NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

HEALTH TECHNOLOGY APPRAISAL

APPEAL HEARING

Advice on Erlotinib monotherapy for the maintenance treatment of advanced or metastatic non-small cell lung cancer.

Decision of the Panel

Introduction

1. An Appeal Panel was convened on 16 May 2011 to consider an appeal against the Institute's Final Appraisal Determination (FAD), to the NHS, on erlotinib for the maintenance treatment of advanced or metastatic non-small cell lung cancer.

2. The Appeal Panel consisted of Mr Jonathan Tross (Chair and non-executive director of NICE), Ms Jenny Griffiths (non-executive director of NICE), Mr Bob Osborne (lay representative), Dr Lindsay Smith (NHS representative), and Dr David Webster (industry representative). None of the members of the Appeal Panel had any competing interests to declare.

3. The Panel considered an appeal submitted by the company, Roche Pharmaceuticals. The company was represented by Dr Adela Williams (Legal Counsel, Arnold and Porter) and from the company Dr Max Summerhayes, Ms Lee Moore, and Mr Simon McNamara.

4. In addition the following individuals involved in the appraisal were present and available to answer questions from the Appeal Panel: Professor Peter Clark (Committee Chair), Professor Jonathan Michaels (Committee Vice Chair), Mr Meindert Boysen (Programme Director, Centre of Health Technology Evaluation) and Dr Elisabeth George (Associate Director, Centre of Health Technology Evaluation).

5. The Panel's legal adviser Mr Stephen Hocking (Partner, 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 under which an appeal can be lodged:

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

8. The Chair of the Appeal Committee (Dr Maggie Helliwell) in preliminary correspondence had confirmed that the appellant Roche Pharmaceuticals had potentially valid grounds of appeal as follows (the numbering follows the numbering used in the appeal letter)

Ground 1

> 1.3. The Appraisal Committee's failure to investigate adequately the potential uncertainty surrounding the cost-effectiveness of erlotinib compared to pemetrexed in those patients eligible for both treatments is unfair.
>
> 1.4. NICE's approach to the calculation of small patient populations, to which the end of life criteria may be applied, lacks transparency and is unfair both in general and in the context of this appraisal.
>
> 1.6 It is unfair for the Appraisal Committee to decline to make a recommendation on the use of an intervention relative to a comparator described in the Scope for the appraisal because they conclude that the use of the comparator is declining.

Ground 2 (Three points of appeal listed have been re-allocated from Ground 1 but, for the sake of transparency, the original appeal numbering has been retained).

> 1.1. The Appraisal Committee's conclusion that the benefit of maintenance treatment with erlotinib seen in the SATURN trial was likely to be lower in routine clinical practice is not evidence based and is therefore unfair.

1.2. Failure to consider the authorised indication for erlotinib as a whole rather than only as squamous and non-squamous subgroups is inappropriate and unfair.

1.5. The Appraisal Committee's determination that the evidence for erlotinib does not demonstrate an extension to life of at least three months is inadequately explained in the context of the available data.

2.1. The Appraisal Committee's conclusion that the results from the stable population in the SATURN trial are too uncertain, simply because they are based on post hoc analyses is not reasonable.

2.2. The decision of the Appraisal Committee not to recommend an intervention which, when assessed by the Independent Evidence Review Group using consistent methodology, is more cost–effective than the recently NICE-approved alternative, pemetrexed is perverse.

Ground 3

9. No appeal was made under this ground.

10. Erlotinib (Tarceva, Roche Products) is an orally active inhibitor of the epidermal growth factor receptor (EGFR) tyrosine kinase. It has a UK marketing authorisation 'as monotherapy for maintenance treatment in patients with local advanced or metastatic non-small cell lung cancer with stable disease after four cycles of standard platinum-based first-line chemotherapy'. Undesirable side effects of erlotinib treatment include diarrhoea, rash, anorexia, gastrointestinal bleeding, liver test abnormalities and keratitis. For further information see the summary of product characteristics. Erlotinib is given orally at a recommended dose of 150mg/day. The manufacturer of erlotinib has agreed a patient access scheme with the Department of Health. The appraisal that is the subject *o*f the current appeal provided advice to the NHS on the use of erlotinib monotherapy for the maintenance treatment of advanced or metastatic non-small cell lung cancer.

11. Before the Appeal Panel inquired into the detailed complaints, Dr Summerhayes on behalf of the appellant and Professor Peter Clark on behalf of the Appraisal Committee made preliminary statements.

12. For the company Dr Summerhayes said that the FAD was a missed opportunity to recommend a life extending treatment. For non-squamous groups erlotinib was more cost effective than its comparator, pemetrexed; for squamous groups there was no alternative maintenance treatment. The conclusion in this case was not consistent with that reached in the pemetrexed guidance in respect of maintenance treatment (TA 190). The two reasons for rejection were that the Appraisal Committee did not accept that the survival benefit shown in the SATURN trial would be replicated (was "generalisable") in English and Welsh patients; and did not accept that erlotinib met the small population criterion in the Institute's guidance on End of Life Treatment (EoL).

13. On generalisability it was inevitable that there would be differences between global trials and UK patients for whom the precise impact could only be shown after NHS use. It would only be reasonable to distinguish between trial benefits and patient population benefits where there is likely to be a clear difference in outcome in treatment, which it is plausible to attribute to identified differences in population. The company had shown that such differences as there were would not affect the likely benefits that patients would receive.

14. On population size, other appraisals had taken suitability or eligibility for treatment as the measurement criterion, rather than licensed populations per se. The same approach should be adopted for erlotinib, and this was the approach taken for its comparator (and competitor) pemetrexed. The two treatments have very similar patient populations, yet one is deemed small and the other is not, which cannot be correct. Given the extension of life offered by erlotinib (accepted by the ERG as 4.2 months) erlotinib should have been accepted as more cost-effective than pemetrexed for those with non-squamous disease and as the only maintenance option available for those with squamous disease.

15. For the Committee Professor Clark said this was a common cancer with poor outlook and small benefits from current treatment. Drugs which improve the treatment options are needed. The Institute had approved a number of cancer treatments to improve availability. However the Committee had been unable to find the robust evidence to enable approval in this case. The problematic issues were the generalisability of the SATURN trial to English and Welsh patients who had received first line chemotherapy, the linked uncertainties generated by reliance on post hoc analyses and other issues, and that the point estimates of benefit came with wide confidence intervals. Disappointingly, added together, these factors did not enable a positive conclusion on cost-effectiveness. The estimates were outside the usual bands which would have applied even with the EoL guidance.

16. The Committee had taken comfort from the fact that authoritative clinical interests such as the British Thoracic Oncology Group, the Royal College of Physicians and the Royal College of Radiology, had supported the Committee's conclusions.

Appeal Ground 1: The Institute has failed to act fairly

Appeal Point 1.3

17. In their appeal letter the Company had argued two main points.

    - All the evidence available indicates that at best pemetrexed maintenance is only marginally more effective than erlotinib in patients with non-squamous disease. At no points in this appraisal were the Committee presented with any scenario which would show that erlotinib was anything other than cost-effective compared to pemetrexed maintenance for this group. At no point did the Committee seek to obtain cost-effectiveness analyses to investigate this uncertainty

    - The Appraisal Committee's concern that data from JMEN and SATURN may not be generalisable to UK practice is clearly not a strongly held view in circumstances where the Appraisal Committee relied upon the JMEN trial to support its recommendation for use of pemetrexed as maintenance treatment in patients with non-squamous non-small cell lung cancer (TA 190).

18. For the company at the hearing Mr McNamara said it was not sufficient to argue there was uncertainty, without doing further work to investigate it. It was necessary to ask what the consequence of uncertainty was. A range of plausible scenarios presented by the company and comparing erlotinib and pemetrexed all showed erlotinib as more cost effective than pemetrexed for stable non-squamous cases. The Committee did not accept this or explore it further.

19. Professor Clark for the Appraisal Committee highlighted the considerable uncertainties in the comparisons between the two technologies. The company accepted that there was a lack of head to head comparisons and had originally said that indirect comparisons were not appropriate. It then presented its scenarios. The committee felt these were based on "strong" assumptions[1]. ERG had accessed additional data from a pemetrexed trial

[1] which the Panel understood to mean both contestable and favourable to erlotinib

(JMEN) and there were further analyses. (The Appeal Panel notes that the company raised no concern with the use of this data per se). Even with this additional data, the ERG commented that its results should be looked at with great caution, and that a true comparison between products was not possible, albeit that it preferred its results to the manufacturer's scenarios. The Committee concluded that all analyses had great uncertainty.

20. Professor Clark noted that the Committee had been asked to approve a drug that, while less costly, was also less effective in terms of extending life. In other words, a recommendation would save the NHS money, but at the expense of reduced life expectancy for patients. This made this appraisal an unusual case (the typical scenario being an appraisal of a drug which extends life compared to its comparator, but is more costly.) NICE placed greater weight on small extensions of life in its End of Life criteria, but it must follow that small reductions in life expectancy must also be given weight. In this case the Committee would need a good basis to recommend a clinically less effective drug. The revised ERG analysis showed a life extension benefit of 2.2 months for erlotinib. Given the uncertainties and the concerns about generalisability, it was not possible to reach a robust conclusion.

21. In response to questions from the Panel the company stressed their appeal point was that the uncertainty should have been investigated further as a matter of fair process. While accepting there might be arguments for a broad range of possible efficacy, the cost-effectiveness comparison was clear. On what analyses the company thought the committee could commission further, the company pointed to lack of testing the uncertainties around the ICER estimate of £84k for erlotinib against best supported care for those with squamous disease.

22. The Panel in their consideration noted that, as this point is brought under fairness, the point at issue is whether the Committee failed to follow the required process adequately in terms of seeking to reduce the uncertainties and whether the company was unfairly disadvantaged in making its case, rather than whether the Committee reached a reasonable conclusion on the evidence presented. They also noted that there is an interest in an appraisal process reaching a conclusion within a reasonable time. While a committee should seek to minimise uncertainty, if it is satisfied that the data and analyses before it have taken matters as far forward as is reasonably possible, it is permissible to move on to considering the material and taking a decision, even if uncertainties remain.

23. The Panel noted that this was an appraisal conducted under the Single Technology Appraisal (STA) process, intended to be an expedited process, where the starting point is data and evidence submitted by the manufacturer

on which an Evidence Review Group (ERG) comments to aid the Committee's consideration, rather than an analysis initiated by and conducted on behalf of the Appraisal Committee. In this case indirect analysis to compare erlotinib and pemetrexed had been presented both in the company's scenarios and using data from a separate trial. Given that, and the reliance on post hoc sub-group analysis for which the SATURN trial had not been powered, (considered as a separate issue below), it was difficult to see what other data could have been found to reduce the uncertainties and aid the Committee's judgement further. Nor was the Panel persuaded that any further analysis would have reduced uncertainty to any material degree.

24. There would still remain the question of opportunity to comment on uncertainty. The issue of uncertainty was flagged by the Committee in the second Appraisal Consultation Document (ACD – paragraph 4.15). In terms of fairness the appellant was able to make a response to the point and did so. The Panel therefore did not accept that the company had been disadvantaged in its response or that the Committee could have been expected to do more analysis before reaching a conclusion.

25. Finally, the Panel agreed that, where an appraisal is considering a treatment which provides less clinical benefit to patients than the alternative, it is right for a committee to place greater importance on the need for certainty on clinical and cost-effectiveness. In order to receive clinical and public support such a recommendation would need to be reached on robust grounds.

26. The Appeal Panel therefore dismissed this appeal point.

Appeal Point 1.4

27. In their letter the company made five more detailed points in support of this appeal point.

- Lack of clear guidance as to the definition of a 'small patient population' prejudices manufacturers in preparing submissions to NICE in relation to the application of the end of life criteria.
- The lack of guidance to Appraisal Committees as to the meaning of 'small patient populations' results in inconsistent approaches in different appraisals.
- The interpretation of 'small patient population' by the Appraisal Committee includes patients who are not in fact eligible for erlotinib therapy.
- The interpretation of 'small patient population' by the Appraisal Committee is inconsistent with that followed in other appraisals.

- The basis for the Appraisal Committee's conclusion that almost 7,000 patients with pancreatic cancer are eligible for treatment is unclear.

28. The Chair of the Panel noted that the Panel had commissioned more information on the application of the criterion on population size in previous appraisals. A table containing that information had been circulated in advance equally to the company and the Committee. The former had provided further comment on the table, which the Panel has taken into account in their consideration. The Committee had not commented on the table but the Chair did not accept that the Committee had been disadvantaged in its ability to comment.

29. Dr Williams for the company at the hearing accepted that the EoL guidance applied only where there was a small patient population. The EoL guidance did not provide a specific figure. While accepting the principle of cumulation, the judgement in this case was not transparent to the appellant and thus prejudiced their ability to focus their arguments. The table showed a range of approaches to cumulating data, ranging from the total population covered by all licensed indications of the technology to a definition based on those eligible for treatment. She contrasted the approach to erlotinib to that accepted for pemetrexed in TA 190. Dr Summerhayes further challenged the Committee's comment that the majority of the 7000 patients with metastatic pancreatic cancer would be eligible for erlotinib. He believed the figure would be less than 1,000. The company's best estimate of the eligible population covered by the two indications was 4,100, which should have been accepted under the criteria.

30. For the Committee Professor Clark stressed the time the Committee had spent on this issue. There were three licensed indications for erlotinib: the indication covered by this appraisal, second line treatment after failure of a chemotherapy regimen (these two overlapping) and for metastatic pancreatic cancer. The first two covered some 6,700 patients. Of the 6,800 cases of pancreatic cancer some 70% would have metastatic disease for whom erlotinib was indicated; around 5,000. While not disputing the estimate of actual use, the Committee had been guided by the appeal decision on TA 178 that it should cumulate the populations on the basis of licensed populations rather than eligibility for treatment. The result was an estimate in excess of that which could be accepted under the EoL criteria. In questioning, Dr Williams for the company argued that NICE's procedures were unfair; either there should be a figure on the size of population or there should be clear guidance on the process to cover the alternatives of licensed or eligible populations. It was clear from the table that the criteria were not being applied consistently. On pressing, the company re-iterated their judgement that the correct figure was around 4,000 based on eligibility, but did not offer a figure for the total populations covered by the licensed indications.

31. For the Committee Professor Clark said that they had considered the approach adopted in the pemetrexed appraisal but had considered that their approach to cumulation was the better judgement in line with the TA 178 appeal. Mr Boysen also pointed out that the table could mislead – there was a difference between the eligible population used for the purpose of costing estimates and any judgement on the total population covered.

32. The Panel considered the points made and the table of supplementary information carefully. They noted the relevant sections of the EoL guidance state 'the treatment is licensed or otherwise indicated for small patient populations' and ' The Appraisal Committee will take into account the cumulative population for each product in considering the strength of any case' (that is for using the EoL criteria to depart from the normal cost-effectiveness judgement).

33. The issue of the absence of a precise numerical criterion was considered in a previous appeal in relation to TA 178 (also involving the current company, the current Appeal Chair, and one appellant representative), which is publicly available. In that appeal the panel had noted the drawbacks of any hard edged threshold, looking to greater clarity as more appraisals were made. The current Panel accepted the drawbacks of hard and fast rules in making the difficult judgement to depart from normal criteria in cost effectiveness in end of life cases. This is not an issue where over rigidity is appropriate. It therefore agrees with the earlier panel that the absence of a threshold per se is not unfair.

34. On the issue of cumulation, the Appeal Panel in TA 178 concluded that it was appropriate under the advice to cumulate the populations in terms of the potential population covered by licences rather than on the basis of actual or recommended use. The Committee followed this approach in their consideration of the applicability of EoL criteria to erlotinib. As the Committee has followed the publicly available guidance of a previous appeal panel, the Panel does not find that its approach to cumulation looked at in isolation is unfair. The Company had suggested that the Committee may have been internally inconsistent, in as much as it had considered only lung cancer patients who had received first line chemotherapy, and not all patients. However as erlotinib is only licensed for lung cancer patients who have received first line chemotherapy, the Committee had consistently applied a licensed population approach. Nor was there a suggestion that the Committee had calculated the population on a "licensed indication" basis, but then applied a small population criterion suitable only for the "eligible patients" approach.

35. The Panel then considered the question of consistency. The Panel accepts that broad consistency between appraisals is a requirement (although it notes

that it is a requirement of fairness only in as much as unexpected or opaque inconsistency may affect the ability to engage with an appraisal). The Panel takes the view that it is consistency with overall past practice and published appeals which is required, and that it is not correct to pick one or a few past appraisals only for comparison. This is in substance an attempt to generate a formal threshold, albeit from past practice rather than Institute guidance, and as noted above, the Panel considers this inappropriate. (However, it considers that pemetrexed is a special case for this appraisal and one that does merit individual consideration, see below.)

36. The Panel reviewed the application of the population criterion in a number of cases. Judgements had varied. It is clear that population size is one factor in making the case for a positive recommendation. The committees had not in all cases made an explicit judgement on the population criterion and the Panel accepted that caution must be applied in assuming the costing estimate necessarily represented a committee view on the issue. However in no case has there been an approval that would call into question the conclusion reached in TA 208 that 7000 individuals was at the upper end of the population size for the EoL criterion, and considering all of the past appraisals in which the EoL criteria were applied, it appeared that even 4,100 could be seen as above the typical population previously accepted. Therefore there had not been unfair inconsistency.

37. Finally, there was the issue of the pemetrexed appraisal, which had a particular relevance to this appraisal. The Panel accepted that the Committee had considered their judgement carefully, including the approach adopted in pemetrexed. The Chair of the Committee explained that they were aware of the approach taken by their sister committee in the pemetrexed appraisal, but felt this Committee's approach, guided by the previous Appeal Panel conclusion was better, and that "two wrongs do not make a right". Recognising the formal consideration of the issue, the Panel did not feel that this was an unfair approach to have taken.

38. In conclusion the Panel did not feel that unfairness could be shown in this case, given that the Committee had consciously followed the guidance confirmed in a previous appeal hearing where this had been tested, which is the only formal comment from an appeal panel on this matter. In terms of impact on the outcome they further noted in relation to the EoL criteria that the survival benefit for non squamous disease where the comparison with pemetrexed was relevant was 2.2 months and that the Committee had not accepted there was a robust estimate of cost effectiveness on which to base a conclusion, and so the small patient population was not the only reason to conclude that the EoL policy did not apply. Accordingly, given the adoption by the Committee of an approach endorsed by a previous appeal panel, the Panel dismissed the appeal on this point.

39. The Panel in this case did understand however the point of concern in relation to possible variation in approaches to calculation of patient population in terms of use of total licensed populations or smaller actual or eligible populations. They recommend that, given the number of EoL judgements that have been made, the Institute should review the experience of relevant appraisals and consider whether, (without introducing rigid criteria inappropriate to a judgement to vary positively the normal approach to judging cost effectiveness), further guidance and clarification on this matter would aid appraisal committees.

Appeal Point 1.6

40. In their letter the Company had argued that, in the FAD, one of the reasons for not recommending erlotinib over pemetrexed for the non squamous group was because such patients increasingly received pemetrexed as part of first-line treatment. The fact that small numbers of patients may be affected was not a valid reason for declining to issue guidance. If pemetrexed was not seen as a valid comparator, the logic was to compare the whole population with best supportive care.

41. For the company Dr Williams pointed out the scope required a comparison with pemetrexed. One of the reasons given in the FAD for non approval of erlotinib was the declining use of pemetrexed in maintenance therapy following its recommendation for first line treatment. This had not been consulted on and it was not appropriate to reach a decision on this basis.

42. Professor Clark explained the overlapping timescales on the respective appraisals of pemetrexed and erlotinib which had complicated matters. The reason not to recommend erlotinib was the absence of a robust estimate of clinical and cost effectiveness, entirely based on the uncertainties shown by the evidence (see 4.27 of the FAD). He accepted that it may have been an error to include the observation on declining use in paragraph 4.18. He could see that this may be taken as a reason, which was not the Committee's intention.

43. In the Panel's consideration they accepted that it was clear that the reasons for non approval were expressed in terms of the problems with a robust estimate of cost effectiveness, concerns about comparability and generalisability of the trial populations and lack of a plausible estimate of cost savings per QALY lost through the displacement of pemetrexed by erlotinib, rather than reliance on the observation that the maintenance use of pemetrexed was declining. Given the actual basis of the Committee's judgement, it was not the case that the Committee had declined to assess pemetrexed as a comparator (see also the comment on appeal point 1.2). Accordingly, they dismissed the appeal on this point. They did however

observe that, in preparing the final FAD, it would be helpful to amend the detailed wording of paragraph 4.18 to avoid future misunderstanding.

Appeal Ground 2: NICE has formulated guidance which cannot be reasonably justified in the light of the evidence submitted

Appeal Point 1.1 (reallocated)

44. In its appeal letter the company had pointed out that licensing trials are conducted on an international basis and that it is inevitable that the trial population will not be identical in every respect to the English and Welsh patient population.

45. For the company at the hearing Dr Summerhayes argued that no evidence had been presented of difference in populations of the SATURN and JMEN trials which had any impact on the clinical outcome for patients. Indeed, the Company had presented evidence to show that any differences did not matter. The Company accepted that the SATURN trial population did not have the same profile as UK patients, a fact of life of global trials. The SATURN trial population had been selective, but this would be true of patients eligible for maintenance therapy also. The exact clinical population could be estimated only with NHS use. They believed uncertainty in relation to applicability to the UK could in some cases work in favour of erlotinib; for example the fact of second line treatment for the SATURN population might dilute the survival benefits shown for erlotinib. The fact that UK patients might have a worse prognosis did not mean the drug would not be effective in those patients. The conclusion that the benefits in the trial were unlikely to be replicated in the UK was not evidence based and therefore unreasonable.

46. For the Committee Professor Clark said the difference in population itself was not important. What was problematic was the difference between the type of patients entering the trial and those who have first line chemotherapy in the UK. The issues concern the relative proportion of never smokers, the numbers of patients of Asian origin and the percentage of patients who had subsequent treatment which indicated a fitter population; all factors which it was reasonable to conclude would not work in the drug's favour in terms of replication of benefits in the UK. Even allowing for all that, the limitations of post hoc analysis further applied to sub-groups did not provide a sufficient basis for confidence.

47. The Panel noted that the Committee had considered in depth a number of characteristics relevant to the generalisability of the SATURN trial data to patients in England and Wales. These were; being Asian (FAD paragraphs 3.5, 3.8, 4.5, 4.9), smoking (3.5, 3.8, 3.9, 4.9), fitness (3.5, 3.9, 4.5), age (4.5), EGFR status (3.5, 3.8, 4.8, 4.9), gender (3.8, 4.6), second line treatment (3.5, 4.5, 4.10, 4.12) and lack of prior treatment with permetrexed (3.21, 4.6,

4.10.12). Both the Company and the ERG had commented on whether some of these characteristics were related to prognosis and/or differed between the trial and NHS patients The Panel noted that the Committee had considered the following factors. Asian patients were noted to have better overall survival. There were more never-smokers in the trial, and such patients do better. Two of the relevant company models submitted were not based on the relevant trial populations. Younger, female and fitter patients do better. The trial patients had more second line treatment than NHS patients would usually receive. It was accepted that the issue of EGFR positivity only applied to the non-squamous subgroup; but that EGFR status did improve outcome for the squamous group. None of the SATURN patients had received prior first line treatment with permetrexed as would now occur for most in the NHS. The Company had presented arguments on these points, and it was clear to the Panel that the Committee had considered the evidence carefully. On whether the Committee had been reasonable to stress the uncertainty in the results for sub-group analyses they had sought, the Panel noted that the SATURN trial had planned analysis based on EGFR as a prognostic factor and that the scope required consideration of the non-squamous group given the need to compare with pemetrexed.

48. The Panel reminded itself that the question was whether the guidance could reasonably be justified in light of the evidence, and not whether the panel agreed with the Committee. The Panel concluded that the Committee had acted reasonably in questioning the generalisability of the SATURN trial results to patients in England and Wales. They noted that the Committee had identified issues on sub-group balance, model data inputs, interaction data, adjustment for prognostic factors, lack of trial inclusion of patients receiving standard NHS first line treatment and higher second line treatment use. The Committee had made a reasonable judgement that, taken together, these factors caused uncertainty so that the data was not robust enough to enable them to reach a positive recommendation.

49. Accordingly, the panel dismissed the appeal on this point.

Appeal Point 1.2 (reallocated)

50. In their letter the Company had argued that it was not justified not to consider the total stable population (squamous and non-squamous groups together). While the ERG had originally estimated an overall survival benefit for the whole population, they had subsequently restricted their estimates to each histological sub-group.

51. For the company Dr Summerhayes pointed out that the FAD failed to give an estimate of the cost-effectiveness of use of erlotinib for the whole patient group, only for the squamous and non-squamous sub-groups, and that

splitting into smaller groups inevitably increased the uncertainty for each group. The ERG's first analysis had estimated 4.2 months extended life benefit (comparable to the Company's own estimate of 3.9, the difference being the approach to discounting) with an ICER of £40,000. That was a reasonable base for a positive recommendation.

52. For the Committee Professor Clark explained the histology of the disease produced a split between squamous and non-squamous groups. As there was now a new optimal first line treatment for the non-squamous group, the histology was now clinically relevant and drove a need to consider the groups separately. That was re-enforced by the need to compare with pemetrexed given the scope. There was a problem with post hoc sub-group analyses since the trial was (necessarily) not designed for these. Further the Committee found it difficult to reconcile the estimate of 3.9 months for the whole population in the light of estimates of 4.5 and 4.2 months respectively for the squamous and non-squamous groups. The ERG had adopted a revised approach to further data after their first analysis using less modelling. That had produced estimates of 3.4 (squamous) and 2.2 (non-squamous) months, both with wide confidence intervals. Given the differences between the two groups, the ERG was clear it was wrong to put the two together. However as the non-squamous group was the larger, it was reasonable to assume that any overall conclusion would be nearer 2.2 than 3.4 months.

53. The Panel noted, as on the previous point of appeal, that the scope required a disaggregation into sub-groups to produce a comparison with the use of pemetrexed in relation to the non-squamous sub-group. The Committee had reasonably considered the clinical relevance of the histology. The Panel further noted that the ERG had not provided an estimate for the whole population and that the manufacturer's estimate for the overall population by comparison to those produced for the two sub-groups within the total group was paradoxical. They further noted the likelihood that an overall estimate would fail the three months' extension of life criterion in the EoL guidance. The Panel found that the Committee had considered the issue and reached a reasonable judgement.

54. Accordingly the Panel dismissed the appeal on this point.

Appeal Point 1.5 (Reallocated)

55. In their letter the Company had stated that the evidence that erlotinib does not demonstrate an extension to life of at least three months is inadequately explained in the context of available data and was inconsistent with the available evidence.

56. Dr Summerhayes for the company argued that the survival benefits from the different estimates for the squamous group were all over 3 months and were therefore a reasonable basis for a positive recommendation.

57. For the Committee Professor Clark highlighted the concerns about generalisability of the results and the degree of uncertainty about the prospective benefits given the rate of post trial treatment in the trial population. He also pointed out that the majority of benefit in the squamous group came after treatment was discontinued.

58. In response to questioning the Company pointed out that the criterion qualified the 'at least an additional 3 months' with the addition of 'normally', so some flexibility needed to be considered. The way to deal with uncertainty was through more analysis rather than reaching the judgement made.

59. The Panel noted that, while a figure below 3 months cannot be ruled out automatically, the presumption in the guidance is a figure of at least 3 months, so there should be a clear reason for a lower figure as an exception. In the case of the squamous group the Panel accepted that the judgement that the likely ICER for erlotinib compared to best supportive care (the comparator) as well as the uncertainty around the extent of life extension itself (given the wide confidence intervals) had made it a reasonable judgement to decline to recommend erlotinib. In the non-squamous group the estimate available to the Committee was 2.2 months, proportionately some way short of the 3 months criterion and it had been reasonable not to make an exception to the normal criterion. They accepted the reason of the Committee not to reach a judgement on the overall group and noted that, had an estimate been made, it would be likely to have been nearer 2.2 than 3.4 months given the relative size of the two sub-groups in the analysis (297 for the non-squamous against 197 for the squamous group).

60. Accordingly they dismissed the appeal on this point.

Appeal Point 2.1

61. In their letter the Company had argued that the conclusion that the benefits of erlotinib in the stable patient population for patients in both groups were uncertain simply because of their basis in post hoc analysis was unreasonable.

62. For the Company Dr Summerhayes said that it was not acceptable to dismiss the results of an analysis merely because it was post hoc, although he accepted that caution in use of post hoc analyses was justified, because, for example, the groups defined post hoc may lack balance for known and for unknown confounding factors. Further, it was inconsistent with the request to

the ERG to do a further analysis of sub groups within the overall post hoc analysis then to reject those analyses as post hoc.

63. For the Committee Professor Clark stressed that the reason for the conclusion that the results of the analysis in terms of the patient benefit from treatment was uncertain was not 'simply' because the analysis was post hoc. It was the degree of benefit that was uncertain not whether erlotinib had an effect itself.

64. In questioning, Dr Williams for the company argued that due account had not been taken of the ruling in the judicial review brought by Servier against NICE [2010] EWCA Civ 346. She added that it was not enough that the Committee had other reasons not to make a recommendation, or to regard the results of the analysis as uncertain; all reasons had to be reasonable. Professor Clark further said that most post hoc analyses have to be treated with some caution. However, other reasons had added to the key concern, which was the absence of a basis for a robust estimate. The fact of post hoc analysis was a factor in that, not the sole reason.

65. The Panel noted that the Committee had given the issue careful consideration including the points made by the Company in consultation. The Panel accepted that the judgement made was not simply because of the analytical basis. There were other factors taken into account. It was however reasonable to take the fact that the analysis was post hoc from a trial not powered for the purpose and further split into sub groups by histology, again for which the trial was not designed, into account when making the overall conclusion as to whether a robust estimate and conclusion on which to base a positive recommendation could be made.

66. So far as the Servier judgement is concerned, the Court of Appeal stated that, as a matter of fairness (and not of reasonableness) it would not be enough to explain reduced weight to be given to a post hoc analysis merely by reference to the fact that it was post hoc. Whilst the Panel naturally accepts the Court's finding, Dr Summerhayes' own evidence to the panel illustrated one difficulty with it. It is common ground that one weakness in a post hoc subgroup analysis is that the sub-group may lack balance for known and unknown factors. By definition, no committee will ever be able to state that a post hoc sub-group has lost balance for an unknown factor. The Servier judgement is not of great assistance in the context of a challenge to the rationality of concerns about a post hoc subgroup analysis, which is essentially a scientific question. On the facts, the analyses here differed in kind from the analyses in Servier (for example, no issue could be taken with the definition of the sub-groups per se, not least because the Committee had requested them, whereas this had been an issue in Servier.) Most importantly, in the Servier case the only reason to place reduced weight on the contested analysis was that it was post hoc, whereas here there are a series of reasons to approach

the results of the analyses with caution, only one of which was that they were post hoc. For example, there were issues that the trial was not powered for the analyses undertaken, which would have been true even had the analysis been pre-specified. The Panel did not agree that every one of those reasons would itself have to be a sufficient reason to approach the analyses with caution. It is enough that taken in the round all of the reasons for caution collectively can justify the weight given to the analyses. Nor did the Panel agree that the fact that the Committee had itself requested the analyses made it unreasonable then to approach them with caution: it is reasonable for the Committee to have requested the analyses in the hope that they might have been informative.

67. Accordingly the panel dismissed the appeal on this point.

Appeal Point 2.2

68. In their appeal letter the Company argued that it was perverse not to recommend erlotinib over the recently approved pemetrexed given its greater cost-effectiveness.

69. For the Company Mr McNamara emphasised the relative cost effectiveness of erlotinib against pemetrexed for the non-squamous sub-group. Given the advantage to the NHS from substituting erlotinib for pemetrexed – a saving of £84k per QALY lost – it was unreasonable not to make a positive recommendation for this group.

70. For the Committee Professor Clark said that they had noted and considered the previous cost effectiveness estimate for pemetrexed and the results indicating both a lower cost and lower clinical effectiveness. He accepted that different approaches and different models could produce different results. However the Committee had concluded that the results were so uncertain that the Committee concluded they lacked a robust basis to make a judgement in favour of erlotinib.

71. In questioning, Mr McNamara for the company highlighted the need for an opportunity cost basis for making a comparison of the two products. Dr Summerhayes stressed the absence of a head to head comparison and the value of increasing patient choice through availability of erlotinib. If a different Appraisal Committee had accepted an estimate of £47k as the ICER and 5.2 months as the survival benefit from the use of pemetrexed as a maintenance treatment, it was unreasonable to reject erlotinib given its cost effectiveness advantage.

72. The Panel considered carefully the basis of the decision. The relevance of opportunity cost was accepted. They accepted that, while consistency needed to be given due weight in comparable analyses, different models

could produce different results as the basis for judgement without there being any unreasonableness. This was amplified here when the starting points in the two appraisals of pemetrexed and erlotinib were different trials and separate submissions under the single technology appraisal process. The comparison of the two products depended on an indirect analysis of the two trials, not designed for that purpose, which increased uncertainty about the results. They noted the issue of recommending a less effective treatment than one already approved, and accepted as justifiable the Committee judgement that they would need a more robust basis for doing so than the analysis here produced (see also the Panel comment on Appeal Point 1.3).

73. The Panel noted that, in terms of accepting a higher than normal cost under the EoL criteria, the normal criterion of at least three months had not been satisfied here; the Committee estimate of 2.2 months being reasonably based on analysis using more actual data and less modelling than in the Company submission. They further noted that the survival benefit in favour of pemetrexed noted by the Company as 'only 6 weeks longer' was not insignificant as a proportion of the 3 months starting basis for application of the End of Life criteria. The Panel also noted that authoritative clinical comment and views from the NHS had supported the Committee's conclusion.

74. It was clear from the FAD and the previous consultations that the matter had been well exposed and carefully considered. The Panel accepted that the conclusion reached by the Committee - that the difficulties of reaching a robust comparison given the nature of the evidence and the uncertainties were such they considered they had not been presented with a plausible estimate of the cost savings per QALY lost from the use of erlotinib – was reasonable.

75. Accordingly the Panel dismissed the appeal on this point.

Appeal Ground 3: The Institute has exceeded its powers

76. There was no appeal under this ground.

Conclusion and effect of the Appeal Panel's decision

77. The Appeal Panel therefore dismissed all the grounds for appeal in this appraisal.

78. There is no possibility of further appeal against this decision of the Appeal Panel. However, this decision and NICE's decision to issue the final guidance may be challenged by applying to the High Court for permission to apply for a judicial review. Any such application must be made within three months of publishing the final guidance.