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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) for the treatment of diffuse large B-cell lymphoma (DLBCL).

Specific Changes: Consider revising the number of Rituxan treatment cycles to "up to eight cycles" for the treatment of DLBCL based on the recently presented data from the RICOVER-60 trial at the 2011 American Society of Clinical Oncology (ASCO) Annual Meeting and data from three pivotal, Phase III studies on the use of Rituxan in combination with chemotherapy.

FDA Clearance: The FDA has approved Rituxan in combination with cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) or other anthracycline-based chemotherapy regimens for the use in patients with previously untreated DLBCL. The recommended dose for Rituxan is 375 mg/m² on Day 1 of each cycle of chemotherapy for up to eight cycles. Please refer to the enclosed prescribing information (PI) for the full FDA-approved indications and safety information.

Rationale: Seven-year follow-up data from the RICOVER-60 trial was recently presented at the 2011 ASCO Annual Meeting in Chicago, Illinois.^{1,2} The randomized RICOVER-60 trial evaluated the safety and efficacy of 6 or 8 cycles of CHOP-14 both with and without 8 cycles of Rituxan in elderly patients with DLBCL. All Rituxan containing arms of the RICOVER trial utilized 8 cycles of Rituxan. At both the 3-year and 7-year follow-up, event-free survival and progression-free survival were significantly greater with 6 cycles of CHOP in combination with 8 cycles of Rituxan than with 6 cycles of CHOP alone.¹⁻³ At the 7-year follow-up, OS was significantly better with either 6 or 8 cycles of CHOP in combination with 8 cycles of Rituxan than with 6 cycles of CHOP alone at 7 years. The authors concluded that 6 cycles of CHOP in combination with 8 cycles of Rituxan is the preferred regimen for elderly patients with DLBCL. Adverse events were reported at 3 years.³ There were 92 treatment-related deaths, occurring in 8% (n=50) of the 8-CHOP cycle arms and 7% (n=42) of patients in the 6-CHOP cycle arms. More patients in the 8-CHOP cycle treatment arms experienced anemia, mucositis, red-blood-cell transfusions, and interventional antibiotics compared with those in the 6-CHOP cycle arms.

Additional data from two Phase III studies evaluating 8 cycles of Rituxan in combination with CHOP was also presented at the 2011 ASCO Annual Meeting.⁴⁻⁵

Data from three pivotal, Phase III studies on the use of Rituxan combined with CHOP or CHOP-like chemotherapy in previously untreated patients with DLBCL was previously submitted to the NCCN panel on March 14, 2011.⁶⁻¹³

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

- Coiffier B, Thieblemont C, Van Den Neste E, et al. Long-term outcome of patients in the LNH-98.5 trial, the first randomized study comparing rituximab-CHOP to standard CHOP chemotherapy in DLBCL patients: a study by the Groupe d'Etudes des Lymphomes de l'Adulte. *Blood* 2010;116:2040-2045.
- Cunningham D, Smith P, Mouncey P, et al. R-CHOP14 versus R-CHOP21: result of a randomized phase III trial for the treatment of patients with newly diagnosed diffuse large B-cell non-Hodgkin lymphoma. *J Clin Oncol* 29: 2011;29(suppl):abstract 8000.
- Habermann TM, Weller EA, Morrison VA, et al. Rituximab-CHOP versus CHOP alone or with maintenance rituximab in older patients with diffuse large B-cell lymphoma. *J Clin Oncol* 2006;24:3121-3127.
- Pfreundschuh M, Schubert J, Ziepert M, et al. Six versus eight cycles of bi-weekly CHOP-14 with or without rituximab in elderly patients with aggressive CD20+ B-cell lymphomas: a randomized controlled trial (RICOVER-60). *Lancet Oncol* 2008;9:105-116.
- Pfreundschuh M, Ziepert M, Zeinalova S, et al. Six versus eight cycles of biweekly CHOP-14 with or without R in elderly patients (pts) with aggressive CD20+ B-cell lymphomas: seven-year FU of RICOVER-60 trial of the DSHNHL. Presented at the 2011 American Society of Clinical Oncology (ASCO) Annual Meeting in Chicago Illinois; June 3-7, 2011. ASCO Poster #8029.
- Pfreundschuh M, Ziepert M, Zeinalova S, et al. Six versus eight cycles of biweekly CHOP-14 with or without R in elderly patients (pts) with aggressive CD20+ B-cell lymphomas: seven-year FU of RICOVER-60 trial of the DSHNHL. *J Clin Oncol* 2011;29(suppl):abstract 8029.
- Pfreundschuh M, Trümper L, Österborg A, et al. CHOP-like chemotherapy plus rituximab versus CHOP-like chemotherapy alone in young patients with good-prognosis diffuse large-B-cell lymphoma: a randomised controlled trial by the MabThera International Trial (MInT) Group. *Lancet Oncol* 2006;7:379-391.
- Stiff PJ, Unger M, Cook J, et al. Randomized phase III U.S./Canadian intergroup trial (SWOG S9704) comparing CHOP ± R for eight cycles to CHOP ± R for six cycles followed by autotransplant for patients with high-intermediate (H-Int) or high IPI grade diffuse aggressive non-Hodgkin lymphoma (NHL). *J Clin Oncol* 29: 2011;29(suppl):abstract 8001.
- Rituxan Prescribing Information

Cited References

1. Pfreundschuh M, Ziepert M, Zeinalova S, et al. Six versus eight cycles of biweekly CHOP-14 with or without R in elderly patients (pts) with aggressive CD20+ B-cell lymphomas: seven-year FU of RICOVER-60 trial of the DSHNHL. Presented at the 2011 American Society of Clinical Oncology (ASCO) Annual Meeting in Chicago Illinois; June 3-7, 2011. ASCO Poster #8029.
2. Pfreundschuh M, Ziepert M, Zeinalova S, et al. Six versus eight cycles of biweekly CHOP-14 with or without R in elderly patients (pts) with aggressive CD20+ B-cell lymphomas: seven-year FU of RICOVER-60 trial of the DSHNHL. *J Clin Oncol* 2011;29(suppl) abstract 8029.
3. Pfreundschuh M, Schubert J, Ziepert M, et al. Six versus eight cycles of bi-weekly CHOP-14 with or without rituximab in elderly patients with aggressive CD20+ B-cell lymphomas: a randomized controlled trial (RICOVER-60). *Lancet Oncol* 2008;9:105-116.
4. Cunningham D, Smith P, Mouncey P, et al. R-CHOP14 versus R-CHOP21: result of a randomized phase III trial for the treatment of patients with newly diagnosed diffuse large B-cell non-Hodgkin lymphoma. *J Clin Oncol* 29: 2011;29(suppl) abstract 8000.
5. Stiff PJ, Unger M, Cook J, et al. Randomized phase III U.S./Canadian intergroup trial (SWOG S9704) comparing CHOP ± R for eight cycles to CHOP ± R for six cycles followed by autotransplant for patients with high-intermediate (H-Int) or high IPI grade diffuse aggressive non-Hodgkin lymphoma (NHL). *J Clin Oncol* 29: 2011;29(suppl) abstract 8001.
6. Habermann TM, Weller EA, Morrison VA, et al. Rituximab-CHOP versus CHOP alone or with maintenance rituximab in older patients with diffuse large B-cell lymphoma. *J Clin Oncol* 2006;24:3121-3127.
7. Morrison VA, Hong F, Habermann TM, et al. R-CHOP versus (vs) CHOP followed by maintenance rituximab (MR) vs observation in older diffuse large B-cell lymphoma (DLBCL) patients (pts): long-term follow-up of intergroup E4494 / C9793. *Blood* 2010. ASH Abstract #589.

8. Coiffier B, Lepage E, Briere J, et al. CHOP chemotherapy plus rituximab compared with CHOP alone in elderly patients with diffuse large-B-cell lymphoma. *N Engl J Med* 2002;346:235-242.
9. Feugier P, van Hoof A, Sebban C, et al. Long-term results of the R-CHOP study in the treatment of elderly patients with diffuse large B-cell lymphoma: a study by the Groupe d'Etude des Lymphomes de l'Adulte. *J Clin Oncol* 2005;23:4117-4126.
10. Coiffier B, Thieblemont C, Van Den Neste E, et al. Long-term outcome of patients in the LNH-98.5 trial, the first randomized study comparing rituximab-CHOP to standard CHOP chemotherapy in DLBCL patients: a study by the Groupe d'Etudes des Lymphomes de l'Adulte. *Blood* 2010;116:2040-2045.
11. Pfreundschuh M, Trümper L, Österborg A, et al. CHOP-like chemotherapy plus rituximab versus CHOP-like chemotherapy alone in young patients with good-prognosis diffuse large-B-cell lymphoma: a randomised controlled trial by the MabThera International Trial (MInT) Group. *Lancet Oncol* 2006;7:379-391.
12. Pfreundschuh M, Kuhnt E, Trümper L, et al. Randomised intergroup trial of first line treatment for young low-risk patients (<61 years) with diffuse large B-cell non-Hodgkin's lymphoma (DLBCL) with a CHOP-like regimen with or without the anti-CD20 antibody rituximab - 6-year follow-up of the Mint study of the Mabthera International Trial (MInT) group. *Blood* 2010. ASH Abstract #111.
13. Murawski N, Kuhnt E, Grass S, et al. The role of the rituximab partner chemotherapy regimen in young patients with good-prognosis diffuse large B-cell lymphoma (DLBCL): results of the 6-year follow-up of the Mint study of the Mabthera International Trial (MInT) group. *Blood* 2010. ASH Abstract #2826.