Rituximab for the treatment of relapsed or refractory chronic lymphocytic leukaemia

Thank you for the opportunity to respond to the appeal from the UK Chronic Lymphocytic Leukemia (UK CLL) Forum, to the final appraisal determination (FAD) for the above technology appraisal. As is noted in the Appeal Panel Chair's responses to the appellants, all appeal points were assumed to be made on the ground of perversity. The appeal points that were referred to the Appeal panel are addressed in turn below.

FAD section 1.1 recommends that rituximab in combination with fludarabine and cyclophosphamide (R-FC) is 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.

The appellant objects to the second exception; prior treatment with rituximab. They consider that (1) people who have been previously treated with rituximab as a first-line therapy should be able to receive rituximab in combination with fludarabine and cyclophosphamide when the disease relapses. In addition (2), specific concerns are raised about the greater impact of the recommendation on a specific subgroup of people who have previously received rituximab as part of a clinical trial and who may have received what was later identified as a sub-optimal rituximab regimen.

1. People previously treated with rituximab

The appellant identifies four factors (a) phase II second-line trial data ("MDACC"), (b) the exclusion of people previously treated with rituximab but not people previously treated with ofatumumab, (c) national and international

guidelines recommending re-treatment with rituximab, and (d) the approval by NICE of second-line rituximab regimens for follicular lymphoma. The Appeal Committee chair has ruled that points (c) and (d) are not referred to the appeal panel. I am therefore replying to (a) and (b).

a. Phase II second-line MDACC trial data

The UK CLL Forum stated that *"in the MD Anderson phase II trial of R-FC as second line therapy, CR [complete response] and PR [partial response] rates were no worse in patients who had received prior rituximab."*

In essence, notwithstanding the MD Anderson phase II trial (referred to in the FAD as the MDACC study), the Committee agreed that the case was not clinically proven. And, going the extra mile on the grounds that it was clinically plausible, the Committee found that it was not cost-effective either.

The MDACC study was submitted by the manufacturer of rituximab and has been considered by the Committee. The clinical effectiveness data from this study are included in sections 3.9 and 3.10 of the FAD. The manufacturer's cost effectiveness analysis using these data is included in section 3.16. The Committee's consideration of these data is in sections 4.8, 4.9 and 4.19.

In its consideration of the evidence on R-FC in people who had previously received rituximab, the Committee considered the following points:

- The Committee heard from patient experts that anecdotal evidence suggested that people retreated with rituximab may have a good response to treatment, and that retreatment with rituximab is common in other lymphoproliferative conditions where there has been a good response. However, the Committee heard from clinical specialists that there was uncertainty about the degree of benefit of retreatment with rituximab (FAD section 4.8). The uncertainty is reflected in section 4.1 of the Summary of Product Characteristics for rituximab which specifies "only limited data are available on the efficacy and safety for patients previously treated with monoclonal antibodies including MabThera [rituximab]…"

- There was no randomised controlled evidence available on the use of R-FC in people who had previously received treatment with rituximab. The pivotal trial (REACH), that formed the basis of the manufacturer's submission, excluded people who had previously received rituximab (FAD section 3.1). The only evidence for the use of R-FC in this context was from phase II uncontrolled studies the largest of which was the MDACC study from the United States (referred to by the appellant). This included 284 people, 100 of whom had previously received rituximab (FAD sections 3.9, 3.10). The Committee considered these results noting the methodological limitations of the studies (FAD section 4.9).

- Another limitation of the MDACC study was that it included people who had previously received any rituximab-containing regimen and little information was provided about what these rituximab-containing regimens were. However, 2005 data provided by the manufacturer indicated that these included rituximab monotherapy as well as rituximab combination regimens (Wierda et al 2005). This was confirmed by additional 2009 data provided by the manufacturer at consultation on the ACD (Badoux et al 2009). In light of the recommendation by NICE for the first-line use of R-FC (Technology Appraisal guidance TA174, 2009), the Committee was aware that an increasing number of people in the UK will receive R-FC as a first-line treatment. Other rituximab chemotherapy regimens are not recommended in TA174 and are therefore not currently considered to be routine standard care. As the patients in the phase II study could have received rituximab monotherapy or rituximab in combination with chemotherapies other than fludarabine and cyclophosphamide, the Committee was not persuaded that the results from this study could be considered reflective of those which would be seen in a UK population (FAD section 4.9).

Overall, the Committee did not consider that the benefits of R-FC after first line treatment that had included rituximab had been conclusively shown.

However, it agreed to consider the estimates of cost effectiveness provided by the manufacturer (FAD section 4.19). The Committee considered the following:

- The manufacturer's estimate of cost effectiveness for R-FC in people who had not previously been treated with rituximab was £15,593 per QALY gained. This was corrected by the ERG to £16,607 per QALY gained. During consultation on the ACD, the manufacturer provided an estimate of the cost effectiveness of R-FC in a rituximab pretreated population using the MDACC data. This figure was £22,519 per QALY gained (without the ERG correction). The higher estimate of cost effectiveness, compared to that for those who had not previously received rituximab, was caused by a smaller gain in QALYs. The analysis of the MDACC data provided by the manufacturer suggested rituximab was slightly less effective in people who had not previously received rituximab than those who had, although this difference was not statistically significant (hazard ratio for progression-free survival: 1.13, p = 0.431, FAD section 3.10)

- The manufacturer's cost-effectiveness estimates (£15,593 and £22,519 per QALY gained) were associated with two key uncertainties.

    - The first uncertainty was the extent to which the gains in progression free survival translated into a gain in overall survival. The manufacturer modelled the gains in progression free survival as translating into an overall survival gain. The Committee did not consider that this was shown in the clinical trial data. Although it accepted that there would be some gain in overall survival, the Committee was not persuaded that the evidence supported a gain as large as the one the manufacturer had modelled (FAD 4.16).

    - Second, no appropriate health-related-quality-of-life data were provided by the manufacturer. The data available did not reflect

the NICE reference case (specifically using preference-based methods) and instead, were estimated by the authors of a 2001 health technology assessment report from condition-specific health-related-quality-of-life data (FAD 4.15).

- The Committee concluded that the manufacturer had underestimated the cost effectiveness of rituximab in the overall population (that is the REACH trial population) and that the corrected base case of £16,607 was more likely to be at the upper end of the range of £20,000 to £30,000 per QALY gained. The Committee was persuaded that even taking into account the uncertainty, the use of R-FC was cost-effective for the population represented in the REACH trial (those who had not previously had rituximab, FAD 4.17, 4.18) i.e. in the range of £20,000 to £30,000. However, the Committee was unwilling to accept the estimate of £22,519 per QALY gained for people who had previously had rituximab because of the added uncertainty in clinical effectiveness as well as in the size of the overall survival gain and the health-related-quality-of-life data. It considered that the combination of these uncertainties meant that the estimate of cost effectiveness for this group would be above the threshold normally accepted (FAD 4.19).

- The Committee recognised the uncertainties in the clinical effectiveness evidence, and considered that further data may affect the decision. Therefore it recommended that rituximab is used only in research for people who have had previously received rituximab (FAD section 1.2 *"Rituximab in combination with fludarabine and cyclophosphamide is recommended only in the context of research for people with relapsed or refractory chronic lymphocytic leukaemia that has previously been treated with rituximab"*) In addition, the Committee recognised the relevance of the first-line treatment appraisal to this appraisal and coordinated the review dates of the two appraisals so that they could be considered together (a review proposal is scheduled for consultation in December 2010).

b. The exclusion of people previously treated with rituximab but not people previously treated with ofatumumab

The UK CLL forum further state within its discussion of the impact of the guidance on people taking part in clinical trials *"this consideration does not apply to patients who have received ofatumumab (a similar CD20 antibody) plus chlorambucil in the GSK phase III trial. I think you will agree that this is a rather perverse situation."*

It is recognised that the summary of product characteristics for rituximab highlights the lack of evidence for the clinical efficacy of rituximab when used after rituximab and other monoclonal antibodies stating that "only limited data are available on the efficacy and safety for patients previously treated with monoclonal antibodies including MabThera [rituximab]…".

Ofatumumab is a CD20 antibody which, although similar to rituximab, is not the same technology, and has a different mechanism of action. It recently (March 2010) received a marketing authorisation for the treatment of chronic lymphocytic leukaemia in patients refractory to fludarabine and alemtuzumab and is currently undergoing a NICE appraisal for this indication. It is not currently part of standard routine care in the NHS as a first-line treatment (first-line treatment options are described in section 4.1 of the FAD). Evidence was not submitted for the use of rituximab after treatment with ofatumumab. However, both clinical and cost effectiveness evidence were submitted for the use of rituximab after previous treatment with rituximab.

2. The specific subgroup of people who have previously received rituximab as part of a clinical trial and who may receive what is later identified as a sub-optimal rituximab regimen

The UK CLL Forum appealed against the recommendation precluding the use of R-FC in people who have previously received rituximab, because *"the FAD 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. The UK CLL Forum refer to a single arm trial of rituximab and chlorambucil for the first line treatment of chronic lymphocytic leukaemia (the CLL208 trial), for which interim data are available (FAD section 4.12).

In making recommendations about the cost effectiveness of rituximab for the treatment of relapsed and refractory chronic lymphocytic leukaemia, one of the key uncertainties was the extent to which the first-line rituximab regimen influenced the efficacy of the second- and subsequent-line regimen. There is currently limited clinical data available demonstrating that for a person who has received rituximab as a first line treatment, the 'gold-standard' subsequent treatment would be a rituximab containing regimen.

The Committee was aware of a number of people involved in clinical trials of rituximab in combination with treatments other than FC but it did not discuss the issue of trial designated sub-optimal doses of rituximab, nor the problems of trial recruitment and perversity that may arise. The Committee do not wish to prejudice recruitment or to inadvertently cause trialists to default on their fairness "contract" with patients. I therefore recommend an amendment to the FAD so that the exclusion of people who have previously been treated with rituximab (in FAD 1.1. bullet 2) would not include patients who have received rituximab only in a clinical trial setting. The revised section 1.1 would read:

Rituximab in combination with fludarabine and cyclophosphamide (R-FC) is 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 <u>other than as part of a clinical trial in which rituximab was given as a suboptimal dose or in a suboptimal combination.</u>*

A considerations section paragraph will be also added to the FAD explaining the rationale for this recommendation and explaining further what is meant by the terms 'suboptimal dose' and 'suboptimal combination'.

Yours sincerely

[redacted]

Chair of the Appraisal Committee