Kate Moore
Technology Appraisal Project Manager
National Institute for Health and Clinical Excellence
Level 1A, City Tower
Piccadilly Plaza
Manchester
M1 4BD

BY EMAIL

16 December 2010

RE: 2nd ACD on erlotinib for the maintenance treatment of mNSCLC

Dear Kate,

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:

- 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)

- 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) (see sections 1.3 and 1.4).

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

Roche Products Limited
6 Falcon Way
Shire Park
Welwyn Garden City
Hertfordshire
AL7 1TW

Health Economics and
Strategic Pricing

Tel. +44(0)[redacted]
Fax +44(0)[redacted]

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, in section 1.2.

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).

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.

We hope the Committee considers carefully the evidence presented in this document. We firmly believe NICE's final decision on erlotinib should be based 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.

Yours Sincerely,

[redacted]

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 (as detailed in section 1.2 of this document) 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 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. SQ SD Overall Survival Means from SATURN

	Truncated Mean	ERG	Roche	Committee
Erlotinib	14.4 months	14.0 months	15.3 months	-
Best Supportive Care	10.8 months	10.7 months	10.8 months	-
Incremental	3.6 months	3.4 months	4.6 months	Less than 3 months

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.

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 1sr ACD on erlotinib maintenance, this information has never been considered by the Committee. We believe that this may be the source of the inconsistency between the conclusions reached by the Committee in the 2nd ACD and the information provided below.

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.

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.

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 (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.

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.

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 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.

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.

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.

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.

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 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 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.

1.4. 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 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.

1.4.1. 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.

1.4.2. 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 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.

1.4.3. 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.

i)

ii)

iii)

Table 2 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 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 2. The populations deemed 'small' in other NICE appraisals

Appraisal	Technology	Indication	Date of Issue	Population Estimated	A Small Population?

TA190	Pemetrexed (Alimta)	Maintenance mNSCLC	June 2010	5,215 (Roche) 3,426 (Lilly)	Yes
TA208	Trastuzumab (Herceptin)	mGC	November 2010	7,000	Yes
Ongoing	Erlotinib (Tarceva)	Maintenance mNSCLC	Ongoing	4,127	No

1.5. 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 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.

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.

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.

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 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.

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 modeling the data, as the OS HR associated with that analysis is better than that of the unstratified squamous stable disease analysis (0.63 compred 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).

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.

1.6. 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. The Stable Disease Overall Survival Curves Fitted by the ERG

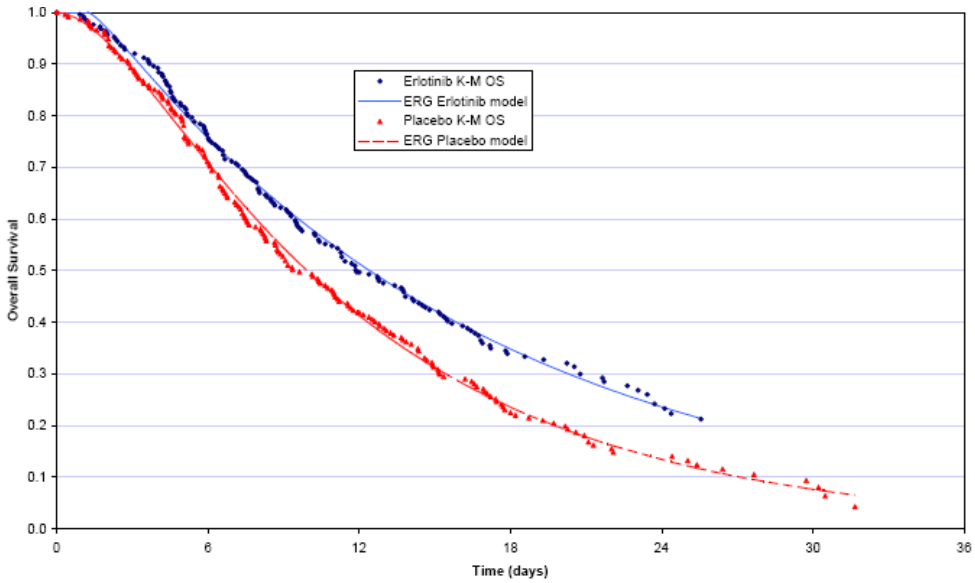


Table 3 below provides the cost-effectiveness results in the whole stable disease group produced via the utilisation of the PFS and OS curves estimated by the ERG, the amendments approved in the previous ACD and the two additional amendments made by the ERG to the two histology split models (i.e. correcting 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 3. The results of the whole stable disease analysis (LYs not discounted)

Comparator	Life Years	QALYs	Cost	Cost per QALY
Erlotinib	1.427	0.789	£17,312	-
BSC	1.081	0.600	£9,574	-
Incremental	0.346 (4.2 months)	0.190	£7,737	£40,792

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.

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 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 4 below.

Table 4. The mean survival advantage in each group as estimated by the ERG

Group	Stable Disease	Stable Disease Squamous	Stable Disease Non-Squamous
ERG	4.2 months	3.4 months	2.2 months

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).

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.

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

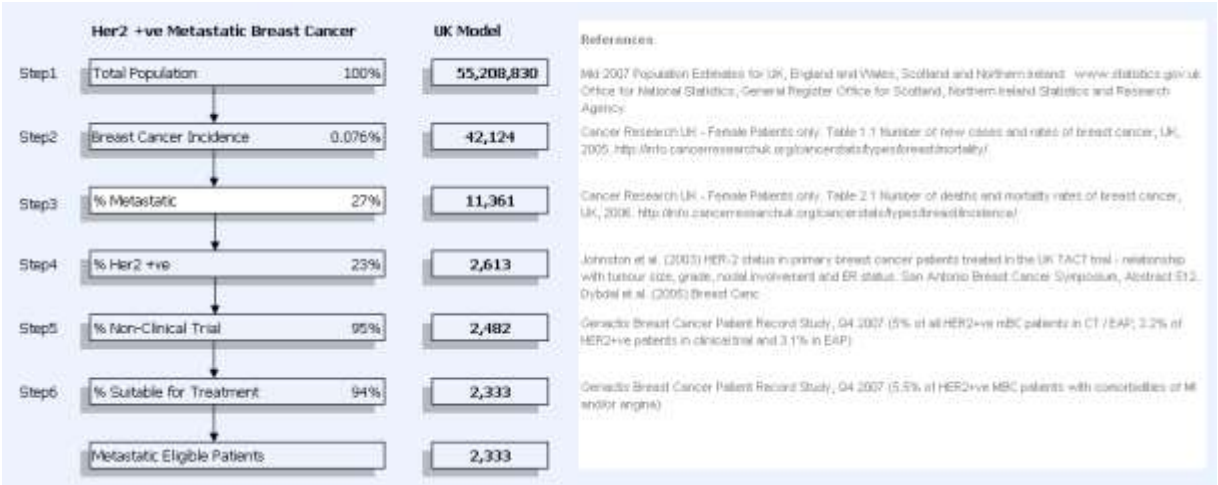
NICE 2010. TA208. Trastuzumab for the treatment of metastatic gastric cancer. http://guidance.nice.org.uk/TA208 (accessed on 09/12/2010)

NICE 2010. TA192. Gefitinib for the treatment of metastatic non-small cell lung cancer. http://guidance.nice.org.uk/TA192 (accessed on 09/12/2010)

NICE 2010. TA190. Pemetrexed for the maintenance treatment of metastatic non-small cell lung cancer. http://guidance.nice.org.uk/TA190 (accessed on 09/12/2010)

NICE 2001. TA25. Gemcitabine for the treatment of metastatic pancreatic cancer http://guidance.nice.org.uk/TA25 (accessed on 09/12/2010)

Appendix 1


Her2 +ve Metastatic Breast Cancer
UK Model
Step1
Total Population
100%
55,208,830
Step2
Breast Cancer Incidence
0.076%
42,124
Step3
% Metastatic
27%
11,361
Step4
% Her2 +ve
23%
2,613
Step5
% Non-Clinical Trial
95%
2,482
Step6
% Suitable for Treatment
94%
2,333
Metastatic Eligible Patients
2,333
References
Mid 2007 Population Estimates for UK, England and Wales, Scotland and Northern Ireland www.statistics.gov.uk Office for National Statistics, General Register Office for Scotland, Northern Ireland Statistics and Research Agency
Cancer Research UK - Female Patients only. Table 1.1 Number of new cases and rates of breast cancer, UK, 2005. http://info.cancerresearchuk.org/cancerstats/types/breast/mortality/
Cancer Research UK - Female Patients only. Table 2.1 Number of deaths and mortality rates of breast cancer, UK, 2006. http://info.cancerresearchuk.org/cancerstats/types/breast/incidence/
Johnston et al. (2003) HER-2 status in primary breast cancer patients treated in the UK TACT trial - relationship with tumour size, grade, nodal involvement and ER status. San Antonio Breast Cancer Symposium, Abstract 512. Dybdal et al. (2005) Breast Canc
Genactis Breast Cancer Patient Record Study, Q4 2007 (5% of all HER2+ve mBC patients in CT / EAP; 3.2% of HER2+ve patients in clinical trial and 3.1% in EAP)
Genactis Breast Cancer Patient Record Study, Q4 2007 (5.5% of HER2+ve MBC patients with comorbidities of MI and/or angina)

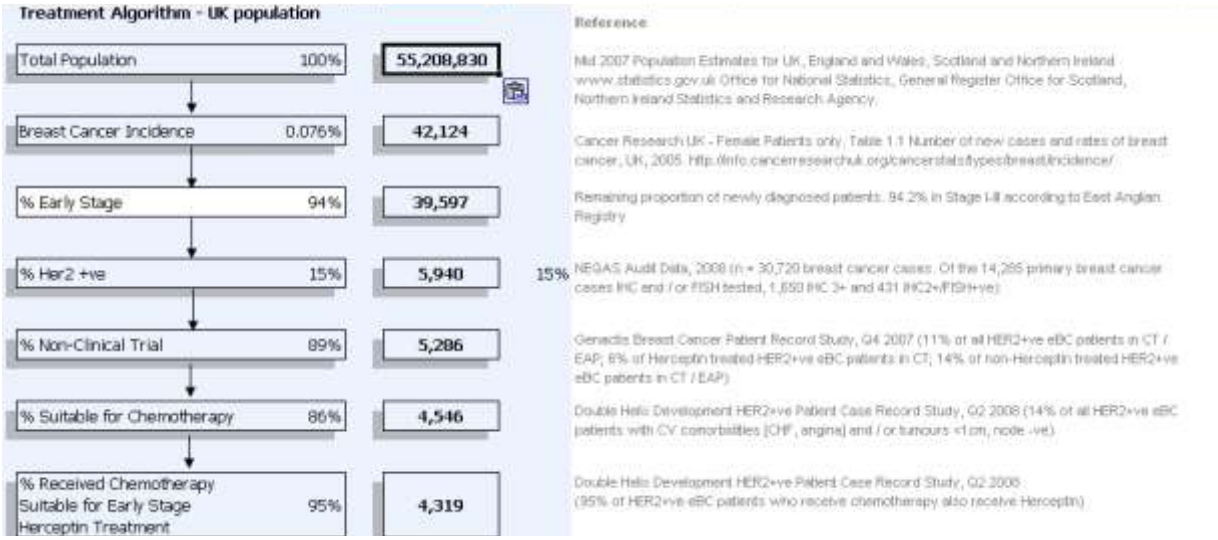

Treatment Algorithm - UK population
Total Population
100%
55,208,830
Breast Cancer Incidence
0.076%
42,124
% Early Stage
94%
39,597
% Her2 +ve
15%
5,940
15%
% Non-Clinical Trial
89%
5,286
% Suitable for Chemotherapy
86%
4,546
% Received Chemotherapy Suitable for Early Stage Herceptin Treatment
95%
4,319
Reference
Mid 2007 Population Estimates for UK, England and Wales, Scotland and Northern Ireland www.statistics.gov.uk Office for National Statistics, General Register Office for Scotland, Northern Ireland Statistics and Research Agency.
Cancer Research UK - Female Patients only. Table 1.1 Number of new cases and rates of breast cancer, UK, 2005. http://info.cancerresearchuk.org/cancerstats/types/breast/incidence/
Remaining proportion of newly diagnosed patients. 94.2% in Stage I-II according to East Anglian Registry
NEQAS Audit Data, 2008 (n = 30,720 breast cancer cases. Of the 14,285 primary breast cancer cases IHC and / or FISH tested, 1,650 IHC 3+ and 431 IHC2+/FISH+ve)
Genactis Breast Cancer Patient Record Study, Q4 2007 (11% of all HER2+ve eBC patients in CT / EAP; 8% of Herceptin treated HER2+ve eBC patients in CT; 14% of non-Herceptin treated HER2+ve eBC patients in CT / EAP)
Double Helix Development HER2+ve Patient Case Record Study, Q2 2008 (14% of all HER2+ve eBC patients with CV comorbidities [CHF, angina] and / or tumours <1cm, node -ve)
Double Helix Development HER2+ve Patient Case Record Study, Q2 2008
(95% of HER2+ve eBC patients who receive chemotherapy also receive Herceptin)

Table 44. Estimated number of patients eligible to receive treatment in England

Assumptions	%	Value 2010	Value 2011	Value 2012	Value 2013	Value 2014
Local population		52,198,207	52,577,102	52,953,960	53,331,991	53,709,928
Gastric Cancer Incidence	0.0122%	6,368	6,414	6,460	6,507	6,553
Proportion of patients with metastatic disease	80%	5,095	5,132	5,168	5,205	5,242
Proportion IHC2+/FISH+ or IHC3+	16.88%	860	866	873	879	885
Proportion receiving chemotherapy	53%	458	462	465	468	472
Eligible population		458	462	465	468	472

Table 45. Estimated number of patients eligible to receive treatment in Wales

Assumptions	%	Value 2010	Value 2011	Value 2012	Value 2013	Value 2014
Local population		3,010,623	3,024,218	3,039,845	3,055,659	3,071,554
Gastric Cancer Incidence	0.0165%	497	499	502	504	507
Proportion of patients with metastatic disease	80%	397	399	401	403	405
Proportion IHC2+/FISH+ or IHC3+	16.88%	67	67	68	68	68
Proportion receiving chemotherapy	53%	36	36	36	36	36
Eligible population		36	36	36	36	36

Appendix 2

Table A2. Patients suitable 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