THE NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE
Health Technology Appraisal
Appeal Hearing

Advice on lapatinib for the treatment of women with previously treated advanced or metastatic breast cancer

Decision of the Panel

Introduction

1. An Appeal Panel was convened on 8th June 2009 to consider an appeal against the Institute's Final Appraisal Determination, to the NHS, on the use of lapatinib for the treatment of women with previously treated advanced or metastatic breast cancer.

2. The Appeal Panel consisted of Mr Jonathan Tross (chair of the Panel), Dr Margaret Helliwell (non-executive director of the Institute), Mr Peter Sanders (lay representative), Dr Peter Brock (industry representative), and Professor Robin Ferner (NHS representative).

3. The Panel considered appeals submitted by GlaxoSmithKline Limited.

4. In addition, the following individuals involved in the appraisal were present and available to answer questions from the Appeal Panel: Professor David Barnett (chair of the Appraisal Committee), Dr Carole Longson (Director, Centre for Health Technology Evaluation), Dr Louise Longworth, Ms Zoe Garrett, Mr Meindert Boysen, and Dr Nicholas Murray.

5. The Institute's legal advisor (Stephen Hocking, Beachcroft LLP) was also present.

6. 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.

7. There are three grounds on which an appeal can be lodged:
   - The Institute has failed to act fairly and in accordance with its published procedures as set out in the Institute's Guide to the Technology Appraisal Process;
   - The Institute has prepared guidance that is perverse in light of the evidence submitted;
   - The Institute has exceeded its legal powers.

8. The Chair of the Appeals Committee (initially Mr Mark Taylor, subsequently Dr Maggie Helliwell), in preliminary correspondence, had confirmed that the

appellants had potentially valid grounds of appeal as follows: GlaxoSmithKline Limited: grounds 1 and 2.

Appeal by GlaxoSmithKline Limited
Appeal Ground 1: The Institute has failed to act fairly and in accordance with its procedures

Point 1.1 The Appraisal Committee's refusal to base its recommendations on a comparison with trastuzumab (a standard treatment for advanced or metastatic breast cancer) is contrary to NICE's procedures

9. Dr Dominy Browning, for GlaxoSmithKline, stated that the Final Appraisal Determination was not based on a comparison with the treatment most widely used in this setting, namely trastuzumab, and failed to take into account a key component of the NICE Guideline Development Group recommendations, which she argued were to continue trastuzumab in patients with metastatic breast cancer where there was progression of metastatic tumours in the central nervous system.

10. Professor David Barnett explained that the proportion of clinicians using trastuzumab in this situation differed considerably from one region to another. He accepted, however, that it was used in this situation. The Appraisal Committee understood that trastuzumab was not licensed in this indication, but that did not prevent the Appraisal Committee from considering trastuzumab as a comparator, and the Committee had in fact considered it.

11. Dr Longson directed the Appeal Panel's attention to paragraph 4.3 of the Final Appraisal Determination, where this consideration was stated explicitly.

12. Dr Longworth explained to the Appeal Panel that the data for trastuzumab had been included in an incremental analysis of cost-effectiveness, and this was the standard approach to such decision problems.

13. Dr Browning accepted that trastuzumab had initially been included as a comparator, but emphasized that it had subsequently been eliminated from the analysis on the grounds that it was not cost-effective.

14. Dr Alison Jones, appearing as a clinical expert on behalf of the Appellants, expressed the view that trastuzumab combined with a taxane now represented the standard of care for women with metastatic or locally advanced breast cancer. This was recommended by her local cancer treatment guideline group. However, in response to questioning she agreed that the local guideline group had made the recommendation without information on the cost-effectiveness of this regimen.

15. Professor Barnett explained that the tests of an appropriate comparator were: was it used in clinical practice? Was there a body of information to support that use? And was it clinically and cost-effective?

16. Dr Longson emphasized that incremental cost-effectiveness analysis was the correct way of analyzing the data, and the Appraisal Committee had to examine how the technology was being applied in the NHS.

17. The Appeal Panel concluded that trastuzumab was an appropriate comparator to consider. Although the degree to which it was in use within the NHS in this context was uncertain, it clearly was in use to a material degree. The Panel felt that the use amounted to "routine UK care" referred to in paragraph 2.2.3.1 of the 2004 Methods Guide. That paragraph describes the content required in a scope. It may be open to the Institute to define what it considers to be "routine UK care" more specifically in each scope. However in this case the scope referred to "appropriate chemotherapy regimens in standard practice in England and Wales" which did not seem to the Panel to take the matter any further. Given that trastuzumab was in use, the panel was sceptical that it would have been permissible for the committee to have excluded it from consideration altogether purely on the grounds that it is not cost-effective. First, although it might be reasonable to suppose that it is not cost-effective in this use, no formal technology appraisal had been conducted to establish that. Secondly, if a treatment is in routine use, it is not obvious that it may be excluded as a comparator on the grounds of its own cost-effectiveness.

18. However, it was clear from the Final Appraisal Determination and the Committee's evidence that trastuzumab had indeed been considered as a comparator. Provided they had acted fairly, and consistently with published procedures, it was for the Committee to decide in what way a product should be assessed against a comparator. The Appraisal Committee had been fair and consistent with published procedure in using an incremental cost-effectiveness analysis to determine whether the clinical benefits offered by lapatinib were cost-effective for the NHS. The panel did not agree that it was correct for Dr Browning to argue that this amounted to "excluding" trastuzumab from the analysis. It could be argued that the "final" comparison was with a treatment other than trastuzumab, but that is how an incremental cost-effectiveness analysis operates. Trastuzumab was considered in the overall analysis, but it did not form part of the final comparison because it was much less cost-effective than some other treatments in the comparison.

19. The Appeal Panel therefore dismissed the appeal on this point.

Point 1.2 The procedure for the appraisal of lapatinib should have been modified to reflect the change in approach resulting from the new

supplementary advice from NICE in relation to the appraisal of treatments which may extend the life of patients with a short life expectancy

20. The Institute adopted the supplementary advice on End of Life treatments ("The Supplementary Advice") in its final version in January 2009. Although the Appraisal Committee had essentially completed its appraisal of lapatinib by the time the new advice was adopted, lapatinib was considered in the context of the Supplementary Advice. GlaxoSmithKline complained that they had not been asked to make a specific submission to the Appraisal Committee to address the question of whether lapatinib should benefit from this new policy. Dr Browning explained that the Company did not know precisely what question the Appraisal Committee was considering, and could not fully contribute. They had not been invited to submit data. They did submit some data in the hope that it would be considered, but had not had the chance to do so in a properly structured and fair way.

21. Mr Boysen stated that the new information containing a subgroup analysis had arrived from the Company the day before the final meeting of the Appraisal Committee.

22. Dr Longson explained that the Appraisal Committee had adopted the Final Appraisal Determination in November 2008, after the second Appraisal Consultation Document and the second round of consultations. At that time, a draft policy on End of Life medicines had been released for consultation but had not been adopted as Institute policy. The Guidance Executive, knowing that the Supplementary Advice was about to be issued, had asked the Appraisal Committee to reconsider the Final Appraisal Determination in the context of the new policy. The Appraisal Committee had not expected to reconsider this appraisal, or to receive further information after the November 2008 meeting. The Appraisal Committee had seen the data that were relevant to deciding whether the Supplementary Advice criteria applied, and decided, on the basis of those data, that the criteria were not met.

23. Dr Longson stated that the draft of the Supplementary Advice had not specified how long 'significant' survival represented, while the final version had specifically stated that survival benefit should be "normally of at least an additional 3 months, compared to current NHS treatment." Otherwise the draft policy and the Supplementary Advice were very similar.

24. Mr Simon Jose, for GlaxoSmithKline, acknowledged that the sub-group data that the Company had used to support its case on the survival benefit of lapatinib had been submitted late in the process, but noted that there was no formal mechanism to allow the Company to contribute to the debate on whether lapatinib met the criteria for recommendation under the Supplementary Advice. They had done the best they could in the circumstances.

25. Dr Adela Williams, on behalf of GlaxoSmithKline, indicated that the Company should not have had to "guess" what was expected under new rules. In any event, they had had insufficient time to prepare a case fully.

26. The Appeal Panel did not accept that GlaxoSmithKline had been required to "guess" at the new criteria. These were published in early January. The policy as adopted was very close to the policy consulted on. GlaxoSmithKline would have had a good idea what the new policy would be during the consultation period, and would have known exactly what the new policy was from publication at the beginning of January. The Appeal Panel considered that the Company was sufficiently aware of the new policy.

27. However, it was accepted by both sides that GlaxoSmithKline had not been invited to make a submission regarding the application of that policy to lapatinib.

28. It might have been reasonable for the Institute not to apply the new policy to lapatinib at all, on the basis that the Final Appraisal Determination had been finalised before the policy was adopted. They should not be criticised for having in fact taken a more generous approach. However, having decided to apply the policy, the policy had to be applied fairly. That would ordinarily require the manufacturer to have an opportunity to make a submission going to the application of the policy. That opportunity would usually arise in the ordinary course of an appraisal. Where, as in this case, a policy was introduced that the Institute asked the Appraisal Committee to consider after all ordinary opportunities for consultation were past, the manufacturer should have been given a opportunity to make a separate submission. The opportunity had not been given at all here. That was unfair.

29. .The Appeal Panel noted that the Company had made a submission, but felt this did not correct the unfairness. The reasons were the limited time allowed for preparation of that submission, the considerable confusion over whether or not it would be considered, and the very limited time available for the Committee to have considered the submission. Taken together, these three factors raised sufficient doubt in the Panel's mind as to whether the submission made was the Company's "best case", and whether it was fairly considered.

30. In the light of the submission actually made, the Appeal Panel also considered whether this was the rare case where it could be sure that, if a fair process had been followed, the outcome would still have been the same. The Appeal Panel accepted the Appraisal Committee's evidence that, insofar as the Company had made a submission and the Committee had reviewed it, the survival advantage offered by lapatinib fell some way short of satisfying the criteria of the Supplementary Advice, and it was not easy to see how the Company could overcome that issue. However the Panel concluded that it could not be sure that the unfairness had made no difference. While it might be considered unlikely that the Company could improve on the submission that it had made, it was not

impossible. Even if the submission could not be improved, the Committee should be required to reconsider the issue in the light of a correct understanding of the Supplementary Advice (see point 1.3 below)

31. The Appeal Panel decided it could not exclude the possibility that, if the Company had been given clear directions and adequate opportunity to engage in the process, and the Appraisal Committee had had more time to consider the Company's submissions, then the Appraisal Committee might have reached a different conclusion. Whether or not it does so on reconsideration is entirely a matter for the Committee.

32. The Appeal Panel therefore upheld the appeal on this point.

Point 1.3 The Appraisal Committee's application of NICE's Supplementary Advice in relation to the appraisal of treatments which may extend the life of patients with a short life expectancy was overly restrictive and unfair

33. Dr Bu Siakpere, for GlaxoSmithKline, in arguing that the Appraisal Committee had been over-restrictive in its interpretation of the guidance that increased survival should 'normally' exceed three months, expressed the view that it was crucial to take into account that lapatinib increased survival by two months on average in the entire group, who otherwise had a life-expectancy of fifteen months; which was proportionately the same as an increase of three months for a patient with a life expectancy of 24 months, (the "proportionality argument ") and in the subgroup of women who had received less intensive prior treatment, it increased survival by an average of seven months (the "subgroup argument"). The trial had been concluded early on the advice of the independent data monitoring committee, so the true overall survival would in fact have been higher. Furthermore these data could not now be improved on as it would be unethical to conduct a similar trial in future

34. Professor Barnett accepted that, for the individual woman with metastatic or advanced breast cancer, any extension of life could be considered important and worthwhile; but that the Appraisal Committee had to consider what was reasonable. The Committee did not consider that the proportionality argument was what the Supplementary Advice had intended. It was most straightforward and logical to establish whether a three-month survival advantage existed for the average patient regardless of life expectancy at the time of commencing treatment. The subgroup argument did not help when applied to the patient population as a whole, in that if there were patients in whom life extension was above average, it followed that for the remainder of patients life extension was below average. Overall the argument was not moved forward. The Appraisal Committee was aware that the basic trial results did not provide a robust estimate of the overall survival. They considered the problem of early termination of the trial, cross-over, extrapolation of the data, and the subgroup analysis. Taken together, the Appraisal Committee concluded that the overall survival was

improved by approximately two months on average, which was less than the three months required by the Supplementary Advice.

35. Dr Siakpere reiterated that the average figure referred to patients who had been very heavily pretreated before receiving lapatinib. The subgroup suggested that overall benefit might be greater than the trial data showed, bearing in mind that the trial was terminated early.

36. Dr Browning argued that the criterion of three months' survival advantage had been very rigidly applied, and that there was an important and identifiable subgroup of patients in whom the advantage was greater. Admittedly, that subgroup had not been pre-specified, and was small.

37. Dr Williams assured the Appeal Panel that no pre-specified analyses had been withheld from the Appraisal Committee.

38. Professor Barnett confirmed that the Appraisal Committee had considered the subgroup analysis, but there were concerns. The analysis showed that a small group (66 of 399) had a more prolonged increase in overall survival of about seven months. That must mean that the remaining patients had a shorter than average increase in overall survival.

39. Mr Jose recognized that the subgroup analysis had been undertaken post hoc, but it was clinically relevant.

40. Dr Williams explained that the intention was that the Appraisal Committee should be persuaded to consider the benefits in the whole group, strengthened by the data from the subgroup; not that the Appraisal Committee should consider allowing lapatinib for the subgroup of women who had received only a small number of pretreatments.

41. Prof Barnett repeated that to suggest, as Dr Siakpere had done, that one might apply a sliding scale to the increase in survival in proportion to the expected overall survival, was not right.

42. Mr Hocking asked Professor Barnett what he understood by 'normally at least three months'.

43. Professor Barnett replied that a mean of three months extension was the minimum requirement.

44. As regards the proportionality argument, the Appeal Panel found that the Committee's approach was correct. The amount of life extension required by the Supplementary Policy is not to be varied relative to the overall life expectancy of the patients in question. First, there is no sanction for this in the policy itself. Secondly, it would have the result of placing an ever increasing value on shorter

and shorter periods of extension, depending on how close to a patient's probable death the extension was obtained. Although, as Professor Barnett had himself rightly observed, it was very understandable that a patient and their family and friends might argue for this, it was not a logical position from a broader NHS perspective.

45. As regards the subgroup argument, in light of the Company's position that all patients should be considered alike in terms of the Supplementary Advice, the Appeal Panel again found that the Committee's approach was correct. Notwithstanding the acknowledged limitations in the data, the possible greater benefit in the subgroup did not lead to a conclusion that the overall survival benefit for all patients was more than three months.

46. However, the Appeal Panel did not accept the Committee's approach to the meaning of the requirement that life extension should be 'normally of at least an additional 3 months, compared to current NHS treatment.' The Appeal Panel concluded that the Appraisal Committee was not correct to have read that as requiring a minimum of an average of three months in absolutely every case. It would, in compelling circumstances, be open to the Appraisal Committee to accept an average value of less than three months.

47. In deciding what constitutes a compelling circumstance, it would have to be borne in mind first that all patients to whom the Supplementary Advice might be applied are in what Professor Barnett correctly described as a parlous situation. All will be facing the end of life, with all that that entails. That is not a "compelling circumstance" in itself. Something over and above the features common to all or many end of life cases would be required before the Committee could justify accepting a mean benefit of less than three months. The Supplementary Advice is itself already a policy dealing with a departure from normal policy in exceptional circumstances. Clear and strong justification would be required for an exceptional departure from what is already an exceptional policy, particularly if the departure is more than nominal. It might be that such compelling circumstances would almost never be present. Nonetheless, the Committee was mistaken to have thought that it had no discretion at all to apply the Supplementary Advice where the mean survival benefit is shown to be less than three months.

48. The Appeal Panel therefore allowed the appeal on this point in so far as the Committee should consider whether, exceptionally, a life extension of less than three months might be acceptable in this case.

49. The Appeal Panel dismissed the appeal as it related to the proportionality argument or the subgroup argument.

Point 1.5 The failure to consider fully the additional evidence provided by GlaxoSmithKline in response to the publication of supplementary advice from NICE regarding the appraisal of end of life treatments is unfair

50. The discussion of this appeal point had been encompassed by the discussion of point 1.2 above, which had been upheld.

51. The Appeal Panel therefore made no additional finding on this point.

Ground 2 Appeal points

Point 1.3 The Appraisal Committee's application of NICE's Supplementary Advice in relation to the appraisal of treatments which may extend the life of patients with a short life expectancy was overly restrictive and unfair

52. During discussion of the Ground 1 Appeal under this heading, the Appeal Panel had explored with the Company and the Appraisal Committee the meaning of the phrase 'normally of at least an additional 3 months, compared to current NHS treatment' in relation to the extent to which life was extended.

53. As discussed at point 1.3 above, the Appeal Panel found that the Committee had correctly rejected a proportionate approach, and the argument that greater benefit should be attributed to all patients in the light of the subgroup analysis provided. It was not necessary to make a finding in respect of perversity on the question of proportionality, as that was an issue of the meaning of the Supplementary Advice, and not a judgement reached under that advice.

54. On the subgroup analysis, the Panel found that it was reasonable for the Committee to have concluded that this did not mean that the true benefit of treatment for all patients was greater than the 1.9 months shown in the trial data. The committee had acknowledged the limitations of the trial data and the reason for early termination of the trial. However it had observed that the subgroup was small, and that there were inherent difficulties in arguing for greater overall average benefit from the existence of a subgroup which demonstrated greater benefit. The reasoning and approach expressed by the Committee were tenable and not perverse.

55. The Committee had not considered whether or not it should apply the Supplementary Advice notwithstanding that the benefit shown was less than three months. The panel therefore makes no finding on perversity as it would relate to that issue.

56. The Appeal Panel therefore dismissed the appeal on this point.

Point 1.4 The Appraisal Committee's rejection of the subgroup of patients who had received fewer than three prior treatment regimens lacks transparency

57. The Appeal Panel considered this matter when it was discussed under Ground 1.

58. The Appeal Panel noted that the Final Appraisal Determination at paragraph 4.21 had 'considered that the data analysis could, at this stage, generate a useful hypothesis for future research but it could not materially affect the conclusion that lapatinib should only be used in the context of clinical trials.'

59. Professor Barnett had explained the reasoning behind this view, that the subgroup was small, and not pre-specified, and Dr Siakpere had accepted that the analysis had not been pre-specified, and had involved only a minority of the patients recruited. Dr Williams had explained that the Company had sought to introduce the subgroup analysis so as to strengthen the case for the whole group, and not so that it was considered independently.

60. The Appeal Panel had already decided that it could not exclude the possibility that, if the Company had been given clear directions and adequate opportunity to engage in the process, and the Appraisal Committee had had more time to consider the Company's submissions, then the Appraisal Committee might (but, equally, might not) have reached a different conclusion. This was unfair. As a reconsideration must now take place , the Appeal Panel considers that it would be inappropriate to make a further finding on this point in the context of perversity.

Point 2.1 The refusal of the Appraisal Committee to make recommendations based on a comparison with trastuzumab has the effect of promoting use of a product which is unlicensed for this indication and less cost-effective than lapatinib

61. Dr Browning told the Appeal Panel that the guidance in the Final Appraisal Determination had not been based on a comparison between lapatinib and trastuzumab. The perverse result was that the guideline, by failing to recommend lapatinib, implicitly condoned the use of trastuzumab, even though the treatment was unlicensed, more expensive, and less effective.

62. Professor Barnett maintained that incremental analysis was the appropriate way to examine this question. He accepted that, while trastuzumab was licensed, it was not licensed for this indication. That was not relevant to the Appraisal Committee's analysis of the cost-effectiveness of lapatinib.

63. Dr Murray confirmed that the off-label usage of trastuzumab had emerged because trastuzumab was available. There had been no analysis of its cost-effectiveness in this indication. Therefore to accept that it should be the base case,

rather than one of the comparators in an incremental analysis, would be contrary to the whole NICE process of establishing the costs and benefits of treatments.

64. Dr Longworth told the Appraisal Committee that trastuzumab had been assessed at the same time as the other treatments in the incremental analysis. The method used had been consistent with the *Guide to the methods of technology appraisal.* The 'blended approach,' which the Company had suggested, masked differences in cost-effectiveness between comparators.

65. Dr Longson reminded the Appeal Panel that trastuzumab had been accepted by the Appraisal Committee as a comparator.

66. Dr Browning stated GlaxoSmithKline acknowledged that trastuzumab had been used as a comparator, but the analysis used did not reflect the way that trastuzumab was given in clinical practice, while the blended comparator did, at least at the time that the manufacturer's case was submitted.

67. Professor Barnett reported that the Appraisal Committee had agreed that when lapatinib was compared with trastuzumab, lapatinib was 'highly' relatively cost-effective.

68. Mr Jose contended that there was significant use of trastuzumab in this unlicensed indication, and that therefore the failure to recommend lapatinib, which cost less and was likely to be more effective against brain metastases, was perverse.

69. The Appeal Panel decided that the Appraisal Committee was reasonable to use incremental analysis, and to include trastuzumab in that analysis in the way it had. The Appeal Panel noted the use of trastuzumab by the NHS. There was evidence to suggest that use might not be cost-effective and that replacement of trastuzumab with lapatinib in some situations might result in an improvement in cost-effectiveness. However, this was a Single Technology Appraisal of lapatinib, not an appraisal of trastuzumab. It would not be possible in this appraisal, nor in this appeal, to make any recommendation on the use of trastuzumab. Nor was it possible to express any definitive views on the clinical and cost-effectiveness of that use. It was not correct to describe any recommendation relating to lapatinib as amounting to a promotion of trastuzmab. Furthermore, although the Panel understood the argument that substituted use of lapatinib in some situations might be a relatively more cost-effective use of resources than current practice, it did not follow that it would reach conventionally accepted absolute levels of cost-effectiveness. The Committee had reasonably concluded that it did not reach those levels. The Panel was doubtful whether it would have been open to the Committee in a Single Technology Appraisal to make a recommendation based only on relative improvements in cost-effectiveness against one comparator, where the technology appraised was not cost-effective when set against other comparators. In any case, the Panel did not feel that the Committee could be regarded as having acted perversely in allowing its finding on cost-effectiveness

using the incremental approach to guide its recommendation in relation to lapatinib.

70. The Appeal Panel therefore dismissed the appeal on this point.

Point 2.2 The approach of the Appraisal Committee to the use of lapatinib in patients who have central nervous system metastases is inconsistent with that followed in the Clinical Guideline on breast cancer in relation to trastuzumab and creates a situation that is arbitrary and therefore perverse

71. Dr Jones explained that brain metastases occurred in 20% of patients with HER2-positive breast cancer. The recent guideline issued by the Institute recommended continuing trastuzumab treatment beyond progression in such patients.

72. Professor Barnett explained that the guideline actually recommended that 'For patients who are receiving treatment with trastuzumab for advanced breast cancer, discontinue treatment with trastuzumab at the time of disease progression outside the central nervous system. Do not discontinue trastuzumab if disease progression is within the central nervous system alone.' This recommendation was given because the Guideline Development Group considered that trastuzumab might still be suppressing disease outside the central nervous system, even if relapse had occurred within the central nervous system: trastuzumab was a large molecule and unlikely to cross the blood-brain barrier.

73. By contrast, Professor Barnett told the Appeal Panel, lapatinib represented a potentially important advance in treatment, because it was a small molecule and it was plausible to suppose that it might cross into the brain. Whether it did in fact reduce the incidence or progression of metastases within the central nervous system was not known. The European Medicines Evaluation Agency (EMEA) had asked for a further clinical trial to examine this question.

74. Dr Siakpere drew attention to the trial by Lin *et al* in which the effects of lapatinib had been examined in patients with brain metastases. This had shown that lapatinib was effective. She agreed that the authors had described the effects of lapatinib as 'modest;' that 7% of patients had responded to treatment; and that the authors had concluded that further studies were warranted.

75. Dr Jones described the treatment of patients with brain metastases. Usually they would be offered surgery or radiotherapy when metastases first appeared, but they would be treated with chemotherapy if metastases recurred.

76. Dr Murray had chaired the Committee responsible for producing the NICE guideline on the treatment of advanced breast cancer. He supported Professor Barnett's understanding of the guidance.

77. The Appeal Panel accepted that the guideline on the treatment of advanced breast cancer did not advocate trastuzumab for the treatment of brain metastases, but rather confirmed that development or progression of brain metastases was not of itself a reason to discontinue trastuzumab treatment. That was a logical conclusion and could not cast any doubt on whether the Appraisal Committee had reached a reasonable conclusion in this appraisal. The Committee had clearly been aware that it was plausible that lapatinib would enter the brain, and had felt that the evidence currently available supported further research to investigate the effect of lapatinib on metastatic tumours in the brain, but did not go so far that as to support a recommendation for use (other than in research). That was a reasonable position to take on the evidence.

78. The Appeal Panel therefore dismissed the appeal on this point.

Point 2.3 The Appraisal Committee's refusal to consider the use of lapatinib in patients with brain metastases was based on an error and is therefore perverse

79. Dr Siakpere emphasized that EMEA had asked that the Company study lapatinib's ability to prevent brain metastases, not to treat metastases after they had occurred, as stated in the Final Appraisal Determination.

80. Dr Williams stressed that the appeal related not simply to the wording of the Final Appraisal Determination, but also to the possibility that the Appraisal Committee had reached the wrong conclusion because they mistakenly believed that EMEA had requested a study in patients who already had metastatic disease of the central nervous system.

81. Professor Barnett assured the Appeal Panel that the Appraisal Committee was well aware of the recommendations of EMEA, and had not misled itself into believing that EMEA had requested a trial of lapatinib in patients who already had brain metastases. Section 4.5 of the Final Appraisal Determination clearly stated in part that 'The manufacturer will conduct a phase III randomised, controlled clinical study to evaluate the incidence of brain metastases as the site of relapse with a lapatinib-containing therapy compared with an appropriate trastuzumab-containing therapy as part of the conditional approval of marketing authorisation.' He agreed, however, that the wording of section 4.5 of the Final Appraisal Determination could have been misconstrued, and would be happy to remove any ambiguity.

82. The Appeal Panel decided that the Appraisal Committee had considered the question of treatment in patients with brain metastases in a reasonable way. The Appraisal Committee had clearly understood what study EMEA had requested, and this was reflected in the Final Appraisal Determination. The Final Appraisal Determination could however have been more clearly worded.

83. The Appeal Panel dismissed the appeal on this point, but observed that, as the guidance is to be reconsidered in any event, the opportunity should be taken to express the relevant paragraph of the guidance more clearly.

Point 2.4 The Appraisal Committee's recommendation that trials should be conducted to compare lapatinib in sub groups of patients that included all appropriate treatment comparisons is unethical and therefore perverse

84. Dr Siakpere explained that it was unethical to conduct any trial in this group of patients that did not include an agent targeted at the HER2 receptor. It was therefore now impossible to conduct any trial comparing lapatinib with, say, capecitabine monotherapy. Indeed such a trial had been halted early on ethical grounds.

85. Mr Jose commented that any 'gaps' in the evidence base could not be filled. The committee should have considered the existing evidence more favourably. Had it realised the 'gaps' could not be filled it would possibly have reached a different conclusion.

86. Professor Barnett maintained that recommendations for research contained in section 6 of a Final Appraisal Determination were not part of the guidance and ought not to be the subject of an appeal. The EMEA had called for further research and the Panel had been told that trials were under way or in preparation and so it could not be said that no further research of any kind was possible.

87. The Appeal Panel noted that the Institute's consistent position was that research recommendations are not part of its guidance to the NHS and cannot be appealed. However, in the context of a recommendation for use in research only, which was contained within the guidance itself, the assertion that there was no further research that could ethically be carried out was a potentially valid appeal point. The Company had been entitled to raise the issue.

88. The Panel did not accept the argument that, if there was no possibility of further research, such evidence as there was should be given additional weight. The Appraisal Committee had to accord the evidence the weight it merited.

89. In any event it was clear that the Committee had not been prescriptive as to the form that additional research might take, and it was also clear that there was additional research that was ethical, which was under way or in preparation, and which would provide more information regarding the decision problem. The Appeal Panel noted that it was in the interests of all concerned to undertake trials that provided secure evidence on primary outcomes, and that such research would contribute to the assessment of cost-effectiveness of treatments.

90. The Appeal Panel dismissed the appeal on this point. .

Conclusion and effect of the Appeal Panel's decision

91. The Appeal Panel upheld under Ground 1 appeal point 1.2, and Ground 1 appeal point 1.3 in part. It makes no finding under Ground 1 appeal point 1.5, and ground 2 appeal point 1.4. It dismisses the appeal on all other grounds.

92. .GlaxoSmithKline must now be asked to provide a submission on the question of whether and how lapatinib falls within the Supplementary Advice. They must be given a reasonable time to prepare that submission.

93. Although no appeal was received on this point, in the interests of even-handed treatment, the Panel recommends that the same opportunity should be given to the other consultees and commentators in this appraisal.

94. The Appraisal Committee must then review the Final Appraisal Determination after due consideration of the Company's submissions, and any submissions from consultees or commentators, and in the light of the guidance given in this decision as to the meaning of the Supplementary Advice.

95. The Appraisal Committee need not invite comments on or reconsider any other aspect of the Final Appraisal Determination.

96. The Panel wishes to stress that the outcome of this reconsideration is entirely a matter for the Appraisal Committee, and the Panel expresses no view as to what that outcome may be.

97. The Appeal Panel also welcomed Professor Barnett's suggestion that section 4.5 of the Final Appraisal Determination be reworded and this should be done.

98. There is no possibility of further appeal within the Institute against this decision of the Appeal Panel. However, the decision of the Appeal Panel and the Institute's decision to issue the Guidance may be challenged by an interested party through an application to the High Court for permission to apply for judicial review. Any such application must be made promptly and in any event within three months of this Decision.