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Sent by e-mail only: xxxxxxxxxxxxxxxxxx

24 January 2023

Dear xxxxxxxx

**Re: Final Appraisal Document — Daratumumab in combination for untreated systemic amyloid light-chain amyloidosis [ID3748]**

Thank you for your letter of 17 January 2023 responding to my initial scrutiny views. This is my final decision on initial scrutiny.

I consider the ground 1(a) points followed by the grounds 1(b) and then the ground 2 points.

***Ground 1(a): In making the assessment that preceded the recommendation, NICE has failed to act fairly***

**Appeal point 1(a).3** **In making the assessment that preceded the recommendation, NICE has failed to act fairly by neglecting to consider inequalities of healthcare provision caused by its decision**

I explained in my letter of 22 December 2022 that I was not minded to refer this appeal point to the Appeal Panel because:

“*The existence of geographical inequalities in existing healthcare provision is not a factor that the committee is required to consider under NICE’s Guide to the methods of technology appraisal 2013 (the “****Methods Guide 2013****”). This point can therefore be considered as a challenge against the appraisal process itself as set out in the Methods Guide, rather than against the final draft guidance, and as such would fall outside the scope of an appeal.*

*Accepting for the sake of argument that existing health inequalities can properly be considered as part of the evaluation process in this appraisal, I nevertheless still consider that you have not put forward an arguable case under ground 1a (or any other ground). MyelomaUK has not identified health inequalities beyond the simple fact that provision may vary on a regional basis. Differing regional or local approaches to commissioning and provision are commonly found in instances where NICE evaluates a technology. No argument has been put forward as to why regional variation gives rise to particular unfairness for patients living with AL amyloidosis as compared to other conditions where such variation is seen or why the approach taken by the committee in this appraisal is procedurally unfair.*

*Such inequalities as may be related to current differences in approach to the management of AL amyloidosis are not attributable to NICE.”*

Your response letter of 17 January 2023 accepts the above points regarding existing inequalities and regional variations in clinical practice but adds that you:

“*want to highlight that people from minority groups, and those from lower socioeconomic backgrounds are more likely to experience issues accessing optimal care. This is more common when there are no guidelines or approved treatment pathways to guide patients and clinicians. There are no routinely approved treatments for AL amyloidosis.”*

I cannot agree or disagree with your additional comment that an absence of guidelines will make it more common for people from minority groups and lower socioeconomic backgrounds to experience issues accessing optimal care.

However, even if I were to accept that to be true, I cannot see any arguable case that NICE has failed to act fairly. It may assist for me to explain that “unfair” under ground 1(a) relates to procedural fairness, for example did the committee follow NICE’s procedures, did stakeholders have an opportunity to comment, are there adequate reasons in the FAD for stakeholders to understand the decision, and so on.

I can see no procedural requirement for the Committee to “consider inequalities of healthcare provision caused by its decision” in the way you describe. You appear to be suggesting that, having determined that all the cost-effectiveness estimates for daratumumab are in a range higher than what NICE considers an effective use of NHS resources, the Committee ought to have gone on to consider whether the continuation of the status quo (i.e. the absence of positive NICE guidance) might represent a missed opportunity to improve inequalities of access for certain groups, and to have made a positive recommendation on that basis. I have identified nothing that would require (or indeed permit) the Committee to take such an approach.

***Ground 2:******the recommendation is unreasonable in the light of the evidence submitted to NICE***

**Appeal point 2.1** **The Appraisal Committee’s conclusion that “both ALchemy and EMN23-UK may be representative of UK clinical practice” is unreasonable in light of the evidence submitted**

Thank you for your response letter which provides helpful clarification.

I explained in my letter of 22 December 2022 that I was not minded to refer this appeal point to the Appeal Panel because I considered the appeal documents show the committee had a sufficient basis on which to conclude that both Alchemy and EMN23-UK may be representative of UK practice. I highlighted that the ERG Report states that the ALchemy patients are “likely to be the cohort that most closely reflects the current UK clinical population and treatment context” and that ALchemy reports response at 1 month, an increasingly common point at which treatment decisions are made.

I note that, while you agree that the patients enrolled in the two studies (EMN23-UK and ALchemy) largely overlap and are representative of the UK AL amyloidosis patient population, you do not believe that the data outputs and subsequent models created from this data are “equally accurate or representative” of UK patient outcomes.

You make two points.

First, you submit that “it is unreasonable to conclude on the basis of the evidence submitted that the ALchemy data is representative of UK clinical practice” because:

* the ERG’s view that the “ALchemy study interpretation [of response criteria] is the same as the interpretation in the UK clinical care” was not validated or underpinned by evidence or reviewed by experts; and
* the Committee did not explore the implications of evidence submitted that the ALchemy study uses an older definition of response which is no longer used in UK clinical practice.

Secondly, you submit “it is unreasonable to conclude that the ALchemy data as published can produce overall survival models that are accurate or representative of UK patient outcomes” because:

* none of the data from the ALchemy study was re-categorised in terms of the criteria used to define each response category (which the ERG’s clinical advisor indicated would be important as the older criteria used in the analysis of ALchemy were problematic); and
* the models produced from the data failed to show face validity at the second committee meeting where the clinical expert stated that overall survival curves from ALchemy were not clinically representative because they were not clinically plausible due to the lack of separation observed between complete haematologic response (CR), and very good partial response (VGPR).

In summary, you say:

*“The evidence submitted showed that the response criteria used in the ALchemy data is older and not representative of clinical practice, that the data outputs were not representative of UK clinical practice due to lack of recategorization, and that the models produced from the data are not clinically plausible and therefore the ALchemy data cannot be considered representative of UK patient outcomes.”*

Having considered these arguments, it appears that your appeal point is that it was unreasonable for the Committee to conclude that ALchemy “may be representative of UK clinical practice”. That is because you consider the ALchemy data cannot be representative and should either be completely discounted or given little weight. I’m mindful that the Committee has put it no higher than the ALchemy data “may be” representative and that the actual weight given to ALchemy by the Committee with regard to modelling haematological response and survival is detailed in the following paragraphs of the FAD. The Committee note weaknesses in the ALchemy data, concluding that the choice of data set (that is, EMN23-UK or Alchemy) is uncertain when assessing haematological repsonse (FAD para 3.11) and that there is high uncertainty in extrapolations for overall survival in the longer term using **either** the re-categorised EMN23-UK or ALchemy datasets (FAD para 3.13). This is reflected in the Committee’s preferred assumptions (at para 3.21) that both the distribution of haematological response for standard care and the extrapolated overall survival “may lie between the Alchemy data and the censored and re-categorised EMN23-UK data”. I am also mindful that, in any event, the company's own ICERs were above the range NICE considers an acceptable use of NHS resources. Nonetheless, I will refer this point the Appeal Panel to consider if the Committee could reasonably conclude that ALchemy “may be representative of UK clinical practice”, such that ALchemy could be taken into account along with other evidence such as EMN23-UK.

**Appeal point 2.2 The Appraisal Committee’s conclusion that “Potential confounding factors between haematological response and overall survival are not appropriately explored” is unreasonable in light of the evidence submitted**

I explained in my letter of 22 December 2022 that I was not minded to refer this appeal point to the Appeal Panel because I considered the committee’s explanation at paragraph 3.12 of the FAD read together with the committee papers show a sufficient basis on which the Committee could reasonably reach the above conclusion, and I had identified no evidence to support an arguable case that the committee’s conclusion was unreasonable.

I note your response that:

*“Myeloma UK continues to submit that the committee's conclusions regarding the issue of possible confounding between haematological response and overall survival are not relevant or reasonable. There is no evidence of confounding. The analysis submitted by the company (consultation response, point 6) identified no confounding issues. It is unreasonable to conclude that confounding is inadequately explored when there is no evidence that confounding exists.”*

The difficulty with your above argument is that it assumes that an absence of evidence of confounding is equal to evidence of absence of confounding. I consider it is clear from the papers that the absence of evidence in this case was not sufficient for the committee to support a conclusion of no confounding.

In particular, the papers show that, while the company presented analysis which identified no confounding issues, the ERG considered potential confounding had not been explored appropriately by the company. Owing to concerns about the company’s approach and a lack of reliable results from the analysis, which the ERG considered “do not appear to be adequately estimated”, the ERG was unable to comment on the results. It therefore considered that confounding remained an area of uncertainty (see excerpt from page 13 of the committee papers[[1]](#footnote-1) quoted in my letter of 22 December 2022).

Paragraph 3.12 of the FAD recognises that the company’s response to the ACD provided results identifying no evidence of confounding and that the ERG considered those results unreliable. The Committee agreed with the ERG that the analyses were not appropriately conducted. Therefore uncertainty about the potential confounding factors remained.

In light of the above, I consider your point that “*it is unreasonable to conclude that confounding is inadequately explored when there is no evidence that confounding exists*” is unarguable. To the contrary, the Committee’s very concern here was that the company’s results identifying no evidence that confounding exists could be given little weight due to the inadequate exploration of the issue.

**Appeal point 2.3 The Appraisal Committee’s conclusion that “Some utilities derived from ANDROMEDA EQ-5D-5L data lack face validity and comparison with utilities from ALchemy is preferred” is unreasonable in light of the evidence submitted.**

I explained in my letter of 22 December 2022 why I was not minded to refer this point to the Panel. You have provided no further comment or argument and I therefore confirm this point will not be referred.

**2.4 The Appraisal Committee’s conclusion that “an acceptable ICER is £20,000 per QALY gained” is unreasonable in light of the evidence submitted**

Thank you for confirming that Myeloma UK is content for this point of appeal to proceed under ground 1a. It will henceforth be referred to as your appeal point 1(a).4: NICE has failed to act fairly when applying the criteria for determining an acceptable ICER value under the Methods Guide 2013.

Conclusion

Therefore the valid appeal points are:

* 1(a).1 (NICE has failed to act fairly by not taking into account the advice and experience of haematologists at every stage of the appraisal process)
* 1(a).2 (NICE has failed to act fairly by failing to allow the National Amyloidosis Centre to nominate its own clinical expert for committee meetings)
* 1(a).4 (NICE has failed to act fairly when applying the criteria for determining an acceptable ICER value under the Methods Guide 2013)
* 2.1 (The Appraisal Committee’s conclusion that “both ALchemy and EMN23-UK may be representative of UK clinical practice” is unreasonable in light of the evidence submitted) as far as this relates to ALchemy only.

NICE shares the valid appeal grounds of each appellant with the other appellants to assist with preparation for the hearing. These will be included in the appeal papers when they are circulated.

NICE will be in contact with you regarding the administration of the appeal, which will be held orally.

Yours sincerely

Dr Mark Chakravarty

Lead Non-Executive Director for Appeals & Vice Chairman

National Institute for Health and Care Excellence

1. <https://www.nice.org.uk/guidance/gid-ta10656/documents/committee-papers-3> - see pages 74-75 of 86 [↑](#footnote-ref-1)