17 January 2023

Dr Mark Chakravarty

Lead non-executive director for appeals

National Institute for Health and Care Excellence

2nd Floor

2 Redman Place

London E20 1JQ

Dear Dr Chakravarty,

Re: Appeal against the final appraisal determination for daratumumab in combination for untreated systemic amyloid light-chain amyloidosis [ID3748]

Thank you for your letter of 22 December 2022, responding to Myeloma UK’s appeal against the above Final Appraisal Document (FAD).

In response to this initial scrutiny letter, we would like to make the following comments regarding whether each appeal point should be referred to the Appeal Panel.

Myeloma UK

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

1a.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.

 We are pleased that you agree that this is a valid appeal point.

1a.2 NICE has not acted fairly by failing to allow the National Amyloidosis Centre to nominate its own clinical expert for committee meetings.

We are pleased that you agree that this is a valid appeal point.

1a.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.

Thank you for your comments regarding this appeal point. We accept your points regarding existing inequalities and regional variations in clinical practice.

However, we 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,

therefore, this decision could exacerbate the inequalities faced by AL amyloidosis patients in England and Wales.

Ground 2 – The recommendation is unreasonable in light of the evidence submitted.

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

Thank you for your comments regarding this appeal point.

Whilst we agree that the patients enrolled in both the ALchemy and EMN23-UK studies largely overlap and are representative of the UK AL amyloidosis patient population we do not believe the data outputs and subsequent models created from this data are equally accurate or representative of UK patient outcomes.

The methodology and data analyses from these studies are significantly different. Most importantly there are significant differences in how complete haematological response is categorized and analysed. These differences impact the validity of the overall survival curves generated from these studies.

The issues with the ALchemy data and the lack of face validity in the overall survival models generated from the data were highlighted at several points during the appraisal.

1. A difference in the measurement of haematological response was highlighted in the Evidence Review Group’s Report. Section 3.5.1.1 “The EMN23 study also interprets the internationally recommended response criteria in a different way from the ALchemy study, leading to slightly different results.”

Whilst they cited the ERG’s clinical expert and concluded that the “ALchemy study interpretation is the same as the interpretation in the UK clinical care.” There was no evidence provided, other than this statement, to confirm this is the case. This assumption was not confirmed or reviewed by independent clinical experts during the committee meeting or technical engagement steps. Myeloma UK submit that it is unreasonable to conclude on this basis that the interpretation in the ALchemy study is representative of UK clinical practice.

In fact, in subsequent discussions between the ERG and their clinical advisors it was made clear that the ALchemy study used an older, out of date, definition of response which is no longer used in UK clinical practice. (ERG’s Critique of the Company’s Response to the Appraisal Consultation Document Papers, point 2.2 which stated: “the older criteria used in the analysis of ALchemy were problematic.”) In summary:

* + Clinical opinion given to the ERG about the applicability of ALchemy was not validated or underpinned by evidence and was not reviewed by nominated experts at any point in the process.
	+ The limitations of out-of-date criteria in ALchemy were highlighted to the committee but the implications of this were not explored or taken into account.

We submit that the failure to take these two evidence limitations into account goes beyond a difference of interpretation, but rather constitutes a failure to properly obtain or engage with key evidence.

As a result, it is unreasonable to conclude on the basis of the evidence submitted that the the ALchemy data is representative of UK clinical practice.

1. There is also a significant difference in the data analysis and output from the studies. In their consultation response (point 2) the company stated:

“Following discussion with the UK NAC, it was confirmed haematologic response data from either the ALchemy study or the EMN23 study UK cohort would need to be recategorised to ensure alignment with ANDROMEDA, specifically in terms of: a) The approach to the response categorisation of patients who had switched treatments, and b) The criteria used to define each response category”.

In the ERG’s response it is stated: “ERG’s clinical advisor indicated that the reclassification of response is important as the older criteria used in the analysis of ALchemy were problematic.”

None of the data from the ALchemy study was re-categorised in terms of the criteria used to define each response category.

Therefore, 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.

In fact, the models produced from the data failed to show face validity at the second committee meeting where the clinical expert Mamta Garg 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).

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.

Myeloma UK submit that it is unreasonable to conclude that the ALchemy data, as published, gives an accurate representation of UK patient experience.

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.

Thank you for your comments regarding this appeal point. 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.

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.

Your preliminary view is noted.

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. Conclusion

We are very pleased that you agree that this is a valid appeal point. You suggest that this point of appeal should proceed under Ground 1a. Myeloma UK is content to proceed on that basis.

For the reasons listed above, we believe that the appraisal of daratumumab in combination was both unfair and unreasonable. It is on this basis that we are appealing the FAD, via an oral appeal.

We urge you to make daratumumab in combination available to all those who could benefit from it.

Yours Sincerely,

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Director of Research and Advocacy, Myeloma UK