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June 2, 2010

Submission Request c/o Joan McClure
National Comprehensive Cancer Network
275 Commerce Dr, Suite 300
Fort Washington, PA 19034

Dear Ms. McClure,

Pralatrexate (FOLOTYN®), a folate analog inhibitor of dihydrofolate reductase, was approved by the US Food and Drug Administration in 2009 for the treatment of patients with relapsed/refractory Peripheral T-Cell Lymphoma (PTCL), and was included in the National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines for this aggressive group of lymphomas. The approval of pralatrexate was based on the results of a pivotal phase 2 open label international trial (referred to as PROPEL, N=111). The primary efficacy endpoint was objective response rate using independent central review of response. Patients enrolled in PROPEL had histologically/cytologically confirmed PTCL, using the Revised European American Lymphoma (REAL) WHO disease classification, including transformed mycosis fungoides (TMF).

Mycosis fungoides is the most common histologic type of cutaneous T-cell lymphoma. It often follows an indolent course, and may initially be treated with topical therapies. Histological transformation to a large T-cell lymphoma generally signifies a change to a clinical picture consistent with the more aggressive PTCL. Like other aggressive PTCL subtypes, TMF is a disease associated with a very poor prognosis with a median survival of less than 2 years, and responds poorly to agents used for the treatment of the more indolent CTCL.^{1,2} Because of the histopathological and clinical similarities to aggressive PTCL, TMF is generally considered as a PTCL and systemic therapies used are those employed for the treatment of PTCL. Thus, TMF patients were included in the PROPEL study and the results from PROPEL demonstrated that pralatrexate is active in TMF, with a tumor response rate similar to that observed for other aggressive PTCL subtypes included in PROPEL.^{3,4} Currently, TMF is included in the NCCN treatment guidelines for CTCL, and there is no mention of this more aggressive disease in the PTCL guidelines. Considering the REAL WHO disease classification of TMF, and the documented activity of pralatrexate in this disease, we ask that the NCCN Non-Hodgkin's Lymphoma Guidelines panel kindly consider adding a notation/footnote in the PTCL clinical practice guidelines regarding pralatrexate as a treatment option for patients with TMF.

Key Clinical Data

In the PROPEL trial, a total of 111 patients were evaluated for safety and 109 for efficacy. Patients were heavily pre-treated, with a median of 3 prior systemic therapies. The primary endpoint was objective response rate (ORR) using International Workshop Criteria, evaluated

by both independent central review (ICR) and investigator review. The ORR according to the ICR was 29% (32/109), including 11% complete response/complete response unconfirmed (CR/CRu). According to the investigator review, the ORR was 39% (43/109), including 18% CR/CRu⁴. The most common adverse events were mucosal inflammation and thrombocytopenia. Of the patients enrolled in PROPEL, 12 patients had TMF (according to ICR). The efficacy and safety of pralatrexate in the patients with TMF were similar to that observed in the overall population:

- The ORR in patients with TMF was 3/12 (25%) according to ICR³, and 7/12 (58%) according to the investigators assessment (*Allos database*)
- The adverse events experienced by the TMF patients were similar in frequency to the overall population in PROPEL, except for a lower incidence of thrombocytopenia and anemia in patients with TMF.

Given the similar histopathological and clinical features of TMF and PTCL, and the consistency of the results in the TMF subgroup with that of the overall PTCL population, the available data support broadening of the current NCCN Guidelines for the treatment of TMF to include pralatrexate.

Thank you for your consideration of this request.

Sincerely,



Dvorit Samid, PhD
Vice President, Medical Affairs
Allos Therapeutics, Inc

Cited references (enclosed)

1. Arulogun SO, Prince HM, Ng J, et al. Long term outcomes of patients with advanced-stage cutaneous T-Cell lymphoma and large cell transformation. *Blood* 2008; 112: 3082-3087.
2. Prince HM, Whittaker S, Hoppe RT. How I treat mycosis fungoides and Sezary syndrome. *Blood* 2009; 114:4337-4353.
3. O'Connor OA, Pro B, Pinter-Brown L, et al. PROPEL: A multi-center phase 2 open-label study of pralatrexate (PDX) with vitamin B12 and folic acid supplementation in patients with relapsed or refractory peripheral T-cell lymphoma. *Blood* 2008; 112:103. (ASH Annual Meeting, Abstract 261) and Presentation
4. Shustov AR, Pro B, Horwitz SM et al. Pralatrexate in patients with relapsed/refractory peripheral T-cell lymphoma (PTCL): Relationship between response and survival *J Clin Oncol* 2010; 28:7s (suppl; abstract 8054)