Responses to comments from the manufacturer

1) Rituximab resistance

The manufacturer's submission (MS) provided a discussion on resistance to rituximab based on two references. These studies, which included a mixture of B cell lymphomas, therefore including Diffuse large B-cell lymphoma (DBCL) as well as FL patients, were subject to limitations with respect to interpreting the observed data (see AG report- p. 146-7)

The assessment group (AG) investigated and found other additional references which may illustrate that resistance to rituximab exists based on what was observed in other types of lymphoma in the absence of evidence specific to follicular lymphoma (FL) patients. The AG is aware that DBCL and FL patients are different populations and therefore were cautious in extrapolating conclusions, but rather noted that there remains uncertainty on whether resistance to rituximab is an issue.

We generally agree with the manufacturers that "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.", although question the strength of support for a hypothesis that the relative risk is identical for retreatment as for initial treatment. As such, it was deemed prudent to conduct sensitivity analyses to examine the effects of different assumptions on the incremental cost effectiveness ratio, whilst using an assumption of no resistance within the base case.

2) Overall survival

The AG does not believe that a discussion of confounding factors for overall survival detracts from the statistically significant increase in overall survival reported in three of the four trials. We feel it necessary to highlight this potential limitation whilst acknowledging that it is unethical and not possible to conduct a trial without any subsequent therapies.

3) Complete response (CR) rate in GLSG 2000 trial

Counting unconfirmed complete responses (CRu) as partial responses [PR] thus increasing the numbers of PRs and decreasing the number of complete responses (CRs), might explain or partially explain the discrepancy in the numbers of PRs in the R-CHOP/CHOP trial compared

with the other three trials. However, the AG notes that the R-MCP/MCP trial by Herold et al [1] also counted CRus as PRs but does not have the same reduction in CR. The precise reasons for the difference in the number of CR in the CHOP/R-CHOP trial compared with the other three trials are unclear.

4) BCSH guideline publication date

The AG agrees with the comment made by the manufacturer and have amended the report accordingly.

5) Rituximab license

The AG agrees with the comment made by the manufacturer and will amend the report accordingly.

References

1. Herold, M., Haas, A., Srock, S., Neser, S., Al-Ali, K. H., Neubauer, A., Dolken, G. *et al.* Rituximab added to first-line mitoxantrone, chlorambucil, and prednisolone chemotherapy followed by interferon maintenance prolongs survival in patients with advanced follicular lymphoma: an East German Study Group Hematology and Oncology Study. *Journal of Clinical Oncology* 2007; **25** 1986-1992