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22 March 2011

Dear Dr Longson

Re: 2nd ACD re Rituximab for the first-line maintenance treatment of follicular non-Hodgkin's lymphoma

I write on behalf of the NCRI/RCP/RCR/ACP/JCCO with relation to this ACD consultation. We are grateful for the opportunity to respond and would like to make the following comments.

We are surprised and disappointed to see this document, which reverses the opinion in the initial appraisal consultation document (ACD) issued after the meeting of 4th November 2010. This reversal appears to have been carried out without the benefit of any new evidence, but following the submission of a single objection from an NHS commissioning body, which has been copied verbatim by two others. This contains significant errors of information and interpretation as detailed below.

Following the Appraisal meeting an ACD was produced that reflected expert opinion in the UK and worldwide, that Rituximab maintenance in first remission is both clinically and cost effective. The recommendations in the second ACD are simply not consistent with the first and have been arrived at without the benefit of any expert clinical input.

The reasons for the acceptance of Rituximab maintenance were extensively discussed at the Appraisal panel. We make the following comments upon the revised ACD and the objection from the NHS commissioners:

1) The improvement in progression free survival (PFS) in the Rituximab maintenance arm of the PRIMA study at two and now at three years is both statistically significant and clinically meaningful in this population. There is nothing to suggest that the difference between the two arms diminishes with time. The concerns voiced by the ERG and the suggestion by the NHS commissioners that the initial data would not be sustained with further follow up are not borne out by the evidence that continues to emerge at international scientific meetings and which has now been published in the Lancet
2) A sustained advantage has been observed in all other published studies of Rituximab as first and second line therapy in follicular lymphoma with long term follow up, and there is nothing to suggest the data from the PRIMA study will diverge from this pattern.
3) No single trial in this condition has demonstrated a major survival benefit, since patients are able to receive further treatment at recurrence. However, the continued separation of the PFS curves indicates that Rituximab is contributing to an overall increase in the freedom from symptomatic disease, in what is an incurable cancer

4) Registry studies have clearly demonstrated an improvement in overall survival for patients with follicular lymphoma since 2000. In the absence of any major shifts in the demographics or other major changes in management, this is widely accepted to be due to the impact of Rituximab during this time.
5) NICE have previously accepted PFS as a legitimate endpoint in the other studies of follicular lymphoma and other indolent lymphoid malignancies. It is not correct for the NHS commissioners to suggest that the original ACD recommendation was questionable in the absence of overall survival benefit, given the natural history of this illness and its responsiveness to salvage therapy.
6) The published results of the PRIMA study clearly demonstrate that all subgroups of patients have increased freedom from disease if they receive maintenance Rituximab. This specifically includes those above or below the age of 60. It is not legitimate to require an unplanned retrospective analysis of a subset of patients with median age comparable to that in registry studies for re-analysis of the data. It is sufficient to demonstrate, as the trial clearly does, that both older and younger patients derive benefit from the addition of 2 years maintenance therapy.
7) It must be re-emphasised that the trial was not stopped prematurely, but when the pre-planned endpoints were met. The decision to analyse the data was not taken by the sponsoring company or by the investigators but by the properly constituted independent data monitoring and safety committee.
8) The NHS commissioners suggest in their submission that the recommendations "could increase the use and therefore the overall cost of this drug for a PCT population" as if this undermines the evidence in favour of its use. Treatments should be approved subject to the existing standards of value for money to the NHS, which this treatment has passed. Furthermore, it is unlikely that the implementation of first line maintenance therapy will very substantially increase the use of Rituximab, since the great majority of patients will receive it in any case in second remission or at subsequent relapses.
9) The NHS commissioners suggest that "there is no convincing evidence of improved…quality of life and this calls into question the assumptions of the cost-effectiveness model". This is not the case. The PRIMA study demonstrated clearly that there is no reduction in quality of life during maintenance treatment, as the NHS commissioners point out. The patients who gave evidence at the appraisal hearing were categorical in their view that Rituximab treatment is greatly preferable to the known side-effects of chemotherapy, which is instituted sooner for patients who do not receive maintenance Rituximab. It is thus evident that the application of maintenance Rituximab carries a substantial premium for quality of life, as has been applied in the model. It is not tenable to assert, as the NHS commissioners have, that "the assumption that patients' quality of life is improved by the more manageable side effects of Rituximab maintenance…was not clearly demonstrated..." On the contrary, this is precisely the experience of patients and clinicians alike.
10) The statement by the NHS commissioners that "The ERG agreed to the manufacturer's small changes to the decision problem" is of no relevance. The assessment of benefit only in patients who had received Rituximab as part of induction treatment would if anything have diluted the effect of maintenance treatment and reduced the benefit. Similarly, the omission of an expensive comparator treatment, Ibritumomab tiuxetan, also works against Rituximab rather than in its favour.

This revised ACD runs directly counter to current national and international guidelines and standard practice for the treatment of follicular lymphoma. Maintenance therapy with Rituximab in first remission has now become a universal standard of care, based upon a large well-conducted prospective clinical trial. There are no other studies planned in this indication, since the results of this study are widely recognised as definitive. There is little purpose to trial groups in this country designing and participating in such studies if their globally accepted results cannot be incorporated into clinical practice, and the UK's capacity to participate in future trials designed with the leading independent international groups will be compromised if patients in this country cannot receive the internationally agreed standard of care.

For these reasons we would ask the committee to reverse its opinion in the second ACD and recommend, as it did originally, the use of Rituximab as first-line maintenance therapy for responding patients with advanced stage follicular lymphoma.

Yours sincerely

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Registrar