

Follicular Lymphoma-rituximab (Review of TA110) Assessment Report

Roche Comments

16 June 2011

(1) Rituximab resistance

On pages 149 & 150 of the Assessment Report, there is discussion around the issue of 'rituximab resistance'. The AG expressed concern that the two references^{1,2} provided by Roche in our submission were insufficient to conclude that resistance to rituximab can be ignored.

The AG provided two alternative references^{3,4} to challenge the efficacy of retreatment with rituximab following initial rituximab treatment in diffuse large B-cell lymphoma (DLBCL). The discussion of these two papers is of concern to Roche. DLBCL is classed as an aggressive lymphoma (in contrast to the indolent classification of follicular lymphoma [FL]) and as such has an entirely different treatment paradigm. Cure is possible in a significant proportion of patients with DLBCL⁵, in contrast to the inevitable disease progression in stage III/IV FL⁶. However, patients who are not cured after front-line treatment for DLBCL present a difficult-to-treat subgroup with few treatment options and a poor prognosis, and will require a combination of salvage immunochemotherapy, stem-cell transplant, and/or radiotherapy⁷. As such, relapsed/refractory FL patients differ significantly from relapsed/refractory DLBCL patients, and it is highly inappropriate to form conclusions regarding the efficacy of retreatment with rituximab in FL patients from these data.

The AG also provided a reference which investigated the efficacy of bendamustine, mitoxantrone and rituximab (BMR) in 57 patients with stage III/IV relapsed or refractory indolent lymphomas and mantle cell lymphoma (MCL) with or without prior rituximab containing chemo-immunotherapy treatment⁸. While 29 of these patients had a diagnosis of FL, 18 patients had MCL, 4 patients had B-CLL with plasmacytic differentiation, 3 patients had lymphoplasmacytic lymphoma, and 3 patients had marginal zone lymphoma. These diseases are morphologically different and MCL in particular –like DLBCL– is considered to be an aggressive lymphoma⁹, albeit without the chance of a cure, and with a corresponding poor prognosis. Unfortunately, the data within the paper regarding second-line responses with and without prior rituximab therapy –upon which the AG appear to have formed conclusions– do not discriminate between the different diseases, meaning that again, it is inappropriate to form conclusions regarding the efficacy of retreatment with rituximab in FL patients from these data.

It is possible that, contrary to the AG's concerns, the relative benefit of retreatment with rituximab may be **increased**, rather than decreased. The current European Society for Medical Oncology guidelines state that retreatment with rituximab should only be undertaken if the previous antibody-containing regime resulted in a >6 month duration of remission¹⁰. If there is a subset of patients who are less responsive to rituximab, they would be more likely to fail this requirement, positively selecting rituximab-responding patients for retreatment.

In conclusion, while there is no *definitive* evidence as to the relative benefit of retreatment with rituximab (although there are various studies that point in this direction) neither is there conclusive evidence to the contrary. We would therefore draw attention to the expert clinical opinion sought by the AG, as per p.150 of the TA110 Assessment Report: *“The AG sought clinical advice on this issue which indicated that resistance of rituximab is unknown, however the clinicians believed that there is little or no loss of effectiveness considering its mechanism of action”*. Further clinical expert opinion sought by Roche concurs with this.

(2) Overall Survival (OS)

The Assessment Report contains a number of references to confounding of OS data as a consequence of subsequent treatment in three of the four trials used in our submission. This is an unavoidable consequence of treatment of a disease like FL, with an indolent relapsing remitting course. Roche agrees with the AG’s suggestion that *“it is unlikely that a trial could be ethically undertaken to remove the effect of subsequent therapies”*.

However, this discussion risks detracting from the important point: that three of the four trials under consideration provide clear and statistically significant evidence of the benefit in overall survival from the addition of rituximab to chemotherapeutic induction regimes.

(3) Complete Response (CR) rate in GLSG-2000 trial

On p68 of the AG report, it was noted that *“The number of CRs in the GLSG-2000 trial for both R-CHOP and CHOP (19% and 17% respectively) were notably lower than those reported in the other studies”*.

According to the paper (reference 90 in AG report), the category of unconfirmed complete remission (CRu) was not used. Instead, patients who fulfilled CR criteria but in whom bone marrow biopsy with evaluable negative result was not performed were considered to have achieved PR. This explains the low numbers of CRs in both CHOP and R-CHOP arms. A higher number of PR in both arms compared to other studies supports this conclusion.

(4) BCSH guideline publication date

There appears to be a contradiction in the publication date for the BCSH guidelines for FL in the Assessment Report. On p24 the publication date is given as August 2011, whilst on p30 (and on the BCSH website: www.bcsguidelines.com) they are expected in June 2011.

(5) Rituximab license

On p28, please remove “relapsed/refractory” from the sentence:

- Rituximab maintenance therapy is indicated for patients with relapsed/refractory FL responding to induction therapy with chemotherapy with or without rituximab.

References

- ¹ Johnston, A, Bouafia-Sauvy, F, Broussais-Guillaumot, F, Michallet, AS, Traulle, C, Salles, G, and Coiffier, B. **Re-treatment with rituximab in 178 patients with relapsed and refractory B-cell lymphomas: a single institution case control study.** *Leukemia and Lymphoma* 2010; 51 399-405.
- ² Coiffier, B., Bouafia-Sauvy, F, Thieblemont, C, Hequet, O, Arnaud, P, Dumontet, C, and Espinouse, D **Rituximab re-treatment in B-cell lymphoma patients: efficacy and toxicity in 59 patients treated in one center.** *Blood* 2002; 100 1390 [abstract]
- ³ Borgerding, A., Hasenkamp, J., Glass, B., Wulf, G., and Trumper, L. **Rituximab retherapy in patients with relapsed aggressive B cell and mantle cell lymphoma.** *Annals of Hematology* 2010; 89 283-289.
- ⁴ Martin, A., Conde, E., Arnan, M., Canales, M. A., Deben, G., Sancho, J. M. et al. **R-ESHAP as salvage therapy for patients with relapsed or refractory diffuse large B-cell lymphoma: the influence of prior exposure to rituximab on outcome. A GEL/TAMO study.** *Haematologica* 2008; 93 1829-1836.
- ⁵ Coiffier 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.** *Blood* 2010, Vol 116, No. 12
- ⁶ Horning SJ. **Follicular lymphoma: Have we made any progress?** *Annals of Oncology* 11 (Suppl 1): S23-S27. 2000
- ⁷ Tilly et al. **Diffuse large B-cell non-Hodgkin's lymphoma: ESMO Clinical Recommendations for diagnosis, treatment and follow-up.** *Annals of Oncology* 20 (Supplement 4): iv110–iv112, 2009
- ⁸ Weide et al. **High anti-lymphoma activity of bendamustine/mitoxantrone/rituximab in rituximab-retreated relapsed or refractory indolent lymphomas and mantle cell lymphomas.** *Leukemia & Lymphoma*, July 2007; 48(7): 1299 – 130
- ⁹ Schulz et al. **Immunochemotherapy With Rituximab and Overall Survival in Patients With Indolent or Mantle Cell Lymphoma: A Systematic Review and Meta-analysis.** *J Natl Cancer Inst* 2007;99: 706–14
- ¹⁰ Dreyling et al. **Newly diagnosed and relapsed follicular lymphoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up.** *Annals of Oncology* 21 (Supplement 5): v181–v183, 2010