

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

APPEAL HEARING

Advice on inotuzumab ozogamicin for treating relapsed refractory B-Cell acute lymphoblastic leukaemia

Decision of the panel

Introduction

1. An appeal panel was convened on 3 November 2017 to consider an appeal against NICE's final appraisal determination on inotuzumab ozogamicin for treating relapsed refractory B-Cell acute lymphoblastic leukaemia.

2. The appeal panel consisted of:

Dr Andrew Black	Appeal Panel Chair
Professor Tim Irish	Non-Executive Director NICE
Dr Ashutosh Wechalekar	NHS Representative
Mr Uday Bose	Industry Representative
Mr Paddy Storrie	Lay Representative

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

4. The panel considered appeals submitted by – Pfizer, Leukaemia CARE, joint appellant: Royal College of Pathologists, Royal College of Physicians and the Association of Cancer Physicians.

5. Pfizer was represented by:

Angela Blake	Head of Health and Value
Dr Kathryn Lang	Oncology Medical Affairs
Alex Smith	Senior Health Economist
Dr Adela Williams	Partner, Arnold & Porter

6. Leukaemia CARE was represented by:

Zack Pemberton-Whiteley	Head of Campaigns and Advocacy
Mike Brandon	Volunteer
Dr Dafydd Thomas	Volunteer
Miles McNeile	Volunteer

7. Mr Pemberton-Whiteley declared that the organisation had previously received financial support from Pfizer but not in this financial year.

8. Joint appellant was represented by:

Dr Rachel Hough	Consultant Haematologist
Professor David Marks	Deputy Head NCRI ALL group

9. Both Dr Hough and Professor Marks declared that they had been involved in the INO-VATE 1022 trial and that Professor Marks had been lead investigator for the UK.

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

Professor Andrew Stevens	Chair, Technology Appraisal Committee C
Dr Stephen O'Brien	Vice-Chair, Appraisal Committee C
Meindert Boysen	Programme Director, NICE
Michael Chambers	Committee Member
Marcela Haasova	Technical Analyst, NICE
Susan Griffin	ERG representative

11. No conflicts were declared for these individuals.

12. NICE's legal adviser Stephen Hocking was also present.

13. Under NICE's appeal procedures members of the public are admitted to appeal hearings and several members of the public were present at this appeal.

14. 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
- b) Exceeded its powers.

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

15. The Vice Chair of NICE (Dr Rosie Benneworth) in preliminary correspondence had confirmed that:

- Pfizer had potentially valid grounds of appeal as follows: Ground 1a NICE has failed to act fairly and Ground 2 the recommendation is unreasonable in the light of the evidence submitted.
- Leukaemia CARE had potentially valid grounds of appeal as follows: Ground 2 the recommendation is unreasonable in the light of the evidence submitted.
- The joint appellant had potentially valid grounds of appeal as follows: Ground 2 the recommendation is unreasonable in the light of the evidence submitted.

16. The appraisal that is the subject of the current appeal provided advice to the NHS on inotuzumab ozogamicin for treating relapsed or refractory B-cell acute lymphoblastic leukaemia [ID893].
17. Before the appeal panel inquired into the detailed complaints, the following made a preliminary statement: Angela Blake on behalf of Pfizer, Mr Zack Pemberton-Whiteley on behalf of Leukaemia CARE and Dr David Marks on behalf of the joint appellant. Professor Andrew Stevens also made a preliminary statement on behalf of the appraisal committee.

Appeal by Pfizer

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 seemingly failed to consider the cost effectiveness of inotuzumab applicable to UK clinical practice when used in accordance with its marketing authorisation

18. Dr Kathryn Lang for Pfizer started the discussion by stating Pfizer's case that inotuzumab would only be used for transplant eligible patients in the UK. The committee had only considered up to 6 cycle scenario based on the INO-VATE trial. She agreed that in some cases 6 cycles were effective and might be used in some health care systems but that the company was not advocating palliative use in the NHS. There has been arbitrary assessment and no consideration of a preferred use case scenario (2+1 cycles only as a bridge to transplant).
19. Professor Andrew Stevens, on behalf of the appraisal committee, stated that the committee had considered a median of 3 cycles but allowing up to a maximum of 6 cycles. This was in keeping with the marketing authorisation.
20. Dr Adela Williams, representing Pfizer, responded that the marketing authorisation was broad reflecting the INO-VATE trial. However, what was examined in the trial and what is actually practiced is different. The product is expected to be a bridge to transplant in the UK. The committee's considerations were at variance with the clinical experts. It would be wrong to say that identification of transplant eligible patients was not possible in advance. The marketing authorisation considers more than 3 cycles but in the bridge to transplant scenario in the UK, no more than 3 cycles would be used.
21. The appeal panel sought clarity from Pfizer as to why this scenario only appeared towards the end of its response to the ACD.
22. Dr Williams, representing Pfizer, clarified that the response to ACD consisted firstly of points raised in the ACD and then the three vs. six cycles scenario. This was not intended as an order of priority by Pfizer. Pfizer's response was in keeping with procedure and the debate on cycles had not been considered in the ACD.

23. The appeal panel sought further clarification from Pfizer with regards to planned UK usage compared to marketing authorisation which allows up to 6 cycles in individuals not undergoing transplant, compared to the 2+1 cycles envisaged for in the UK.
24. Dr Lang, from Pfizer, agreed that the marketing authorisation was for up to 6 cycles which reflected a broad range of clinical practice worldwide. However, the UK practice is more specifically to use this as a bridge to transplant. Hence the base case based on marketing authorisation fails to consider UK practice.
25. Professor Stevens, on behalf of the appraisal committee, responded that the base case had been clearly defined and there were no grounds to separate base case from practice. In the trial, there was no pre-defined "transplant" subgroup to allow such an analysis and hence there was no specific evidence for this use case.
26. The appeal panel explored further with the committee its understanding of the scenarios, particularly in light of clinical opinion.
27. Professor Stevens, on behalf of the appraisal committee, clarified that their understanding was based on the INO-VATE trial data where there was no evidence for consideration of a different treatment scenario. He stated that the case in focus was on the base case scenario as this was clearly tied with the evidence available to inform costing scenarios. There was no evidence for post-hoc analyses of patients where the aim of treatment was transplant and more importantly, there had been no suggestions for rules for stopping treatment.
28. Pfizer and the joint appellant questioned whether this was the case and were concerned about the level of discussion surrounding real world usage. Professor Marks, on behalf of the joint appellant, clarified the difficulties of undertaking clinical trials in a rare disease particularly the challenge of a trial in an even rarer sub-group. He appealed for flexibility over methodological purity. He contended that 77 patients in the cohort he was familiar with went on to transplant and, in this context, was a large number.
29. The appeal panel considered the points raised in the discussions. It reminded itself that the issue here was whether the consideration of the 2+1 cycle bridge to transplant scenario was fair, and that the reasonableness of that consideration fell to be considered under ground 2. The panel felt that the key issue was whether the committee had considered inotuzumab within the marketing authorisation and did they consider this as per the scope. There was the issue raised about number of cycles as per UK practice, but it was unclear to the appeal panel that this issue was raised to the same extent as was the base case in the initial discussions. Committees have been criticised in the past for considering only a subset of treatment covered by the scope and it was not unfair not to have adopted this approach at the outset, nor to have considered the bridge to transplant use case only when raised. When the bridge to transplant scenario had been raised in the response to the ACD the Committee had

considered it. Its record of the point was perilously brief, but the point had not been pressed on them as a central consideration and in that context the approach taken was not unfair. The panel felt that the appraisal committee had a clear understanding of the evidence presented and had considered the marketing authorisation appropriately as per the scope. The panel felt that this consideration was fair. As noted above whether it was reasonable falls to be considered elsewhere.

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

31. Appeal Ground 1a.2: The fact that the clinical experts were not invited to the second meeting of the Appraisal Committee meant that important clinical evidence was not available to guide the preparation of the FAD

32. Dr Kathryn Lang, from Pfizer, said that this was a rare disease and there was paucity of good quality evidence, and there was need for a clinical expert to clearly interpret available evidence. The FAD committee hearing discussed cycle numbers, mortality and costs. There were key changes that had to be considered. The 2+1 cycle scenario was not considered at the first meeting. Hence, Pfizer contended that it was unfair on the part of the appraisal committee not to invite a clinical expert to the second meeting.

33. Professor Andrew Stevens, on behalf of the appraisal committee, said that it was, in general, unusual to have an expert at the second committee meeting. This would only be needed if there had been a need for further clarification on the disease pathophysiology. He added that the clinical expert had indeed responded to the ACD. To clarify any clinical issues raised, he commented that the committee had 6 medically qualified physicians. One of the new issues raised was mortality after stem cell transplantation being similar to general population and similarities were raised to another agent blinotumumab. There was nothing in the response to ACD or in discussion on point which was unclear to the appraisal committee. The committee gave careful consideration to the response to ACD. There was no specific request at any point from ACD or its response from Pfizer or any other group to request presence of a clinical expert at the second hearing.

34. The appeal panel sought clarification from both the appellant and the appraisal committee as to the areas where there was disagreement on the value of further clinical expert input, based on submissions received in response to the ACD.

35. The appeal panel considered previous appeals on this point in particular an appeal concerning ranibizumab in 2011. In that appeal, the appeal panel said:

“The panel considered when fairness may require committee to seek additional expert opinion. There are two possibilities. The first is if the evidence presented to the committee has obvious gaps which could reasonably be filled by expert opinion. In that case a committee which does not seek expert opinion may have taken a decision without having had regard to material considerations. The second possibility is where the evidence

before the committee is such that the committee cannot properly evaluate the evidence without expert assistance.

“The appeal panel considered this in light of the discussion and evidence it received. It was satisfied that the Appraisal Committee reviewed responses to the ACD and there was nothing in the ACD responses that was radically different to previous evidence it had heard. There were no clearly identifiable gaps or any clinical evidence that were unclear to the Appraisal Committee. There had been a clear expert response to ACD and the expert response did not raise any further points needing clarification. There had been no explicit request by any party for further clinical expert input at second hearing. The Appeals Panel concluded that the decision of the Appraisal Committee in not inviting an expert to the second hearing was not unfair.”

36. The appeal panel is not bound by its previous decisions but all other things being equal it does try to take a broadly consistent approach. It therefore adopted the same approach to the question of whether it might have been unfair not to have a clinical expert at the FAD meeting. The panel was satisfied that by this stage if not sooner the committee had all of the relevant evidence before it. Without casting doubt on the panel's conclusions under ground 2 below the panel was also satisfied that the evidence was not so technical or so unusual that the committee lacked the skills properly to evaluate it. The panel felt that the ground of appeal amounted to a desire for the clinical expert to participate in rather than to inform decision making, and that fairness did not require, and NICE's processes did not permit, this.

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

Appeal Ground 1a.3: The Committee has provided no explanation for its decision to reject the utilities proposed in the revised Pfizer base case for post-HSCT period and submitted in response to the consultation

38. Given the overlap with Pfizer appeal ground 2.2 the appeal panel considered both these appeal grounds together. **The ground for appeal 2.2 was: The Committee has seemingly misunderstood the utilities submitted by Pfizer in response to consultation on the ACD**

39. Mr Alex Smith, from Pfizer, contested that there was no explanation from the committee for choosing the utility value used for the quality of life after 3 years post transplantation (when patients are considered cured). Pfizer were unclear on the rationale for choosing this value. Pfizer argued the better value was the one published in the blinotumumab NICE appraisal. No rationale was given for difference between the values accepted for the two appraisals – the lack of rationale is unfair. Furthermore, the "headline" applied value is 0.88 and the committee said that the company did not adjust that value for variables which would have reduced it. This statement was included in the FAD and indicated a misreading of the evidence submitted or that the committee was unclear on the assumptions applied by the company.

40. Professor Andrew Stevens, on behalf of the appraisal committee, said that the committee was entirely clear on the choice of the utility values, which were based on Pfizer's base case and a clear evidence base. The committee had considered and were not convinced by the case for utility value of 0.88 even though this value had been accepted by another NICE appraisal committee. The committee considered that there was a need to be consistent with the approach based on the evidence throughout the appraisal process and not change later in the course of the process without due evidence. The committee did understand that the initial values were not age adjusted and Pfizer age adjusted the utility values at request of the committee. The committee knew that the value therefore took a range and decreased to 0.55 at the end of that range.
41. The appeal panel sought clarification from the appraisal committee as to its choices and understanding of the utility values used in particular when compared to those used in the blinotumumab appraisal that had been undertaken by NICE. Further discussion of this issue was considered under Pfizer appeal ground 2.1.
42. Mr Meindert Boysen, Programme Director for NICE's technology appraisal programme, intervened that it was for the appraisal committee to make the decision based on the evidence that had been reviewed. It was not expected of one committee to connect evidence from a different technology appraisal. The committee was free to judge from the evidence presented and come to evidence based conclusions. It would be a bit unfair on the appraisal committee chair to expect to comment on outcomes of another appraisal.
43. Further opinions were heard from the appraisal committee and Pfizer concerning the role and presence of the clinical expert Professor Fielding at the first meeting and the input she had had in the discussion of possible utility values and the point in the discussion that Professor Fielding had left.
44. The appeal panel was not in a position to question Professor Fielding as she was not in attendance at the appeal hearing.
45. The appeal panel, having heard the viewpoints, considered its opinion for the grounds separately in regards to Ground 1a and Ground 2.
46. Pfizer appeal ground 1a.3: The appeal panel heard various viewpoints discussed. Pfizer's argument was essentially based on consistency: it said that NICE having accepted a particular set of utility values for post-transplant post "cure" patients in one appraisal, ought either to accept those same values in this appraisal or give reasons to depart from them.
47. Appeal panels have in the past been wary of consistency arguments, not because they disagree that broad consistency may not be an element of fairness or reasonableness, but because each appraisal turns so closely on its specific evidence base that true inconsistency is hard to make out. Further the appeal panel agrees with Mr Boysen that an appraisal committee cannot generally be expected to be familiar with the evidence or considerations in another appraisal.
48. However this was a rare case where a lack of consistency was made out.

49. The appeal panel feels that that it is not incumbent on any NICE technology appraisal committee to accept or use the assumptions of another technology appraisal committee and indeed the committees have the freedom (and the duty) to individually come to independent conclusions. However, in the rare instance where patient population to which the technology is applied exactly the same (not just similar), and where the treatment under consideration has no direct impact on the assumptions used, then it is incumbent on the later appraisal committee to explicitly clarify why they have chosen assumptions different from assumptions used (and accepted) for the same population by a previous committee. This is particularly the case where the treatment under consideration has no direct impact on the assumptions used.

50. The appeal panel therefore upheld appeal point 1a.3.

51. Pfizer appeal ground 2.2: The appeal panel heard the various viewpoints. The appeal panel was satisfied that the appraisal committee had clearly understood the utilities submitted by Pfizer in relation to the consultation on ACD. They had reviewed the evidence available for the utilities and chosen to proceed with a value different from that suggested by Pfizer. The reason expressed by Professor Stevens at the appeal hearing for doing so was rational, and the appeal panel therefore dismissed appeal point 2.2. However the appraisal committee (as opposed to its chair) will now have to consider which utility values to use and give a reason for that choice, and the panel can express no view as to the rationality of that future decision.

52. No valid appeal points were made under Ground 1a by either Leukaemia CARE or the joint appellant.

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

53. There was no appeal under this ground by either Pfizer, Leukaemia CARE or the joint appellant.

Appeal by Pfizer

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

Appeal Ground 2.1: The appraisal committee's reasons for disregarding key assumptions used for the purposes of the NICE blinotumumab appraisal did not explain the choices made in relation to inotuzumab

54. Dr Kathryn Lang, from Pfizer, stated that it was reasonable to suppose that the modelling of treatment for patients treated with different agents would differ during treatment, and for some time thereafter if they were still subject to disease or if the effects of disease and treatment were yet to make themselves manifest. However, the period sufficiently long after stem cell transplantation is different. Three to four years post stem cell transplant, there can be no impact of the

therapies prior to transplant. The patient is considered cured at this point. The modelling should be fixed and should be the same. The chair of the appraisal committee had in fact invited a blinotumumab treated patient at the inotuzumab appraisal committee meeting. There are no clear reasons given by the committee for modelling post cure patients differently depending on their pre-cure treatment and the decision is arbitrary.

55. Professor Andrew Stevens, on behalf of the appraisal committee, responded that the inotuzumab appraisal was a single technology appraisal. The company did not provide any comparison with blinotumumab. The two appraisals, inotuzumab and blinotumumab, are different. The available evidence for the two drugs is different, the mechanisms are different. Additionally, the survival gain from blinotumumab is seen irrespective of stem cell transplantation and hence the modelling is very different. The analysis post transplantation in the inotuzumab case is a post hoc analysis of CR/Cri after stem cell transplantation. There was no similarity to blinotumumab modelling. Hence, there was a difference between the two agents in terms of modelling, evidence and remission.
56. The appeal panel sought clarification from the appraisal committee about the main issue being post the point of cure and the assumptions made post cure point – to understand why the inotuzumab patient population would have a different behaviour to that of the blinotumumab appraisal and thus have different modelling assumptions.
57. Professor Stevens, chair of the appraisal committee, responded that there had been discussion about these utilities. He contested the term “cure” since the post-transplant patients are not truly back to “normal”. The committee had considered post-transplant mortality and utilities. The committee had considered the evidence and were confident that their conclusions were evidence based.
58. The appeal panel sought further clarification from the appraisal committee concerning the concept of “cure” point and patient mortality post this point.
59. Professor Stevens, on behalf of the appraisal committee, replied that the analysis post inotuzumab was post hoc which was different from the analysis in blinotumumab. Hence, finding a cure point in inotuzumab relied on a different modelling. In any case a cure point at 3 to 4 years did not make any difference to the ICER. He also restated the committee’s opinion that mortality remained elevated in patients post-transplant beyond this “cure” point compared to general population.
60. Mr Alex Smith, from Pfizer, responded that there had been many reasons given for differences between the two patient populations pre-transplant and in the immediate post-transplant period. Hence, Pfizer had allowed for a higher mortality in these populations. However, the key issue was that both models for inotuzumab and blinotumumab have the same cure points. At that point drug treatment is some time in the past as is the “curative” transplant. Hence the models and assumptions post cure point need to be same.

61. At this point Mr Boysen, on behalf of NICE, interjected and Mr Stephen Hocking, legal representative for the appeal panel, intervened to clarify to the appellants and appeal panel that while different committees can make different decisions on the same evidence or in similar situations, the committee needs to be able to explain they why have taken a different viewpoint and that this explanation needs to “stack-up”.
62. Dr Adela Williams, representing Pfizer, agreed with the analysis and said that Pfizer attempted to find the reasons why there was a difference in approach, but all the reasons given relate to the treatment in question. It is still unclear why the modelling is different after the cure point, well after treatment has been completed. This is unreasonable.
63. Professor Stevens, on behalf of the appraisal committee, said that the committee was confident that their modelling was correct. When there was a question of choosing between evidence based parameters vs. non-evidence based assumptions, the committee chose to follow the evidence based parameters with robust analysis.
64. The appeal panel considered the discussion on this point. The key issue was whether the reasoning for differences between the two appraisals “stacked up”. There was considerable force in the company's argument that once a sufficient number of years have passed post treatment and post-transplant, patients treated with either agent might be expected to have the same health trajectory. The panel is well aware that that would only be a starting position and that it might be departed from in the light of evidence. The panel was clear that there is a good explanation of differences up to the “cure” point but it was unclear why there were different assumptions after the “cure” point. The panel felt that it was important for the appraisal committee to have considered and explained the differences in assumptions post “cure” point explicitly. The panel cannot say that such an explanation does not exist nor that it would necessarily be unreasonable when given its conclusion is simply that this aspect of the appraisal is presently unsupported by relevant reasons and so is unreasonable.
65. The appeal panel therefore upheld appeal point 2.1.
66. The appeal panel felt that scenario post the point of cure needs to be clarified, the assumptions discussed and a case made clearly for the assumption chosen (similar or different as may the case be from other appraisals).

Appeal Ground 2.2: The Committee has seemingly misunderstood the utilities submitted by Pfizer in response to consultation on the ACD

67. The grounds and discussion of this appeal point was considered with the appellants ground 1a.3.
68. A fuller description of the points, discussion and appeal panel’s considerations is given previously in this document (para 39-45, 51).

69. As previously stated in this document (para 51) the panel dismissed this appeal point.

Appeal by Leukaemia CARE

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

Appeal Ground 2.1: An incorrect assumption on the number of cycles of inotuzumab ozogamicin

Appeal by Joint Appellant

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

Appeal Ground 2.1: An incorrect assumption on the number of cycles of inotuzumab ozogamicin

70. As both Leukaemia CARE and the joint appellant appealed the decision on exactly the same point, their appeal was considered jointly.

71. Dr Rachel Hough, on behalf of the joint appellant, stated that inotuzumab is primarily used as a means of getting a patient ready for an allogenic bone marrow transplant. Although it can be used for up to 6 cycles, the median is 3 cycles even when all patients (transplant eligible or ineligible) are considered. There was a specific mention of the SMPC for use of only 2 cycles (and need of an additional third cycle in some cases) in transplant eligible patients. In the UK, there is no intention to use this agent as a palliative treatment – a setting where more than 3 cycles may need to be administered as was reported in the INOVATE clinical trial but that was not the ambition for UK clinicians. Data was presented to the ERG about the use of the number of vials needed per cycle and this would be much lower than considered by the ERG as per UK standard practice. The appellants were unclear on the justification for a 6 cycle model used by the appraisal committee and lack of clarity on why consideration or otherwise of a 3 cycle scenario. A 6 cycle model was at odds with the UK practice and data presented to the ERG.

72. Mr Mike Brandon, Dr Dafydd Thomas and Mr Miles McNeile, on behalf of Leukaemia CARE, presented their (in case of Dr Dafydd Thomas – his daughter's) experience with inotuzumab used before they had a bone marrow transplant. Mr Brandon explained he had progressive leukaemia despite intensive chemotherapy and the only option was a trial agent with chimeric T cells. He had inotuzumab as preparation for a potentially curative treatment. He had an excellent response to inotuzumab which was very well tolerated with minimal side effects. Dr Thomas represented his daughter who as an inpatient undergoing an allogenic stem cell transplant could not attend. She had recurrent leukaemia which was progressive after standard chemotherapy. Her disease was highly refractory and progressed after another novel therapy with blinotumumab. She responded well to inotuzumab in just two cycles only and did

not need additional cycles. This has allowed her to receive a potentially curative allo-transplant. He made a plea that this life saving treatment was not denied to other suitable patients. Mr McNeile had ALL which relapsed at the end of his maintenance treatment. He received two cycles of inotuzumab. The first cycle was given as an inpatient as a precautionary measure and the other cycle was as an outpatient. He had no significant side effects. He had a complete response with inotuzumab and had a transplant a couple of months before this hearing. He emphasised the markedly superior quality of life during treatment with inotuzumab compared to his experience with standard chemotherapy.

73. Professor Andrew Stevens responded on behalf of the appraisal committee and clarified that the model used was based on the INO-VATE clinical trial which has a median of 3 cycles and the modelling was consistent with numbers of vials as mentioned by the appellants. He made the point that the use case scenario of 2+1 cycles was not evidenced and based on post hoc analysis of a randomised trial. He raised a point that there was no clarity on which patients would be proceeding to transplant and that in the trial ■■■ of all patients received more than 4 cycles and even ■■■ of transplant patients received more than 3 cycles in addition to ■■■ who did not proceed to transplant despite a response. Hence 6 courses was considered as the upper limit range.
74. The appeal panel sought clarification from the appellants as to whether it was possible to identify potentially those patients eligible for transplant before starting inotuzumab.
75. Professor Marks, from the joint appellant, addressed the eligibility for transplant and mentioned that only 80% will respond to inotuzumab and essentially all of these will be transplant eligible. The decision for selection for transplantation is based on the number of complex factors including age, performance status, and adequacy of organ function and availability of a donor (the latter is not a real problem in the modern transplant era). Based on these factors, a patient can be identified in advance as highly likely to proceed to transplant or as unlikely to be suitable for transplantation. Non-responders can also be identified early in treatment.
76. The panel asked Professor Marks to clarify the likely use of inotuzumab in UK NHS practice and in particular if he could envisage a scenario where more than 3 cycles would be used.
77. Professor Marks, on behalf of the joint appellant, responded that it was most unlikely that more than 3 cycles would ever be used since the risk of side effects of the drug (such as hepatic veno-occlusive disease) markedly increases after three cycles. The key issues were getting a patient to transplant quickly without toxicity. In his view, this could be achieved with inotuzumab in 7 weeks (4 weeks for first cycle and 3 weeks for second cycle). There was seldom a need for even a third cycle – and occasionally can proceed to transplant after 1 cycle.
78. The appeal panel sought clarity from the appraisal committee as to what it had assumed the most appropriate or likely use of inotuzumab in relation to UK clinical practice.

79. Professor Stevens, on behalf of the appraisal committee, clarified the role of the appraisal committee in assessing the cost and the effectiveness of any agent. He explained the challenges of giving very lengthy explanations when data was clear and of discussion of sub-groups. The committee's view was that the INOVATE trial scenario was not materially different from the base case and that in either case it would not have substantially impacted the ICER. The base case ICER was on a median of 3 cycles whilst the UK use was less than 3 cycles – in either scenario, the ICER was still very high.
80. The appeal panel expressed a feeling that in a potential life and death situation it might be said that the obligation for giving clarity around explanations may need to be higher than in other cases.
81. Professor Stevens, on behalf of the appraisal committee, felt that it would be a change from usual policy to have detailed explanation for every sub-group. To do this, there needed to be something "a bit special" and that this specific sub-group ideally highlighted in advance. He conceded that perhaps the committee could have been more explicit in the writing of the FAD but would routinely not expect it to do so.
82. Dr Adela Williams, representing Pfizer, requested Pfizer to allow to comment on this appeal point as much had been discussed about inotuzumab and the INOVATE trial design.
83. Mr Alex Smith, from Pfizer, clarified that INOVATE trial allowed up to a maximum of 6 cycles of inotuzumab whilst the UK practice is to use 2 cycles and maximum of 3 cycles. He also clarified that the median of 3 cycles for the base case came from using a maximum of 6 cycles. However, the costs would be considerably lower if 3 cycles were considered. Since, only [REDACTED] of patients went up to 6 cycles, there would be a significant cost difference. His recollections of the discussions at the committee meeting were at variance with those of the appraisal committee.
84. The appeal panel asked Pfizer why they had not used a maximum of 3 cycles in their base case scenario.
85. Dr Williams, representing Pfizer, clarified that when the appraisal process started, there was no marketing authorisation and hence there was no other alternative to consider a different base case scenario.
86. Professor Stevens, on behalf of the appraisal committee, responded that the draft marketing authorisation, on the basis of which the initial application was made, and the final marketing authorisation, were essentially the same. Even after the final marketing authorisation the base case scenario remained as per the INOVATE study.
87. The appeal panel considered these points. The appeal panel accepted that the initial case scenarios were based on a median of 3 cycles and a maximum of six

cycles. However, in response to ACD, a key point was raised about the maximum of 3 cycles.

88. As the panel noted under ground 1a above, this scenario was not highlighted by the company. It may well be that it is only with the wisdom of hindsight, and indeed the contributions of the appellants at the appeal hearing, that the importance of this scenario has become fully apparent. To that extent the committee should not be over criticised. Nor can the committee be criticised for seeking to base its recommendations only on the evidence before it or (in general terms) of being wary of post hoc analyses.

89. However the appeal panel considered that a potentially curative use is so clearly different to a palliative use, and the importance of a potentially curative use is so high that every effort should have been made to analyse that use and to see whether a recommendation in respect of that use alone could be made. If Professor Stevens is right that a sub group must be "a bit special" before the risks of a post hoc analysis of the data become acceptable, then this group would pass that test. Notwithstanding the additional clarity given by hindsight this should have been apparent at the time. Not all of the committee's reasons for not having considered this group of patients at length "added up". The fact that the use case was raised late in the day was unfortunate, but the significance of the scenario was such that if more time was needed to consider it then that time should be found. The suggestion that it was difficult to identify transplant eligible patients in advance was difficult to sustain in the light of Professor Marks' comments (and indeed this caused the appeal panel some concern under appeal ground 1a.2 above, although it was content that the correct approach was to deal with this defect under rationality rather than unfairness). The panel could see no reason why appropriate and simple to implement stopping rules could not be devised. The panel was not in a position to say whether the concern that the trial data did not support use as a bridge to transplant only was reasonable, because the committee's stated reasons on the point were so telegraphic.

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

91. The appeal panel felt it was not reasonable to fail to consider properly and rigorously a model of treatment which is the norm in UK practice. Whether following such consideration it will be possible to make a recommendation for use will be a matter for the appraisal committee.

92. Having heard all appeal points, the panel heard closing statements from Professor Andrew Stevens on behalf of the appraisal committee, Angela Blake on behalf of Pfizer, Mr Zack Pemberton-Whiteley on behalf of Leukaemia CARE and Professor Marks on behalf of the joint appellant.

Conclusion and effect of the appeal panel's decision

93. The appeal panel therefore upheld the appeal on the grounds that the appraisal committee acted unfairly in regards to ground 1a.3 (appellant Pfizer) that the committee has provided no explanation for its decision to reject the utilities proposed in the revised Pfizer base case for the post HSCT period and submitted

in response to consultation. In addition it upheld the appeal on the grounds that the appraisal committee acted unreasonably in the light of the evidence submitted to NICE with regards to ground 2.1 (appellant Pfizer) that the appraisal committee's reasons for disregarding key assumptions used for the purpose of NICE's appraisal of blinatumomab do not explain the choices that were made in relation to inotuzumab.

94. The appeal panel also upheld the appeal on the grounds that the appraisal committee's recommendation is unreasonable in the light of the evidence submitted to NICE with regards to ground 2.1 (appellants Leukaemia CARE and the joint appellant).
95. The appeal panel dismissed all other grounds for appeal.
96. The appraisal is remitted to the appraisal committee who must now take all reasonable steps to explain clearly its decision to reject utilities proposed by Pfizer in response to the ACD. The appraisal committee needs to consider and explain the differences in assumptions post cure point made in this appraisal explicitly compared to previously published guidance on blinatumomab. The appraisal committee should reconsider inotuzumab in the context of the UK practice of 2 cycles plus an additional third, if needed, and a costing model based on appropriate stopping rules may be considered
97. 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 3 months of NICE publishing the final guidance.