NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

APPEAL HEARING

Advice on Daratumumab in combination for untreated systemic amyloid light-chain amyloidosis [ID3748]: Decision of the panel

Introduction

1. An appeal panel was convened on 27 April 2023 to consider an appeal against NICE's final appraisal document, to the NHS, on daratumumab in combination for untreated systemic amyloid light-chain amyloidosis [ID3748].

2. The appeal panel consisted of:

• Professor Jonathan Cohen	Chair
• Alina Lourie	Non-executive director
• Dr Biba Stanton	Health service representative
• Dr Rachel Russell	Industry representative
• David Chandler	Lay representative

3. None of the members of the appeal panel had any competing interest to declare.

4. The panel considered appeals submitted by Janssen and Myeloma UK.

5. Janssen was represented by:

• Dr Margaret Wan	Medical lead, Haematology
• Amanda Cunnington	Senior Director, Patient Access
• Nicola Trevor	Director of Health, Economic, Market Access and Reimbursement

- Andrew Ternouth — Head of Health, Economic, Market Access and Reimbursement
- Dr Adela Williams — Legal Representative

6. Myeloma UK was represented by:

- Shelagh McKinlay — Director of Research and Advocacy
- Professor Ashutosh Wechalekar — Consultant Haematologist
- Dr Mamta Garg — Consultant Haematologist
- Michael Jameson — Patient representative
- Sarah Love — Legal representative

7. In addition, the following individuals involved in the appraisal were present and available to answer questions from the appeal panel:

- Dr Charles Crawley, chair — Technology appraisal committee B
- Baljit Singh, vice chair — Technology appraisal committee B
- Henry Edwards — Associate Director, technology appraisals, NICE
- Yelan Guo — Technology assessment adviser, NICE

8. The appeal panel's legal adviser Amy Smith was also present.

9. Under NICE's appeal procedures, members of the public are admitted to observe appeal hearings and several members of the public and NICE staff observed the proceedings which were held via Zoom.

10. There are two grounds under which an appeal can be lodged:

Ground one: In making the assessment that preceded the recommendation, NICE has:

(a) Failed to act fairly; and/or

(b) Exceeded its powers.

Ground two: The recommendation is unreasonable in light of the evidence submitted to NICE.

11. Dr Mark Chakravarty, NICE's lead non-executive director for appeals, in preliminary correspondence had confirmed that:

- Janssen had potentially valid grounds of appeal as follows: Grounds 1a and 2
- Myeloma UK had potentially valid grounds of appeal as follows: Grounds 1a and 2

12. The appraisal that is the subject of the current appeal provided advice to the NHS on daratumumab in combination for untreated systemic amyloid light-chain amyloidosis [ID3748].

13. Before the appeal panel inquired into the detailed complaints the following made a preliminary statement: Amanda Cunnington on behalf of Janssen, Sarah Love and Michael Jameson on behalf of Myeloma UK and Dr Charles Crawley on behalf of the appraisal committee.

14. The appeal panel were very grateful for Michael Jameson's eloquent and moving description of his experience as a patient with this condition.

15. The remainder of this document sets out the panel's decisions in the following order:

a. Janssen's ground 1a points;

b. Myeloma UK's ground 1a points;

c. Janssen's ground 2 points; and

d. Myeloma UK's ground 2 points.

Appeal by Janssen

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

Appeal Ground 1a.1: The appraisal committee has failed to take into account factors other than uncertainty when defining the ICER threshold for this appraisal.

16. This appeal point was considered alongside Myeloma UK appeal point 1a.4 at the hearing, so the following should be read in conjunction with that section of this decision letter. In determining this point 1a.1 the panel had regard to the full discussion at the hearing in relation to this point and Myeloma UK appeal point 1a.4.

17. Nicola Trevor, for Janssen, stated that paragraph 3.20 of the final appraisal document (FAD) says that the high level of uncertainty led the committee to conclude that an acceptable ICER would be well below £30,000. She stated that amyloid light-chain (AL) amyloidosis is an "ultra-rare" condition and that such a low ICER threshold is completely at odds with the flexibility afforded by the highly specialised technologies (HST) programme. She acknowledged that the FAD refers to the severity of the condition, unmet need, the potential uncaptured benefits and the innovative nature of the technology in different places. However, where the ICER threshold is discussed at paragraph 3.20, the only factor mentioned as a rationale for the ICER threshold is uncertainty. She said it is therefore unclear how these other factors were taken into account. She submitted it is procedurally unfair not to give adequate consideration to these other factors or – if such consideration was given – to give an adequate explanation in the FAD of how.

18. Henry Edwards, for NICE, said that there was an editorial error in the FAD. The strapline for paragraph 3.20 should have been but was not updated from the appraisal consultation document (ACD) and was incorrect in stating that "an acceptable ICER threshold is £20,000 per QALY gained". The statement in the body of the paragraph that an acceptable ICER would be "well below £30,000 per QALY gained" was the correct one. He referred to 6.3.1 of NICE's Guide to the methods of technology appraisal 2013 and explained NICE has a duty to consider the opportunity cost of approving a technology.

He drew attention to the places in the FAD where innovation and potential additional benefits of daratumumab are mentioned. He said that the rarity of AL amyloidosis and the unmet need for treatments were considered at the committee meetings and are mentioned in the slides. He said that even having considered uncertainty, uncaptured benefits and rarity, the committee still could not recommend daratumumab. He said that the change in the ICER threshold between the ACD and the FAD demonstrated that the committee had given further consideration to the factors mentioned by the appellants. He also said that the committee had not been provided with any ICER within the range normally considered an acceptable use of NHS resources.

19. In response to questions from the panel, Henry Edwards acknowledged that rarity was not mentioned in the FAD. He referred to section 6.2.16 of the methods guide that refers to evidence necessarily being weaker for a rare disease. In fact, in this case Janssen described the evidence as “robust” and the committee judged that this was by no means the weakest evidence they have seen in the context of rare diseases.

20. Dr Charles Crawley, for NICE, said that the main issue regarding rarity is how it impacts on the evidence: if appraising a treatment for a very rare condition with little evidence to support it, the committee are mindful not to penalise those with the condition because it is not possible to provide the usual standard of evidence. He stated that the committee understood that AL amyloidosis is a rare condition. However, he agreed that the evidence provided was quite impressive, so the rarity of the condition did not appear to have impacted on the ability to provide evidence.

21. In response to questions from the panel noting that innovation is referenced at paragraph 3.19 of the FAD, Dr Adela Williams, for Janssen, said that the issue is not only whether the committee considered additional factors in determining the ICER threshold but how they took them into account in their analysis. She acknowledged that it is clear the committee knew about the degree of clinical need and rarity of AL amyloidosis, but it was not clear how these factors were taken into account in setting the cost-effectiveness threshold. She submitted that the ICER threshold was set so low that it was almost impossible for a treatment for such a rare disease to meet it. Taking

into account the rarity of AL amyloidosis along with unmet need and innovation, it was hard to understand how the committee could ever have suggested a £20,000 per Quality Adjusted Life Year (QALY) ICER threshold.

22. In response to questions from the panel, Nicola Trevor said that rarity is important and should lead to more flexibility around uncertainty because it makes it challenging to generate evidence, and the fact that companies have to invest more to generate evidence in a rare disease. The degree of clinical need in this case arises from the fact that there is no other licensed treatment for this severe, life-threatening condition.

23. Henry Edwards said that the committee considered that an acceptable ICER threshold would be well below £30,000. The committee are asked to determine an ICER threshold for what ICERs they would be willing to consider an acceptable use of NHS resources. He said that the committee are asked to take a deliberative rather than quantitative approach when considering most plausible ICERs against that threshold in any given appraisal. In this case the committee did not see any ICERs below £30,000, so they could not consider something that was not on the table. If they had, it would have been a more challenging decision. They did not set a strict threshold of £20,000 but after taking everything into account felt that it could not be as high as £30,000. If there had been an ICER within the range of £20,000 to £30,000 it would have been something the committee could deliberate on. In response to the appellant's comments about transparency, he said that the FAD is trying to summarise many pages of documents over a long appraisal process. He agreed that there had to be enough information for a reader to understand the decision making, and said the committee would be happy to edit the FAD if needed.

24. Dr Charles Crawley reiterated that the committee considers ICERs presented to them and asks itself whether these are plausible and whether there is one within a cost-effective range. While the committee must determine an acceptable ICER threshold/range for the purpose of considering the ICERs put to them, the ICER threshold is not fixed and is always up for discussion if for example the evidence changes. In this appraisal, the committee did not see an ICER within an acceptable range.

25. Dr Adela Williams said that she was puzzled by the statement that no cost-effective ICERs had been presented as this was not her understanding.

26. Henry Edwards confirmed that the committee had not seen ICERs in the cost-effective range once confidential discounts for the competitor products had been applied. The lower end of the ICER range was £34,000 but the upper end was considerably higher.

27. Nicola Trevor said that the editorial error in the FAD that stated an acceptable ICER threshold was £20,000 had impacted on the company's ability to consider a managed access arrangement. This threshold would have set the bar ridiculously high.

28. Henry Edwards said that the editorial error in the FAD would have been corrected as part of factual accuracy checking before the FAD was published and would have been corrected in any commercial discussions with NHS England. He stated that for a technology to enter the cancer drugs fund there has to be a plausible ICER below £30,000 which was not the case here.

29. The appeal panel concluded as follows. The panel accepted that the committee had been aware of the rarity of AL amyloidosis, the unmet clinical need in this condition and the potential for benefits that were not fully captured in the model, and that this was clear from the papers. However, the panel was concerned that in paragraph 3.20 of the FAD – which sets out how the ICER threshold was decided – the only factor mentioned was uncertainty. The panel did not judge that the committee was obliged to discount uncertainty in the data solely because of the rarity of the condition. However, the panel judged that rarity is a relevant factor to consider when committees weigh the importance of uncertainty in modifying the ICER threshold. The panel were not persuaded by the committee's argument that rarity was less important in this appraisal because of the high quality of the data, as this seemed at odds with their focus on the uncertainty in the data. The panel was also concerned by the implication at the hearing that the committee may have given less detailed consideration to these points because they had not seen any ICERs below £30,000 (particularly given that they had seen ICERs close to this). The panel concluded that the reasoning in the FAD was not

sufficient for the reader to understand how the ICER threshold was reached, in particular how rarity had been weighed in the committee's consideration of uncertainty, but also with regard to how factors other than uncertainty had been weighed in the decision-making.

30. The appeal panel therefore upheld the appeal on this point.

Appeal Ground 1a.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

31. This appeal point was considered alongside Janssen appeal point 2.2 at the hearing, so the following should be read in conjunction with that section of this decision letter. In determining this point 1a.2 the panel had regard to the full discussion at the hearing in relation to this point and point 2.2.

32. Dr Adela Williams, for Janssen, said that the conclusion in section 3.7 of the FAD that "it had not been shown if daratumumab in combination improves overall survival" (OS) appeared to disregard important evidence submitted by Janssen. Firstly, the importance and clinical significance of complete haematological response (CR) to overall survival that had been acknowledged by the Scottish Medicines Consortium as the basis of its recommendation. Secondly, the importance of major organ deterioration progression free survival (MOD-PFS) that was approved as an endpoint by the Food and Drug Administration and the European Medicines Agency. Thirdly, additional data from the ANDROMEDA trial at a median follow-up of 20.3 months showing a modest numerical survival benefit. Whilst some of this evidence was described in the FAD there was no indication that it was taken account of by the committee. Further, she stated the text at the beginning of the FAD appeared to suggest daratumumab in combination does not improve overall survival.

33. Dr Charles Crawley, for NICE, said that the committee accepted the strong correlation between haematological response and OS and accepted that this was a surrogate marker for OS. They did have some concerns about whether confounding factors might influence this relationship. They brought this back

to the second committee meeting, but further analysis did not resolve the issue. The committee therefore concluded that they had not seen evidence proving that daratumumab improves OS, but there was no evidence that it did not do so: this was a case of absence of evidence rather than evidence of absence of effect. A projected survival benefit was incorporated into the economic model used at the first committee meeting. At the second meeting, the company presented data applying an increased survival benefit based on an updated analysis of the ANDROMEDA data. The committee was not happy with this approach, as the company had applied this increased benefit to all response groups (not just those with a complete or very good partial response). In fact, even with this increased projected survival benefit, there were no ICERs within the range normally considered an acceptable use of NHS resources.

34. In response to questions from the panel, Dr Adela Williams said that the question about the relevance of complete haematological response is front and centre of this appraisal. The committee's acceptance that this is a surrogate marker of OS is inconsistent with stating that no OS benefit of daratumumab has been shown. She did not argue that the committee had not been aware of the relevant data, but rather that they did not explain whether or how this linked to their conclusion on whether daratumumab has an OS benefit.

35. Henry Edwards, for NICE, said that the FAD is a short document that attempts to summarise complex issues with a goal of helping patients and clinicians to understand the decision making. He stated that the committee had given careful consideration to this issue, but they would be happy to explain this more clearly in the FAD if needed. He went on to emphasise that the committee has not stated that there is not or may not be an OS benefit from daratumumab, only that it had not seen one.

36. The appeal panel concluded as follows. They accepted that the committee had been aware of the totality of data relevant to whether daratumumab improves OS, and did not accept that they had disregarded this. The panel noted that paragraph 3.7 of the FAD sets out reasoning for the committee's conclusions on overall survival, and accepted that the statement that "it had

not been shown if daratumumab in combination improves overall survival" was intended to mean that this has not been demonstrated definitively with primary data rather than that it was not likely. However, the panel was concerned that this statement appeared inconsistent with the committee's view that complete response is a surrogate marker of OS, and could imply to readers of the FAD that economic modelling had assumed no survival benefit (although this was not the case). The panel were also concerned by the statement in the lay summary of the FAD that "the treatment has not been shown to increase how long people live". The prominence given to this statement in a summary of the document implied that this may have been a key factor in decision making. Overall, the panel concluded that the drafting of the FAD was sufficiently unclear to make it difficult for the reader to understand how a decision had been reached without further information from the committee, and therefore constituted unfairness.

37. The appeal panel therefore upheld the appeal on this point.

Appeal Ground 1a.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 haematological response were not discussed.

38. This appeal point was considered alongside Myeloma UK appeal point 1a.1 at the hearing, so the following should be read in conjunction with that section of this decision letter. In determining this point 1a.3 the panel had regard to the full discussion at the hearing in relation to this point and Myeloma UK appeal point 1a.1.

39. Dr Margaret Wan, for Janssen, stated that there are only a handful of haematologists in the UK who specialise in this condition, so it was crucial that one of these was present at the committee meetings. Dr Jenny Pinney, consultant nephrologist, highlighted this deficiency during the consultation phase. Without this expertise, the committee would find it more difficult to interpret the treatment goal or the association between CR and overall survival. This was a critical factor in the committee's conclusion that there was uncertainty about the effectiveness of daratumumab. The attempt to address this by inviting Dr Mamta Garg to the second committee meeting

failed because the fundamental importance of haematological response was not revisited. Although Dr Mamta Garg was asked about plausibility of the modelling, there was a superficial discussion and lack of context, and it was not clear that her contribution was fully considered. Dr Margaret Wan suggested that, had there been a discussion of the correlation between CR and OS, this would have demonstrated the effectiveness of daratumumab.

40. Henry Edwards, for NICE, said that input from clinical and patient experts is truly valued by NICE. He pointed out that the committee meeting is not the only opportunity to engage with the appraisal process. He also explained the process for sourcing clinical input. A stakeholder list is drafted at the start of an appraisal process. NICE then asks for nominations of clinical experts from consultees. The chair then selects experts from the nominees, taking into account the NICE policy concerning conflicts of interest. For this appraisal, the committee understood that this is a multi-system disease, with multiple specialties involved in treatment. NICE did receive two nominations of haematologists, but concluded that they were too conflicted to participate in the committee meetings. Dr Charles Crawley pointed out that the decision not to accept the two nominations had been made by his predecessor who had stepped down as committee chair. The committee then sought to mitigate this by selecting three clinical experts rather than two as is usual and by ensuring these experts played a very active role at the first committee meeting. Dr Charles Crawley acknowledged that none of these experts were haematologists. They invited Dr Mamta Garg to the second committee meeting, even though clinical experts are not usually invited at this stage in the process. In addition, a haematologist was involved in the scoping workshop, a haematologist advised the company on their submission and a haematologist gave advice to the Evidence Review Group (ERG). Furthermore, he asserted that the committee did understand the value of CR and its relationship with OS. He explained that the reason this was not revisited was because the committee had already accepted CR as a surrogate marker. While it was unfortunate there was no haematologist at the first meeting as the chair felt those nominated were conflicted, the committee considered the expert input received was adequate.

41. Dr Charles Crawley, for NICE, explained that NICE is dependent on stakeholders for nominating experts and this can be difficult, particularly regarding conflicts. He said the committee discussed three time points and the reason the committee did not return in the second committee meeting to the question of the time point to assess haematological response was that it had already agreed to consider both 3 and 6 months. He acknowledged that he is a consultant haematologist but confirmed that this was not relevant as it was not his role when working for NICE as committee chair.

42. In response to questions from the panel, Henry Edwards confirmed that the committee would have liked to have a treating clinician (i.e. a haematologist) present at the first meeting. He was unsure whether, after the nominated experts had been rejected based on conflicts of interest, NICE had sought alternative suggestions. He confirmed that the three specialists at the first committee meeting had expertise in AL amyloidosis (including one who is a consultant in renal medicine at the National Amyloidosis Centre).

43. In response to questions from the panel, Nicola Trevor, for Janssen, explained the key questions they felt should have been posed to a haematologist that were not asked of Dr Mamta Garg at the second meeting. She said that Dr Mamta Garg was asked about plausibility of the OS curves and clinical extrapolation, but the committee did not revisit the importance of haematological response. Concerning the relationship between haematological response and OS, she agreed the committee had accepted haematological response as a surrogate for OS but said the depth of questioning of Dr Mamta Garg was superficial: the committee should have asked a clinical expert about how important confounding is likely to be and what the importance of response categorisation is. She also explained that Janssen were not informed that their nominations had not been accepted and only became aware that there was no haematologist attending when they arrived at the first committee meeting.

44. Dr Charles Crawley agreed that it would have been desirable to have a haematologist in the first committee meeting but they had decided to proceed when there was not one available given that they had other specialists in AL amyloidosis (albeit not those primarily involved in treatment). He emphasised

that the absence of a haematologist at the first committee meeting had not had an impact on decision making. In particular, the committee recognised the importance of CR as a surrogate marker of OS and understood there was a strong correlation there. They looked in detail at the time point for assessing response. He judged that there were no clinical questions that could have materially affected the committee's conclusions or the recommendation that was reached.

45. The appeal panel concluded as follows. The panel noted the importance of clinical expert advice throughout the technology appraisal process, and agreed that a clinical expert would normally be a treating physician with specific expertise in the condition being considered. The panel judged that it was reasonable for NICE to reject nominated experts based on conflicts of interests, but noted that it may be hard to identify experts without any conflict of interest in a rare disease, so felt it would have been helpful if the basis for this decision had been documented. The panel noted that there was no evidence that NICE had sought an alternative haematologist to participate at the first meeting. The company did not have the opportunity to make an alternative nomination as they were not aware their nominees had been rejected until they arrived at the meeting. The panel commented that NICE may wish to consider amending their procedures to ensure that stakeholders are informed when nominated experts are rejected. The panel noted Dr Charles Crawley's statement that the lack of clinical expert advice at this stage did not affect decision-making but were struck by Professor Ashutosh Wechalekar's description of the clinical expert at the meeting feeling unable to answer the questions posed (see the section of this decision regarding Myeloma UK appeal point 1a.1). The panel agreed that inviting a haematologist to the second meeting could have addressed this deficiency, but in fact Dr Mamta Garg clearly felt that she did not have the opportunity to fully explain her point of view on issues of importance to the appraisal. Overall, the panel therefore concluded that the absence of a treating physician at the first committee meeting amounted to unfairness in this case.

46. The appeal panel therefore upheld the appeal on this point.

Appeal by Myeloma UK

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

Appeal Ground 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.

47. This appeal point was considered alongside Janssen appeal point 1a.3 at the hearing, so the following should be read in conjunction with that section of this decision letter. In determining this point the panel had regard to the full discussion at the hearing in relation to this point and Janssen appeal point 1a.3.

48. Sarah Love, for Myeloma UK, submitted that what procedural fairness requires depends on the particular circumstances of this appraisal. In particular, management of AL amyloidosis is normally co-ordinated by a haematologist with a special interest in this disease so only a specialist haematologist can give advice on important issues like categorisation of treatment response. She confirmed Myeloma UK agree with Janssen's arguments under Janssen point 1a.3 regarding why a haematologist was required as a matter of procedural fairness from the outset of the appraisal. She quoted parts of NICE's Principles and the methods guide regarding the need for a comprehensive evidence base, emphasising the importance of utilising specialist clinical expertise at all stages of an appraisal.

49. Shelagh McKinlay, for Myeloma UK, explained that she has extensive experience of attending NICE committee meetings, but has never previously encountered a scenario where a treating physician did not participate in every meeting. Although clinical experts were present at the first committee meeting, they were not haematologists with primary responsibility for treating patients with this disease. The presence of a haematologist was vital to validating both the company and ERG cases and critical to ensure that the decision-making was fully informed. Although Dr Mamta Garg attended the second committee meeting, this did not address misconceptions that were by then built into the committee's consideration (specifically concerning how

haematological response should be defined, which dataset to extrapolate OS from and the importance of speed and depth of haematological response).

50. Dr Mamta Garg, for Myeloma UK, confirmed that she attended the second committee meeting. She recalls being shown extrapolated survival curves for different response categories from both ALchemy and EMN23 and asked which better represented clinical practice. She said EMN23, but was not given adequate context or time to elaborate. In particular, she felt that the vital importance of how CR is defined, which renders the ALchemy data inadequate, was not understood by the committee.

51. In response to questions from the panel, Shelagh McKinlay said that Myeloma UK do not normally nominate experts as they expect other consultees to do this. She went on to say that she was concerned about the lack of haematology input at technical engagement as well as at the first committee meeting. She pointed out that the role of a clinical expert at the committee meetings is different from the role of an expert advising the company or ERG, so the fact that there was haematology input into the company case and ERG report did not mitigate the unfairness caused by the absence of a haematologist at the first meeting.

52. Professor Ashutosh Wechalekar, for Myeloma UK, (who did not attend the first committee meeting), stated that a clinical expert who was present at the first committee meeting had communicated with him at the time of the meeting saying that she was being asked questions that she could not answer.

53. Dr Charles Crawley and Henry Edwards, for NICE, responded as set out in paragraphs 40-42 above.

54. The appeal panel concluded, for the reasons set out in paragraph 45, that the absence of an expert haematologist at the first committee meeting did amount to procedural unfairness in this appraisal.

55. The appeal panel therefore upheld the appeal on this point.

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

56. Sarah Love, for Myeloma UK, referred to her points set out in paragraph 48 about the importance of utilising specialist clinical expertise at all stages of an appraisal. She argued that the decision not to include the National Amyloidosis Centre (NAC) as a commentator is a stark and surprising example of difficulties in the process of this appraisal.

57. Professor Ashutosh Wechalekar, for Myeloma UK, explained that the NAC is a national referral centre, funded by the Department of Health and Social Care, which sees the majority of patients with this condition nationally. They undertake an assessment and then patients can go back to their local centre for treatment. They have been involved in all new treatments for the condition and have detailed retrospective databases. A key role of the haematologist in the multidisciplinary team is in the assessment of treatment response. This is particularly important because the evaluation of treatment response has changed over time, and it was a challenge to put this into context for the committee. He said that the ERG also struggled with this and he was last contacted by the ERG about it ten minutes before the second committee meeting. Having an expert nominated by the NAC at the first committee meeting would have helped everyone to understand how response evaluation matters.

58. Henry Edwards explained that NICE engages with hundreds of patients and clinical organisations in 150-200 appraisal scopes every year. In this case, in drafting the scope / stakeholder list, the NAC were omitted. This was an omission rather than a deliberate act. Stakeholder lists typically include 50-70 organisations so organisations can be and are missed mistakenly. Many stakeholders do not contribute, so despite reference in the appraisal to NAC guidance, NICE did not realise the NAC had been omitted. The consultation on the scope provides an opportunity for such an omission to be pointed out to NICE. It specifically asks consultees to let NICE know if they have missed any organisations from the stakeholder list. If anyone had alerted NICE to the absence of the NAC from this list, they would certainly have been added. NICE are not experts on the conditions, so they rely on stakeholders to alert

them to any errors. He emphasised that NICE did not intend to prevent the NAC from participating or nominating its own clinical expert for committee meetings.

59. Shelagh McKinlay, for Myeloma UK, acknowledged that they did not highlight to NICE that the NAC had not been included in the list of stakeholders.

60. Professor Ashutosh Wechalekar stated that he asked the ERG whether he or another NAC haematologist could attend the first committee meeting but was told this was not possible owing to NICE's conflict of interest procedure. He accepted this request was made to the ERG, not to NICE.

61. The appeal panel concluded as follows. The committee agreed during the hearing that not including the NAC as a stakeholder was an omission. The panel acknowledged the challenge that the NICE scoping team face in identifying all relevant stakeholders, and noted that the opportunity for consultees to point out any omissions from this list at consultation is a useful part of the process. It was unfortunate that none of the consultees alerted NICE to the omission of the NAC on this occasion. However, AL amyloidosis is a rare disease where almost every patient is assessed in a single centre. It was therefore of particular importance to include this organisation, the NAC, as a stakeholder. Whilst a clinician from the NAC was present at the first committee meeting, this was not a haematologist. As discussed under Janssen appeal point 1a.3 and Myeloma UK appeal point 1a.1, the panel judged that that the absence of specialist haematology advice throughout the process was unfair. If the NAC had been appropriately included as a stakeholder, they would have had the opportunity to nominate an expert haematologist. The panel therefore concluded that the omission of the NAC as a stakeholder was unfair.

62. The appeal panel therefore upheld the appeal on this point.

Appeal Ground 1a.4: NICE has not acted fairly when applying criteria for determining an acceptable ICER value under the Methods Guide 2013

63. At the hearing, this point was taken together with Janssen's appeal point 1a.1, so this section should be read in conjunction with that section of the decision

letter. In determining this point the panel had regard to the full discussion at the hearing in relation to this point and Janssen appeal point 1a.1.

64. Shelagh McKinlay, for Myeloma UK, stated that paragraph 3.20 of the FAD where the ICER threshold is discussed, fails to discuss all the factors that should have been taken into account in addition to uncertainty. Instead there is a long list of bullet points about the sources of uncertainty. She referred to section 6 of the Methods Guide which says that cost-effectiveness is not the sole basis for decision-making, and subsection 6.2 which notes that the evidence for rare diseases is necessarily weaker. She referred to section 6.3.1 of the methods guide which states the committee does not use a precise maximum acceptable ICER and that consideration of the cost effectiveness of a technology is a necessary, but is not the sole, basis for decision-making. She then referred to section 6.3.3 which sets out factors to be considered in deciding whether a most plausible ICER above £20,000 per QALY gained is an effective use of NHS resources and said that the committee failed to take account of these. She said that setting a low ICER threshold is out of keeping with the approach to rarity in the HST programme and that the committee could have chosen to apply flexibility but did not.

65. Henry Edwards and Dr Charles Crawley, for NICE, responded as set out in paragraphs 18-20 above. Submissions were also made for Janssen, as set out above.

66. Sarah Love, for Myeloma UK, stated that there was a significant transparency issue. It was not enough for the committee to list factors it was aware of and assert these featured in the ICER threshold conclusion. Instead, it should explain how these factored into decision making. It was also not enough for the committee to consider factors in the meeting but not refer to those factors in the FAD or explain how those factors influenced their conclusion.

67. In response to questions from the panel about the clinical need in this condition, Professor Ashutosh Wechalekar, for Myeloma UK, explained that patients with AL amyloidosis are often diagnosed late and this adversely affects their median survival. He described the clinical need as desperate.

68. Shelagh McKinlay pointed out that the ACD stated that the committee had seen ICERs between £34,000 and £62,000. She argued that £34,000 is not a million miles away from £30,000 so it is not the case that the ICERs were nowhere close to being acceptable. Regarding unmet need, she stated that not only is AL Amyloidosis a severe condition but that there is no treatment.

69. Sarah Love said that while £20,000-£30,000 is the usual range of acceptable ICERs, there is no absolute threshold and there should always be an assessment in the round for that particular appraisal. She also referred to 6.3.5 of the Methods Guide ("Above a most plausible ICER of £30,000 per QALY gained, the committee will need to identify an increasingly stronger case for supporting the technology as an effective use of NHS resources, with regard to the factors listed in section 6.3.3") and the fact that in the HST process, ICERs of >£100,000 can be acceptable. She quoted the HST guidance which states "a simple utilitarian approach…is unlikely to produce guidance which would recognise the particular circumstances of these very rare conditions" and addresses the vulnerability of small patient groups as well as the extent of evidence and challenges for a company in making a reasonable return. She argued that the vulnerability of a small patient group was applicable to AL amyloidosis even if the other factors may be less so in this case. She suggested it would be very unfortunate if daratumumab "falls between two stools" given the high need / vulnerability of the patient group.

70. Henry Edwards, responded as set out in paragraphs 19, 23 and 26 above.

71. The appeal panel concluded as set out in paragraph 29 above that the reasoning in the FAD was not sufficient for the reader to understand how the ICER threshold was reached, in particular with regard to how rarity had been weighed in the committee's consideration of uncertainty, but also with regard to how factors other than uncertainty had been weighed in the decision-making. The appeal panel therefore upheld the appeal on this point.

Appeal by Janssen

Appeal Ground 1b: In making the assessment that preceded the recommendation, NICE has exceeded its powers.

72. There was no appeal under this ground.

Appeal by Myeloma UK

Appeal Ground 1b: In making the assessment that preceded the recommendation, NICE has exceeded its powers.

73. There was no appeal under this ground.

Appeal by Janssen

Appeal Ground 2: The recommendation is unreasonable in the light of the evidence submitted to NICE.

Appeal Ground 2.1: The appraisal committee's conclusions that "both ALchemy and EMN23-UK may be representative of UK clinical practice" are unreasonable.

74. At the hearing, this point was taken together with Myeloma UK appeal point 2.1, so this section should be read in conjunction with that section of the decision letter. In determining this point the panel had regard to the full discussion at the hearing in relation to this point and Myeloma UK point 2.1.

75. Nicola Trevor, for Janssen, explained that in this appraisal, real world evidence was used to model the response in the standard of care arm, and the impact of haematological response on OS. The reason for this is that ANDROMEDA necessarily excluded patients with more severe disease, so did not capture the full licensed population. At the first committee meeting, the committee considered two sources of data (ALchemy and EMN23). It became clear that neither were appropriate because of confounding by treatment switching, and because both used an older approach to categorising haematological response than the ANDROMEDA trial. The committee therefore asked Janssen to adjust the analysis to bring the approach to categorisation of response in line with ANDROMEDA. Janssen could not do this for the ALchemy dataset as they did not have access to patient level data. However, they were able to do this for the UK patients in the EMN23 dataset (EMN22-UK). She pointed out that there is 95% overlap between the patients in ALchemy and EMN23-UK.

76. Dr Charles Crawley, for NICE, explained how the committee approached reaching its conclusions. They were presented at the first committee meeting with two sets of real world data to extrapolate survival beyond the data from ANDROMEDA: ALchemy and EMN-23. They first asked themselves which was most representative of UK clinical practice and then asked which should be used in the economic model. At the first committee meeting they were presented with the original EMN-23 cohort, of which only 38% were UK patients and many of which did not receive bortezomib based treatment regimens. They therefore concluded that ALchemy was more representative of UK practice. They did note the difference in response categorisation between ANDROMEDA and ALchemy and asked for this to be addressed. At the second meeting they had access to the ALchemy data, and the EMN23-UK data which contained exclusively UK patients and had been re-classified to use the current criteria for haematological response. The committee concluded that both are representative of UK practice, particularly as they include virtually the same patients. They then went on to ask themselves which data should be used in the modelling. EMN23-UK was preferred in the modelling because the committee recognised the importance of the re-classification of the data. However, they did have some concerns about the 18-22% missing data in this sample, and asked themselves whether the data were missing at random. The committee asked for further data on how this might impact the validity of the data but were not able to obtain it. They therefore used ALchemy as a scenario analysis or “sense check”, but EMN-23 was the primary basis for the economic model. He added that none of the ICERs the committee saw were in the range normally considered an acceptable use of NHS resources. He reiterated the committee considered this issue in two stages: first, what was representative of UK clinical practice; second, what should be used in the modelling? They felt they could not say ALchemy did not reflect UK clinical practice.

77. Henry Edwards, for NICE, emphasised that the committee did not state a preference for ALchemy in the FAD, and that using the term “may” be representative of UK practice reflected uncertainty about both data sources. He found it challenging to understand how this statement could be considered

unreasonable when the two cohorts are made up of essentially the same patients.

78. In response to questions from the panel about where the committee's preference for EMN23-UK in the economic model appears in the papers, Nicola Trevor said that the papers suggest that ALchemy and EMN23-UK were given equal weight.

79. The appeal panel concluded as follows. The panel were aware of the importance of how CR is defined, as explained by Professor Ashutosh Wechalekar. They agreed that the patients in both the ALchemy and EMN23-UK cohorts were representative of UK practice (and indeed they were essentially the same patients) but noted that the criteria for assessing haematological response in ALchemy are not representative of current UK practice. The approach Dr Charles Crawley described at the hearing (preferring EMN23-UK for economic modelling, but using ALchemy as a "sense check" given uncertainty arising from missing data in EMN23-UK) seemed reasonable to the panel. However, the panel could find no documentation in the papers to show that EMN23-UK was preferred for modelling, nor were the committee able to point out such a reference during the hearing. In a section of the FAD concerning modelling, at paragraph 3.11, the committee conclude that "the choice of dataset, that is, EMN23-UK or ALchemy is uncertain". In the slides from the second committee meeting there is no indication that the ICERs on slide 37 using EMN23-UK were preferred. If anything, the title of slide 38 (which includes "committee preferred assumptions") seems to imply that these ICERs using ALchemy were preferred. Overall, the panel judged that the FAD gave the impression that the committee weighted EMN23-UK and ALchemy approximately equally. This seemed strikingly at odds with the clear reasons for preferring EMN23-UK given by the committee themselves at the hearing, as well as Professor Ashutosh Wechalekar's opinion that ALchemy should not be given any weight (see paragraph 94). The panel therefore concluded that the conclusion that both ALchemy and EMN23-UK may be representative of UK clinical practice did not adequately capture how the committee handled these two datasets and was so unclear as to be unreasonable.

80. The appeal panel therefore upheld the appeal on this point.

Appeal Ground 2.2: The committee's conclusion that "it had not been shown if daratumumab in combination improves overall survival" conflicts with the balance of available evidence.

81. This appeal point was considered alongside Janssen appeal point 1a.2 at the hearing, so the following should be read in conjunction with that section of this decision letter. In determining this point the panel had regard to the full discussion at the hearing in relation to this point and point 1a.2.

82. Andrew Ternouth, for Janssen, described the (OS) data from ANDROMEDA. Median OS was not reached in either arm but at 18 months and 20 months survival was higher in the daratumumab group. Commonly, mature OS data are not available at the time of an appraisal, so a submission is made using a surrogate endpoint. NICE uses three levels of data: Level 3 (biological), Level 2 (non-interventional studies) and Level 1 (Randomised Controlled Trials (RCTs)). Janssen presented a substantial amount of Level 3 and 2 data to support the relationship between timing and depth of haematological response and OS. He argued that this position is consistent with guidelines that recommend CR as a treatment target and with expert testimony during the appeal hearing. He concluded that the totality and consistency of evidence supports an OS benefit from daratumumab.

83. During discussion of Myeloma UK appeal point 2.1, Professor Ashutosh Wechalekar, for Myeloma UK, explained that one reason no survival benefit has yet been seen in ANDROMEDA is because patients with more advanced disease could not be included in the trial. He said there are three clear facts: that CR (as currently defined) translates into OS, that this applies at all stages of disease, and that the rate of CR with daratumumab in combination is much higher than with standard of care.

84. Dr Charles Crawley, for NICE, responded as set out in paragraph 33 above.

85. In response to questions from the panel, Dr Charles Crawley, said that the committee accepted that complete response was a well-established surrogate marker of OS. They also noted the association between MOD-PFS and OS.

However, they did have concerns about potential confounders that were not addressed by additional analysis. In terms of implementation in the model, the committee did take OS into account. He referred to slide 16 from the second committee meeting where all the modelled survival curves show a survival benefit and explained that this informed the model and calculations of cost-effectiveness. They also considered the additional survival benefit modelled by Janssen as a scenario. As neither of these produced an acceptable ICER, they did not have to make a final conclusion on this point. However, the committee did conclude that they could not say that primary data had demonstrated a survival benefit.

86. Yelan Guo, for NICE, said that whilst the committee recognised in the FAD that complete response is a surrogate marker the question was how strong this association is. She said that the ratio of 1.066 for OS reported in the 12 month landmark analysis of the ANDROMEDA trial was a post-hoc analysis without confidence intervals. Therefore, from a technical perspective, there is uncertainty about whether daratumumab has an OS benefit based on current data.

87. Henry Edwards, for NICE, said that the committee has not stated that there is not or may not be an OS benefit from daratumumab, only that it had not seen one.

88. The appeal panel concluded as follows. During the hearing there seemed to be a consensus on two points, with which the panel also agreed. On the one hand, the data from ANDROMEDA are not mature, so it is not possible to say unambiguously that daratumumab improves overall survival. On the other hand, CR and MOD-PFS are valid and appropriate surrogate markers of overall survival. The panel accepted that the committee intended their statement to mean that an OS benefit had not been definitively shown with primary data. However, the panel also accepted that the statement could be read to mean that the balance of evidence was not in favour of an overall survival benefit from daratumumab. Whilst the slides from the second committee meeting made clear that an overall survival benefit had been incorporated into economic modelling, this was not clear in the FAD. The panel also noted that the statement that “the treatment has not been shown to

increase how long people live" is in the lay summary, implying it may have been a key factor in decision-making. The panel found it particularly hard to reconcile the committee's conclusion that daratumumab has no overall survival benefit with the committee's acknowledgement that CR was a close surrogate of survival and that the drug clearly benefited MOD-PFS, given that the committee accepted that organ failure was the commonest cause of death. Overall, the panel felt that the strength of the evidence taken together made it unreasonable to conclude it had not been shown if daratumumab in combination improves overall survival, as this was likely to be read by the intended audience as suggesting that daratumumab does not have an OS benefit, even if this is not the meaning the committee intended.

89. The appeal panel therefore upheld the appeal on this point.

Appeal by Myeloma UK

Appeal Ground 2: The recommendation is unreasonable in the light of the evidence submitted to NICE.

Appeal Ground 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.

90. At the hearing, this point was taken together with Janssen appeal point 2.1, so this section should be read in conjunction with that section of the decision letter. In determining this point the panel had regard to the full discussion at the hearing in relation to this point and Janssen point 2.1.

91. Sarah Love, for Myeloma UK, said that it is important not to overstate what it means in law to say that a decision is unreasonable, and referred to relevant judgements. In particular, where a technical error is made, the error does not have to "jump off the page" or be readily explained to a lay person to be unreasonable, but it should be incontrovertible once explained. She argued that the conclusion that both ALchemy and EMN23-UK may be representative of UK practice was central to the decision not to recommend daratumumab, because it informed the committee's conclusion about OS.

92. Professor Ashutosh Wechalekar, for Myeloma UK, explained that ALchemy is a UK observational study of over 1600 patients since 2007. EMN23 is a

cohort bringing together data from a number of European centres including the UK. The UK patients in both datasets are the same. He explained that the International Society of Amyloidosis have used different criteria for the definition of haematological response over time (2005, 2012 and 2020). The data in the published ALchemy cohort uses the 2012 criteria. The criteria were updated in 2020 because clinicians had noted that some patients were getting a deep haematological response to novel therapies, and had excellent outcomes, even though did not quite meet the 2012 criteria for "complete response". Once the criteria were updated, it became clearer that depth of haematological response was a strong predictor of outcome. For instance, in the original analysis of EMN23 data (using the 2012 criteria) there appeared to be little difference in survival between patients with CR and very good partial response (VGPR). Once the 2020 criteria were used, there was a dramatic difference in survival between these two groups. After the first committee meeting, Janssen asked Professor Ashutosh Wechalekar's team for re-categorised EMN-23 data using the 2020 criteria. This necessarily resulted in some missing data, but the dataset still included over 900 patients.

93. Dr Charles Crawley and Henry Edwards, for NICE, responded as set out in paragraphs 76and 77 above.

94. Professor Ashutosh Wechalekar, stated that despite the missing data, the re-analysis of EMN23-UK was very rigorous and included a large number of patients. He said that it would be unreasonable to attach any weight to the ALchemy data.

95. The appeal panel concluded as set out in paragraph 79 that the committee's conclusion that both Alchemy and EMN23-UK may be representative of UK clinical practice was unreasonable.

96. The appeal panel therefore upheld the appeal on this point.

Conclusion and effect of the appeal panel's decision

97. The appeal panel therefore upholds the appeal on the following grounds: Janssen 1a.1, 1a.2, 1a3, 2.1, 2.2 and Myeloma UK 1a.1, 1a.2, 1a.4 and 2.1.

98. The appraisal is remitted to the appraisal committee who must now take all reasonable steps to correct the issues identified above. Specifically:

99. **Janssen 1a.1 and Myeloma UK 1a.4:** the committee should reconsider the significance and relevance of rarity and other factors listed in the methods guide to ensure they have been properly taken into account in determining the ICER threshold for this appraisal. Should this result in a change to the threshold, the committee will need to assess the impact of this (if any) on the overall recommendation. In any event the decision-making around the ICER threshold should be adequately explained in the FAD.

100. **Janssen 1a.2, Janssen 1a.3, Myeloma UK 1a.1, Myeloma UK 1a.2 and Janssen 2.2:** the committee should re-evaluate the data on surrogate markers of OS and reconsider to what extent they might inform a judgement on OS. To assist in this they should take steps to obtain further advice from a specialist haematologist, or from specialists at the National Amyloidosis Centre. In the light of this they should reconsider the balance of evidence on the effect of daratumumab on overall survival and ensure that their review of these data is clearly explained in the FAD.

101. **Janssen 2.1 and Myeloma 2.1:** the committee should reconsider whether both ALchemy and EMN23-UK may be representative of UK practice, and clarify in the FAD how they used these data for the purpose of economic modelling.

102. There is no possibility of further appeal against this decision of the appeal panel. However, this decision and NICE's decision to issue the final guidance may be challenged by applying to the High Court for permission to apply for a judicial review. Any such application must be made within three months of NICE publishing the final guidance.

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