NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Health Technology Appraisal

Second 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 17th August 2010 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 (vice-chair of the Institute), Mr Robert Osborne (lay representative), Dr Peter Brock (industry representative), and Professor Robin Ferner (NHS representative).

3. None of the members of the Appeal Panel had any competing interest to declare, although Mr Tross, Dr Helliwell, Dr Brock, and Professor Ferner recorded that they had heard the appeal against the first Final Appraisal Determination issued for this drug.

4. The Panel considered appeals submitted by GlaxoSmithKline Limited.

5. In addition, the following individuals involved in the appraisal were present and available to answer questions from the Appeal Panel: Professor Phillip Home (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.

6. Professor Home declared a non-personal, non-specific interest, as his University and NHS Trust received financial support from the Appellant; and Dr Nicholas Murray declared an interest as he had previously been an investigator in a clinical trial assessing the efficacy of lapatinib.

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

8. 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.

9. There are three grounds on which an appeal can be lodged:
    i. 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;
    ii. The Institute has prepared guidance that is perverse in light of the evidence submitted;
    iii. The Institute has exceeded its legal powers.

10. The Chair of the Appeal Committee (Dr Maggie Helliwell), in preliminary correspondence, had confirmed that the appellant GlaxoSmithKline Limited had potentially valid grounds of appeal as follows: Grounds 1 and 2.

11. Lapatinib is an orally active tyrosine kinase inhibitor. It has a marketing authorization for the treatment, in combination with capecitabine, of patients with advanced or metastatic breast cancer whose tumours over-express ErbB2 (HER2), and who have progressive disease after therapy which must include anthracyclines, taxanes, and therapy with trastuzumab in the metastatic setting.

12. Both the appellant and the Committee made opening statements, summarising their respective positions. The content of those statements is discussed against the relevant appeal points below.

Appeal by GlaxoSmithKline Limited

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

13. The substantial parts of the Appeal under Ground 1 related to alleged unfairness arising out of correspondence between the Guidance Executive and the Chair of the Appraisal Committee after the Appraisal Committee had provided a draft of the Final Appraisal Determination to the Guidance Executive.

14. Dr Adela Williams, for GlaxoSmithKline, explained that the Appellant considered the letter from the Guidance Executive to the Chair of the Appraisal Committee to represent a specific direction to the Appraisal Committee on how to consider the appraisal. It represented a supplement to the published guidance on the appraisal process, and the Company could expect that the Appraisal Committee would consider and act on the direction in the Guidance Executive's letter. While only the Final Appraisal Determination is the subject of appeal, the letter from Professor Home in response to the Guidance Executive's letter confirmed and amplified the thought processes and discussion that had taken place in the Appraisal Committee during the formulation of the Final Appraisal Determination, and thus constituted a proper subject for appeal.

15. Dr Longson, for the Institute, told the Appeal Panel that the Guidance Executive was a formally constituted body that held powers delegated from the Institute's Board. These powers were, in essence, to ensure that any guidance finally issued by the Institute should have been formulated in accordance with the processes and methods laid down in the Guide to Methods of Technology Appraisal.

16. Dr Longson was not aware of a previous instance in which the Guidance Executive had written formally to the Chair of the Appraisal Committee, but on this occasion, the Executive was anxious to ensure that the Appraisal Committee had considered the extent of the current use of trastuzumab in the absence of a determination in favour of lapatinib. The issue had already been aired. The Guidance Executive had not considered the letter a direction and did not believe it had power to issue direction to an Appraisal Committee. After it had received Professor Home's reply, the Guidance Executive was content that the Appraisal Committee had discharged its duties.

17. The Panel considered the letter, the reply, and also the Guidance Executive's terms of reference available on the Institute's website. The Panel concluded that the Guidance Executive is right to say that it has no power to instruct the Appraisal Committee, and therefore the letter cannot be read as such an instruction. Further, although the exchange of letters had rightly been made public after the event, they were internal communications between two aspects of the Institute. They were not addressed to or intended to be relied on by GlaxoSmithKline. Even if the letter had been an instruction, this would have been a matter between the Guidance Executive and the Committee. The Panel did not accept that that would have founded procedural expectations on which GlaxoSmithKline were entitled to rely.

18. However the Panel did accept that the reply from Professor Home was evidence as to the Committee's state of mind in formulating the guidance. If that state of mind revealed an appealable error, then this was a matter on which GlaxoSmithKline were entitled to rely.

Point 1a The final paragraph of Professor Home's letter suggests that the Appraisal Committee has misunderstood the treatment pathway for use of lapatinib

19. Dr Bu Siakpere, for GlaxoSmithKline, stated that Professor Home, in his reply to the Guidance Executive, indicated that a decision to recommend lapatinib would involve ‘a drug used out of licensed indication and against NICE guidelines.’ This was untrue, as lapatinib was licensed, and the Company had been denied a fair opportunity to clarify what had been misunderstood.

20. Professor Home, for the Appraisal Committee, put forward the view that all understood that the relevant phrase in his letter referred not to lapatinib, but to trastuzumab. The Appraisal Committee knew that lapatinib was licensed for the use described.

21. The Appeal Panel noted that the Final Appraisal Determination of May 2010 at paragraph 2.1 stated explicitly that ‘Lapatinib, in combination with capecitabine, has a marketing authorisation for the treatment of patients with advanced or metastatic breast cancer whose tumours over-express ErbB2 (HER2).’ The Panel accepted that the only reasonable interpretation of the phrase in question was that it referred to taking account of the use of trastuzumab, as Professor Home had clearly intended, not lapatinib. The Panel could not find any evidence that Professor Home had misunderstood the treatment pathway for the use of Lapatinib.

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

Point 1b No stated basis for concluding that replacing trastuzumab with lapatinib would be difficult to implement

23. Professor Home had written of the Committee’s concern that it would be difficult to ensure the implementation of any recommendation that lapatinib should replace trastuzumab in a defined population of women progressing on the drug.

24. Dr Siakpere told the Appeal Panel that there was no evidence in the Final Appraisal Determination to support the assertion that there would

be difficulties in implementation. The process had been unfair because the Company had been denied the opportunity to understand the difficulty in implementation or to respond to the concerns.

25. Professor Home responded that paragraphs 4.1 to 4.4 of the Final Appraisal Determination dealt with the difficulties of defining which subgroup at present received trastuzumab. In any event, the advice of the Final Appraisal Determination to use lapatinib treatment only in the setting of clinical trials was based on concerns over effectiveness and cost-effectiveness, and not over any perceived difficulties in implementation of a recommendation to use more widely.

26. Dr Longson said that the Appraisal Committee was obliged to consider both clinical effectiveness and cost-effectiveness.

27. Professor Home reminded the Appeal Panel that GlaxoSmithKline had already noted the difficulties of defining subgroups of women in whom treatment would be beneficial (at page 23 of the Response to consultee, commentator and public comments on the Appraisal Consultation Document, 2009), where they themselves had said *For patients who are more likely to be continued on a trastuzumab regimen beyond progression, lapatinib plus capecitiabine is a clinically and cost effective alternative…In its original submission, GSK presented an argument that the subset of patients that is more likely to receive treatment with trastuzumab beyond progression includes* [various groups…] *However we acknowledge such an approach presents a number of challenges:* [including] ***the difficulty in creating clear and unambiguous clinical criteria with which to define such a subgroup*** (emphasis supplied).

28. The Final Appraisal Determination recommended that these issues be resolved through research.

29. Professor David Cameron, for GlaxoSmithKline, stated that teams of clinicians could define patients as suitable for trastuzumab or lapatinib on a patient specific or local policy basis.

30. Dr Williams agreed, in response to a question from the Appeal Panel, that the Appraisal Committee was the appropriate body to provide guidance to the NHS on these matters, but noted that at present, multidisciplinary teams were in fact making decisions on whether patients should have trastuzumab.

31. The Appeal Panel considered that the difficulties of defining a subgroup of women who would benefit from lapatinib treatment had been discussed previously, and that GlaxoSmithKline had entered into the debate and had indeed accepted that there were difficulties. The issue was not a new one. There had been no new examination of the sub-group problem after the Guidance Executive letter, there were no new data, and so there had been no unfairness.

32. Furthermore, Professor Home's evidence was that even if it had been possible to define a subgroup sufficiently rigorously, recommended use would still have been restricted to clinical trials, due to concerns over clinical and cost-effectiveness, even in a hypothetically closely defined 'trastuzumab' subgroup. The issue had not, therefore, borne on the final recommendation.

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

Point 2 The effect of the direction from the Guidance Executive was that the committee should have considered the cost-effectiveness of lapatinib vs trastuzumab in the context of the lapatinib patient access scheme

34. Dr Siakpere explained to the Appeal Panel that the Company's July 2008 submission showed a saving of £2000–£3000 for every patient

who had lapatinib under the patient access scheme in place of trastuzumab. There was no indication in the Final Appraisal Determination that the Appraisal Committee had considered these cost savings.

35. Professor Home told the Appeal Panel that the patient access scheme had been in place prior to the first appeal on lapatinib. The Appraisal Committee had always been aware of the impact of the patient access scheme on the incremental cost-effectiveness ratio as calculated, and had taken this into account. The Appraisal Committee had also considered the 'blended comparator' put forward by GlaxoSmithKline, but had decided to use an incremental analysis. The concept of incremental analysis had been discussed in detail at the previous appeal, and the Appeal Panel had held at that time that it was reasonable for the Appraisal Committee to adopt that analysis.

36. Dr Williams reminded the Panel that, in a previous appeal on azacitidine, the Appeal Panel had in fact recommended that use of a blended comparator.

37. Dr Louise Longworth, for the Appraisal Committee, told the Appeal Panel that a blended comparator was unconventional. The incremental analysis that the Appraisal Committee had chosen allowed the examination of all the relevant comparators.

38. Dr Longson stated that the Guidance Executive had received technical advice that a blended comparator is inappropriate in examining cost-effectiveness.

39. Dr Dominy Browning, for GlaxoSmithKline, reiterated that there would be 'considerable savings' if lapatinib under the patient access scheme were used in place of trastuzumab as currently given to women with progressive disease.

40. Professor Home agreed with Dr Browning that lapatinib under the patient access scheme cost less than trastuzumab. However, there still remained a great deal of uncertainty over the relative clinical effectiveness of the two agents. That could materially influence the outcome of a comparison. In any event, the Appraisal Committee had chosen to use an incremental analysis.

41. The Appraisal Committee had been asked by the Guidance Executive to assure itself that its analyses and computations were appropriate, and it had met and had been able to assure itself that it had acted correctly.

42. The Appeal Panel accepted that the Appraisal Committee had acted fairly in choosing the incremental analysis, and that the matter had been extensively debated. The Company had been able to put forward its views at the appraisal consultation stage, and at the previous appeal. The Appraisal Committee's position had not changed since the last Appeal.

43. The facts of the azacitidine appraisal referred to by Dr Williams had been rather different from those in this case. In that appeal, the rejected comparator was not shown to be cost-ineffective, but had rather been rejected for reasons which the Appeal Panel found unclear and/or unsatisfactory. Here the Appeal Panel has already stated (and restates in this decision) that the reason for not carrying trastuzumab into the final comparison is clear, and is one which a reasonable committee might rely on. In any event, in the azacitidine appeal the Appeal Panel had left it open to the Appraisal Committee to continue to rely on only Best Supportive Care as a comparator after reconsidering its guidance for azacitidine, provided it gave clear and detailed reasons for doing so. It was not right to say that the Appeal Panel had required use of a blended comparator, although it had required consideration of a blended comparator. Here, however, the blended comparator had clearly been considered. Therefore although of interest the Appeal

Panel did not consider that its previous decision in the azacitidine appeal cast doubt on the approach taken in this appeal.

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

Point 3 No explanation is given for the concern that a positive recommendation would potentially displace capecitabine and vinorelbine and this appears to be a matter for implementation not clinical or cost-effectiveness

45. Dr Siakpere advised the Appeal Panel that GlaxoSmithKline had become aware for the first time of concerns over implementation, rather than guidance, on reading Professor Home's letter. There was no explanation for the concern that lapatinib would displace capecitabine and vinorelbine. If GlaxoSmithKline had been aware of the Appraisal Committee's thoughts on this matter, the company would have been able, in concert with the Institute, to formulate guidance that was capable of being implemented. The Company had been denied this opportunity.

46. Professor Home explained that it was not relevant to consider advice on implementing a recommendation that the Appraisal Committee had not made. The fact that the Committee had adopted an incremental analysis made it superfluous to consider how lapatinib might be used in place of trastuzumab, as neither was cost-effective in the current setting. The Committee had not been convinced that use of lapatinib was cost-effective even in people progressing or who would have progressed on trastuzumab. Concern about displacement, although real, was not the reason not to recommend use.

47. Dr Siakpere advanced the view that the Appraisal Committee had made a number of assumptions on the matter of 'drift,' that is, the tendency to displace capecitabine or vinorelbine treatment with lapatinib treatment. In fairness, GlaxoSmithKline should have been shown those assumptions.

48. Professor Home stated that these matters were part of the discussion of the previous Final Appraisal Determination and subsequent appeal. The Appraisal Committee's decision flowed from the use of incremental analysis.

49. Dr Siakpere characterized the incremental analysis with which the Appraisal Committee had approached the decision problem for lapatinib as 'a very formal health economics approach.' There would have been advantages for the NHS in pragmatic guidance to switch from trastuzumab to lapatinib after disease progression.

50. The Appeal Panel considered the submissions under this point, but noted that, in light of its acceptance of the validity of the incremental analysis and the Appraisal Committee's demonstration that neither trastuzumab nor lapatinib was cost-effective in that analysis, the Committee had not relied on concerns about 'drift' in formulating its recommendation, and so the Committee had acted fairly.

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

Point 1.4 Even if substitution occurs this should be balanced against cost savings associated with replacement of trastuzumab

52. After discussion between legal representatives, it was agreed that the Appeal Panel should consider this point under both Ground 1 and Ground 2.

53. Dr Browning expressed the Company's view that it would be cost-effective for lapatinib to replace trastuzumab in those patients with progressive disease who currently receive trastuzumab. There would be savings even if lapatinib were additionally given to up as many as half of those patients who currently receive capecitabine or vinorelbine. That is, the NHS would benefit even if 'drift' were up to 50%. The blended analysis had been disregarded by the Appraisal Committee,

but should have been reconsidered in the light of the Guidance Executive's letter.

54. Professor Home assured the Appeal Panel that he considered he had received no instructions from the Guidance Executive, as opposed to a request to confirm all relevant issues had been considered, and the Appraisal Committee did not re-open the question of the blended comparator. This had been carefully considered in previous discussions. In particular, the Appeal Panel had previously held that it was open to the Appraisal Committee to use the incremental approach, as it had in fact done. The incremental analysis made the consideration of the costs and savings of displacement irrelevant, since neither trastuzumab nor lapatinib was cost-effective by that analysis. The question was the cost-effectiveness of lapatinib against capecitabine alone, not against a blend of actual current or possible future therapies. The Appraisal Committee had, however, assured themselves that they had adequately considered all relevant issues.

55. The Appeal Panel considered the submissions on this appeal point. It accepted that the incremental approach made a discussion of the displacement of trastuzumab by lapatinib irrelevant. It reminded itself and reaffirmed that it had in its previous decision accepted that the use of the incremental approach was fair and reasonable.

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

Appeal under Ground 2

Point 4 Even if substitution occurs this should be balanced against cost savings associated with replacement of trastuzumab

57. Dr Browning asked the Appeal Panel to consider that, while the Guidance Executive's letter was not an instruction to the Appraisal Committee, it did raise an important point regarding the potential savings to the NHS if lapatinib were used in place of trastuzumab. As

had been stated, this would save substantial sums of money. The letter suggested that the Appraisal Committee explore this possibility, but it had not done so. It had not even considered the extent of displacement of capecitabine and vinorelbine by lapatinib.

58. Professor Home replied that the Appraisal Committee had been satisfied that it had all the information necessary to come to a decision on the problem before it. The Appraisal Committee did not require information on the displacement or on the cost-savings from substitution, because the incremental analysis made that information redundant.

59. The Appeal Panel examined whether the Appraisal Committee was unreasonable in considering that it required no information on substitution or displacement. Since the incremental analysis made it clear that neither trastuzumab nor lapatinib would be cost-effective against capecitabine, the Appeal Panel was satisfied that the Appraisal Committee's stance was one that was reasonably open to it.

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

Conclusion and effect of the Appeal Panel's decision

61. The Appeal Panel dismisses the appeal on all points under both Ground 1 and Ground 2.

62. However, the Panel makes the following observation. The Panel could readily understand the concern, which it felt was shared to a greater or lesser degree by all of the Appellant, the Guidance Executive, the Committee, and the Panel itself, that cost-ineffective use of NHS resources is occurring, and that, had lapatinib been recommended, it is possible (acknowledging always the Committee's doubts on this point) that overall cost-effectiveness would to a degree be improved.

63. The Panel does not in any way cast doubt on the conclusions above that incremental cost-effectiveness analysis is a reasonable approach, or that none of the issues raised amount to a valid appeal ground. It is mindful that this was a Single Technology Appraisal of lapatinib and not a Multiple Technology Appraisal including trastuzumab.

64. It notes that *Clinical Guideline CG81 Advanced breast cancer: full guideline* (03 March 2009) recommends 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.' The Institute has, therefore, discouraged cost-ineffective use of trastuzumab.

65. It also has in mind that the role of the Institute is to promote cost-effective use of resources, which is not the same as promoting marginally less cost-ineffective uses, and that the answer to unrecommended cost-ineffective use of one product is not necessarily positively to recommend cost-ineffective use of a different product.

66. Nevertheless, the Panel suggests that the issue of how the Institute should respond when a cost-ineffective use of NHS resources is identified, during an appraisal or otherwise, should be considered corporately by the Institute. Particular attention might be given to trastuzumab, and whether, by virtue of having been the first to market and not having been appraised in all indications, this product is now enjoying an unsatisfactory advantage over rivals.

67. In the course of the appeal, the company indicated that it is willing to contribute to such further consideration.

68. There is no possibility of further appeal against the decision of the Appeal Panel. However, this decision and NICE's decision to issue the

final guidance may be challenged by applying to the High Court for permission to apply for a judicial review. Any such application must be made within 3 months of publishing the final guidance.