

June 8, 2010

Submission Request to the NCCN Guidelines Panel for Non-Hodgkin's Lymphoma

For your consideration, data is available on the use of maintenance Rituxan[®] (Rituximab) for the treatment of follicular non-Hodgkin's lymphoma (NHL). The Phase III, international, multicenter, randomized PRIMA study evaluated maintenance Rituxan in patients with previously untreated advanced follicular NHL who responded to initial treatment with Rituxan plus chemotherapy.^{1,2} The primary endpoint, progression free survival (PFS), was significantly longer in patients who received maintenance Rituxan compared with patients who did not receive maintenance Rituxan (hazard ratio [HR]=0.50; 95% CI: 0.39-0.64). Two-year PFS was 82% (95% CI: 78-86%) in patients who received Rituxan maintenance compared with 66% (95% CI: 61-70%) in patients who did not receive Rituxan maintenance. Grade 3/4 adverse events were reported in 22% of patients who received maintenance Rituxan compared with 16% of patients who did not receive Rituxan maintenance; and included neutropenia (4% vs. 1%, respectively) and infections (4% vs. 1%, respectively).

Long-term outcomes of the Phase III EORTC 20981 trial, which evaluated maintenance Rituxan therapy following induction with cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) or Rituxan plus CHOP (R-CHOP) in patients with relapsed/resistant follicular NHL, have recently been published.³ With a median follow-up of 6 years, the primary endpoint, PFS, was 3.7 years in patients who received maintenance Rituxan compared with 1.3 years in patients who did not receive maintenance Rituxan (HR=0.55; p<0.001). The 5-year overall survival, a secondary endpoint, was 74% in patients who received maintenance Rituxan and 64% in patients who did not receive maintenance Rituxan, but the difference was not statistically significant (p<0.07). In the Rituxan maintenance arm, Grade 3/4 neutropenia and infection were reported in 11.5% and 9.4% of patients compared with 6.0% and 2.4% in the observation arm, respectively.

In addition, the Phase III ECOG 1496 study (Study 5 in the Rituxan PI), which evaluated the use of Rituxan following induction with CVP chemotherapy has been enclosed for your review.⁴

Rituxan is not FDA-approved for the use of maintenance following induction with Rituxan plus chemotherapy for the treatment of follicular NHL. Please refer to the enclosed prescribing information for the full FDA-approved indications and safety information.⁵

The enclosures listed below are included for your review (copyright-paid where applicable). The 2010 ASCO oral presentation on the PRIMA study will be sent in a follow-up communication as soon as copyright permissions have been obtained.

- Hochster H, Weller E, Gascoyne RD, et al. Maintenance Rituximab after cyclophosphamide, vincristine, and prednisone prolongs progression-free survival in advanced indolent lymphoma: results of the randomized phase III ECOG1496 study. *J Clin Oncol*. 2009;27:1607-1614.
- Salles GA, Seymour JF, Feugier P, et al. Rituximab maintenance for 2 years in patients with untreated high tumor burden follicular lymphoma after response to immunochemotherapy. *J Clin Oncol* 2010;28(7 suppl):ASCO Abstract 8004.
- Van Oers MHJ, Van Glabbeke, Giurgea L, et al. Rituximab maintenance treatment of relapsed/resistant follicular non-hodgkin's lymphoma: long-term outcome of the EORTC 20981 phase III randomized intergroup study. *J Clin Oncol* 2010. E-pub Date: May 3, 2010. DOI #10.1200/JC.2009.26.5827.
- Rituxan Prescribing Information

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Cited References

1. Salles GA, Seymour JF, Feugier P, et al. Rituximab maintenance for 2 years in patients with untreated high tumor burden follicular lymphoma after response to immunochemotherapy. *J Clin Oncol* 2010;28(7 suppl):ASCO Abstract 8004.
2. Salles GA, Seymour JF, Feugier P, et al. Rituximab maintenance for 2 years in patients with untreated high tumor burden follicular lymphoma after response to immunochemotherapy. Presented at the American Society of Clinical Oncology in Chicago, IL; June 4-8, 2010. ASCO Oral Presentation.
3. Van Oers MHJ, Van Glabbeke, Giurgea L, et al. Rituximab maintenance treatment of relapsed/resistant follicular non-hodgkin's lymphoma: long-term outcome of the EORTC 20981 phase III randomized intergroup study. *J Clin Oncol* 2010. E-pub Date: May 3, 2010. DOI #10.1200/JCO.2009.26.5827.
4. Hochster H, Weller E, Gascoyne RD, et al. Maintenance Rituximab after cyclophosphamide, vincristine, and prednisone prolongs progression-free survival in advanced indolent lymphoma: results of the randomized phase III ECOG1496 study. *J Clin Oncol*. 2009;27:1607-1614.
5. Rituxan Prescribing Information