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NCCN Guidelines Panel: Non-Hodgkin's Lymphoma

On behalf of Genentech, I respectfully request the NCCN Non-Hodgkin's Lymphoma (NHL) Guideline Panel to review the enclosed data for Rituxan[®] (Rituximab) maintenance for the treatment of mantle cell lymphoma.

Specific Changes: Consider the recently presented data on Rituxan maintenance for the treatment of mantle cell lymphoma for your updating purposes.

FDA Clearance: The FDA has not approved Rituxan for the treatment of mantle cell lymphoma. Please refer to the enclosed prescribing information (PI) for the full FDA-approved indications and safety information.

Rationale: Results from an open-label, randomized, Phase III trial evaluating Rituxan for the treatment of mantle cell lymphoma were recently presented at the 11th International Conference on Malignant Lymphoma (ICML) on June 15-18 in Lugano, Switzerland.^{1,2} In the trial, elderly patients with mantle cell lymphoma were randomized to receive Rituxan in combination with cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) or Rituxan in combination with fludarabine and cyclophosphamide (R-FC). Patients who responded were further randomized to Rituxan maintenance or interferon-alfa, given until progression. Overall response rates were 78% in the R-CHOP arm and 87% in the R-FC arm ($p=0.0581$). Complete remission rates were similar for the R-CHOP and R-FC arms (38% vs. 34%, respectively). Remission duration was significantly longer in the Rituxan maintenance arm compared with the interferon-alfa arm (51 months vs. 24 months, respectively; $p=0.012$). Hematologic Grade 3/4 adverse events were reported more frequently in the R-FC arm, including thrombocytopenia. Reported non-hematologic Grade 3/4 adverse events included neutropenic fever and infections.

The long-term follow-up of a separate, single armed, Phase II study was recently published in Leukemia and Lymphoma.³ This study evaluated Rituxan maintenance following Rituxan in combination with hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone (hyperCVAD) chemotherapy in patients with mantle cell lymphoma. The primary endpoint, complete response to induction was 64%. With a follow-up of 62 months, the median progression-free survival and overall survival were 38 months and 70 months, respectively. During the induction phase, the major toxicity was myelosuppression. No late toxicities were noted in the long-term follow-up.

Additional data on Rituxan maintenance therapy in mantle cell lymphoma has been previously reported.³⁻¹⁶

The following enclosures are included for your review (copyright-paid where applicable):

- Kluin-Nelemans JC, Hoster E, Hermine O, et al. R-CHOP versus R-FC followed by maintenance with rituximab or IFN: first results of a randomized trial for elderly patients with mantle cell lymphoma. *Ann Oncol* 2011;22(suppl 4):iv86-iv89. ICML Abstract #016.
- Kenkre VP, Long WL, Eickhoff JC, et al. Maintenance rituximab following induction chemo-immunotherapy for mantle cell lymphoma: long-term follow-up of a pilot study from the Wisconsin Oncology Network. *Leuk Lymphoma*. 2011;[epub]:1-6.
- Rituxan Prescribing Information

Cited References

1. Kluin-Nelemans JC, Hoster E, Hermine O, et al. R-CHOP versus R-FC followed by maintenance with rituximab or IFN: first results of a randomized trial for elderly patients with mantle cell lymphoma. *Ann Oncol* 2011;22(suppl 4):iv86-iv89. ICML Abstract #016.
2. ClinicalTrials.gov. Induction chemotherapy (R-CHOP vs. R-FC) followed by interferon maintenance versus rituximab maintenance in MCL (NCT00209209). Available at: www.clinicaltrials.gov. Accessed June 20, 2011.
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4. Ghielmini M, Schmitz SF, Cogliatti SB, et al. Prolonged treatment with rituximab in patients with follicular lymphoma significantly increases event-free survival and response duration compared with the standard weekly x 4 schedule. *Blood* 2004;103:4416-4423.
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8. Dreyling M, Hoster E, Hermine O, et al. European Mantle Cell Lymphoma Network: an update on current first line trials. Presented at the 10th International Conference on Malignant Lymphoma in Lugano, Switzerland; June 4-7, 2008. ICML Poster #300.
9. Dreyling M, Hoster E, Hermine O, et al. European Mantle Cell Lymphoma Network: an update on current first line trials. *Ann Oncol* 2008;19(suppl 4):iv173. ICML Abstract #300.
10. Angona A, Saumell S, Sánchez-González B, et al. Rituximab maintenance after first line immunochemotherapy achieves excellent high disease control in both de novo follicular and mantle cell lymphomas. *Haematologica* 2010. EHA Abstract #1570.
11. Blum K, Baiocchi RA, Alinari L, et al. A phase II trial of induction plus maintenance rituximab and bortezomib in patients with relapsed/refractory mantle cell (MCL) and follicular (FL) non-Hodgkin's lymphoma. *Blood* 2008;112. ASH Abstract #3053.
12. Kahl BS, Longo WL, Eickhoff JC, et al. Maintenance rituximab following induction chemoimmunotherapy may prolong progression-free survival in mantle cell lymphoma: a pilot study from the Wisconsin Oncology Network. *Ann Oncol* 2006;17:1418-1423.
13. Kahl BS, Peterson C, Blank J, et al. A feasibility study of VcR-CVAD with maintenance rituximab for untreated mantle cell lymphoma. *J Clin Oncol* 2007;25. ASCO Abstract #8062.
14. Rupolo M, Michieli M, Manuele R, et al. Maintenance immunotherapy after autologous bone marrow transplantation (ABMT) in relapsed follicular (R-FL) and mantle cell (R-MC) lymphomas (NHL). A monoinstitutional experience. *J Clin Oncol* 2008;26. ASCO Abstract #18012.

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16. Lim SH, Esler WV, Periman PO, et al. R-CHOP followed by consolidative autologous stem cell transplant and low dose rituxan maintenance therapy for advanced mantle cell lymphoma. *Br J Haematol* 2008;142:482-484.