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Sent by e-mail only: xxxxxxxxxxxxxxxx

24 January 2023

Dear xxxxxx

**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).2 The Appraisal Committee’s conclusion that “it had not been shown if daratumumab in combination improves overall survival” disregards substantial evidence submitted by Janssen in support of complete haematological response as a surrogate endpoint for overall survival**

I explained in my initial scrutiny letter that I was not minded to refer this appeal point to the Appeal Panel because *“There was no direct evidence in respect of overall survival. The committee was invited to consider complete haematological response as a surrogate endpoint and gave detailed consideration to this submission...”.*

I understand from your response that your appeal point is (in essence) that the Committee’s consideration of haematological response as a surrogate endpoint - and in particular its conclusion at para 3.7 of the FAD that “it had not been shown if daratumumab in combination improves overall survival” - was procedurally flawed / unfair because the Committee failed “to take into account relevant evidence or to explain why important evidence has not been relied upon (lack of transparency)”. In particular you say there is no evidence in the FAD that the Committee took into account that:

1. substantial delay in major organ deterioration is an endpoint closely linked to survival; and
2. the additional survival results from the ANDROMEDA safety data at a median follow up of 20.3 months (which were used to update the economic model and submitted in response to the ACD, with the agreement of NICE), while immature, provide directional (direct) evidence of a survival advantage in patients receiving daratumumab in combination (a 6.6% higher survival at 20.3 months median follow-up in patients treated with DBCd as compared with patients on BCd only (point 4 Janssen response to ACD).

I remain of the view that it is unarguable that the Committee unfairly failed to take into account important relevant information. I note that:

* + - * The Committee was clearly aware of the evidence on major organ deterioration and haematological response, as the FAD (under “clinical evidence”) states that “daratumumab in combination is an effective treatment for improving haematological response and reducing major organ deterioration”. It was also aware that the company used haematological response as a surrogate end point for overall survival (FAD para 3.6 and 3.9). I see no arguable case that there that the Committee has failed to consider these matters. There is evidence that the Committee considered the company’s position on surrogate end points.Whether the Committee’s conclusion, having considered the evidence, that “it had not been shown if daratumumab in combination improves overall survival” may be unreasonable is a different appeal point: see point 2.2 below.
* The ANDROMEDA additional survival results you reference (showing a 6.6% higher survival at 20.3 months median follow-up in patients treated with DBCd as compared with patients on BCd only), were expressly considered by the ERG stating (p75 of the committee papers):

*“The observed ratio of surviving patients in ANDROMEDA at a median follow-up of 20.3 months was 1.066 for DBCd versus BCd, while the equivalent ratio between treatment arms in the model (based on the re-categorised EMN23 UK cohort data) was 1.021. Consequently, the company uplifted the per-cycle survival probabilities for all response categories in the DBCd treatment arm from cycle 7 onwards by a factor of 1.044, indicating a 4.4% higher survival in patients treated with DBCd as compared with patients on BCd only. The implications for the cost-effectiveness results are shown in Section 3.2. In the absence of mature OS data from ANDROMEDA, the ERG considers the company’s general approach to be acceptable but there remains uncertainty surrounding the predicted treatment-specific OS over time.”*

* The Committee itself was aware of and considered the ANDROMEDA results in detail. In particular:
	+ slide 23 from the FAD slide deck shows that the committee considered the Andromeda data and specifically the 6.6% increase in overall survival and the inclusion of that in the company’s economic model[[1]](#footnote-1);
	+ para 3.7 of the FAD explains the Committee’s conclusions relating to the ANDROMEDA data, stating: “*The committee noted that ANDROMEDA is an ongoing trial and that the data on overall survival presented by the company, a secondary outcome in the trial, is immature at the planned interim and 12- month landmark analyses, and only data on haematological response was available at the 18-month landmark analysis”.*
* I see no arguable case that the Committee has failed to consider these matters. Whether the Committee’s conclusion, having considered the evidence, that “it had not been shown if daratumumab in combination improves overall survival” may be arguably unreasonable is a different appeal point: see point 2.2 below.

You appear to raise an additional argument in your response letter that the FAD unfairly fails to “explain why important evidence was not relied upon (transparency)”. While I think it is clear that the evidence you raise was taken into account, I accept there is an arguable point about whether the weight given to the evidence was appropriate (i.e. whether the conclusion that “it had not been shown if daratumumab in combination improves overall survival” was reasonable – see appeal point 2.2 below) and whether that has been adequately explained in the decision. I will refer this aspect of your point to the Appeal Panel.

***Appeal point 2.1 The Appraisal Committee’s conclusions that “both ALchemy and EMN23-UK may be representative of UK clinical practice” are unreasonable***

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 you say that the ERG Report is not relevant because it considered only the EMN23 data rather than EMN23-UK. I disagree that this undermines my previous reasoning as regards to whether the Committee had a sufficient basis to conclude that ALchemy may be reflective of UK clinical practice per se, rather than being relatively more reflective in comparison to EMN23 (or indeed EMN23-UK).

I have nonetheless considered your more detailed arguments set out in your response letter. You explain that appeal point 2.1 is, in summary, that:

*“the unbalanced reference to the views of the clinical experts together with the failure to consider the implausible Kaplan Meier curves from ALchemy, the inconsistency between the haematologic response criteria used by ALchemy and in ANDROMEDA and the lack of access to patient level data from ALchemy indicate that the approach of the Committee in concluding that both ALchemy and EMN23-UK may be representative of UK clinical practice, is unreasonable.”*

More specifically you say:

* Paragraph 3.10 of the FAD is “unbalanced and misleading”, as:
	1. the statement that “the clinical experts agreed with the ERG that ALchemy better reflects NHS practice” relates to the experts’ consideration of EMN23 only and is factually inaccurate so far as the experts’ comments on EMN23-UK is concerned; and
	2. paragraph 3.10 does not reflect concerns expressed by experts at the second Committee meeting regarding the data from ALchemy;
* The Committee disregarded the fact, drawn to its attention by Janssen (Point 2, Janssen ACD Response) and also noted by the ERG’s expert, that the haematologic response criteria from ALchemy were not aligned with the response criteria used in ANDROMEDA. Specifically, the ERG’s clinical advisor stated that *“the reclassification of response is important as the older criteria used in the analysis of ALchemy were problematic”* (Page 8, Evidence Review Group’s Critique of the Company’s Response to the ACD);
* A further issue with ALchemy was the potential risk of confounding due to treatment switching. This was discussed in the first appraisal committee meeting and referred to in Section 3.11 of the ACD: *“However, in ALCHEMY , response status at 6 months was reported irrespective of previous treatment changes – for instance, a person who switched treatments after 3 months and whose condition subsequently responded would be reported as having a response. This suggests that the response categorisation at 6 months in ANDROMEDA does not match the response categorisation from ALCHEMY..”;* and
* Patient level data from ALchemy were not available to you so the inconsistencies identified above could not be corrected. You say this “provides a clear reason why EMN23-UK should have been preferred.”

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 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 Committee’s conclusion that “it had not been shown if daratumumab in combination improves overall survival” conflicts with the balance of the available evidence***

Having considered the additional arguments made in your letter of 17 January 2023 I agree that this is a valid appeal point.

Conclusion

Therefore the valid appeal points are:

* 1(a).1 (The Appraisal Committee has failed to take into account factors other than uncertainty when defining the ICER threshold for this appraisal);
* 1(a).2 (The Appraisal Committee’s conclusion that “it had not been shown if daratumumab in combination improves overall survival” disregards substantial evidence submitted by Janssen in support of complete haematological response as a surrogate endpoint for overall survival) only so far as this relates to whether the FAD provides adequate reasons;
* 1(a).3 (The fact that an expert haematologist was not invited to the first meeting of the Committee was not adequately corrected by inviting such an expert to the second meeting because issues such as the significance of complete haematologic response were not discussed);
* 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; and
* 2.2 (The Appraisal Committee’s conclusion that “it had not been shown if daratumumab in combination improves overall survival” conflicts with the balance of the available evidence).

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/1-2> [↑](#footnote-ref-1)