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APPLICATION NUMBER:

22-468

OFFICE DIRECTOR MEMO

Office Director Memo

Date	September 21, 2009
From	Richard Pazdur, MD
Subject	Office Director Memo
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/ Folotyn 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

Summary:

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:

Due to the lack of confirmatory scans according to IWC, the duration of response (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.

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.

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 evaluation of 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.

Regulatory Background

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 recommended a phase 2 trial be conducted. 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.

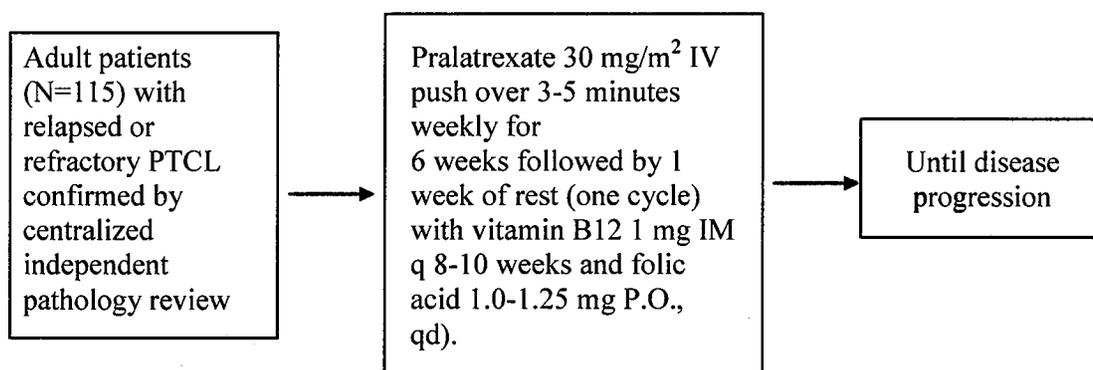
In July 2006, under the special protocol assessment (SPA), FDA recommended that a minimum of 100 patients be studied to support efficacy and safety in the NDA. FDA recognized that although peripheral T cell lymphoma is a heterogeneous disease, it is also a rare one. The eligibility criteria as proposed 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.

Clinical Study

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

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

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.

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.

Recommendations/Risk Benefit Assessment

- **Recommended Regulatory Action: Accelerated approval for pralatrexate as single agent in the treatment of patients with relapsed or refractory PTCL**
- **Risk Benefit Assessment:** 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. 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 likely to 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.

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. Datasets and analyses that support this updated duration of response data and subsequent therapies received by responding patients were requested to be submitted to FDA. Data and analyses on the response to subsequent therapies in these patients were requested.
 - 2) Updated survival data for all patients enrolled was requested to be submitted to FDA.
 - 3) Clinical protocols for at least two trials to confirm the clinical benefit of pralatrexate treatment in patients with peripheral T-cell lymphoma (PTCL) and/or related disease, such as cutaneous T-cell lymphoma were requested. These trials must be randomized trials demonstrating an effect on a clinically meaningful endpoint.

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/s/

RICHARD PAZDUR
09/21/2009