Comments on Rituximab Second Line- Evaluation Report and appraisal Consultation document.

[redacted]

By recommendation-
1.1a.
This recommendation is a fair appraisal of the evidence submitted by the manufacturer and analysed by the ERG.
I welcome the fact that second line patients who are not refractory to fludarabine (and are otherwise suitable) will be treated with FCR.

1.1.b- …'and have not been previously treated with rituximab.'
I realise that there is insufficient evidence at this stage to support second line FCR after first line FCR though anecdotal evidence suggests that this is a valid treatment. I believe that data will accrue to support FCR second line after FCR first line.

1.2 The evidence given in the consultation document indicates that the addition of Rituximab to other chemotherapy regime shows a distinct advantage in progression free survival for CLL patients. Many of the studies were with 'salvage' patients, patients for whom there were no standard treatment options due to the progression of the disease. The following recently available (post appraisal) paper, while an interim report, supports the supposition that R+ other chemo has an advantage
'An Open-Label Phase II Study to Investigate the Safety and Efficacy of Rituximab Plus Chlorambucil in Previously Untreated Patients with CD20-Positive B-Cell Chronic Lymphocytic Leukaemia (CLL) Hilllmen et al, ASH Programme and abstracts, '09'
Analysis shows an improvement in the percentage of patients achieving a PR with this conservative treatment. It is likely that as the data matures this advantage will become more clear cut. This is a trend that has been seen in CLL trials studies.

1.3
'Option of stopping treatment…….'
The evaluation report documentation provided has shown unequivocally that rituximab in addition to any other chemotherapy has, statistically, an advantage to the patient.

I am uneasy as to the ethics of withdrawing rituximab after 1 or more cycles since in my limited understanding the earlier a patient receives rituximab in the sequence of treatments (first, second, third etc) the better effect that it has. As the patient is sequentially re-treated, the clinical picture is even less straightforward, and remissions shorter. I understand that the balance between autonomy, beneficence and justice are finely balanced here.

I would be interested in also seeing the opinion of the medical advisers on the advisability of withdrawing rituximab for these patients, and what effect this may have on resuming monoclonal antibody treatment at a later date.

Then by question;

Has all of the relevant evidence been taken into account?

The studies quoted in the appraisal document were certainly representative and most probably all the available reviewed pertinent evidence.

Further evidence has been published; see the paper by Hillmen et al above.

Also as described by the Medics present at the committee, actual life extension has now been reported, see

'First-Line Treatment with Fludarabine (F), Cyclophosphamide (C), and Rituximab (R) (FCR) Improves Overall Survival (OS) in Previously Untreated Patients (pts) with Advanced Chronic Lymphocytic Leukemia (CLL): Results of a Randomized Phase III Trial On Behalf of An International Group of Investigators and the German CLL Study Group'

Halleck et al , ASH Programme and abstracts, '09'.
This information can realistically be extrapolated to this appraisal. (see also 4.10)

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

As a lay person, I believe that the clinical summary of FCR second line is reasonable overall.

As a lay person, I believe that the clinical summary of R + other chemo is reasonable given the data but would urge the committee to re-examine in the light of the Hillmen paper which I believe gives more credence to the picture overall, and the claim that R does indeed add qol to other chemotherapies. If R+ other chemo is not approved now, I would urge re-examination of this aspect as data accumulates. This has particular relevance to the patient population who acquire CLL late in life, as it is in this population that often have more co-morbidities.

I support the supposition that quality of life in remission is greatly better than qol in the illness before treatment, both from the qol studies and anecdotally, and the fact that this supposition was used in financial calculations.

I have no further comment on the financial calculations.

‘and that the preliminary views on the resource impact and implications for the NHS are appropriate?

As far as I can determine, the cost of the resources are correct, but I am not able to comment on impact and implications. I would point out again that this is a relatively small number of people, and that justice is not served if patients were excluded from resources that other groups have already been granted.

Do you consider that the provisional recommendations of the Appraisal Committee are sound and constitute a suitable basis for the preparation of guidance to the NHS?

See 1.1, 1.2, and 1.3.

Equality related Issues.

To the best of my knowledge and belief there are no grounds that would lead to
any aspects of the recommendations that need particular consideration to ensure unlawful discrimination against any group of people on the grounds of gender, race, disability, age, sexual orientation, religion or belief, since treatment should be determined by the individual’s fitness.

Date of next appraisal; I would urge NICE to bring the date of the appraisal forward as soon as more supporting information becomes available.