[redacted]

8th July 2010

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BY E-MAIL

Re: Erlotinib monotherapy for the maintenance treatment of non-small cell lung cancer ACD

Dear Kate,

Please find below Roche's comments on the ACD on the use of Erlotinib monotherapy for the maintenance treatment of non-small cell lung cancer. As previously agreed a supplementary evidence submission and 3 associated economic models are also provided separately for the appraisal committee's consideration..

Our commentary on the ACD relates to 3 key areas:

1. Rationale for and results of submission of new evidence
2. Erlotinib and NICE End of Life Criteria
3. Comments on specific summaries of the evidence within the ACD

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

Yours Sincerely,
[redacted]

1. Has all relevant evidence been taken into account?

As the wording of the EMA Marketing Authorisation (MA) for Tarceva (erlotinib) is different from that originally sought by Roche and anticipated during scoping and preparation of the Manufacturer's Submission, key evidence about the clinical and cost-effectiveness were not included in the original submission or reviewed by NICE or the ERG. Without proper consideration of this new evidence guidance based upon the most relevant evidence cannot be formulated.

Specifically, the committee have yet to consider:

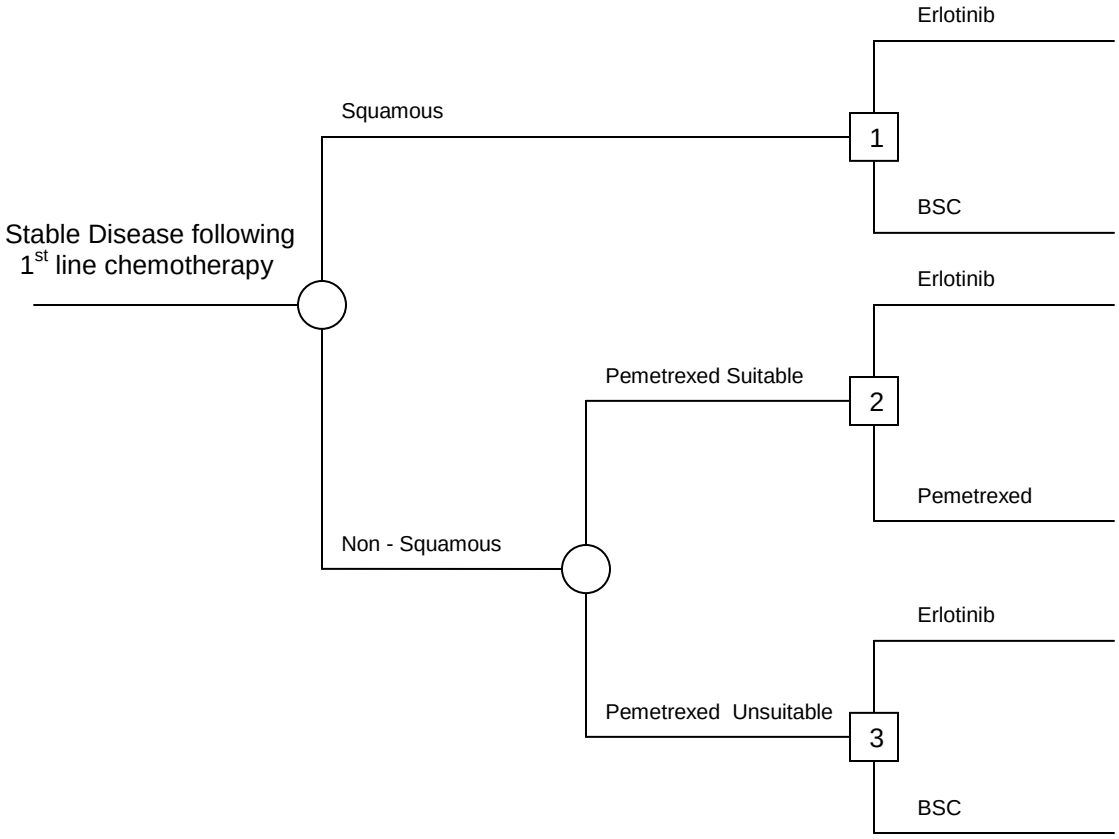
1. The comparison of erlotinib vs best supportive care (BSC) in patients with squamous (SQ) histology and stable disease as best response to induction

2. The comparison of erlotinib vs pemetrexed in patients with non-squamous (NSQ) histology and stable disease (SD) as best response to induction for whom maintenance with pemetrexed is suitable

3. The comparison of erlotinib vs pemetrexed in patients with non-squamous histology and stable disease as best response to induction for whom maintenance with pemetrexed is unsuitable

These three required comparisons are illustrated in the decision tree below.

Figure 1. Summary of decision problem



As noted in section 4.4 of the ACD, whilst an analysis was presented in which erlotinib was compared to pemetrexed in patients with non-squamous histology this analysis incorporated patients with a best response to induction other than 'stable disease'. As the license for erlotinib restricts the use of erlotinib in maintenance treatment to those patients with stable disease as best response following induction, this analysis is no longer relevant. The evidence required to enable the comparison of erlotinib to pemetrexed in the NSQ SD population has not yet been presented to the committee.

Whilst in the original submission an analysis comparing erlotinib to best supportive care in patients with stable disease following induction was provided this patient population was not analysed in terms of a patient's underlying disease histology. The absence of this analysis was noted by the committee in section 4.4 of the ACD. Neither the evidence needed to compare erlotinib to best supportive care in those patients with squamous SD

or those patients with non-Squamous SD has therefore been considered by the committee.

Also during the development of these new models the opportunity was taken to incorporate improvements and modifications suggested by the ERG during their initial review and correct certain errors which became apparent.

1.1 Evidence previously submitted

In support of its application to the EMEA to extend the MA for Tarceva (erlotinib) to cover maintenance therapy of patients with non-small-cell lung cancer (NSCLC) after first-line platinum-doublet chemotherapy, Roche conducted a single, large randomised, placebo-controlled, clinical trial (RCT), SATURN. This met its primary end-point of improving progression-free survival (PFS) and also significantly improved overall survival (OS) in patients with NSCLC non-progressive after completing first-line platinum-based chemotherapy.

During its review, the EMEA – possibly sensitised by recent appraisals of NSCLC treatments that work only in tumours of a particular histology (pemetrexed) or epidermal growth factor receptor (EGFR) genotype (gefitinib) – expressed an interest in limiting the maintenance indication for erlotinib to those patients gaining most benefit. Various predictors of benefit were discussed by Roche and the EMEA – both histology and EGFR genotype were considered and rejected as neither could be used to select patients without excluding a considerable proportion of those benefiting from treatment.

However, analysis of outcomes in SATURN, according to patient response to first-line platinum-based chemotherapy (objective response *versus* disease stabilisation; SD), revealed that although all SATURN entrants obtained similar extensions in time to disease-progression, OS benefit was largely confined to those with a poorer (SD) response to their induction chemotherapy. As a consequence, the European maintenance indication for erlotinib was limited to this group (in the USA the FDA recommended erlotinib as a maintenance treatment for all patients achieving at least disease stabilisation after platinum-based chemotherapy).

Discussions between Roche and the EMEA about the wording of the erlotinib maintenance indication were ongoing at the time of the Decision Problem Meeting (teleconference) between Roche and the NICE project team on 10th December 2009. At this point there was also uncertainty around what the appropriate comparators should be – the Scope stated that "*for people with non-squamous NSCLC: Pemetrexed monotherapy may be included as a comparator, dependent on the outcome of the ongoing STA: pemetrexed for maintenance treatment of non-small cell lung cancer"* , but an ACD for pemetrexed was not published until 17th December 2009, the FAD was released on 1st April 2010 and the Final Guidance only published in June 2010, four months after the deadline for submissions in the erlotinib appraisal.

With more than usual uncertainty around the erlotinib indication and the relevance of pemetrexed as a comparator (a particularly problematic comparator given the lack of a head-to-head comparison and a paucity of data from which to construct any type of network analysis) Roche requested at the Decision Problem Meeting permission to defer submission. This permission was not granted and so Roche made a submission which included the following comparisons:-

Table 1. Patient groups and comparators in the original manufacturer's submission

Patient Group	Comparator	Relevance to Decision Problem
1. SATURN ITT population	Best supportive care (BSC)	**This comparison is now irrelevant.** The ITT patient group includes patients with objective response after chemotherapy who have limited OS benefit from maintenance and are outside of the erlotinib Marketing Authorisation
2. SD patients in SATURN	Best supportive care (BSC)	This comparison is still relevant if one concludes histology is not a sub-group of relevance in the use of erlotinib and is therefore included in the response. However amendments have been made in light of ERG feedback and errors identified by Roche that justify further consideration by the committee (i.e. use of an inappropriate post-progression BSC cost)

3. Non-squamous patients from SATURN	Pemetrexed	**This comparison is now irrelevant.** The non-squamous patient group includes patients with objective response after chemotherapy who are outside of the erlotinib Marketing Authorisation

As can be seen from Table 1, only one of the combinations of patient group and comparator included in the original Roche submission are relevant to both the Marketing Authorisation for erlotinib and the clinical situation pertaining in England and Wales following the approval by NICE of pemetrexed maintenance therapy for non-squamous NSCLC at least stable after 4 cycles of platinum-based chemotherapy. Furthermore as the new comparisons presented in the supplementary evidence submission accompanying this response incorporate substantial refinements and corrections, largely based on ERG comments, these have also been incorporated into the original stable disease comparison where they make a substantial difference to cost-effectiveness estimates. The required additional economic and clinical evidence is supplied in the attached supplementary evidence submission.

1.2 Results

1. The ICER of erlotinib compared to best supportive care in those patients unsuitable for pemetrexed (either due to histology or due to pemetrexed based induction) is £39,936. This equates to a cost per life year gained of £24,029 with a 3.9 month expected life extension in a patient population with a typical prognosis of around 12 months.

2. The base-case ICER of erlotinib compared to best supportive care in patients with squamous histology and stable disease following induction is £35,491. This ICER is largely driven by the significant 4.3 month life extension provided by erlotinib in a histological group in which overall survival is around 10 to 11 months. This OS gain amounts to an over 40% extension in a patients life expectancy at a cost per life year gained of £20,433.

3. The ICER of erlotinib compared to best supportive care in patients with non-squamous histology and stable disease as best response following induction is £40,020.

4. The Non-squamous SD analysis demonstrates conclusively that despite the uncertainty surrounding the relative efficacy of pemetrexed compared to erlotinib in this specific population erlotinib is cost effective compared to pemetrexed (NICE approved in TA190). The total cost of pemetrexed maintenance is around double the cost of erlotinib maintenance. Base-case results varied from erlotinib being more effective and less costly than pemetrexed to pemetrexed being more effective and more costly than erlotinib.

2. Are the summaries of clinical and cost-effectiveness reasonable interpretations of the evidence?

2.1 Clinical Effectiveness

2.1.1. Impact of pemetrexed availability at first-line on benefit of erlotinib maintenance

Section 3.11 of the ACD reports the ERG's concerns about the generalisability of SATURN because *"no patients had first-line treatment with pemetrexed, which is becoming a more common first-line treatment for patients with non-squamous disease"*. This appears to have caused concern to the appraisal committee as in the ACD's "Consideration of the Evidence Section" (Section 4.10 specifically) it is stated that *"The committee noted that no one in the SATURN trial had received first-line treatment with pemetrexed and cisplatin, which is now becoming a commonly used combination chemotherapy regimen for patients with non-squamous disease. It therefore concluded that there was uncertainty about the clinical benefit of erlotinib in patients who had previously received pemetrexed and cisplatin"*

Although true that the SATURN population did not include patients who had received first-line pemetrexed, the underlying concern does not seem valid for four reasons:-

1. The concept underpinning SATURN was that patients should all have received a standard platinum-based chemotherapy prior to randomisation and a list of regimens was provided covering those widely used around the world. The intent was to ensure that patients had received optimal first-line therapy so that any benefit associated with erlotinib could be attributed to maintenance and not to remediation of sub-optimal first-line therapy. At the time that SATURN was planned and recruiting pemetrexed was not approved as a first line treatment for non-squamous NSCLC and was not included in the list of treatment options. If SATURN were being started today it would undoubtedly have included pemetrexed-cisplatin in the menu of suitable chemotherapy regimens.

2. The entry criterion for SATURN was “at least stable disease after platinum doublet chemotherapy” i.e. entry was defined by disease status not, primarily, by prior treatment history. An interaction between erlotinib maintenance and the prior chemotherapy used to achieve at least stable disease was not part of the hypothesis underpinning the study, nor is such an interaction plausible given the entirely different modes of action of non-specific cytotoxic chemotherapy and EGFR directed therapy with erlotinib

3. As demonstrated in Figure 9 of the original Manufacturer’s Submission for this appraisal, retrospective analysis of treatment outcome in the SATURN study by first-line chemotherapy showed no difference according to whether patients received the predominant chemotherapy (gemcitabine plus cisplatin) or another platinum doublet.

4. A more important difference between SATURN and UK clinical practice lies not in the availability of pemetrexed first-line but in its availability at relapse. In SATURN 18-21% of SD patients received pemetrexed at second-line. Since pemetrexed is known to be active at second-line its availability is likely to have diluted the OS benefit seen in the study compared with that which would be seen in the UK, where the only proven and NICE approved second-line agent (apart from erlotinib) is docetaxel – this is too toxic for many patients and, effectively, limits post first-line treatment.

2.1.2. Lack of statements from patient experts

Section 4.7 of the ACD states that *“The Committee noted that no statements were received from patient experts”*. This may be factually correct but should not, as appeared to be the case when this matter was raised during the AC meeting, be taken as evidence that patients and their representatives do not value erlotinib maintenance therapy sufficiently to make a submission. The deadline for submissions to NICE for this appraisal fell before a Marketing Authorisation had been received for erlotinib as maintenance therapy. This being the case, it is very unlikely that any clinician working within the NHS would have discussed erlotinib maintenance as a treatment option with patients prior to the submission deadline. As such it is unlikely that many individual patients would have been aware of the data supporting erlotinib maintenance therapy

and sought further information about the treatment or help in accessing it from the relevant patient groups. Under these circumstances statements from patient experts are far less likely. Even if patients were aware of the SATURN study and the results that had, up to the time of submission, been made public they could not of have been aware of the magnitude of benefit achieved with erlotinib maintenance in its approved (SD) group as the analysis of outcomes according to response to first-line chemotherapy was only presented for the first time at the ELCC in May 2010 (Coudert *et al* 2010). Lack of awareness of the SD results may also have influenced the desire of other stakeholders to submit to NICE and would certainly have had an impact on the content of any submission that they made.

2.2 Cost Effectiveness

As the summary of cost-effectiveness evidence contained within the ACD is founded upon an incomplete evidence base whilst, it may be an accurate summary of the evidence presented to the committee it does not represent an accurate summary of all the relevant economic evidence associated with erlotinib in 1LM.

2.2.1. The true cost of erlotinib to the NHS

In section 4.16 of the ACD it is noted that 'the committee was persuaded that the costs of erlotinib in the manufacturer's model had been underestimated and that the ERG's revisions more closely estimate the true costs than those in the manufacturers submission'. This statement is of doubtful accuracy for one key reason. In deriving their expected cost of erlotinib to the NHS the ERG assumed that a patient would be dispensed a pack of erlotinib every 30 days of PFS.

Whilst the ERG's methodology is thorough it ignores the disparity between treatment cessation and disease progression observed in SATURN (and in clinical practice) and therefore over-estimates the mean cost of erlotinib per patient.

Whilst it does appropriately calculate the mean per protocol cost of erlotinib it fails to account for the fact that if a patient has ceased treatment (due to adverse event, patient

preference etc) prior to progression they will not in practice be dispensed an additional pack of erlotinib every 30 days despite being in PFS. The ERG's method effectively assumes that a patient who has completely ceased treatment will continue to be dispensed packs of erlotinib whilst still in PFS. This is clearly incorrect and brings into doubt the notion that the ERG's method estimates the true cost of erlotinib to the NHS.

In the additional analyses presented by Roche in response to the ACD, the method of the ERG was followed with the substitution of the proportion of patients in PFS every 30 days with the proportion of patients yet to cease treatment every 30 days. This more accurately estimates the true cost of erlotinib to NHS including tablet wastage and potential disparities between disease progression and treatment cessation. Further detail on the approach used in the new analyses presented is provided in the attached supplementary evidence submission.

2.2.2. Half Cycle Correction

In section 3.7 of the ACD when summarizing the Roche economic models submitted it is noted that patients within the model moved health states 'at the end of each cycle'. This is factually incorrect as a half cycle correction was applied within all 3 models previously submitted and so a patient transitioned mid-cycle rather than at the end of each cycle.

3. Are the provisional recommendations sound and a suitable basis for guidance to the NHS?

The provisional recommendations are not a sound and suitable basis for guidance to the NHS for two key reasons:

1. As discussed previously the ACD and provisional recommendations contained within the ACD were founded upon an incomplete evidence base and one containing errors that significantly affect the estimate of the most plausible ICER. (in terms of the SD economic evidence submitted).

2. Erlotinib was not granted consideration under NICE's supplementary end of life (EoL) guidance on the grounds of population size and the validity of the OS advantage provided by erlotinib despite the patient population eligible for erlotinib being smaller than that for pemetrexed (in which EoL status was granted in appraisal TA190) and the ERG conducting independent analysis on the overall survival data from SATURN and estimating that the expected OS advantage provided by erlotinib in the SD population was approximately 4.2 months

Regarding Point 1 above, the additional evidence submission enables the committee to address these issues in full.

Regarding point 2, Roche believes that the reasoning behind the conclusion that erlotinib should not be considered in the light of NICE's supplementary end of life guidance is flawed and entirely inconsistent with the recent decision to apply EoL consideration to pemetrexed as a maintenance therapy. Each of the issues identified by NICE in rejecting erlotinib's potential consideration under end of life is discussed in turn below.

3.1 Number of patients covered by the licensed indications for erlotinib (relapsed NSCLC, 1LM after platinum-based chemotherapy for NSCLC and pancreatic cancer)

A starting point is to consider the number of patients covered by each license indication assuming all patients diagnosed with a condition represent “eligible” patients, though is clearly not the case. This has been done for both erlotinib and pemetrexed in the “All licensed patients” column of Table 6 below.

However even if no other eligibility criteria are applied it is wrong to count patients at successive lines of therapy as discrete eligible patients – a patient who progresses *on* maintenance therapy with erlotinib or pemetrexed will not receive the drug as their treatment for relapsed disease. Similarly, a patient who receives pemetrexed at first line is precluded (by the pemetrexed Marketing Authorisation) from receiving the drug at maintenance. In short, patients will not receive erlotinib or pemetrexed as more than one line of treatment for NSCLC. Therefore, the “Assuming drug used in only one line of therapy” column of Table 6 represents the absolute maximum eligible patient population for the two drugs based solely on diagnosis.

Table 6. Numbers of patients eligible for erlotinib and pemetrexed within their licensed indications assuming diagnosis is the only factor defining eligibility

Indication	All licensed pts		Assuming drug used in only one line of therapy	
	Erlotinib	Pemetrexed	Erlotinib	Pemetrexed
Pancreatic cancer	6,866[1]	N/A	6,866[1]	N/A
NSCLC -1st line SIII/IV -1st line maint. - relapsed	 N/A 6,333[2] 25,330[3]	 16, 464[4] 7,573[5] 16,464[6]	 N/A 0 25,330[3]	 16,464[4] 0 0
Mesothelioma	N/A	2,063[7]	0	2,063[7]
Total	38,529	40,501	32,196	18,527

[1.] New cases of pancreatic cancer in England and Wales 2007 ISD on-line. Conservative assumption that all pancreatic cancer cases are diagnosed as or become metastatic

[2.] Assumes:

- 33,835 new cases of lung cancer in England and Wales (ISD online, 2010)

- 80% of lung cancer cases are NSCLC resulting in 27,068 cases of NSCLC (CRUK 2010 a).
- 10.7% of NSCLC cases (2,896) are diagnosed early and treated with radical surgery (National Lung Cancer Audit, 2009) with 60% (1,738) cured by surgery (CRUK, 2010b) leaving 25,330 patients diagnosed with or developing inoperable disease
- All cases of advanced disease receive platinum based chemotherapy as recommended by NICE for suitable patients (NICE, 2005)
- 25% of patients treated with platinum based chemotherapy achieve stable disease (required for erlotinib maintenance) (SATURN study; Cappuzzo *et al,* 2010)

[3.] Assumes all cases of advanced NSCLC get first-line chemotherapy and all receive erlotinib at disease progression (see 2)
[4.] Same assumptions as 2 plus additional assumption that 35% of advanced NSCLC (8,892) has squamous histology and is unsuitable for pemetrexed treatment (CRUK, 2010a)
[5.] Assumes 46% of patients have at least stable disease after 1st line chemotherapy and all non-squamous patients get pemetrexed maintenance therapy (SATURN study; Cappuzzo *et al* 2010)
[6.] Assumes all cases of advanced NSCLC get first-line chemotherapy and all non-squamous patients receive pemetrexed at disease progression
[7]. Assumes all new cases (ISD online, 2010)get pemetrexed and cisplatin

However, patients with pancreatic cancer, NSCLC and mesothelioma have high levels of comorbidity and low levels of general fitness which in many cases preclude them for being candidates for any systemic therapy and it is misleading to leave these "treatment unsuitable" patients in the eligible treatment pool when determining whether EoL considerations apply. Table 7 gives an estimate of the patients actually capable of receiving treatment in each of the licensed indications.

Table 7 Patients actually eligible for treatment with erlotinib and pemetrexed

Indication	Patients eligible for treatment	
	Erlotinib	**Pemetrexed**
Pancreatic cancer	600-800 pa[1]	N/A
NSCLC -1st line SIII/IV -1st line maint. - relapsed	 N/A 1,672[2] 1,655[3]	 4,347[4] 0[5] 0[5]
Mesothelioma	N/A	846[6]
Total	4,127	5,215

[1.] NICE (2001) Guidance on first-line use of gemcitabine for advanced pancreatic cancer (TA25)

[2.] This figure adjusts the 25,330 new cases of inoperable NSCLC in the UK each year (see Table 6, Note 2) to account for:

- Only 55% (13,932) being PS 0-1 and suitable for first-line platinum-based chemotherapy (Peak, 2010)
- Only 48% (6,687) of PS 0-1 patients receiving chemotherapy (National Lung Cancer Audit, 2009)
- 25% of first-line chemotherapy recipients (1,672) achieving Stable Disease and being eligible for maintenance (SATURN study; Cappuzzo et al, 2010)

[3.] This figure adjusts the 25,330 new cases of inoperable NSCLC in the UK each year (see Table 6 Note 2) to account for:

- Only 55% (13,932) being PS 0-1 and suitable for standard first-line chemotherapy (National Lung Cancer Audit, 2009)
- Only 48% (6,687) of PS 0-1 patients receiving first-line chemotherapy (National Lung Cancer Audit, 2009)
- Of those patients receiving chemotherapy 25% (1,672) achieve SD and are eligible for erlotinib maintenance an indication mutually exclusive with second-line treatment
- 75% (5,015) of patients receiving first-line chemotherapy show disease progression or objective response (i.e. not stable disease) and so are eligible for second-line therapy but not maintenance (which is a mutually exclusive indication)
- 33% of patients relapsing after first-line chemotherapy in the UK receive second-line systemic therapy (Peak, 2010; see also Manufacturer's response to ERG question E5 arising from Roche's original Manufacturer's submission for further discussion of this figure)

[4.] This figure adjusts the 25,330 new cases of inoperable NSCLC in the UK each year (see Table 6, Note 2) to account for:

- Only 55% (13,932) being PS 0-1 and suitable for standard first-line chemotherapy (National Lung Cancer Audit, 2009)
- Only 48% (6,687) of PS 0-1 patients receiving first-line chemotherapy (National Lung Cancer Audit, 2009)
- 35% (2,340) of patients have squamous tumours and so are ineligible for pemetrexed

[5.] If all non-squamous patients received pemetrexed at first line none would be expected to receive at maintenance or second-line

[6.] Costing template for NICE guidance on pemetrexed disodium for the treatment of mesothelioma (TA135) (NICE, 2008) assumes 41% of patients with mesothelioma will receive pemetrexed

Overall it can be seen from Table 7, that using realistic assumptions (mostly taken from or derived from NICE's own guidance or national registry or audit sources) to estimate the number of patients eligible for treatment with erlotinib, the number falls well below that at which EoL considerations can be applied. Furthermore, using the same (where appropriate) or similarly conservative assumptions a similar but slightly higher eligible patient pool is revealed for pemetrexed, where EoL considerations *were* applied during its recent appraisal as a maintenance therapy in NSCLC.

Implicit in the new guidance allowing maintenance therapy with pemetrexed in non-squamous NSCLC is, firstly, NICE's acceptance of the drug's manufacturer's estimate

of the total in-license eligible patient pool of 3,426, which is clearly much lower than the combined incidence of non-squamous non-small-cell lung cancer and mesothelioma in England and Wales and, secondly, that eligible patient pools do not equate to all patients with the diagnosis covered by the Marketing Authorisation.

If approaches based purely on cancer incidence figures and taking no account of factors which exclude many patients from treatment are used to calculate the eligible patient pool – then neither erlotinib or pemetrexed would qualify for EoL considerations, with pemetrexed patient numbers the highest of the two treatments.

The exclusion of erlotinib from EoL considerations based on numbers of patients eligible to receive the drug is not only illogical, but inconsistent with the approach taken by NICE when appraising a competitor product in, essentially, the same indication within the last 6 months.

3.2. Survival benefit of greater than 3 months

In its submission, Roche claimed a survival benefit exceeding 3 months (the threshold for EoL consideration) whilst the independent ERG concluded that Roche had been conservative and that the benefit actually exceeded 4 months. However the AC rejected the survival benefit claim on the basis that it was “modelled” and “not taken directly from the trial”. There are only two approaches to estimating mean survival (the preferred survival metric for the calculation of cost-effectiveness) in a clinical trial:-

1. Wait until all patients recruited into the study have died and calculate the true mean survival (which will still only be a true mean if no patients were lost to follow-up). This approach is clearly impractical, given that even amongst patients with the most deadly illnesses there are long-term survivors. Roche is unable to identify a single NICE appraisal of an oncology product where true mean survival has been available.

2. Carry out some form of modelling to account for those patients still alive at the time of the analysis.

As the overall survival data in SATURN is not complete there is no other alternative to deriving the expected overall survival advantage via modelling. An area under the curve estimate cannot be created if the curve itself does not touch the x axis. To reject the ERGs own analysis of the OS advantage provided by erlotinib as it was 'modelled' is therefore unreasonable in the context of both the NICE Guide to methods and the generic limitations of oncology clinical trials.

An alternative survival metric to the mean, that *can* be taken directly from studies is median survival. This has severe limitations as an overall measure of survival benefit:-

- It is a point estimate and may be greatly influenced by any lack of linearity or symmetry in survival curves which may cause them to come closer together or further apart at a given point thus depressing or inflating the apparent survival benefit

- The degree of separation at the median will depend heavily on the distribution of survival benefit amongst the treated population – if half get no benefit and half get substantial benefit it is possible to have minimal impact on median survival despite a substantial benefit in mean survival

- If a trial population consists of two populations with differing prognosis at baseline (e.g. NSCLC patients with squamous and non-squamous tumours) the median survival advantage for the study population as a whole may be less than for either group individually

Despite these limitations, the median survival benefit in both groups of patients of interest for this submission - patients with squamous tumours and SD after 1st-line platinum based chemotherapy and patients with non-squamous tumours and SD after 1st-line platinum-based chemotherapy increases by 3 months or more (3.0 and 3.1 months respectively) as a result of erlotinib maintanence. The mean OS benefit for these patient groups is 4.5 and 4.2 months respectively.

Thus, in addition to the estimate of 3.3 - 4.2 months improvement in OS in the whole SD population, the improvement in SD in the two populations now of interest reaches 3

months whether measured as median (taken directly from the trial, but a less appropriate metric) or mean (which inevitably involves a degree of modelling).

As such it clear that the survival benefit associated with erlotinib maintenance therapy in the populations under consideration meets the 3 month landmark required for EoL considerations to apply. Therefore Roche finds this conclusion within the ACD an unreasonable conclusion by the committee.

4 Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of gender, race, disability, age, sexual orientation, religion or belief?

Roche are unaware of any such issues with the preliminary recommendations made.