



Submitted by:

Emily Costerison, Pharm.D., Scientist
Medical Communications, Medical Affairs
Genentech, Inc.

1 DNA Way

South San Francisco, CA 94080

Phone: (650) 225-8084

Email: mc-mc-d@gene.com

Date of request: February 29, 2012

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) plus fludarabine and cyclophosphamide (FC) for the treatment of mantle cell lymphoma (MCL) presented at the 53rd American Society of Hematology (ASH) Annual Meeting on December 10-13, 2011, in San Diego, California.

Specific Changes: Consider the recently presented data on Rituxan plus FC for the treatment MCL.

FDA Clearance: Rituxan is not FDA-approved for the treatment of patients with MCL. Please refer to the enclosed prescribing information for the full FDA-approved indications and safety information.

Rationale: In a Phase III, randomized trial, Rituxan plus FC was compared with FC in newly diagnosed patients with MCL (n=370).^{1,2} Overall survival, the primary endpoint, was significantly longer in the patients who received Rituxan plus FC compared with patients who received FC (hazard ratio=0.73 (95% CI: 0.54-0.97; p=0.03).² More patients in the Rituxan plus FC arm experienced Grade 3 or 4 leukopenia, neutropenia, and thrombocytopenia compared with patients on the FC arm. The number of deaths on trial was 113 patients in the FC arm and 91 patients in the Rituxan plus FC arm. A greater number of patients on the FC arm died of disease progression compared with the Rituxan plus FC arm (80 patients vs. 59 patients, respectively).

Additional data on Rituxan in combination with fludarabine-containing regimens,³⁻¹¹ cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP)-based regimens,¹²⁻¹⁸ hyper-fractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone (HCVAD),¹⁹⁻³⁰ and bendamustine,^{16,17,31-34} as well as Rituxan maintenance^{9,18,29,35-41} in the treatment of MCL has been previously reported.

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

- Rule S, Smith P, Johnson PW, et al. The addition of rituximab to fludarabine and cyclophosphamide (FC) improves overall survival in newly diagnosed mantle cell lymphoma (MCL): results of the randomized UK National Cancer Research Institute (NCRI) trial. Blood 2011;118. ASH Abstract #440.
- Rule S, Smith P, Johnson PW, et al. The addition of rituximab to fludarabine and cyclophosphamide (FC) improves overall survival in newly diagnosed mantle cell lymphoma (MCL): results of the randomized UK National Cancer Research Institute (NCRI) trial. Presented at the American Society of Hematology (ASH) December 10-13, 2011. ASH poster #440.
- Rituxan Prescribing Information

Cited References

1. Rule S, Smith P, Johnson PW, et al. The addition of rituximab to fludarabine and cyclophosphamide (FC) improves overall survival in newly diagnosed mantle cell lymphoma (MCL): results of the randomized UK National Cancer Research Institute (NCRI) trial. *Blood* 2011;118. ASH Abstract #440.
2. Rule S, Smith P, Johnson PW, et al. The addition of rituximab to fludarabine and cyclophosphamide (FC) improves overall survival in newly diagnosed mantle cell lymphoma (MCL): results of the randomized UK National Cancer Research Institute (NCRI) trial. Presented at the American Society of Hematology (ASH) December 10-13, 2011. ASH poster #440.
3. Rule S, Burton C, Waleski J, et al. A randomised phase II study of fludarabine/cyclophosphamide +/- rituximab in patients with untreated mantle cell lymphoma. *Ann Oncol* 2005;16:v95. ICML Abstract #198.
4. Eve H, Smith P, Qian W, et al. Toxicity of fludarabine and cyclophosphamide (FC) +/- rituximab (R) as initial therapy for patients with previously-untreated mantle cell lymphoma: results of a randomised phase II study. *Br J Haematol* 2007;137:19. BSH Abstract #56.
5. Rummel MJ, Kaiser U, Balser C, et al. Bendamustine plus rituximab versus fludarabine plus rituximab in patients with relapsed follicular, indolent and mantle cell lymphomas - final results of the randomized phase III study NHL 2-2003 on behalf of the StiL (Study Group Indolent Lymphomas, Germany). *Blood* 2010. ASH Abstract #856.
6. Forstpointner R, Dreyling M, Repp R, et al. The addition of rituximab to a combination of fludarabine, cyclophosphamide, mitoxantrone (FCM) significantly increases the response rate and prolongs survival as compared with FCM alone in patients with relapsed and refractory follicular and mantle cell lymphomas: results of a prospective randomized study of the German Low-Grade Lymphoma Study Group. *Blood* 2004;104:3064-3071.
7. Dreyling MH, Forstpointner R, Ludwig W, et al. Combined immuno-chemotherapy (R-FCM) results in superior remission rates and overall survival in recurrent follicular and mantle cell lymphoma follow-up of a prospective randomized trial of the German Low Grade Lymphoma Study Group (GLSG). *Proc Am Soc Clin Oncol* 2005;23:567s. ASCO Abstract #6528.
8. Dreyling M, Forstpointner R, Ludwig W, et al. The addition of rituximab to fludarabine combination (R-FCM) significantly improves remission rates and overall survival in recurrent follicular as well as mantle cell lymphoma - follow-up of a prospective randomized trial of the German Low Grade Lymphoma Study Group (GLSG). *Ann Oncol* 2005;16:v110-v111. ICML Abstract #252.
9. Dreyling M, Forstpointner R, Gramatzki M, et al. Rituximab maintenance improves progression-free and overall survival rates after combined immuno-chemotherapy (R-FCM) in patients with relapsed follicular and mantle cell lymphoma: final results of a prospective randomized trial of the German Low Grade Lymphoma Study Group (GLSG). *J Clin Oncol* 2006;24. ASCO Abstract #7502.
10. Thomas W, Owen RG, Johnson SAN, et al. Fludarabine/cyclophosphamide (FC) with or without rituximab is more active than CHOP in mantle cell lymphoma (MCL). *Br J Haematol* 2003;121:25. BSH Abstract #73.
11. Levine AM, Tulpule A, Smith L, et al. Results of a pilot trial of fludarabine, mitoxantrone and Rituxan in mantle cell lymphoma. *Blood* 2005;106:278a. ASH Abstract #945.
12. Drach W, Hopfinger G, Fridrik M, et al. R-CHOP plus thalidomide for previously untreated mantle cell lymphoma. *Haematologica* 2008;93:394-395. EHA Abstract #0991.
13. Elonen E, Raty R, Honkanen T, et al. Elderly patients with mantle cell lymphoma (MCL) – efficacy and feasibility of prolonged immunochemotherapy with rituximab, cytarabine and fludarabine added to CHOP and followed by rituximab maintenance treatment. A prospective study by the Finnish Lymphoma Group. *Blood* 2008;112. ASH Abstract #1001.
14. Ruan J, Martin P, Furman RR, et al. CHOP-R + bortezomib as initial therapy for mantle cell lymphoma (MCL). *Blood* 2009;114. ASH Abstract #2682.
15. Grant C, Dunleavy K, Tweiito M, et al. Bortezomib plus DA-EPOCH-rituximab followed by bortezomib maintenance versus observation in previously untreated mantle cell lymphoma (MCL). *J Clin Oncol* 2011;29. ASCO Abstract #8022.

16. Rummel MJ, Niederle N, Losem C, et al. Bendamustine plus rituximab vs CHOP plus rituximab in the first-line-treatment of patients with follicular, indolent and mantle cell lymphomas: second interim analysis of a randomized phase III study - NHL 1-2003 - of the StiL (Study Group indolent Lymphomas, Germany). Presented at the American Society of Hematology December 6-9, 2008, 2008. ASH Poster #2596.
17. Rummel MJ, von Gruenhagen U, Niederle N, et al. Bendamustine plus rituximab versus CHOP plus rituximab in the first-line-treatment of patients with follicular, indolent and mantle cell lymphomas: results of a randomized phase III study of the Study group indolent Lymphomas (StiL). *Blood* 2008;112. ASH Abstract #2596.
18. 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:iv87. ICML Abstract #016.
19. Romaguera JE, Fayad L, Rodriguez MA, et al. High rate of durable remissions after treatment of newly diagnosed aggressive mantle-cell lymphoma with rituximab plus hyper-CVAD alternating with rituximab plus high-dose methotrexate and cytarabine [published correction appears in *J Clin Oncol* 2006;24:724]. *J Clin Oncol* 2005;23:7013-7023.
20. Romaguera JE, Fayad L, Rodriguez MA, et al. Blastoid mantle cell lymphoma (MCL): 5-yr failure free survival (FFS) rate of 50%, without failures after 2.5 years following treatment with rituximab (R)-HyperCVAD alternating with R-methotrexate/cytarabine (M/A). *Blood* 2006;108. ASH Abstract#2749.
21. Fayad L, Thomas D, Romaguera J. Update of the M.D. Anderson Cancer Center experience with hyper-CVAD and rituximab for the treatment of mantle cell and Burkitt-type lymphomas. *Clin Lymphoma Myeloma* 2007;8:S57-S62.
22. Romaguera JE, Fayad LE, Feng L, et al. Ten-year follow-up after intense chemoimmunotherapy with rituximab-HyperCVAD alternating with rituximab-high dose methotrexate/cytarabine (R-MA) and without stem cell transplantation in patients with untreated aggressive mantle cell lymphoma. *Br J Haematol* 2010;150:200-208.
23. Kahl B, Li H, Smith MR, et al. The VcR-CVAD regimen produces a high complete response rate in untreated mantle cell lymphoma (MCL): first analysis of E1405 - a phase II study of VcR-CVAD with maintenance rituximab for MCL. *Blood* 2009;114. ASH Abstract #1661.
24. Feldman T, Mato AR, Zielonka T, et al. Effect of front-line therapy with either high-dose therapy and autologous stem cell rescue (HDT/ASCR) or dose-intensive therapy (R-Hypercvad) on outcome in mantle cell lymphoma (MCL). *J Clin Oncol* 2010;28. ASCO Abstract #8067.
25. Epner EM, Unger J, Miller T, et al. A multi center trial of hyperCVAD+Rituxan in patients with newly diagnosed mantle cell lymphoma. *Blood* 2007;110. ASH Abstract #387.
26. Merli F, Luminari S, Ilariucci F, et al. Rituximab plus hypercvad alternating with high dose methotrexate and cytarabine for patients with newly diagnosed mantle cell lymphoma. A multicenter trial from GISL. *Blood* 2008;112. ASH Abstract #3050.
27. Galimberti S, Palumbo GA, Caracciolo F, et al. The efficacy of rituximab plus hyper-CVAD regimen in mantle cell lymphoma is independent of FC γ R11a and FC γ R11a polymorphisms. *J Chemother* 2007;19:315-321.
28. 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.
29. Kenkre VP, Long WL, Eickhoff JC, et al. Maintenance rituximab following induction chemoimmunotherapy for mantle cell lymphoma: long-term follow-up of a pilot study from the Wisconsin Oncology Network. *Leuk Lymphoma* 2011;52:1675-1680.
30. Wang M, Fayad L, Cabanillas F, et al. Phase 2 trial of rituximab plus hyper-CVAD alternating with rituximab plus methotrexate-cytarabine for relapsed or refractory aggressive mantle cell lymphoma. *Cancer* 2008;113:2734-2741.
31. Weide R, Hess G, Köppler H, et al. High anti-lymphoma activity of bendamustine/mitoxantrone/rituximab in rituximab pretreated relapsed or refractory indolent lymphomas and mantle cell lymphomas. A multicenter Phase II study of the German Low Grade Lymphoma Study Group (GLSG). *Leuk Lymphoma* 2007;48:1299-1306.

32. Rummel MJ, Heine K, Bodenstein H, et al. Efficacy and safety of bendamustine and rituximab in the treatment of indolent and mantle cell lymphomas in older patients. *J Clin Oncol* 2008;26. ASCO Abstract #8572.
33. Robinson KS, Williams ME, van der Jagt RH, et al. Phase II multicenter study of bendamustine plus rituximab in patients with relapsed indolent B-cell and mantle cell non-Hodgkin's lymphoma. *J Clin Oncol* 2008;26:4473-4479.
34. Borgerding A, Hasenkamp J, Glaß B, et al. Rituximab retherapy in patients with relapsed aggressive B cell and mantle cell lymphoma. *Ann Hematol* 2010;89:283-289.
35. 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.
36. Ghielmini M, Schmitz SF, Cogliatti S, et al. Effect of single-agent rituximab given at the standard schedule or as prolonged treatment in patients with mantle cell lymphoma: a study of the Swiss Group for Clinical Cancer Research (SAKK). *J Clin Oncol* 2005;23:705-711.
37. Ghielmini M, Rufibach K, Salles G, et al. Single agent rituximab in patients with follicular or mantle cell lymphoma: clinical and biological factors that are predictive of response and event-free survival as well as the effect of rituximab on the immune system: a study of the Swiss Group for Clinical Cancer Research (SAKK). *Ann Oncol* 2005;16:1675-1682.
38. Witzens-Harig M, Benner A, Rieger M, et al. Rituximab maintenance therapy in CD20 B-cell non-Hodgkin-lymphoma - final results of a multicenter prospective randomised Phase II study. *Haematologica* 2011.EHA Abstract #0950.
39. 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.
40. 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.
41. 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.