April 5, 2010

Submission Request c/o Joan McClure
National Comprehensive Cancer Network
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RE: Request for Addition of Oforta (oral fludarabine phosphate) for Use in 1st Line CLL and 1st and 2nd Line NHL

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Date of request: April 5, 2010
NCCN Guidelines Panel: NHL

Dear Ms. McClure:

As the National Comprehensive Cancer Network (NCCN) non-Hodgkin's lymphoma (NHL) Panel reviews the NCCN Clinical Practice Guidelines in Oncology for NHL, we respectfully request consideration of the inclusion of Oforta™ (oral fludarabine phosphate) as a treatment option for first-line chronic lymphocytic leukemia (CLL) and first- and second-line NHL.

Request for Addition of Oforta (oral fludarabine phosphate) for Use in 1st Line CLL and 1st and 2nd Line NHL

Oforta (oral fludarabine phosphate) is approved for use in adult patients with B-cell CLL whose disease has not responded to or has progressed during or after treatment with at least one standard alkylating-agent containing regimen.[1] Additionally, data exists evaluating the use of oral fludarabine phosphate as a single agent in the treatment of first line (previously untreated) CLL, including two studies summarized within the Oforta product labeling.[2-5] Patients received oral fludarabine phosphate 40 mg/m^2 daily for 5 days, every 28 days in both studies.[2-4] In Study 2 of the Oforta product labeling, the overall response rate according to NCI criteria was 80.2%, and 71.6% according to IWCLL criteria.[2] Myelosuppression was the most frequent grade 3/4 toxicity (granulocytopenia, 32.1%; anemia, 9.9%; thrombocytopenia, 4.9%). In Study 3, the overall response rate according to modified NCI criteria was 74%.[3-4] There was no significant difference in main toxicities between oral and IV fludarabine in this study. Data also exists for the use of oral fludarabine phosphate (24-30 mg/m^2) plus oral cyclophosphamide (150-250 mg/m^2) given for 3-5 days every 4 weeks in previously untreated CLL patients that demonstrate efficacy and acceptable toxicity.[3,6-8] The use of oral fludarabine phosphate in patients with NHL has also been evaluated, and includes previously treated and untreated patients with small lymphocytic, lymphoplasmacytic, follicular, marginal zone (including MALT lymphoma), and mantle cell lymphoma.[9-12] These data include the use of oral fludarabine phosphate (40 mg/m^2) as a single agent[9], oral fludarabine phosphate (25 mg/m^2) plus oral cyclophosphamide (150 mg/m^2)[10], as well as oral fludarabine phosphate (40 mg/m^2) plus intravenous rituximab.[11-12]

Specific change recommended

Consider the addition of Oforta (or listed Oforta-containing regimen) as a suggested treatment regimen in the following:

- CLL: First-line single agent therapy[2-5] and combined with oral cyclophosphamide[6-8] (CSLL-D)
- Follicular Lymphoma: First-line therapy combined with oral cyclophosphamide[10] (low dose regimen in elderly patients) or combined with rituximab[11] (FOLL-B)
- Follicular Lymphoma: Second-line and subsequent therapy as single agent[9] and in combination with rituximab[12] (FOLL-B)
- Mantle Cell Lymphoma: Second-line single agent therapy[9] (MANT-A)

FDA Status

Oforta (oral fludarabine phosphate) is approved for use in adult patients with B-cell CLL whose disease has not responded to or has progressed during or after treatment with at least one standard alkylating-agent containing regimen,[1] and is not approved for use in 1st line CLL or 1st or 2nd line NHL.

Rationale for recommended change

Multiple phase II studies evaluating the use of oral fludarabine phosphate as a single agent and in combination with oral cyclophosphamide or rituximab provide evidence for use in patients with CLL and NHL by demonstrating efficacy and acceptable toxicity.

Literature support

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4. Hillmen P, Richards S, Catovsky D. Comparison of oral and intravenous fludarabine in the LRF CLL4 trial. *Blood*. 2005,2006: Abstract 722.
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12. Tobinai K, Ishizawa K, Ogura M, et al. Phase II study of oral fludarabine in combination with rituximab for relapsed indolent B-cell non-Hodgkin lymphoma. *Cancer Sci*. 2009;100:1951-1956.