16 December 2022

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,

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

Introduction

Myeloma UK is appealing against the recent decision by NICE not to recommend daratumumab in combination for untreated systemic amyloid light-chain amyloidosis, as set out in Final Appraisal Determination [ID3748].

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22

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Myeloma UK is appealing this decision because we believe it is unacceptable and sets a dangerous precedent.

AL amyloidosis is a rare, complex and very individual condition. It is incurable and whilst it can be successfully treated it will inevitably come back. The median life expectancy ranges from years to months. Effective treatments which help patients achieve complete responses are critical for patient survival and quality of life. However, there are no routinely commissioned treatments for AL amyloidosis patients, they have to rely on the off-label use of myeloma treatments. The off-label use of treatments is not guaranteed and is dependent on regional guidance and procedures. Therefore, there is a very high unmet need for AL amyloidosis patients.

This decision prevents patients from accessing the first AL amyloidosis-specific treatment. This treatment is seen internationally as the most effective treatment for newly diagnosed AL amyloidosis patients because it is significantly more likely to deliver deep responses, preventing further organ damage. Without these treatments patients in England and Wales will not be receiving an international standard of care, which will further impact patients since it is a disincentive for companies to run clinical trials. Therefore, this decision forces AL amyloidosis patients to depend on off-label use of treatments and puts them at an international disadvantage.

Appeal points

There are several points on which we base this appeal, covering the following grounds:

* Ground 1a – NICE has failed to act fairly
* Ground 2 – The recommendation is unreasonable in light of the evidence submitted.

Examining these in greater detail:

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.

AL amyloidosis is a plasma cell dyscrasia and although it affects other organs in the body it is a haematological condition.

Haematologists are the treating physicians for AL amyloidosis patients and therefore the most relevant clinicians to comment and give advice on treatment, treatment response and clinical practice in AL amyloidosis.

However, no haematology clinical experts provided written evidence as consultees at any point in the appraisal process. Furthermore, they did not participate in the first committee meeting and therefore were unable to clarify issues or provide expert testimony about the evidence base to Committee members.

The input from clinical experts is fundamental to the way in which NICE conducts its appraisals. Clinical experts validate and scrutinise both company and ERG evidence reviews and assumptions helping to ensure the discussions are balanced and representative of clinical practice and patient need. It is established practice that the findings and advice of the ERG are considered by the Committee alongside expert written and oral evidence by treating physicians. This expert opinion is a fundamental “check and balance” in the evidence base presented to the Committee. Without the perspective of a treating physician, Myeloma UK submits that the proceedings were not subjected to the clinical scrutiny that NICE applies as standard in its practice.

We also submit that the exclusion of a haematologist from scoping, technical engagement, written submissions, the first committee meeting and response to the Appraisal Consultation Document (ACD) was an exclusion of important evidence and testimony. AL amyloidosis is a rare, complex, incurable condition. It is estimated that there are only 500-600 people diagnosed with AL amyloidosis every year and around 3000 people in the UK living with AL amyloidosis. The patient population is highly diverse due to the variation in organ involvement. This makes it harder to collect meaningful data and run clinical trials in the UK patient population. This means that clinical experts are even more important for the validation of scoping, evidence and modelling.

Myeloma UK, Janssen and clinical expert (consultant nephrologist) Dr Jenny Pinney highlighted this issue during the consultation phase. Although, a haematologist was invited to the second committee meeting this was too late in the process because many discussions had already taken place and the Committee had taken significant decisions and set the context for its consideration without the proper expert input.

During technical engagement stakeholders are given the opportunity to comment on and submit evidence to address the key issues driving uncertainty in the ERG evidence review and subsequent cost-effectiveness calculations. In the first committee meeting all the evidence submissions from the company, Janssen, the ERG and technical engagement are discussed and reviewed. The committee discussed and made decisions about standard clinical practice, how and when complete haematological response should be measured, and which data sets should be used for overall survival.

As the treating physician, a haematologist is better placed to answer committee questions on significant issues such as the generalisability of patient population data to UK NHS clinical practice and the assessment of haematological response. Furthermore, the data sets being discussed were from trials and studies where haematologists were the principal investigators.

Although some of these topics were discussed in the second committee meeting the discussion and questions were tailored based on the ACD consultation comments. The haematological expert was only asked a couple of very specific questions. They did not have the opportunity to give their expert perspective on the issues surrounding the differences in overall survival criteria and the data they believe should have been used. They were also denied the opportunity to expand upon what actually happens in clinical practice and the challenges many clinicians face accessing myeloma treatments for their AL amyloidosis patients, as this use is an off-label use of these treatments.

It is submitted there is a legitimate expectation a haematology clinical expert ought to have been engaged for the reasons stated above given the terms of 3.1.1 of the NICE health technology evaluations: the manual (published 31 January 2022). 3.1.1 states that "A comprehensive evidence base is fundamental to the evaluation process… To ensure that the guidance issued by NICE is appropriate and robust, the evidence and analysis, and their interpretation, must be of the highest standard possible and transparent". A similar requirement is incorporated into NICE's Guide to the process of technology appraisal (Published: 02 September 2014, Last updated: 30 May 2018) by the reference in 3.3.8 to

NICE's Guide to the methods of technology appraisal (Published: 04 April 2013). Paragraph 3.1.1 of the latter contains this requirement in terms which, although not identical, are not substantively different.

In addition, it is further submitted that excluding a haematology clinical expert also goes against the principles that guide the development of NICE guidance and standards. Principle 4 (NICE, Our Principles) states that NICE will take into account the advice and experience of people using services and their carers or advocates, health and social care professionals, commissioners, providers and the public. We submit that the absence of participation by a haematologist, as a treating physician, at any stage other than the final committee meeting means that the Committee was not properly able to take into account the advice and experience of the key healthcare professionals responsible for the treatment and care of people with AL amyloidosis.

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

The National Amyloidosis Centre (NAC) is the biggest amyloidosis clinical and research facility in the UK. It is based at the University of College London. The majority of AL amyloidosis patients in England and Wales will be referred to the NAC for specialist review after diagnosis. It is the biggest AL amyloidosis research group in the UK.

NICE failed to include The National Amyloidosis Centre or University College London (UCL) as a stakeholder in this appraisal although it had been in a previous amyloidosis treatment appraisal [TA696]. This meant they could not nominate clinical experts or provide independent written evidence. It is submitted that this, along with the NICE resources quoted in the final two paragraphs of the previous appeal ground (1a.1) combine to create a legitimate expectation that NAC would have been a stakeholder in this appeal too.

The NAC was considered a stakeholder, as a relevant research group, in a previous amyloidosis appraisal, the Single Technology Appraisal for Tafamidis for treating transthyretin amyloid cardiomyopathy [ID1531], where a clinical expert was nominated by UCL. The value of NAC input in the current appraisal was acknowledged because they were consulted by the Evidence Review Group (ERG). The unpublished data from the ALchemy study used within the ERG’s assessments of utilities and overall survival was provided by the NAC.

However, there was no NAC or UCL-nominated AL amyloidosis clinical expert at the committee meeting. The committee, therefore, was not able to consider their expert opinion during the complex discussion and debate surrounding the data and subsequent models.

Furthermore, AL amyloidosis is rare and therefore there is a very small group of AL amyloidosis experts to draw upon for guidance and opinion. NICE rules governing participation of clinical experts can prevent clinicians who support the ERG review from also appearing as clinical experts. This supports our argument that consultee clinical experts are essential to provide scrutiny and/or validation of ERG finding and evidence.

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.

There are no NICE guidelines for the management of AL amyloidosis and no routinely commissioned treatments for either newly diagnosed or relapsed AL amyloidosis patients. Patients are currently treated with drugs and drug combinations used to treat myeloma. This is considered an off-label use of these drugs. In the absence of standard commissioning, the off-label use of drugs is managed at the clinical commissioning group (CCG) level. Therefore, access to approved myeloma treatments for AL amyloid patients is determined on a regional basis by local CCG guidance rather than national guidance. This means that there are geographical inequalities in access with some patients accessing innovative myeloma treatments like daratumumab and others not. In some CCGs, AL amyloidosis patients are denied access to myeloma treatments due to stricter protocols for the off-label use of innovative anti-myeloma drugs.

AL amyloidosis patients need routinely commissioned treatments to guarantee the equity of access to the most effective treatments. By failing to recommend this treatment the committee has failed to uphold NICE’s commitment to reduce health inequalities through their work, as outlined in NICE’s 5-year strategy (2021 to 2026) through their work, as outlined in NICE’s 5-year strategy (2021 to 2026), (Section 6, page 20, Strategic pillar 1: Rapid, robust and responsive technology evaluation) which states NICE will “ensure all aspects of [their] approach - product selection, methods and adoption - are aligned to help reduce health inequalities.”.

Therefore, NICE has acted unfairly by neglecting to consider regional inequalities in healthcare provision caused by its decision.

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. In ‘FAD Section 3.10 the Committee concluded that ALchemy and EMN23-UK may be representative of UK clinical practice.

Myeloma UK submits that this conclusion is unreasonable because we do not believe the ALchemy data is representative of UK clinical practice. This is because the data doesn’t plausibly reflect the overall survival estimates for people defined as achieving a complete haematological response in clinical practice today.

The ALchemy study used a different definition of response than the internationally recognised standard for haematological response in AL amyloidosis and has a shorter followup to the EMN data. As a result, the ALchemy data as published underestimates the effect complete response has on overall survival. These differences mean the separation between the overall survival curves for those achieving complete haematologic response (CR), and those with very good partial response (VGPR) is reduced and thus the curves underestimate the overall survival benefit of the treatment.

This difference 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 conclude that “The ERG’s clinical advisor familiar with both studies noted that ALchemy study interpretation is the same as the interpretation in the UK clinical care, using a strict interpretation of the response criteria, whilst EMN23 has a looser interpretation.” This was not the case at the one- and three-month time points.

The FAD did not address the implausibility of the overlapping overall survival curves raised by the pharmaceutical company in their response to technical engagement which stated “the overlapping Kaplan-Meier curves for patients achieving CR and VGPR at the three-month analysis timepoint, with expert clinical opinion indicating that this clinically implausible result is likely to be reflective of immature data. The lack of face validity for the CR and VGPR survival at the three-month timepoint therefore represents a limitation of the ERG base case approach.”

The FAD also did not attach sufficient weight to the clinical expert evidence from by Mamta

Garg received at the second committee meeting stating that the 3-month results 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). Not attaching weight to this expert opinion renders the recommendation unreasonable.

Therefore, it is submitted that the committee’s conclusion is unreasonable because the ALchemy data as published is not representative of UK clinical practice due to the differences in the criteria used and the lack of plausibility due to the overlapping KaplanMeier curves.

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.

As set out in the FAD Section 3.12 the committee felt that “potential confounding factors between haematological response and overall survival are not appropriately explored”. Myeloma UK submits that this conclusion is unreasonable.

It is acknowledged that the level of organ damage caused by AL amyloidosis affects patient survivability (Company Submission, Section B1.3.1, Prognosis and Staging). This is particularly true for patients with severe cardiac involvement. (FAD Section 3.1 and 3.5)

However, it is also acknowledged that sustained complete haematological response improves organ function and reduces organ damage. (FAD section 3.9, Company Submission Section B1.3.1: Treatment pathway for AL amyloidosis in the UK and B.2:

Haematological response)

In FAD section 3.7 The committee concludes that daratumumab in combination is an effective treatment for improving haematological response and reducing major organ deterioration in people with newly diagnosed systemic AL amyloidosis.

Therefore, confounding factors such as renal and cardiac involvement would be reduced in the DVCD arm. Therefore, Myeloma UK submits the committee's points and focus on the issue of possible confounding between haematological response and overall survival are not relevant or reasonable. Thus, it is therefore unreasonable to attribute this to an increase in overall uncertainty and to conclude that the confounding factors are not appropriately explored.

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.

In ‘FAD Section 3.15 the Committee concluded that utilities derived from ANDROMEDA EQ5D-5L data lack face validity and comparison with utilities from ALchemy is preferred. Myeloma submits that this conclusion is unreasonable because the ALchemy Quality of Life data is not publicly accessible and as such not available to the company. This data set can therefore not be used by the company to model for utilities and it is therefore unreasonable for the committee to request this analysis.

In the FAD Section 3.7, the committee acknowledges that the data from ANDROMEDA is immature and that longer follow-ups are required to assess treatment benefits. The evidence reviewed by the committee also highlighted that improvements in quality of life are not typically observed immediately after successful treatment and can take up to one-year for patients to experience the QoL gains as a result of successful treatment. Therefore, due to the short follow-up from ANDROMEDA it is unreasonable to expect sufficient QoL data from current ANDROMEDA analysis.

Thus, Myeloma UK also submit that the Committee did not attach sufficient weight to the scenario analysis included in the original Company submission which provided health state utility values estimated by a panel of six UK-based clinicians at a clinical Advisory Board and more accurately reflects the quality-of-life improvement expected as a result of the significant deepening of haematologic responses on the DVCD arm.

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

As set out in the FAD Section 3.20 the committee determined that “because of the uncertainty … an acceptable ICER is £20,000 per QALY gained”

Myeloma UK submits that the explicit imposition of the lower threshold of £20,000 is unreasonable in this context, setting a dangerous precedent. AL amyloidosis is a rare, complex and incurable condition and therefore uncertainty would be expected. There are no routinely commissioned treatments for AL amyloidosis and due to the rarity of the condition there is limited clinical data, particularly in patients with advanced cardiac or renal

involvement due to short life expectancies, therefore most of the available data is observational data.

As set out in the NICE’s guide to the methods of technology appraisal (at 6.2.16) uncertainty is a key factor underpinning the judgements of the Committee. However, it explicitly states that “the evidence base will necessarily be weaker for some technologies, such as technologies used to treat patients with very rare diseases.” Given the rarity of this condition, unmet need, and limited treatment options for these patients we submit the imposition of this lower threshold to be unreasonable.

Conclusion

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 wish to appeal 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