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BY EMAIL

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RE: Obinutuzumab in combination with chlorambucil for previously-untreated chronic lymphocytic leukaemia [ID650]

Dear Nicole,

Thank you for providing the opportunity to comment on the above ACD.

Whilst we are disappointed with the decision reached we are fully cognisant of the fact that any comparison of obinutuzumab plus chlorambucil to a bendamustine-containing regimen is extremely challenging and highly uncertain. This is primarily due to the absence of evidence on the relative effectiveness of bendamustine-based regimens and their chlorambucil-based counterparts in the population of interest (adults with untreated chronic lymphocytic leukaemia who have comorbidities that make full-dose fludarabine-based therapy unsuitable for them).

Although the ERG and ourselves have both made attempts at making these comparisons using unproven assumptions it appears clear that these indirect comparisons are largely ‘guesses’ made due to an absence of relevant data. Examples of these attempts include the linking of complete response rates to progression free survival outcomes using an unproven assumed linear relationship and, in the case of bendamustine, a comparison made through extrapolation from differing and incompatible patient populations.

Due to this inherent uncertainty we accept it will be challenging for the Committee to evaluate the cost-effectiveness of obinutuzumab plus chlorambucil compared to bendamustine-based regimens.

In light of this we request that the Committee consider the clinical and cost effectiveness of obinutuzumab plus chlorambucil in two different fludarabine-unsuitable patient populations:

1) Those suitable for treatment with a bendamustine-based regimen - for which the relevant comparators are bendamustine and rituximab plus bendamustine, chlorambucil or rituximab plus chlorambucil.

2) Those unsuitable for treatment with a bendamustine-based regimen - for which the relevant comparators are chlorambucil and rituximab plus chlorambucil (the comparators for which there is direct evidence available from the CLL11 trial).

These two groups are distinct populations as not all patients within scope are suitable for bendamustine-based therapy.

Even though it is clear that the comparison of obinutuzumab plus chlorambucil to bendamustine-based regimens is highly uncertain, there is relatively low uncertainty associated with the estimated cost-effectiveness of obinutuzumab plus chlorambucil in patients unsuitable for bendamustine-based regimens. As a result this may be a population in which the Committee could consider issuing a positive recommendation.

We would also like to draw the Committee's attention to the fact that failure to consider these populations as distinct groups may be interpreted as discriminatory and in breach of the public sector equality duty ("PSED"). This is a general equality duty which came into force on 5 April 2011 and is enshrined in law (section 149 of the 2010 Equality Act[1]) (the "Act"). As a public body, NICE must, amongst other things, have due regard to the need to eliminate unlawful discrimination and other conduct prohibited by the Act. This involves removing or minimizing disadvantages suffered by people due to their protected characteristics, in this instance, the relevant protected characteristic under the Act being disability as defined in the Act. If a patient unsuitable for a bendamustine-based therapy were denied access to obinutuzumab plus chlorambucil on the basis that it was not cost effective compared to a bendamustine-based regimen this would clearly present a serious risk of that decision being considered discriminatory and in breach of the PSED.

In addition to this request for consideration of the decision problem in two distinct populations the following has occurred since the issuance of the ACD:

1) We have submitted a simple patient access scheme to the Department of Health (a [redacted]% discount on the current list price of obinutuzumab).

2) The submitted economic model has been updated with the assumptions preferred by the Committee in the ACD.

3) New evidence has been presented for PFS off treatment utility values

4) An error in the costing of neutropenia has been corrected. This change and the utility values noted above are detailed as an appendix to this response.

Following these changes, and the introduction of the PAS the ICERs in patients unsuitable for bendamustine are detailed on page 4 of the appendix to the ACD. It should be noted that the uncertainty associated with these ICERs is relatively small as all comparisons are based upon data available directly from CLL11.

Given these cost-effectiveness results, the innovative nature of obinutuzumab (with an extremely impressive PFS HR of [redacted] [95% CI [redacted] – [redacted]] compared to chlorambucil alone) and the relatively low uncertainty associated with these comparisons there appears to be a strong case for a positive committee decision in this population.

The equivalent ICERs in patients suitable for bendamustine-based therapy are also presented in the appendix to the ACD. In this case the ICERs associated with comparisons against bendamustine-based therapies are above the range typically considered acceptable in NICE Technology Appraisals. It should be noted that these values are highly uncertain due to the fact that it is not possible to conduct a robust comparison of these therapies against obinutuzumab plus chlorambucil.

In light of the evidence above, and significant uncertainty associated with the comparison against bendamustine-based regimens, we suggest the Committee consider issuing a restrictive positive recommendation supporting use of obinutuzumab plus chlorambucil in patients unsuitable for bendamustine-based therapy.

Whilst the above supports a restrictive approval for obinutuzumab we are committed to working with NICE to expand access to obinutuzumab to every eligible patient who has the capacity to benefit from this treatment. With time, more data on the relative efficacy of bendamustine-based therapies and chlorambucil-based therapies is likely to be produced – with new data this uncertainty is likely to be resolved and we hope the Committee may be in a position to issue a broader positive recommendation for use of obinutuzumab at that point.

The above changes and analyses are presented under the standard headings below. If any further information is required we would be happy to provide it in order to aid the Committee's decision making.

Kind Regards

Jennifer Cozzone
Head of Health Economics and Strategic Pricing

1) Has all the relevant evidence been taken to account?

New data became available during consultation regarding PFS off-treatment utility values for the Committee to consider. A factual accuracy has also been corrected in the valuation of the adverse event of neutropenia. Details of these are provided in the appendix to the ACD.

In addition a simple PAS have been submitted to the Department of Health which provides [redacted]% discount to list price.

This amendment to our base case is in addition to incorporation of the Appraisal Committee's preferred values in regard to the five points raised during the ACD (detailed below).

1. Utility whilst on obinutuzumab after first cycle of therapy
2. Utility PFS off treatment decreased from 0.82 to 0.71
3. Mean dose of bendamustine and rituximab in bendamustine + rituximab arm
4. PFS hazard ratio between obinutuzumab + chlorambucil and bendamustine + rituximab increased from 0.68 to 0.76
5. PFS hazard ratio obinutuzumab + chlorambucil vs. bendamustine from 0.40 to 0.55

Patient population

As detailed in the covering letter, the scope for this appraisal covers two distinct fludarabine-unsuitable patient populations. We believe that it is necessary for the Appraisal Committee to consider the following populations separately:

1) Those suitable for treatment with a bendamustine-based regimen - for which the relevant comparators are bendamustine and rituximab plus bendamustine. By default if the patient can tolerate regimens including bendamustine they are also suitable for chlorambucil or rituximab plus chlorambucil).

2) Those unsuitable for treatment with a bendamustine-based regimen (for which the relevant comparators are chlorambucil and rituximab plus chlorambucil (the comparators for which there is direct evidence available from the CLL11 trial).

These populations are distinct. Not all patients suitable for treatment with obinutuzumab in combination with chlorambucil are suitable for treatment with a bendamustine-based regimen (primarily due to their ability to tolerate treatment with bendamustine).

Failure to treat these patient populations as distinct groups could be interpreted as discriminatory under public sector equality duty.

Further detail on these points is provided in the final section of this ACD response and the covering letter.

Impact on ICERs

Following the changes detailed above and the introduction of the PAS, the ICERs in patients unsuitable for bendamustine are shown on page 4 of the appendix to the ACD. The uncertainty associated with these ICERs is relatively small as all comparisons are based upon data available directly from CLL11.

The equivalent ICERs in patients suitable for bendamustine-based therapy are also presented in the appendix to the ACD. These values are highly uncertain due to the fact that it is not possible to conduct a robust comparison of these therapies against obinutuzumab plus chlorambucil. Whilst the ERG and ourselves have both made attempts at making these comparisons using unproven assumptions it appears clear that these indirect comparisons are largely 'guesses' made due to an absence of relevant data. Examples of these attempts include the linking of complete response rates to progression-free survival outcomes using an unproven assumed linear relationship and, in the case of bendamustine, a comparison made through extrapolation from differing and incompatible patient populations.

In this case the ICERs associated with comparisons against bendamustine-based therapies are above the range typically considered acceptable in NICE Technology Appraisals.

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

In addition to incorporation of the Committee's preferred values as detailed in the ACD, three further changes have been made, for the Committee to consider incorporating into their decision making. These are:

- New evidence has been submitted in an appendix to this ACD response - corrected neutropenia cost
- New evidence been submitted in an appendix to this ACD response – PFS off treatment utility values
- Submission of a simple PAS

In addition we have identified a few typographical errors that should be corrected:

A minor typographical error in our submission should be highlighted. The HR for stage 1a on page 8 and 10 in our submission is incorrect, it should be HR 0.18 (95% CI 0.13-0.24) and not HR 0.19 (95% CI 0.14 -0.27). It should be noted that this is only a typographical error and has no impact on the economic analysis.

Roche sent a pro-forma response to the ERG report which included factual inaccuracies to which the ERG responded in 'Errata 22nd August' which listed the changes to be made to the original ERG report. There was one error highlighted by Roche that was wrongly amended in the 'Errata' publication and remains incorrect. On page 21 of the original ERG report the cost of rituximab plus bendamustine is shown as £12,000. It was pointed out that as rituximab + chlorambucil is listed as £10,000, chlorambucil as £300 and bendamustine as £7,000 the rituximab plus bendamustine figure therefore cannot be correct.

In the 'Errata' document on page 24 the cost of bendamustine has been changed to £16,000 and the cost of rituximab plus bendamustine remains as £12,000 which is incorrect. We believe that the figure for rituximab plus bendamustine should be £16,000 and the figure for bendamustine monotherapy should revert to £7,000.

In addition the ACD page 13 section 3.21 refers to 'Knauf et al. (bendamustine alone and rituximab plus bendamustine)'. This should be corrected as the Knauf study does not involve rituximab plus bendamustine but compares bendamustine alone with chlorambucil alone.

3) <u>Are the provisional recommendations sound and a suitable basis for guidance to the NHS?</u>

Incorporation of the additional evidence detailed above, coupled with the consideration of two distinct patient populations would provide a sound and suitable basis for guidance to the NHS.

4) <u>Are there any aspects of the recommendations that need particular consideration to ensure avoidance of unlawful discrimination?</u>

We propose that NICE should consider issuing guidance in the following fludarabine-unsuitable patient populations:

1) Those suitable for treatment with a bendamustine based regimen - for which the relevant comparators are bendamustine and rituximab plus bendamustine, chlorambucil or rituximab plus chlorambucil.

2) Those unsuitable for treatment with a bendamustine-based regimen - for which the relevant comparators are chlorambucil and rituximab plus chlorambucil (the comparators for which there is direct evidence available from the CLL11 trial).

There is a lack of alternative therapies for patients who are unsuitable for fludarabine and are also unsuitable for bendamustine-based regimens. If implemented this guidance has the effect of preventing patients who are unsuitable for bendamustine-based therapies from having access to obinutuzumab on the basis that it is not cost-effective compared to bendamustine or rituximab-bendamustine.

Clinical rationale

There are fludarabine-unsuitable patients for whom bendamustine is not appropriate; these patients currently receive chlorambucil with or without rituximab in accordance with British Committee for Standards in Haematology (BCSH) Guidelines[2].

This view was echoed by the clinical expert during the Committee meeting, is acknowledged on page 23 of the ACD and is also in line with the view of the ERG clinical expert (page 163 of the ERG report[3]).

Public Sector Equality Duty

Failure to consider these populations as distinct groups may be interpreted as discriminatory and in breach of the public sector equality duty ("PSED"). This is a general equality duty which came into force on 5 April 2011 and is enshrined in law (section 149 of the 2010 Equality Act[1]) (the "Act"). As a public body, NICE must, amongst other things, have due regard to the need to eliminate unlawful discrimination and other conduct prohibited by the Act. This involves removing or minimizing disadvantages suffered by people due to their protected characteristics, in this instance, the relevant protected characteristic under the Act being disability as defined in the Act. If a patient unsuitable for a bendamustine-based therapy were denied access to obinutuzumab plus chlorambucil on the basis that it was not cost-effective compared to a bendamustine-based regimen this would clearly present a serious risk of that decision being considered discriminatory and in breach of the PSED.

References

1 Equality Act 2010. Part 11, chapter 1, section 149. Available at http://www.legislation.gov.uk/ukpga/2010/15/section/149

2 Oscier D et al. for the British Committee for Standards in Haematology. Guidelines on the diagnosis investigation and management of chronic lymphocytic leukaemia Brit J Haem. 2012, 159: 541–564

3 Hoyle, M., Long, L., Huxley, N., Crathorne, L., Briscoe, S., Rudin, C. Obinutuzumab in combination with Chlorambucil for previously untreated chronic lymphocytic leukaemia: a critique of the submission from Roche. PenTAG, University of Exeter, 2014.