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RESEARCH**

APPLICATION NUMBER:

22-468

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	September 16, 2009
From	Ke Liu, MD, PhD
Subject	Cross-Discipline Team Leader Review
NDA/BLA #	NDA 022-468
Supplement#	Supplements # 0-25
Applicant	Allos Therapeutics, Inc.
Date of Submission	March 23, 2009
PDUFA Goal Date	September 23, 2009
Proprietary Name / Established (USAN) names	Pralatrexate/ Foloty TM
Dosage forms / Strength	Intravenous
Proposed Indication	Single agent for the treatment of patients with relapsed or refractory peripheral T-cell lymphoma
Recommended:	Accelerated Approval

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1. Introduction

This NDA submission is based on overall response rate (ORR) from a single arm phase 2 trial (PDX-008) using pralatrexate as a single agent in the treatment of patients with relapsed or refractory PTCL.

One hundred fifteen (115) patients were enrolled in this multi-center international trial. One hundred and nine (109) eligible patients received pralatrexate at 30 mg/m² via intravenous push over 3-5 minutes once weekly for 6 weeks followed by a one week interval (one cycle). Intramuscular injection of 1 mg vitamin B12 was administered every 8-10 weeks along with 1.0 mg folic acid given orally once a day. The imaging scans were performed at Week 7 (end of cycle 1) to assess the disease status. Patients who had tumor responses or stable disease continued to receive additional cycles of pralatrexate. Subsequent tumor assessments were performed by scheduled imaging scans every 14 weeks.

The primary efficacy endpoint was response rate, based on the assessment from central review of imaging and clinical data according to the International Workshop Criteria (IWC) developed by the National Cancer Institute (NCI) sponsored International Working Group. 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.

The sponsor reported an overall response rate of 27% according to IWC (n = 29). This response rate was mostly driven by partial responders (20 out of 29 responders, or 18% of 109 evaluable patients). Nine patients (8%) achieved a CR. The median duration of response was 287 days.

The main review issues with this NDA that have been resolved include the following:

A. Duration of response (DOR)

Due to the lack of confirmatory scans according to IWC, the DOR in 16 of 29 responders (55%) was found to be less than 14 weeks, the time interval between two consecutive scans. Although, the Applicant-reported median DOR cannot be verified, the clinical/statistical team verified that thirteen of 29 responders (12% of 109 evaluable patients) had a DOR \geq 14 weeks.

This issue was resolved because 12% response rate with a DOR \geq 14 weeks was considered to be clinically significant in a rare, uncommon disease without currently available therapies.

B. Uncertain of response determination for the responders

In 52% of responders, tumor responses were adjudicated due to the disagreement between central readers 1 and 2 of independent image review committee. Determination of responses in some patients was also confounded by the possibility that the tumor shrinkage in these patients might have been due to the delayed effect of radiation rather than a treatment effect from pralatrexate, by the waxing and waning nature of lymphomas, by concomitant medication such as steroids and by inflammation and infections that could have affected the nodal sizes.

This issue was resolved after reviewing the source data showing that the adjudication was for the determination of partial responses vs. complete responses. The overall adjudication rate for all 109 evaluable patients was 34%. Case report form reviews indicated that there were 3 patients whose response determination was uncertain, representing a small percentage that would not change the conclusion of the review.

C. Inherent problems with single arm phase 2 study

Inherent with single arm studies are difficulties in interpreting the time to events endpoints of the study such as progression-free survival (PFS), time to progression (TTP), or overall survival (OS). In addition, lack of comparator arms in single arm trials makes it difficult to interpret the risk/benefit. The applicant has no on-going phase 3 clinical trials for pralatrexate in any indication.

This issue was resolved because of a prior special protocol assessment (SPA) agreement between the Applicant and FDA on the design of the single arm phase 2 trial to support the application.

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 committee was asked the following question: "Are the response rate and duration of response results "reasonably likely" to predict for clinical benefit? Clinical benefit in lymphomas would be defined as an improvement in overall survival or a robust effect on progression-free survival." The committee voted 10 Yes to 4 No.

2. Background

2.1 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's (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). In general, PTCL has worse prognosis compared to their B-cell counterparts. However, anaplastic large cell has better survival than any other subtypes (4, 6).

Patients with a higher International prognostic Index (IPI) score have a shorter survival. 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).

Currently, there are no approved therapies and no standard of care for the treatment of PTCL. 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). 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).

2.2 Major Regulatory Milestones for Pralatrexate Development

In February 2006, the sponsor communicated to FDA that a positive signal was identified in a subset of lymphoma patients (PTCL) in a phase I trial. 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.

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 Overall Response Rate (ORR) is acceptable, however, stated that 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.

2.3 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 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).

3. CMC/Device

There are no unresolved CMC issues

4. Nonclinical Pharmacology/Toxicology

There are no unresolved nonclinical Pharmacology/Toxicology issues

5. Clinical Pharmacology/Biopharmaceutics

5.1 Demographic Interactions

Data from 54 patients from two Phase 1 (PDX-007, PDX-99-083) and one Phase 2 (PDX-008) studies were pooled to evaluate the effects of pharmacokinetics by age, gender, and race. Integrated covariate analysis was performed. 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, 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.

5.2 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.

5.3 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.

5.4 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 several studies (including lymphoma studies PDX-008 and PDX-009). However, no ECGs were performed postdose 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), 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.

5.5 Remaining Clinical Pharmacology Issues

- Perform *in vitro* studies to determine if transporters are involved in the elimination of pralatrexate.
- A clinical trial in patients with renal impairment to include patients with severe renal impairment.

These issues have been discussed with the Applicant and the Applicant has agreed to perform these studies and the trial described above.

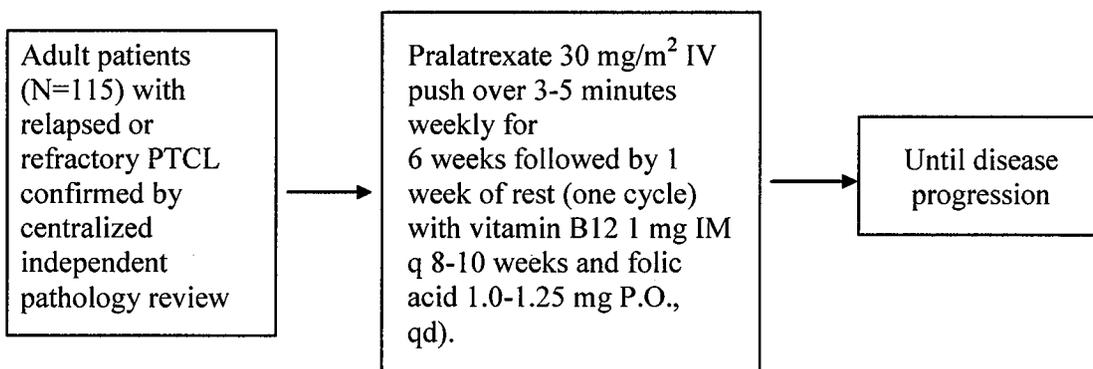
6. Clinical Microbiology

No issues.

7. Clinical/Statistical- Efficacy

This NDA submission is based on one single arm trial (PDX-008). The design of this trial was based on the results of a phase 1 trial where a 65% ORR rate with 56% CR was observed in 16 patients with PTCL.

PDX-008 trial design is shown below in the following Figure.



Histologic subtypes of patients enrolled were shown in Table 1

Table 1. Tumor Histologies

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%

Responses were shown in Table 2

Table 2. FDA's Analyses of Responses

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

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, FDA cannot verify these responses and their duration in these 13 responders except that these responses lasted < 14 weeks.

FDA 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 (Table 4 above bold and underlined) with 6 CR (5%), 1 CRu (1%) and 6 PR (5%). Median duration of response in these patients cannot be assessed due to few events and data censoring.

This 12% response rate with a DOR \geq 14 weeks was considered to be clinically significant.

8. Safety

Safety assessments were performed on 111 enrolled patients who had received at least one dose of pralatrexate. Mucositis (70%) and thrombocytopenia (41%) were the most common AEs (Table 3). AEs were the reason for dose reductions in 31%, dose omission in 69% and treatment withdrawal in 22% of the patients

There were a total of 49 Serious Adverse Events (SAEs) reported and those reported in \geq 3 patients were pyrexia (8 patients), mucosal inflammation (6 patients), febrile neutropenia (5 patients), sepsis (5 patients, 1 septic shock), and thrombocytopenia (3 patients).

Eight deaths were reported within 30 days of their last dose of pralatrexate. Seven were attributed to PD and 1 was due to cardiopulmonary arrest (possibly related to pralatrexate).

Table 4 lists reasons for off-study treatment. The most common reason was due to disease progression in 64 patients. Twenty-five patients discontinued pralatrexate treatment due to adverse events.

Table 3. AEs Occurring in $\geq 20\%$ of Patients (N = 111)

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

Table 4. Reasons for off-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%)

There are no notable safety issues outstanding. The profile of pralatrexate toxicities has no significant differences from other anti-metabolite chemotherapeutic agents of similar class such as methotrexate.

9. 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 committee was asked the following question: "Are the response rate and duration of response results "reasonably likely" to predict for clinical benefit? Clinical benefit in lymphomas would be defined as an improvement in overall survival or a robust effect on progression-free survival." The committee voted 10 Yes to 4 No.

10. Pediatrics

Since the pralatrexate has orphan drug designation, the pediatric requirement is waived.

11. Other Relevant Regulatory Issues

No other regulatory issues remain at this time.

12. Labeling

See the labeling. The review team plans to approve the Prescribing Information for this review cycle since there is not enough time to review the Patient Counseling Information. The Applicant was informed about this decision and the request for the submission of Patient Counseling Information will be included in the Action Letter to be sent to the Applicant.

13. Recommendations/Risk Benefit Assessment

- Recommended Regulatory Action

I recommend an accelerated approval for pralatrexate as single agent in the treatment of patients with relapsed or refractory PTCL

- Risk Benefit Assessment

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 ≥ 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 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 on the question "Are the response rate and duration of response results were "reasonably likely" to predict for clinical benefit?"

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, was considered to most likely predict clinical benefit in patients with PTCL, a rare disease without currently available therapies.

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 anti-metabolite class.

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

- Recommended Comments to Applicant
 - 1) Updated data on duration of response was presented at the Oncologic Drugs Advisory Committee Meeting on September 2, 2009. Provide updated datasets and analyses that support this updated duration of response data and subsequent therapies received by responding patients. Provide data and analyses on the response to subsequent therapies in these patients.
 - 2) Provide updated survival data for all patients enrolled.
 - 3) Submit clinical protocols for at least two trials to confirm the clinical benefit of pralatrexate treatment in patients with peripheral T-cell lymphoma (PTCL).
 - A) 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.
 - B) Another trial could be a randomized controlled trial of single agent pralatrexate vs. an appropriate control in patients with relapsed or refractory PTCL.

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