NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Health Technology Appraisal

Appeal Hearing

Rituximab for the treatment of relapsed or refractory chronic lymphocytic leukaemia

Decision of the Panel

Introduction

1. An Appeal Panel was convened on 25th May 2010 to consider an appeal against the Institute's Final Appraisal Determination, to the NHS, on the use of rituximab for the treatment of relapsed or refractory chronic lymphocytic leukaemia

2. The panel comprised Dr Maggie Helliwell (Chair of the Appeal Panel and Non-executive director of NICE), Professor Patrick Morrison (Non-executive director of NICE), Mr Peter Sanders (Lay representative), Dr David Webster (Industry representative), and Professor Robin Ferner (NHS representative)

3. The Panel considered an appeal submitted by the UK Chronic Lymphocytic Leukaemia Forum, and a joint appeal submitted by the Royal College of Pathologists, and the British Society for Haematology.

4. The Appeal Panel met without representatives of the Appellants, the Appraisal Committee, or the Institute being present.

5. The Appeal Panel considered written submissions from the Appellants and from the chair of the Appraisal Committee. The chair of the Appeal Panel had also received a late letter from the Institute's Centre for Health Technology Evaluation. This letter provided evidence on a point of principle in relation to the Institute's approach to the scope of guidance in relation to the use of drugs in a clinical setting. The Appeal Panel saw that letter but did not take it into account in arriving at its conclusions.

6. The Institute's legal advisor (Mr Stephen Hocking, Beachcroft LLP) was available by telephone.

7. No other people were present.

8. There are three grounds on which an appeal can be lodged:
   - The Institute has failed to act fairly and in accordance with its published procedures as set out in the Institute's Guide to the Technology Appraisal Process;
   - The Institute has prepared guidance that is perverse in light of the evidence submitted;
   - The Institute has exceeded its legal powers.

9. The chair of the Appeal Committee (Dr Helliwell), in preliminary correspondence, had confirmed that the appellant had potentially valid grounds of appeal as follows:

   Ground 2 only

10. The Final Appraisal Determination considered at this appeal provided guidance on the use of rituximab, a biological medicinal product that acts against certain lymphocytes in the blood, as a treatment for the disorder relapsed/refractory chronic lymphocytic leukaemia.

Ground 1: The Institute has failed to act fairly and in accordance with its procedures

11. There was no appeal on this ground.

Ground 2: The Institute Final Appraisal Determination is perverse in the light of the evidence submitted

Appeal under Ground Two

First appeal point under Ground 2

12. It was said that in the MD Anderson phase II trial of rituximab with fludarabine and cyclophosphamide (R-FC) as second-line therapy, complete response (CR) and partial response (PR) rates were no worse in patients who had received prior rituximab. It was therefore perverse not to recommend second-line use.

13. The Appeal Panel noted that the Appraisal Committee had considered whether patients who had been treated with rituximab and then subsequently relapsed would benefit from further treatment with rituximab, as described in paragraph 4.8 of the Final Appraisal Determination. The only clinical trial evidence presented to the Appraisal Committee on this question came from a study, known as the MD Anderson Cancer Centre (MDACC) study, in which treatment allocation was open, and patients were not allocated treatment at random. [Wierda et al 2005]

14. At the time the Appraisal Committee considered the MDACC study, only 22 of 177 patients had received treatment with rituximab prior to entry, and of that small number, some at least had received regimens other than R-FC. While the Company later submitted more complete data, the Appeal Panel was clear that the Appraisal Committee had to make a decision on the best evidence available in the submission.

15. After considering Professor Stevens's written submission and the Final Appraisal Determination, the Appeal Panel understood that the reasons why the Appraisal Committee regarded the evidence on re-treatment with rituximab as insufficient were as follows: the trial was open-label; it was not randomised; the number of enrolled patients previously treated with rituximab was small; those patients had received various rituximab regimens; and neither the patients, who were often younger than in UK clinical practice, nor the regimens gave information sufficient on which to base guidance to the NHS.

16. The Appeal Panel considered that these reasons were sufficient for the Committee reasonably to have concluded that the trial was not a robust basis to recommend second-line use, and that the decision of the Appraisal Committee on the basis of the available evidence could therefore not be characterised as perverse.

17. The Appeal Panel therefore dismissed the appeal on this point.

18. However, the Appeal Panel advises the Guidance Executive that the opportunity should be taken to state more clearly the reasoning that led the Appraisal Committee's recommendation in the Final Appraisal Determination.

Second appeal point under Ground 2

19. It was said that the Final Appraisal Determination in its current form discriminates against patients who have already received rituximab as part of their first-line treatment with chlorambucil as part of the Roche phase II trial, which may or may not show a benefit of rituximab in this setting. Paradoxically, this consideration does not apply to patients who have received ofatumumab (a similar CD20 antibody) plus chlorambucil in the GSK phase III trial.

20. The Appeal Panel discussed Professor Stevens's response to this point. The Appraisal Committee had accepted that the recommendations as drafted might cause difficulties in relation to clinical trials, and that the recommendation should be amended as a result.

21. The Appeal Panel noted that there was consensus between the Appraisal Committee and the Appellants on this point. Although UK CLL had queried the exact new wording proposed by the Appraisal Committee, the panel did not think that there was a disagreement in substance as to what the position should be. It had some sympathy with UK CLL's view that the use of "suboptimal" in the reworded guidance might cause confusion. It therefore proposes a slightly different amendment below.

22. The Appeal Panel therefore upheld the appeal by agreement between the parties on this point.

Ground 3 The Institute has exceeded its legal powers

23. There was no appeal on this ground.

Conclusion

24. The Appeal Panel dismissed the appeal on the first point.

25. The Appeal Panel asked, however, that the reasons it had established as being behind the Appraisal Committee's decision to exclude those who had previously had treatment with rituximab from further treatment with rituximab, in combination with fludarabine, and cyclophosphamide, should be clarified by the Guidance Executive in consultation with the Appraisal Committee.

26. The Appeal Panel upheld the appeal on the second point, as had been agreed between the Appraisal Committee and the Appellants.

27. The Appeal Panel therefore asks that the relevant section of the Final Appraisal Determination be suitably reworded to overcome the agreed difficulty. The rewording should be overseen by the Guidance Executive, and this would overcome the difficulty without the need for a referral back to the Appraisal Committee.

28. The Appeal Panel suggests that the suitable amendment of paragraph 1.1 of the Final Appraisal Determination is that it should read:

    1.1 Rituximab in combination with fludarabine and cyclophosphamide is recommended as a treatment option for people with relapsed or refractory chronic lymphocytic leukaemia except when the condition:

    - is refractory to fludarabine (that is, it has not responded to fludarabine or has relapsed within 6 months of treatment) or
    - has previously been treated with rituximab, except
        i. in the context of a clinical trial, or
        ii. at a dose lower than the dose currently licensed for chronic lymphocytic leukaemia or
        iii. in combination with chemotherapy other than fludarabine plus cyclophosphamide.

29. The Appeal Panel also suggests that the Guidance Executive might further consider minor modification in respect of the wording of paragraph 1.2 of the FAD in the light of the Appeal Panel's suggested modification to paragraph 1.1.

30. The Appeal Panel welcomed the stated intention of Paragraph 8.1 of the FAD to review the evidence in December 2010.

31. There is no possibility of further appeal within the Institute against this decision of the Appeal Panel. However, the decision of the Appeal Panel may be challenged by an interested party through an application to the High Court for permission to apply for judicial review. Any such application must be made promptly and in any event within three months of this decision or the issuing of the Guidance.