NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

APPEAL HEARING

Dinutuximab for treating high-risk neuroblastoma [ID799]

Introduction

1. An Appeal Panel was convened on 30 September 2016 to consider an appeal against the Institute's final appraisal determination in the single technology appraisal of dinutuximab for treating high-risk neuroblastoma [ID799].

2. The Appeal Panel consisted of:

Professor Alan Silman	Chair
Tim Irish	NICE Non-Executive Director
John Morris	Lay Representative
David Tyas	Industry Representative
Dr Anthony Emmerson	NHS Representative

3. None of the members of the Appeal Panel had any competing interest to declare.

4. The Appeal Panel considered the appeal submitted by Solving Kids Cancer (SKC also "the Appellant").

5. The Appellant was represented by:

Nick Bird	Patient Representative and Trustee SKC
Donna Ludwinski	Director of Research programmes, SKC
Leona Knox	Research and Partnership Coordinator, SKC
John Rogers	Scientific Advisor, SKC
Grant Castle	Legal Representative, Covington & Burlington, LLP, acting pro bono

6. In addition the following individuals involved in the appraisal were present and available from the Appraisal Committee ("the Committee") to answer questions from the Appeal Panel:

Professor Gary McVeigh	Technology Appraisal Committee Chair
Helen Knight	Associate Director, HTE Appraisals
Meindert Boysen	Programme Director, HTE Appraisals
Nwamaka Umeweni	Technical Advisor
Richard Diaz	Analyst, HTE Appraisals

7. The Appeal Panel's legal adviser, Mr Stephen Hocking, DAC Beachcroft LLP was also present.

8. Under the Institute's appeal procedure members of the public are admitted to appeal hearings and several members of the public were present at this appeal. In addition, several observers were present, but took no part in the proceedings.

9. 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 2: The recommendation is unreasonable in the light of the evidence submitted to NICE

10. The Vice Chair of NICE (Mr Andy McKeon) in preliminary correspondence has confirmed that the appellant had two valid grounds of appeal under grounds 1(b) and 2.

11. Dinutuximab (Unituxin, United Therapeutics) is an immunotherapy treatment; a human–mouse monoclonal antibody produced in a myeloma cell line (SP2/0) using recombinant DNA technology. It has a marketing authorisation for treating 'high-risk neuroblastoma in patients aged 12 months to 17 years who have previously received induction chemotherapy and achieved at least a partial response, followed by myeloablative therapy and autologous stem cell transplantation'. Dinutuximab is given as part of a 6course regimen that includes granulocyte-macrophage colony-stimulating factor (GMCSF), interleukin2 and isotretinoin. It is administered at a daily dose of 17.5 mg/m2 on days 4–7 during courses 1, 3 and 5 (each course lasting approximately 24 days) and on days 8–11 during courses 2 and 4 (each course lasting approximately 28 days). Course 6 consists of treatment with isotretinoin alone.

12. The appraisal that is subject to the current appeal process is to provide advice to the NHS on the use of dinutuximab for the treatment of high-risk neuroblastoma.

13. Before the Appeal Panel enquired into the details of the appeal points the following made preliminary statements: Grant Castle, Leona Knox, Donna Ludwinski and Nick Bird for SKC and Professor Gary McVeigh for the Appraisal Committee.

Appeal by Solving Kids Cancer

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

Ground 1b There has been a breach of Section 11 of the Children Act 2004, Article 3 of the UN Convention on the Rights of the Child and human rights legislation.

14. The Appellant had been asked to set out its argument in writing under this ground, and it did so. The appraisal committee was given the opportunity to make any observations it wished in writing, but was content to leave the matter to the Panel. The Panel considered the initial written submission from the Appellant, the written advice note received from its own legal advisor, and a supplemental paper prepared for the Appellant by Covington and Burling LLP.

15. The Panel also briefly heard from Mr Grant of Covington and Burling LLP and from Mr Hocking. Neither wished to make further detailed legal submissions. Although they differed on some points of detail in the legal analysis, they agreed there was little benefit exploring these in the hearing. They agreed that on any view of the law, the fundamental issue for the panel expressed in lay terms was whether NICE's processes had properly accounted for the fact that the target population for this technology was a paediatric patient group.

16. Mr Grant additionally stated that there was no evidence in the committee papers that the Committee had considered the special position of children, or treated their best interests as a primary concern.

17. Professor McVeigh explained that the Committee understood both that the Methods Guide existed to ensure consistency, and that the Committee was not restricted to a rigid adherence to it. He gave an example of a previous appraisal where End of Life ("EoL") criteria had been applied flexibly. He stated that the benefit of a response to treatment in children could be greater than in adults, and an extension to life could be valued more highly in that group. The Committee had considered that not all quality of life benefits of treatment had been captured in the data before it; it recognised the toxicity of existing treatments and the stress and anxiety caused to patients. It also considered the impact of bereavement on the parents.

18. He said that he was confident the Committee had been prepared to be as flexible as possible and would have accepted a higher ICER for this population than it would have done for an adult population. He said he had emailed NICE in a personal capacity to that effect. However the Committee had to strike a fair balance between the population targeted for this technology and other similar populations in other areas of health. The Committee had not in fact been presented with an ICER that approached the maximum it would have considered

acceptable. Nor had it been given quantifiable data on issues such as quality of life.

19. Turning to the Appellant's specific complaint about the EoL policy, Professor McVeigh said that the median survival of the patient group was twice the usual upper limit allowed for the policy to apply. The Committee had not thought it would be correct to apply the policy on the assumption that a sub-group of patients were within two years of the end of life, as there was no way to know which patients that would be.

20. The Panel considered the points made to it. As the Panel is not legally qualified, and as in any case any view on the law it may express would only be provisional, it does not see great benefit in setting out and dealing with the legal arguments at length here. In summary:

    - the Panel was not persuaded that the United Nations Convention on the Rights of the Child applied to the work of the Committee[1].
    - The Panel was not persuaded that there was as such a requirement to document a specific consideration of what was in the interests of children.
    - The Panel agreed with its legal advisor that articles 2, 8 and 14 of the European Convention on Human rights were engaged, and accepted what it understood to be a broadly jointly shared view between Mr Hocking and Mr Castle as to what the legal content of those articles was.
    - Finally the Panel understood that the status of the patients as children could be relevant purely on ordinary public law principles, and it noted the application of the Public Sector Equality Duty.

21. Turning to the Committee's work: the Panel was not satisfied, given the lack of specific evidence in the FAD that sufficient consideration had been given to the position of the patients as children. The Panel accepted that the law did not require that status to have a paramount or even a primary weight. However it did consider that it was a relevant issue, and one that had to rank as one among the many important considerations that the Committee had to deal with. It was not satisfied that the Committee's treatment of the issue met that requirement.

22. The Panel did accept that the absence of written evidence of specific consideration did not mean that those issues had not been considered. A written consideration was not a requirement in itself. However in the absence of any

[1] At the hearing Mr Grant raised a point concerning the legislative history of s.11 of the Children Act 2004 and its application to NICE. Whether he was right or wrong about parliament's intentions in that regard, the Panel felt constrained by the fact that as currently enacted s.11 does not apply to NICE.

contemporaneous documents the Panel felt it should be cautious in accepting later evidence that the relevance of childhood was considered. In this case Professor McVeigh had been clear about the extent of the Committee's considerations: he himself had expressed a personal view to the Institute, and he had felt confident what the Committee would have done if it had been presented with certain evidence. Coupled with the lack of contemporaneous documentation of consideration of the position of the patients as children, the Panel felt there was no evidence that explicit discussion had taken place. The Panel appreciated that the Committee could not but have been aware in general terms that the patients were children, (and it does not suggest that the Committee was insensitive to their plight) but the Panel did not feel this awareness was sufficient. Nor did it feel able to speculate what the Committee might have agreed had the issue been discussed.

23. This lack of demonstrable evidence of consideration was of particular significance to the EoL policy. The Institute's guidance on the EoL policy describes only when that policy will "normally" apply. Professor McVeigh clearly and correctly understood that the guidance could be departed from, and gave an example of a fairly small departure as regards the short life expectancy criterion in the case of adult pancreatic cancer patients. It appeared to the Panel that because the departure from that criterion that would be required in this case would have been of an order of magnitude more than for the pancreatic cancer case, the issue was not considered. However the Panel felt this assumed that the EoL policy for children was considered to apply as it would apply to adults, and the Committee treated the magnitude of the departure from the usual (ie adult) criterion as the determinative issue.

24. That may ultimately be the correct approach - it is not for the Panel to say - but the Panel felt a discussion was needed, with reasons for whatever the eventual conclusion would be. The EoL policy itself reflects a departure from NICE's standard approach to reflect a societal value placed on treatment at the end of life. The Panel felt it could not lawfully go unexamined whether that value was the same or different in the case of children. For example, the view might be taken that much larger departures to the short life expectancy criterion could be justified in children, to reflect a possible opinion that additional years in a short life have exceptional value to the children and their parents/carers.

25. The Panel appreciated that the Committee had not been given quantifiable data (indeed, in some cases, had not been given any data) as regards important factors that may differ as between adult and child patients (such as quality of life, the bereavement of parents, the value of additional life years when the patient is still developing). It understood that in an STA it is not for the Institute to assemble evidence and that in the absence of evidence a Committee may face difficult choices in how to proceed. Ultimately it may have to conclude that a factor is potentially relevant but wholly unevidenced, and so be unable to give it

any weight. Nevertheless the Panel remained of the view that a discussion of the point by the whole Committee was a requirement and should be documented in the FAD.

26. In the absence of that discussion the Panel did not consider whether the FAD breached any of Articles 2, 8 or 14 ECHR or the Public Sector Equality Duty (PSED) in any detail. This is because the Committee must first have the opportunity to consider whether there is anything particular to this patient group as children that should be taken into account in the appraisal. Further if there is something particular to take it into account then there is a requirement to consider whether the outcome of the appraisal is different, and if there is not, to say so with reasons. It would be premature to determine the substantive compliance of any guidance with the ECHR or the PSED until this extra consideration had taken place. The Panel did not consider that guidance in its current form must necessarily be in breach of any of those provisions, but it went no further in its deliberations.

27. Provided the Committee asks itself whether its approach should change to reflect the fact that the population targeted for this technology are children, and gives a reasoned answer, it will have corrected the error identified by the Panel. What it should then do will be a matter for its judgement and will depend on whether or not it considers a different approach is needed, and the evidence available to it.

28. Given especially Point (25) above the Panel upheld this appeal point.

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

Appeal point 2.2 It was unreasonable for the Institute to use a 10-year cure point, given the evidence before it.

29. Mr Castle for SKC expressed the view that the Appraisal Committee had acted very unreasonably by selecting a 10 year cure point because, in SKC's view, the data by 10 years were very sparse and hence statistically unstable. He commented that scientific bodies were given discretion on which data sets they use and how they interpreted the data. He conceded that it was relatively easy for an expert body to justify their processes.

30. Nick Bird for SKC noted that there had been several data cuts after the end of the [ANBL0032] trial in 2009, 2012 and 2014. He agreed that in general terms, the longer term follow up data the better, and that there was no dispute over the use of the 5 year outcome data following the data analysis requested by the European Medicines Agency in 2014. However SKC considered that the Appraisal Committee had taken an unreasonable approach by using 10 year

data as the confidence intervals at 10 years were very wide due to the very low patient numbers and thus the point estimate was therefore unstable and unreliable.

31. He quoted the advice given by Dr Wendy London, the US Children's Oncology Group statistician for the ANBL0032 trial. He gave the example that at 10 years the point estimate for overall survival was 58% but the confidence interval, given the very small number of patients was very wide, ranging between 34% and 83%. It was thus inappropriate to use this point estimate. He noted that before 5 years, only 11 of the 114 patients in the immunotherapy group had been censored while 58 were censored after 5 years. SKC's view was thus that it was scientifically unsound and unreasonable to have used a 10 year cure point.

32. Prof Gary McVeigh for the Appraisal Committee referred to Figures 4 and 5, (page 45) of the ERG report to show that events continue to occur after 5 years. He considered that most of these events would inevitably be in the dinutuximab arm of the study. He referred to Table 7 (page 44) and Table 8 (page 46) showing that the confidence intervals overlapped at 2, 3, and 5 years and acknowledged that in appraisals, where there are few patients, the tail of the group can markedly influence the ICER. He noted that curves were fitted to the observed data points and referred and drew the panel's attention to Table 40 (page 117) where 2 models had been used to analyse the [10 year] data and showed that the ICER didn't change between the methods used. He emphasised that to accept a 5 year cure point was contrary to the evidence as there were clearly events occurring after 5 years.

33. He stated that on the basis of previous evidence with standard therapy where the cure point was 5 years then if further events were to occur these would, in his opinion, be in the dinutuximab group and that would have the effect of increasing the ICER.

34. Nick Bird for SKC pointed out that neither the EMA nor the company had used 10 year data and the ERG had used the Kaplan-Meier curve which was wholly unscientific as the data was unclear with wide confidence intervals. He pointed out that some patients will relapse after 5 years in the standard therapy arm also.

35. David Tyas asked Professor McVeigh what the Committee had made of the Company's Submission (page 138 bullet point 2) that 6.5 years was the "upper" cure point based on best fitting curves.

36. Professor McVeigh said that the Appraisal Committee had not discussed a 6.5 year cure point and commented that the longest follow up of patients suggested that event free survival plateaued at about 8 years and overall survival at 10 years. He commented that the manufacturer had accepted both the 2014 data and the 10 year cure point in their revised submission. He said that the ICER for an 8 year cure point would be lower but this data had not been presented.

37. David Tyas asked how certain the ERG or the Appraisal Committee had been and why had an 8 year plateau not been assessed.

38. Professor McVeigh said that the ICER for 8 years would only be a few thousand pounds less than the 10 year ICER.

39. Professor Alan Silman expressed the view that there appeared to be arbitrariness in the use of a 10 year cure point especially when the 2014 data showed that a proportion was cured.

40. Professor McVeigh responded that instability of small numbers is a feature of survival data and that the Committee had looked at earlier data and the ICERs would have been higher.

41. Tim Irish asked for clarification of the cause of difference between the ICER values at 5 and 10 years (table 38 page 116).

42. Professor McVeigh agreed that there was volatility but for the analysis there was a need to capture all the costs and benefits. The advantage of the 10 year cure point was that there was identification of patients that were cured so the correct discount rate could be applied. He considered that the Committee had been reasonable and any other Committee would have made the same decision.

43. Nick Bird for SKC expressed the view that the "data should speak for itself" and that the data out to 10 years, with very small numbers, was not sufficient to do that. He was concerned that parents are advised that clinical trials are important to provide the data to make correct decisions yet here the data out to 10 years was not mature and should not be prejudged. He expressed concern over the advice given to the Committee by clinicians who had not actually used dinutuximab. He also stated that while the 5 year cure point was used to inform parents of the likely long term outlook if no events had occurred by then, nevertheless that was not the same as saying there would be no events after that.

44. Donna Ludwinski gave her personal experience of her son who relapsed 13 years later on standard therapy.

45. Helen Knight for the Appraisal Committee pointed out that the outcome data in the model applied to both arms so there were some patients on standard therapy that relapsed after 5 years.

46. In his closing remarks Professor McVeigh said that the Committee had considered all aspects of this rare cancer and recognised the significant extension to life and noted that all the data for health related quality of life had not been fully captured. He expressed the view that, although not discussed, the Committee would have been willing to extend the ICER to the maximum

allowable. However he remained of the view that the Appraisal Committee could not have done other than use the longest possible time for the cure point.

47. Nick Bird for SKC commented that the committee had not considered whether there were subgroups such as those with MYC amplification who had a poor prognosis may have benefitted and fulfilled the end of life criteria.

48. Grant Castle in closing for SKC commented that he had heard during the Appeal Hearing that the Appraisal Committee were prepared to use discretion and apply the maximum possible ICER allowance but that he did not see evidence of this in the FAD. There was no documented reasoning for the Appraisal Committee's decisions. He commented that he found the debate about the end of life criteria to be nonsensical. He accepted that the Appraisal Committee was bound by the methods guide and that there was discretion as the guide used the word "normally" when referring to the two year criterion for end of life treatment. He said that this treatment will give on average a 3 year extension to life yet had not been used as exceeded the 2 year cut off. The STA process of appraisal was bound to make the approval of dinutuximab fail and, in SKCs view, this should have been done through a HST process.

49. John Rogers for SKC stated that only £1M would be required to fund this treatment and put in a plea for review through the HST process.

50. The Appeal Panel in its deliberations accepted that the cure point was longer than 5 years and that there were likely to be some events in both groups beyond that. The Panel considered that the case had not been made that the data out to 10 years was so robust for this to be the only cure point and acknowledged that the ICER was highly influenced by the small numbers in the data out to that point.

51. The Panel felt that there were a number of other possible cure points that could have been explored and that there was a balance between the desire to have the longest time period to capture all the benefits and costs and the weakness of the data out to 10 years. The panel felt that the Committee should look for a range of clinical views on the appropriateness of different cure points. The Panel felt that the approach of taking the 10 year cure point alone was unreasonable: more reasonable approaches might have been to consider a range of plausible cure points, and then to exercise judgement informed by an appreciation of the strengths and weaknesses of each, for example, that estimates based on the ten year cure point span a very wide range of possible values but is reasonably complete, that estimates based on the five year cure point will be blind to events that are known to occur after that time but give better defined values, and so on.

52. The Panel also felt that the FAD should have included the Committee's reasoning for accepting / rejecting a range of different cure points including the 6.5 years suggested by the manufacturer in their submission.

53. The Panel therefore upheld this appeal point.

Conclusion and effect of the Appeal Panel's Decision

54. The Appeal Panel upheld both appeal points made by Solving Kids Cancer. The Appraisal Committee should have the opportunity to consider whether there is anything particular to this patient group as children that should be taken into account in the appraisal, and if there is, to take it into account and to see whether the outcome of the appraisal is different, and if there is not, to say so with reasons.

55. The Committee should also review a range of cure points and associated ICERs between 5 and 10 years and should outline in the FAD the balanced reasoning for their choice.

56. 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 publishing the final guidance.