Single technology appraisal (STA)

Rituximab for the treatment of relapsed or refractory chronic lymphocytic leukaemia

Appeal points that were referred to the appeal panel on behalf of the Royal College of Pathologists and the BSH

Thank you for the opportunity to respond to the joint appeal from the Royal College of Pathologists (RCP) and the British Society for Haematology (BSH) 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. First, they raise specific concerns about the 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. Second, they state that rituximab in combination with fludarabine and

cyclophosphamide should be available to people who have been previously treated with rituximab as a first-line therapy.

The scrutiny letter indicates that the Appeal Committee Chair has ruled that only the first of these points will go forward to the appeal panel. Therefore this second point will not be addressed in this response.

The specific subgroup of people who have previously received rituximab as part of a clinical trial

The appellant refers to three clinical trials. First, they refer to the ARTIC trial in which people are randomized to two treatment groups in which one group receive a smaller dose of rituximab than is currently licensed. Second they 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 results are available (FAD 4.12). Finally, the appellant refers to a trial in which people receive ofatumumab and who would be eligible under the current guidance for treatment with rituximab.

The scrutiny letter indicates that that the Appeal Committee Chair has ruled that this last point will not go forward to the appeal panel. Therefore it will not be addressed in this response.

The RCP and BSH state that *"patients coming out of current clinical trials including rituximab are potentially being discriminated against by this policy. The reasons are as follows:*

- *half of the patients in the NCRI-badged ARCTIC Trial are treated with FCM-miniR in which they only receive a total of 100mg rituximab with each cycle of treatment compared to approximately 1000mg in FCR (the standard arm). We do not know that miniR is as good (hence the trial) and if it isn't these patients would be denied "full dose" rituximab at any stage of their disease! The*

ARCTIC Trial is testing a significantly economic question and is therefore funded by the HTA. If the guidance is unchanged then it is difficult to enter patients in the ARCTIC trial knowing that R-FC now has an overall survival advantage and entering the trial will deny them this therapy later

- *100 patients in the UK have received chlorambucil+rituximab in a clinical trial and this is not as effective as R-FC (we know this from the interim results). These patients should be able to receive the acknowledged gold-standard treatment at some point in their disease - i.e. R-FC."*

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 fludarabine and cyclophosphamide 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 other than as part of a clinical trial in which rituximab was given either at a dose lower than that licensed for CLL or in combination with chemotherapy other than fludarabine plus cyclophosphamide*
- 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