NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Multiple Technology Appraisal

Lapatinib and trastuzumab in combination with an aromatase inhibitor for the first-line treatment of metastatic hormone receptor positive breast cancer which over-expresses HER2

Decision of the Appeal Panel

Introduction

1. An appeal panel was convened on 8th September 2011 to consider an appeal against the Institute's Final Appraisal Determination (FAD), to the NHS, on the use of lapatinib and trastuzumab in combination with an aromatase inhibitor for the first-line treatment of metastatic hormone receptor positive breast cancer which over-expresses HER2

2. The appeal panel consisted of Professor Patrick Morrison, Chair of the panel, Ms Linda Seymour, Non-Executive Director of NICE, Dr Frank McKenna, NHS Representative, Dr Mercia Page, Industry representative, and Mr Peter Sanders, Lay representative.

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

4. The panel considered an appeal submitted by Roche Products Ltd.

5. The appellant was represented by Mr Gavin Lewis, Dr Julian Cole, Ms Lee Moore, Ms Sarah Jones and Dr Adela Williams, the legal representative for the appellant.

6. In addition the following individuals involved in the appraisal were present and available to answer questions from the Appeal Panel – Dr Jane Adam, Committee Chair, Professor Philip Home, Committee Vice Chair, Ms Janet Robertson, NICE Associate Director, Ms Joanne Holden, Technical Advisor and Ms Sally Doss, Technical Lead**.**

7. All the above declared that they did not have any conflicts of interest except for Professor Home who declared a non personal pecuniary interest in that his institution had received research funding from Roche, though he had not personally done so.

8. The Institute's legal adviser Mr Stephen Hocking from Beachcroft LLP was in attendance as the legal representative to the panel.

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

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

- **The Institute has failed to act fairly**
- **NICE has formulated guidance which cannot reasonably be justified in the light of the evidence submitted**
- **The Institute has exceeded its powers**

11. The Chair of the Appeal Committee (Dr Maggie Helliwell) in preliminary correspondence had confirmed that: the appellant, Roche Products Ltd, had potentially valid grounds of appeal under Ground 1 that "The Institute has failed to act fairly" as follows:

1.1 The Appraisal Committee's conclusions in relation to (a) the life expectancy of people eligible for trastuzumab in combination with an aromatase inhibitor for first line treatment of metastatic hormone receptor positive breast cancer that over expresses HER2 and (b) the survival gain associated with trastuzumab therapy, are not stated and it is unclear whether the Committee concluded that these criteria for the 'End of Life' advice were met.

In addition the Chair of the Appeal Committee in preliminary correspondence had also confirmed that: The Appellant, Roche Products Ltd, had potentially valid grounds of appeal under Ground 2 that "The Institute has formulated guidance which cannot be reasonably justified in light of the evidence submitted" as follows:

2.1 The Appraisal Committee's addition of a further 2,000 patients to the 7,000 population figure estimated by Roche for trastuzumab equates to double counting of patients. These calculations suggest that nearly twice as many mBC patients are potentially eligible for trastuzumab as there are HER2+ mBC patients in the UK. This cannot be reasonably justified in light of the evidence presented and is not a sound a suitable basis for the issuance of guidance to the NHS.

2.2 The Appraisal Committee's statement regarding the overall survival of patients who received aromatase therapy monotherapy in the TAnDEM trial failed to allow for patient cross over

2.3 The Appraisal Committee's statements regarding the overall survival benefit associated with trastuzumab therapy are unreasonable in light of the totality of the data presented.

2.4 The conclusion by the Appraisal Committee that estimates of progression free survival for the aromatase inhibitor monotherapy in the TAnDEM trial were likely to be too low disregards the fact that the patient population in TAnDEM was different from that in EGF30008

No appeal was made in relation to lapatinib; and no appeal in relation to trastuzumab was made under ground 3.

12. The Panel were made aware in documentary evidence that trastuzumab (Herceptin, Roche Products) is a recombinant humanised IgG1 monoclonal antibody directed against HER2. Trastuzumab is indicated (inter alia) for the treatment of patients with HER2+ metastatic breast cancer 'in combination with an aromatase inhibitor for the treatment of postmenopausal patients with hormone-receptor positive metastatic breast cancer, not previously treated with trastuzumab'.

13. Before the Appeal Panel inquired into the detailed complaints the following made preliminary statements: Mr Gavin Lewis on behalf of the appellant and Professor Phillip Home on behalf of the appraisal committee. Mr Lewis gave a brief overview of the treatment of breast cancer. He described how breast cancer was defined by the presence or absence of HER2 and that patients' option to receive Herceptin (trastuzumab) had become the standard of care for HER2 positive breast cancer. Mr Lewis explained that trastuzumab was licensed for the treatment of metastatic gastric cancer in addition to early and metastatic breast cancer. He described how there is a small patient population with both HER2 positive and estrogen receptor (ER) positive breast cancer who were not suitable for chemotherapy who would be suitable for dual therapy with an aromatase inhibitor and trastuzumab. These patients were in a poor prognostic category. Roche had estimated that only approximately 50 patients per annum in England and Wales would be in this category and that treatment offered an increase in survival of over 6 months. Mr Lewis described the data from the TAnDEM study which evaluated this patient population and explained that because 70% of patients on placebo crossed over to active treatment it was a difficult analysis. A specific statistical model was therefore used that indicated there was an overall increase in survival of 6.5 months. Mr Lewis explained that to Roche, there was little commercial interest in such a small patient population but they felt that this appeal was important as a matter of principle as the conclusions of the appraisal committee may set an unfair precedent for future appraisals. Mr Lewis also stated that Roche had serious concern that appeal point 1.2, *The lack of guidance issued by the Institute in relation to the calculation of small patient populations for the purposes of the End of Life advice is unfair*, made in Roche's initial notice of appeal was not allowed as a valid point of appeal.

14. Mr Lewis summarised by stating that although the appeal points were under 5 separate headings there were 2 key issues which were the End of Life criteria and the interpretation of the TAnDEM study. On both these areas Mr Lewis argued that the appraisal committee were opaque and ambiguous and that this had prejudiced any consultation. Mr Lewis explained how the appellant

considered their feedback on the ACD had been ignored and that the assessment of survival gain by the appraisal committee had failed to take into account the crossover onto treatment in those on placebo.

15. Before inviting the appraisal committee to respond Professor Morrison explained that appeal point 1.2 could not be discussed as it was not accepted in previous correspondence by Dr Helliwell, the appeal panel Chairman, as a valid point of appeal. However Janet Robertson on behalf of NICE explained that the Methods guide was currently under review and the issue of clarity regarding the End of Life criteria was under discussion. Professor Morrison then invited the committee to make any introductory remarks.

16. For the committee Professor Home stated that the appraisal committee were very familiar with metastatic breast cancer having recently reviewed other treatments for this condition. He also stated that this was a more complex appraisal as it was a multiple technology and not a single technology appraisal and the committee had spent time reviewing each technology separately. Professor Home described how all the ICERs for both technologies were greater than £51,000. He also described that the committee were aware that this was a frailer population that were being considered for this indication but that the problems were on the economic modelling. Professor Home stated that the committee did make conclusions on each of the End of Life Criteria and these were described in the FAD. He concluded his remarks by noting that an appeal was not lodged by the manufacturers of lapatinib.

Ground 1

1.1 The Appraisal Committee's conclusions in relation to (a) the life expectancy of people eligible for trastuzumab in combination with an aromatase inhibitor for first line treatment of metastatic hormone receptor positive breast cancer that over expresses HER2 and (b) the survival gain associated with trastuzumab therapy, are not stated and it is unclear whether the Committee concluded that these criteria for the 'End of Life' advice were met.

17. For the appellant, Dr Adela Williams suggested that points a) and b) could be considered together. Dr Williams stated that the committee had failed to conclude whether either the first 'End of Life' criterion (a life expectancy that is normally less than 24 months) or the second 'End of Life' criterion (overall survival gain greater than 3 months) were met. She considered the FAD to be unclear and ambiguous. Dr Williams referred to 4.3.16 in the FAD and the statements that *"people with HER2+ status have a worse prognosis"* and *"would be expected to have a life expectancy of less than 24 months".* She then referred to the statement that *"it noted that the mean overall survival in the aromatase inhibitor monotherapy arm of the EGF30008 trial and in the ITT population of the TAnDEM trial exceeded 24 months."* Dr Williams said that the overall flavour of these comments appears to support the satisfaction of the first End of Life criterion but it was unclear. In addition if the committee

decided that patients would not meet this criterion because of the results in the TAnDEM trial then this would be unfair.

18. Professor Home for the committee explained that they were unable to reach a firm conclusion on this aspect of the End of Life criteria. He said that the committee were aware that all the criteria had to be satisfied and because the committee had concluded that other End of Life criteria were not met then they did not feel it necessary to draw a firm conclusion on the first criterion. They were aware that this was a particularly frail population and felt that they probably would not have an expected survival of greater than 24 months but they did not feel it possible on the evidence to reach a firm conclusion. Professor Home stated that 4.3.16 in the FAD did not suggest the committee had reached a conclusion but that 4.3.17 did conclude that the second criterion was not met by stating that the increase in survival was not statistically significant.

19. For the appellant Dr Williams stated that it was therefore unfair for the committee not to explain in the FAD that they were unable to make a conclusion on the first End of Life criterion rather than making an ambiguous statement. In relation to statistical significance and the second criterion, Dr Williams stated that although the increase in survival was not statistically significant in the trial, this was not the primary endpoint of the trial. She noted that in 4.3.17 the committee commented on the gain in progression free survival but implied that this was a 1 to 1 ratio to overall survival and this was also unclear and unfair.

20. For the committee Professor Home disagreed and thought it was clear that the committee had concluded that the second End of Life criterion was not met. The panel asked Professor Home to consider the statement in 4.3.14 of the ACD *"The Committee noted that the trial data did not show a statistically significant overall survival gain, but that the ITT analysis indicated a median overall survival benefit of 4.6 months, suggesting that trastuzumab plus an aromatase inhibitor compared with an aromatase inhibitor alone may offer a 3-month survival gain"* and if he agreed that the phrasing suggested that the committee felt the second EOL criterion was met. Professor Home did not agree and felt that although the committee wrestled with the overall survival gain, the statement that there was not a statistically significant survival gain indicated that the second criterion was not met.

21. In considering this appeal point, the panel discussed in particular whether the appellant may have been compromised in making appropriate submissions to the committee by the conclusions expressed in the ACD. The panel agreed that it was necessary for any consultee to understand whether the End of Life policy would or would not be applied. In this case it was clear that the policy was not being applied. It is also necessary for consultees to understand why the policy is not being applied. The panel accepted Professor Home's statement that all three EOL criteria have to be met in order to consider the supplementary advice for EOL technologies and that the committee therefore did not always need to reach conclusions on all the criteria if at least one failed. The panel also considered the argument from the appellant that the committee's conclusions were unclear and ambiguous. In relation to the

conclusions on the first criterion, the panel considered that the statements in the ACD and FAD in relation to anticipated survival without treatment were lacking in clarity. The panel considered that although this may have reflected the committee's failure to reach a conclusion on this point, that fact, and a reason for it, should have been explicit in the ACD. The Panel agreed that it was unclear from the ACD and FAD whether the committee was finding that the first criterion was satisfied, was not satisfied, or whether, as they clarified at the appeal hearing, they had felt it unnecessary to reach a conclusion. The panel concluded that this lack of clarity did not enable the appellant to make an appropriate response to the committee both on this particular criterion and on the application of the End of Life policy overall, and that this was unfair.

22. In relation to the second criterion, the panel compared the statements in the ACD and FAD in addition to considering the responses made by Professor Home. The panel considered that the natural implication of the wording in the ACD was that the committee had accepted the second criterion was satisfied, perhaps with some reservation regarding the lack of a statistical significance. The panel considered the supplementary advice for End of Life treatments and the advice to appraisal committees in 2.3.1 is that they need to be satisfied that *"the estimates of the extension to life are robust and can be shown or reasonably inferred from either progression free survival or overall survival (taking account of trials in which cross-over has occurred and been accounted for in the effectiveness review)".* The panel considered that this advice does not infer that the benefit must always be statistically significant. The panel considered that if the committee considered the second criterion was not met then this should have been expressed more clearly in the ACD, and the reason given. The panel did not accept Professor Home's argument that the lack of statistical significance meant (and would be understood as meaning) that the second criterion could never be met. That would be a question for the committee's judgement, and therefore the consultees must have a fair chance to persuade the committee that, unusually, evidence that is not statistically significant should nevertheless be relied on. The panel concluded that the ACD appeared to indicate that the committee accepted the second EOL criterion was satisfied, that as a result the appellant had not commented on that issue and this lack of clarity may well have unfairly compromised the appellant in submitting an appropriate response. Appeal point 1.1 was therefore upheld on both points (a) and (b).

Ground 2

2.1 The Appraisal Committee's addition of a further 2,000 patients to the 7,000 population figure estimated by Roche for trastuzumab equates to double counting of patients. These calculations suggest that nearly twice as many mBC patients are potentially eligible for trastuzumab as there are HER2+ mBC patients in the UK. This cannot be reasonably justified in light of the evidence presented and is not a sound a suitable basis for the issuance of guidance to the NHS.

23. For the appellant Ms Moore argued that the FAD contained a factual error related to the available population for Herceptin. She stated that there are approximately 2,500 patients with metastatic breast cancer in the UK of whom approximately 50 will not have had chemotherapy and so are suitable for Herceptin with an aromatase inhibitor. Using the calculations submitted to NICE by Roche indicated that there are a total of approximately 7000 patients who could be treated with Herceptin in its various licensed indications. Ms Moore suggested that the committee had double counted by adding the 2,500 metastatic breast cancer patients to the total of 7000 whereas they were already included in calculating this population. She therefore argued that this figure was in keeping with the third EOL criteria in being a small patient population.

24. For the committee, Professor Home said that the committee had not double counted and had considered that the number of patients suitable for treatment probably ranged between 7,000 and 9,000 but although they accepted that it could be 7,000 they felt this figure exceeded what could be considered to be a small population and on this basis concluded that the third criterion was not satisfied.

25. The panel asked if the committee was aware of the conclusions on TA 208 of another committee that a population of 7000 was at the upper end of the "small population size" criterion. Professor Home said that the committee were aware of this when finalising the FAD, though not when drafting the ACD, but drew a different conclusion. The panel asked him whether the committee considered the previous conclusion to have been wrong. Professor Home felt that they did not consider whether another committee's conclusions were right or wrong but considered the criteria independently.

26. In considering this appeal point, the panel were conscious of the conclusions of the appraisal committee considering the treatment of trastuzumab for the treatment of HER2 positive metastatic gastric cancer. In TA 208 paragraph 4.25 of the guidance stated that "*The Committee considered that 7000 was at the upper end of the population size for which it understood the supplementary advice to apply"* and *"concluded overall that applying the supplementary advice on end-of-life was appropriate."* The panel accepted Professor Home's comment that the current committee were not guilty of double counting, and were aware of the conclusions of TA208 before the guidance was finalised, and his concession that that the cumulated patient population was identical. The panel were also in agreement that taken in isolation, the view that 7000 patients was not a small patient population was justifiable.

27. However, the panel felt that the question was not only whether approximately 7000 patients was a small patient population per se, but whether the population covered by trastuzumab's current licensed indications is, as has previously been held, a small population. That is not a question of where the boundaries of a small population may be, but of what the requirements of consistency between appraisals are.

28. A previous appeal panel set out its general approach to consistency between appraisals in TA227 at paragraphs 35-37 of its appeal decision, and this panel agreed with that reasoning. It specifically notes and agrees that one appraisal committee may differ from a decision of another appraisal committee. Notwithstanding this, the panel finds that in this appraisal the committee acted unreasonably in so doing. There are two reasons.

29. First, in TA227, the committee had carefully discussed the position taken by its sister committee before disagreeing with it. Here, the initial departure was made without discussion (because at ACD stage the Committee was not aware that it was making a departure at all), and no reassurance was offered that the issue was discussed in detail before the FAD was finalised. This would be a requirement where, as here, the committees are considering precisely the same drug and precisely the same patient population.

30. Second, the panel considered that this appraisal raises an issue of fair treatment of this particular patient population. They comprise a small subset of the patients with HER2+ metastatic breast cancer. They differ from that cohort in an inability to receive chemotherapy, but not in their underlying disease, nor in the expectation that trastuzumab will benefit them. It was clear that, but for the inability to receive chemotherapy, these patients would have been considered for treatment with trastuzumab, in common with the broader patient cohort. The panel stresses that even so it is not necessarily unreasonable that these patients should be treated differently, but that it is essential that there are clear and convincing reasons for any difference in treatment, which can be tested in consultation or on appeal and which if need be can be expressed by a supervising clinician to a patient. In this special case, if a clinician is unable to understand and to explain what may otherwise seem a counterintuitive decision to a patient, it is difficult to see how he or she could implement the guidance. In this case one part of the reason for a difference in treatment was the committee's disagreement that the patient population for trastuzumab was "small". The panel felt this alone would be an inadequate reason for the difference in treatment.

31. Appeal Point 2.1 was therefore upheld. However the Panel repeats the comment made by the appeal panel in TA227 that it would be desirable for the Institute to consider reviewing the application of the EoL policy, and to consider whether any further guidance or clarification would assist committees.

Ground 2

2.2 The Appraisal Committee's statement regarding the overall survival of patients who received aromatase therapy monotherapy in the TAnDEM trial failed to allow for patient cross over

32. For the appellant, Ms Moore described the analysis of the TAnDEM study and why this was complicated by the crossover of patients from placebo to active treatment. She argued that using the placebo arm to determine the overall survival of untreated patients was therefore inappropriate and without taking

this into consideration, this would indicate a survival of greater than 24 months.

33. In response, Professor Home stated that the committee did take the crossover design into account and agreed that the overall survival of this patient group without treatment is probably less than 24 months but because of the uncertainty and in the interests of time, the committee did not reach a conclusion. For the committee, Ms Holden added that the crossover analysis could be criticised by being a post hoc analysis. However, for the appellant, Ms Moore explained that the statistical techniques in crossover analysis had not been developed when the study was designed. For the committee, Professor Home also expressed concern that the study population was multinational and did not necessarily reflect a UK population.

34. The panel asked the committee whether they considered that FAD 4.3.16 adequately reflected these concerns and whether the committee had difficulty with the crossover analysis. Professor Home said that the committee were used to reviewing this type of analysis. He also considered that because the committee did not make a decision on the first criterion of the EOL criteria, that he considered the FAD to be appropriate. For the appellant, Mr Lewis agreed that data need to be relevant to an NHS setting but there was an obligation to consider observations of the likely survival when treated just with an aromatase inhibitor. Professor Home said that he didn't disagree but that the committee did not reach a conclusion.

35. The panel in considering this appeal point had accepted the arguments put forward by Professor Home that because other EOL criteria were in the committee's view not met, the committee did not necessarily need to have reached a conclusion on the first criterion. Although this point was considered under fairness, the panel also considered whether this meant that the guidance could not be justified on this basis. The panel considered that the FAD was ambiguous in relation to the first EOL criterion and considered that the decision not to reach a conclusion by the committee should have been expressed in the FAD. However, the panel did not feel it had been unjustifiable on the evidence available not to reach a conclusion on this criterion (although this would not be the case if the other criteria had been satisfied). The committee should carefully consider the way forward here, in light of the panel's findings under appeal point 2.1. Point 2.2 was dismissed.

Ground 2

2.3 The Appraisal Committee's statements regarding the overall survival benefit associated with trastuzumab therapy are unreasonable in light of the totality of the data presented

36. Ms Moore for the appellant accepted that the increase in survival in the TAnDEM study was not statistically significant but this could be explained by the crossover design of the study and when adjusting for the crossover, the mean increase in survival exceeded 6 months. Ms Moore also suggested that the progression free survival of 2.4 months that is described in the FAD could be considered to be a surrogate measure of increase in survival that is double

that of progression free survival. In addition a final analysis concluded that the statistically significant progression free survival was 8.6 months.

37. For the committee, Professor Home said that if the analysis of survival benefit of greater than 3 months was not statistically significant then it would fail to meet the second EOL criterion. In relation to trastuzumab, the data were not independent and was not statistically significant. He explained how the committee also considered the progression free survival as a surrogate measure of survival benefit. The median progression free survival was 2.4 months, the committee considered that the mean could be greater but there was uncertainty and the conclusion in 4.3.17 of the FAD followed robust discussion. For the appellant, Mr Lewis considered that it was a worrying precedent if the lack of statistical significance meant that there was held to be no benefit. In addition he raised a concern whether the mean or the median is considered as the data may be skewed because some patients have a prolonged response. Professor Home agreed that in some data the median may be more important than the mean. Mr Lewis then suggested that the approach taken by the committee implied that progression free survival was more important than overall survival. Dr Adam explained that the committee decided to choose the progression free survival as a more robust analysis of the cross over data. Mr Lewis asked why the median rather the mean was then the preferred method used by NICE. Ms Seymour for the panel asked the appellant whether they had more data. Ms Moore explained that they now had a final dataset that found a group of strong performers reflected better in the mean than the median. The final dataset found that the overall survival was approximately double the progression free survival. Professor Home said that the committee were not informed of any other relationship other than 1 to 1, but Dr Williams said that the appellant was not given an opportunity to respond as the failure to meet the second EOL criterion was not expressed prior to the FAD.

38. The panel considered the evidence available to the committee and also the supplementary advice relating to End of Life treatment. The panel considered the comments made by Professor Home that the interpretation of the EOL advice was that there was a need for a statistically significant increase in survival for greater than 3 months. The panel also considered the information from the appellant that the final analysis of the TAnDEM study found a progression free survival that was approximately half the overall survival. The panel considered that 4.3.14 in the ACD implied that the committee accepted the second EOL criterion. The panel considered the supplementary advice for End of Life treatments and that the advice to appraisal committees in 2.3.1 is that they need to be satisfied that *"the estimates of the extension to life are robust and can be shown or reasonably inferred from either progression free survival or overall survival (taking account of trials in which cross-over has occurred and been accounted for in the effectiveness review)".* The panel considered that this advice does not infer that the benefit must necessarily be statistically significant and considered that if the committee considered the second criterion was not met then this should have been expressed more clearly in the ACD. Although the final dataset was not available to the committee, the panel considered it was unjustifiable to apply the strict criterion

of statistical significance without any possibility of establishing robust estimates in any other way, and to assume that progression free survival equated to a 1 to 1 ratio when other data suggested it was likely that there was a survival benefit of greater than 3 months. Point 2.3 was upheld.

39. The panel stresses, as a general observation, that ordinarily a committee will be justified in refusing to place weight on evidence that lacks statistical significance, and that it will not need to give reasons for doing so. It is sufficient that statistical significance is taken as the degree of confidence in a result that is conventionally required. However, more care may be needed where:

    a. there is a general lack of statistically significant results, and no likelihood of any being generated;

    b. the results closely approach statistical significance;

    c. the statistically insignificant results are inherently plausible, not the result of possible "data mining", and are supported by other data;

    d. the question before the committee is a pass/fail criterion, rather than a freestanding exercise of judgement. (In this case it may have been reasonable to take account of a lack of statistical significance when forming a view on confidence in an overall ICER, but it was not reasonable (without more discussion) to rely on it to exclude trastuzumab from consideration under the EoL policy at all.)

Ground 2

2.4 The conclusion by the Appraisal Committee that estimates of progression free survival for the aromatase inhibitor monotherapy in the TAnDEM trial were likely to be too low disregards the fact that the patient population in TAnDEM was different from that in EGF30008

40. Dr Cole for the appellant expressed concern that the committee appeared to base their decision on the comments of clinical experts rather than on the data from the TAnDEM study. In addition the committee compared the outcome of the patients in the EGF30008 trial without taking into account that the patient population in the TAnDEM study had different prognostic factors. In response, Professor Home said that the committee had accepted the populations in the 2 studies were different and did not attempt to compare populations but were unhappy with the uncertainty from the different data sets. Ms Williams asked whether Professor Home could identify another breast cancer population where the prognosis on aromatase inhibitors alone indicated a good survival. Professor Home explained that the uncertainty relating to these populations was the concern of the clinical experts who had given evidence to the committee. Ms Moore stated that there had only been 3 trials that had evaluated HR2 positive patients with aromatase inhibitors and the lapitinib study had included HER2 positive and negative patients, so patients with a better prognosis were included.

41. Ms Seymour for the panel asked the committee whether they had considered expert opinion to equate to robust evidence. In response, Professor Home said that there were times when it was useful particularly when there is concurrence between expert opinion and the Evidence Review Group. In this appraisal there was uncertainty because of the protocol design in the TAnDEM study offering a crossover to treatment for those on placebo and because of potential variability in randomisation leading to bias. Dr Cole pointed out that bias could occur in other studies to which Professor Home agreed. Dr Adam also agreed that this added to the uncertainty of the data. For the appellant, Ms Williams suggested that a crossover design is best practice. Mr Lewis added that there was concern that the committee accepted the median data but then ignored the outcome.

42. In considering this appeal point, the panel noted that the committee did not attempt a limited meta-analysis with the studies and assessed the data in tandem with opinion from the clinical experts. The panel considered that the committee were informed of the differences in the patient population between the 2 studies and that this did not materially affect the conclusions of the study relating to the EOL criteria as this was dictated by the lack of statistically significant increase in survival. Point 2.4 was dismissed.

Conclusion

43. The Appeal Panel therefore upholds the appeal on the grounds that the Institute has failed to act fairly in relation to point 1.1 and has formulated guidance which cannot be reasonably justified in the light of the evidence submitted in relation to points 2.1 and 2.3. The appeal is dismissed on all other grounds.

44. The appraisal is remitted to the Appraisal committee who must now take all reasonable steps to acknowledge the comments made by the Panel. What form those steps take will be for the committee to decide, but the panel suggests that it would be advisable to consider the application of the EoL policy (and all of its criteria) de novo, and stresses the need for the appellant and other consultees to have an opportunity to comment during that reconsideration.

45. There is no possibility of further appeal against this decision of the Appeal Panel. However, this decision 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 this decision letter.