NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Erlotinib for the maintenance treatment of non-small-cell lung cancer

Response to consultee, commentator and public comments on the Appraisal Consultation Document (ACD)

Definitions:

Consultees – Organisations that accept an invitation to participate in the appraisal including the manufacturer or sponsor of the technology, national professional organisations, national patient organisations, the Department of Health and the Welsh Assembly Government and relevant NHS organisations in England. Consultee organisations are invited to submit evidence and/or statements and respond to consultations. They are also have right to appeal against the Final Appraisal Determination (FAD). Consultee organisations representing patients/carers and professionals can nominate clinical specialists and patient experts to present their personal views to the Appraisal Committee.

Clinical specialists and patient experts – Nominated specialists/experts have the opportunity to make comments on the ACD separately from the organisations that nominated them. They do not have the right of appeal against the FAD other than through the nominating organisation.

Commentators – Organisations that engage in the appraisal process but that are not asked to prepare an evidence submission or statement. They are invited to respond to consultations but, unlike consultees, they do not have the right of appeal against the FAD. These organisations include manufacturers of comparator technologies, NHS Quality Improvement Scotland, the relevant National Collaborating Centre (a group commissioned by the Institute to develop clinical guidelines), other related research groups where appropriate (for example, the Medical Research Council and National Cancer Research Institute); other groups (for example, the NHS Confederation, NHS Information Authority and NHS Purchasing and Supplies Agency, and the *British National Formulary*).

Public – Members of the public have the opportunity to comment on the ACD when it is posted on the Institute's web site 5 days after it is sent to consultees and commentators. These comments are usually presented to the appraisal committee in full, but may be summarised by the Institute secretariat – for example when many letters, emails and web site comments are received and recurring themes can be identified.

Comments received from consultees

Consultee	Comment	Response
British Thoracic Oncology Group (BTOG)	Thank you for the opportunity to comment on this ACD. BTOG members have been consulted by email on this matter. The replies received were unanimously positive and supportive of this ACD and therefore BTOG does not have any further comments.	Comment noted. No change to the ACD required.
British Thoracic Society	Thanks for the opportunity to comment on this ACD. We believe that NICE has taken all the relevant evidence into consideration and that this is an appropriate decision.	Comment noted. No change to the ACD required.
CSAS	On behalf of the Commissioning Support, Appraisal Service (CSAS), Solutions for Public Health, I would like to submit our comments on the appraisal consultation document for Erlotinib monotherapy for the maintenance treatment of non-small cell lung cancer. We are in agreement with the recommendations in the ACD not to recommend erlotinib for this indication as on the basis of the evidence considered it is unlikely that this treatment can be considered clinically and cost effective in real life clinical practice.	Comment noted. No change to the ACD required.
CSAS	The key trial presented by the manufacturer (SATURN trial) may not be representative of the UK population. The population in this trial was not typical of UK clinical practice. It had a higher proportion of South East Asians, a slightly younger, probably slightly fitter patient population, a higher proportion of never smokers and a small proportion with a positive EGFR status than would be seen in UK clinical practice. All these factors would be associated with better outcomes. In addition, EGRF positive patients in the UK would not be treated with erlotinib.	Comment noted. The Committee discussed whether the results of the SATURN trial could be generalised to UK clinical practice and concluded that the results from the trial had limited generalisability to UK clinical practice, therefore adding further uncertainty to the true magnitude of the benefits of erlotinib that would be achieved for UK patients. See FAD section 4.5.
CSAS	The SATURN trial required very frequent scans that would be unlikely to be replicated in routine clinical care.	Comment noted. The Committee noted that the RECIST criteria used in the SATURN trial were based on 6-weekly CT scans and considered that such frequent scans were not likely in the routine care of lung cancer patients in the UK. See FAD section 4.11.

Consultee	Comment	Response
CSAS	No patients in the SATURN trial received the most common and more effective first line treatment in the UK (pemetrexed and cisplatin for patients with non squamous disease).	Comment noted. The Committee discussed the first-line treatments received by patients in the SATURN trial, and noted that no patients received first-line treatment with pemetrexed and cisplatin, a regimen that is now commonly used as combination chemotherapy for patients with non-squamous disease because of its superiority to the regimens used in the SATURN trial. See FAD section 4.10.
CSAS	Evaluation of patients with small cell and non small cell disease was based on post hoc stratification in this trial. CSAS agrees with the ERG's comment that this trial was not designed for these analysis and the results of this analysis should be interpreted with caution.	Comment noted. The Committee was aware that the results for patients with stable disease were based on a post hoc subgroup analysis of 55% of the SATURN trial population. Furthermore, 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 and there were relatively small numbers of patients in each subgroup (190 and 297 respectively). The Committee was aware that the SATURN trial had not been designed for such analyses. It therefore regarded that the true magnitude of the benefits of erlotinib in these patient populations was uncertain. See FAD section 4.4.
CSAS	CSAS supports the view of the Appraisal Committee that the true Incremental Cost Effectiveness Ratio (ICER) was greater than those estimated by the manufacturers and the Evidence Review Group (ERG), and well above £50,000 per QALY even after consideration the patient access scheme. The true benefit is also likely to be	Comment noted. The Committee considered that the most plausible ICERs for erlotinib compared with best supportive care would be higher than those estimated

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	even lower than that estimated by the ERG.	by the ERG (£44,800 and £68,100 per QALY gained for treatment of patients with stable, squamous disease and with stable, non-squamous disease respectively) and considerably above £50,000 per QALY gained for treatment of the whole stable disease population. The Committee agreed that the end-of-life criteria were not met in this appraisal, but it noted that even if they were taken into account, the most plausible ICERs were higher than those normally considered to be associated with cost effective treatments. See FAD section 4.23.
CSAS	Cost effectiveness was not demonstrated for erlotinib compared with pemetrexed in patients with stable, non-squamous disease.	Comment noted. The Committee considered that erlotinib was likely to be associated with cost savings per QALY lost compared with pemetrexed in patients with stable non-squamous disease, but that it was not possible to establish a robust estimate. See FAD section 4.23.
CSAS	End of life criteria did not apply as the potential population eligible to receive erlotinib is large and there was no robust evidence of an extension of life of three months.	Comment noted. The Committee considered that the true size of the cumulative population potentially eligible for treatment with erlotinib according to its UK marketing authorisations was not small and was considerably higher than the manufacturer's estimate. See FAD section 4.21. The Committee did not consider that robust evidence had been provided to demonstrate

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		an extension to life of at least 3 months and taken together with the consideration on population size, therefore concluded that the end-of-life criteria were not met in this appraisal. See FAD section 4.22.
NHS Cornwall and Isles of Scilly	On behalf of NHS Cornwall and Isles of Scilly, I would like to submit our comments on the appraisal consultation document for Erlotinib monotherapy for the maintenance treatment of non-small-cell lung cancer. We are in agreement with the recommendations in the ACD not to recommend erlotinib for this indication as on the basis of the evidence considered it is unlikely that this treatment can be considered clinically and cost effective in real life clinical practice.	Comment noted. No change to the ACD required.
NHS Cornwall and Isles of Scilly	The key trial presented by the manufacturer (SATURN trial) may not be representative of the UK population. The population in this trial was not typical of UK clinical practice. It had a higher proportion of South East Asians, a slightly younger, probably slightly fitter patient population, a higher proportion of never smokers and a small proportion with a positive EGFR status than would be seen in UK clinical practice. All of these factors would be associated with better outcomes. In addition, EGFR positive patients in the UK would not be treated with erlotonib.	Comment noted. The Committee discussed whether the results of the SATURN trial could be generalised to UK clinical practice and concluded that the results from the trial had limited generalisability to UK clinical practice, therefore adding further uncertainty to the true magnitude of the benefits of erlotinib that would be achieved for UK patients. See FAD section 4.5.
NHS Cornwall and Isles of Scilly	The SATURN trial required very frequent scans that would be unlikely to be replicated in routine clinical care.	Comment noted. The Committee noted that the RECIST criteria used in the SATURN trial were based on 6-weekly CT scans and considered that such frequent scans were not likely in the routine care of lung cancer patients in the UK. See FAD section 4.11.
NHS Cornwall and Isles of Scilly	No patients in the SATURN trial received the most common and more effective first line treatment in the UK (pemetrexed and cisplatin for patients with non-squamous disease).	Comment noted. The Committee discussed the first-line treatments received by patients in the SATURN trial, and noted that no patients received first-line treatment with pemetrexed and cisplatin, a regimen that is

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		now commonly used as combination chemotherapy for patients with non-squamous disease because of its superiority to the regimens used in the SATURN trial. See FAD section 4.10.
NHS Cornwall and Isles of Scilly	Evaluation of patients with small cell and non small cell disease was based on post hoc stratification in this trial. CSAS agrees with the ERG's comment that this trial was not designed for these analysis and the results of this analysis should be interpreted with caution.	Comment noted. The Committee was aware that the results for patients with stable disease were based on a post hoc subgroup analysis of 55% of the SATURN trial population. Furthermore, 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 and there were relatively small numbers of patients in each subgroup (190 and 297 respectively). The Committee was aware that the SATURN trial had not been designed for such analyses. It therefore regarded that the true magnitude of the benefits of erlotinib in these patient populations was uncertain. See FAD section 4.4.
NHS Cornwall and Isles of Scilly	CSAS supports the view of the Appraisal Committee that the true Incremental Cost-Effectiveness Ratio (ICER) was greater than those estimated by the manufacturers and the Evidence Review Group (ERG), and well above £50,000 per QALY even after considering the patient access scheme. The true benefit is also likely to be even lower than that estimated by the ERG.	Comment noted. The Committee considered that the most plausible ICERs for erlotinib compared with best supportive care would be higher than those estimated by the ERG (£44,800 and £68,100 per QALY gained for treatment of patients with stable, squamous disease and with stable, non-squamous disease respectively) and considerably above £50,000 per QALY

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		gained for treatment of the whole stable disease population. The Committee agreed that the end-of-life criteria were not met in this appraisal, but it noted that even if they were taken into account, the most plausible ICERs were higher than those normally considered to be associated with cost effective treatments. See FAD section 4.23.
NHS Cornwall and Isles of Scilly	Cost effectiveness was not demonstrated for erlotinib compared with pemetrexed in patients with stable, non-squamous disease.	Comment noted. The Committee considered that erlotinib was likely to be associated with cost savings per QALY lost compared with pemetrexed in patients with stable non-squamous disease, but that it was not possible to establish a robust estimate. See FAD section 4.23.
NHS Cornwall and Isles of Scilly	End of life criteria did not apply as the potential population eligible to receive erlotinib is large and there was no robust evidence of an extension of life of three months.	Comment noted. The Committee considered that the true size of the cumulative population potentially eligible for treatment with erlotinib according to its UK marketing authorisations was not small and was considerably higher than the manufacturer's estimate. See FAD section 4.21. The Committee did not consider that robust evidence had been provided to demonstrate an extension to life of at least 3 months and taken together with the consideration on population size, therefore concluded that the end-of-life criteria were not met in this appraisal. See FAD section 4.22.

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NHS Cornwall and Isles of Scilly	On this basis, and on considering the competing demands for funding in the current economic climate, we would not consider Erlotinib monotherapy for the maintenance treatment of non-small-cell lung cancer to be a priority for funding for our local population.	Comment noted. No change to the ACD required.
Roche Products	Thank you for giving us the opportunity to comment upon the 2nd ACD on the use of erlotinib for the maintenance treatment of patients with metastatic non-small cell lung cancer. In general we are disappointed with the conclusions detailed within the ACD and feel the Committee appear to have overlooked, or perhaps not fully considered, key pieces of information in the derivation of the provisional guidance. It is our belief that the ACD contains several conclusions which appear unreasonable in light of the evidence available and conclusions that appear to be inconsistent with previous NICE technology appraisals. Our key points are summarized below.	Comment noted.
Roche Products	The Committee have dismissed the greater than 3 month survival gains observed in SATURN as not generalisable to UK clinical practice for reasons that appear invalid given the evidence available (See section 1.1 and 1.2)	Comment noted. The Committee agreed with comments from the ERG that the mean survival figures were more informative because they were based on all available data for all patients across the whole trial period. The Committee also heard from the clinical specialists that some patients have significantly longer responses to treatment with erlotinib, which was another reason to consider the mean rather than the median values. Although the ERG had not provided an overall survival estimate for the whole stable disease population, the Committee heard from the ERG that this figure was likely to be closer to the mean overall survival estimate for patients in the non-squamous

Consultee	Comment	Response
		group (2.2 months). The Committee did not consider that robust evidence had been provided to demonstrate an extension to life of at least 3 months. See FAD section 4.22.
Roche Products	The Committee have determined that erlotinib does not have a 'small population' due to their belief that 'most' metastatic pancreatic cancer (mPC) patients are potentially suitable for erlotinib. This conclusion would appear to be inconsistent with NICE's own guidance on the treatment of mPC (TA25) and two recent NICE appraisals in which technologies with larger populations than erlotinib were granted consideration under the 'End of Life' guidance (TA208, TA190).	Comment noted. The Committee discussed written evidence from a previous NICE technology appraisal appeal and noted that the Appeal Panel had concluded that it was appropriate, according to the supplementary advice, to add together the patient populations covered by the marketing authorisation for different indications rather than on the basis of actual or recommended use. The Committee therefore considered 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. See FAD section 4.21.
Roche Products	In the squamous histology stable disease group Roche, the ERG and the truncated mean survival advantage direct from SATURN are all clearly above 3 months (4.6 months, 3.4 months, and 3.6 months, respectively). Only the Committee estimated a survival gain less than 3 months for a rationale that appears to be unfounded. Both the ERG and Roche estimate an ICER comfortably below £50,000/QALY in this patient population with the Committee being the only group who estimate an ICER 'above £50,000'. The only apparent reason for this conclusion is the Committee's concerns that the SATURN results would not be replicated in clinical practice due to the issues detailed, and refuted (below).	Comment noted. The Committee acknowledged that the manufacturer had provided additional information about the patient characteristics of the squamous disease population in the SATURN trial during consultation and accepted that these data showed that the number of patients with a prognostic factor was small and was unlikely to significantly bias the estimate of overall survival for this subpopulation. See FAD section 4.9.

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		The Committee agreed that end-of-life criteria were not met in this appraisal, but it noted that even if they were taken into account, the most plausible ICERs were higher than those normally considered to be associated with cost effective treatments. See FAD section 4.23.
Roche Products	For the reasons outlined in section 1.5 it is our belief that in the group of non-squamous histology stable disease patients, erlotinib does provide an overall survival advantage of greater than 3 months at an ICER of less than £50,000/QALY in those patients who in practice would be most likely to receive erlotinib maintenance (i.e. those with EGFR wild type disease).	Comment noted. See above response.
Roche Products	If the guidance issued by NICE in other appraisals is followed (TA25, TA190 and TA208) it would appear that erlotinib does have a 'small population' and could be considered under the supplementary end of life guidance and may therefore be regarded as being a cost-effective use of NHS resources.	Comment noted. The Committee discussed written evidence from a previous NICE technology appraisal appeal and noted that the Appeal Panel had concluded that it was appropriate, according to the supplementary advice, to add together the patient populations covered by the marketing authorisation for different indications rather than on the basis of actual or recommended use. The Committee therefore considered 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. See FAD section 4.21.
Roche Products	We hope the Committee considers carefully the evidence presented in this document. We firmly believe NICE's final decision on erlotinib should be based	Comment noted. The Committee did not consider that robust evidence had been

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	upon the best evidence available, should be consistent with other decisions made by NICE and should reflect the views of society with regards to end of life technologies. In this case we strongly believe that the current ACD is inconsistent with existing NICE guidance, contains erroneous conclusions based upon a series of unfounded assumptions and is therefore not a sound and suitable basis for the issuance of guidance to the NHS. Furthermore we do not believe the current ACD is a sound and suitable basis for denying patients, and their families, access to a highly valued life extension of nearly 4 months when they will otherwise die within 12 months. If any further clarification or analyses are required in order to aid the Committee's deliberations we would be more than happy to provide them.	provided to demonstrate an extension to life of at least 3 months and taken together with the consideration on population size, therefore concluded that the end-of-life criteria were not met in this appraisal. See FAD section 4.22.
Roche Products	Section 1. Has all the relevant evidence has been taken into account? It is our belief that the Committee have overlooked, or have not yet considered, evidence that appears to be vital given the decision problem at hand. Some of this evidence has only become pertinent in light of the Committee's most recent conclusions, and thus explains why it was not presented earlier. 1.1. The truncated mean survival advantage provided by erlotinib in squamous histology stable disease group directly from the SATURN study In the 2nd ACD the Committee dismissed the mean overall survival advantage for squamous histology stable disease patients estimated by Roche and the ERG (ACD Section 4.13). As it appears the rationale for dismissing these estimates may be flawed it may be of interest to the Committee to consider the overall survival advantage of erlotinib in this group directly from the SATURN study itself (i.e. with no extrapolation). Because a true mean cannot be determined until all patients in a clinical trial have died, it is common practice to present estimates based on Kaplan-Meier estimation methods and this has already been presented to the Committee. An alternative is to calculate a "truncated" mean – this uses the actual duration of survival for patients known to be dead and the time up until last follow-up for patients not known to be dead. In a study like SATURN where most patients in both arms have died, this will give a close approximation to the true mean but is likely to underestimate treatment benefit because the treatment and control curves are diverging with time. As can be	Comment noted. The Committee concluded that the ERG's approach to estimating survival was more appropriate because it was based as much as possible on data directly from the trial and used modelling only when necessary. See FAD section 4.16.

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	seen from Table 1, the truncated mean survival benefit for squamous SD patients in SATURN is well above 3 months and sits comfortably between the extrapolated survival estimates of Roche and the ERG. (Table 1-Not replicated here) Because of the tendency of truncated means to underestimate survival benefit when survival curves are diverging, Table 1 supports a true survival advantage of somewhere between Roche's and the ERG's estimates. Given the evidence above it is clear that all evidence based estimates of the survival gain offered in SATURN are over 3 months.	
Roche Products	1.2. The generalisability of the SATURN squamous histology stable disease results in UK clinical practice In the ACD the Committee opted to discard both Roche and the ERG's estimates of the overall survival advantage offered by erlotinib in stable disease patients with squamous histology. The primary reason for this dismissal is detailed in section 4.13 of the ACD: "The Committee considered that the overall survival benefit of erlotinib in clinical practice was likely to be even lower than that estimated by the ERG because of ….the high proportion of Southeast Asian patients and patients who had never smoked, as well as the inclusion of patients with EGFR mutations and patients with stable disease and relatively good performance status despite having had four cycles of platinum based chemotherapy" 2nd ACD, section 4.13 In addition to the above the Committee expressed their concern that the overall survival advantage seen in SATURN may not hold in practice due to the utilization of 2nd line treatments not typically seen in England and Wales and due to the nature of the analysis undertaken (i.e. the use of a post-hoc identified subgroup). Each of these concerns, and their relevance in the squamous histology stable disease group, is discussed below. It is apparent that whilst the demographics of the squamous histology stable disease group were provided in one of the economic models submitted following the 1st ACD on erlotinib maintenance, this information has never been considered by the Committee. We believe that this may be the source of the inconsistency	Comment noted. The Committee acknowledged that the manufacturer had provided additional information about the patient characteristics of the squamous disease population in the SATURN trial during consultation and accepted that these data showed that the number of patients with a prognostic factor was small and was unlikely to significantly bias the estimate of overall survival for this subpopulation. See FAD section 4.9.

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	between the conclusions reached by the Committee in the 2nd ACD and the information provided below.	
Roche Products	1.2.1 The proportion of squamous histology stable disease patients with EGFR mutations In SATURN itself only 1 of the 190 squamous histology stable disease patients randomized had an EGFR mutation. This equates to an EGFR mutation incidence of 0.005%. Given this extremely small incidence the notion that the OS advantage observed in SATURN would not hold in UK clinical practice due to the exclusion of patients with EGFR mutations is unreasonable.	Comment noted. See above response.
Roche Products	1.2.2 The proportion of squamous histology stable disease patients who were 'never smokers' In fact, in SATURN only 13 or the 190 squamous histology stable disease patients (6.86%) in the study were never smokers, this is not unusually high for lung cancer patients under treatment in the UK. In any case, the reason that the proportion of 'never-smokers' in SATURN would be of interest to the Committee when discussing the reproducibility of the SATURN results is that it represents a surrogate for patients with a high rate of EGFR mutations which as noted above is an invalid concern in the squamous histology group. Given the small magnitude of the percentage of squamous patients who were never smokers in SATURN and the contents of section 1.1.1 the Committee's concerns on the validity of the survival gain observed in SATURN due to the study containing too many 'never-smokers' appear unfounded.	Comment noted. See above response.
Roche Products	1.2.3 The proportion of squamous histology stable disease patients who were 'Asian' In the squamous histology group of SATURN only 7.9% patients were Asian and over 92% were White. This percentage is considerably less than the proportions of Asian patients in studies that have recently been accepted by NICE in support of other positive appraisals (notably the IPASS study in the appraisal of gefitinib in mNSCLC (TA192) and the ToGA study in the appraisal of trastuzumab in mGC	Comment noted. See above response.

Consultee	Comment	Response
	(TA208)). If the Committee's concerns on this proportion are due to the increased likelihood of Asian patients having tumours harboring activating EGFR mutations, the 0.005% EGFR mutation incidence noted above should allay that concern. Overall it is unreasonable to suppose that the percentage of Asian patients in the squamous SD group in SATURN will have any appreciable impact on the efficacy seen relative to what might be achieved in clinical practice in England and Wales.	
Roche Products	1.2.4 The performance status of squamous histology stable disease patients in SATURN It was a requirement of the SATURN protocol that patients had an ECOG Performance Status (PS) of 0-1 to be eligible for randomization between maintenance and no maintenance. Although it is not a requirement of the erlotinib maintenance license that patients are of at least PS 1 to be eligible for treatment, it is unlikely that clinicians would be enthusiastic about treating patients whose PS had declined during chemotherapy (both the SATURN protocol and the NICE guidance in this area state that patients should have at least PS1 to start platinum doublet chemotherapy). As maintenance treatment with erlotinib is only indicated for patients with stable disease as best response to induction, it is highly likely that the vast majority of erlotinib maintenance candidates will have a PS maintained at 0 or 1 at the point of completing induction therapy. Against this background, NICE may wish to recommend erlotinib maintenance only in patients with SD and ECOG PS 0-1. In practice this restriction will have little impact since clinicians are unlikely to want to prescribe maintenance for patients who have failed to benefit from first-line chemotherapy and have experienced declining PS during induction.	Comment noted. See above response.
Roche Products	1.2.5 The second line treatments received by squamous histology stable disease patients in SATURN In the ACD the Committee note their concerns that overall survival advantage offered by erlotinib as observed in SATURN may not hold in clinical practice due to the utilization of 2nd line therapies not typically seen in the United Kingdom within the study. Such concerns are not new in NICE appraisals and are the product of the	Comment noted. The Committee noted that a high proportion of patients in the SATURN trial received a range of post-progression treatments, some of which would not be routinely used in the UK. It also observed that only a small proportion of patients in the

Consultee	Comment	Response
	divide between the decision problem as defined by typical practice in the NHS and that in the rest of the world. What matters in such situations is not the fact that patients went on to receive 2nd line treatments which are not given in the United Kingdom but the balance between those arms. If the utilization of those medicines was equal then there is no reason to believe each arm will have benefited more than the other and so it would appear unreasonable to assume the overall survival advantage observed in the study of interest would not hold in clinical practice. To do otherwise would be to penalize UK patients two-fold. Firstly in terms of the denial of access to a second line treatment on the basis of cost-effectiveness and secondly in terms of the denial of a new first line treatment due to the utilization of the denied second line treatment within the registration study for the new treatment. In the case of the squamous histology stable disease population of SATURN the second line treatments are indeed balanced and so the Committee's logic that the overall survival gain seen in SATURN would not hold in UK in practice appears unreasonable.	placebo group had received erlotinib after progression. It considered that the post-progression treatments and the small proportion of patients in the placebo group who had received erlotinib after progression would affect the estimates of overall survival in the erlotinib and placebo groups. The Committee was aware that it is unclear whether patients would benefit more from receiving erlotinib as maintenance treatment or for treatment of relapsed disease. The Committee concluded that there was very considerable uncertainty that the benefit or erlotinib seen in the trial would be translated into routine practice. See FAD section 4.10.
Roche Products	1.2.6 The absence of pemetrexed as a first line treatment in SATURN As pemetrexed is only indicated as a first line treatment in patients with non-squamous histology the Committee's concerns on the applicability of the SATURN data in UK practice due to the absence of induction containing pemetrexed within the study are not applicable for squamous histology stable disease patients. Therefore the absence of pemetrexed induction is no reason to suspect that the overall survival advantage observed in the squamous histology stable disease group in SATURN would not hold in UK clinical practice.	Comment noted. The Committee considered that there were several factors that led 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. See FAD section 4.12.
Roche Products	1.2.7 The utilization of a post-hoc defined subgroup for the purposes of economic modeling In the ACD the Committee express their concern that the squamous histology stable disease group was post-hoc defined. Given the prime reason for presenting this group was because in first ACD it was noted that the decision problem was different for the stable disease group split by histology it appears unreasonable this is raised as an issue within the 2nd ACD.	Comment noted. The Committee was aware that the results for patients with stable disease were based on a post hoc subgroup analysis of 55% of the SATURN trial population. Furthermore, the results for the subgroups of patients with squamous and non-squamous disease were also post hoc

Consultee	Comment	Response
	There is a clear rationale as to why the cost-effectiveness of erlotinib may be different if the stable disease group is split by histology (the different prognostic baselines of the two groups) and the demographics of patients in the squamous histology stable disease group appear well balanced across the two arms. Therefore it seems unlikely that the ICER estimated for erlotinib in squamous histology stable disease patients is the product of simply 'trawling' the data (one potential concern with the utilization of post-hoc subgroups) or confounded due to imbalances in prognostic factors (the other prime reason for caution when dealing with post-hoc subgroups). Therefore it would appear unreasonable for the Committee to deny squamous histology stable disease patients access to erlotinib on the basis that this group was post-hoc defined. It should be noted that Roche's case comparing erlotinib maintenance in all SD patient was dismissed by the ERG and appears to have been given limited consideration by the Appraisal Committee. Although this was also based on post hoc analysis, this SD analysis was one which had been closely scrutinized by the EMEA for regulatory purposes and included a much larger proportion of the SATURN patients, reducing the associated risks.	analyses based on a disaggregation of the stable disease population and there were relatively small numbers of patients in each subgroup (190 and 297 respectively). The Committee was aware that the SATURN trial had not been designed for such analyses. It therefore regarded that the true magnitude of the benefits of erlotinib in these patient populations was uncertain. See FAD section 4.4.
Roche Products	Summary of point 1.1 and 1.2. The Committee's concerns on the generalisability of the overall survival gain observed in SATURN are unfounded in the squamous histology stable disease group. Given the evidence presented in section 1.1. above it is unclear as to how the Committee could conclude that in UK patients with squamous histology and stable disease, erlotinib provides an overall survival advantage of less than 3 months. 1.3. The truncated mean survival advantage provided by erlotinib in squamous histology stable disease group directly from the SATURN study In the 2nd ACD the Committee dismissed the mean overall survival advantage for squamous histology stable disease patients estimated by Roche and the ERG. As it appears the rationale for dismissing these estimates may be flawed (as detailed in section 1.1 of this document) it may be of interest to the Committee to consider the	Comment noted. See previous responses.

Consultee	Comment	Response
	overall survival advantage of erlotinib in this group directly from the SATURN study itself (i.e. with no extrapolation). Because a true mean cannot be determined until all patients in a clinical trial have died, it is common practice to present estimates based on Kaplan-Meier estimation methods and this has already been presented to the Committee. An alternative is to calculate a "truncated" mean – this uses the actual duration of survival for patients known to be dead and the time up until last follow-up for patients not known to be dead. In a study like SATURN where most patients in both arms have died, this will give a close approximation to the true mean but is likely to underestimate treatment benefit because the treatment and control curves are diverging with time. As can be seen from Table 1, the truncated mean survival benefit for squamous SD patients in SATURN is well above 3 months and sits comfortably between the extrapolated survival estimates of Roche and the ERG. Because of the tendency of truncated means to underestimate survival benefit when survival curves are diverging, this supports a true survival of somewhere between Roche's and the ERG's estimate. (Table 2 – Not replicated here) When the contents of section 1.1 of this document are combined with the above overall survival gains and those estimated by Roche and the ERG it is unclear as to how the Committee could conclude that erlotinib offers an overall survival advantage less than 3 months and an ICER above £50,000/QALY (and not simply an OS gain of between 3.4 and 4.6 months and an ICER between £36,000 and £44,800 as suggested by the estimates generated by Roche and the ERG).	
Roche Products	1.4. The number of metastatic pancreatic cancer patients suitable for treatment as defined by NICE In the ACD the Committee conclude that 'most' metastatic pancreatic cancer patients would potentially be indicated for treatment with erlotinib (ACD section 4.17). The consequence of this conclusion is that erlotinib is considered not to have a 'small population' and so is not eligible for consideration under NICE's supplementary end of life guidance. The Committee has provided no reasoning as to why this would be the case and appear to have made an unsupported assumption with the consequence that erlotinib is not considered to be eligible for	Comment noted. The Committee discussed written evidence from a previous NICE technology appraisal appeal and noted that the Appeal Panel had concluded that it was appropriate, according to the supplementary advice, to add together the patient populations covered by the marketing authorisation for different indications rather than on the basis of actual or recommended

Consultee	Comment	Response
	consideration under the end of life guidance. We would like to bring to the attention of the Committee NICE's previous own estimates on the number of patients suitable for treatment in metastatic pancreatic cancer from NICE TA25 ('The use of Gemcitabine for the treatment of pancreatic cancer'). In TA25 the Committee estimated that of the 6,000 patients diagnosed with pancreatic cancer per annum approximately 80% would have metastatic or locally advanced disease and of these only 600-800 would actually be offered and receive gemcitabine (erlotinib's partner when utilised in mPC). This figure of between 10% and 13.3% of patients diagnosed with mPC appears far from the 'most' assumed by the Committee in the 2nd ACD for erlotinib and would suggest that erlotinib's patient population has been significantly over-estimated when assessing it's applicability for consideration under the end of life guidance. The current ACD suggests the Committee were not aware of, or did not consider fully, NICE's own estimates of the proportion of mPC patients suitable for treatment and so made an unsupported assumption which appears to be inconsistent with the guidance issued in TA25. In light of this we would ask that the Committee reconsider their conclusion on the size of erlotinib's population using an evidence based estimate of the number of mPC patients suitable for treatment, consistent with what was estimated in TA25 (as provided by Roche in response to the first ACD in this appraisal) rather than the assumption made in the development of the 2nd ACD.	use. The Committee therefore considered 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. See FAD section 4.21.
Roche Products	1.5. The populations of other technologies granted consideration under NICE's supplementary end of life guidance In the ACD the Committee conclude that erlotinib does not have a 'small population' and is therefore not eligible for consideration under the supplementary end of life guidance (section 4.17 of the ACD). This conclusion appears counter to the recent technology appraisal of trastuzumab in metastatic gastric cancer (NICE TA208, issued in November 2010). In this appraisal the Committee determined that trastuzumab had a 'small population' and could therefore be considered under the supplementary end of life guidance. If the same methodology as was used in TA208 is followed in determining the	Comment noted. See above response and FAD section 4.21.

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	population size for erlotinib it is clear that erlotinib has a smaller population than trastuzumab. Furthermore if the methods used in TA208 were similarly followed for TA190, it is clear that erlotinib also has a smaller treatment population than another technology granted consideration under the end of life guidance in 2010 and thus approved for essentially the same indication: pemetrexed. The methods followed and conclusions reached in TA208 and TA190 are detailed below (see points 1.4.1 and 1.4.2 below). Point 1.4.3. demonstrates the number of patients indicated for treatment with erlotinib if the methods followed in TA208 and TA190 are replicated.	
Roche Products	1.5.1. The patient population considered 'small' in TA208 (trastuzumab in mGC) In TA208 when discussing the applicability of trastuzumab for consideration under NICE's supplementary end of life guidance the Committee noted the following: 'The Committee considered the size of the patient population. Treatment with trastuzumab would be suitable for approximately 7000 people who have one of the diseases for which trastuzumab is licensed (that is, HER2-positive metastatic gastric cancer, HER2- positive early and locally advanced breast cancer and HER2- positive metastatic breast cancer). The Committee considered that 7000 was at the upper end of the population size for which it understood the supplementary advice to apply. However, the Committee concluded overall that applying the supplementary advice on end-of-life was appropriate.' NICE 2010, TA208, Trastuzumab mGC FAD, Section 4.25 This conclusion was based upon the four algorithms provided in appendix 1 with an estimated total population of 7,144 patients per annum. Crucially, the Committee utilized the number of patients 'suitable' for treatment in determining trastuzumab's applicability for consideration under the end of life guidance including the removal of patients ineligible for chemotherapy from the relevant algorithms.	Comment noted. See previous response and FAD section 4.21.
Roche Products	1.5.2. The patient population considered 'small' in TA190 (pemetrexed in mNSCLC) In TA190 the Committee granted pemetrexed consideration under the end of life guidance based upon the following population estimate: 'Appendix 6 shows the patients eligible to receive pemetrexed treatment across all	Comment noted. See previous response and FAD section 4.21.

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	licensed indications (i.e., maintenance NSCLC, first and second-line NSCLC and mesothelioma). The total number of patients eligible to receive pemetrexed for any indication is 3,426.' Eli Lily 2009, Pemetrexed in maintenance NSCLC NICE STA submission, p49 What is notable about this appraisal is that the Committee determined that it was inappropriate to consider patients ineligible for treatment when determining pemetrexed applicability for consideration under the end of life guidance and utilised evidence based estimates of the number of patients actual suitable for treatment (including removing a significant proportion (77%) of non-squamous metastatic NSCLC patients from the algorithm when assessing a patients suitability for first line chemotherapy containing pemetrexed). Roche estimate that if the method used in TA208 is replicated for pemetrexed the number of patients suitable for pemetrexed is approximately 5,215 per annum. The algorithm utilised to generate this value is provided in appendix 2. It should be noted that the disparity between the treatment of pemetrexed and erlotinib with regard to end-of-life considerations was raised in Roche's response to the first ACD in this appraisal and it is unclear how the comments made have been considered by the Committee during preparation of the second ACD.	
Roche Products	1.5.3. The erlotinib patient population utilizing the methods used in TA190 and TA208 If the methods used in TA190 and TA208 are replicated for erlotinib Roche estimate 4,127 patients per annum are suitable for treatment with erlotinib (see appendix 2). Of these a total of 3,327 are suitable for erlotinib's 2nd line and stable disease first line maintenance lung cancer indications (with around 1,500 patients suitable for maintenance treatment per annum) with 800 metastatic pancreatic cancer patients suitable for treatment. Table 3 below highlights the inconsistency between erlotinib's applicability for consideration under the end of life guidance due to the 'small population' criteria and the decisions made in TA190 and TA208. If the 7,144 patients considered 'small' in TA208 are assumed to mark the upper limit of what denotes a small population in the eyes of an Appraisal Committee it is	Comment noted. See previous response and FAD section 4.21.

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	clear that nearly 4,000 mPC patients per annum would have to be suitable for treatment with erlotinib for erlotinib to be considered to not have a small population. TA25 (NICE guidance on Gemcitabine in mPC) would suggest this figure is between 600 and 800 patients per annum. We believe the current conclusion of the Committee, that erlotinib does not qualify for end of life criteria because of it's large patient population size, is inconsistent and illogical given that two technologies with larger populations have been approved for use on the NHS under the end of life guidance. Furthermore, we believe that the intervention is exactly the sort for which end-of-life considerations were intended – those offering a substantial improvement in survival to groups of patients, whose prognosis is otherwise very poor. (Table 3 – Not replicated here)	
Roche Products	1.6. The generalisability of the SATURN non-squamous histology stable disease results to UK clinical practice As was the case for squamous histology patients the Committee also expressed their concerns on the generalisability of the SATURN results in non-squamous histology stable disease patients (ACD section 4.13). The majority of these concerns appear to be the same as those refuted in section 1.1. (post-progression treatments, PS status of patients etc) or focused around the proportion of patients with tumours harboring activating EGFR mutations (either explicitly or via concern around the proportion of patients with characteristics one would typically associate with such patients (asians, never-smokers etc)). Whilst NICE approval of gefitinib in TA192 will likely mean that the vast majority of candidates for erlotinib will not harbor activating EGFR mutations we do not believe that the removal of these patients would make erlotinib any less cost-effective. Roche would like to bring to the Committee's attention data on the efficacy of erlotinib in those patients without EGFR mutations (those with EGFR wild type disease) in order to better aid the Committee's determinations. Moreover, it is important to consider how aspects of the study population may result is a smaller as well as a greater treatment effect being observed in the SATURN study relative to UK clinical practice. In the case of the SATURN study it is important to remember that when looking at a small sub-population such as the	Comment noted. The Committee acknowledged that the manufacturer provided updated analyses during consultation on the appraisal consultation documents, which adjusted for some of the prognostic factors (such as ECOG status and smoking history) which the manufacturer suggested may have biased the results against erlotinib in the SATURN trial. However, the Committee was concerned about the reliability of the data because of the small numbers of patients included in these further subgroup analyses. The Committee heard from the ERG that the differences in ECOG status and smoking history between the erlotinib and best supportive care groups were not statistically significant in the non-squamous population and that the differences in these baseline characteristics would not artificially

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	non-squamous SD patients, much of the benefit of randomization is lost and imbalances in patient characteristics can appear between treatment groups diminishing or exaggerating the observed treatment effect. Although the squamous SD group show a reasonably good balance being maintained between treatment arms in terms of patient characteristics of known prognostic significance, this is not true of the non-squamous SD group.	decrease the overall survival estimate for erlotinib. See FAD section 4.6.
Roche Products	The imbalance in ECOG Performance Status In SATURN all patients were either ECOG status 0 (better performance status and prognosis) or ECOG status 1 (worse performance status and prognosis). In the NSQ SD group of SATURN 38% of patients randomized to placebo were ECOG status 0 whilst only 30% of those randomized to erlotinib had an ECOG status of 0. In effect those patients randomized to placebo were over 25% more likely to be ECOG status 0 than those randomized to erlotinib and therefore the overall survival advantage attributable to erlotinib is group is confounded in favor of the comparator arm due to the misattribution of this imbalance to best supportive care following induction.	Comment noted. See previous response and FAD section 4.6.
Roche Products	The balance of 'never smoker' status between arms in the SATURN non-squamous histology stable disease population In SATURN 31% of non-squamous histology stable patients randomised to placebo were 'never-smokers' (better prognosis) whilst only 25% of patients randomised to erlotinib were 'never-smokers'. A NSQ SD patient randomised to placebo was therefore more than 25% more likely to be of the better prognosis 'never-smoker' group than an equivalent patient randomised to erlotinib. This imbalance in a known prognostic factor will likely have biased the raw treatment effect observed in SATURN to the discredit of erlotinib.	Comment noted. See previous response and FAD section 4.6.
Roche Products	Adjusting for these imbalances Roche would suggest the true OS advantage offered by erlotinib in this group is significantly underestimated by SATURN with the impact of these known prognostic factors mistakenly being credited to the comparator arm. This hypothesis is supported by the results of a stratified analysis of overall survival (including ECOG status and smoking status as covariates) in which the OS hazard	Comment noted. See previous response and FAD section 4.6. The Committee also acknowledged comments from the ERG that no adjustments for other prognostic factors that

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	ratio produced was 0.71 [0.54, 0.93] (compared to 0.76 [0.59, 1.00] in the unstratified analysis). If the aforementioned overall stratified analysis is repeated in solely those patients with EGFR wild type disease (n=113, i.e. the patients who will likely receive erlotinib in clinical practice due to the growing use of gefitinib in patients with an EGFR mutation) the overall survival hazard ratio generated falls further to 0.63 [0.41, 0.96]. This result suggests that the overall survival advantage that would be offered by erlotinib in patients with non-squamous stable disease in UK clinical practice may be significantly underestimated by SATURN.	could have had an impact on overall survival, such as gender and disease stage, had been made in these analyses by the manufacturer. See FAD section 4.6. The Committee was also aware that EGFR mutation status was not recorded in almost half of the SATURN patients. It considered that patients with EGFR mutations would usually receive gefitinib and would therefore not be eligible for maintenance treatment with erlotinib in UK clinical practice. See FAD section 4.8.
Roche Products	Whilst it is difficult to predict what the results of an economic evaluation based upon a stratified analysis of solely EGFR wild type patients would be without actually modelling the data, as the OS HR associated with that analysis is better than that of the unstratified squamous stable disease analysis (0.63 compared to 0.67) yet based upon a higher prognostic baseline, Roche would suggest that this analysis would almost certainly produce an absolute overall survival advantage higher than that observed for squamous patients (certainly over 3 months) and an ICER less than the £44,800 determined by the ERG for squamous patient (i.e. well below £50,000/QALY).	Comment noted. See previous response. The Committee agreed that end-of-life criteria were not met in this appraisal, but it noted that even if they were taken into account, the most plausible ICERs were higher than those normally considered to be associated with cost effective treatments. See FAD section 4.23.
Roche Products	Furthermore the Committee's concerns on the generalisability of the SATURN non-squamous stable disease results due to the absence of pemetrexed as an induction treatment in SATURN appear to be misplaced. Since randomization into SATURN was based on achieving at least SD after any then accepted first-line platinum doublet rather than on receiving a particular chemotherapy regimen, it is hard to understand the rationale for this objection. Roche see no plausible reason as to why the first line induction regimen utilised would have a particular influence upon the efficacy of erlotinib maintenance.	Comment noted. The Committee discussed the first-line treatments received by patients in the SATURN trial, and noted that no patients received first-line treatment with pemetrexed and cisplatin, a regimen that is now commonly used as combination chemotherapy for patients with non-squamous disease because of its superiority to the regimens used in the

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		SATURN trial. See FAD section 4.10.
Roche Products	1.7. Consideration of the ICER of erlotinib in its approved indication i.e. the whole stable disease group In reaching their conclusion on the cost-effectiveness of erlotinib as a maintenance treatment the Committee appear to have overlooked the evidence presented by Roche for the whole stable disease group after the previous ACD instead opting to focus on the two 'by histology' models. Given the confounding in the non-squamous stable disease population as highlighted in section 1.5 (above) we feel it is essential the Committee consider this whole stable disease analysis and the ICER of erlotinib in its licensed population prior to the development of a FAD. Following the first ACD we provided a revised version of the whole group stable disease analysis originally submitted utilising the survival curves fitted by the ERG with a series of amendments either suggested by the ERG in the first ERG report or later approved of by the Committee in the 2nd ACD (best supportive care costs, time horizon etc). The overall survival advantage estimated by the ERG in this as per license patient population, and therefore the OS advantage included in this revised model, was 4.2 months (note: not 3.3 months are erroneously reported in section 4.18 of the 2nd ACD). These survival curves were utilized by the Committee in the first ACD in order to determine the 'most plausible ICER' for erlotinib in the stable disease group (see sections 4.18 and 4.19 of the first ACD) yet have seemingly disappeared from consideration in the 2nd ACD despite the Committee's reservations around the analyses split by histology (section 4.12 of the 2nd ACD). It should be remembered that the stable disease group as a whole is the one for which erlotinib has regulatory approval and which has been subject to greatest scrutiny by the EMEA. The face validity of these overall survival curves is demonstrated in Figure 1 below. (Figure 1- Not replicated here)	Comment noted. The Committee agreed it was more appropriate to consider the cost effectiveness of erlotinib in the subgroups of patients with squamous disease and non-squamous disease separately, rather than in the stable disease population as a whole, because of heterogeneity between the subgroups. However the Committee was concerned about the subgroup analyses because the trial population had not been stratified by histology and analyses for these histological subgroups and for the stable disease population as a whole had not been predefined, which added uncertainty to the survival estimates and therefore also to the ICERs. See FAD section 4.15. The overall survival advantaged of 4.2 months estimated by the ERG was based on data from the original submission from the manufacturer. Following consultation on the first ACD, the manufacturer provided a revised submission, from which the ERG estimated that the overall survival was 3.3 months. Therefore this figure has not been incorrectly reported in section 4.18 of the second ACD.
Roche	Table 4 below provides the cost-effectiveness results in the whole stable disease	Comment noted. See previous response.

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Products	group produced via the utilisation of the PFS and OS curves estimated by the ERG, the amendments approved in the previous ACD and the two additional amendments made by the ERG to the two histology split models (i.e. correcting the discounting error of the application of the terminal care cost and slightly reducing the PFS utility for each comparator due to the inclusion of solely those patients with stable disease following induction). (Table 4 – Not replicated here) In this analysis, which features a series of components of which all have been individually accepted by the Committee as being appropriate, the incremental cost of erlotinib maintenance is £7,737 and the incremental QALY gained is 0.190. This equates to an ICER of £40,792 with an overall survival gain of 4.2 months. Given the Committee have considered all of the components of this analysis individually as being appropriate and the fact that the non-squamous analysis is confounded (as highlighted above) and possibly even irrelevant due to the apparent impossibility of a formal indirect comparison against pemetrexed (the only possible rationale for splitting the decision problem by histology) we feel it would be inappropriate if this analysis were not to be fully considered in the production of a FAD.	Comment noted. The Committee noted that manufacturer's ICERs for erlotinib compared with best supportive care of £40,800 per QALY gained for all patients with stable disease. See FAD section 4.14.
Roche Products	Section 2. Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? No. The overall survival advantage utilized by Roche for the whole stable disease population in the supplementary evidence submission provided following the previous ACD has been misunderstood making the evidence we presented in the additional submission look inconsistent. In the ACD it is noted that in Roche's supplementary evidence submission a survival advantage of 3.3 months was estimated for the whole stable disease group (section 4.18 of the ACD). This value is simply not correct and suggests the Committee have misunderstood the evidence submitted on the whole stable disease group following the ACD. As noted in section 1.5 above, in the supplementary evidence submission provided following the previous ACD Roche utilised the survival estimates generated by the ERG when estimating the ICER of the whole stable disease group. In the first ERG	Comment noted. The overall survival advantaged of 4.2 months estimated by the ERG was based on data from the original submission from the manufacturer. Following consultation on the first ACD, the manufacturer provided a revised submission, from which the ERG estimated that the overall survival was 3.3 months. Therefore this figure has not been incorrectly reported in section 4.18 of the second ACD. The Committee noted that in new analyses provided by the manufacturer during

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	report on erlotinib maintenance the ERG estimated a survival benefit of 4.2 months for erlotinib in the stable disease group and it was this survival estimate that was utilised by Roche in the supplementary evidence submission. For clarity the overall survival gains estimated by the ERG in each of the 3 populations are provided in Table 5 below. (Table 5 –Not replicated here) What is clear from the table above is that the ERG's overall survival estimates differ significantly and illogically between the populations of interest and that whilst the Committee express their confusion at the overall survival estimates used by Roche in our supplementary evidence submission it is in fact the ERG's estimates that are confusingly differentiated. In the supplementary evidence submission Roche estimates that the aforementioned populations have less than 0.5 months deviation between them whilst the ERG's 'by histology' estimates are both sizeably lower than those they estimated for the whole stable disease population (nearly one month less for patients with squamous histology and two months less for patients with non-squamous histology).	consultation, the manufacturer estimated the mean overall survival benefit of erlotinib compared with best supportive care to be 3.3 months in the whole stable disease population, 4.2 months in the stable squamous disease group and 4.5 months in the stable non-squamous disease group. It also noted that the ERG estimated the mean overall survival benefit to be 3.4 months and 2.2 months in the squamous and non-squamous disease groups respectively. The Committee had previously concluded that the overall survival benefit of erlotinib in clinical practice was uncertain and likely to be less than the ERG's estimates. See FAD section 4.22.
Roche Products	Section 3. Are the provisional recommendations a sound and suitable basis for guidance to the NHS? Roche believe that the Committee have overlooked, or not been privy to, key pieces of information which mean the current recommendations are not a sound and suitable basis for the preparation of guidance. Furthermore it is our belief that the Committee's current assessment of erlotinib's applicability for consideration under the end of life guidance in the squamous histology stable disease group is unfounded (in terms of the reproducibility of the study results and the assessment of the number of metastatic pancreatic cancer patients suitable for treatment with erlotinib) and potentially in conflict with the rulings of the Appraisal Committee's in NICE TA208 and TA190 and so it is our belief that the current ACD is not a sound basis for guidance.	Comment noted. The Committee discussed written evidence from a previous NICE technology appraisal appeal and noted that the Appeal Panel had concluded that it was appropriate, according to the supplementary advice, to add together the patient populations covered by the marketing authorisation for different indications rather than on the basis of actual or recommended use. The Committee therefore considered 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

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		estimate. See FAD section 4.21.
Roche Products	Section 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? If the proposed guidance stands it will mean that whilst patients with non-squamous NSCLC have a maintenance option, those with squamous cell tumors do not. Although legislation does not specifically prohibit discrimination on grounds of histology, it must be understood that the histological mix of NSCLC shows a gender imbalance with squamous cell cancers making up a substantially larger proportion of NSCLC in men. As such the guidance has a disproportionate impact on men with lung cancer and can be seen as discriminatory. This is particularly concerning given that men with lung cancer have an inherently worse prognosis than women. Furthermore if the Committee maintain their current stance on erlotinib's applicability for consideration under the end of life guidance due to its population not being 'small' whilst having a smaller population than both trastuzumab and pemetrexed (utilizing the methods used in TA208) which were both granted consideration under the end of life guidance the final guidance produced may unfairly discriminate against maintenance patients eligible for erlotinib who, had this appraisal been conducted by an alternative Committee, may have been granted access to a much needed extra line of treatment. (References and Appendices-Not replicated here)	Comment noted. The Committee considered that it was justified in considering the squamous and non-squamous populations separately on clinical grounds. See FAD section 4.16. The Committee noted that no data on gender distribution based on histology were provided by the manufacturer and therefore this assertion was impossible to substantiate. However, the Committee noted that any possible differences in maintenance treatment access referred to by the manufacturer were related to TA190, rather than possible to be addressed in this appraisal. The Committee agreed that its decision about erlotinib maintenance treatment needed to be based on the evidence seen in this appraisal. Furthermore, the final decision not to recommend erlotinib maintenance treatment was made because erlotinib was not cost-effective in either of the squamous or non-squamous subgroups compared with best supportive care. The Committee concluded that its recommendations do not make it more difficult in practice for a specific group to access erlotinib maintenance treatment compared with other groups. See FAD

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		section 4.24.
Royal College of Nursing	Has the relevant evidence has been taken into account? The evidence considered seems comprehensive.	Comment noted. No change to the ACD required.
Royal College of Nursing	Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence, and are the preliminary views on the resource impact and implications for the NHS appropriate? We would ask that the summaries of the clinical and cost effectiveness of this appraisal should be aligned to the clinical pathway followed by patients with lung cancer. The preliminary views on resource impact and implications should be in line with established standard clinical practice.	Comment noted. No change to the ACD required.
Royal College of Nursing	Are the provisional recommendations of the Appraisal Committee sound and do they constitute a suitable basis for the preparation of guidance to the NHS? Nurses working in this area of health have reviewed the recommendations of the Appraisal Committee and do not have any other comments to add. The RCN would welcome guidance to the NHS on the use of this health technology.	Comment noted. No change to the ACD required.
Royal College of Nursing	Are there any equality related issues that need special consideration that are not covered in the ACD? We are not aware of any specific issue at this stage. We would however, ask that any guidance issued should show that equality issues have been considered and that the guidance demonstrates an understanding of issues concerning patients' age, faith, race, gender, disability, cultural and sexuality where appropriate. Any guidance on the use of this technology should also be mindful of the impact it may have on reducing socio-economic inequalities.	Comment noted. The Committee discussed whether NICE's duties under the equalities legislation required it to alter or add to its recommendations in any way. The Committee concluded that its recommendations do not make it more difficult in practice for a specific group to access erlotinib maintenance treatment compared with other groups. In addition. The Committee noted that, following the publication of TA181, the proportion of patients who would be eligible to receive pemetrexed maintenance treatment was declining quickly over time (because they are receiving pemetrexed as a first-line

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		treatment instead) and therefore the manufacturer's concern that pemetrexed is currently only available as a maintenance option of non-squamous disease was becoming less relevant. See FAD section 4.24.
Royal College of Physicians	Has all of the relevant evidence been taken into account? Yes. We are not aware of any evidence that has been omitted, and all relevant data has been analysed critically.	Comment noted. No changes to the ACD required.
Royal College of Physicians	Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? Yes. With the proviso that modelling for cost effectiveness is always contentious, the summaries are a reasonable interpretation of the evidence.	Comment noted. No changes to the ACD required.
Royal College of Physicians	Are the provisional recommendations sound and a suitable basis for guidance to the NHS? We believe that the recommendations are sound.	Comment noted. No changes to the ACD required.
Royal College of Physicians	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? No.	Comment noted. No changes to the ACD required.
Royal College of Physicians	Are there any equality-related issues that need special consideration and are not covered in the appraisal consultation document? No.	Comment noted. No changes to the ACD required.
Roy Castle Lung Cancer Foundation	We are disappointed that the recently issued second ACD on the use of Erlotinib monotherapy for the maintenance treatment of non-small cell lung cancer, reveals that the Committee is minded not to recommend this therapy.	Comment noted. No changes to the ACD required.
Roy Castle Lung Cancer Foundation	We believe that the Committee may have overestimated the numbers of pancreatic cancer patients suitable for Erlotinib, this overestimation having made Erlotinib ineligible within NICE's 'End of Life' Guidance criteria. Furthermore, we understand that the manufacturer will be submitting detail of the patient characteristics in the SATURN study, showing them to be representative of the general population. We	Comment noted. The Committee discussed written evidence from a previous NICE technology appraisal appeal and noted that the Appeal Panel had concluded that it was appropriate, according to the supplementary

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	hope that the implications of these observations will be considered by the Committee.	advice for end-of-life treatments, to add together the potential patient populations covered by the marketing authorisation for different indications rather than on the basis of actual or recommended use. The Committee therefore considered that the true size of the cumulative population potentially eligible for treatment with erlotinib according to the indications in its UK marketing authorisation was not small and was considerably higher than the manufacturer's estimate. See FAD section 4.21. Comment noted. The Committee discussed whether the results of the SATURN trial could be generalised to UK clinical practice and concluded that the results from the trial had limited generalisability to UK clinical practice, therefore adding further uncertainty to the true magnitude of the benefits of erlotinib that would be achieved for UK patients. See FAD section 4.5.
Roy Castle Lung Cancer Foundation	Once again, we remind the Committee of the overall poor prognosis and low survival rates for this patient group. Even relatively small improvements in survival and quality of life, as compared with the current established therapy, are of real importance to patients. We hope, that during its further deliberations, the Appraisal Committee will be mindful of this and take it in to account.	Comment noted. The Committee considered evidence on the nature of non-small-cell lung cancer and the value placed on the benefits of erlotinib by people with the condition, those who represent them, and clinical specialists. See FAD section 4.1. The Committee also noted a statement from

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		a patient group which emphasised that even relatively small improvements in survival and quality of life afforded by new treatments compared with current treatment options is of real importance to patients. See FAD section 4.3.

Comments received from members of the public

NHS Professional 1	Appraisal Committee's preliminary recommendations	The accessibility of an effective, well tolerated oral maintenance therapy for NSCLC patients within the homecare setting should be given due consideration. Pemetrexed has recently received regulatory and NICE approval as a maintenance agent after first-line chemotherapy, but only in patients with non-squamous histology who have not previously received pemetrexed. Erlotinib is the only maintenance agent with a license which includes patients with squamous histology and for patients who have already received pemetrexed as part of first-line chemotherapy. After first line chemotherapy, most patients currently experience a break in their active treatment until their disease returns. This is when second line treatment is considered. For many patients this is a less than ideal approach, as only a minority of UK patients (around one-third) actually receive second-line treatment at relapse. This is usually because disease progression is identified too late, performance status has already declined and further treatment would not be appropriate. Therefore the ability to administer erlotinib in the first line maintenance setting should be seen as an opportunity to prolong survival for advanced NSCLC patients by ensuring that patients who can benefit from therapy receive it.	Comment noted. The Committee considered evidence on the nature of non-small-cell lung cancer and the value placed on the benefits of erlotinib by people with the condition, those who represent them, and clinical specialists. See FAD section 4.1. The Committee was aware that maintenance treatment after first-line treatment is still a relatively new concept in lung cancer and that its aim is to prolong the benefits of first-line treatment and to maximise quality of life for as long as possible. See FAD section 4.2. The Committee heard from the clinical specialists that erlotinib may provide a maintenance treatment option for patients who cannot receive pemetrexed maintenance treatment because they have squamous disease and/or they have had pemetrexed as a first-line treatment. See FAD section 4.3.

NHS Professional 1	The technologies	Erlotinib is also well suited to the maintenance setting as it has been shown to delay disease and therefore symptom progression, is orally administered (does not require hospital resources for I.V administration) and is generally well tolerated. Because of its toxicity profile – it is devoid of the myelosuppresion and other non-specific toxicities of conventional cytotoxic drugs and its main side-effects are mild-moderate rash and diarrhoea. These can usually be managed by simple symptomatic interventions or by dose modification. As an oral agent erlotinib offers benefits to patients who do not wish to attend the hospital regularly for the intravenous (IV) administration required with pemetrexed and to hospital departments already struggling to deliver the volumes of IV chemotherapy treatments.	Comment noted. The Committee noted views from the clinical specialists that erlotinib is an oral drug with adverse effects that are well known and relatively well tolerated. See FAD section 4.3.
NHS Professional 1	Consideration of the evidence	Unless erlotinib receives NICE guidance for maintenance therapy, patients who received pemetrexed as part of their first line treatment (rapidly becoming the majority of non squamous patients) or who have squamous histology will not have the opportunity for life extending maintenance therapy.	Comment noted. The Committee heard from the clinical specialists that erlotinib may provide a maintenance treatment option for patients who cannot receive pemetrexed maintenance treatment because they have squamous disease and/or they have had pemetrexed as a first-line treatment. See FAD section 4.3. The Committee was also aware that the proportion of patients who would be eligible for pemetrexed maintenance treatment was declining quickly over time as more patients receive pemetrexed first-line (following publication of TA181). See FAD sections 4.18 and 4.24.
NHS Professional	Appraisal Committee's preliminary	The preliminary recommendation is incorrect given the data and the discrepancy between the JMEN pemetrexed and SATURN erlotinib assessments. The confusion and	Comment noted. The Committee discussed whether the results of the SATURN trial could be generalised to UK clinical practice and

2	recommendations	difference of opinion between the local ERG and the Licensing Authority re the robustness of the SATURN data and subsequent statistical analysis needs resolution. The ERG and other comments reveal confusion and unsupported opinions which have produced a negative effect. Some will be detailed. There seems to be an inherent prejudice in this ACD against erlotinib.	concluded that the results from the trial had limited generalisability to UK clinical practice, therefore adding further uncertainty to the true magnitude of the benefits of erlotinib that would be achieved for UK patients. See FAD section 4.5.
NHS Professional 2	The technologies	The erlotinib side effect profile detailed above is remarkably slight given the toxicity of cytotoxic drugs. An oral convenient drug without cytotoxic side effects is a very welcome option after 1st line chemotherapy. It should be noted that in the maintenance, 2nd and 3rd line settings there is no evidence that the Overall Survival is dependent on EGFR mutation status (which captures the sensitivity of SE Asian and never/light smoker population) commented in section 3 and 4.Therefore in this setting the UK population will be similar to the global study population.	Comment noted. The Committee discussed whether the results of the SATURN trial could be generalised to UK clinical practice and concluded that the results from the trial had limited generalisability to UK clinical practice, therefore adding further uncertainty to the true magnitude of the benefits of erlotinib that would be achieved for UK patients. See FAD section 4.5.
NHS Professional 2	The manufacturer's submission	It is intriguing as to why the methodology and estimations of the local ERG is always chosen in preliminary ACDs over that of other submissions e.g manufacturers, EMEA etc. Where is the evidence to support this systematic choice? The ERG view that the results are not generalised within the UK is nonsense. SATURN is not a 1st line trial but a maintenance trial and by definition the patients will be fitter. Furthermore there is no evidence that other than EGFR mutation status which captures smoking history/SE asian ethnicity etc that global patients are any different from the UK patients in terms of treatment survival in advanced NSCLC. Paclitaxel/vinorelbine has never been compared against pemetrexed. The comment on post progression treatment (PPT) as not having marketing authorisation is common, even in JMEN pemetrexed trial which NICE	Comment noted. The Committee concluded that there was very considerable uncertainty that the benefit of erlotinib seen in the SATURN trial would be translated into routine practice. See FAD section 4.10. The Committee agreed that 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 considered that there were several

		approved. From randomised trials there is no evidence that one cytotoxic is superior overall for survival nor was pemetrexed vs. erlotinib, therefore the OS gain is not due to PPT. The stable disease subgroup was determined as robust by the licensing authority, perhaps the ERG should reconsider its view.	factors that led 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. These included the small numbers of patients in the post hoc subgroup analyses informing the survival estimates for the squamous and non-squamous disease groups and the use of post-progression treatments in the SATURN trial, which are not routinely used in the UK; and the lack of explanation as to why most of the survival benefit for erlotinib in the squamous disease group occurred after treatment was discontinued (in the post-progression period). See FAD section 4.12.
NHS Professional 2	Consideration of the evidence	Currently patients wait for progression and then some receive 2nd line. Maintenance assists a group of patients who would drop out and never receive any 2nd line. Thus fewer patients will benefit from 2nd line cf.to maintenance The S124 pemetrexed trial result may show benefit after first line pemetrexed. Re relatively small numbers in subgroups these are LESS in the gefitinib 1st line trial wrt EGFR mutation status. The proportion of patients from South East Asia and the never smokers are LESS than the number of other recent trials, particularly the JMEN trial. Thus SATURN has fewer favourable patients. The 30% of stable disease patients with PS0 is a very realistic value in a maintenance (not 1st) trial. Erlotinib overall survival is not dependant on mutation status either in the maintenance setting or 2nd 3rd line. Mutation testing in UK is not comprehensive, it is inconceivable that all mutation positive	Comment noted. See above response. The Committee was concerned that some of the survival benefit of maintenance treatment with erlotinib demonstrated in the SATURN trial would not be seen in clinical practice because patients with EGFR mutations would usually receive gefitinib (in line with TA192) and would therefore not be eligible for maintenance treatment with erlotinib. See FAD section 4.8.

		patients would be given first line gefitinib, these remaining patients could well benefit from erlotinib.	