[redacted]
**Health Economics and Strategic Pricing Director**

24th March 2011

**NOTICE OF APPEAL**

[redacted]
Chair, Appeal Committee
National Institute for Health and Clinical Excellence
MidCity Place
71 High Holborn
London WC1V 6NA

**RE: FINAL APPRAISAL DETERMINATION FOR ERLOTINIB MONOTHERAPY FOR THE MAINTENANCE TREATMENT OF ADVANCED OR METASTATIC NON-SMALL CELL LUNG CANCER**

Dear [redacted],

Roche Products Ltd would like to appeal against the Final Appraisal Determination for the above mentioned technology appraisal on the following two grounds:

**Ground one**: The Institute has failed to act fairly.
**Ground two**: The Institute has formulated guidance which cannot reasonably be justified in the light of the evidence submitted

If you require any further information or clarification then please do not hesitate to contact us.

Yours Sincerely,

[redacted]
Health Economics and Strategic Pricing Director

# ERLOTINIB MONOTHERAPY FOR THE MAINTENANCE TREATMENT OF ADVANCED OR METASTATIC NON-SMALL CELL LUNG CANCER

# NOTICE OF APPEAL

## EXECUTIVE SUMMARY

### 1. Ground 1: The Institute has failed to act fairly

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

1.3 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.

1.5 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

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: The Institute has formulated guidance which cannot reasonably be justified in the light of the evidence submitted

2.1 The Appraisal Committee's conclusion that the results from the licensed stable patient population in the SATURN study 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.

## BACKGROUND

Roche Products Limited ("Roche") is responsible for the sale and marketing of erlotinib (Tarceva) in the UK. The indications for use of erlotinib include maintenance treatment in patients with locally advanced or metastatic non-small cell lung cancer with stable disease after 4 cycles of standard platinum-based first-line chemotherapy; this is the therapy considered in this appraisal.

## HISTORY OF THE APPRAISAL

The appraisal of erlotinib has been complex, as shown by the following chronology:

2009: referral to NICE and commencement of single technology appraisal process.

17 November 2009: Final Scope issued.

19 January 2010: Submissions by consultees, including Roche. Roche estimate a survival advantage of 3.3 months for erlotinib in the stable disease population. This estimate is derived via the fitting of single parametric curves to the SATURN OS data.

19 March 2010: The European Medicines Agency's CHMP approves a variation to the authorisation for erlotinib to include monotherapy for maintenance treatment in patients with locally advanced or metastatic non-small cell lung cancer with stable disease after 4 cycles of standard platinum-based first-line chemotherapy (following a favourable opinion of the CHMP on 19 March 2010). This indication, limited to patients with stable disease, is different from that originally proposed by Roche and which formed the basis for Roche's submission to NICE.

23 March 2010: Liverpool Reviews and Implementation Group (LRiG), produces an ERG report, based on the original submission by Roche. LRiG estimate a survival advantage attributable to erlotinib of 4.2 months in the stable disease population and an ICER of £60k. This modelling was undertaken using 'piece-wise' fitting of the time to event curves from SATURN.

April 2010: Roche proposes a patient access scheme for erlotinib maintenance treatment, comprising a discount on the list price.

1 April 2010: NICE issue a positive Final Appraisal Determination (FAD) for the utilisation of pemetrexed as a maintenance treatment for patients with non-squamous tumours. This determination confirms pemetrexed as a comparator to erlotinib in non-squamous stable disease patients in the decision problem for the appraisal of erlotinib as a maintenance treatment.

27 April 2010: The European Commission grants a variation to the authorisation for erlotinib as approved by the CHMP on 19 March 2010.

27 April 2010: The Appraisal Committee proceeds to consider erlotinib based on the original submission by Roche, despite the changes to the proposed indication for erlotinib made by the CHMP and the FAD issued for pemetrexed as a maintenance treatment in non-squamous patients.

June 2010: An Appraisal Consultation Document (ACD) is issued. This states at paragraph 1.1:

> "*Erlotinib monotherapy is not recommended for the maintenance treatment of people with locally advanced or metastatic non-small-cell lung cancer with stable disease after platinum-based first-line chemotherapy*".

8 July 2010: Roche submits its response to the ACD including, as agreed by NICE, a supplementary evidence submission and three additional versions of its economic model. An error in the costing of the best-supportive care is noted and amended. This brings the ICER of erlotinib in its licensed population using LRIG's survival curves and the analysis felt 'most plausible' by the Committee in the first ACD down to £40k. Roche attempt to replicate the 'piece-wise' survival curve fitting methodology utilised by LRiG for the two 'by-histology' models. Roche estimate ICERs of £36k and a survival for the squamous histology group and £40k in the non-squamous group. Roche acknowledge the limitations with an indirect comparison against pemetrexed in non-squamous stable disease patients due to a lack of publicly available data on pemetrexed in the stable disease population. Instead a series of plausible relative efficacy scenarios are provided.

September 2010: LRiG produces a supplementary ERG report. They reject the projective modelling of OS employed by themselves in their previous analysis and the OS modelling undertaken by Roche. They derive estimates of the overall survival advantage offered by erlotinib via discrete analyses of progression free and post-progression survival. No attempt is made to estimate the OS advantage offered by erlotinib based upon the overall survival curves from the SATURN study. No attempt is made to estimate an ICER of erlotinib in its licensed indication. LRiG conduct an indirect comparison of erlotinib to pemetrexed utilising data from the JMEN trial (the pemetrexed maintenance registration study) that Roche were unaware of at the point of their supplementary evidence submission. LRiG produce the following estimates:

- The ICER of erlotinib vs BSC in squamous patients with stable disease is £44k with a 3.4 month survival advantage

- The ICER of erlotinib vs BSC in non-squamous patients with stable disease is £68k with a 2.2 month survival advantage

- For every QALY lost by switching a non-squamous patient with stable disease from pemetrexed to erlotinib the NHS will save £84k

27 October 2010: The Appraisal Committee meets for a second time and agrees the content of a second ACD.

November 2010: A second ACD is issued. The content of paragraph 1.1 reflects that in the first ACD. The Committee reject all ICERs and survival estimates derived by Roche and the ERG.

16 December 2010: Roche provides comments in relation to the second ACD. This response focuses on allaying the Committee's concerns on the generalisability of the SATURN results. Roche demonstrate that the concerns on the SATURN population expressed by the Committee in the second ACD are either unfounded (in the squamous stable disease population) or in favour of the comparator arm (in the non-squamous population). Roche demonstrate that the removal of patients with an EGFR mutation has no appreciable impact upon the survival estimate derived for erlotinib in the non-squamous population.

25 January 2011: The third meeting of the Appraisal Committee takes place and a FAD is agreed.

March 2011: The FAD is issued to consultees. The content of the proposed guidance in paragraph 1.1 is the same as that in the first ACD.

## GROUNDS OF APPEAL

Roche's grounds of appeal in relation to the FAD for erlotinib for maintenance treatment of non-small cell lung cancer are set out below.

### 1. Ground 1: The Institute has acted unfairly

#### 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

At paragraphs 4.5 - 4.11 of the FAD, the Appraisal Committee expresses concerns about the generalisability of trial results to UK clinical practice because of differences between trial subjects and those in the UK. The Committee summarised its conclusions at paragraph 4.12 of the FAD "the benefit of maintenance treatment with erlotinib seen in the SATURN trial was likely to be lower in routine clinical practice when considering that the trial population represented patients who are likely to have a better prognosis than the average patient treated in the UK". In addition, the Committee identified three factors which it concluded "lead to considerable uncertainty about the magnitude of overall survival gain expected from erlotinib maintenance treatment in the stable population and in the squamous and non-squamous disease subpopulations. For the reasons set out below, Roche believes the Committee's conclusions are not consistent with the available evidence or are otherwise unfair:

(a) Licensing trials are conducted on an international basis and accordingly it is inevitable that the population of patients studied will not be identical in all respects to the population of patients who may receive treatment in England and Wales.

In circumstances where it is unrealistic to expect that all major trials used for licensing purposes are conducted in the UK, it is unfair for the Appraisal Committee to criticise the data for not reflecting precisely the UK population. If the Committee believes the trial population is materially different from the relevant UK population, it is necessary for the Committee to identify such differences and assess systematically the likely impact on the trial results.

- The high proportion of Asian patients, never smokers and EGFR mutations in SATURN

The relatively high proportion of south-east Asian patients and never smokers in SATURN might be expected to be significant because such patients harbour a high frequency of EGFR mutations that sensitise to EGFR tyrosine kinase inhibitors. However, these mutations are vanishingly rare in squamous cancers and there is no reason to suppose such characteristics are important in this group. Furthermore the Committee accepted that the number of patients with squamous disease with an activated EGFR mutation or who were of Asian origin or who had never smoked was

small and it "agreed that these prognostic factors were unlikely to significantly bias the estimate of overall survival for this subpopulation" (paragraph 4.9 of the FAD).

While the Appraisal Committee concluded that the imbalances would therefore be greater in the non-squamous subgroup, there is no indication that they considered how such imbalances would be likely to affect the data for erlotinib. This constitutes a flaw in the appraisal procedure and is unfair. By way of example, while there was an imbalance in the number of patients who had never smoked between the erlotinib and best supportive care groups, this favoured the best supportive care group and accordingly the overall survival benefit from erlotinib in the non-squamous disease patients would be confounded in favour of best supportive care Similarly a cox regression analysis of survival in patients without EGFR mutations (Section 1.6 of Roche's response to the second ACD) showed that removing patients with EGFR mutations does not reduce the survival benefit associated with maintenance erlotinib. Thus, whether or not the mutation rate in patients in the SATURN study or sub-populations from is the same as that encountered in UK clinical practice is largely irrelevant to the efficacy of the intervention under review. Finally, no plausible reason has been given by the Appraisal Committee for considering that any overrepresentation of Asian patients in the evidential trial, relative to UK clinical practice, limits the generalisability of trial data to the UK clinical population – although. Although such patients have a higher rate of EGFR mutations in their tumours, these have been shown not to be associated with differential survival benefit during this appraisal.

- The proportion of patients who were fit after first line chemotherapy

The high proportion of trial patients who are fit (PS 0) after 4 cycles of first-line therapy was considered by the Committee to reflect a population of patients fitter than those in UK clinical practice (FAD paragraph 4.5). However, while the trial population was certainly fitter than the average patient presenting with advanced NSCLC (around two-thirds of whom are too unfit to treat), there is no evidence that the patients who participated in SATURN were any more fit than the patients who receive chemotherapy in clinical practice in England and Wales. UK patients do not receive chemotherapy unless they are fit (PS 0-1) and with the symptomatic relief that is associated with chemotherapy those who have not progressed can also expect to be relatively fit. In these circumstances, the basis for the conclusion of the Committee that patients in SATURN were more fit than those in UK clinical practice, is unclear and Roche does not believe it is correct.

In any event, there is no evidence that level of fitness impacts on benefit from maintenance erlotinib or that this would otherwise affect the generalisability of the results from SATURN to the UK population.

- The fact that the trial participants were relatively young

Again the relatively young age of trial participants is noted by the Committee as a reason why the results of SATURN may have limited generalisability to the UK population (FAD paragraph 4.5). However no evidence is provided that this population will be younger than patients successfully treated with first line chemotherapy in the UK (who will be younger than the average newly diagnosed patient) and no plausible reason is given as to why, even if the population of patients in SATURN was younger than in UK practice, this would impact on benefit from erlotinib.

- Trial participants received a variety of follow-on treatments not available in the UK

The Committee also suggested that the fact that a high proportion of patients received a variety of follow-on treatments not available in the UK, could impact generalisability of results to the UK (FAD paragraph 4.5). While it is true that a range of follow-on treatments were used in the study, while second-line treatment rates in the UK are very low (an argument for making maintenance treatments more widely available), more ready access to a range of salvage therapies will have no impact on the PFS effect of maintenance therapy as measured in SATURN and would be expected to dilute the overall survival benefit relative to what might be seen in UK practice. In these circumstances, the reasoning of the Committee is not understood and it seems that it has not, in any event considered that this factor would, if anything, increase the potential benefits of erlotinib in the UK population.

- The SATURN trial did not include patients with non-squamous tumours who had received first line chemotherapy with pemetrexed and cisplatin

At paragraph 4.6 of the FAD, the Committee casts doubt on the benefits arising from erlotinib in patients with non-squamous tumours because the SATURN trial did not allow the use of the (then unproven) pemetrexed/cisplatin combination that many would now receive. However, the SATURN maintenance trial was designed to recruit patients according to their disease status after first-line chemotherapy rather than which first-line treatment they received. The Appraisal Committee has not explained why first line use of pemetrexed would influence the efficacy of subsequently administered erlotinib. Given the completely different modes of action of erlotinib and cytotoxic drugs, such as pemetrexed, cross-resistance between first-line treatment and erlotinib maintenance seems unlikely and NICE have not given a plausible rationale for their concerns in this area.

- The small numbers of patients in the post hoc analyses for the squamous and non-squamous disease subgroups

The Committee identifies the small numbers of patients in the histologically defined subgroups as a reason for uncertainty in relation to the benefits of erlotinib (paragraph 4.12 of the FAD). Roche believes this criticism is unfair, both because the company did

not require such subgroups (see point 1.2 below) and because the data for the squamous subgroup reached statistical significance in any event (see point 2.1 below).

Overall, it is unfair to assume that differences between the evidential trial and UK clinical practice exist, without appropriate evidence and it is unfair to reject trial evidence because of differences between trials and clinical practice when there is no good reason to assume they will affect outcomes. The lack of explanation for the Appraisal Committee's conclusions in this respect has prejudiced Roche in its ability to respond to the Committee's conclusions and does not form a credible basis for guidance.

Furthermore, the rejection of trial survival benefits in this appraisal is not consistent with the approach adopted in the closely related appraisal TA190 (and others) where almost all of the same "criticisms" of the generalisability of trial data could be made, but did not prevent NICE accepting survival estimates based on the trial results.

### 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

While the Committee express the view that it was justified in considering the squamous and non-squamous populations separately on clinical grounds (paragraph 4.15 of the FAD), in circumstances where they conclude that the use of the squamous and non-squamous subgroups introduces substantial uncertainty in relation to the benefits of erlotinib, it was unfair for the Committee not to consider the total stable patient population in circumstances where this reflects the licensed indication for use of erlotinib.

In their first report in this appraisal the ERG estimated an overall survival advantage of 4.2 months for erlotinib in its licensed population. In their first ACD the Committee concluded that the ICER for erlotinib estimated by the ERG in this population (£60k) using this survival advantage was 'the most plausible' (section 4.18 and 4.19 of the first ACD). Following the correction of a costing error within the model the ICER based upon this analysis fell to £40k (see page 70 of Roche's supplementary evidence submission). The ERG and Committee then both withdrew their support for these estimates despite their earlier advocacy instead preferring to estimate ICERs for each histological subgroup. The Committee then dismissed/rejected the ICERs estimated by both Roche and the ERG in each of these histological subgroups for the reasons discussed elsewhere in this document.

The ERG have sought to justify the histological subgroups on the basis that they are producing more homogeneous populations. However this is directly contrary to the clinical trial design which attempts to include a population heterogeneous for a wide variety of prognostic and predictive factors (known and unknown) and that by randomisation, such heterogeneity will be more or less equally divided between the groups. The approach of the ERG removes these benefits and, by attempting to introduce homogeneity, may mean that unidentified differences between the subgroups confound the results. In these circumstances, and particularly in the context of the concerns raised

by the Committee in relation to uncertainty arising from the subgroup analyses, it was incumbent on the Committee to consider the whole stable population from SATURN and to take this into account when reaching its conclusions.

For completeness the Appeal Panel should be aware that the ICER calculated by Roche for the comparison of erlotinib with best supportive care in the stable disease population utilizing the survival curves fitted by the ERG and a series of amendments, of which all have individually been accepted by the committee, was £40,792 per QALY, which is within the range normally recommended by NICE for use in NHS patients under the end of life criteria.

### 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.

Pemetrexed maintenance treatment was recommended by NICE in June 2010 in TA190, for use in patients with non-squamous non-small cell lung cancer, who have not received pemetrexed induction. It is the only treatment recommended by NICE for use in the maintenance setting.

Pemetrexed therefore forms a comparator for erlotinib in this appraisal, as provided in the Scope issued in November 2009. There are however, no clinical trial data directly comparing the two therapies in patients with non-squamous stable disease (the group where both pemetrexed and erlotinib are indicated) and Roche were unable to conduct a formal indirect comparison based on a suitably homogenous populations, as we did not have access to the data from the JMEN study (the pemetrexed maintenance registration study) on the efficacy of pemetrexed in non-squamous stable disease patients.

The ERG however did have access to these data and were able to conduct such an analysis. They independently came to the conclusion that the SATURN and JMEN studies indicated that whilst pemetrexed was associated with an improved PFS compared to erlotinib this was not the case for OS (HR=0.93 [0.66, 1.30]) (ERG Report Addendum, Page 11).

When this information was utilised by the ERG in an economic model this resulted in a conclusion that, for every QALY lost due to a patient being switched from pemetrexed to erlotinib the NHS would gain over £84,000. By the ERG's own estimates pemetrexed offers only 6 weeks longer survival than erlotinib at an incremental cost of over £8,000 (ERG Report Addendum, Page 20). Put another way, with an assumed displacement threshold of £30,000/QALY the current determination of the Committee not to recommend erlotinib, equates to guidance recommending that the NHS should opt to forgo 2.8 QALYs derived from somewhere else in the healthcare system in return for 1 QALY derived through use of pemetrexed over erlotinib in patients with stable, non-squamous, non-small cell lung cancer.

Against this background, the conclusion of the Appraisal Committee that it had "not been presented with a plausible estimate of the cost savings per QALY lost that would be associated with use of erlotinib maintenance compared with pemetrexed" (paragraph 4.18 of the FAD) without investigating the effects of uncertainty surrounding the analysis of comparative effectiveness is unfair. Roche supplied evidence of cost-effectiveness over a range of relative efficacy assumptions, including relative overall survival lower than that estimated by the ERG. In all cases erlotinib was very much more cost-effective than pemetrexed. It seemed unnecessary to formally model even lower levels of erlotinib efficacy as this work demonstrated that using any plausible efficacy measure erlotinib, would still be cost-effective compared to pemetrexed.

(a) All the evidence available indicates that at best pemetrexed maintenance, the only NICE approved regimen in this setting, is only marginally more effective than erlotinib in patients with non-squamous stable disease. At no point in this appraisal were the Committee presented with any scenario in which erlotinib would be considered anything other than cost-effective compared to pemetrexed maintenance in this group and at no point did the Committee seek to obtain cost-effectiveness analyses with alternative relative efficacy scenarios, to investigate uncertainty.

(b) 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 (TAG 190). Generalisability of trial data could not therefore constitute a valid reason for refusing to investigate other aspects of uncertainty.

It is therefore unfair for the Committee to refuse to recommend erlotinib as maintenance therapy in non-squamous patients who have not received pemetrexed based induction, without considering sensitivity analyses to determine the cost-effectiveness consequence of assuming different relative efficacy scenarios of erlotinib compared to pemetrexed, in circumstances where erlotinib would have to be very considerably less effective than suggested by the trial data and the indirect comparison with pemetrexed for erlotinib not to be cost-effective in these patients. Such analyses were provided by Roche in the first ACD response yet it appears unclear as to how these analyses have been considered by the committee.

Should this appeal by upheld, Roche propose to provide NICE with further analyses and real-number Kaplan-Meier data from the SATURN study in order to inform further sensitivity analysis of erlotinib compared to pemetrexed in stable disease patients with non-squamous histology. It is Roche's belief that such analyses will demonstrate conclusively that the relative efficacy of pemetrexed compared to erlotinib would have to be implausibly far from that indicated by the ERG's current indirect comparison for erlotinib to not be considered cost-effective in this group and that therefore, irrespective of any uncertainty, erlotinib should be recommended in this group.

**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.**

NICE's supplementary advice "Appraising life-extending, end of life treatments" provides that the advice should be applied when three listed criteria are satisfied. One of these is that "the treatment is licensed or otherwise indicated, for small patient populations (Paragraph 2.1.3). When assessing the application of these criteria "the Appraisal Committee will take into account the cumulative population for each licensed indication …" (Paragraph 3.4).

NICE has issued no guidance as to the proper interpretation of "small patient populations" save for the information at Paragraph 3.4. This lack of transparency produces results that are unfair in general and in the context of NICE's appraisal of erlotinib in particular.

(a) 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.

In circumstances where the criteria which determine whether the end of life criteria may be applied are unclear, companies cannot assess how these criteria will be applied to their products, whether there is any purpose making a submission to NICE at all or, if so, how a submission should be presented. The NICE Appeal Panel which considered the appeal in respect of treatments for renal carcinoma, suggested that it would not be appropriate to specify a fixed patient population to determine eligibility for the end of life criteria. If this is the position then fairness requires that it should be formally stated by NICE and the Institute should identify the threshold number to be "normally" applied, as it does in relation to the other criteria, namely the life expectancy of eligible patients and the number of months of additional life provided by the technology under consideration.

It is a fundamental part of a fair procedure that the test to be applied by the decision making body should be stated so that an applicant is not "shooting in the dark", but is aware of the threshold he has to meet. In this case, the lack of transparency in relation to the Institute's definition of "small patient populations" means that, in practice, manufacturers can have no certainty as to whether their product will be eligible. This is unfair.

(b) The lack of any guidance to Appraisal Committees as to the meaning of "small patient populations" results in inconsistent approaches in different appraisals; this is also unfair.

The lack of any guidance on the proper approach to "small patient populations" results in different approaches being applied in different appraisals. There seems

to be no reason why "small patient populations" should be interpreted differently in different appraisals; accordingly, as a matter of fairness, NICE should ensure that its Appraisal Committees apply consistent standards when determining whether the end of life criteria should apply and, in that context, clear guidance as to the meaning of a "small patient population" is required.

If, contrary to Roche's view, Appraisal Committees are intended to exercise discretion in determining whether a product is indicated for a "small patient population" for the purposes of the end of life criteria, based on particular features of an appraisal, then fairness requires that the factors to be taken into account by the Committee in exercising their discretion, should be clearly stated.

(c) The interpretation of "small patient population" by the Appraisal Committee includes patients who are not, in fact, eligible for erlotinib therapy.

At paragraph 4.21 of the FAD, the Appraisal Committee concludes that erlotinib does not satisfy the "small patient population" criteria. The reason given by the Committee is based on its approach to the cumulation of patients who may receive erlotinib therapy for any of its authorised indications.

The Committee therefore referred to the 6,700 patients who receive first line chemotherapy for non-small cell lung cancer in the UK, some of whom would subsequently receive erlotinib as maintenance treatment rather that as second-line therapy. In addition, the Committee noted that erlotinib is authorised for the treatment of patients with metastatic pancreatic cancer and stated "most of the 7,000 patients with pancreatic cancer present with metastatic disease and erlotinib would potentially be indicated for this population". While the Committee did not state its conclusions regarding the size of the patient population who might receive erlotinib, the Committee expressed the view that "the true size of the cumulative population potentially eligible for treatment with erlotinib according to its UK marketing authorisation was not small and was considerably higher than the manufacturer's estimate" of around 4,100 patients.

In support of its approach, the Appraisal Committee referred to the decision of the Appeal Panel which considered the appeal against the FAD for treatments for advanced and/or metastatic renal cell carcinoma. In that appraisal, an appeal had been based on whether, in determining the size of a patient population, it was appropriate for the Appraisal Committee to cumulate the patients for which a product was actually used or recommended by NICE or whether it was simply appropriate to consider the population eligible in accordance with the marketing authorisation. The Appeal Panel in that case based its decision on the terms of the marketing authorisation. What the Appeal Panel was not asked to consider in that case however, was how the population of patients eligible for treatment in accordance with a marketing authorisation should be determined. In particular, whether the population should be determined simply by reference to all those patients with the condition identified as an indication in the authorisation or

whether the eligible patient population should be limited to those who could potentially receive therapy in fact (e.g. taking into account the fact that patients will receive treatment as maintenance or second line, but not both and the fact that a proportion of patients will be excluded from receiving treatment as a result of, for example, performance status).

If, as NICE say, the rationale for limiting the scope of the end of life advice to products indicated for a small patient population, is the fact that "higher prices and therefore reduced cost effectiveness are more likely to be justified, given the need to recoup the costs of development of the product from more limited licences", then the size of the patient population should be determined by the number of patients who may potentially receive treatment in reality - i.e. excluding the proportion of patients who, while theoretically eligible for treatment in accordance with the marketing authorisation, could never receive such such therapy.

If that approach is applied to erlotinib then, even though the Committee does not explain its calculation of the patient population who may receive the product for non-small cell lung cancer, its conclusions set out at paragraph 4.21 are nevertheless incorrect. In particular, while the Committee states that "most of the 7,000 patients with pancreatic cancer…. and erlotinib would potentially be indicated for this population", most patients who are diagnosed with pancreatic cancer are not fit enough to receive treatment with erlotinib. It is relevant that NICE's appraisal of gemcitabine, indicated for both locally advanced and metastatic pancreatic cancer, concluded that only approximately 600-840 patients per year would receive therapy. This is broadly consistent with a total use of erlotinib in approximately 4,100 patients, which Roche believes should be viewed as a small patient population.

(d) <u>The interpretation of "small patient population" by the Appraisal Committee considering erlotinib is inconsistent with that followed in other appraisals.</u>

As stated at paragraph 4.21 of the FAD, Roche calculated that, if all patients fit for treatment in its licensed indications were to receive erlotinib, around 4,120 patients would be eligible for treatment each year. This figure compares very closely with that for pemetrexed calculated in the same way (5,215 patients, see table 7 Roche's response to the ACD, submitted 8 July 2010). Nevertheless, pemetrexed was found to satisfy the small patient population criterion in TAG 190, whereas the Committee found that erlotinib did not.

The reason for the different outcome is the fact that different approaches have been taken by the Appraisal Committees considering different appraisals. Examples of these were provided by Roche in its response to the second ACD dated 16 December 2010. In summary:

- In the appraisal of trastuzumab in metastatic gastric cancer (TAG 208), the Appraisal Committee calculated the size of the patient population by reference to the patients suitable for treatment, excluding patients who could not in practice receive chemotherapy. In that appraisal a patient population of 7,000 was found to be "small".
- In the appraisal of pemetrexed for maintenance treatment of non-small cell lung cancer (TAG 190) the Appraisal Committee calculated the size of the patient population by reference to those patients who were "suitable" for therapy across all the licensed indications - i.e. excluding a significant proportion of patients with non-squamous metastatic disease from the first line indication
- In contrast the Appraisal Committee considering erlotinib has adopted a different approach, seemingly cumulating all patients who may fall within the wording of the authorisation irrespective of, for example, performance status and eligibility for treatment in fact.

Regardless of how patient numbers for end of life criteria are calculated, the approach should be consistent. It has not been consistent in this case; that is unfair.

(e) <u>The basis for the Appraisal Committee's conclusion that almost 7,000 patients with pancreatic cancer are eligible for treatment with erlotinib is unclear</u>

The Appraisal Committee relies upon an assertion that "most of the 7,000 patients with pancreatic cancer" would be eligible for erlotinib therapy. The basis for this figure is not explained and, while Roche believes it is incorrect, the company has been prejudiced in its ability to respond to it.

In any event however, the majority of patients presenting with pancreatic cancer are not fit enough to receive therapy with erlotinib and are not, in fact eligible for treatment (see paragraph (c) above).

**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**

At paragraph 4.22 of the FAD, the Committee states that it "did not consider that robust evidence had been provided to demonstrate an extension to life of at least 3 months". However this is inconsistent with the available evidence, is unexplained or is otherwise unfair.

(a) The mean overall survival benefit associated with erlotinib therapy compared with best supportive care for the whole stable disease population was estimated at 3.3 months by Roche in our initial submission and 4.2 months by the ERG in their first ERG report.

(b) In relation to the squamous population, the extension to life modelled by Roche was 4.6 months (response to the Second ACD table 1) and modelled by the ERG was 3.4 months (paragraph 3.4 of the FAD). In addition, Roche provided NICE with details of a truncated (unmodelled) mean survival gain of 3.6 months (Table 1 from the response to the second ACD). All of these analyses show a survival advantage significantly in excess of 3 months. (For completeness, in addition an analysis of median survival data (unmodelled and not representative of the magnitude of survival benefit given divergent survival curves) shows an overall survival benefit associated with erlotinib treatment of 3 months (paragraph 3.7 of FAD) .

**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**

At Section 4.18 of the FAD one of the reasons given for not recommending erlotinib as an alternative to pemetrexed in patients with non-squamous stable disease after first-line chemotherapy is because non-squamous patients increasingly receive pemetrexed as part of first-line treatment, precluding its use at second-line.

Although this may be a small patient group, it was included in the Scope and Roche's submission, critiqued by the ERG, showed erlotinib to be more cost-effective and cost saving compared with pemetrexed. In the context of the Scope and the improved cost effectiveness of erlotinib, the fact that small numbers of patients may be affected, does not constitute a valid reason for declining to issue guidance.

For completeness, if the Appraisal Committee concludes that pemetrexed is not a valid comparator, the logical and fair result is that there is no longer any reason to split the stable disease population and guidance should be based on a comparison of erlotiniob with best supportive care across the licensed indication for erlotinib.

2. **Ground 2: The conclusions of the Institute are not reasonable based on the evidence available to it**

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

At paragraph 4.4 of the FAD, the Appraisal Committee refers to the fact that the results for patients with stable disease were based on a post hoc subgroup analysis of 55% of the SATURN trial population and that the results for the subgroups of patients with squamous and non-squamous disease were also post hoc analyses based on a disaggregation of the stable disease population. The Committee comments that there were "relatively small numbers of patients" in the squamous and non-squamous subgroups and states that it was aware that "the SATURN trial had not been designed for such analyses". As a result of these matters, the Committee states "it therefore regarded that the true magnitude of the benefits of erlotinib in these patient populations was uncertain".

While the fact that an analysis was not pre-defined may mean that the results are unreliable, that is not always the case. The stable patient population from the SATURN trial was one identified by the European Medicines Agency (EMA) during their consideration of the application for a variation to the marketing authorisation for erlotinib to include maintenance therapy as an indication. The squamous and non-squamous subgroups were accepted by the Appraisal Committee on the basis that it concluded "it was justified in considering the squamous and non-squamous populations separately on clinical grounds" (paragraph 4.15 of the FAD).

It is unreasonable to conclude that analyses required by the EMA and by the Appraisal Committee are unreliable or uncertain simply because they are defined post hoc. .

In these circumstances, the Appraisal Committee's conclusions at paragraph 4.4 of the FAD, that the benefits of erlotinib in the stable patient population, in patients with squamous and with non-squamous disease are uncertain due to the post hoc nature of the analyses and, without considering the results, due to relatively small patient numbers, are not reasonable. The position is directly comparable to that considered by the Court of Appeal in R ota Servier Laboratories Ltd v NICE (2010).

**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.**

Following their assessment of Roche's submissions, the ERG produced an ICER for pemetrexed as maintenance treatment in non-squamous non-small cell lung cancer of £75,000 per QALY and ICERS of £68,000 and £44,000 per QALY for erlotinib versus

best supportive care in patients with non-squamous and squamous tumours, respectively (Table 12 of Addendum to ERG report). In other words, the ERG calculated (when applying a similar modelling approach) that erlotinib is *more* cost effective than the recently NICE approved maintenance agent pemetrexed in non-squamous tumours and provides *substantially* better value for money in those individuals with squamous tumours, who currently have **no** maintenance option.

The only reason given by the Appraisal Committee to justify this surprising decision is their concern that the results from erlotinib shown in SATURN are unlikely to be reflected in the UK population, where patients are less fit and have different prognostic characteristics. As explained at point 1.1 above, Roche does not understand the basis for the Committee's concerns and believes they are unfounded. In these circumstances NICE's rejection of erlotinib as not cost-effective, despite being found to be more cost effective than another product recommended by NICE is not reasonable.

## REMEDIES

As a result of the matters raised in this appeal, Roche respectfully requests the Appeal Panel to return this appraisal to the Appraisal Committee for further consideration with the following directions:

- The Committee to reconsider the SATURN data, identifying the evidence relied upon to support any conclusion that the trial population may not be generalisable to the patients who would receive therapy with erlotinib in England and Wales and explaining why any differences in the trial population may affect the outcomes of treatment in the English population.

- That the results of the stable disease population from the SATURN trial (the majority of the trial participants and a group defined by the regulatory authority) are not necessarily unreliable because they are based on a post hoc analysis.

- The Committee to investigate and consider basing guidance on an analysis of the cost-effectiveness of the full stable disease population, consistent with the approach followed by the regulatory authority.

- The Committee to obtain and consider analyses investigating potential uncertainty surrounding the estimates of overall survival associated with erlotinib treatment and pemetrexed treatment and their effects on the cost effectiveness of treatment.

- That the Committee should not refuse to issue guidance based on a comparison with pemetrexed simply because the Committee believes that use of pemetrexed is declining, in circumstances where NICE has recently recommended use of pemetrexed for this indication and the comparison is identified in the Scope.

- That the Committee would require cogent reasons not to recommend use of erlotinib rather than pemetrexed in patients eligible for both treatments, in circumstances where Roche and the ERG have found erlotinib to be of similar effectiveness but less cost.

- The Committee to reassess erlotinib in the context of the advice on end of life treatments:

    - Defining “small patient populations” and following the same approach as applied in TAG 190;

    - Reconsidering the extension to life associated with erlotinib maintenance treatment, particularly in the context of the full stable disease population.

## REQUEST FOR ORAL HEARING

Roche requests an oral hearing for the determination of this appeal.