2 diastereomers are referred to as follows: PDX-10a {(2S)-2-[[4-[(1S)-1-[(2,4-diaminopteridin-6-yl)methyl]but-3-ynyl]benzoyl]amino]pentanedioic acid} and PDX-10b {(2S)-2-[[4-[(1R)-1-[(2,4-diaminopteridin-6-yl)methyl]but-3-ynyl]benzoyl]amino]pentanedioic acid}.

Figure 3 Structural Formula of Pralatrexate



2.3 Currently available treatment for PTCL

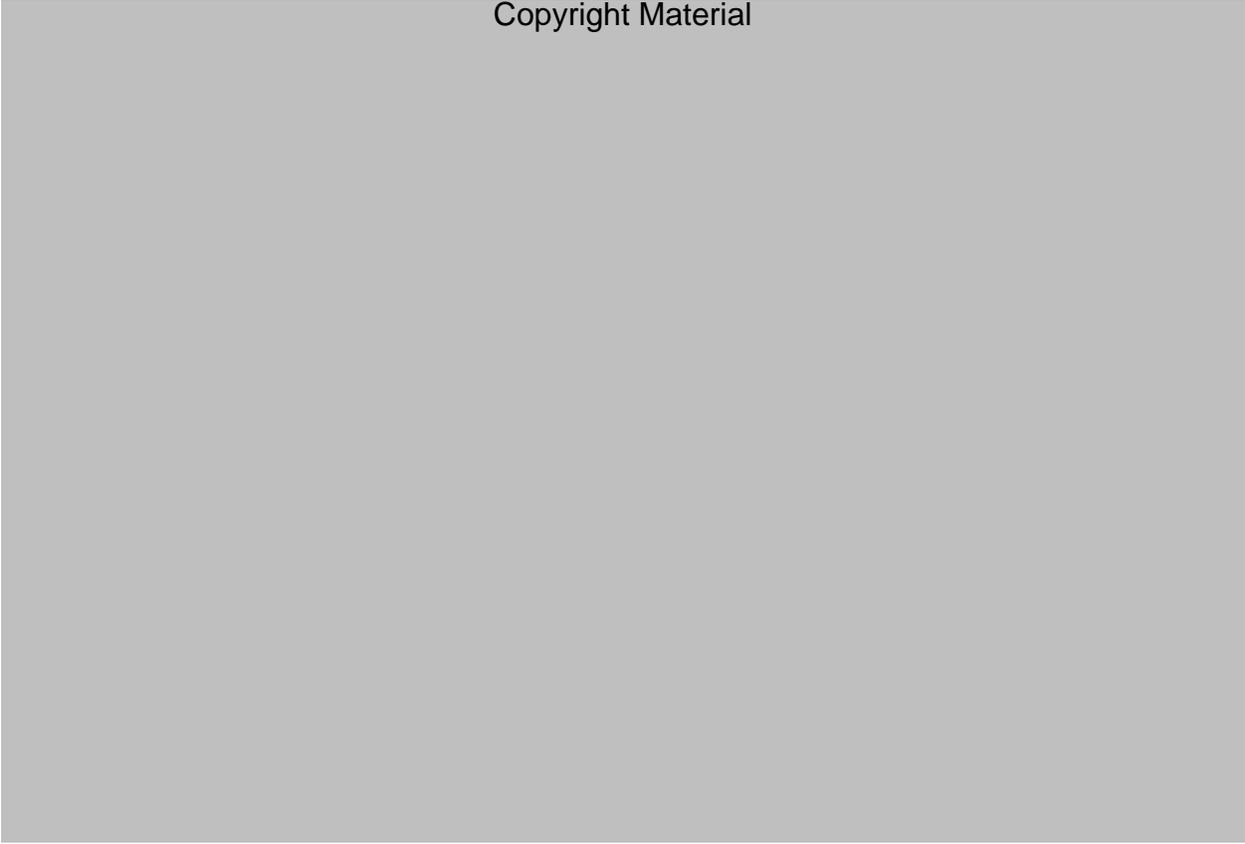
Currently, there are no therapies specifically approved for PTCL; however, there are a multitude of therapies available to these patients. Randomized trials are lacking. Most published series are difficult to interpret partly because of the inclusion of heterogeneous subtypes and because of small number of patients enrolled. Prognosis after conventional treatment is poor. The impact of more aggressive treatment approaches such as stem cell transplant (SCT) has not been determined yet, as most series are retrospective.

CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) is the most commonly used initial therapy. More aggressive combination chemotherapy regimens, such as hyper-CVAD (fractionated cyclophosphamide, vincristine, doxorubicin, dexamethasone, methotrexate, cytarabine) and VIP-ABVD (etoposide, ifosfamide, cisplatin, doxorubicin, bleomycin, vincristine, dexamethasone), have not been shown to be superior to CHOP and were significantly more toxic (9, 10). For relapsed/refractory disease, salvage combination chemotherapy followed by auto SCT is typically offered, but few patients experience a durable benefit from this approach (11, 12).

Multiple phase 1/2 trials have been conducted using agents such as pentostatin, gemcitabine, alemtuzumab, denileukin diftitox, bortezomib, nelarabine, and lenalidomide for the treatment of patients with relapsed or refractory PTCL. The number of patients enrolled to these trials ranged from 2 to 27 with responses reported from 12.5% to 75% (13) (Figure 4). Pralatrexate was reported to result in an overall response rate of 62% CR rate of 56% in a phase 1 trial of 16 patients with PTCL (14).

Figure 4 Other Therapies for Patients with Relapsed or Refractory PTCL

Copyright Material



The authors at that time stated that an international confirmatory trial of these data was ongoing (14).

2.4 Availability of Proposed Active Ingredient in the United States

Please refer to CMC review

2.5 Important Safety Issues with Consideration to Related Drugs

Safety assessments were performed on 111 enrolled patients who had received at least one dose of pralatrexate in the trial PDX-008 that supports the current submission. Mucositis and thrombocytopenia were the most common adverse events (AEs). AEs were the reason for dose reductions in 31%, dose omission in 69% and treatment withdrawal in 22% of the patients. These adverse events were not different from those seen with the same class drug methotrexate. No specific safety issues were identified.

2.6 Summary of Presubmission Regulatory Activity Related to Submission

On August 17, 1998, IND # 052604 was activated to study Pralatrexate in humans, and the IND sponsorship was transferred from Memorial Sloan Kettering to Allos Therapeutics, INC. in December 23, 2002.

In February 2006, the sponsor communicated to FDA that a positive signal was identified in a subset of lymphoma patients (PTCL) in a phase 1 trial. The trial was a dose escalation trial conducted at Memorial Sloan Kettering Cancer Center, NY, in patients with lymphoproliferative malignancies. The pralatrexate was administered on every other week (QOW) and weekly (QW) schedules in patients **with non-Hodgkin's and Hodgkin's Lymphoma**. The maximum tolerated dose (MTD) of pralatrexate (PDX) was determined to be 30 mg/m² weekly intravenous(IV) push for 6 weeks with 1 week rest (one cycle). The dose-limiting toxicity (DLT) was primarily hematologic, including thrombocytopenia. Among the 16 patients with T-cell lymphoma (TCL), who completed at least 2 cycles of therapy, 10 were reported as having had a major remission with an overall response rate (ORR) of 62%; 9 complete remissions (CR) and 1 partial remission (PR). The results were reported at the annual 2006 ASH meeting. The authors at that time stated that an international confirmatory trial of these data was ongoing.

FDA responded that a phase 1 study cannot be the major trial for approval. The phase 2 part of the study could potentially be acceptable, if the population for which the approval will be sought is pre-specified and the population of interest is homogenous and well-defined, with an adequate sample size.

February 2006 Meeting minutes are shown below:

QUESTIONS for DISCUSSION with FDA RESPONSE and DECISIONS REACHED:

Clinical

1. Does the FDA concur that the positive signal identified in a subset of lymphoma patients (peripheral T-cell lymphoma [PTCL]) in the ongoing clinical study 02-078 conducted at Memorial Sloan-Kettering Cancer Center is in a patient population which could be pursued for marketing approval? Clinical Study 02-078 is a dose escalation Phase 1 study to determine a maximum tolerated dose (MTD).

FDA Response:

Please clarify your question. The patients that were studied in 02-078 represent a variety of different diseases. In addition, it is not clear whether you propose that the phase 2 part of 02-078 is intended to be a registration trial. It appears that additional studies are warranted and that PTCL is a potential population.

A phase 1 study cannot be the major trial for approval. The phase 2 part of the study could potentially be acceptable, if the population for which the approval will be sought is prespecified. The population of interest should be homogenous and well-defined, with an adequate sample size. We suggest that you include diseases with similar natural history. Please provide a rationale for the patient population proposed for inclusion in the phase 2 portion of the study. Please submit a special protocol assessment if you intend to proceed with this protocol as your registration study.

Discussion Point: The sponsor clarified that study 02-078 was not intended to be a registration trial. FDA recommends that the patient population be as homogenous as possible e.g., similar prior therapy and prognosis.

2. Does the FDA agree that the efficacy endpoints outlined in the Phase 2 protocol would be acceptable to support a New Drug Application (NDA) of pralatrexate administered as a single agent to patients with PTCL?

FDA Response: Yes, if the efficacy endpoints are objective. Clinical evaluations will not be acceptable as part of response evaluation. All lymph nodes, spleen and liver can be imaged and skin lesions should be photographed with a ruler. There should be a centralized radiologic assessment. The magnitude and duration of responses should be convincing and will be a review issue. In a single arm study, results for time to event endpoints such as progression-free survival and overall survival are not interpretable.

Discussion Point: Allos plans to submit an SPA for study 008. FDA recommends that Allos includes a plan for a standardized objective response evaluation in the SPA submission. FDA suggested considering a randomized superiority trial design with physician's choice as the comparator (limited number of choices should be defined). Alternatively, an add on trial design can be considered (e.g., Gemcitabine + PDX vs. Gemcitabine alone). In a randomized trial time to event endpoints such as PFS and OS could be evaluated.

Allos intends to utilize PET scans as part of the response evaluation. FDA stated that the primary response evaluation should be based on objective criteria such as CT scans but would be interested in seeing PET results. The proposed role of the PET scans will be evaluated during the review of an SPA submission. Please include a complete statistical analysis plan with the SPA submission.

3. If the answer to Question 2 is positive, does the FDA agree that a 20% response rate (complete response and partial response) and a 3-6 months' duration of response is a sufficiently long duration to establish a clinical benefit (efficacy) in this heavily pre-treated patient population?

FDA Response: The magnitude and duration of response that will suffice for an approval will be a review issue. This application will likely be discussed in an ODAC meeting.

4. There are many subcategories of T-cell lymphoma within PTCL, each having various incidence/frequency rates. Would the FDA consider a positive study in these patients to be representative of expected effectiveness across all subcategories of T-cell lymphoma included in the protocol?

FDA Response: No. You should attempt to enroll a more homogenous population to your phase 2 study.

Discussion: Discussed under question #1 above.

5. Should the proposed Phase 2 be submitted under the Special Protocol Assessment (SPA) procedure? (This protocol will be included in the briefing package to be submitted 1 month prior to the meeting date.)

FDA Response: Yes, please submit the protocol and a sample of CRF for a special protocol assessment.

Please also consider having an independent central response review for the study and submit a charter for review.

(End of Meeting Minutes)

In July 2006, under the special protocol assessment (SPA), FDA recommended that a minimum of 100 patients be studied to support efficacy and safety in the NDA. FDA recognized that although peripheral T cell lymphoma is a heterogeneous disease, it is also a rare one. The eligibility criteria as proposed to include a mixture of histologies were acceptable. FDA agreed that the primary endpoint of ORR was acceptable; however, the magnitude of response rate, duration of response and safety profile required to support approval would be a review issue.

FDA also indicated that the primary analysis should be based on patients with central pathology review and confirmation of the diagnosis of PTCL at screening. A secondary analysis could include patients who did not have sufficient biopsy material for central review. FDA recommended that the duration of response for a responder who receives subsequent therapy (including transplant) before documented progressive disease (PD) should be censored at the date of last assessment prior to receiving subsequent therapy.

2.6 Other Relevant Background Information

July 20, 2006 Orphan-drug designation
Sept 28, 2006 Fast track designation

Clinical Review
Shakun Malik, MD
NDA 022468
Folotyn (Pralatrexate)

July 16, 2008 Exempted from PREA requirement
January 28, 2008 and Sep 11, 2008 Statistical Analytic Plan (SAP) Type A, Phase 2

Meeting minutes of January 28, 2008

Request for FDA Feedback

We request FDA written feedback to the following questions regarding the statistical analysis plan and public disclosure:

Statistical Analysis Plan

1. PDX-008 Protocol Version 1.5, Section 15.3.2, states that "Initial study analyses will be conducted after all patients have been followed for a minimum of 1 year after enrollment or until study endpoints are met, whichever occurs first." In planning for these analyses, we realize that this definition is not precise, and would like to offer further clarification. Specifically, we propose to conduct the initial study analyses, i.e., the analyses that will form the primary basis for the clinical study report, once all patients have completed the Cycle 3 assessment (or terminated prior to the Cycle 3 assessment). This clarification appears in Section 11.2 of the enclosed Statistical Analysis Plan. Does the agency agree with this proposal?

FDA Response: No. We recommend that you conduct your analyses after a minimum of 1 year follow up for all patients. As previously communicated, both the response rate and duration of response will be taken into consideration for determination of clinical benefit.

2. Section 15.2 of PDX-008 Protocol Version 1.5 defines the primary analysis population. Specifically, it states: "The primary and secondary efficacy endpoints will be analyzed using the evaluable patient population. A patient will be considered evaluable if he/she receives at least 1 dose of pralatrexate and meets the major inclusion criterion # 1, i.e., the diagnosis of allowed PTCL histopathological subtype is confirmed by central pathology review." There may be some instances where there is insufficient material at the site to send to the central pathology review. In these cases, we would rather be inclusive of the patient and assume the treating physician is correct than to make the assumption that the patient is not eligible. This clarification appears in Section 5.0 of the enclosed Statistical Analysis Plan. Does the FDA agree with this proposal?

FDA Response: No. Including patients for analysis based on the treating physician's assumption, without definitive histopathological classification from the central pathology review, is not acceptable. Please make sure you keep all central pathology review reports and include them in the NDA submission.

Public Disclosure

Clinical Review
Shakun Malik, MD
NDA 022468
Folotyn (Pralatrexate)

Separately, Protocol PDX-008 incorporates three pre-specified data analyses, which will be conducted and reviewed by Allos and an independent Data Monitoring Committees. These consist of 2 analyses for safety and 1 for efficacy and safety. These assessment are planned at the following intervals: (1) review of the safety data on the first 10 treated patients after their completion of Cycle 1; (2) review of data on the first 35 treated patients for safety and efficacy after their completion of Cycle 1 (efficacy evaluation after stage 1 of a Simon design which mandates that at least 4 responses must have occurred to proceed to Stage 2), and (3) review of the safety data on the first 65 treated patients after their completion of Cycle 1. However, legal counsel has advised Allos that

(b) (4)

(b) (4)

(b) (4) Does the FDA agree that public disclosure of such safety or efficacy data is acceptable after all patients have been enrolled in the study?

FDA: DDOP has no comment. If you have any concerns that this disclosure may be considered promotional you should contact DDMAC for advice.

Additional Comments:

- 1. Please be aware that time to event endpoints such as PFS and OS are not interpretable in a single arm study and no claims can be made based on these endpoints.**
- 2. Duration of response for a responder who receives subsequent therapy (including transplant) before documented PD should be censored at the date of last assessment prior to receiving subsequent therapy.**

MEETING MINUTES

MEETING DATE: September 11, 2008

MEETING OBJECTIVES: To discuss the preliminary efficacy data from PDX-008 and the statistical simulation based on these data.

QUESTIONS for DISCUSSION with FDA RESPONSE and DECISIONS REACHED:

Duration of Response

- 1. Based on the more mature efficacy data from PDX-008, does the Agency agree that follow-up through the cycle 3 response assessment for the last responding patient is sufficient to accurately determine the duration of response for patients enrolled in study PDX-008 for submission in the initial NDA?**

Clinical Review
Shakun Malik, MD
NDA 022468
Folotyn (Pralatrexate)

FDA Response: We reiterate our recommendation that a minimum of 6 months of follow-up for the last responding patient to ensure that the duration of response data is mature.

DISCUSSION: Although a submission in February 2009 based on a cutoff in November of 2008 would potentially be fileable, a submission in March 2009 with a cutoff in December 2008 would provide a more complete database due to the expected completion of at least 6 months follow up for duration of response in all responders. Although a submission in December 26, 2008, is possible it is not desirable from a FDA perspective.

Follow-up Questions to the 16 Jul 2008 Type B Pre-NDA Meeting

2. In the Type B Pre-NDA meeting held with the DDOP on 16 Jul 2008, the Division indicated that they would prefer that photographs for patients with skin lesions who were enrolled into PDX-008 be submitted in PDF format in the NDA. The Agency requested that Allos provide the projected PDF file size of these photographs so that a determination could be made as to whether a subset of patients would be preferable. Allos estimates that the size of the PDF file of all photographs of patients with skin lesions is 214,200 Kbytes. This was calculated by multiplying the average size of each photograph (200 Kbytes) by the number of photographs (1,071). Would the Agency confirm whether this is an acceptable file size or should only a subset of patients be provided?

FDA Response: You should try to keep your PDF documents to a maximum of 100 MB per document. For example, you should submit 2 documents of around 100 MB each rather than a single document of approximately 209 MB.
DISCUSSION: The sponsor agrees.

3. In the Type B Pre-NDA meeting held with the DDOP on 16 Jul 2008, the Agency indicated that they cannot archive scan images. Upon request, they would like a short turn-around for the CT/PET scans of selected patients. (b) (4) responsible for the central review for this study, has an established procedure with the Agency for submission of scans for review within 10 days of request as digitized pictures. Please clarify if the requested scans are to be provided in digitized format upon request or as PDF files.

FDA Response: FDA is no longer accepting digitized scans. The scans should be submitted as PDF files.

4. If the PDF files of CT/PET are preferred, would it be acceptable to provide PDF files of the patients who have had a response, either by Central or Investigator assessment, in the NDA rather than upon request?

FDA Response: This is acceptable.

5. If the Division prefers the digitized format of CT/PET scans, will the Division also

Clinical Review
Shakun Malik, MD
NDA 022468
Folotyn (Pralatrexate)

require digitized photographs of patients with skin lesions in addition to PDF files?

FDA Response: No.

ACTION ITEMS: None.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

- Submission contains all components of e-CTD
- Overall quality and integrity are reasonable good

3.2 Compliance with Good Clinical Practices

Submission contains the statement that the Investigators agreed to conduct the study in accordance with national, state, and local laws intended to protect the rights and welfare of patients participating in medical research. These included the US Code of Federal Regulations (CFR, Title 21 CFR § 50, 54, 56, and 312), the Canadian Institutes of Health Research Act, the ethical principles that have their origins in the Declaration of Helsinki (48th World Medical Association General Assembly, Somerset West, Republic of South Africa, Oct 1996), and International Conference on Harmonization (ICH) Good Clinical Practices (GCP) guidelines. Where applicable, Ministries of Health reviewed and approved the protocol and amendments in their countries.

3.3 Financial Disclosures

Pralatrexate was developed in Memorial Sloan Kettering and the IND was later transferred to Allos.

(b) (4)

(b) (4) \$298,026.25 compensation for Pre-clinical work

(b) (4) for the drug.

Allos Therapeutics, Inc. in exchange for patent and other rights related to pralatrexate, had agreed to pay the following royalties and milestone payments Sloan-Kettering Institute (SKI), Southern Research Institute and SRI International (SRI).

Royalties on worldwide annual net product sales of pralatrexate include the following:

(b) (4)

Milestones that have been paid include the following:

[REDACTED] (b) (4)

[REDACTED] (b) (4)

As per disclosure by the applicant, the PI of the trial has not and will not receive any royalties or milestone payments from Allos in connection with the development, approval or sales of pralatrexate or any other product. The disclosable financial arrangement between PI and the sponsor is shown in Table 1.

PI is named as an inventor of the technology claimed in U.S. patent application No. 11/141,868; however, he has assigned his ownership in this patent application to SKI.

The trial that the sponsor submitted to support this NDA was a multi-institutional global trial and number of patient enrollment at Sloan or Columbia was not found to drive the efficacy data.

This reviewer did not identify Conflict of interest.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

Refer to CMC review. No issues.

4.2 Clinical Microbiology

Refer to Clinical Microbiology review. No issues

4.3 Preclinical Pharmacology/Toxicology

Refer to Pre-clinical pharm/tox review. No issues

4.4 Clinical Pharmacology

Clinical Review
 Shakun Malik, MD
 NDA 022468
 Folutyn (Pralatrexate)

Table 1 Disclosable Financial Arrangements

Form FDA 3455 Disclosable Financial Arrangements

Disclosable Financial Arrangements

Institution/Investigator	Contract Number	Activity	Amount Paid	Date of Payment
(b) (6)			\$100,000.00	6-Jul-07
			\$66,008.75	31-Jan-08
			\$132,017.50	11-Jun-08
			\$298,026.25	
			Amount Paid	Date of Payment
			\$258.00	28-Apr-08
			\$864.71	15-Jan-07
			\$3,000.00	20-Feb-07
			\$500.00	29-Aug-07
			\$180.00	20-Mar-06
			\$3,000.00	22-Oct-06
			\$2,000.00	2-Nov-05
			\$300.42	31-Oct-05
			Total	

Steps to Minimize Potential Bias of Clinical Study Results

Clinical Study PDX-008

- Response was assessed by an independent data monitoring committee
- Multiple Investigators at multiple study sites participated in the study

Clinical Studies PDX-02-078 and PDX-010

These studies do not provide primary basis of safety and efficacy for approval.

4.4.1 Mechanism of Action:

Pralatrexate is a structural analogue of the anti-folate drug methotrexate. The applicant claims that, compared to methotrexate, pralatrexate is more effectively taken up by the cancer cells through increased affinity for the 1-

carbon reduced folate carrier (RFC-1) and more efficiently polyglutamylated by folylpolyglutamyl synthetase (FPGS). The main target of pralatrexate is the dihydrofolate reductase (DHFR).

4.4.2 Pharmacodynamics

Refer to Clin Pharm review

4.4.3 Pharmacokinetics

Refer to Clin Pharm review

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

Table 2 summarizes all 12 clinical trials the applicant has conducted prior to the NDA submission. All of them except for 1 (PDX-012) were single arm phase 1, 2 trials. Patient population in these trials included Adults with relapsed or refractory PTCL, advanced solid tumors, Stage IIIB (pleural or pericardial disease) or IV NSCLC lung cancer, relapsed or refractory aggressive NHL or Hodgkin's disease.

Table 2 Tables of Studies/Clinical Trials

Type of Study/ Study Identifier	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Patients	Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
PDX-008 Phase 2	<p>Primary</p> <p>1. Determine the efficacy of pralatrexate with concurrent vitamin B12 and folic acid supplementation.</p> <p>Secondary</p> <p>1. Determine the safety of pralatrexate.</p> <p>2. Determine the PK profile of pralatrexate.</p>	Non-randomized, open-label	<p>Initial dose: pralatrexate 30 mg/m²/wk for 6 wks in a 7-wk cycle by IV; dose reductions to 20 mg/m²/wk for treatment-related AEs.</p> <p>Patients receive vitamin B12 and folic acid supplementation.</p>	<p>Planned: a minimum of 100 evaluable patients</p> <p>Enrolled: n = 115</p> <p>Treated: n = 111</p>	Adults with relapsed or refractory PTCL	Patients continue on treatment until protocol-defined criteria for removal from study are met.	Enrollment complete; study ongoing; full report

Clinical Review
Shakun Malik, MD
NDA 022468
Folotyn (Pralatrexate)

<p>PDX 97-006 Phase 1/ Clinical Pharmacologic</p>	<p>Primary 1. Establish a tolerable weekly IV dosage and schedule of pralatrexate that will produce a reliable biologic effect.</p> <p>Secondary 1. Seek evidence of therapeutic activity</p> <p>2. Define the nature of drug-induced adverse effects and seek means of reducing them.</p> <p>3. Measure pralatrexate concentration and examine the relationship between pharmacodynamic parameters and toxicities.</p>	<p>Non-randomized, open-label</p>	<p>6 patients: 30 mg/m² pralatrexate (IV bolus) weekly for 3 wks of a 4-wk cycle. 27 patients: pralatrexate dose escalation (15-170 mg/m²; IV bolus) q 2 wks of a 4-wk cycle. No vitamin B12 or folic acid supplementation during study.</p>	<p>Planned: n = 40 Enrolled: n = 35 Treated: n = 33</p>	<p>Adults with advanced solid tumors</p>	<p>Patients continued on treatment until protocol-defined criteria for removal from pralatrexate treatment were met</p>	<p>Study completed; abbreviated report</p>
<p>PDX 99-053 Phase 2</p>	<p>Primary 1. Determine the efficacy of pralatrexate as first- or second-line chemotherapy.</p> <p>Secondary 1. Characterize AEs. 2. Determine the duration of survival. 3. Measure QoL. 4. Perform pharmacodynamic studies.</p>	<p>Non-randomized, open-label</p>	<p>29 patients: 150 mg/m² pralatrexate (IV bolus) q 2 wks of a 4-wk cycle. 10 patients: 135 mg/m² pralatrexate (IV bolus) q 2 wks of a 4-wk cycle. Folic acid supplementation for significant stomatitis.</p>	<p>Planned: n = 19 initially; maximum n = 39 if response observed Enrolled: n = 39 Treated: n = 39</p>	<p>Adults with Stage IIIB (pleural or pericardial disease) or IV NSCLC</p>	<p>Patients continued on treatment until protocol-defined criteria for removal from pralatrexate treatment were met.</p>	<p>Study completed; abbreviated report</p>

Clinical Review
Shakun Malik, MD
NDA 022468
Folotyn (Pralatrexate)

<p>PDX 99-083 Phase 1</p>	<p>1. Determine the optimal dose of pralatrexate when combined with a taxane (paclitaxel or docetaxel).</p> <p>2. Characterize safety profile of pralatrexate when combined with a taxane.</p> <p>Secondary</p> <p>1. Evaluate efficacy of pralatrexate in combination with a taxane.</p> <p>2. Evaluate potential markers of response to pralatrexate and taxane.</p> <p>3. Evaluate potential correlates of stomatitis.</p>	<p>Non-randomized, open-label</p>	<p>Pralatrexate w/ docetaxel 42 patients: pralatrexate (60-140 mg/m²; IV) on day 1 q 2 wks, followed by 50 or 35 mg/m² docetaxel on day 1 or 2, q 2 wks, or on days 1,8, and 15 q 4 wks. Vitamin B12 and folic acid supplementation implemented part way through study.</p> <p>Pralatrexate w/ paclitaxel 6 patients: pralatrexate dose escalation (60-110 mg/m²; IV) on day 1 q 2 wks, followed by 175 mg/m² paclitaxel on day 1 or 2 q 2 wks.</p>	<p>Planned: 3-6 patients enrolled at each dose until the MTD was found. Enrolled: n = 51 Treated: n = 48</p>	<p>Adults with advanced cancer</p>	<p>Patients continued on treatment until protocol-defined criteria for removal from study were met.</p>	<p>Study completed; abbreviated report</p>
<p>PDX 01-014 Phase 1/Clinical Pharmacologic</p>	<p>1. Establish a tolerable biweekly dose and schedule of IV pralatrexate along with IV probenecid that will produce a reliable biologic effect.</p> <p>2. Seek evidence of therapeutic activity at tolerable drug dosages.</p> <p>3. Characterize adverse effects and seek means of reducing them.</p> <p>4. Measure pralatrexate concentration in blood and urine. Evaluate effect of probenecid initial plasma concentration on pralatrexate PK.</p>	<p>Non-randomized, open-label</p>	<p>17 patients: probenecid dose escalation (70-233 mg/m²; IV bolus) with pralatrexate dose at 40 mg/m²; IV bolus, q 2 wks of a 4-wk cycle. No vitamin B12 or folic acid supplementation during the study.</p>	<p>Planned: n = 40 Enrolled: n = 17 Treated: n = 17</p>	<p>Adults with advanced solid tumors not curable by standard chemotherapy, RT, or surgical procedure who had failed first-line therapy</p>	<p>Patients continued on treatment until protocol-defined criteria for removal from study were met.</p>	<p>Study completed; abbreviated report</p>

Clinical Review
Shakun Malik, MD
NDA 022468
Folotyn (Pralatrexate)

PDX 01-076 Phase 2	Primary 1. Determine the efficacy of pralatrexate as first-line chemotherapy. Secondary 1. Characterize AEs. 2. Measure QoL. 3. Evaluate potential markers of response to pralatrexate. 4. Evaluate potential correlates of toxicity (stomatitis).	Non-randomized, open-label	16 patients: 135 mg/m ² pralatrexate (IV bolus), q 2 wks of a 4-wk cycle Patients received vitamin B12 and folic acid supplementation.	Planned: n = 12 initially; maximum n = 37 if response observed Enrolled: n = 17 Treated: N = 16	Adults with unresectable malignant pleural mesothelioma	Patients continued on treatment until protocol-defined criteria for removal from study were met.	Study completed; abbreviated report
PDX 02-078 Phase 1/2	Primary 1. Determine the efficacy of pralatrexate. 2. Determine impact of PK on AEs and drug elimination. 3. Optimize a weekly schedule of pralatrexate with vitamin B12 and folic acid supplementation. Secondary 1. Characterize AEs. 2. Evaluate influence of prior chemotherapy response duration on pralatrexate response. 3. Evaluate potential correlates of stomatitis. 4. Evaluate potential markers of response.	Non-randomized, open-label	Phase 1 Pralatrexate doses and schedules: 135 mg/m ² (IV) with 15 mg/m ² increases q 2 wks of a 2-wk cycle. 30mg/m ² weekly for 3 wks of a 4-wk cycle. 30 mg/m ² weekly for 6 wks of a 7-wk cycle. 45 mg/m ² weekly for 6 wks of a 7-wk cycle. Phase 2 Pralatrexate 270 mg/m ² q 2 wks in a 4-wk cycle. The dose may be reduced to 230 mg/m ² , based on defined criteria. Patients receive vitamin B12 and folic acid supplementation.	Planned: Phase 1: 3-6 patients will be enrolled at each dose level until the MTD is found Phase 2: minimum of 15 patients and a maximum of 35 based on response Treated: n = 56	Adults with relapsed or refractory aggressive NHL or Hodgkin's disease	Patients continue on treatment until protocol-defined criteria for removal from study are met.	Enrollment ongoing; interim report

Clinical Review
 Shakun Malik, MD
 NDA 022468
 Folutyn (Pralatrexate)

<p>PDX-007 Phase 1</p>	<p>1. Evaluate the safety and tolerability of escalating doses of pralatrexate.</p> <p>2. Determine the MTD of pralatrexate.</p> <p>3. Determine the PK profile of pralatrexate.</p>	<p>Non-randomized, open-label</p>	<p>Treatment Group A: pralatrexate by IV push, starting dose 15 mg/m² on day 1 and gemcitabine 400 mg/m² on day 2 weekly x 3 wks followed by 1 wk of rest (4-wk cycle), with protocol-specified dose reduction to minimum of 5 mg/m² pralatrexate and 200 mg/m² gemcitabine in the event of intolerance.</p> <p>Treatment Group B: pralatrexate starting dose 10 mg/m² on day 1, gemcitabine 300 mg/m² on day 2 q 2 wks (4-wk cycle) with escalation to 30 mg/m² pralatrexate and 1000 mg/m² gemcitabine maximum.</p> <p>Treatment Group C same starting doses and escalation as Group B, but gemcitabine administered on same day as pralatrexate (day 1) q 2 wks (4-wk cycle). Patients receive vitamin B12 and folic acid supplementation.</p>	<p>Planned: Phase 1: 3-6 evaluable patients will be enrolled into each cohort until the MTD is determined for each treatment group.</p> <p>Phase 2a: 30 additional evaluable patients will be enrolled per expanded cohort; 15 with relapsed or refractory PTCL and 15 with B-cell lymphoma.</p> <p>Treated: n = 17</p>	<p>Adults with Stage IIIB-IV NSCLC</p>	<p>Patients continue on treatment until protocol-defined criteria for removal from study are met.</p>	<p>Enrollment complete; study ongoing; interim report</p>
----------------------------	--	-----------------------------------	--	---	--	---	---

Clinical Review
Shakun Malik, MD
NDA 022468
Folotyn (Pralatrexate)

<p>PDX-009 Phase 1/2a</p>	<p>1. Determine the MTD and recommended Phase 2 dose of IV pralatrexate and gemcitabine. 2. Evaluate the safety and tolerability of escalating doses of pralatrexate and gemcitabine. 3. Determine the PK profile of pralatrexate and gemcitabine. 4. Confirm tolerability and assess preliminary efficacy in patients with relapsed or refractory PTCL and B-cell lymphoma.</p>	<p>Non-randomized, open-label</p>	<p>Planned: Maximum of 56 evaluable patients. A maximum of 9 evaluable patients are to be enrolled into each cohort until an effective and well-tolerated dose and schedule is achieved, at which point, up to 20 evaluable patients are to be enrolled at the optimal dose and schedule. Treated: n =15</p>	<p>Planned: Maximum of 56 evaluable patients. A maximum of 9 evaluable patients are to be enrolled into each cohort until an effective and well-tolerated dose and schedule is achieved, at which point, up to 20 evaluable patients are to be enrolled at the optimal dose and schedule. Treated: n =15</p>	<p>Adults with relapsed or refractory lymphoproliferative malignancies</p>	<p>Patients continue on treatment until protocol-defined criteria for removal from study are met.</p>	<p>Enrollment ongoing; interim report</p>
<p>PDX-010 Phase 1</p>	<p>• Determine an effective and well-tolerated dose and schedule of pralatrexate with vitamin B12 and folic acid supplementation that can be administered safely to patients with relapsed or refractory CTCL. • Characterize the safety profile of pralatrexate in this group of patients.</p>	<p>Non-randomized, open-label</p>	<p>Pralatrexate will be given IV over 1 hr on days 1 and 15 of a 4-wk cycle. The initial dose will be 190 mg/m² q 2 wks, which is to be decreased to a minimum of 150 mg/m² per defined criteria in the protocol. Patients will receive vitamin B12 and folic acid supplementation.</p>	<p>Planned: At least 41 evaluable patients. 21 evaluable patients will be entered in Stage 1 and if the Stage 1 Criteria for continuing the study are met, an additional 20 evaluable patients will be entered. Treated: n = 0</p>	<p>Adult patients with relapsed or refractory CTCL</p>	<p>Patients continue on treatment until protocol-defined criteria for removal from study are met.</p>	<p>Enrollment ongoing; interim report</p>

Clinical Review
 Shakun Malik, MD
 NDA 022468
 Folutyn (Pralatrexate)

<p>PDX-011 Phase 2</p>	<p>1. Determine the objective response rate (CR + PR). 2. Determine the duration of response, clinical benefit rate, PFS and OS. 3. Evaluate safety and tolerability.</p>	<p>Non-randomized, open-label</p>	<p>Patients randomized to the Pralatrexate Arm receive pralatrexate IV push over 3-5 min on days 1 and 15 of a 4-wk/28-day cycle. The initial dose of pralatrexate was 230 mg/m². However, the protocol was amended to a starting dose of 190 mg/m², which, based on defined criteria, may be increased to 230 mg/m² or reduced to 150 mg/m² (minimum).</p> <p>Patients randomized to the Erlotinib Arm receive erlotinib 150 mg/day orally 1 hr before or 2 hrs after eating. Dosing is continuous. Patients receive vitamin B12 and folic acid supplementation.</p>	<p>Planned: ~ 160 patients randomized 1:1 to pralatrexate or erlotinib. Treated in the Pralatrexate Arm: n = 3</p>	<p>Adult patients with advanced or metastatic relapsed TCC of the urinary bladder</p>	<p>Patients continue on treatment until protocol-defined criteria for removal from study are met.</p>	<p>Open to enrollment; interim report</p>
----------------------------	---	-----------------------------------	---	--	---	---	--

Clinical Review
 Shakun Malik, MD
 NDA 022468
 Folutyn (Pralatrexate)

PDX-012 Phase 2b	<p>Primary</p> <ul style="list-style-type: none"> • Estimate the efficacy of pralatrexate as assessed by OS compared with that of erlotinib. <p>Secondary</p> <ul style="list-style-type: none"> • Estimate the efficacy of pralatrexate as assessed by RR compared with that of erlotinib. • Estimate the efficacy of pralatrexate as assessed by PFS compared with that of erlotinib. • Evaluate the safety and tolerability of every-other-week administration of pralatrexate in patients with Stage IIIB/IV NSCLC. 	Randomize d, open- label			Adult patients with Stage IIIB/IV NSCLC who are or have been cigarette smokers.	Patients continue on treatment until protocol-defined criteria for removal from study are met.	Enrollment ongoing; interim report
---------------------	---	--------------------------------	--	--	---	--	---

5.1.1 Study PDX-02-078

Was an ongoing Phase 1/2 study at the time of data submission in patients with **relapsed or refractory aggressive non-Hodgkin's lymphomas (NHLs) or Hodgkin's disease**. In the initial version of the study, the starting dose of pralatrexate was 135 mg/m² given on an every (q) 2 weeks basis with inpatient dose escalation. A higher than anticipated incidence of Grade 3 or 4 stomatitis occurred at this dose in patients with homocysteine (Hcy) and methylmalonic acid (MMA) concentrations greater than 10 µmol/L and 200 µmol/L, respectively. The study was then amended to become a Phase 1/2 study with an outpatient dose-escalation scheme starting at 30 mg/m² weekly for 3 weeks of a 4-week cycle with subsequent increases in number of consecutive doses and dose amount. Because of the observation of cytotoxic failures, the more frequent weekly schedule was adopted, which is concordant with well-established theories regarding the important pharmacokinetic (PK) parameters and dosing schedules known to be critical in the use of antimetabolites (ie, larger area under the curve [AUC] exposures are more important than a larger maximum concentration [C_{max}]). This amendment to the protocol also added vitamin B12 and folic acid supplementation in order to normalize Hcy and MMA and evaluate whether vitamin supplementation enabled tolerance of higher doses of pralatrexate. When dose-limiting toxicities (DLTs) occurred at the dose of 45 mg/m² for 6 weeks of a 7-week cycle, the maximum tolerated dose (MTD) was determined to be 30 mg/m²/week for 6 weeks on a 7-week cycle. The study was still enrolling patients at the time of NDA submission with an emphasis on those with B-cell lymphoma evaluation at a higher dose of 270 mg/m² administered q 2 weeks, with dose reduction allowed to 200 mg/m² if protocol-defined AEs are experienced.

5.1.2 Study PDX-008

was 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 B12 and folic acid supplementation to patients with relapsed or refractory PTCL. The clinical study is the basis for this new

5.1.4 Study PDX-009

As per submission by the sponsor Study PDX-009 is an ongoing Phase 1/2a, non-randomized, open-label, multi-center study of pralatrexate and gemcitabine administered on sequential days, or the same day depending on cohort, with vitamin B12 and folic acid supplementation to patients with relapsed or refractory lymphoproliferative malignancies. The objectives of the study are: 1) to determine the MTD and recommended Phase 2 dose of the combination of pralatrexate and gemcitabine; 2) to evaluate the safety and tolerability of escalating doses of pralatrexate and gemcitabine; 3) to determine the PK profile of the combination of pralatrexate and gemcitabine; and 4) to confirm tolerability and assess preliminary efficacy in patients with relapsed or refractory PTCL and B-cell lymphoma.

The initial dose of pralatrexate in Treatment Group A was 15 mg/m²; the maximum dose for the study is 30 mg/m². The initial dose of gemcitabine in the study was 400 mg/m². The minimum and maximum gemcitabine doses for the study are 200 and 1000 mg/m², respectively. Pralatrexate and gemcitabine will be administered weekly x 3 weeks followed by 1 week of rest for Treatment Group A and q 2 weeks for Treatment Groups B (sequential-day dosing) and C (same-day dosing). The Phase 1 component of the study will be the determination of the MTD, which is defined as the highest dose level at which = 33% of patients experience a DLT. Three to 6 evaluable patients will be enrolled into each cohort until the MTD is determined. After the MTD is established for both dosing on sequential days q 2 weeks of a 4-week cycle (Treatment Group B), and same day dosing q 2 weeks of a 4-week cycle (Treatment Group C), 1 or both treatment groups will be expanded at this dose level. The Phase 2a component of the study will enroll 30 additional evaluable patients who will be enrolled per expanded cohort (15 with relapsed or refractory PTCL and 15 with B-cell lymphoma) to obtain information on preliminary efficacy for subsequent clinical trials.

5.2 Review Strategy

Clinical review is mainly based on CSR for PDX-008 trial, sponsor's presentation slides, CRF's, primary data sets for efficacy and toxicity submitted and literature review of PTCL.

5.3 Discussion of Individual Studies/Clinical Trials

This NDA is based on an over all tumor response rate from a single arm phase II trial (PDX-008).

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

Objectives:

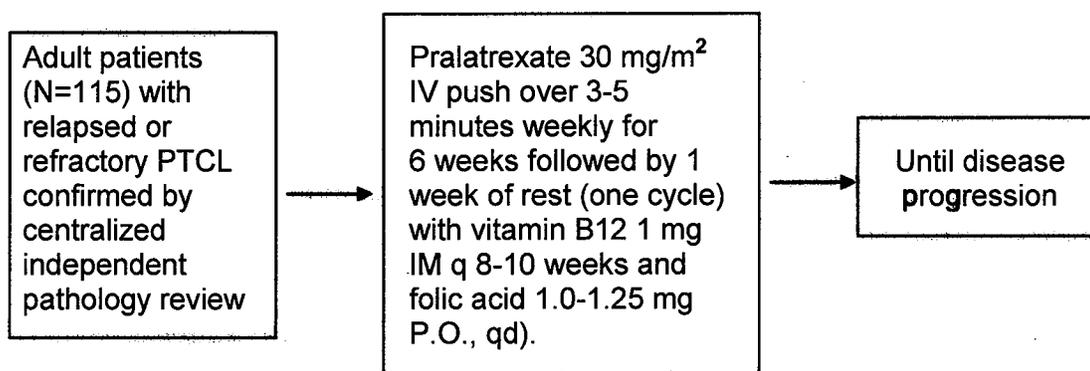
The primary objective of the study was to determine the efficacy of pralatrexate with concurrent vitamin B12 and folic acid supplementation when administered to patients with relapsed or refractory PTCL.

The secondary objectives were to determine the safety and the pharmacokinetic (PK) profile of pralatrexate with concurrent vitamin B12 and folic acid supplementation when administered to patients with relapsed or refractory PTCL.

5.3.1 Study Design

The study is an open label, multi-center Phase 2 trial of pralatrexate with vitamin B12 and folic acid supplementation in patients with relapsed or refractory peripheral T-cell lymphoma (PTCL).

Figure 5 Study design schema



5.3.2 Study Drug administration and schedule

Pralatrexate was administered at a dose of 30 mg/m²/week IV push for 6 weeks in a 7-week cycle. The weekly pralatrexate dose could be reduced to 20 mg/m² for toxicities.

Vitamin Administration

Vitamin supplementation began after a patient's blood has been collected for methylmalonic acid (MMA) and homocysteine (Hcy) analysis at screening based on the following:

- If the patient's MMA level was > 200 nmol/L and/or Hcy was > 10 µmol/L at screening, vitamin supplementation was initiated at least 10 days prior to pralatrexate administration on cycle 1, dose 1.
- If, however, MMA and Hcy results were within normal range, pralatrexate dosing could be started immediately (it was not necessary to wait 10 days).

Vitamin supplementation consisted of vitamin B12 1 mg intramuscular (IM) every (q) 8-10 weeks, and folic acid 1.0-1.25 mg, orally (PO) every day (QD). Vitamin B12 and folic acid were supplied by the site pharmacy/equivalent. Site staff administered 1 mg IM q 8-10 weeks to each patient for the duration of the treatment phase of the study. Site staff provided patients with a prescription for folic acid and instructed patients to take 1.0-1.25 mg, PO QD for the duration of the treatment phase of the study. Once pralatrexate was permanently discontinued, vitamin supplementation continued at least 1 month after the last pralatrexate dose, or longer at the discretion of the investigator.

5.3.3 Study Endpoints

The primary efficacy endpoint was

- Overall Response Rate (ORR)
 - including Complete Response (CR),
 - Complete Response Unconfirmed (CRu) and
 - Partial Response (PR).

Secondary efficacy endpoints included

- duration of response,
- progression-free survival (PFS), and
- overall survival (OS).

5.3.4 Eligibility criteria

Each patient had to meet the following criteria to be eligible for the study:

- 1) Patient had histologically/cytologically confirmed PTCL, using the Revised American Lymphoma (REAL) WHO disease classification:
 - T/NK-cell leukemia/lymphoma

- Adult T-cell lymphoma/leukemia (human T-cell leukemia virus [HTLV] 1+)
- Angioimmunoblastic T-cell lymphoma
- Blastic NK lymphoma (with skin, lymph node, or visceral involvement)
- Anaplastic large cell lymphoma (ALCL) , primary systemic type
- **PTCL – unspecified**
- **T/NK-cell lymphoma – nasal**
- Enteropathy-type intestinal lymphoma
- Hepatosplenic T-cell lymphoma
- **Extranodal peripheral T/NK-cell lymphoma – unspecified**
- Subcutaneous panniculitis T-cell lymphoma
- Transformed mycosis fungoides

Reviewer's comment:

As described in section 2.1 Peripheral T-cell lymphoma (PTCL), NK-cell malignancies are considered separate from PTCL. Inclusion of patients with these histologies would not be consistent with the indication sought.

- 2) Patient had to have documented progressive disease (PD) after at least 1 prior treatment. Patients may not have received an experimental drug or biologic as their only prior therapy. Patient must have had clear PD after the last treatment received. Patient had at least 1 biopsy from initial diagnosis or in the relapsed setting to confirm the diagnosis PTCL. Patients had recovered from the toxic effects of prior therapy. Patients treated with a Food and Drug Administration (FDA)-approved monoclonal antibody therapy could be enrolled regardless of the timeframe of the therapy if they had PD.
- 3) Eastern Cooperative Oncology Group (ECOG) performance status ≤ 2 .
- 4) At least 18 years of age.
- 5) Adequate hematological, hepatic, and renal function:
 - a. Platelets $\geq 100,000/\mu\text{L}$
 - b. ANC $\geq 1,000/\mu\text{L}$
 - c. Bilirubin $\leq 1.5 \text{ mg/dL}$
 - d. ALT/AST $\leq 2.5 \times$ Upper Limits of Normal (ULN)
 - e. Creatinine $\leq 1.5 \text{ mg/dL}$
6. Women of childbearing potential must have agreed to practice a medically contraceptive regimen from study treatment initiation until at least 30 days after the last administration of pralatrexate and had to have a negative serum pregnancy test within 14 days prior to the first day of study treatment. Patients who were postmenopausal for at least 1 year (> 12 months since last menses) or were sterilized did not require this test.
7. Men who were not surgically sterile had to have agreed to practice a medically acceptable contraceptive regimen from study treatment initiation until at least 90 after the last administration of pralatrexate.

8. Patient gave written Informed Consent (IC).

Exclusion Criteria Patients who met any of the following criteria were excluded from the study:

1. Patients had

- a. Precursor T/NK neoplasms, with the exception of blastic NK lymphoma
- b. T-cell prolymphocytic leukemia (T-PLL)
- c. T-cell large granular lymphocytic leukemia
- d. Mycosis fungoides, other than transformed mycosis fungoides
- e. Sézary syndrome
- f. Primary cutaneous CD30+ disorders: ALCL and lymphomatoid papulosis

2. Active concurrent malignancy (except non-melanoma skin cancer or carcinoma in situ of the cervix). If there was a history of prior malignancy, the patient must have been disease-free for ≥ 5 years.

3. Congestive heart failure Class III/IV according to the New York Heart Association's Heart Failure Guidelines.

4. Uncontrolled hypertension.

5. Human immunodeficiency virus (HIV)-positive diagnosis and was receiving combination anti-retroviral therapy.

6. Patient had, or had history of, brain metastases or central nervous system (CNS) disease.

7. Patient had undergone an allogeneic SCT.

8. Patient had relapsed less than 75 days from time of an autologous SCT.

9. 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.

10. Patient had major surgery within 2 weeks of study entry.

11. Receipt of any conventional chemotherapy or radiation therapy (RT) within 4 weeks (6 weeks for nitrosoureas or mitomycin C) prior to study treatment or planned use during the course of the study.

12. Receipt of corticosteroids within 7 days of study treatment, unless patient had been taking a continuous dose of no more than 10 mg/day of prednisone for at least 1 month.

13. Use of any investigational drugs, biologics, or devices within 4 weeks prior to study treatment or planned use during the course of the study.

5.3.5 Duration of treatment

Patients continued to receive pralatrexate until the following was met.

- 1) Development of PD
- 2) Initiation of radiotherapy or systemic chemo/biologic therapy for T-cell lymphoma
- 3) Development of an AE indicating intolerance of the lowest study dose allowed
- 4) Omission of 3 sequential doses of pralatrexate due to a treatment-related AE
- 5) > 3 week lapse between pralatrexate doses
- 6) Development of an AE, intercurrent illness, condition, or procedural complication that may have interfered with the patient's participation
- 7) Withdrawal of consent
- 8) Death of patient
- 9) Investigator decision
- 10) Sponsor decision
- 11) Treatment with pralatrexate for 24 months

Table 3 Schedule of Events

Visit	CYCLE 1					SUBSEQUENT CYCLES			FOLLOW-UP			
	21 Days Prior to Pralatrexate Dose 1	10 Days Prior to Pralatrexate Dose 1 through Cycle 1, Dose 1	24, 48, 72 hours post-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	Rescue FU	Survival & Subsequent Treatment FU
Eligibility Criteria/Informed Consent/Privacy Authorization	X											
Medical/Surgical History	X											
Document Histopathology	X ¹											
Unilateral bone marrow biopsy and aspirate	X ²					X ³		X ⁴	X ⁵	X ⁶	X ⁷	
CT of Chest, Neck, Abdomen, Pelvis (CNAP)	X					X ⁸		X ⁹	X ¹⁰	X ¹¹	X ¹²	
Other imaging of disease site other than CNAP ⁸	X ³					X ⁴		X ^{5, 6, 7}	X ^{8, 9}	X ^{10, 11}	X ¹²	
PET (base of skull to mid-thigh)	X ³					X ⁴		X ⁵	X ⁶	X ⁷	X ⁸	
Medical photography with ruler measurement of cutaneous lesions ⁹	X ³					X ⁴		X ^{5, 6, 7}	X ⁸	X ⁹	X ¹⁰	
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 ¹	X ²	X ³
Record ECOG Performance Status	X				X ⁴	X			X	X		
Physical Examination	X				X ⁵	X			X	X		
Record Height in cm		X ⁶										
Record Weight in kg		X ⁶				X						

Best Available Copy

5.3.6 Primary endpoint evaluation

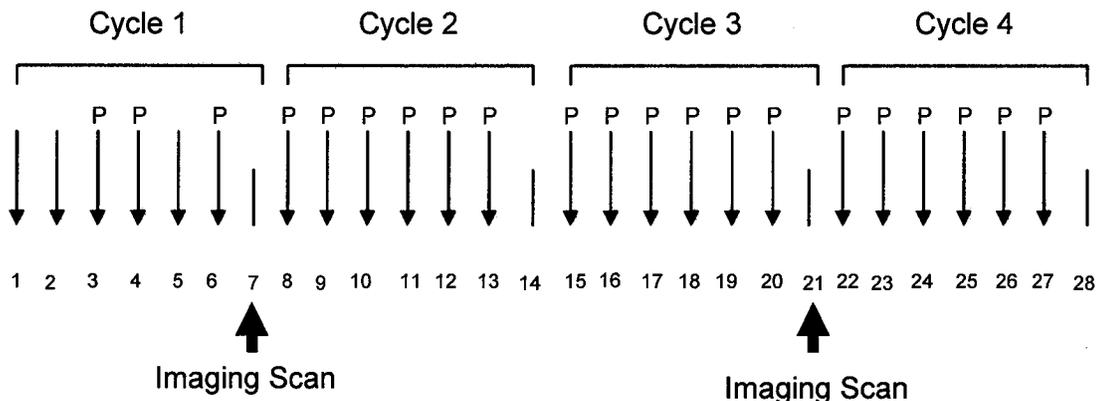
Efficacy: Response assessment was conducted by an independent central review using the International Workshop Criteria (IWC) developed by the National Cancer Institute (NCI) sponsored International Working Group. Investigator assessment of response was also collected.

Evaluation Methods

- Imaging Modality
 - CT or MRI and/or medical photography with ruler measurement of cutaneous lesions.
 - PET (only for exploratory analysis, not for primary endpoint)
- Bone Marrow Biopsy
- Clinical Evaluation

Patients were designated as responders when their nodal shrinkage met the IWC criteria on a given scan. Tumor status of all patients enrolled was evaluated by imaging scans.

Figure 6 Imaging Scheduling Evaluation Schema



- Cycles repeat until disease progression or condition met as described in section 6.3
- After cycle 1, scans every 14 weeks just prior to the first dose of an even cycle
- P = pralatrexate

After starting the study treatment drug, 1st imaging evaluation was done after cycle 1 i.e. at week 7. If patient showed a response or stable disease, they continued the study drug and the next scan was performed after every 2 cycles of therapy at 14 wks interval prior to the first dose of an even cycle.

5.3.7 Criteria for Primary Endpoint

The primary efficacy endpoint was assessed according to the International Working Group Criteria (IWC).

- Overall Response Rate (ORR) including
 - Complete Response (CR),
 - Complete Response Unconfirmed (CRu) and
 - Partial Response (PR)

Response assessment was conducted by an independent central review using the International Workshop Criteria (IWC) developed by the National Cancer Institute (NCI) sponsored International Working Group. Investigator assessment of response was also collected.

Table 4 The International Workshop Response Criteria (IWC)

Response Category	Physical Examination	Lymph Nodes	Lymph Node Masses	Bone Marrow
CR	Normal	Normal	Normal	Normal
CRu	Normal	Normal	Normal	Indeterminate
	Normal	Normal	> 75% decrease	Normal or indeterminate
PR	Normal	Normal	Normal	Positive
	Normal	≥ 50% decrease	≥ 50% decrease	Irrelevant
	Decrease in liver/spleen	≥ 50% decrease	≥ 50% decrease	Irrelevant
Relapse/progression	Enlarging liver/spleen; new sites	New or increased	New or increased	Reappearance

Complete Response (CR)

1. Complete disappearance of all detectable clinical and radiographic evidence of disease and disappearance of all disease-related symptoms if present before therapy.
2. All lymph nodes and nodal masses assessed must have regressed to normal size: If > 15 mm before treatment, decreased to < 15 mm in their greatest transverse diameter (GTD); if 11 mm to 15 mm in GTD before treatment, must have decreased to <10 mm in GTD (or by more than 75% in the sum of products of the greatest diameters).

3. If the spleen and other organs are considered to be enlarged on CT before therapy, these organs must have regressed in size and must not be palpable on physical examination.
4. If bone marrow was involved by lymphoma before treatment, the infiltrate must be cleared on repeat aspirate and biopsy of same site.
5. No new sites of disease.
6. Normalization of biochemical abnormalities (e.g., lactate dehydrogenase [LDH] definitely assignable to NHL).

CR/Unconfirmed (CRu) Response includes those subjects who fulfill Complete Response criteria but include one or more of the following features:

1. A residual lymph node mass >15 mm in GTD that has regressed by > 75% in sum of the products of the greatest diameters (SPD).
2. Individual nodes previously confluent must have regressed by > 75% in SPD compared with the size of the original mass.
3. Indeterminate bone marrow (increased number or size of aggregates without cytologic or architectural atypia).

Partial Response (PR)

1. 50% decrease in SPD of the six (6) largest dominant nodes or nodal masses. These nodes or masses should be selected according to the following features: They should be clearly measurable in at least two (2) perpendicular dimensions; They should be from as disparate regions of the body as possible; and They should include mediastinal and retroperitoneal areas of disease whenever these sites are involved.
2. No increase in the size of the other nodes, liver, or spleen. Splenic and hepatic nodules must regress by at least 50% in the SPD. With the exception of splenic and hepatic nodules, involvement of other organs is considered assessable and not measurable disease.
3. Bone marrow assessment is irrelevant for determination of a PR because it is assessable and not measurable disease; however, if positive, the cell type should be specified in the report, e.g., large-cell lymphoma or low-grade lymphoma (i.e., small, lymphocytic small cleaved, or mixed small cleaved, or mixed small and large cells).
4. No new sites of disease.

Stable Disease (SD) Less than a PR but not PD.

Progressive Disease (PD) In this study, both Relapsed Disease and Progressive Disease were reported by Central Imaging Reading Contractor as Progressive Disease.

1. >50% increase from nadir in the SPD of any previously identified abnormal node.
2. A new node that is > 15 mm in its GTD has appeared.
3. A new non-nodal lesion of any size has appeared.
4. A bone marrow that was previously negative becomes positive.

5.3.8 Evaluations for Secondary Endpoints(s)

- **Duration of response** was measured from first day of documented response until PD or death.
- **Progression-free survival (PFS)**, was measured from treatment day 1 until event (i.e. the earliest of the following: death from any cause or PD or censoring, whichever occurred first). Patients undergoing transplant or any other subsequent therapy prior to documentation of PD were censored for duration of response and/or PFS.
- **Overall survival (OS)** was measured from treatment day 1 until death or censoring, whichever occurred first.

5.3.9 Major protocol amendments

Table 5 Major Protocol Amendments

NO	Date	Amendment
1	05 Jun 2006	To increase the maximum number of planned patients from 75 to 100, incorporating the appropriate adjustments to the statistical analysis section. To increase the number of planned study centers from 20 to 35. To incorporate safety monitoring at specific time points by a Data Monitoring Committee (DMC). To add flow cytometry at baseline and in cases of CR or PR.
2	15 Jun 2006	To provide guidance to the investigator regarding known incidence and treatment of nausea/vomiting.
3	23 Jun 2006	To clarify that a minimum of 100 evaluable patients will be enrolled. To extend central review of response assessment beyond 1 year if applicable, until PD, start of subsequent therapy, study termination, or study completion, whichever occurs first.

Clinical Review
 Shakun Malik, MD
 NDA 022468
 Folutyn (Pralatrexate)

4	04 Oct 2006	<ol style="list-style-type: none"> 1. To clarify that peripheral blood and bone marrow aspirate flow cytometry are not required protocol procedures for each patient, but must be considered when evaluating disease status if done per standard of care. 2. To delete the addition of the wording "any new lymph node = 1 cm should be considered a new lesion" from the definition of progressive disease. The published response criteria in Appendix 2 and Appendix 3 will be utilized. 3. To clarify pralatrexate administration in the event of delays due to administrative reasons (eg, vacation, holiday, etc.). 4. To provide guidance for missed or vomited doses of folic acid. 5. International Prognostic Index (IPI) classification was . 6. To include complete response unconfirmed (CRu) in the definition of responders according to the published response criteria
5	03 Jan 2007	<p>This amendment to Protocol PDX-008 was made after review of the data from the first 10 patients enrolled, to modify the treatment plan in the event of Grade 3, 4 thrombocytopenia.</p> <p>Folic acid requirements was changed to allow a dose range of 1.0-1.25 mg to accommodate country variability without posing safety concerns to patients.</p>

6 Review of Efficacy

Efficacy Summary

This NDA submission is based on an overall response rate from a single arm trial using pralatrexate as a single agent in the treatment of 109 patients with relapsed or refractory PTCL. Tumor status was assessed by imaging scans performed at week 7 after initiation of pralatrexate treatment and subsequently every 14 weeks. The responses were evaluated by an independent imaging review committee (IRC).

- The applicant reported an overall response rate of 27% (95% CI: 19-36%) according to the International Workshop Criteria (IWC) for malignant lymphoma.
- Response determination was adjudicated in 52% of responders because of the disagreement between central readers 1 and 2 of the IRC.
- After initial response designation according to IWC, the duration of response (DOR) in 55% of responders was found to be < 14 weeks. Only 12% of 109 evaluable patients (13 responders) had a DOR ≥ 14 weeks (6 CR, 1 CRu and 6 PR). Nine of these 13 responders (69%) had their response determination adjudicated. Median duration of response cannot be assessed in these 13 patients due to few events and data censoring.
- Seventy percent of patients received subsequent therapies after pralatrexate treatment.

6.1 Indication

The proposed indication is pralatrexate as a single agent for the treatment of patients with relapsed or refractory peripheral T-cell lymphoma.

6.2 Methods

Clinical review is based mainly on CSR for PDX-008 trial, sponsor's presentation slides, CRF's, primary data sets for efficacy and toxicity submitted and literature review of PTCL.

6.3 Demographics and baseline characteristics

6.3.1 Demographics

The demographics of the pivotal study (PDX-008) are presented in

Table 6. 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%).

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.

Table 6 Patient Characteristics

Category	Parameter	Pralatrexate Treated (N = 111)	
		N	Percent
Gender	Males	76	68
	Females	35	32
Race	White	80	72
Age (years)	< 65	71	64
	≥ 65	40	36
ECOG PS	0	43	39
	1	49	44
	2	19	17

6.3.2 Histology

Patient histopathology by central review and by investigator for all treated patients is in Table. Histopathology was recorded by the investigator on the CRF, and was confirmed by central review by (b) (4) (b) (4) was provided with tissue slides to confirm histopathology, and bone marrow aspirate and core biopsy slides to confirm presence or absence of bone marrow involvement, along with any supporting documentation.

In cases where (b) (4) could not confirm the diagnosis of histopathological subtype provided by the investigator, the relevant slides and pathology reports were provided to (b) (4) for a third party pathology assessment.

Table 7 Histology

Histopathology	Per Independent Central Review (N = 111)	
	N	Percent
PTCL-unspecified	59	53
Anaplastic large cell lymphoma, primary systemic	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
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
Mycosis fungoides (not transformed)	1	< 1
Inconsistent with T-cell lymphoma	1	< 1

Table 7 lists the histologies that were enrolled in the trial. The prevalence of the various histopathological subtypes reflects that with the majority (n = 59, 53%) having 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.

Reviewer's Comment:

In general NK-cell malignancies are not considered as PTCL. Seven such patients were enrolled in this trial indicated by the asterisks in Table 7.

6.3.3 Source of tumor specimen used for histologic diagnosis

Eligibility Criteria of the clinical protocol stated that the patient must have had clear progression of disease (PD) after the last treatment received. Patient must have had at least 1 biopsy from initial diagnosis or in the relapsed setting to confirm the diagnosis of PTCL.

All 109 evaluable patients had diagnosis and REAL/WHO classification of PTCL confirmed by central pathology. However,

- Eighty-six out of 115 enrolled (77%) patients had pathology confirmation from previous tissue blocks prior to multiple treatment modalities (up to 3 yrs old).
- Twenty-five patients out of 115 enrolled (21.7%) underwent tumor re-biopsy after disease progression and received pathologic confirmation of PTCL diagnosis by central pathological reading.

6.3.4 Prior PTCL therapies

Table 8 Prior Therapies

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

Table 8 summarizes the therapies that the patients had received prior to the study enrollment. 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). There were diverse** number and types of prior therapies.

Approximately, 21 % of the patients had received only 1 therapy while 19% had received more than five. Sixteen percent of the enrolled were after Auto SCT.

6.4 Subject disposition

One hundred and fifteen (115) patients with relapsed or refractory PTCL were enrolled. Four patients were never treated with pralatrexate and were excluded from all analyses. Two of these patients were considered not evaluable due to their histopathology assessment by the site. The investigator decided not to treat 1 patient due to the presence of B-cell lymphoma and another developed PD prior to starting pralatrexate treatment.

Table 9 Reasons for Discontinuing Study Treatment

Patients who discontinued study treatment	102 (92%)
Reason for discontinuing study treatment	
Disease Progression	64 (58%)
Adverse Event	25 (23%)
Investigator Decision	7 (6%)
Patient Decision	5 (5%)
Other	1 (< 1%)

An additional 2 patients were treated in the study but excluded from the efficacy analysis set as their histopathology assessment by central pathology review could not confirm the diagnosis of PTCL. Safety analysis was thus done on one hundred eleven (111) patients who had received at least 1 dose of pralatrexate and out of these 111 patients, 109 patients were evaluable.

As of the data cut-off date, 102 patients were off study and 9 patients remained on therapy. Table 9 summarizes patient disposition of treated patients.

6.5 Primary endpoint results

According to the protocol defined IWC response criteria, the sponsor reported an overall response rate of 29% (27 responders out of 109 evaluable patients) **based on IRC's assessment Responders were defined as those patients whose imaging scans showed tumor shrinkage that met IWC response criteria.** Follow up scans were not performed to confirm the responses (Table 10).

Table 10 Applicant-reported ORR

	Central Review (IWC)	Central Review (IWC+PET)	Investigator
CR+CRu+PR	29 (27%) (95%CI: 19%, 36%)	26 (24%) (95%CI: 16%, 33%)	42 (39%) (95%CI: 29%, 48%)
CR	7 (6%)	14 (13%)	15 (14%)
CRu	2 (2%)	--	4 (4%)
PR	20 (18%)	12 (11%)	23 (21%)

6.5.1 Issues with the primary endpoint results

- Uncertain clinical significance of tumor response and duration of response

Tumor status in all 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.

Out of 29 responders reported, 15 (51.7%) had their responses adjudicated because of the disagreement between central readers 1 and 2 of the independent imaging review committee (IRC). Thirteen (13) of these 29 were designated as responders on the response evaluation scans, but their response status cannot be confirmed. Ten of these 13 had subsequent scans 14 weeks later showing disease progression, and 3 of 13 did not have subsequent imaging scans because of off-study treatment due to consent withdrawal (2 patients) and serious adverse event resulting in death (1 patient).

Due to this long interval (14 weeks) between scans together with the fact that there were no confirmatory scans for responders after initial response designation according to IWC, this reviewer cannot verify these responses and their duration in these 13 responders except that these responses lasted < 14 weeks.

This reviewer evaluated and confirmed that 16 of these 29 responders had confirmatory scans after initial designation of response. Three of the sixteen patients had an unscheduled scans that confirmed their responses with DOR of 41 – 69 days. **Thirteen of these 16 (12% of 109 evaluable patients)**

had a DOR of at least 14 weeks with 6 CR (5%), 1 CRu (1%) and 6 PR (5%) (Table 11). Median duration of response in these patients cannot be assessed due to few events and data censoring.

Table 11 FDA Analysis of PDX-008 Response Results

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

- **Uncertainty of response determination**
 As stated above, there was a high adjudication rate for response determination in responders (15 of 29 responders). This reviewer made subsequent inquiry to the Applicant regarding the adjudication, Applicant responded that adjudication was for designation of CR vs. PR and the overall adjudication among central readers of the IRC was 34%. Given this high rate of adjudication, the designation of CR is questionable.
- **Overall response rate was driven by partial responders**
 Out of 29 responders, 20 were partial responders accounting for 18% of 109 evaluable patients (Table 10). It is not clear what is the clinical significance of partial responses in this disease setting.
- **Reliability of response determination for individual patients**
 In addition, this reviewer questions the response designation for some responders. Some examples are provided below:
 - a. **Pralatrexate treatment effect or delayed radiation Effect?**

Prior to study enrollment, patient #10 received radiation therapy (XRT) for an axillary mass that was the only site of disease. One month later, fine needle aspiration of this mass revealed necrotic tissue with some viable cells only. Patient was subsequently started on pralatrexate. After 1 cycle of pralatrexate treatment, imaging scans showed stable disease 3 months after radiation. After 3 cycles of pralatrexate treatment, imaging scans showed a PR 5 months after radiation at which time the patient was taken off study treatment for stem cell

transplant. An unscheduled scan done 2 months after patient was taken off the study drug (7 months after radiation) showed a CR.

Patient #29 received CHOP/XRT for a lesion in the pharyngeal wall before the start of pralatrexate. Biopsy was performed within 60 days of XRT. Patient was designated as CR based on resolution of the pharyngeal mass that was radiated and a mediastinal lymph node of 2.0 X1.1 cm which was not biopsy proven.

- b. Tumor regression after limited exposure to pralatrexate (1,2 or 3 doses only)

Patient # 49 received CHOP for nodal PTCL and was enrolled for PD with biopsy of tissue sent to central path performed prior to CHOP. He received 1 dose of IV push of pralatrexate and was taken off study treatment when he was admitted to the hospital ICU for sepsis. An unscheduled imaging scan was done prior to SCT and patient was designated PR.

Patient # 64 went off study due to grade 3 neutropenia and fatigue after receiving only 2 doses in cycle 1. An unscheduled scan within 6 weeks showed patient to be in PR. Patient continued to remain in PR for approximately 287 days prior to developing PD.

Patient #41 received 1 full dose of pralatrexate during week 1, reduced doses during weeks 3 and 5 because of mucositis that led to treatment discontinuation. Patient was designated as CR on an unscheduled scan about 7 weeks later. Patient remained in CR with no subsequent therapy until the data cut off date with a DOR noted to be 351 days.

6.5.2 Clinical reviewer's analysis of complete responders (CRs)

Table 12 Clinical Reviewer's Analysis of Complete Responders (CRs)

	Previous Therapy	Histological Subtype	Response to Pralatrexate Adjudicated
CR 6	3 pts ≥ 3 2 pts ≥ 2 1 pt ≥ 1	2 pts: ALCL 1 pt: T/NK cell 3 pts: PTCL (NOS)	CR in 5 of 6 patients were adjudicated
CRu 1	4	PTCL (NOS)	Yes

Table 12 Clinical Reviewer's Analysis of Complete Responders (CRs) shows the clinical reviewer's analysis of CRs. Out of 6 CRs and one CRu, With respect to the prior therapy, 4 patients had more than 2 prior

treatment regimens; 2 patients had 2 and 1 had only one chemo regimen, respectively.

In terms of histology subtypes, 2 patients had tumor histology consistent with anaplastic large cell lymphoma (the subtype with long natural history); 1 patient had T/NK cell lymphoma that is usually not considered to be PTCL and 4 out of these 7 CRs had PTCL(NOS).

Responses to pralatrexate were adjudicated in all 7 patients with CR and CRu except for one.

6.5.3 Clinical Reviewer's conclusion on the primary endpoint of ORR

The analyses above indicated that 27% of the patients had a response. The response lasted >14 weeks in 12 % and a small subset of patients (7 out of 109 patients, 6%) experienced CR that lasts more than 14 weeks.)

6.5.4 Exploratory analyses for the primary endpoint

A. Types of tumor histology

Because PTCL is a heterogenous mixture of tumors with different prognosis, the overall response rate could have been driven by some histologies that have a better prognosis. To examine this possibility, responses were analyzed against tumor histology types.

Table 13 Response analysis according to tumor histology type

	Pralatrexate (N = 109)		Response Rate IWC
	n	Percent of Patients	
PTCL NOS	59	54%	31%
Angioimmunoblastic	13	12%	8%
Anaplastic LC	17	16%	29%
Transformed MF	12	11%	25%
Other	8	7%	25%

As can be seen from Table 13 response rate by histopathology was similar among the subtypes, with the possible exception of angioimmunoblastic T-cell lymphoma in which there was only 1 responder out of 13 patients with this histological subtype for a response rate for that subtype of 8%. This data is inconsistent with literature results in which AITL had better response and better prognosis. However, overall, responses were not driven by a particular tumor histology.

B. Prior therapies

This reviewer also examined whether the responses were influenced by the prior systemic or local therapies that patients received before pralatrexate

Table 14 shows that the response rates ranges from 21% 35% regardless of the number or type of prior therapies that the patients had received.

Table 14 Response analysis according to prior therapy

		Pralatrexate (N = 109)		
		n	Percent of Patients	Response Rate IWC
Prior systemic therapy	1 regimen	23	21%	26%
	2 regimens	29	27%	21%
	> 2 regimens	57	52%	30%
Prior transplant	Yes	18	17%	33%
	No	91	83%	25%

C. Response analysis incorporating PET Scans.

The role of PET scans is not established in Lymphomas especially in T-cell lymphomas. PET was used for exploratory analysis only in this trial. The response rate by IWC plus PET scans was 24% (n = 26), with 14 patients (13%) with a CR. Twelve patients (11%) had a best response by IWC plus PET of PR.

6.6 Analysis of Secondary Endpoints

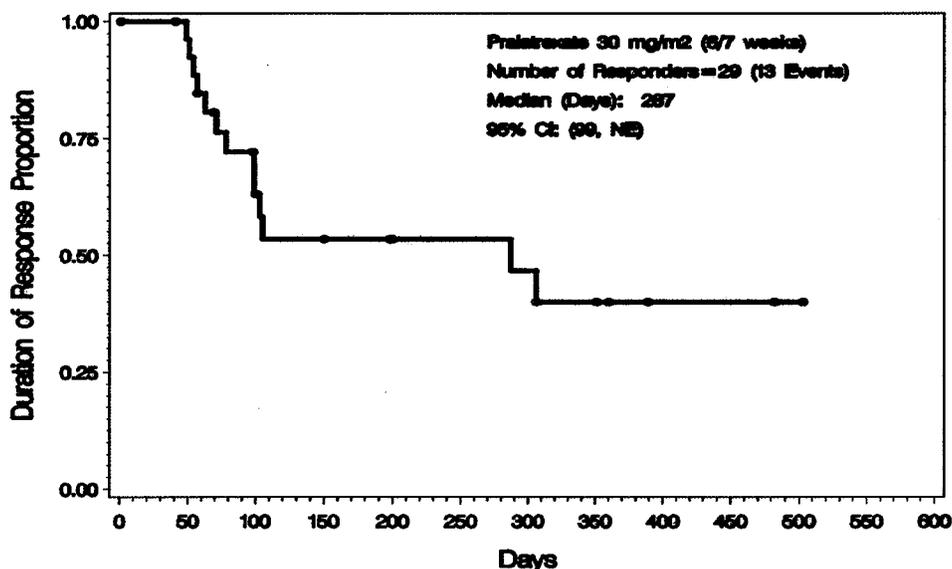
6.6.1 Duration of response

The applicant's duration of response reported was based on response assessed by IWC and estimated by the Kaplan-Meier method Figure 7. 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** .

However, this reviewer cannot verify this duration of response. As described in section 5.3.6 Primary endpoint evaluation), there was no confirmatory scans performed for responders. Patients were designated as responders if their tumor shrinkage met the IWC criteria seen from a given scan, and next scans would not happen until 14 weeks later or short for unscheduled scans. Thirteen (13) of 29 responders were designated as responders on the response evaluation scans, but their duration of response status cannot be confirmed. Ten of these 13 had

subsequent scans 14 weeks later showing disease progression, and 3 of 13 did not have subsequent imaging scans because of off-study treatment due to consent withdrawal (2 patients) and serious adverse event resulting in death (1 patient).

Figure 7 Applicant's Kaplan-Meier Estimate of Duration of Response



Due to this long interval (14 weeks) between scans together with the fact that there were no scans for responders after initial response designation according to IWC, FDA cannot verify these responses and their duration in these 13 responders except that these responses lasted < 14 weeks.

Table 15 describes in detail the duration of response for each of 29 responders reported by the sponsor. Note that duration of response in 13 responders cannot be verified according to IWC (bold and italicized).

6.6.2 PFS and OS

The median PFS reported by the applicant 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.** The median PFS was based on response assessed by IWC plus PET as 141 days (95% C`I, 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.

Clinical Review
Shakun Malik, MD
NDA 022468
Folotyn (Pralatrexate)

Table 15 Clinical Reviewer's Analysis of Duration of Response

Pt #	Treatment Duration (days)	Status	Best Response	Date of First Response	Status	Type	End Date	Duration days
26	484	Off	PR	24-Dec-07	Event	PD	24-Oct-08	306
64	8	Off	PR	18-Oct-07	Event	PD	30-Jul-08	287
103	135	Off	CRu	30-Apr-08	Event	PD	12-Aug-08	105
7	132	Off	PR	9-Nov-06	Event	PD	19-Feb-07	103
38	183	Off	PR	31-Jul-07	Event	PD	6-Nov-07	99
45	245	Off	PR	20-Dec-07	Event	PD	27-Mar-08	99
17	92	Off	PR	21-May-07	Event	PD	6-Aug-07	78
72	342	Off	PR	24-Sep-08	Event	PD	3-Dec-08	71
80	75	Off	PR	8-Jan-08	Event	PD	10-Mar-08	63
12	86	Off	PR	18-Apr-07	Event	PD	13-Jun-07	57
44	189	Off	PR	27-Nov-07	Event	PD	16-Jan-08	51
87	82	Off	PR	23-Jan-08	Event	PD	11-Mar-08	49
48	78	Off	PR	4-Sep-07	Event	Death	(b) (6)	54
59	179	Off	CR	1-Oct-07	Censored	Transplant	27-Feb-08	150
67	162	Off	CR	6-Nov-07	Censored	Transplant	13-Feb-08	100
49	1	Off	PR	30-Aug-07	Censored	Transplant	6-Nov-07	69
10	127	Off	CR	4-Mar-07	Censored	Transplant	13-Apr-07	41
29	442	Off	CR	1-Oct-07	Censored	Other Therapy	1-Aug-08	306
43	246	Off	PR	4-Mar-08	Censored	Other Therapy	4-Mar-08	1
60	135	Off	PR	22-Jan-08	Censored	Other Therapy	22-Jan-08	1
92	84	Off	PR	31-Jan-08	Censored	Study Term	27-Mar-08	57
35	540	On	CRu	25-Jul-07	Censored	Continuing	8-Dec-08	503
36	529	On	CR	25-Jul-07	Censored	Continuing	17-Nov-08	482
57	477	On	PR	2-Oct-07	Censored	Continuing	24-Oct-08	389
52	414	On	CR	11-Sep-07	Censored	Continuing	4-Sep-08	360
41	29	Off	CR	15-Aug-07	Censored	Continuing	30-Jul-08	351
113	232	On	PR	20-May-08	Censored	Continuing	5-Dec-08	200
105	254	On	PR	13-May-08	Censored	Continuing	26-Nov-08	198
86	346	On	PR	22-Aug-08	Censored	Continuing	27-Nov-08	98

The median OS for the efficacy analysis set, estimated by the Kaplan-Meier method as per applicant 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.

Reviewer's comment: this trial is a single arm non-randomized trial and thus response rate is the only endpoint that can be evaluated. Time to event endpoints cannot be reliably evaluated in single arm trials.

6.6.3 Subsequent therapies

After pralatrexate 70% of the patients received subsequent therapy that was available to these refractory patients. The therapies ranged from 1-7 different regimens With a median of 2 regimens (Table 16). Thirteen patients underwent stem cell transplant.

Table 16 Subsequent therapies after pralatrexate treatment

	Subsequent Therapy	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)
	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)

6.6.4 Analysis of Clinical Information Relevant to Dosing Recommendations

The dose of pralatrexate was 30 mg/m² (the recommended Phase 2 dose from the PDX-02-078 study), administered IV once weekly for 6 weeks followed by 1 week of rest for a 7 week cycle. All patients received vitamin supplementation consisting of vitamin B12 and folic acid. Dose reductions to 20 mg/m² due to toxicity were allowed.

If the patient developed an AE indicating intolerance of this lowest dose of 20 mg/m²/week, the patient was to be discontinued from study treatment. Re-escalation of the pralatrexate dose once a dose reduction occurred was not allowed.

AEs were the reason for dose reductions in 31%, dose omission in 69% and treatment withdrawal in 22% of the patients.

The majority of all dose modifications were due to mucosal inflammation.

7 Review of Safety

Safety Summary

All patients (n=111) experienced at least 1 AE. The most frequently reported AEs regardless of causality were mucosal inflammation (70%), thrombocytopenia (41%), and nausea (40%). The other frequently reported AEs (reported in > 25% of patients) were fatigue (36%), anemia (34%), constipation (33%), pyrexia (32%), edema (30%), cough (28%), and epistaxis (26%). The Grade 3 or 4 AEs regardless of causality reported most frequently were thrombocytopenia (32%), mucosal inflammation (21%), neutropenia (20%), and anemia (17%).

7.1 Methods

Pre-clinical, Phase I/II clinical studies as noted in efficacy section. In addition, this reviewer evaluated the safety datasets that were contained in the NDA submission.

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

PDX-008

7.1.2 Categorization of Adverse Events

AE's, (Adverse Events), SAE's (Serious Adverse Events) and Deaths.

Toxicities were graded according to the Common Terminology Criteria for Adverse Events (CTCAE) scale, Version 3.0.

7.2 Adequacy of Safety Assessments

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 Terminology 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.

. AEs were coded by body system using a medical dictionary for regulatory authorities (MedDRA®). Safety assessments appear to be adequate..

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

Out of 111 patients who received at least one dose of pralatrexate, 45/109 (41%) were off before cycle 2 or week 8; 85/109 (78%) were off before cycle 4 or 21 weeks (64% due to PD).

7.2.2 Explorations for Dose Response

According to clinical pharmacology review, there appears that there was no relationship of response with respect to drug exposure, i.e., responses in patients who had achieved a higher serum concentration of pralatrexate were not higher than those who had lower serum concentration of pralatrexate.

7.3 Major Safety Results

Safety assessments were performed on 111 enrolled patients who had received at least one dose of pralatrexate. Certain AEs were reported with similar preferred terms (e.g., mucosal inflammation, stomatitis) were grouped. Mucositis (70%) and thrombocytopenia (41%) were the most common AEs. The overall incidence of AEs regardless of causality was 100%. A total of 106 patients (95%) experienced AEs considered possibly, probably, or definitely related to pralatrexate treatment. Under the collective term of mucosal inflammation, 75 patients (68%) had a pralatrexate-related event. The severity was Grade 1 – 2 (n = 52, 47%), Grade 3 (n = 19, 17%), and Grade 4 (n = 4, 4%). Nausea and fatigue occurred in 36 (32%) and 33 (30%) patients, respectively, and most events were mild or moderate. Most hematological AEs were considered treatment-related, which is also consistent with the expected safety profile for pralatrexate. Under the collective term of thrombocytopenia, 44 patients (40%) had a pralatrexate-related event. The severity was Grade 1 – 2 (n = 9, 8%), Grade 3 (n = 16, 14%), and Grade 4 (n = 19, 17%). Under the collective term of anemia, 36 patients (32%) had a pralatrexate-related event. The severity was Grade 1 – 2 (n = 20, 18%), Grade 3 (n = 14, 13%), and Grade 4 (n = 2, 2%).

7.3.1 Deaths

Eight deaths were reported within 30 days of their last dose of pralatrexate were reported. Seven were attributed to PD and review of narrative death reports could not exclude the causality as progression of disease in these patients. One was attributed to cardiopulmonary arrest, possibly related to pralatrexate.

Narratives of Deaths

PATIENT 004

Patient was a 77-year-old white male initially diagnosed with angioimmunoblastic T-cell lymphoma on 19 Dec 2005. A report was received from the site when this patient died from PD 28 days after initiating study therapy with pralatrexate. The patient was hospitalized on (b) (6) for fever with a subsequent diagnosis of PD. The study drug was permanently discontinued. The patient was discharged to hospice on (b) (6). He subsequently died on (b) (6).

Clinical Review
Shakun Malik, MD
NDA 022468
Folotyn (Pralatrexate)

PATIENT 008

Patient was a 62-year-old white male initially diagnosed with unspecified peripheral T-cell lymphoma (PTCL-U) on 09 Jan 2006. A report was received from the site when this patient died from PD 47 days after initiating study therapy with pralatrexate. The patient was admitted to the hospital on (b) (6) secondary to thrombocytopenia and treated with red blood cell and platelet transfusions. A bone marrow biopsy revealed hypercellular marrow with near-total replacement by large-cell lymphomatous infiltrate, 90% of marrow cellularity, and markedly reduced myeloid, erythroid, and megakaryocytic maturation. A computed tomography (CT) scan of the abdomen and pelvis identified soft tissue masses in the inguinal, iliac, and aortocaval regions as well as splenomegaly with multiple low-density regions in the spleen. The patient's condition stabilized and he was discharged on (b) (6). However, he ultimately died on (b) (6).

PATIENT 042

Patient was a 78-year-old white male initially diagnosed with angioimmunoblastic T-cell lymphoma in Dec 2005. Prior to the initiation of study treatment, the patient was hospitalized from (b) (6) for fever and fatigue. Three days after discharge, he was re-hospitalized (preplanned admission) for the administration of study drug. The patient received the first dose of pralatrexate (30 mg/m², dosing weight 70.8 kg) on (b) (6). He remained hospitalized at that time due to fatigue. One week later, the (b) (6) patient developed Grade 2 mucositis and the second dose of pralatrexate administered on (b) (6) was reduced to 20 mg/m². On (b) (6), the patient's mucositis worsened to Grade 4 and he began to develop pancytopenia as evidenced by Grade 4 thrombocytopenia and Grade 3 anemia. Three days later, he was noted to have Grade 4 neutropenia. On (b) (6), the patient developed DYSPNEA secondary to PD. Laboratory test results and treatment details were not provided. The study drug was permanently discontinued. The mucositis and pancytopenia were considered resolved on (b) (6). The patient remained hospitalized until his death due to PD or (b) (6). The sponsor assessed the event as not related to pralatrexate.

PATIENT 048

Patient was a 64-year-old white male initially diagnosed with PTCL-U on 16 Aug 2006. A report was received from the site when this patient was hospitalized on (b) (6), for neutropenic fever and mucositis 82 days after initiating study treatment with pralatrexate. Despite treatment with broad-spectrum intravenous (IV) antibiotics, IV fluids, and granulocyte colony-stimulating factor, the events persisted. The patient remained hospitalized until the time of his death on (b) (6) due to cardiopulmonary arrest. The investigator assessed the neutropenic fever as severe in intensity and as probably related to pralatrexate. The sponsor assessed the neutropenic fever as probably related to pralatrexate.

Clinical Review
Shakun Malik, MD
NDA 022468
Folotyn (Pralatrexate)

PATIENT 066

Patient was a 41-year-old black male initially diagnosed with transformed mycosis fungoides on 03 Jul 2007. A report was received from the site when this patient was hospitalized for PD 28 days after initiating study treatment with pralatrexate. The patient received the last dose of pralatrexate 30 mg/m² on (b) (6). He was hospitalized on (b) (6) with persistent fever, decreased performance status, diffuse erythroderma, and edema secondary to PD and its metabolic impact. The patient subsequently died due to PD on (b) (6).

The investigator assessed the PD as not related to pralatrexate. The sponsor assessed the event as not related to pralatrexate.

PATIENT 077

Patient was a 24-year-old white male initially diagnosed with anaplastic large-cell lymphoma (ALCL) on 22 Dec 2006. A report was received from the site when this patient was hospitalized for PD and acute renal failure 21 days after initiating study treatment with pralatrexate. The patient received the first dose of pralatrexate (30 mg/m²) on (b) (6) and last received study drug on (b) (6) at a reduced dose (20 mg/m²) due to Grade 3 mucositis. After receiving study treatment on (b) (6), the patient was hospitalized with acute renal failure secondary to bilateral ureterohydronephrosis due to PD. The study drug was discontinued. The patient remained hospitalized until his death due to PD on (b) (6).

The investigator assessed the PD and acute renal failure as very severe/life-threatening in intensity and as not related to pralatrexate.

PATIENT 087

Patient was a 40-year-old white female initially diagnosed with PTCL-U on 07 Aug 2007. A report was received from the site when this patient was hospitalized for neutropenic fever and shortness of breath secondary to PD 97 days after initiating study treatment with pralatrexate. The patient was hospitalized from (b) (6) for fever and shortness of breath, and the study drug was discontinued due to PD. On (b) (6) the patient was re-admitted for neutropenic fever and shortness of breath. A CT scan and chest x-ray revealed marked progression of disease. Despite treatment with antibiotics and chemotherapy, the patient died from PD on (b) (6).

PATIENT 095

Patient was a 65-year-old hispanic female initially diagnosed with PTCL-U on 19 Jul 2007. A report was received from the site when this patient died from PD 73 days after initiating study treatment with pralatrexate. The study drug had been permanently discontinued, with the last dose received on 26 Feb 2008. She was hospitalized several times throughout the study before she was transferred to hospice and subsequently died from PD on (b) (6).

7.3.2 Nonfatal Serious Adverse Events

Forty-nine patients (44%) experienced 107 SAE's while on study or within 30 days after their last dose of pralatrexate. The SAEs reported for > 3 patients that usually resulted in hospitalization included

- Pyrexia 8
- Mucosal Inflammation 6
- Febrile Neutropenia 5 (1 septic shock)
- Sepsis 5
- Thrombocytopenia 3

The most common SAEs were pyrexia, mucosal inflammation, febrile neutropenia, sepsis, dehydration, and dyspnea.

7.3.3 Dropouts and/or Discontinuations

Table 17 Reasons for Treatment Discontinuation

Patients who discontinued study treatment	102 (92%)
Reason for discontinuing study treatment	
Disease Progression	64 (58%)
Adverse Event	25 (23%)
Investigator Decision	7 (6%)
Patient Decision	5 (5%)
Other	1 (< 1%)

In total, 102 (96%) of patients were off study treatment at the time of data cut off. More than half were due to disease progression, 23% adverse events, 6% investigator decision and 5% was due to patient decision (Table 17).

7.3.4 Significant Adverse Events

The AEs reported as the reason for withdrawal from treatment with pralatrexate most frequently were mucosal inflammation (n = 7, 6%) and thrombocytopenia (n = 5, 5%).

Clinical Review
 Shakun Malik, MD
 NDA 022468
 Folutyn (Pralatrexate)

Patients underwent weekly physical examination 6/7 during the treatment period, re weekly while patients were on the study

Under the collective term of mucosal inflammation, 78 patients (70%) had an event, which was the most frequently occurring AE when analyzed by grouping similar preferred terms. The severity was Grade 1 – 2 (n = 55, 50%), Grade 3 (n = 19, 17%), and Grade 4 (n = 4, 4%). The AE that occurred second most frequently when similar preferred terms were combined was thrombocytopenia. Thrombocytopenia occurred in 45 patients (41%) and the severity was Grade 1 – 2 (n = 9, 8%), Grade 3 (n = 15, 14%), and Grade 4 (n = 21, 19%). Only 5 patients (5%) had platelet counts on study of < 10,000/ μ L. The other frequently reported AE terms (reported in > 25% of patients) were nausea (n = 44, 40%), fatigue (n = 40, 36%), anemia (n = 38, 34%), constipation (n = 37, 33%), pyrexia (n = 36, 32%), edema (n = 33, 30%), cough (n = 31, 28%), and epistaxis (n = 29, 26%). These events were mainly mild to moderate in severity and none resulted in dose reduction other than in 1 patient with fatigue.

Table 18 AEs Occurring in \geq 20% of Patients (N = 111)

Adverse Event	Grade 1	Grade 2	Grade 3	Grade 4	Total
Mucosal inflammation (grouped)	20%	30%	17%	4%	70%
Thrombocytopenia (grouped)	1%	7%	14%	19%	41%
Nausea	24%	12%	4%	--	40%
Fatigue	19%	11%	5%	2%	36%
Anemia (grouped)	4%	14%	15%	2%	34%
Constipation	24%	9%	--	--	33%
Pyrexia	23%	8%	1%	1%	32%
Edema (grouped)	18%	11%	1%	--	30%
Cough	23%	4%	1%	--	28%
Epistaxis	24%	2%	--	--	26%
Vomiting	16%	7%	2%	--	25%
Neutropenia (grouped)	--	5%	13%	7%	24%
Diarrhea	13%	6%	2%	--	21%

7.3.5 Electrocardiograms (ECGs)

QT/QTc effects of pralatrexate As per applicant in vitro findings suggest that it is unlikely that pralatrexate would induce QT prolongation in vivo conditions. Screening ECGs were performed as a clinical safety measure prior to dosing with pralatrexate in

Clinical Review
Shakun Malik, MD
NDA 022468
Folotyn (Pralatrexate)

several studies (including lymphoma studies PDX-008 and PDX-009). However, no ECGs were performed post dose in these studies, unless clinically indicated. Therefore, there is no comparison of QT/QTc effects of pralatrexate available for these trials. In PDX-008, all patients had an ECG within 21 days prior to the projected start of pralatrexate administration. If clinically indicated at anytime during study, an ECG was to be repeated; however, no repeat ECGs were reported.

A QTc assessment was completed in a subgroup of 14 evaluable patients who received pralatrexate doses of 190 or 230 mg/m² every 2 weeks over 3-5 minutes or over 1 hour in the ongoing Phase 1 clinical trial of patients with NSCLC (PDX-007, **Table 2**), entitled “**A Phase 1 Open-label Study of (RS)-10-Propargyl-10-Deazaaminopterin [PDX] with Vitamin B12 and Folic Acid Supplementation in Patients with Previously-treated Advanced Non-small Cell Lung Cancer**”. Patients received a significantly higher dose of pralatrexate in the dose treatment regimen for NSCLC than for the PTCL indication (190 to 230 mg/m² vs 30 mg/m²). With protocol Version 2.5, there was intensive ECG monitoring correlated with PK plasma sampling of pralatrexate concentrations. A 12-lead ECG was performed at screening, 2 triplicate ECGs at baseline (just prior to pralatrexate injection), and then triplicate ECGs were obtained at the end of infusion and 1, 3, and 6 hours post-infusion in conjunction with pralatrexate plasma PK collections. In addition, single 12-lead ECGs were obtained pre-injection and within 30 minutes post-injection for the first dose of each odd-numbered cycle thereafter. Amendment #6 (Version 2.6) provided for the use of a central laboratory, using a single reader to perform the review and evaluations of the ECGs. Overall, pralatrexate demonstrated only a negligible impact on cardiac repolarization as assessed by changes in the QTcF. With regard to categorical thresholds for arrhythmia risk, no patient exhibited a QTc interval > 500 msec using **either Bazett’s or Fridericia’s correction formula, which represents a threshold of concern for drug-induced arrhythmia risk**. Additionally, no patient exceeded a QTcF of 470 msec and only 1 patient exhibited an absolute QTcF interval > 450 msec. No patient exhibited an absolute increase from baseline in QTcF exceeding 30 msec.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

The most frequent form of dose modification due to AEs was dose omission, which occurred in 77 patients (69%). The target pralatrexate dose in this study was 30 mg/m² for 6 of 7 weeks and the majority of patients (n = 77, 69%) remained at this dose for the duration of treatment. The pralatrexate dose was reduced from 30 mg/m² to 20 mg/m² for 34 patients (31%). Dose reduction below 20 mg/m² was not allowed. Sixty-two percent (n = 69) of the patients missed 1 or more doses in cycle 1, and 21 patients (19%) had their dose reduced in cycle 1. AEs were the reason for dose reductions in 31%, dose omission in 69% and treatment withdrawal in 22% of the patients.

The majority of all dose modifications were due to mucosal inflammation, which was reported as the reason for missed doses for 47 patients (42%) and dose reduction for 25 patients (23%). However, there was overlap in the numbers of dose omissions and dose reductions as some patients had both type of dose modification as a consequence of AEs.

Thrombocytopenia was listed for 28 patients (25%) as the reason for dose omission. The timing and severity of thrombocytopenia did not change to a great extent after dose reduction. Neutropenia was the reason for dose omission for 13 patients (12%) and febrile neutropenia caused 3 patients (3%) to miss doses.

Abnormal liver function tests (ALT and/or AST increases) resulted in dose omission in 3 (3%) patients. Two patients had a dose reduction due to abnormal liver function tests.

7.5.2 Drug-Demographic Interactions

In order to evaluate the effects of PK by age, gender, and race, integrated covariate analysis was performed on pooled data from 54 patients across two Phase 1 (PDX-007, PDX-99-083) and one Phase 2 (PDX-008) studies (Table 2). The final PK study population was 52% (28/54) female and 48% (26/54) male. A total of 81% (44/54) were White, 15% (8/54) Black, 2% (1/54) Asian, and 2% (1/54) of unknown ethnicity. Age ranged from 24 to 77 (mean: 60) years, body weight ranged from 43 to 127 (mean: 77) kg, while creatinine clearance, as calculated by the Cockcroft-Gault formula (CL_{creaCG}) ranged from 53 to 130 mL/min (mean: 89 mL/min), indicating a mostly elderly, mildly renally impaired population of "normal" weight, with considerable dispersion. In addition, a population pharmacokinetic (POPPK) analysis was also performed across the above studies (PDX-007, PDX-99-083, PDX-008) and the database comprised 154 patients.

Gender: in PDX-008, the overall percentage of occurrence of all selected AEs grouped by similar preferred term was identical between genders (91%). However, the frequency of mucosal inflammation, thrombocytopenia, anemia, edema, neutropenia, hypokalemia, pruritus, preferred term was identical between genders (91%). However, the frequency of mucosal inflammation, thrombocytopenia, anemia, edema, neutropenia, hypokalemia, pruritus, dyspepsia, liver function test abnormalities, and leukopenia is greater in female patients. There were no significant gender differences in PK parameters.

Race: covariate analysis did not reveal race as a significant covariate.

Ethnicity: although there are differences in the epidemiology of PTCL worldwide (frequency and distribution of subtypes), with a higher incidence in Asia, the clinical trials of pralatrexate in PTCL did not extend to Asia. The early studies

with pralatrexate were conducted at MSKCC. Subsequently, clinical trials with pralatrexate expanded to include the United States (US), Canada, and Europe. There are no clearly observed differences in the epidemiology of PTCL in these regions. There were no observed clinically significant differences among the geographic regions studied with pralatrexate with respect to clinical safety.

7.5.4 Drug-Disease Interactions

Renal Impairment: the safety and effectiveness of pralatrexate has not been evaluated in patients with moderate and severe renal impairment. Patients with creatinine > 1.5 mg/dL or calculated creatinine clearance < 50 mL/min were routinely excluded from clinical studies. In humans, pralatrexate is substantially excreted unchanged into urine (approximately 34%), while the remainder is cleared nonrenally, presumably by hepatobiliary excretion. Renal clearance (CL_{ren}) values, corrected for plasma protein binding, suggest net renal tubular secretion, while nonrenal clearance (CL_{nonren}) values suggest that pralatrexate is a low-hepatic-extraction ratio drug. POPPK analysis revealed a correlative trend between age and decline in renal function with increased pralatrexate plasma exposure. Because of the relative contribution of renal excretion to pralatrexate clearance in patients, caution is advised when treating patients with moderate and severe renal impairment. It is recommended that patients be monitored for renal function.

Hepatic Impairment; no studies investigating pralatrexate in patients with hepatic impairment have been performed. Pralatrexate was not evaluated in patients with hepatic impairment. Patients with total bilirubin > 1.5 mg/dL, AST and ALT > 2.5 × upper limit of normal (ULN), (AST/ALT > 5 × ULN if documented hepatic involvement with lymphoma) were excluded from PDX-008. Liver function test abnormalities have been observed after pralatrexate administration but are usually not cause for modification of pralatrexate treatment. Persistent liver function test abnormalities may be indicators of liver toxicity and may require evaluation. It is recommended that patients be monitored for liver function.

7.5.5 Drug-Drug Interactions

No formal clinical assessments of pharmacokinetic drug-drug interactions between pralatrexate and other drugs have been conducted. However, the effect of co-administration of the uricosuric drug probenecid on pralatrexate PK was investigated in a Phase 1 clinical study. Co-administration of increasing doses of probenecid resulted in delayed clearance of pralatrexate and a commensurate increase in exposure.

7.6 Additional Safety Evaluations

7.6.1 Human Reproduction and Pregnancy Data

Pralatrexate may cause fetal harm when administered to a pregnant woman.

7.6.2 Pediatrics and Assessment of Effects on Growth

Pediatric patients were not included in clinical studies with pralatrexate. All studies to date have required that patients be more than 18 years of age to meet eligibility criteria. Therefore, the safety of pralatrexate in pediatric patients has not been established. In addition, there have been no nonclinical studies specifically performed in juvenile animals. It is exempted under Orphan Product designation.

8 Appendices

8.1 Literature Review/References

- 1) Ascani S, Zinzani PL, Gherlinzoni F, et al: Peripheral T-cell lymphomas: Clinico-pathologic study of 168 cases diagnosed according to the REAL classification. *Ann Oncol* 8:583-592, 1997.
- 2) Anderson JR, Armitage JO, Weisenburger DD, et al: Epidemiology of the non-Hodgkin's lymphomas: Distributions of the major subtypes differ by geographic locations. *Ann Oncol* 9:717-720, 1998.
- 3) Nakamura S, Koshikawa T, Koike K, et al: Phenotypic analysis of peripheral T-cell lymphoma among the Japanese. *Acta pathol Jpn* 43:396-412, 1993
- 4) Julie M. Vose, MD, Neumann M. and Mildred E. Harris et al: International Peripheral T-Cell and Natural Killer/T-Cell Lymphoma Study: Pathology Findings and Clinical Outcomes *Journal of Clinical Oncology*, Vol 26, No 25 (September 1),pp. 4124-4130 2008.
- 5) Jaffe ES, Harris NL, Stein H, Vardiman JW. *World Health Organization Classification of Tumours: Pathology and Genetics of Tumours of the Haematopoietic and Lymphoid Tissues*. Lyon: IARC Press; 2001.
- 6) Savage KJ, Chhanabhai M, Gascoyne RD, Connors JM. Characterization of peripheral T-cell lymphomas in a single North American institution by the WHO classification. *Ann Oncol* 2004;15:1467-1475.
- 7) 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;92:76-82.**
- 8) Lopez-Guillermo A, Cid J, Salar A, et al. Peripheral T-cell lymphomas: initial features, natural history, and prognostic factors in a series of 174 patients diagnosed according to the R.E.A.L. Classification. *Ann Oncol* 1998;9:849-855.

Clinical Review
Shakun Malik, MD
NDA 022468
Folotyn (Pralatrexate)

- 9) Escalon MP, Liu NS, Yang Y, et al. Prognostic factors and treatment of patients with T-cell non-Hodgkin lymphoma: the M. D. Anderson Cancer Center experience. *Cancer* 2005;103:2091-2098.
- 10) Gressin R, Peoch M, Deconinck E, et al. The VIP-ABVD regimen is not superior to the CHOP 21 for the treatment of non epidermotropic peripheral T-cell lymphoma. Final results of the "LTP95" protocol of the GOELAMS [abstract]. *Blood* 2006;108:Abstract 2464
- 11) Kewalramani T, Zelenetz AD, Teruya-Feldstein J, et al. Autologous transplantation for relapsed or primary refractory peripheral T-cell lymphoma. *Br J Haematol* 2006;134:202-207.
- 12) Chen AI, McMillan A, Negrin RS, et al. Long term results of autologous hematopoietic cell transplantation (AHCT) for peripheral T-cell lymphoma: the Stanford experience [abstract]. *Blood* 2007;110:Abstract 1906
- 13) Andy I. Chen, Ranjana H. Advani, Beyond the Guidelines in the Treatment of Peripheral T-cell Lymphoma: New Drug Development Journal of the National Comprehensive Cancer Network: JNCCN Published: 04/01/2008; Updated: 04/30/2008
- 14) O'Connor OA, Hamlin PA, Gerecitano J, et al. Pralatrexate (PDX) produces durable complete remissions in patients with chemotherapy resistant precursor and peripheral T-cell lymphomas: results of the MSKCC phase I/II experience [abstract]. *Blood* 2006;108: Abstract 400.
- 15) Cheson BD, Horning SJ, Coiffier B, et al. Report of an international workshop to standardize response criteria for non-Hodgkin's lymphomas. NCI Sponsored International Working Group. *J Clin Oncol* 1999;17(4):1244-53.

8.2 Labeling Recommendations

See final labeling.

8.3 Advisory Committee Meeting

An oncologic drug advisory committee meeting (ODAC) was held on September 2, 2009 to discuss the clinical significance of the overall response rate and duration of response as well as the benefit:risk ratio for pralatrexate treatment in patients with relapsed or refractory PTCL.

The discussion revolved around the fact that there was no effective therapy available for patients with relapsed or refractory PTCL and that there was a small subset of patients in this trial who had a long DOR. The committee was asked **"are the response rate and duration of response results were "reasonably likely" to predict for clinical benefit?"** The committee voted 10 Yes to 4 No.

Application
Type/Number

Submission
Type/Number

Submitter Name

Product Name

NDA-22468

ORIG-1

ALLOS
THERAPEUTICS
INC

FOLOTYN

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

SHAKUNTALA M MALIK
09/16/2009

KE LIU
09/17/2009