NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Erlotinib monotherapy for the maintenance treatment of non-small cell lung cancer after previous platinum containing chemotherapy

Roche Supplementary Evidence Submission to the National Institute for Health and Clinical Excellence
8th July 2010

Executive Summary

The requirement for additional analysis

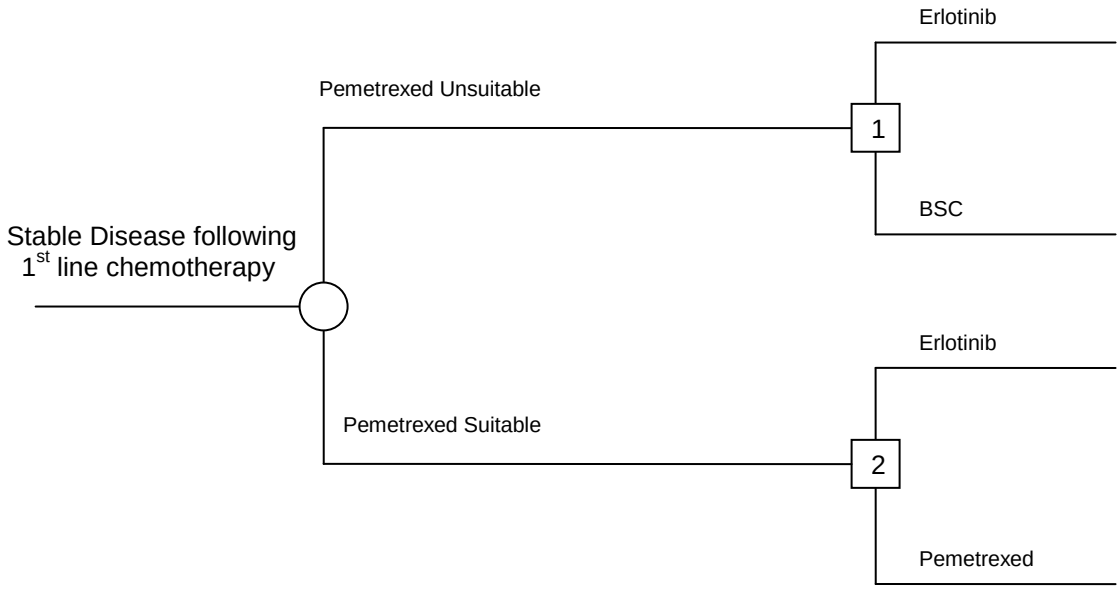
The original Roche erlotinib first line maintenance (1LM) NICE submission was made at a time of considerable uncertainty surrounding the specific license erlotinib would be granted by the EMA and the legitimacy of pemetrexed as a comparator given it's then ongoing NICE 1LM appraisal. Despite Roche's request for a delay in the scheduling of this appraisal at the decision problem meeting for erlotinib in 1LM this request was not and as such significant elements of the submission made are no longer relevant to the decision problem at hand.

EMA approval of erlotinib in the stable disease group and NICE approval of pemetrexed in the non-squamous group has redefined the decision problem of interest by a patient's best response to first line induction, the contents of that induction and by disease histology.

If a patient has stable disease following induction and is not eligible to receive pemetrexed maintenance (either due to having squamous histology or due to having had pemetrexed based induction) they are eligible to receive either erlotinib as a maintenance or no active treatment (best supportive care (BSC)).

If a patient has stable disease following induction and is eligible for pemetrexed maintenance (i.e. has non-squamous histology and received an induction doublet regimen containing gemcitabine, paclitaxel or docetaxel) a clinician faces the decision of whether to utilise pemetrexed (NICE recommended for use in this setting in TA190) or erlotinib. These two scenarios are denoted by decision node 1 and 2 in the decision tree below.

Figure 1. The decision problem defined by the recent decisions of NICE and the EMA



As noted in section 4.4 of the ACD the non-squamous model presented by Roche in our original submission contained patients with a best response to induction other than 'stable disease' thereby rendering the analysis undertaken beyond erlotinib's license and irrelevant to the new decision problem. The committee therefore did not have access to the evidence base required to make an evidence based decision on the cost effectiveness of erlotinib in this group. The required non-squamous stable disease analysis (i.e. 'Pemetrexed Suitable' analysis) is presented within this additional evidence submission.

In addition to this entirely new analysis a revised form of the stable disease model originally submitted to NICE is provided for consideration by the committee. This revised model incorporates refinements and corrections suggested by the ERG and also corrects a significant error made by Roche in costing the best-supportive care associated with the post-progression state. In the original model the extremely expensive resource phase associated with a patients last few months of life was mistakenly applied for the whole period post-progression on first line maintenance. Clearly a patient progressing on first line maintenance will enter a resource use health state more akin to that of the PFS state of a 2nd Line appraisal with an eventual terminal phase at the end of

life rather than being in the extremely expensive terminal phase for the whole 11 months post-first line progression. The erroneous use of such a cost causes the incremental cost associated with a regimen that provides an extension in life (such as erlotinib) to be significantly overstated.

This oversight resulted in the mean monthly post-progression BSC cost utilised in the erlotinib SD 1LM economic model being over 10 times the monthly BSC cost applied to the equivalent health state in the recent pemetrexed first line and first line maintenance appraisals (TA181 and TA190).

This caused considerable over-estimation of the total cost associated with each treatment option with the total cost of the stable disease 'watch and wait' arm estimated via the original Roche SD model being nearly twice (£16,382 compared to £8,318) the almost equivalent non-squamous 'watch and wait' arm of the pemetrexed non-squamous maintenance model (accepted by the ERG and committee in NICE TA190).

As the amendment of this error has significant implications for the estimated cost effectiveness of erlotinib it is imperative that the committee consider the amended analysis presented.

Although histology is not an important determinant of benefit to erlotinib, it has become an important factor in selecting patients for other treatments and so it was felt that the committee may be curious to see the cost effectiveness of erlotinib compared to best-supportive care in stable disease patients according to histology. Therefore, two new further comparisons are presented. The first is a cost utility analysis of erlotinib compared to BSC in stable disease patients with squamous histology and the second is the same comparison but made in stable disease patients with non-squamous histology.

In summary four cost-utility comparisons are provided within this document:

1. Erlotinib compared to best supportive care in patients who are eligible for maintenance with erlotinib yet not eligible for maintenance with pemetrexed (i.e. squamous stable disease patients or non-squamous stable disease patients who have received pemetrexed/cisplatin as induction).

2. Erlotinib compared to best supportive care in patients with squamous histology with stable disease as best response to induction

3. Erlotinib compared to best supportive care in patients with non-squamous histology with stable disease as best response to induction

4. Erlotinib compared to pemetrexed in patients who are eligible for maintenance with erlotinib or pemetrexed (i.e. non-squamous stable disease patients who did not receive pemetrexed/cisplatin as induction).

Clinical Evidence

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

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

However, analysis of outcomes in SATURN, according to patient response to first-line platinum-based chemotherapy (objective response versus disease stabilisation; SD), revealed that although all SATURN entrants obtained similar extensions in time to disease-progression, OS benefit was largely confined to those with a poorer (SD)

response to their induction chemotherapy. As a consequence, the European maintenance indication for erlotinib was limited to this group (in the USA the FDA recommended erlotinib as a maintenance treatment for all patients achieving at least disease stabilisation after platinum-based chemotherapy).

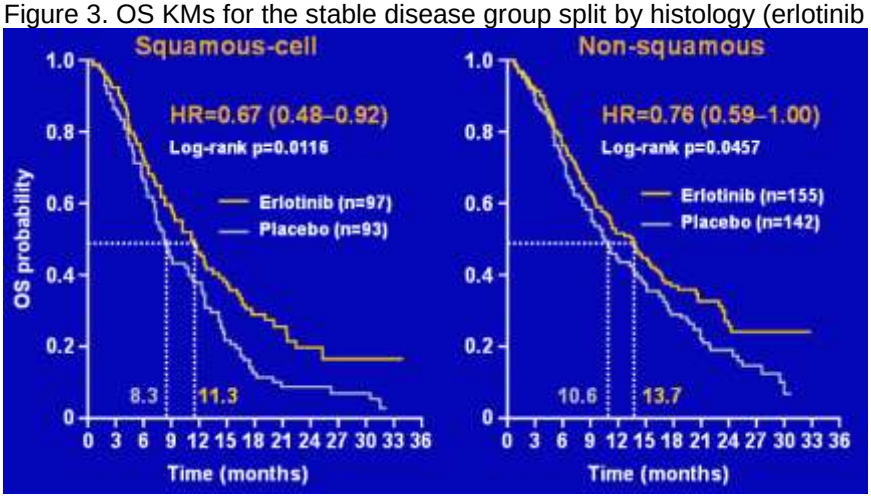
Due to the uncertainty surrounding the specific license erlotinib would be granted at the time of the original Roche erlotinib 1LM submission, Roche omitted clinical data that is now key to the decision problem faced. This clinical data (in particular the efficacy results from the SD group from SATURN stratified by histology) is provided within this document.

Figure 2. HRs for the stable disease group split by histology (erlotinib vs BSC)

	N	PFS	OS
Squamous	190	0.691 [0.513; 0.929]	0.665 [0.484; 0.915]
Non-Squamous	297	0.687 [0.541; 0.873]	0.764 [0.586; 0.996]

Post-hoc analysis of the SATURN data demonstrates that erlotinib provides a significant and clinically meaningful PFS and OS advantage in both patients with squamous histology stable disease and non-squamous histology stable disease. In both cases the median OS advantage provided is just over 3 months. These median values are underestimates of the expected OS gain provided by erlotinib in both groups due to the clear divergence of the erlotinib and BSC OS curves of the SATURN SQ SD and NSQ SD populations over time.

Figure 3. OS KMs for the stable disease group split by histology (erlotinib vs BSC)



Cost Effectiveness Methods

Three models were create to satisfy the four cost utility comparisons required. The first was a revised form of the stable disease model originally submitted with the use of the ERGs suggested amendments in combination with two modifications (discussed in further detail below) in order to facilitate the comparison of erlotinib to pemetrexed in patients for whom treatment with erlotinib is suitable but treatment with pemetrexed is not (either due to histology or due to having received the NICE approved regimen of pemetrexed/cisplatin as induction).
The second was a model founded on the amended SD model with the PFS, OS and dosing fits updated to those of the SATURN squamous histology stable disease population.
The third was a model of the same structure as the above 2 models designed to combine comparisons 3 and 4 within the same model. The PFS and OS curves in the model were updated to those of the non-squamous stable disease population and the pemetrexed comparator arm was generated via the application of a range of plausible pemetrexed vs erlotinib PFS and OS HRs to the erlotinib baseline curves under the assumption of proportional hazards.

The revised models incorporated the majority of the amendments made by the ERG in the additional work they conducted on the original Roche SD model with two key deviations. The ERG amendments incorporated included the use of the ERG's 'spline' based PFS and OS parametric fits (those actually fitted by the ERG in the case of the SD model and those fitted by Roche for the other two models), the correction of the discounting methodology used, the use of the ERG's preferred utility values and the extension of the time horizon.

The two deviations were as follows:

- The use of a slightly modified version of the methodology used by the ERG to derive the mean cost of erlotinib (with the PFS KM curves used by the ERG being replaced by time to complete treatment cessation KM curves in order to reflect the fact that in the SATURN trial, and indeed in clinical practice, a

proportion of patients did/do cease treatment prior to disease progression (due to patient preference, AE etc))

- The amendment of the BSC costing logic applied within the model to that used by the manufacturer of pemetrexed and accepted by the ERG and NICE appraisal committee in NICE TA181 and TA190 following the realisation that in the original model the extremely expensive terminal phase associated with progression on 2nd line treatment from the erlotinib 2nd line appraisal (TA162) had erroneously been applied to the entire period post-progression on first line maintenance.

The NSQ SD and SQ SD models both featured these amendments.

As no stable disease non-squamous hazard ratio is publicly available from the JMEN trial (with only the non-squamous hazard ratio available) a wide range of potential relative efficacy scenarios were tested in the comparison of erlotinib to pemetrexed in those for whom maintenance with pemetrexed is suitable.

The cost of pemetrexed was calculated with consideration of the distribution of BSA around the mean value reported for the SATURN NSQ SD population via the use of a BSA frequency table.

The real number PFS, PPS, OS and time to complete treatment cessation KMs for the two new populations (the NSQ SD and SQ SD populations) are provided as a CIC appendix so that the ERG may validate the results produced and/or make any amendments if deemed necessary.

Results

1. Stable Disease: Erlotinib Vs BSC

The amended base-case ICER of erlotinib compared to best supportive care in patients with stable disease following induction is £39,936. This equates to a cost per life year gained of £24,029 at a mean OS advantage of 3.9 months in a patient population in

which mean survival without maintenance treatment is around 12 months (equivalent to a greater than 30% increase in expected overall survival).

The biggest driver of the difference between this figure and that estimated by Roche and the ERG in the original erlotinib submission and the erlotinib 1LM appraisal is the correction of the erroneous application of the highly expensive end of life phase cost for the entire post-first-line-progression period. If the original PFS BSC supportive care cost used in the model is applied to the complete PFS and PD BSC phase rather than the use of the figure used by the manufacturer of pemetrexed in TA181 and TA190 the base-case ICER rises to £44,475.

The use of the ERG's dosing method that assumes patients are dispensed a pack of erlotinib every 30 days of PFS despite having completely ceased treatment (rather than the method used in this analysis which is linked to time to complete treatment cessation rather than PFS) caused the base case ICER to rise to £44,942.

Sensitivity analysis demonstrates that biggest driver of this ICER is the assumed cost of PD BSC with all plausible value sensitivity analyses producing an ICER well below £50,000 per QALY gained. Whist the ERG's dosing method suggests a higher base-case ICER this method clearly overestimates the true cost of erlotinib to the NHS as if a patient has ceased treatment due to an adverse event or simply patient preference they will not be dispensed another pack of erlotinib every 30 days.

2. Stable Disease with Squamous Histology: Erlotinib Vs BSC

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

This ICER was robust to sensitivity analysis with the use of the TA181 PFS BSC values for the BSC in the model increasing the base case to just over £40,000 per QALY gained.

3. Stable Disease with Non-Squamous Histology: Erlotinib Vs BSC

The base case ICER of erlotinib compared to best supportive care in patients with non-squamous histology and stable disease as best response following induction is £40,020. This ICER is robust to sensitivity analysis with the use of the TA181 PFS BSC values for the BSC in the model increasing the base-case ICER to just under £45,000 per QALY gained.

4. Stable Disease with Non-Squamous Histology: Erlotinib Vs Pemetrexed

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

In the scenarios in which erlotinib was assumed to be equally as effective as pemetrexed and more efficacious than pemetrexed erlotinib dominated pemetrexed.

In the scenarios in which it was assumed pemetrexed was more effective than erlotinib the base-case ICERs ranged from £91,789 to £511,351. Whilst these ICER suggest that erlotinib is not cost-effective compared to pemetrexed it is important to note that these ICERs in fact denote that erlotinib is cost-effective compared to pemetrexed as the ICERs are generated in scenarios in which erlotinib is effectively in the south-west quadrant of a cost-effectiveness plane (i.e. erlotinib is less costly and less effective).

The £511,351 ICER for example demonstrates that if this scenario were true for every QALY lost by switching to erlotinib the NHS would save over £500,000. If this cost-saving were re-invested in more efficient technologies elsewhere in the NHS (such as

erlotinib in SQ SD patients) it is clear that the net health impact of a wholesale switch to erlotinib could be significantly positive.

Conclusions

If granted consideration under NICE's supplementary end of life (EOL) guidance it would appear that erlotinib maintenance is cost effective according to the NICE criteria in the treatment of those patients with stable disease as best response to induction therapy with a most plausible ICER of around £40,000 per QALY gained.

Erlotinib grants an extension in life greater than 3 months (3.9 months), in a stable disease patient population with an extremely short life expectancy (12 months) and is indicated for use in a small population (just over 4,000 patients per annum across the 1LM and 2L NSCLC and metastatic pancreatic licenses) (see the attached ACD response document for further detail on the derivation of these figures).

If the SD group are split by histology the ICER of the SQ SD group improves slightly whilst the NSQ SD group reduces slightly (as one might expect given the marginal OS benefit to squamous patients suggested by the OS HRs for the SD population of SATURN).

In the SQ SD group erlotinib provides a life extension of over 40% (4.3 months) in a patient population with poor prognosis and no alternative maintenance treatment options. The base-case ICER suggests the cost per QALY gained by the use of erlotinib in this patient population is £35,491. This ICER is robust to sensitivity analysis. The base case ICER of erlotinib compared to BSC in the NSQ SD population is £40,020.

The stable disease non-squamous analysis undertaken demonstrates that irrespective of the uncertainty surrounding the relative efficacy of erlotinib and pemetrexed in the specific patient group erlotinib is cost effective relative to the NICE recommended regimen of pemetrexed maintenance. Despite this uncertainty the significant cost-savings provided by erlotinib (around £16,000 per patient treated) are large enough to outweigh QALY differences associated with even the most pemetrexed favourable efficacy scenarios.

If granted consideration under NICE's supplementary end of life guidance erlotinib appears to be cost effective in those patients with stable disease following induction for whom maintenance with pemetrexed is unsuitable. This conclusion is robust to the dichotomisation of this SD population by histology.

Erlotinib is extremely cost effective compared to pemetrexed in NSQ SD patients for whom maintenance with pemetrexed is suitable.

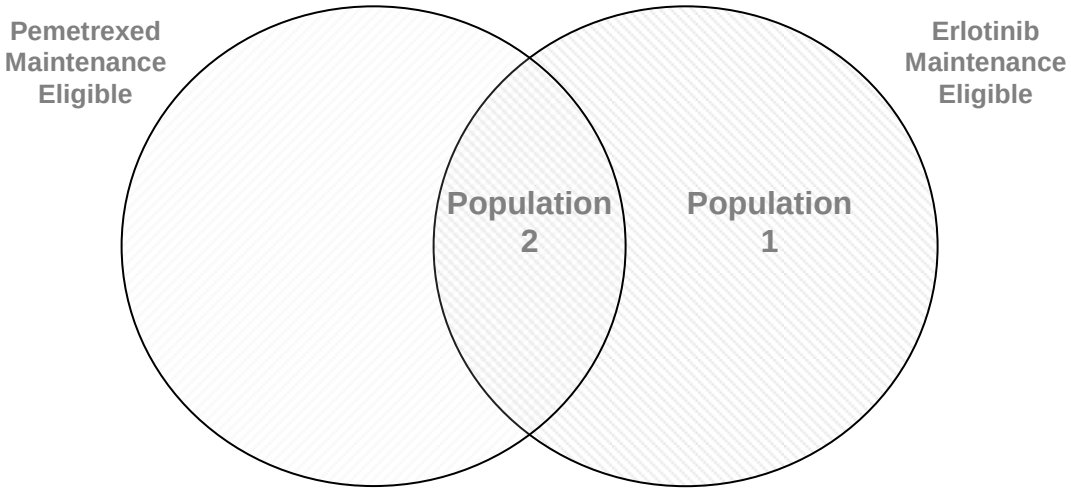
1. The decision problem

1.1. Overview

Two decisions have been made since the original Roche submission for this appraisal; NICE approval of pemetrexed in the 1st line maintenance treatment of non-squamous non-small cell lung cancer (NSCLC) and EMA approval of erlotinib in the 1st line maintenance (1LM) treatment of stable disease (NSCLC) patients. These two decisions have redefined a patients treatment options according to their best response to induction, the contents of that induction and their underlying disease histology.

A patient with non-squamous disease non-progressive following induction with a doublet regimen containing gemcitabine, paclitaxel or docetaxel is eligible for NICE approved maintenance treatment with pemetrexed. A patient with stable disease following four cycles of induction therapy with standard chemotherapy (including pemetrexed) is eligible for erlotinib maintenance.

Figure 4. The decision problem



Therefore there are two primary patient populations that must be considered in any appraisal of erlotinib; those who are eligible to receive erlotinib but not eligible to receive

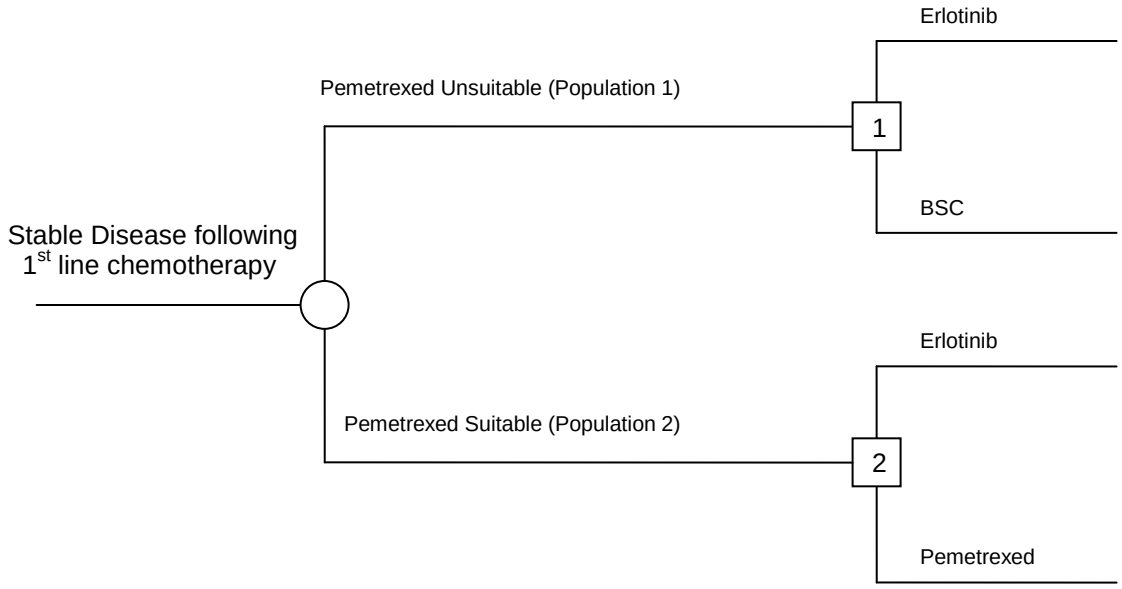
pemetrexed (population 1 in Figure 4) and those who are eligible to receive erlotinib and also eligible to receive pemetrexed (population 2 in Figure 4)

Population 1 is made up of those patients with stable disease following induction for whom maintenance with pemetrexed is unsuitable (be that due to the patient having squamous disease or due to the patient having non-squamous disease with their induction consisting of the NICE recommended doublet of pemetrexed and cisplatin).

Population 2 is made up of those patients with stable disease following induction for whom maintenance with pemetrexed is suitable (i.e. the patient has non-squamous histology and did not receive the NICE recommended pemetrexed/cisplatin doublet regimen as induction).

Figure 5 below demonstrates the treatment options available to each of these patient populations and thereby defines the cost-utility analyses required.

Figure 5. First line maintenance treatment algorithm for stable disease patients



Whilst a cost-utility analysis of decision node 1 (erlotinib vs BSC in those patients with stable disease as best response following induction) was presented in the original Roche submission the analysis undertaken was limited due to the erroneous application of the cost associated with the extremely resource intensive period at the very end of a patients

life for the entire period of post-first line maintenance progression. Therefore an amended model incorporating modifications suggested by the ERG and the methodology and monthly post-progression best supportive care cost values utilised in recent NICE appraisal of pemetrexed in first line maintenance (TA190) in combination with the amendments made by the ERG in their additional work conducted in preparation of the erlotinib 1LM ERG report is provided for the committees consideration.

In addition to this amended evaluation of 'population 1' a new cost utility analysis of erlotinib compared to pemetrexed in those patients in 'population 2' (those patients with non-squamous stable disease) incorporating the amendment described previously is presented so that the appraisal committee may determine the cost-effectiveness of erlotinib in this patient group. This analysis was not provided in the original Roche submission and so has never been presented to the committee.

NICE and EMA approval of pemetrexed maintenance in only those patients with non-squamous disease has brought disease histology to the forefront of the decision a clinician faces when determining which, if any, maintenance treatment to give a patient. Given this importance of histology in determining whether or not a patient is eligible to receive pemetrexed it was felt that it may be of interest to the committee to see the results of the 'pemetrexed unsuitable' analysis described above stratified by underlying histology (i.e. squamous or non-squamous). Therefore 'population 1' was split into those patients with squamous and non-squamous disease in order to determine the cost-effectiveness of erlotinib vs BSC in patients with stable disease by histology.

In summary four cost-utility comparisons are provided within this document:

1. Erlotinib compared to best supportive care in patients who are eligible for maintenance with erlotinib yet not eligible for maintenance with pemetrexed (i.e. squamous stable disease patients or non-squamous stable disease patients who have received pemetrexed/cisplatin as induction).

2. Erlotinib compared to best supportive care in patients with squamous histology with stable disease as best response to induction

3. Erlotinib compared to best supportive care in patients with non-squamous histology with stable disease as best response to induction

4. Erlotinib compared to pemetrexed in patients who are eligible for maintenance with erlotinib or pemetrexed (i.e. non-squamous stable disease patients who did not receive pemetrexed/cisplatin as induction).

1.2 Comparators

As this submission is provided as supplementary evidence to the original Roche submission only a brief summary of the comparators utilised will be provided in the following sections. A more comprehensive overview is provided in the original Roche submission.

1.3.1 Erlotinib

Erlotinib (Tarceva©) is an oral formulation indicated as monotherapy for maintenance treatment in patients with locally advanced or metastatic non-small cell lung cancer with stable disease after 4 cycles of standard platinum-based first-line chemotherapy (Tarceva SmPC). In maintenance treatment a patient receives one 150 mg tablet of erlotinib daily until disease progression. Erlotinib is administered in packs of 30 tablets every 30 days. The BNF 59 list price of a pack of 30 150 mg tablet erlotinib is £1631.53. Under the patient access scheme (PAS) offered by Roche in TA162 (a 14.5% reduction in the price of erlotinib to the NHS) the price of a pack of 30 150 mg erlotinib tablets is £1394.96. This PAS has been extended for use in first line maintenance and has been approved by the Department of Health.

1.3.2 Pemetrexed

Pemetrexed (Alimta©) is an IV administered chemotherapy indicated as monotherapy for the maintenance treatment of locally advanced or metastatic non-small cell lung cancer other than predominantly squamous cell histology (i.e. non-squamous histology) in patients whose disease has not progressed immediately following platinum-based chemotherapy. First-line treatment should have been a platinum doublet with

gemcitabine, paclitaxel or docetaxel (Almita SmPC). Pemetrexed monotherapy is administered once every 21 days until disease progression at a dose of 500 mg per BSA m^2.

Pemetrexed can be purchase in two vial sizes; 500 mg and 100 mg (at a cost of £800 and £160 respectively (BNF 59)). For a typical 1.8m^2 BSA patient this equates to a cost of £1,440 every 21 days and a monthly cost of £2,087. As pemetrexed is IV administered it requires additional administration resources beyond that required for erlotinib monotherapy.

1.3.3. Best Supportive Care

Prior to EMEA approval of pemetrexed and erlotinib in first line maintenance patients completing their initial first line chemotherapy for their locally advanced or metastatic NSCLC had no treatment option beyond waiting for their disease to progress so that they could commence their second line treatment (typically erlotinib or docetaxel in England and Wales). The 'best supportive care' comparator under consideration in the SD analysis undertaken represents this option of 'watching and waiting' for disease progression before instigating second line. It consists of no active treatment and merely attempts to palliate the symptoms of a patients disease.

1.4 Perspective

The NICE reference case was followed throughout the evaluations undertaken. This included the use of the perspective of the NHS/PSS in England and Wales.

2. Clinical Evidence

The following sections will present the additional information required to reach a conclusion on the clinical-effectiveness of erlotinib as first-line maintenance therapy within its licensed indication and reflecting UK clinical practice following recent and NICE guidance on pemetrexed

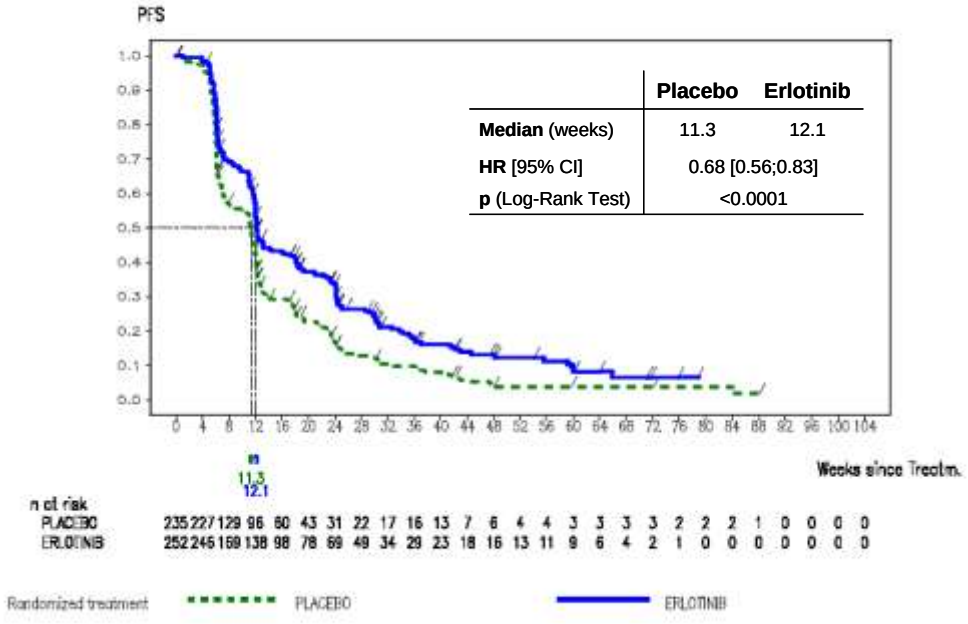
2.1 Clinical efficacy of erlotinib in patients with stable disease after first-line platinum-based chemotherapy

2.1.1 Progression-free and overall survival of stable disease patients

As reported in Roche's original submission to NICE, retrospective analysis of data from the SATURN study demonstrates that amongst patients with an inadequate response (achieving only SD, not objective response) after first-line chemotherapy, PFS benefit from erlotinib maintenance is similar to that seen in the entire SATURN study population, but OS benefit is substantially greater than in unselected patients. More extensive analysis of outcomes in SATURN according to status at the end of first-line chemotherapy was subsequently presented at the European Lung Cancer Congress (Coudert et al 2010).

The hazard ratio (HR) for the primary parameter, progression free survival (PFS), amongst patients achieving SD after first-line chemotherapy was 0.68 (95% CI 0.56 to 0.83) showing a statistically significant benefit for the erlotinib group ($p<0.0001$). The HR of 0.68 corresponds to a 47% improvement in PFS time with erlotinib. Median PFS was 11.3 weeks in the placebo group versus 12.1 weeks in the erlotinib group (See Figure 6). As noted previously, due to the step wise shape of the curve and single-point distortion, the median PFS is not considered to accurately reflect the overall patient benefit.

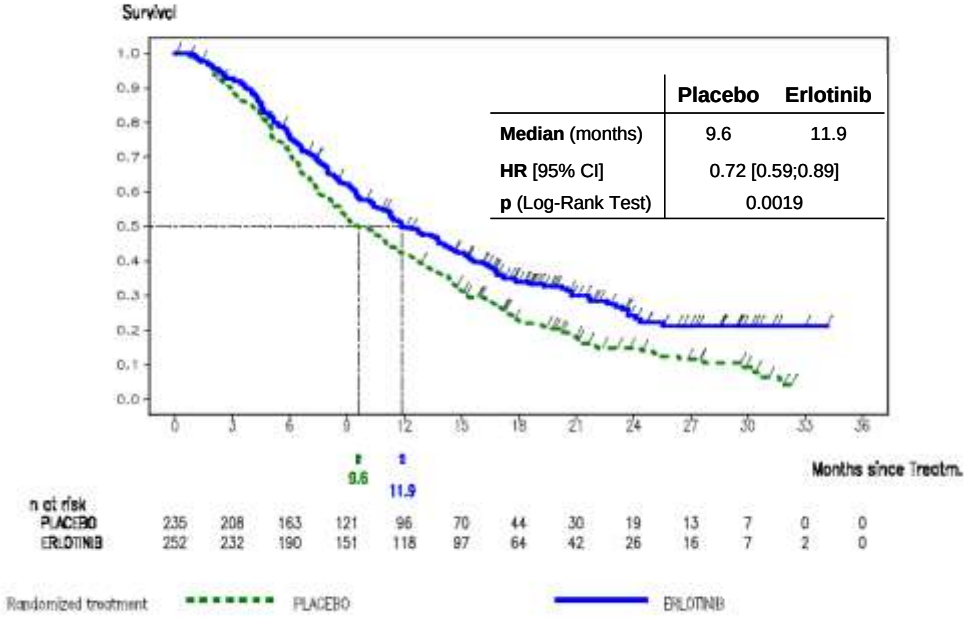
Figure 6. Progression-free survival benefit from maintenance erlotinib or placebo in patients achieving stable disease after first-line platinum chemotherapy in the SATURN study



	Placebo	Erlotinib
Median (weeks)	11.3	12.1
HR [95% CI]	0.68 [0.56;0.83]	
p (Log-Rank Test)	<0.0001	

In the SD population, the HR for OS was 0.72 (95% CI: 0.59;0.89; p=0.0019) (See Figure 7). This survival benefit represents a 39% improvement in OS with erlotinib in the maintenance setting for patients with SD.

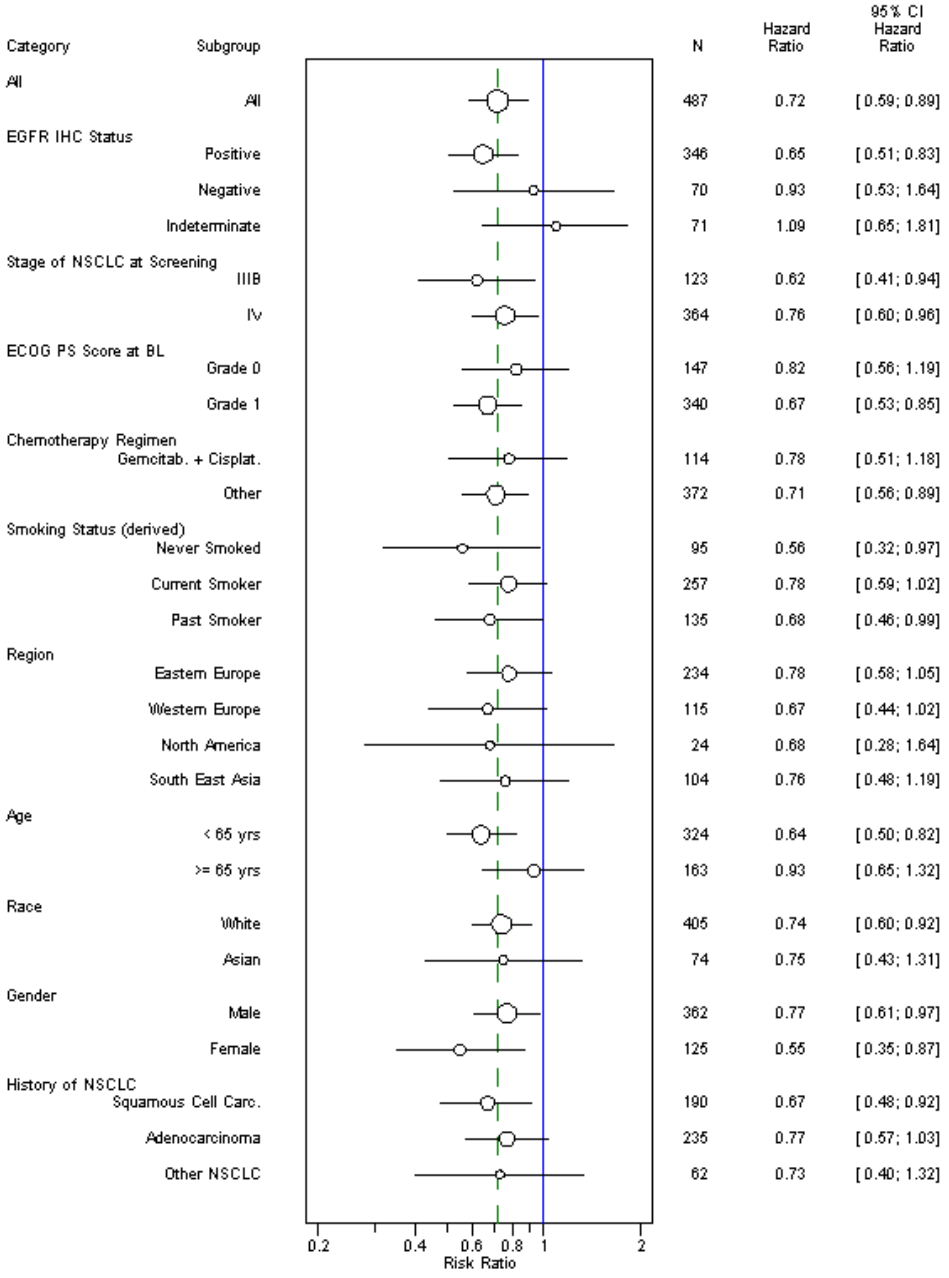
Figure 7. Kaplan-Meier Curve of Survival – Stable Disease Population (ITT analysis)



	Placebo	Erlotinib
Median (months)	9.6	11.9
HR [95% CI]	0.72 [0.59;0.89]	
p (Log-Rank Test)	0.0019	

As shown in Figure 8, subgroup analysis showed robust and consistent overall survival (OS) benefit across subgroups of the SD population. All HRs were below 1.00, except for patients with EGFR IHC status ‘indeterminate’.

Figure 8. SATURN Forest Plot



2.1.2 Progression-free and overall survival of stable disease patients according to histological subtype

EMEA and NICE approval of 1LM with pemetrexed in patients with non-squamous histology has placed tumour histology at the forefront of treatment algorithm facing physicians considering maintenance therapy in England and Wales. Given this growing presence of histology in defining a patients treatment options and therefore the decision that must be made by NICE it is important to consider the degree of benefit erlotinib maintenance affords to patients with both squamous and non-squamous tumours compared to best supportive care in those groups in which it is a relevant comparator (SQ SD patients and NSQ SD patients for whom treatment with pemetrexed is unsuitable) and against pemetrexed in those patients in which treatment with pemetrexed is a viable treatment option (NSQ SD patients for whom treatment with pemetrexed is suitable).

The efficacy results in the SD population according to histological subgroups are summarised in the appropriate sections below. These confirm findings from other studies, including BR.21, the pivotal study of erlotinib in relapsed NSCLC, that patients with both squamous and non-squamous NSCLC benefit to a similar extent, from erlotinib treatment. Additionally, by disaggregating two patient populations with different baseline risk of death a clearer picture of improvement in median survival emerges with erlotinib improving median survival in patients with both squamous and non-squamous tumours by at least 3 months.

So, although histology may be important in this appraisal because it defines patient suitability for other treatments and hence the appropriate comparators, it has little bearing on the efficacy of erlotinib itself.

2.1.2.1 Squamous Cell Stable Disease Patients: Erlotinib vs BSC

Post-hoc analysis of those patients with squamous histology and stable disease as best response to induction therapy in SATURN demonstrates that erlotinib is significantly more efficacious than BSC in terms of both PFS and OS. Table 1 provides the

descriptive statistics of the analysis of this patient population whilst Figure 9 and Figure 10 demonstrate the Kaplan-Meier curves for both PFS and OS.

Table 1. PFS and OS benefit in Squamous Cell Stable Disease Patients

Best Response To Induction	Histology	n	PFS	OS*
Stable Disease	**Squamous**	190	0.691 [0.513; 0.929]	0.665 [0.484; 0.915]

*OS is measured from time of randomisation into the maintenance phase.

Erlotinib was associated with a median OS advantage of over 3 months (3.02) with the shape of the OS curves causing the median gain to underestimate the mean OS gain (due to the steady divergence of the BSC and erlotinib OS curve over time). See the supplementary economic evidence presented for further detail on the derivation of mean time in OS for each of the analyses undertaken (estimated to be 4.3 months in the base-case). This 4.3 months equates to an over 40% extension in life expectancy over that expected without maintenance (figures from SATURN SQ SD economic modeling base case as detailed in the supplementary evidence submission).

Figure 9. Progression free survival for those patients with squamous stable disease

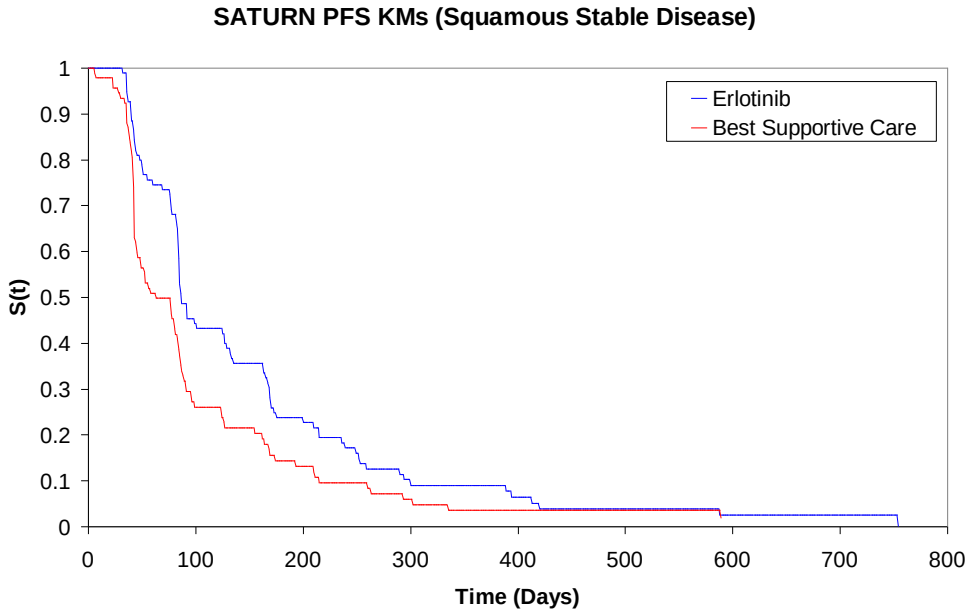
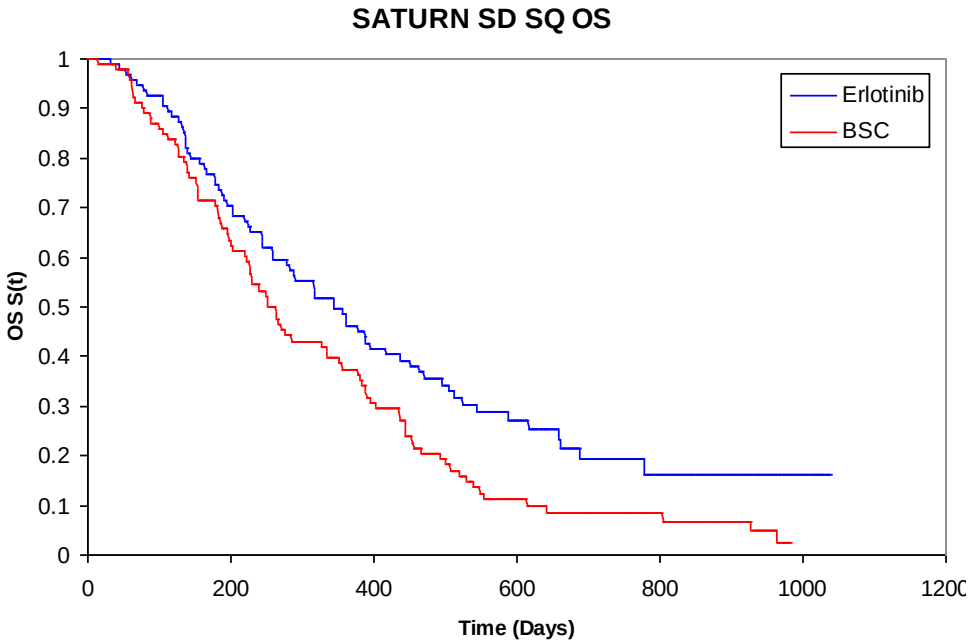


Figure 10. Overall survival for those patients with squamous stable disease



The above results demonstrate that erlotinib maintenance provides a clinically important PFS and OS benefit relative to the relevant comparator (BSC) in those patients with squamous histology with stable disease as best response to induction.

2.1.2.2 Non-Squamous Stable Disease Patients for whom treatment with pemetrexed is unsuitable: Erlotinib vs BSC

Post-hoc analysis of those patients with non-squamous stable disease confirms that erlotinib is significantly more efficacious than BSC in terms of both PFS and OS. This finding confirms that patients with both squamous and non-squamous NSCLC benefit to a similar extent, from erlotinib treatment (as was found in BR.21, the pivotal study of erlotinib in relapsed NSCLC).

The median OS advantage provided by erlotinib in this population is over 3 months (3.1 months) with the mean advantage greater than this figure due to the divergence of the OS curves over time.

Table 3. PFS and OS benefit in Squamous and Non-Squamous Stable Disease Patients

Best Response To Induction	Histology	n	PFS	OS*
Stable Disease	**Non-Squamous**	297	0.687 [0.541; 0.873]	0.764 [0.586; 0.996]

*OS is measured from time of randomisation into the maintenance phase.

Figure 11. SATURN NSQ SD PFS Curves

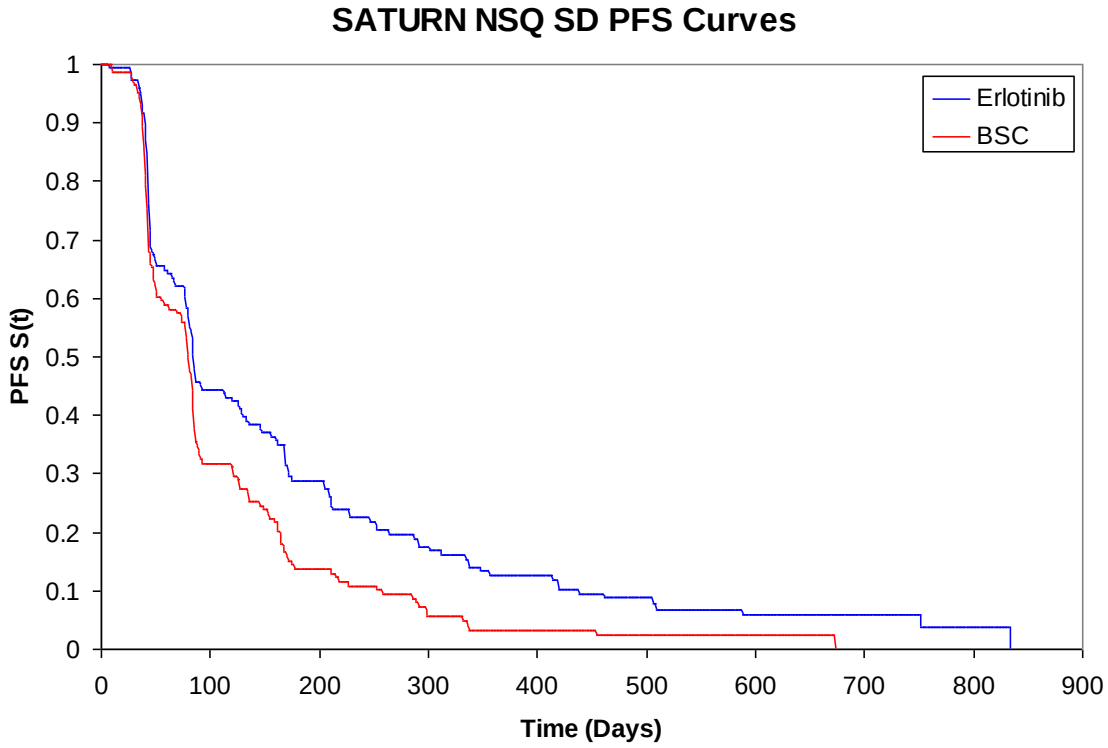
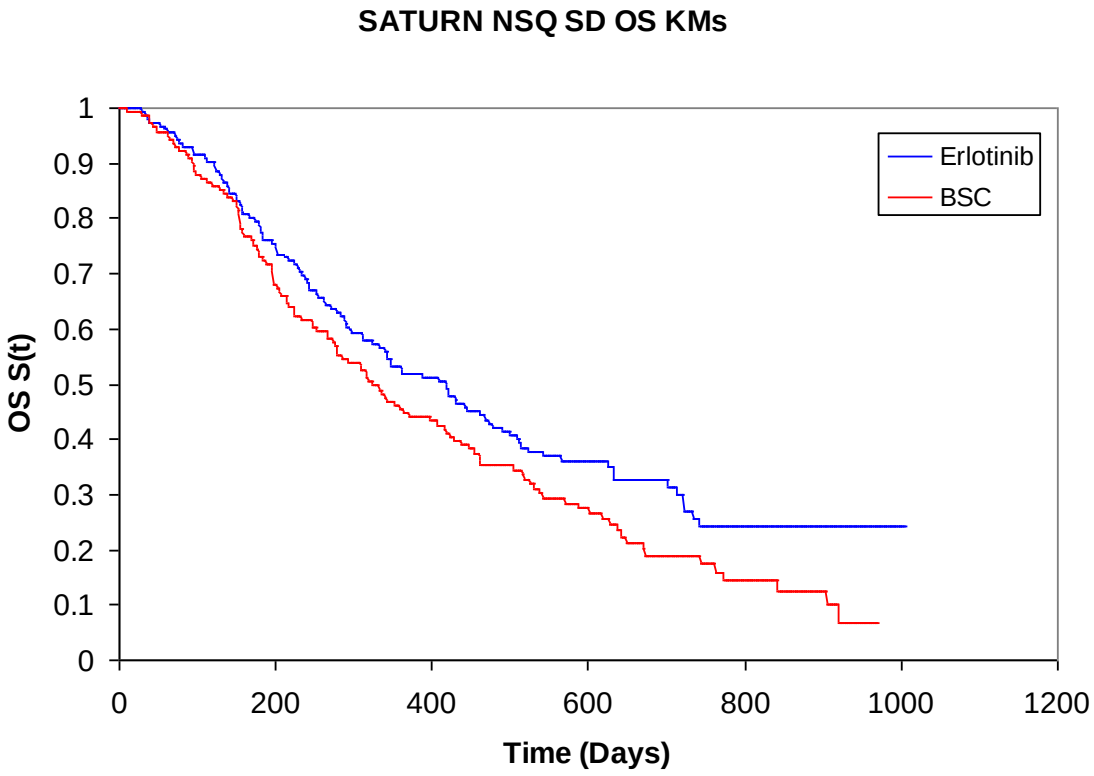


Figure 12. SATURN NSQ SD PFS Curves



As the majority of maintenance candidates with non-squamous stable disease following induction are likely to have received pemetrexed first line (due to NICE approval of pemetrexed in this setting in TA181) they will ineligible to do so in the maintenance setting (pemetrexed SmPc) and will be faced with the option of receiving erlotinib or 'watching and waiting' for disease progression before commencing second line treatment.

The above results demonstrate that erlotinib maintenance provides a clinically important PFS and OS benefit relative to best supportive care (BSC) in both the non-squamous stable disease and squamous stable disease populations (with erlotinib demonstrating moderately better OS efficacy in those patients with squamous cell disease).

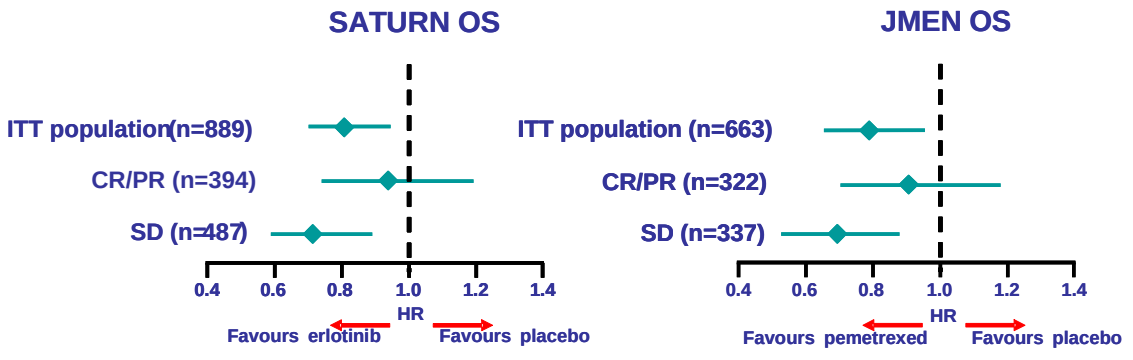
2.1.2.3. Non-Squamous Cell Stable Disease Patients For Whom Treatment with Pemetrexed is Suitable : Erlotinib vs Pemetrexed

For the remaining group of patients eligible for erlotinib-maintenance therapy (those with non-squamous tumours who did *not* receive the optimal pemetrexed-platinum combination at first-line and whose disease was stable at the end of their chemotherapy) two maintenance options are possible – erlotinib and pemetrexed. Whilst the previous sections demonstrate that for these patients erlotinib offers a clinically important benefit over BSC there is considerable difficulty in estimating the relative effectiveness of erlotinib and pemetrexed (the only other active treatment licensed in this treatment positioning).

This comparison is problematic for the following reasons:

- There is no head-to-head study comparing erlotinib and pemetrexed in the maintenance setting
- Although the RCTs used for regulatory approval of erlotinib and pemetrexed have a common comparator (BSC) comparing treatment effects across the two trials is difficult because of marked differences in the characteristics and hence significant heterogeneity of recruited patients and also the post-study treatments (see Section 6.6.10 of the Roche's original submission)
- There are no data in the public domain covering efficacy of pemetrexed in patients with non-squamous tumours *and* SD at the end of first-line chemotherapy

Figure 6. Overall survival by response to first-line chemotherapy in the SATURN and JMEN Studies (not limited by histological subtype)



Adapted from BelaniCP, et al. ASCO 2009 (Abs. CRA8000)

In these circumstances it is very hard to make a robust estimate of the relative efficacy of erlotinib and pemetrexed as maintenance agents in pemetrexed-naïve patients with SD after first-line platinum-based chemotherapy for non-squamous NSCLC. However, it is clear that erlotinib offers a clinically important benefit relative to the current standard of care, BSC with no active maintenance. Since the JMEN study shows benefit from pemetrexed maintenance in the subgroups of NSCLC patients with non-squamous tumours and those with SD after first-line chemotherapy, it is reasonable to assume that this group of SD, non-squamous patients derive enefit too, though it is difficult to quantify.

As the comparison of pemetrexed and erlotinib in terms of efficacy in this patient population is a fundamental component of the cost-utility analysis necessary if NICE are to make a decision on the cost-effectiveness of erlotinib in this setting (irrespective of the availability of the exact evidence required this decision must still be made) this comparison was made quantitatively in the economic evaluation undertaken utilising a range of plausible hazard ratios comparing erlotinib and pemetrexed. This comparison is described in further detail in the attached economic section below.

2.1.3 Impact of erlotinib maintenance on quality of life (QoL) of patients with stable disease at the end of first-line chemotherapy in the SATURN study

The time to symptom progression, time to deterioration in QoL and time to deterioration in Trial Outcome Index (TOI) were similar in erlotinib and placebo groups in the SATURN study (HR=0.92, 95% CI 0.70 to 1.22, p=0.5768; HR=0.97, 95% CI 0.75 to 1.26, p=0.8291; and HR=1.14, 95% CI 0.86 to 1.50, p=0.3534 respectively). Thus, the QoL results observed for the SD population are in line with those observed in the ITT population and described more fully in Section 6.4.5 of Roche's original submission. Further details of QoL outcomes in the SD population can be provided on request. In both cases, no deterioration in QoL was observed for patients receiving treatment with erlotinib compared to those receiving only placebo.

2.1.4 Patient characteristics of SD patients in SATURN

Since disease outcome in patients with SD at the end of first-line chemotherapy was not the primary study end-point in SATURN and stratification at randomisation was not

specifically designed to deliver balanced active and placebo groups amongst the SD patient group, it is important to demonstrate that the benefit to SD patients receiving erlotinib maintenance is not due to an imbalance in base-line characteristics that might be expected to alter baseline risk of progression/death. In fact all patient, treatment and tumour characteristics were well matched between the active and placebo groups of SD patients as shown in Appendix 1.

2.1.5 Tolerability of erlotinib amongst SD patients in SATURN

It is plausible that the enhanced efficacy amongst the SD patients in SATURN might be associated with increased toxicity. In fact, as shown in Table 4, there were no meaningful differences in tolerability between patients in the SATURN study as a whole and those in the SD subgroup.

Table 4. Overview of Adverse Events, Withdrawals, and Deaths During the Treatment Phase – SD and Overall Safety Population

	SD Population		**Overall Population**	
	Placebo N=233 No. (%)	Erlotinib N=250 No. (%)	Placebo N=445 No. (%)	Erlotinib N=433 No. (%)
Total patients with at least one AE	134 (57.5)	196 (78.4)	241 (54.2)	341 (78.8)
Total number of AEs	389	756	700	1268
Deaths	22 (9.4)	23 (9.2)	31 (7.0)	35 (8.1)
Study withdrawal due to an AE	5 (2.1)	15 (6.0)	7 (1.6)	19 (4.4)
Patients with at last one				
AE leading to death	5 (2.1)	7 (2.8)	5 (1.1)	10 (2.3)
Serious AE	23 (9.9)	33 (13.2)	34 (7.6)	47 (10.9)
Related serious AE	0	5 (2.0)	1 (0.2)	10 (2.3)
AE leading to withdrawal from treatment	5 (2.1)	16 (6.4)	7 (1.6)	20 (4.6)
AE leading to dose modification/interruption	8 (3.4)	40 (16.0)	15 (3.4)	70 (16.2)
Related AE	47 (20.2)	165 (66.0)	89 (20.0)	281 (64.9)
Related AE leading to withdrawal from treatment	1 (0.4)	9 (3.6)	2 (0.4)	12 (2.8)

Severe AE	37 (15.9)	64 (25.6)	54 (12.1)	107 (27.7)

Investigator text for Adverse Events encoded using MedDRA version 11.0.
Percentages are based on N.
Multiple occurrences of the same adverse event in one individual counted only once.
Deaths derived from Death page, Withdrawals derived from Study Completion page.
Deaths occurred during treatment phase are counted.

2.1.6 Summary of clinical effectiveness of erlotinib maintenance in SD patients

The SATURN study of maintenance erlotinib in patients with NSCLC non-progressive after 4 cycles of platinum based chemotherapy met both co-primary endpoints with statistical significance. There was a 29% reduction in the risk of progression with erlotinib compared with placebo (HR=0.71, P<0.0001) and a significant improvement in response and disease control. In addition, overall survival was significantly improved versus placebo (HR=0.81, P<0.0088).

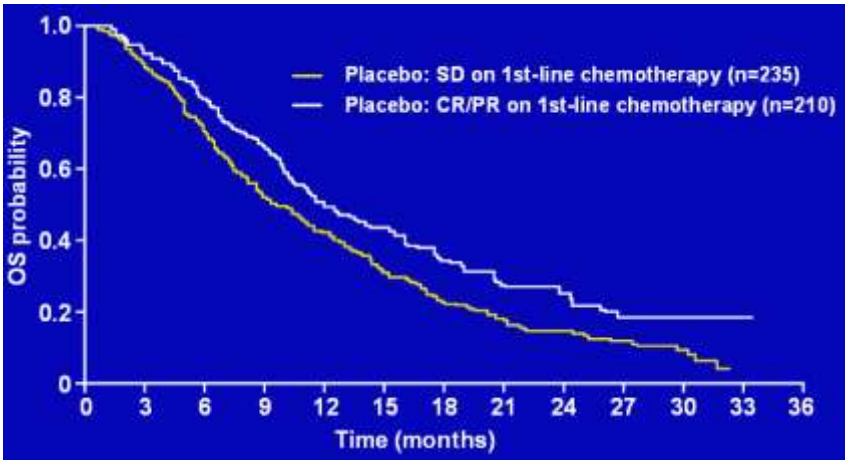
Particular benefit in patients with stable disease (SD)

However, during regulatory review, the EMEA were keen to identify the population of patients deriving most benefit from erlotinib maintenance and further analysis of the SATURN data identified a group of patients that derived greater benefit from receiving erlotinib as maintenance therapy immediately following 1st line treatment, namely patients who only achieved SD after 1st line treatment. Indeed, this group of patients were largely responsible for the overall survival benefits observed in the ITT population.

SD patients still have the same bulk of tumour that they had at the start of chemotherapy and can be expected to experience worsening symptoms with any increase in their tumour volume once the “brake” applied by chemotherapy is removed. As such they might also be expected to benefit more from maintenance treatment than patients whose tumours have been shrunk significantly by chemotherapy and who have bought themselves a little “head room” when tumour growth resumes.

The SATURN study confirms not only that SD patients derive most benefit from erlotinib maintenance, but also that they represent a group with particularly high unmet need – as shown in Figure 7 patients with SD at the end of first-line chemotherapy have a worse prognosis than those whose tumour shows a good degree of shrinkage.

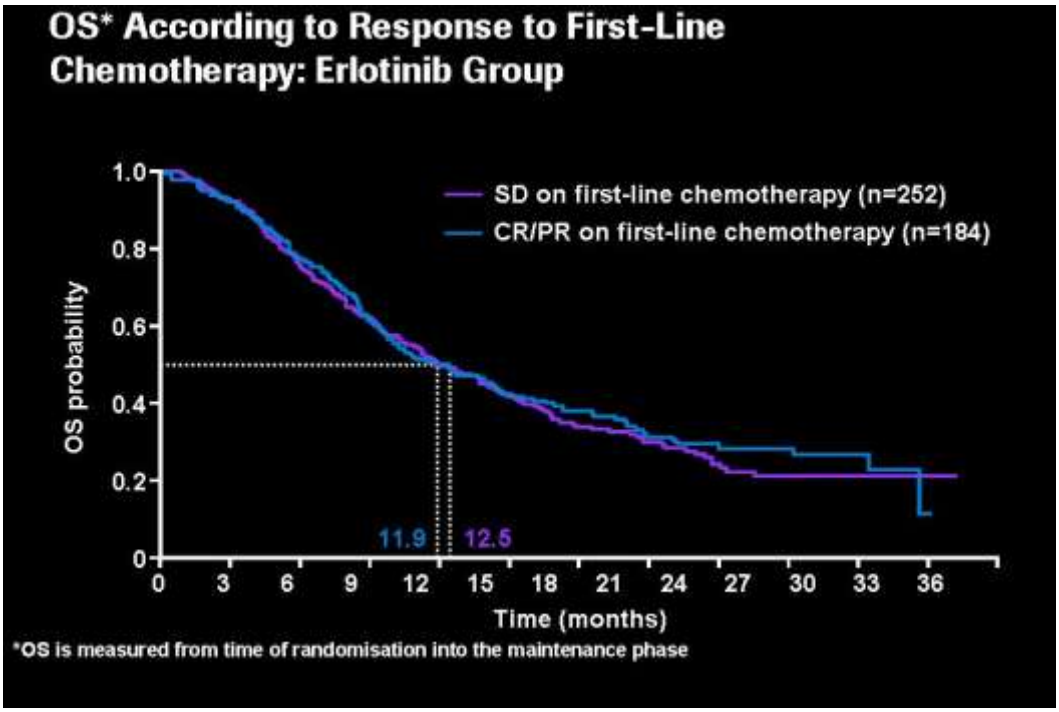
Figure 13. Prognosis of patients in the SATURN study according to their response to first-line*



*Note: both these OS curves are for patients randomized to placebo

As shown in Figure 8 treating SD patients with erlotinib maintenance improves their prognosis to that of patients achieving a good response (CR/PR) to their 1st line chemotherapy.

Figure 14. Maintenance erlotinib in SATURN improves the prognosis of patients with minimal tumour regression after first-line chemotherapy (SD) to that of those achieving a good response to first-line chemotherapy**



**Note: both these OS curves are for patients randomized toerlotinib

Impact of histology on outcomes

For SD patients with both squamous and non-squamous tumours, the improvement in mean OS reaches approximately 4 months (figures from economic analyses), with the median reaching 3.0-3.4 months compared with patients receiving the current standard of BSC between the completion of first-line chemotherapy and relapse. This is a clinically important benefit, particularly for a well tolerated oral therapy which does not impact negatively on quality of life. Moreover, the OS benefit seen in SATURN, where second-line, post-study, treatment rates amongst SD patients were very high (61%-63%) are likely to be less than those that would be seen in the UK where only about one-third of patients get second-line treatment for NSCLC (see section 4.1.2.3 of Roche's original submission and response to ERG Question A5 arising from the original Manufacturer's submission). Whilst analysis of the SD population by histological subtype demonstrates that erlotinib is effective irrespective of histology there is an observed difference in the point estimates of the hazard ratios in those patients with squamous histology than in those with non-squmaous histology (SQ SD OS HR = 0.665 compared to the NSQ SD OS HR = 0.764).

Maintenance treatment options

For most patients eligible for erlotinib maintenance, there are no other active maintenance options available. Patients with squamous tumours do not benefit from pemetrexed maintenance, and there is no evidence and no regulatory approval for using pemetrexed maintenance in patients with non-squamous tumours who have received pemetrexed as part of first-line chemotherapy. For these patient groups, erlotinib maintenance is the only active treatment option and negative NICE guidance for erlotinib in these groups may cause issues of equity to arise as those patients with non-squamous disease who have not received pemetrexed first line have the option of NICE approved maintenance therapy with pemetrexed following TA190 whilst negative NICE guidance for erlotinib would resign those ineligible for pemetrexed to simply 'watch and wait' for their disease to progress with no access to active treatment until this period.

For a small and diminishing group (pemetrexed naïve patients with non-squamous NSCLC achieving SD after first-line chemotherapy) pemetrexed does offer an alternative active maintenance option. As discussed above, both pemetrexed and erlotinib have

useful activity in this setting, though it is hard to say which is the most active due to the lack of head to head evidence comparing the two regimens and the heterogeneity of populations in the only 2 RCTs available as an evidence base on which to base such a comparison. What is clear is that the different delivery schedules, toxicity profiles and requirements for pre-medication of erlotinib and pemetrexed are such that they have very different impact on patients and the health care system (see Table 5), such that the availability of both increases patient choice considerably.

Table 5. Key characteristics of erlotinib and pemetrexed maintenance regimens

Erlotinib	Pemetrexed	Implications for patient	Implications for Health Service
Oral treatment taken by patients at home	IV delivery every 3 weeks in hospital	Although some patients may feel supported by regular visits to the chemotherapy unit for IV chemotherapy, most would prefer an oral treatment that enables them to spend as much of their limited remaining life as possible at home, especially as most have just completed 12 weeks of aggressive IV chemotherapy	IV chemotherapy units often lack physical capacity and/or adequate levels of experienced staff to prepare and deliver IV chemotherapy easily. The addition of IV maintenance therapy to the treatment regimen of patients who would currently be on a treatment break will place substantial stresses on services that oral maintenance will not .
No pre-medication mandated with erlotinib	Oral folic acid and steroids and intramuscular (IM) vitamin B12 are mandatory to prevent severe toxicity	Compliance with required premedication regimens can be taxing, IM B_{12} requires attendance at the hospital or GPs surgery and corticosteroids have significant side-effects	There is the possibility of error in failing to arrange the comparatively complex pre-medication regimen required with the corresponding risk of avoidable toxicity needing management by the NHS. Provision of pre-medication also has a small direct cost and a greater indirect cost in terms of patient education and administration
Main toxicities are those characteristic of a selective EGFR inhibitor: mild-moderate rash and	Main toxicities are those characteristic of non-specific cytotoxic agents: neutropenia, anaemia, nausea,	It is difficult to say that either treatment is clearly superior in this regard, but patients may well have views	

diarrhoea	vomiting and fatigue	on which treatment they would prefer based on prior experiences with chemotherapy and individual preferences	

3. Economic Methods

3.1. Overview

Three models were constructed in order to assess the cost-effectiveness of erlotinib in each of the four comparisons of interest.

Model 1 was an amended version of the stable disease model originally submitted by Roche designed to facilitate the comparison of erlotinib vs BSC in those patients unsuitable for pemetrexed maintenance (either due to disease histology or having received the NICE recommended pemetrexed/cisplatin doublet regimen as induction).

Model 2 was completely de novo and founded upon the squamous histology stable disease population from SATURN designed to facilitate the comparison of erlotinib vs BSC in this patient population.

Model 3 was another de novo model founded upon the non-squamous histology stable disease population from SATURN designed to enable the comparison of erlotinib vs pemetrexed in those patients eligible for NICE approved maintenance with pemetrexed and the comparison of erlotinib vs BSC in those non-squamous stable disease patients ineligible for pemetrexed.

The majority of the ERG's suggested amendments to the original models were made in preparation of these three models. These amendments included:

- The use of the ERG's suggested utility values
- The use of the ERG's preferred annually compounding annual discount rate rather than a monthly compounding annual discount rate
- The use of the PFS and OS parametric curves fitted by the ERG's 'spline' based method (the SD model contains the parametric curves fitted by the ERG in the additional work they conducted in preparation of the erlotinib 1LM ERG report)

- The extension of the models time horizon to 15 years

- The use of the ERG's suggested 2nd line treatment costing methodology

- The calculation of the cost of pemetrexed taking consideration of the distribution of BSA around the recorded mean BSA value from SATURN

In addition to the implementation of these ERG suggested changes the models also feature 2 additional amendments; one which is a slight modification of a technique utilised by the ERG and one in which an oversight on the part of Roche and ERG is corrected. These were as follows:

- The use of the ERG's methodology for the calculation of the cost of erlotinib (including consideration of drug wastage) with substitution of the PFS real number Kaplan-Meier values every 30 days with the equivalent time to complete treatment cessation Kaplan-Meier values.

- The amendment of the BSC costing methodology applied within the model to that used by the manufacturer of pemetrexed and accepted by the ERG and NICE appraisal committee in NICE TA181 and TA190 in correction of the erroneous application of the extremely expensive cost associated with a patients terminal care at the very end of life for the entire post-first-line maintenance progression period (as was mistakenly done in the original Roche SD model presented).

These modifications are described in further detail in the appropriate sections below . The NICE reference case was followed throughout. The PFS, PPS, OS and time to complete treatment cessation real number Kaplan-Meier life-tables for the SATURN NSQ SD and SQ SD population are provided as a Commercial in confidence appendix so that the ERG may validate the results.

Each model is discussed in further detail below.

3.2. The SD model: Erlotinib vs BSC (Population 1)

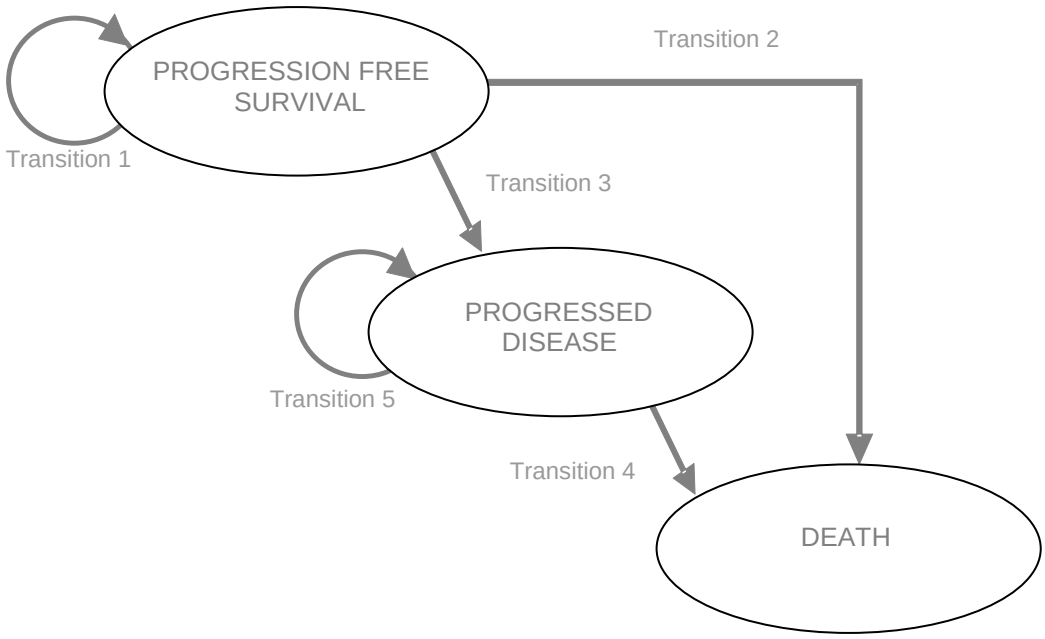
A three state model was constructed in Excel© in order to estimate the cost-effectiveness of erlotinib compared to best-supportive care in patients with stable disease as best response following induction. This model is an amended form of that originally submitted by Roche following the discovery of the PD BSC costing error identified in the original SD model.

This patient group incorporates both those patients with squamous histology and those with non-squamous histology who received the NICE recommended induction regimen of pemetrexed and cisplatin (rendering them ineligible for pemetrexed based maintenance).

Whilst pemetrexed was not one of the induction therapies in the SATURN trial (due to it obtaining EMA approval in this setting after the finalisation of the trial protocol) erlotinib is indicated for maintenance following induction involving 4 cycles of standard platinum-based first-line chemotherapy and so could be given following pemetrexed induction. As there is no clinical or pharmacological rationale to suggest that the relative efficacy of erlotinib and BSC following first line induction with pemetrexed would be any different to that following induction with the regimens in SATURN in the base case analysis it is assumed that the efficacy observed in this group in SATURN would apply to those patients receiving pemetrexed first line induction in practice.

3.2.1. SD Model Structure

A 3 state model of the type typically used in the modelling of metastatic oncology was used to model the decision problem of interest. Patients enter the model in the progression free survival (PFS) state (as they did in SATURN) and in the first month can either progress on their disease (entering the ‘progressed disease’ (PD) health state), enter the absorbing ‘death’ state or remain in the PFS state. In all subsequent months a patient can either move to a ‘worse’ health state, die or remain in the same health state.



A cycle length of one month was used in order to capture patients health state transitions with adequate resolution. A half cycle correction was used where appropriate to simulate mid-cycle patient health state transitions. This same structure was utilised by the ERG their additional work.

3.2.2. SD Model Inputs

3.2.2.1. PFS

The piecewise parametric PFS curves fitted by the ERG in the additional work they conducted as part of their preparation of the erlotinib 1LM ERG report were utilised to determine the proportion of patients in PFS in each month of the model. The models were fitted using a 'spline' based methodology in order to achieve a good fit to the data whilst preserving the observed long term stabilised hazard trend. The derivation of the appropriate 'spline point' (at which the data is essentially split into two halves) was conducted as described in the 'ERG technical details of amendments made to manufacturers model - part B' document. Following the appropriate analysis the ERG determined that the appropriate spline point was somewhere between 10 and 12 months and chose 12 months in their analysis for ease of modelling.

The data was then split at this spline point and OLS was conducted on the SATURN SD cumulative hazard (i.e. –log(S(t)) curves using the following functional forms (phase 1 for the pre-12 month period and phase 2 for post-12 months).

Phase 1

$$\text{Cumulative hazard} = A * \{ 1 - \exp(- B * \text{months}) \} + (C * \text{months})$$

Phase 2 (PFS only)

$$\text{Cumulative hazard} = P + Q * \text{months}$$

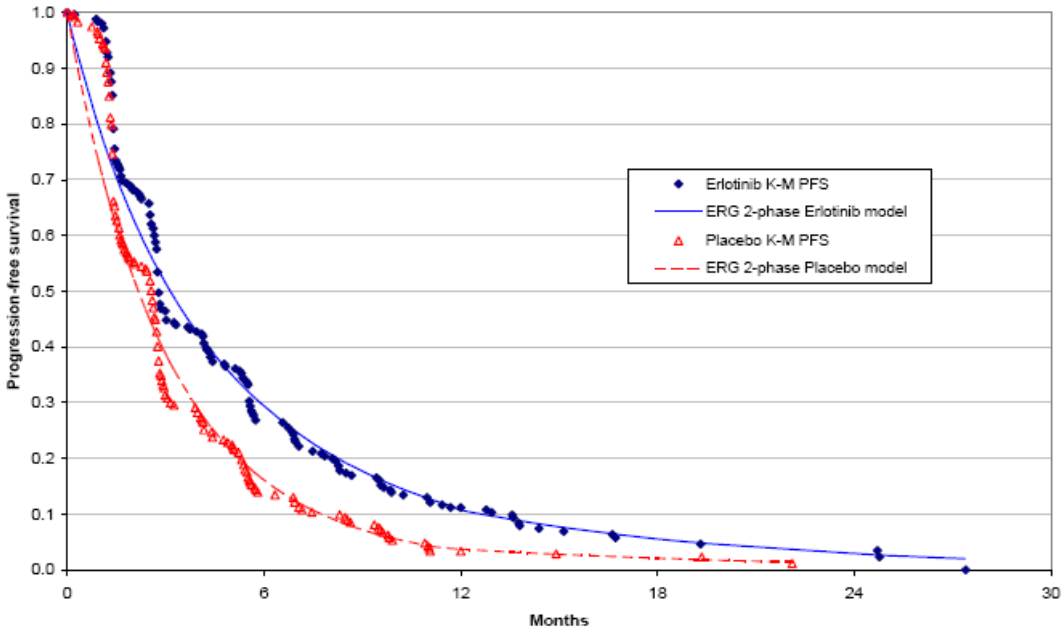
The coefficients estimated by this approach are provided in Table 2 below.

Table 2. PFS parameter estimates estimated by ERG

	A	B	C	P	Q
Placebo	12.619596	0.026037	0.000000	2.110823	0.098147
Erlotinib	0.432279	0.225179	0.150780	0.921091	0.109304

The relationship exp(- (- log (S(t))) = S(t) was then used to derive the S(t) points from the cumulative hazard curves estimated. Figure ? demonstrates the extremely strong face validity of the parametric curves fitted using this technique when compared to the PFS KMs observed in the SATURN SD population.

Figure 15. ERG fitted PFS curves



3.2.2.2. OS

The OS curves fitted by the ERG via OLS conducted on the cumulative OS hazard plots of the SATURN SD population were used directly in the model to derive the proportion of patients alive (and therefore the proportion of patients in the 'Death' health state via the relationship 1 - ALIVE = DEAD) in each month.

This OLS utilised the 'Phase 1' functional form used for the first 12 months of the PFS curve fitting for the entire OS period. This form is provided below:

$$\text{Cumulative hazard} = A * \{ 1 - \exp(- B * \text{months}) \} + (C * \text{months})$$

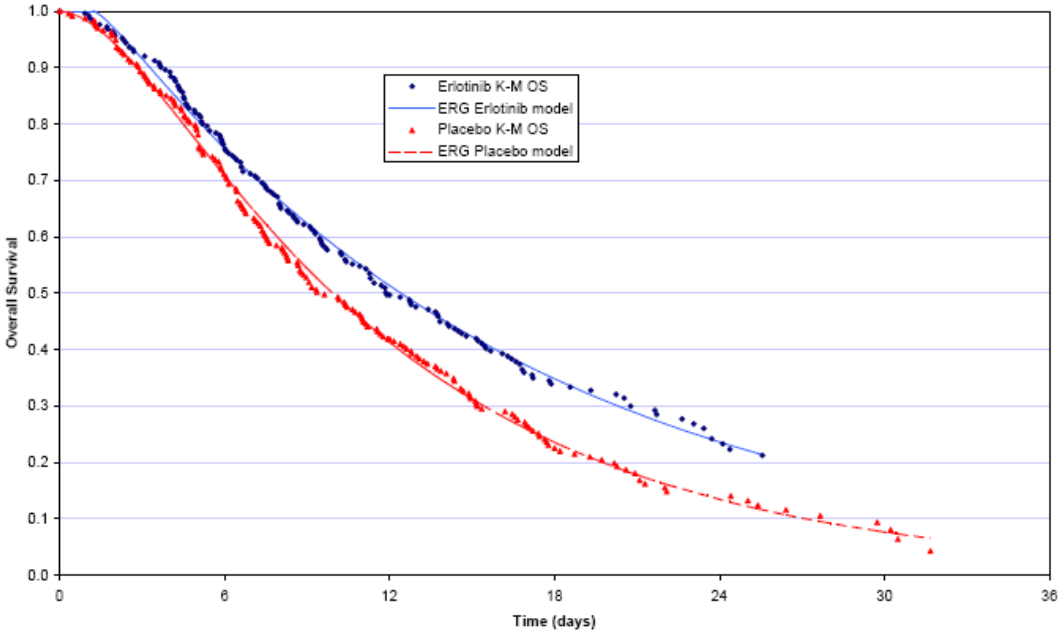
The exponential of the negative fitted cumulative hazard was then taken to derive the fitted OS S(t) value within each month of the model.

The coefficients estimated using this technique are provided in Table 3 below. Figure 16 demonstrates the face validity of the parametric fits produced via this method compared to the observed OS KM curves for the SATURN SD population.

Table 3. OS parameter estimates estimated by ERG

	A	B	C
Placebo	-0.245697	0.368852	0.093994
Erlotinib	-0.109676	1.109700	0.064724

Figure 16. ERG fitted OS curves



As the erlotinib OS curve fitted above exceeds 1 in the very early phase of the model a logical cap was placed on the OS curve so that if the predicted OS was greater than 1 at any time the OS applied in the model would be limited to 1. This same cap was applied by the ERG in the additional assessment they conducted in preparation of the erlotinib 1LM ERG report.

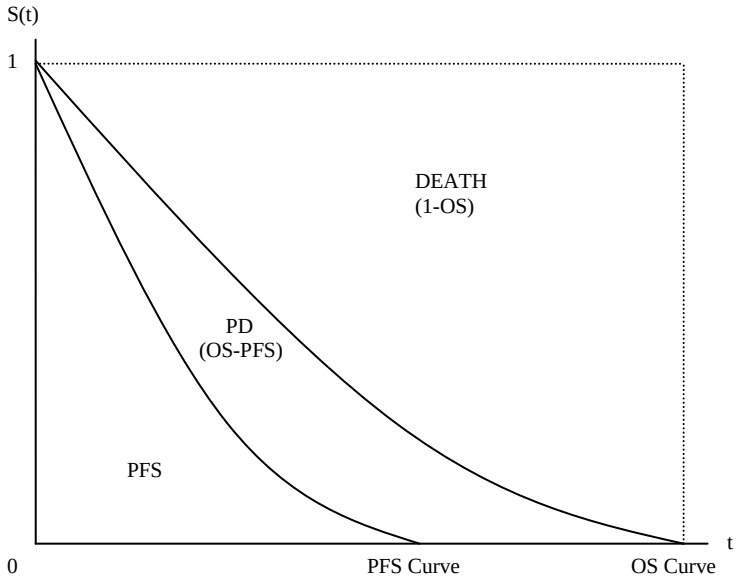
The 'ERG technical details of amendments made to manufacturers model - part B' document provides more detail on both the PFS and OS fitting conducted by the ERG.

3.2.2.3. PD

The proportion of patients in the progressed disease state at any given time was derived via the relationship OS – PFS = PD (i.e. if a patient is still alive but no longer in PFS they must by definition be in the progressed disease health state) in combination with the proportion of patients in the PFS and OS states as derived via the methods described in sections 2.2.2.1. and 2.2.2.2.

Figure 17 below demonstrates the derivation of the proportion of a patients in each health state based upon the PFS and OS curves fitted.

Figure 17. Using PFS and OS curves to derive the proportion of patients in each health state over time



Note: The curves in the above figure are not specific to this appraisal and act only to demonstrate the method used

The modelled outcomes produced as a product of the above technique were assessed for potential logical impossibilities by placing an 'If' statement within the model so that if PD at any point became negative (as it erroneously did in one of the Roche models originally submitted for this appraisal) this error would be highlighted. No such errors were found. For the purposes of PSA a logical constraint was placed on the OS values used within the model so that if any point the probabilistic scenario indicated that PFS exceeded OS (which is clearly impossible) OS would simply equal PFS.

3.2.2.4. Utilities

The utility values utilized by the ERG in the additional work they conducted in assessing the first Roche submission for this appraisal (Dickson, 2009) were used within the model . These values are derived from Nafees et al. 2008 (in which the standard gamble technique was utilized with 100 members of the UK general public) and incorporate the disutility of grade 3 and 4 adverse events associated with each of the treatment options (Dickson, 2009). The utility values used are provided in the table below:

Figure 18. Utility Values Utilised in Model

Health State	Utility Value	Source
PFS (Erlotinib)	0.6732	Erlotinib 1LM ERG report + Nafees 2008
PFS (Best Supportive Care)	0.6628	Erlotinib 1LM ERG report + Nafees 2008
PD	0.53	Erlotinib 1LM ERG report + Nafees 2008

3.2.2.5. Costs

3.2.2.5.1 Drug Costs - Erlotinib

A slightly amended version of the method utilized by the ERG in deriving the mean cost of erlotinib was used in the SD model.

In the ERG's additional analyses the real number PFS KM data provided by Roche was utilized by the ERG to derive the cost of erlotinib in the following way:

1. The proportion of patients in PFS every 30 days was recorded in a table (i.e. proportion of patients in PFS on day 0, day 30, day 60, day 90 etc)

2. It was then assumed that each of these patients would be dispensed a pack of 30 x 150 mg tablets on each of these 'dispensing dates'

3. The above was combined with the cost of a pack of erlotinib (£1,394.96 with the PAS) and discounted appropriately to derive a mean **per protocol** cost of erlotinib per patient

In the amended SD model provided the same approach taken by the ERG has been used with the substitution of the real number PFS KM data for real number time to complete treatment cessation (TTCTC) KM data.

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

Whilst it does appropriately calculate the mean per protocol cost of erlotinib it fails to account for the fact that if a patient has ceased treatment (due to adverse event, patient preference etc) prior to progression they will not in practice be dispensed an additional pack of erlotinib every 30 days despite being in PFS. The TTCTC method accounts for this factor in deriving the mean cost of erlotinib by only assuming a pack of erlotinib will be dispensed on each of the 'dispensing dates' if a patient has yet to completely cease treatment rather than assuming that everyone in PFS on the 'dispensing dates' will receive treatment (as was done by the ERG).

Where the TTCTC Kaplan-Meier exceeded the PFS parametric fit (which occurred in the very start of the model due to the parametric technique employed by the ERG) it was assumed that the proportion of patients in PFS was equivalent to the proportion of patients yet to completely cease treatment. Estimation via this methodology could be improved by the use of a parametric fit analogous to that applied for PFS for the TTCTC curves and would likely produce a lower incremental cost of erlotinib. Table 4 below demonstrates the significant impact omitting consideration of this disparity between PFS and treatment cessation has upon the estimation of the mean cost of erlotinib with the ERGs method over-estimating the mean cost of erlotinib by 13.57%.

Table 4. PFS compared to TTCTC dosing

Mean Packs (PFS Based)	Mean Packs (TTCTC Based)	Mean Discounted Cost (PFS Based)	Mean Discounted Cost (TTCTC Based)	ERG Cost Overestimation
5.85	5.14	£8,118.74	£7,148.44	13.57%

As the objective of this evaluation is to discern the incremental costs and benefits associated with the introduction of erlotinib maintenance into the NHS it is important that the consider the true expected cost of erlotinib to the NHS including the disparity between TTCTC and PFS rather than simply using a per-protocol costing method.

The full derivation of the above figures is provided within the supplementary models submitted.

3.2.2.5.2 Administration Costs - Erlotinib

Erlotinib is an oral formulation and so the only additional administration resources required over BSC are due to the pharmacy time required to dispense a pack of erlotinib every 30 days. This dispensing was implemented in the model at a cost of £13.50 every time a pack of erlotinib was dispensed (NCAT pathway, CPORT 2009). This cost was integrated into the model utilizing the time to treatment cessation methodology used to derive the mean cost of erlotinib rather than the PFS based methodology used by the ERG. The administration cost of pemetrexed is discussed in section 2.3.2.3.3..

Figure 19. The impact of the divergence between PFS and TTCTC in deriving erlotinib administration costs

Mean Packs (PFS Based)	Mean Packs (TTCTC Based)	Mean Admin Cost (PFS Based)	Mean Admin Cost (TTCTC Based)	ERG Cost Overestimation
5.85	5.14	£78.32	£69.42	13. 57%

3.2.2.5.3 Best Supportive Care, Monitoring and Terminal Costs

In the amended SD base case the best supportive care costs utilised in the pemetrexed first line and first line maintenance NICE appraisals (in which pemetrexed was approved for use in both indications) were applied throughout a patients time alive in the model

(apart from in the last cycle in which an extremely expensive 'terminal care' cost was applied). This BSC cost was derived in the following way:

'The BSC and palliative care costs used in the model are based on the publication by NICE/University of Sheffield (2004) which reports the average cost of Specialist Palliative Care to be £3,236 per cancer death per year. This value was inflated to £3,451, based on an inflation index of 1.07 (PSSRU, 2008). We assumed that the bulk of this cost would be incurred in the last 3 months of life (£2588.25) with the remaining £862.75 incurred over the remaining 9 months. This is equivalent to a monthly BSC cost of £95.86' (Text duplicated from pemetrexed manufacturer's 1LM NICE submission).

This BSC costing was founded upon the assumption that 75% of BSC/terminal care costs are accrued in the last 3 months of life as described in pemetrexed first line maintenance submission.

As this BSC cost does not include monitoring costs a regular 3 monthly hospital visit consisting of a face to face meeting with a consultant and an outpatient CT scan was incorporated into the PFS stage of the model using NHS reference costs 2008/2009 (Service Code 800 and RA12Z). This assumption equates to an expected PFS monthly monitoring cost of £85.60 and increases the monthly PFS BSC and monitoring cost utilised in the model to £181.46.

As monitoring for disease progression is only required in the active treatment 1LM and 2L it would be inappropriate to utilise this monitoring cost for the entire post-first-line-maintenance progression period. Therefore it was assumed that monitoring was not required for 25% of a patients post-progression period (approximately equivalent to the last 3 months of a patients life) when calculating the expected monthly cost of monitoring in the PD state. When combined with the BSC cost utilised by the manufacturer of pemetrexed and accepted by the ERG and appraisal committees in TA181 and TA190 the total monthly PD BSC and monitoring cost applied within the model was slightly lower than that for PFS at £160.06.

In the original Roche submission for this appraisal the expensive post-progression terminal care cost derived at an advisory board for Roche's 2nd line erlotinib appraisal

(TA162) was mistakenly applied to the entire post-first-line-maintenance progression period rather than simply in a patient final terminal phase. The erroneous monthly PD BSC cost applied to each month of PD was over 10 times higher than that applied in the only other NICE appraisal in the NSCLC first line maintenance setting (TA190) and resulted in the total cost of the 'watch and wait' arm of the SD model in the original Roche submission being nearly twice that of the equivalent 'watch and wait' arm of the pemetrexed NSQ model (approximately £16,000 compared to £8,000).

In the amended analysis the expensive terminal phase cost was modelled utilising the same technique and cost value used by the manufacturer of pemetrexed (i.e. the application of a cost of £2,588.25 in the last month of a patients life).

The use of the method utilised in the pemetrexed 1LM NICE appraisal rectifies the error found in the original SD model submitted and is consistent with the only other NICE appraisal conducted in the maintenance setting (TA190) and that applied in the post-progression period of the pemetrexed first line appraisal (TA181).

3.2.2.5.4 Adverse Events

Adverse events were incorporated into the amended SD analysis in the same manner as in the original SD model. Further detail on AEs can therefore be found in the original Roche submission. As described in Dickson 2009 the disutilities associated with the adverse events associated with each treatment option are incorporated into the base-case utility values used and so the inclusion of specific AE disutilities is unnecessary.

3.2.2.5.5 2nd Line Treatment Costs

2nd line treatments were incorporated into the model utilising the method described by the ERG in the erlotinib 1LM ERG report. This involved taking the mean cost of a 2nd line course of erlotinib or docetaxel from TA162 (in which it was determined that with Roche's 14.5% price reduction PAS that the mean cost of a course of either docetaxel or erlotinib was the same at £6,800 per patient), multiplying that figure by an assumed proportion of patients receiving 2nd line treatment (28% in the base-case, figure from National Lung Cancer Audit Database) and spreading that value pro-rata across the

period a patient was in PD. Sensitivity analysis utilising higher proportions of 2nd line treatments was conducted.

3.2.3. SD Model Sensitivity Analysis

The deterministic sensitivity analyses conducted are detailed in the table below. Given the substantial amount of new analysis presented and the timelines of the STA process there was insufficient time to conduct probabilistic sensitivity analysis on the 3 models and so only deterministic sensitivity analysis is provided.

Table 5. Deterministic Sensitivity Analysis (SD Model)

Parameter Modified	Base Value	Low Value	High Value	Description
Utilities				
PFS	Erlotinib = 0.6732 BSC = 0.6628	Erlotinib = 0.6059 BSC = 0.5965	Erlotinib = 0.7405 BSC = 0.7291	Base case value from ERG report on erlotinib in 1LM High/Low = +/- 10%
PD	0.53	0.48	0.58	Base case value from ERG report on erlotinib in 1LM High/Low = +/- 10%
Both Utilities	As above	-	1	Cost per LYG
Costs				
Monthly PFS BSC and Monitoring Costs	£181.46	£108.88	£411.67	Base-case cost from pemetrexed 1L and 1LM NICE appraisals (TA181 and TA190) in combination with monitoring cost. Low value is -40%. High Value is value used for PFS BSC in TA162 (Erlotinib 2nd line appraisal) updated using NHS Reference Costs 2008/2009)
Monthly PD BSC Cost	£160.06	£115.69	£411.67	Base-case cost from pemetrexed 1L and 1LM NICE appraisals (TA181 and TA190) in combination with monitoring cost (monitoring assumed to not be required after 2nd line cessation). Low value is -40%. High Value is value used for PFS BSC in TA162 (Erlotinib 2nd line appraisal) updated using NHS Reference Costs 2008/2009)
Both Monthly PFS BSC and Monitoring Costs	As above	Both the above sensitivity	Both the above sensitivity analyses combined	As above. Both base-case values are those used in the only NICE appraisal of a first line maintenance treatment for NSCLC (TA181) with an additional

and Monthly PD BSC Cost		analyses combined		monitoring cost implemented. High/Low values are as described above.
Cost of 2nd Line	£6,800	£4,080	£9,520	Base Case Value from TA162. High/Low values are +/- 40%
Cost of a pack of Erlotinib	£1,394.96	-	£1,631.53	Base Case Value with PAS (14.5% discount). High Value without PAS.
Cost of Terminal Care	£2,588.25	£1,552.95	£3,623.55	Base Case Value from TA181 (Pemetrexed 1L NICE appraisal). High/Low values are +/- 40%
Clinical Practice/Patient Assumptions				
Time in PFS on treatment	Based upon SATURN time to complete treatment cessation data	85% of time in PFS	100% of time in PFS on treatment	Base case value based upon data recorded in SATURN. Low value is a plausible bottom limit for this ratio. High value is ERG's dosing methodology in which it was assumed that patients receive a new pack of erlotinib every 30 days of PFS despite ceasing treatment completely.
Proportion of patients receiving 2nd Line	73%	28%	100%	Base case value is as recorded in SATURN. Low value is from National Lung Cancer Audit Data. 100% is an extreme scenario.
Proportion of packs dispensed that are 150 mg / 100mg	100% 150 mg	90% 150 mg 10% 100 mg	-	Base case value is per protocol. Low value assumes 10% of packs dispensed are 100 mg packs.
Model Parameters				
Time Horizon	15 years	10 years	-	Base case value used as ERG increased time-horizon to 15 years. Low value is designed to demonstrate the sensitivity of the model to this parameter.
Health Discount	3.5%	0%	6%	Base case value is as per guide to methods.

rate				High/Low values designed to demonstrate model sensitivity to alternative values
Costs Discount rate	3.5%	0%	6%	Base case value is as per guide to methods. High/Low values designed to demonstrate model sensitivity to alternative values.
Both Discount rates	3.5%	0%	6%	Base case values are as per guide to methods. High/Low values designed to demonstrate model sensitivity to alternative values.

3.3. Squamous (SQ) SD model: Erlotinib vs BSC

A three state model was constructed in Excel© in order to facilitate the comparison of erlotinib to best supportive care in those patients with squamous histology and stable disease as best response to induction. The model was essentially the same as the SD model described above with the substitution of the PFS, OS and time to complete treatment cessation information for the stable disease population with those for the stable disease squamous population. Given this duplication within the models only the updated data will be discussed in the sections below. For further detail on the SQ SD model inputs not detailed below the reader should refer to section 2.2.

Two assumptions were made in order to simplify the amount of additional work required to convert the SD model to a SQ SD model.

- It was assumed that the expected cost of adverse events would be the same for the SQ SD patients as for the SD patients not stratified by histology

- It was assumed that the proportion of patients receiving 2nd line treatment would be the same for the SQ SD patients as for the SD patients not stratified by histology

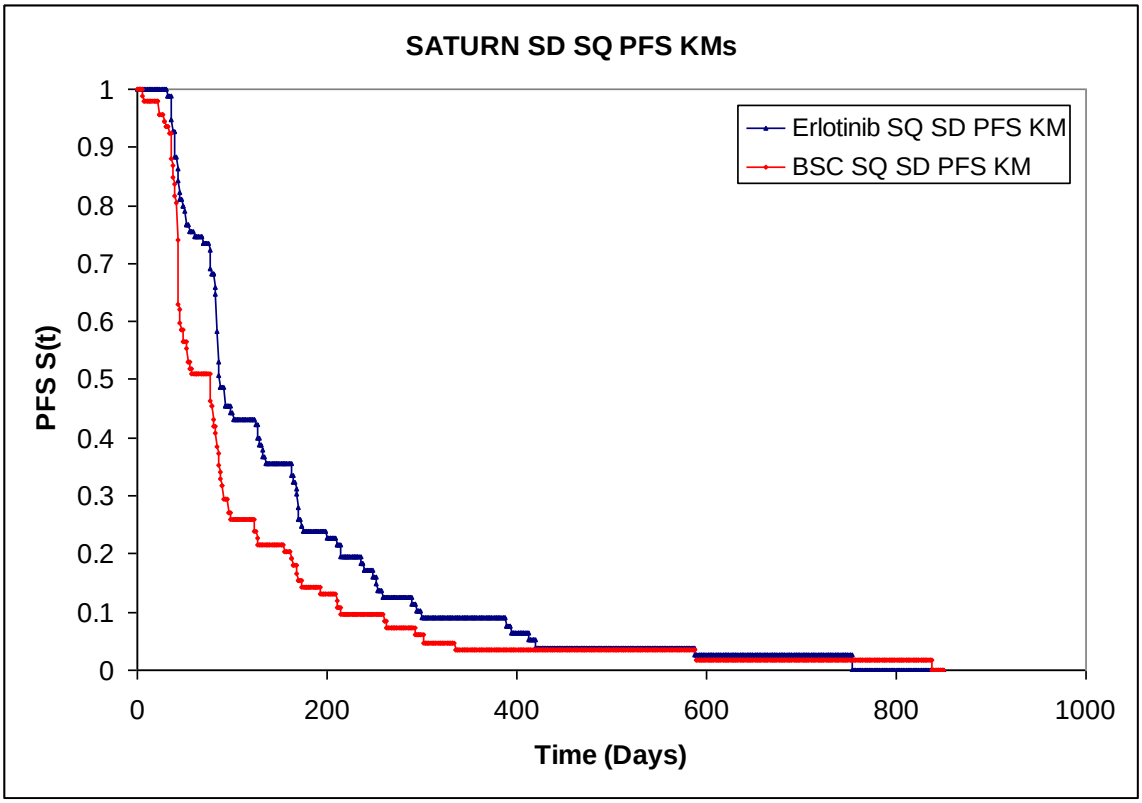
The PFS and OS curves utilised within the model are described below.

3.3.1. PFS

As the PFS KMs for both SQ SD patients randomised to erlotinib and BSC were complete no parametric extrapolation was necessary and the KM curves were used directly within the model. To help validate Roche's 'spline' based fitting approach in any additional work conducted the real number PFS KM curves for the SATURN SQ SD population are provided as a CIC appendix.

The PFS KMs used in the model are presented below:

Figure 20. PFS KMs used in the SQ SD model



3.3.2. OS

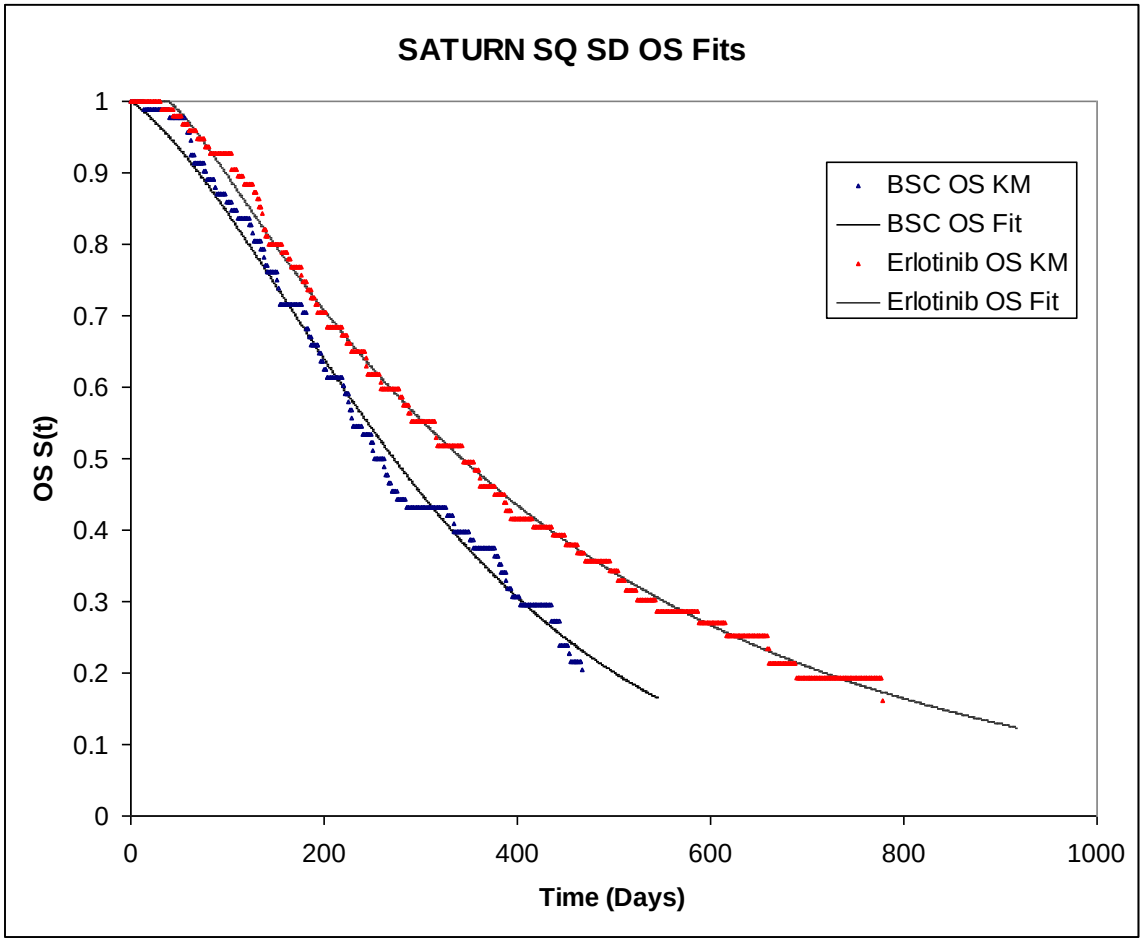
As the overall survival data for the SQ SD population from SATURN was incomplete it was necessary to parametrically fit the OS KM curves in order to determine the expected time a patient would be alive given erlotinib maintenance or simply non-active BSC. This was done using the same functional form used by the ERG in their fitting of the SD OS curves (i.e. the 'Phase 1' form).

Table 6. OS parameter estimates estimated by for the SQ SD population

	A	B	C
BSC	-0.8358	0.1351	0.1432
Erlotinib	-0.1408	0.8732	0.0742

The parametric fits produced via the above parameters are displayed below.

Figure 21. OS parametric fits used in the SQ SD model



3.3.3. Deterministic Sensitivity Analysis

The same sensitivity analysis as was described for the SD model was similarly conducted for the SQ SD model.

3.3. The NSQ SD model

As the NSQ SD model was designed to fulfil two of the comparisons required (erlotinib vs BSC in NSQ SD patients ineligible for pemetrexed maintenance and erlotinib vs pemetrexed in NSQ SD patients eligible for pemetrexed maintenance) each comparison will be discussed in turn in the appropriate section below.

3.3.1. The NSQ SD model: Erlotinib vs Pemetrexed in patients eligible for maintenance with pemetrexed

A three state model was constructed in Excel© in order to facilitate a cost-utility analysis on the use of erlotinib maintenance compared to pemetrexed maintenance in patients with non-squamous stable disease as best response following induction for whom maintenance with pemetrexed is suitable. This model is entirely de novo and has yet to be presented to the appraisal committee.

Pemetrexed maintenance was approved by NICE for use in this patient population in TA190. Given clinicians now have NICE guidance recommending the use to of an active treatment to patients suitable for pemetrexed maintenance best supportive care is not an appropriate comparator in those patients eligible for pemetrexed and not providing an active treatment to a patient suitable (and NICE recommended) to do so would be deemed clinically unethical.

3.3.1.1 SD Model Structure

Structurally the NSQ SD model constructed was equivalent to that for the amended SD model presented. 3 health states were used to model a patients disease progression and eventual death (Progression Free Survival (PFS), Progressed Disease (PD) and an absorbing ‘Death’ state) with patient level data for the SATURN NSQ SD population utilised to inform the proportion of erlotinib patients in each health state at any given time.

3.3.1.2. NSQ SD Model Inputs

3.3.1.2.1. Indirect Comparison

As there is no head to head RCT of erlotinib compared to pemetrexed in the 1LM setting there is considerable uncertainty surrounding the relative efficacy of the two comparators of interest.

There are however two trials comparing each comparator of interest to a 'best supportive care' arm (the SATURN trial in the case of erlotinib and the JMEN trial in the case of pemetrexed) from which an estimate of the relative efficacy of the two regimens can in theory be drawn.

The integration of such a comparison in this scenario is severely hampered by lack of data on the efficacy of pemetrexed in the NSQ SD population. Whilst hazard ratios from the JMEN trial are available in the NSQ population this information is not publicly available by best response to induction therapy.

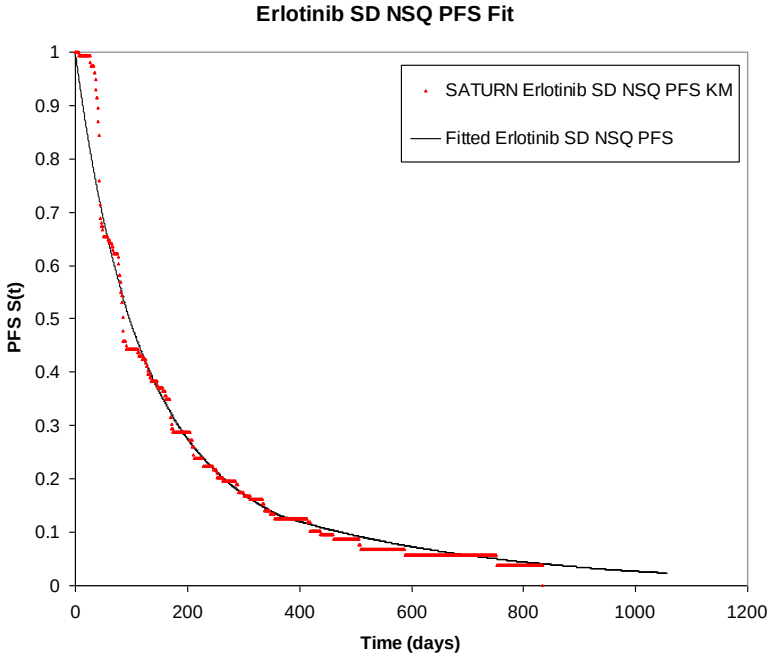
Furthermore as there appears to be significant heterogeneity between the patient populations of the JMEN trial and the SATURN trial in terms of known prognostic and potential predictive factors (namely the proportion of Asians and the proportion of never smokers) the assumption of transitivity is unlikely to hold in this case even if such NSQ SD specific HR information was available. As there is a known association between the efficacy of TKIs and never-smoker and 'asian' status it is clear that the assumption of transitivity is unlikely to hold in this case (making a quantitative indirect comparison based upon the SATURN and JMEN PFS and OS HRs extremely limited).

As both of these demographic imbalances favour pemetrexed in terms of prognosis with the JMEN trial having twice the proportion of asian patients as the SATURN study (32% compared to 16%) and over 50% more never-smokers (26% compared to 17%) it is clear that any indirect comparison of the median survival outcomes from JMEN and SATURN is highly likely to be biased in favour of pemetrexed.

Whilst an indirect comparison of pemetrexed to erlotinib is severely hampered by the above issues one must be conducted if the decision problem is to be fulfilled. Therefore in the base case it was assumed pemetrexed and erlotinib are of equivalent efficacy and a range of plausible relative efficacy scenarios (9 in total) were tested in sensitivity analysis to capture possible uncertainty around this assumption.

3.3.1.2.2. PFS

The 'spline' technique utilised by the ERG for the SD PFS analysis was repeated for the NSQ SD analysis. The same functional forms were used as was the 12 month spline point. The parametric fit produced by this technique is displayed below.



As the specifics of the derivation of the PFS parametric fits have been discussed previously they will not be repeated in this section. The parameters estimated are provided below:

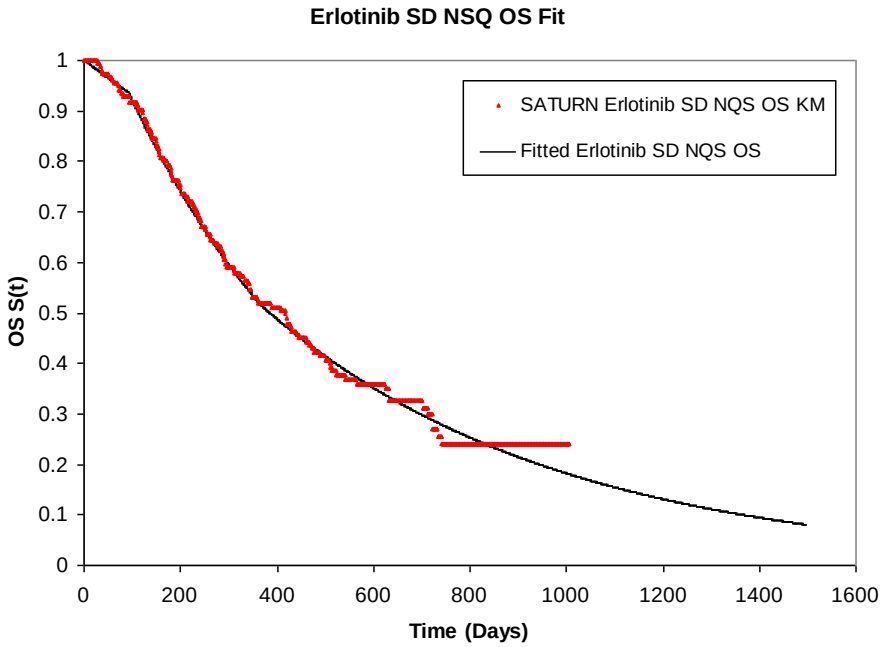
Table 7. NSQ SD PFS parameter estimates

	A	B	C	P	Q
Erlotinib	7.5818	0.0423	-0.0828	1.219042	0.075775

In order to generate a comparison against pemetrexed a range of plausible PFS HRs were applied to this erlotinib PFS baseline under the assumption of proportional hazards (see the previous section for each scenario analysis undertaken). Whilst the erlotinib PFS KMs were complete it was necessary to fit the erlotinib PFS curve parametrically in order to provide a time point in the scenario in which pemetrexed was assumed to be more effective than erlotinib.

3.3.1.2.3. OS

A 3-stage spline model was chosen to model overall survival. This approach was taken as there appeared to be 3 defined stages in the hazard of death of erlotinib NSQ SD patients in SATURN. The first of these two spline sections followed the two parametric forms used by the ERG whilst another exponential model was fitted to the last spline section. The excellent face validity of the fits produced by this methodology is demonstrated below:



The first spline point was fitted at 3 months. This point was chosen as there appeared to be a sharp increase in the hazard of death from this point onwards and it was felt that attempting to fit a curve to both the pre-3 month and post-3 month period was unlikely to produce a satisfactory fit for either section. After conducting initial fitting around this singular spline point it was also noticed that the accelerated hazard observed from 3-

months onwards appeared to slow down at around 12 months. Therefore a second spline point was added at 12 months.

Section 1 (0-3 months) was fitted using the ERG's 'phase 1' function form and section 2 (3-12 months) and section 3 (12 month onwards) were fitted using the ERG's 'phase 2' form (essentially a simple exponential fit).

Table 8. NSQ SD OS parameter estimates

	A	B	C	Phase 2 Hzd	Phase 3 Hzd
Erlotinib	12.0561	0.0000	0.0219	0.0663	0.0499

In order to generate a comparison against pemetrexed the OS HRs outlined previously were applied to this erlotinib OS baseline under the assumption of proportional hazards. Whilst some may argue that the assumption of proportional hazards is a strong one in this case there is little alternative if erlotinib is to be compared to pemetrexed in the absence of a head to head study of the two regimens.

3.3.1.2.4. PD

The proportion of patients in the PD state in any time was derived from the PFS and OS curves in the manner described in section 2.2.2.3 (as was done by the ERG in their additional work).

3.3.1.2.2. SD NSQ Utilities

The utility values used by the ERG in the additional work they conducted in assessing the original non-squamous model submitted by Roche were used within the model. These values are provided below and incorporate the disutility associated with the grade 3/4 adverse events experienced by patients receiving each regimen.

Figure 22. Utility Values Utilised in AUC Model

Health State	Utility Value	Source
PFS (Erlotinib)	0.6732	Erlotinib 1LM ERG report + Nafees 2008
PFS (Pemetrexed)	0.6568	Erlotinib 1LM ERG report + Nafees 2008
PD	0.53	Erlotinib 1LM ERG report + Nafees 2008

3.3.1.2.3. NSQ SD Model Costs

As the majority of costs implemented into the NSQ SD model were the same as those featured in the SD model the explanation of these cost inputs will not be duplicated in this section.

The following costs used the same method and/or values described previously:

- The cost of erlotinib (same methodology as used for SD model but with NSQ SD specific inputs)
- The cost of erlotinib administration (same methodology as described previously founded upon NSQ SD specific inputs)
- The cost of best supportive care, monitoring and end of life
- The cost of erlotinib adverse events (assumed the cost of adverse events for the NSQ SD population would be the same as that for the whole SD population)
- 2^{nd} line treatment costs

Those costs not described previously are related to the cost of pemetrexed, the cost of pemetrexed administration, the cost of pemetrexed associated concomitant medications, pemetrexed pharmacy preparation cost and the cost of adverse events associated with pemetrexed. These are discussed in the sections below.

3.3.1.2.3.1 Pemetrexed Drug Costs

Pemetrexed is IV administered every 21 days at a dose of 500 mg per BSA m^2 . It can be purchase in two vial sizes; 500 mg at a cost of £800 and 100 mg at a cost of £160.

In order to estimate the expected cost of pemetrexed in practice (including consideration of drug wastage) the patient weight and height data recorded in the NSQ SD population of SATURN was combined in order to generate the body surface area (BSA) of each patient. A BSA frequency table was then constructed based upon the BSA bands in which a patient would require a certain number of vials. Table 9 below demonstrates this frequency table.

The frequency table was then combined with the cost of treatment in each vial band in order to derive a weighted average expected cost of one dose of pemetrexed. This technique produced an expected drug cost of £1,492.43 per dose administered.

This cost per dose was then converted into a monthly expected cost by multiplying the expected cost per dose by the number of doses per month (30.4375/21). This conversion produced an expected monthly per protocol cost of pemetrexed of £2,163.14.

As in clinical practice there is often a disparity between disease progression and treatment cessation it is common practice in the economic evaluation of oncology technologies to apply some sort of adjustment factor in order to convert the expected cost per month of treatment generated by a methodology such as that described above into an expected monthly cost of drug per month of PFS. In order to adjust for this factor, and in order to remain conservative with respect to the incremental cost associated with pemetrexed, a proportion of time in PFS on treatment figure of 95% was used within the base case. This value was based upon the mean number of pem/cis cycles reported in the manufacturers pemetrexed first line NICE submission (3.8) relative to the mean number of cycles a patient should have received (4). This adjusted expected monthly PFS cost (£2,055.98) was then applied to each month a patient spent in PFS. As this assumption is clearly subject to uncertainty a range of plausible time in PFS on treatment ratio values were tested in sensitivity analysis.

Table 9. SATURN NSQ SD BSA Frequency Table

BSA Band (m^2)	No. of 500 mg vials required	No. of 100 mg vials required	Number of Patients in Band	Proportion of Patients with record in Band	Cost per dose in BSA Band

BSA ≤1.2m^2	1	1	0	0.00%	£960.00
1.2m^2< BSA ≤1.4m^2	1	2	7	2.36%	£1,120.00
1.4m^2< BSA ≤1.6m^2	1	3	54	18.24%	£1,280.00
1.6m^2< BSA ≤1.8m^2	1	4	109	36.82%	£1,440.00
1.8m^2< BSA ≤2.0m^2	2	0	92	31.08%	£1,600.00
2.0m^2< BSA ≤2.2m^2	2	1	30	10.14%	£1,760.00
2.2m^2< BSA ≤2.4m^2	2	2	3	1.01%	£1,920.00
2.4m^2< BSA ≤2.6m^2	2	3	1	0.34%	£2,080.00
2.6m^2< BSA	2	4	0	0.00%	£2,240.00
Missing Record	N/A	N/A	1	N/A	N/A

3.3.1.2.3.2. Pemetrexed Concomitant Medication

The concomitant medications associated with pemetrexed described in the original submission for this appraisal were similarly applied in the de novo NSQ SD model. CPORT and NCAT were used to derive these costs as explained in the original submission made.

3.3.1.2.3.3. Pemetrexed Administration Costs and Pharmacy Costs

As pemetrexed is intravenously administered a patient receiving pemetrexed maintenance therapy must come into hospital every 21 days (1.45 times a month) to receive their infusion. This was integrated into the model utilising the 2008/2009 NHS reference cost SB12Z (Deliver simple parenteral chemotherapy at first attendance). This value (£272.10) was then combined with the pemetrexed pharmacy preparation cost from the previous submission, converted into a monthly cost multiplied by the proportion of time in PFS on treatment and applied to each month of PFS in the model (£398.21 a month).

3.3.1.2.3.4. Pemetrexed Adverse Events

Pemetrexed related AEs were incorporated into the analysis in the same manner as described in the previous Roche erlotinib 1LM submission. In addition it was assumed the expected erlotinib adverse event cost associated with those patients with non-squamous stable disease would be equivalent to that calculated for the whole SD population.

3.3.1.3. Sensitivity Analysis

Due to the time constraints associated with the provision of such a substantial quantities of new evidence at the ACD stage and the uncertainty surrounding the relative efficacy of erlotinib and pemetrexed only sensitivity analysis surrounding this relative efficacy was conducted.

The matrix below demonstrates the analyses undertaken (all HRs are pemetrexed vs erlotinib). The model is fully editable if the user wishes to update the HRs applied.

Figure 23. Pemetrexed vs Erlotinib scenario analyses undertaken

PFS \ OS	0.9	1.0	1.1
0.9	See Section 3.4 for Results		
1			
1.1			

3.3.2. The NSQ SD model: Erlotinib vs Best Supportive Care in patients ineligible for maintenance with pemetrexed

For the purposes of enabling a comparison of erlotinib vs BSC in those patients with non-squamous histology with stable disease as best response to induction therapy a BSC arm was integrated into the NSQ SD model used to facilitate the comparison of erlotinib to pemetrexed in those NSQ SD patients eligible for pemetrexed maintenance.

This integration took the form of the creation of a new comparator sheet within the model and the updating of the 'model inputs' sheet with those BSC specific inputs not included in the original NSQ SD analysis (i.e. adverse events and utility values).

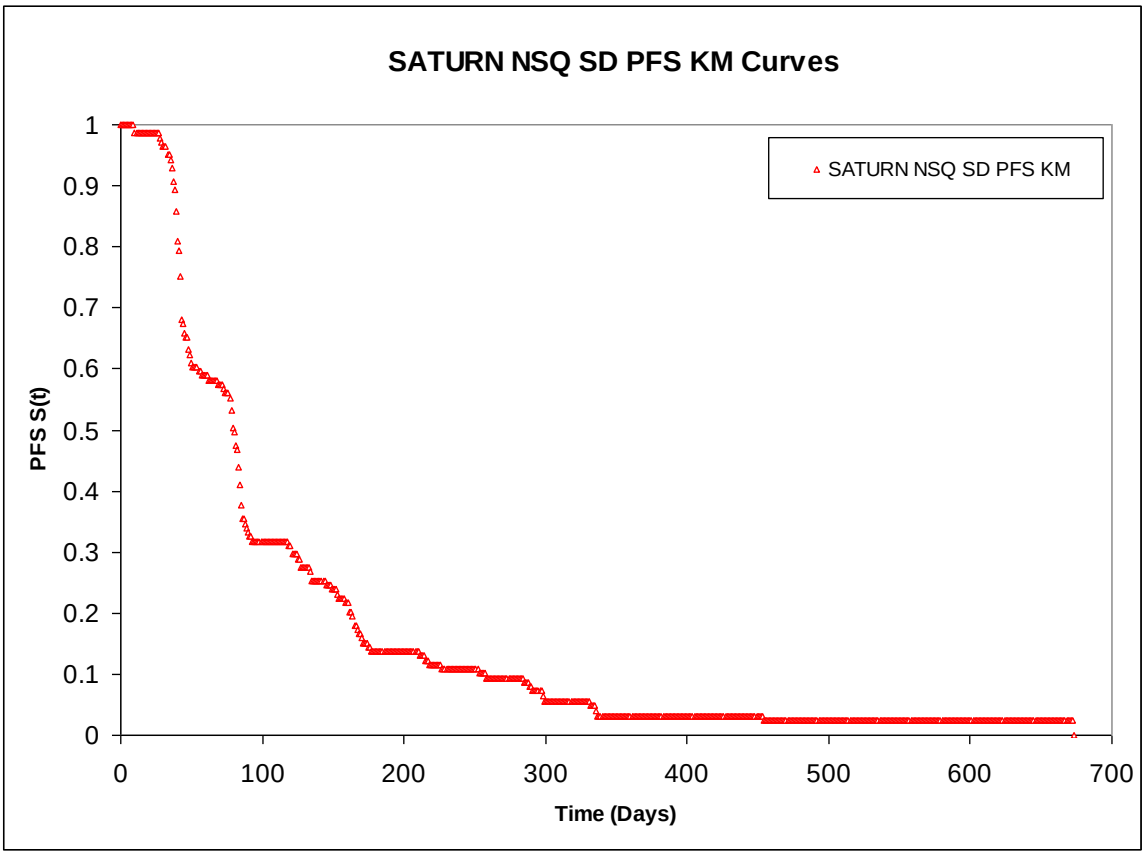
The PFS and OS curves used in the model are presented below.

3.3.2.1. PFS

In order to remain as parsimonious as possible the PFS KMs for the NSQ SD population from SATURN were used directly in the model. As these were complete no parametric extrapolation was required to model the full time horizon of interest. As was the case for

the previous new populations the real number PFS KM data for the NSQ SD is provided in an appendix so that the ERG may validate the results presented.

Figure 24. SATURN NSQ SD BSC PFS KM used in model



3.3.2.2 OS

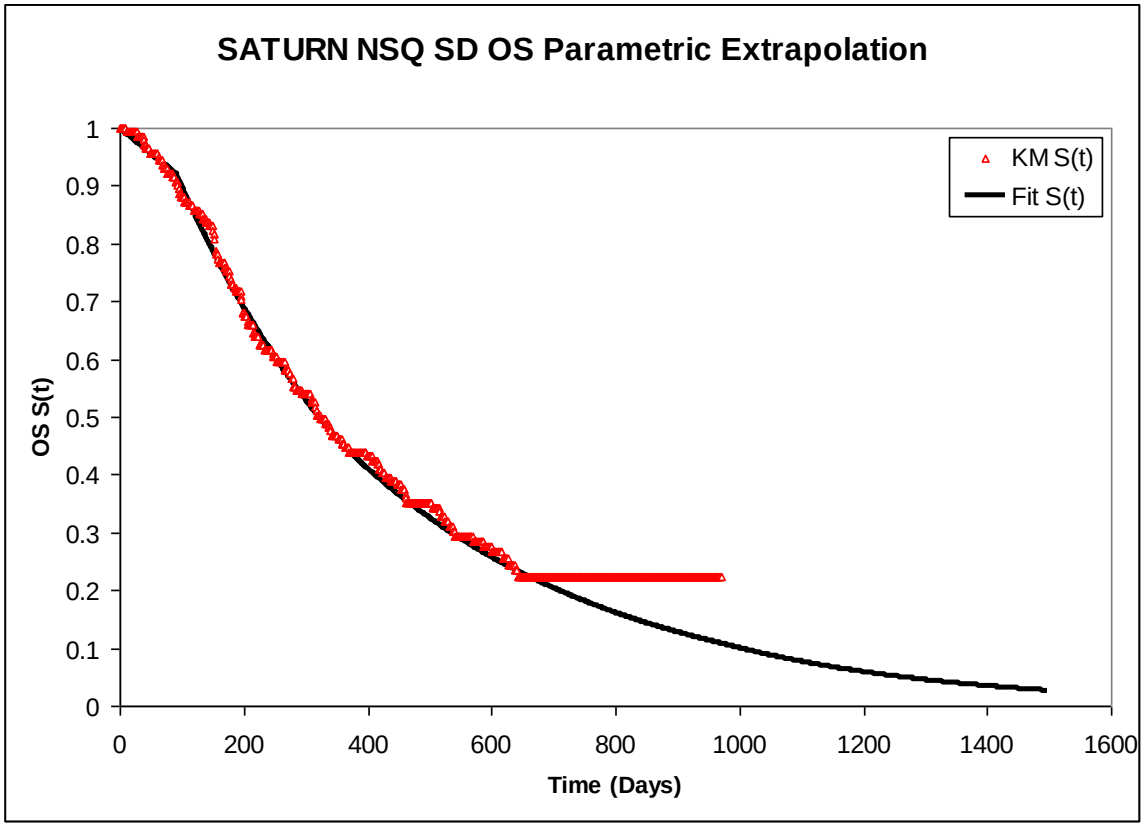
The 3-stage spline based methodology used for the OS fitting of the erlotinib NSQ SD data from SATURN was similarly used for the fitting of the OS BSC arm. The same spline points were used. The parameters estimated via this approach are provided in Table 10 below.

Table 10. NSQ SD OS parameter estimates

	A	B	C	Phase 2 Hzd	Phase 3 Hzd
BSC	63.5239	0.0000	0.0311	0.0806	0.0710

The face validity if the parametric fit generated is demonstrated below:

Figure 25. SATURN BSC NSQ SD OS Extrapolation



3.3.2.3 Sensitivity Analysis

The sensitivity analysis described for the SD model were similarly conducted for the SQ SD model.

4. Results

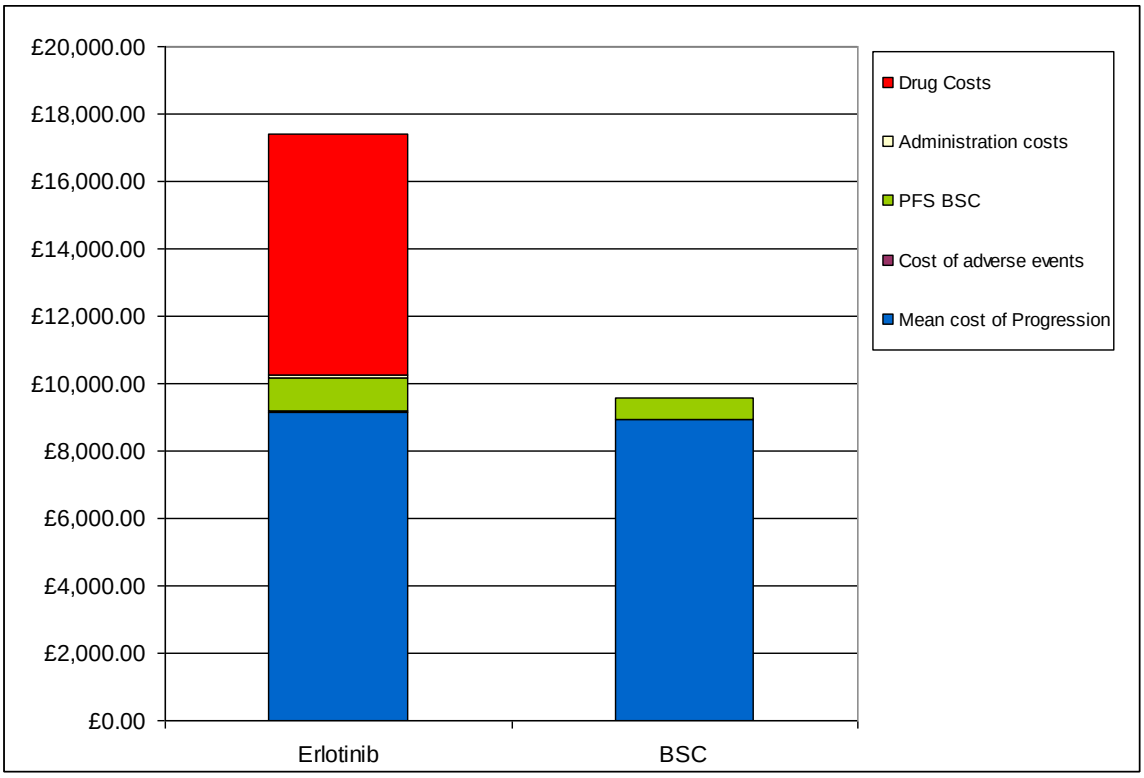
4.1 Erlotinib compared to BSC in Pemetrexed Unsuitable Stable Disease Patients

4.1.1 Costs

Table 11. Stable Disease (Pemetrexed Unsuitable) Costs

Cost Element	Erlotinib	BSC	Incremental (Erlotinib – BSC)
Cost of Erlotinib	£7,148.44	£0.00	£7,148.44
Total Drug Cost	**£7,148.44**	**£0.00**	**£7,148.44**
Cost of Erlotinib Admin	£69.18	£0.00	£69.18
Total Admin Cost	**£69.18**	**£0.00**	**£69.18**
Cost of PFS BSC	£994.42	£651.02	£343.40
Cost of PD BSC, 2nd line treatment and EOL	£9,163.69	£8,923.13	£240.56
Adverse events costs	£11.00	£0.00	£11.00
Total 'Other' Costs	**£10,169.11**	**£9,574.16**	**£594.95**
Total Cost	£17,386.73	£9,574.16	£7,812.57

Figure 26. Stable Disease (Pemetrexed Unsuitable) Costs



4.1.2 Health Outcomes

Table 12. Stable Disease (Pemetrexed Unsuitable) Health Outcomes

	Erlotinib	**BSC**	**Incremental (Erlotinib – BSC)**
Time in PFS (Years)	0.456	0.299	0.158
Time in PD (Years)	0.931	0.764	0.168
Total time alive (Years)	**1.388**	**1.063**	**0.325** **(3.9 months)**
QALYs in PFS	0.307	0.200	0.107
QALYs in PD	0.494	0.405	0.089
Total QALYs	**0.801**	**0.605**	**0.196**

Figure 27. Squamous Stable (Pemetrexed Unsuitable) Disease QALYs

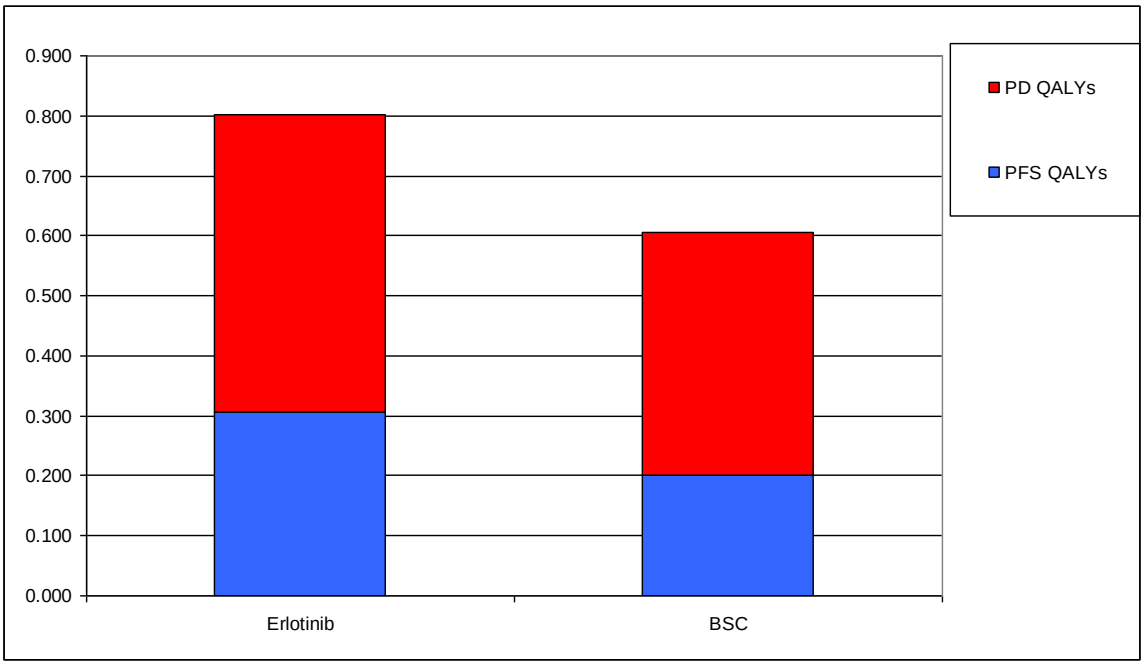
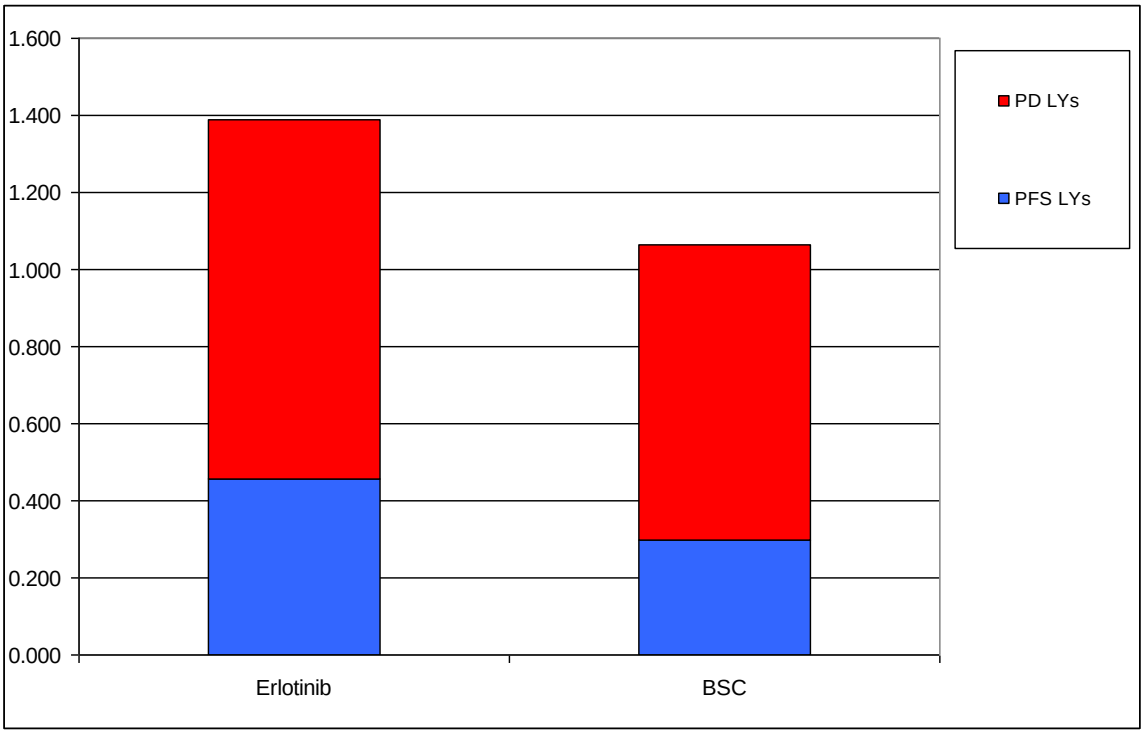


Figure 28. Stable Disease (Pemetrexed Unsuitable) Life Years



4.1.3 ICERs

Table 13. Stable disease (Pemetrexed Unsuitable) cost per QALY gained

Regimen	Cost	QALYs	Cost per QALY gained
Erlotinib	£14,798.50	0.801	£39,935.60
BSC	£6,985.91	0.605	

Table 14. Stable disease (Pemetrexed Unsuitable) cost per life year gained

Regimen	Cost	Lys	Cost per Life Year gained
Erlotinib	£14,798.50	1.388	£24,029.29
BSC	£6,985.91	1.063	

Figure 29. Stable Disease Cost Effectiveness Plane

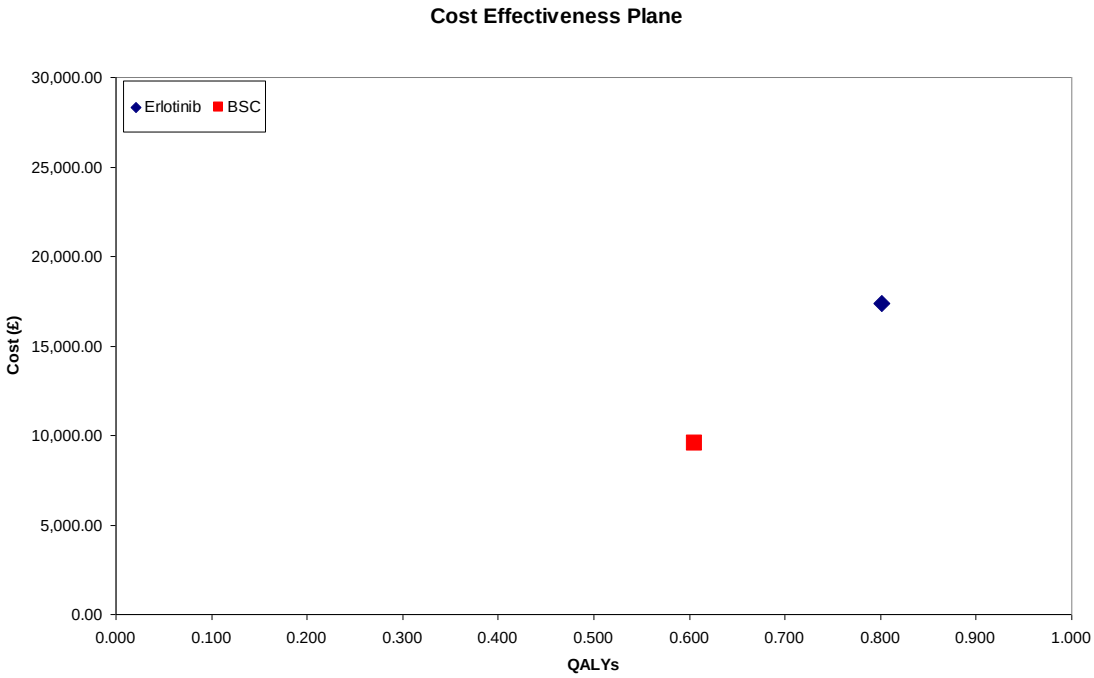
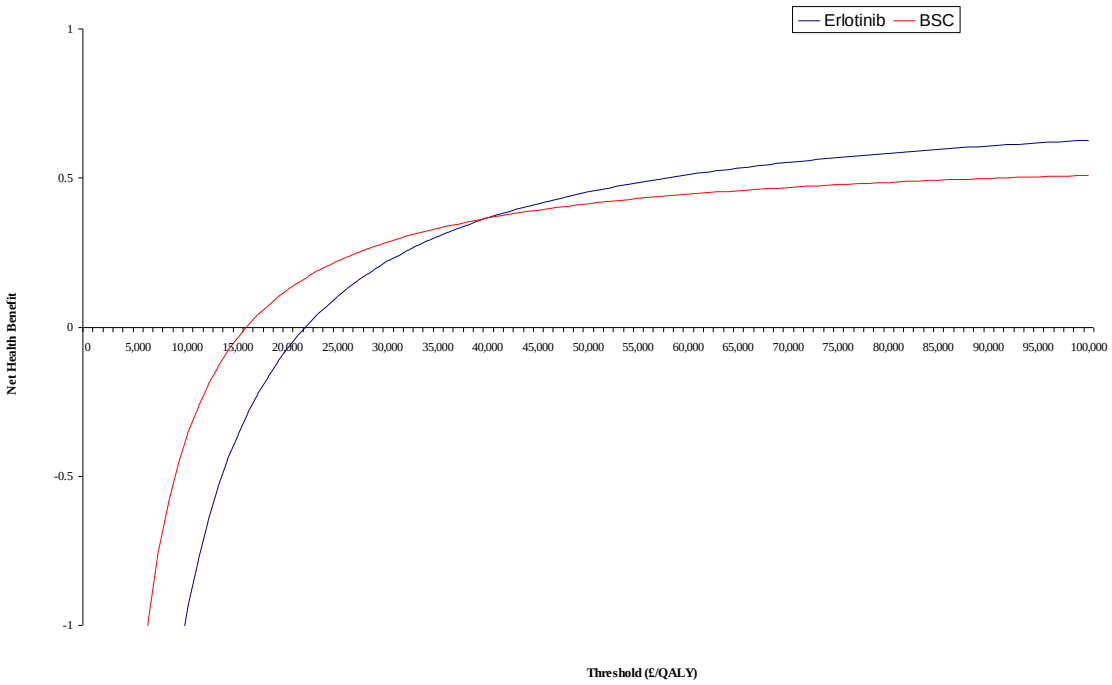


Figure 30. Stable Disease Net Health Benefit Threshold Analysis



4.1.4 Sensitivity Analysis

4.1.4.1 Deterministic Sensitivity Analysis

Deterministic sensitivity analysis demonstrates that given plausible variation of those parameters subject to uncertainty the ICER of erlotinib compared to best supportive care in those patients unsuitable for pemetrexed remains below £45,000 per QALY gained. The biggest drivers of the ICER were found to be the BSC costs used in PFS and PD, the proportion of time in PFS a patient spent on treatment and the PFS utility values used.

Sensitivity analysis demonstrates that without the erlotinib PAS the base-case ICER rises around £7,000 to approximately £46,000 per QALY gained. Utilising the erlotinib 2L PFS BSC costs for PFS and PD BSC (from TA162) resulted in the ICER rising to just below £45,000 per QALY gained (compared to the base-case value of around £40,000 which was founded on the use of the pemetrexed 1L and 1LM BSC cost).

The use of the ERG's PFS based dosing rather than time to complete treatment cessation based dosing demonstrates that if erlotinib were given as per protocol in practise the base-case ICER would be around £45,000 per QALY gained. This sensitivity underlines the need to consider the fact that in practice, and in the SATURN trial, treatment cessation prior to progression occurs/did occur and needs to be accounted for when deriving estimates of the cost effectiveness of erlotinib when used within the NHS.

Due to time constraints probabilistic sensitivity analysis was not conducted.

Table 15. SD (Pemetrexed Unsuitable) Deterministic Sensitivity Analysis Results

Parameter Modified	Base Parameter Value	Low Parameter Value	High Parameter Value	Base Case ICER	Low Parameter Value ICER	High Parameter Value ICER
Utilities						
PFS	Erlotinib = 0.6732 BSC = 0.6628	Erlotinib = 0.6059 BSC = 0.5965	Erlotinib = 0.7405 BSC = 0.7291	£39,936	£42,241	£37,869
PD	0.53	0.48	0.58	£39,936	£41,722	£38,296
Both utilities	As above	-	1	£39,936	-	£24,029
Costs						
Monthly Erlotinib Pharmacy Costs	£13.50	£8.10	£18.90	£39,936	£31,794	£40,077
Monthly PFS BSC and Monitoring Costs	£181.46	£108.88	£411.67	£39,936	£39,233	£42,159
Monthly PD BSC Cost	£160.06	£115.69	£411.67	£39,936	£39,480	£42,521
Both Monthly PFS BSC and Monitoring Costs and Monthly PD	As above	Both the above sensitivity analyses	Both the above sensitivity analyses combined	£39,936	£38,777	£44,745

BSC Cost		combined				
Cost of 2nd Line	£6,800	£4,080	£9,520	£39,936	£40,102	£39,769
Cost of a pack of Erlotinib	£1,394.96	-	£1,631.53	£39,936	-	£46,132
Cost of Terminal Care	£2,588.25	£1,552.95	£3,623.55	£39,936	£39,936	£39,935
Clinical Practice/Patient Assumptions						
Time in PFS on treatment	Based upon SATURN time to complete treatment cessation data	85% of time in PFS	100% of time in PFS on treatment	£39,936	£38,657	£44,942
Proportion of patients receiving 2nd Line	73%	28%	100%	£39,936	£40,192	£34,783
Proportion of packs dispensed that are 150 mg / 100mg	100% 150 mg	90% 150 mg 10% 100 mg	-	£39,936	£39,247	-
Model Parameters						
Time Horizon	15 years	10 years	-	£39,936	£39,975	-
Health Discount rate	3.5%	0%	6%	£39,936	£37,611	£41,562

Costs Discount rate	3.5%	0%	6%	£39,936	£40,700	£39,451
Both Discount rates	3.5%	0%	6%	£39,936	£38,331	£31,058

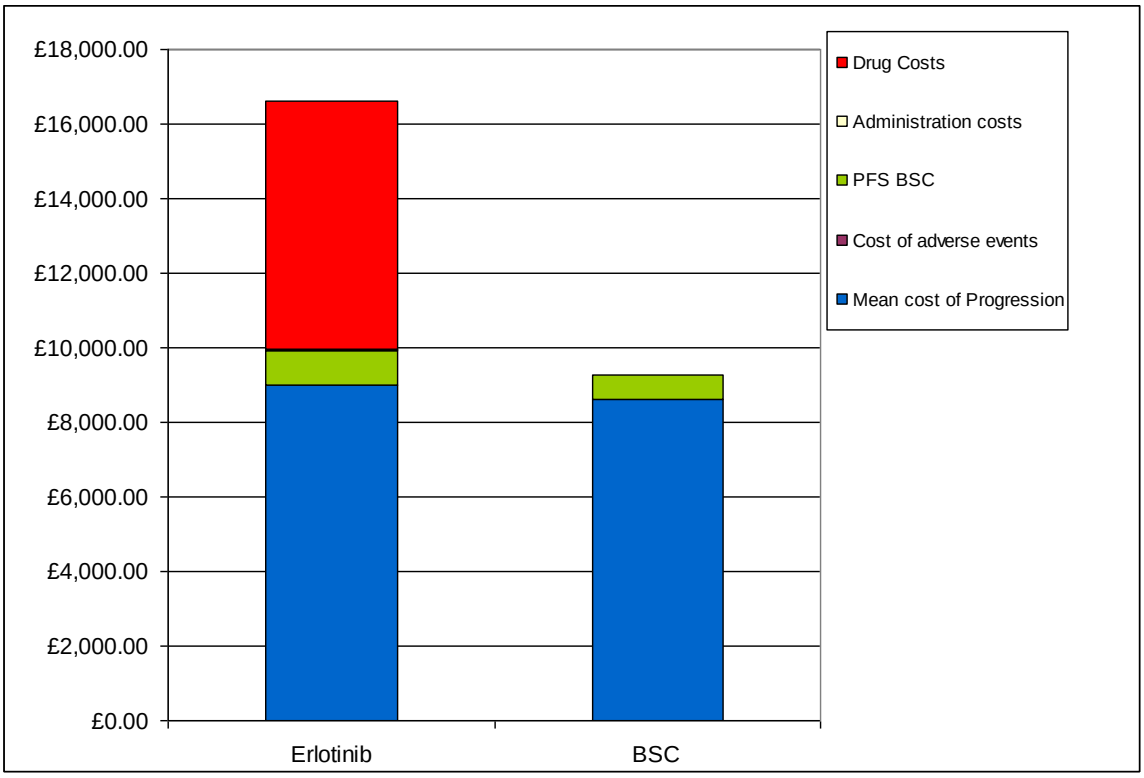
4.2 Erlotinib compared to best supportive care in Squamous histology patients with stable disease as best response induction

4.2.1 Costs

Table 16. Squamous Histology Stable Disease Costs

Cost Element	Erlotinib	BSC	Incremental (Erlotinib – BSC)
Cost of Erlotinib	£6,643.66	£0.00	£6,643.66
Total Drug Cost	**£6,643.66**	**£0.00**	**£6,643.66**
Cost of Erlotinib Admin	£64.30	£0.00	£64.30
Total Admin Cost	**£64.30**	**£0.00**	**£64.30**
Cost of PFS BSC	£899.03	£661.87	£237.16
Cost of PD BSC, 2nd line treatment and EOL	£9,003.66	£8,620.49	£383.17
Adverse events costs	£11.00	£0.00	£11.00
Total 'Other' Costs	**£9,913.69**	**£9,282.36**	**£631.32**
Total Cost	£16,621.64	£9,282.36	£7,339.27

Figure 31. Squamous Histology Stable Disease Costs



4.2.2 Health Outcomes

Table 17. Squamous Histology Stable Disease Health Outcomes

	Erlotinib	BSC	Incremental (Erlotinib – BSC)
Time in PFS (Years)	0.413	0.304	0.109
Time in PD (Years)	0.836	0.586	0.250
Total time alive (Years)	**1.249**	**0.890**	**0.359 (4.3 months)**
QALYs in PFS	0.278	0.204	0.074
QALYs in PD	0.443	0.311	0.133
Total QALYs	**0.721**	**0.514**	**0.207**

Figure 32. Squamous Histology Stable Disease QALYs

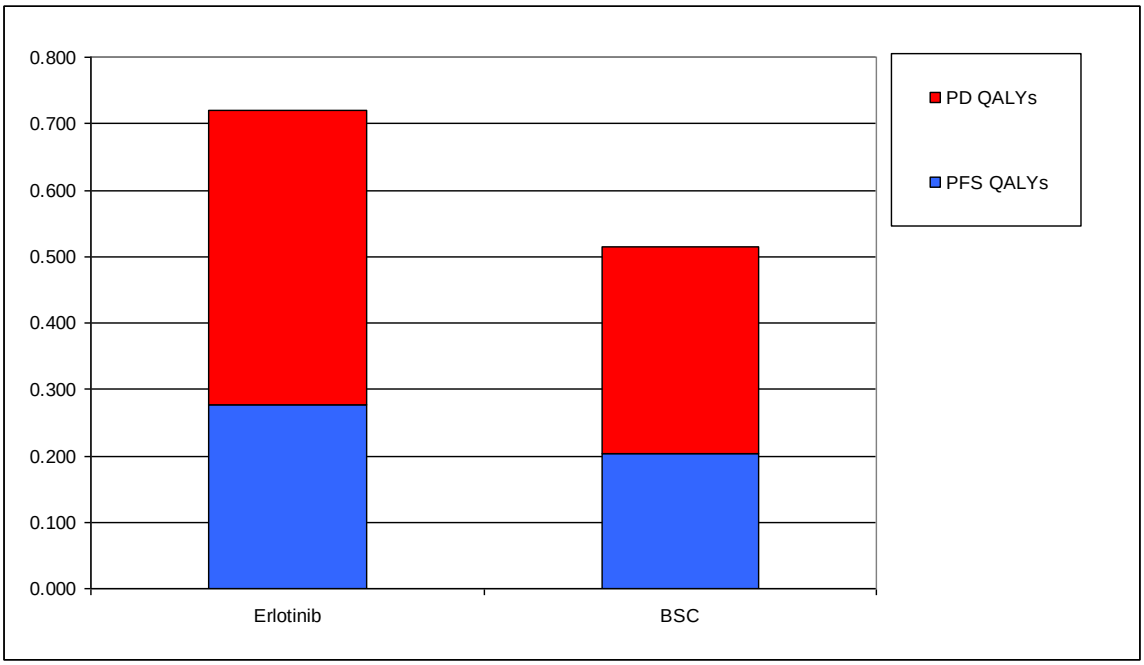
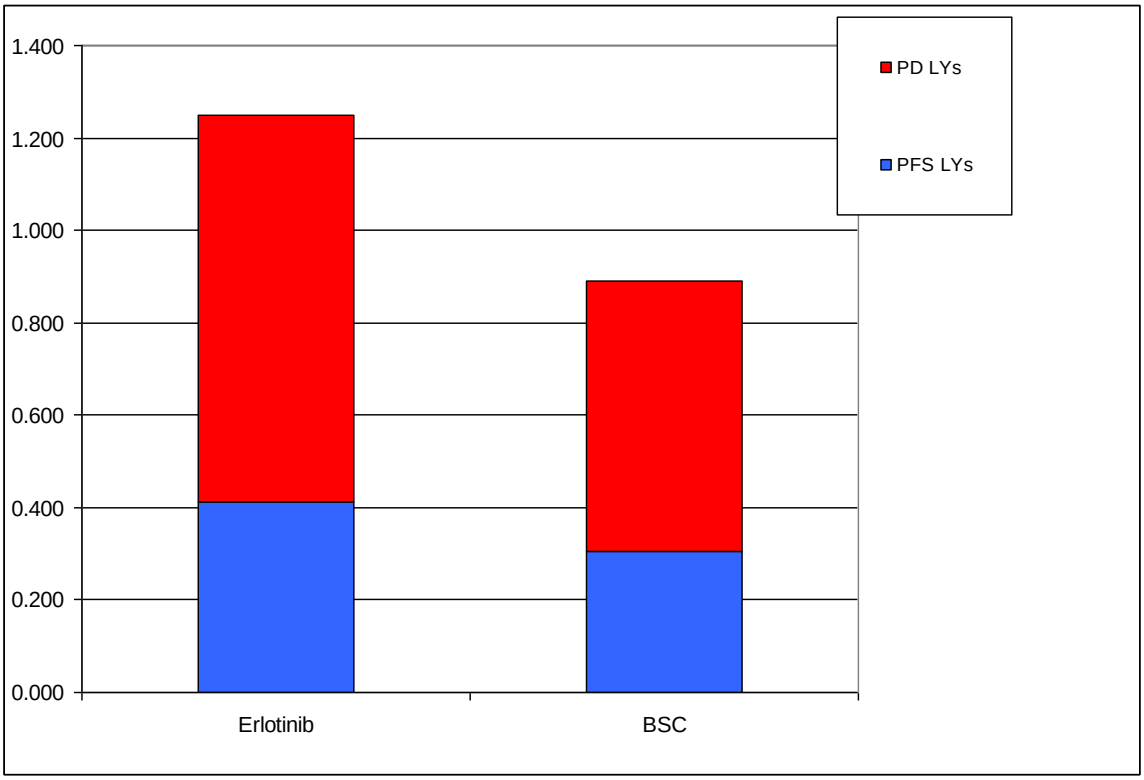


Figure 33. Squamous Histology Stable Disease Life Years



4.2.3 ICERs

Table 18. Squamous Histology Stable Disease cost per QALY gained

Regimen	Cost	QALYs	Cost per QALY gained
Erlotinib	£16,621.64	0.721	£35,491
BSC	£9,282.36	0.514	

Table 19. Squamous Histology Stable Disease cost per life year gained

Regimen	Cost	Lys	Cost per Life Year gained
Erlotinib	£16,621.64	1.249	£20,433
BSC	£9,282.36	0.890	

Figure 34. Squamous Histology Stable Disease Cost Effectiveness Plane

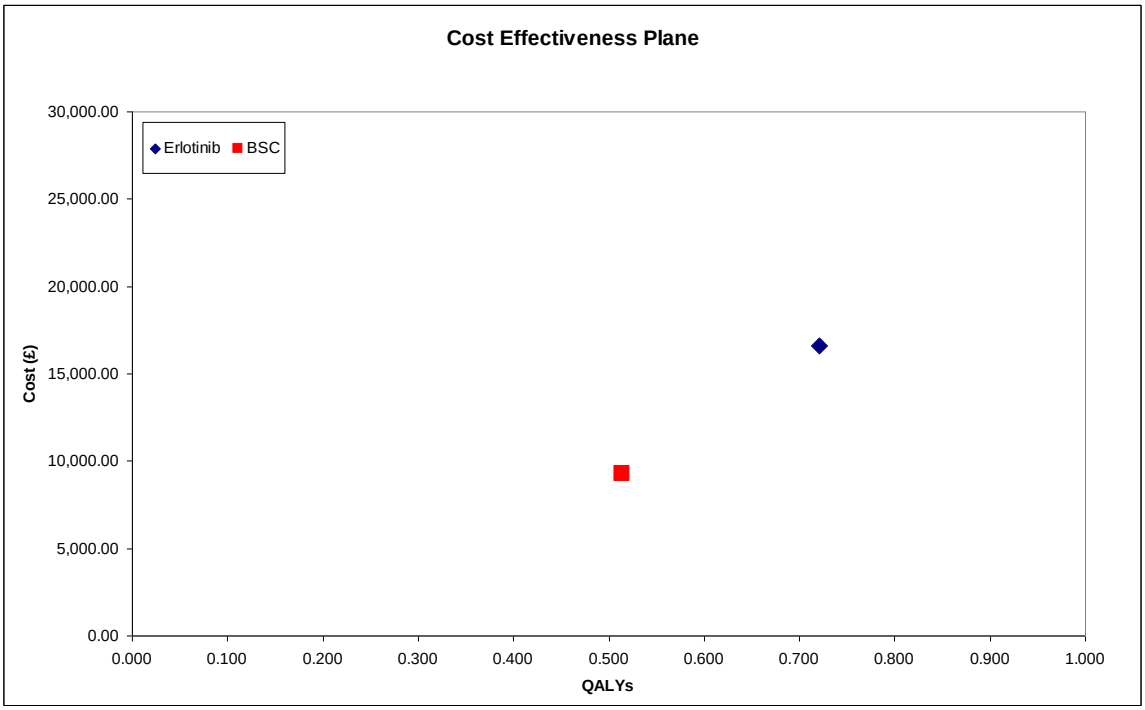
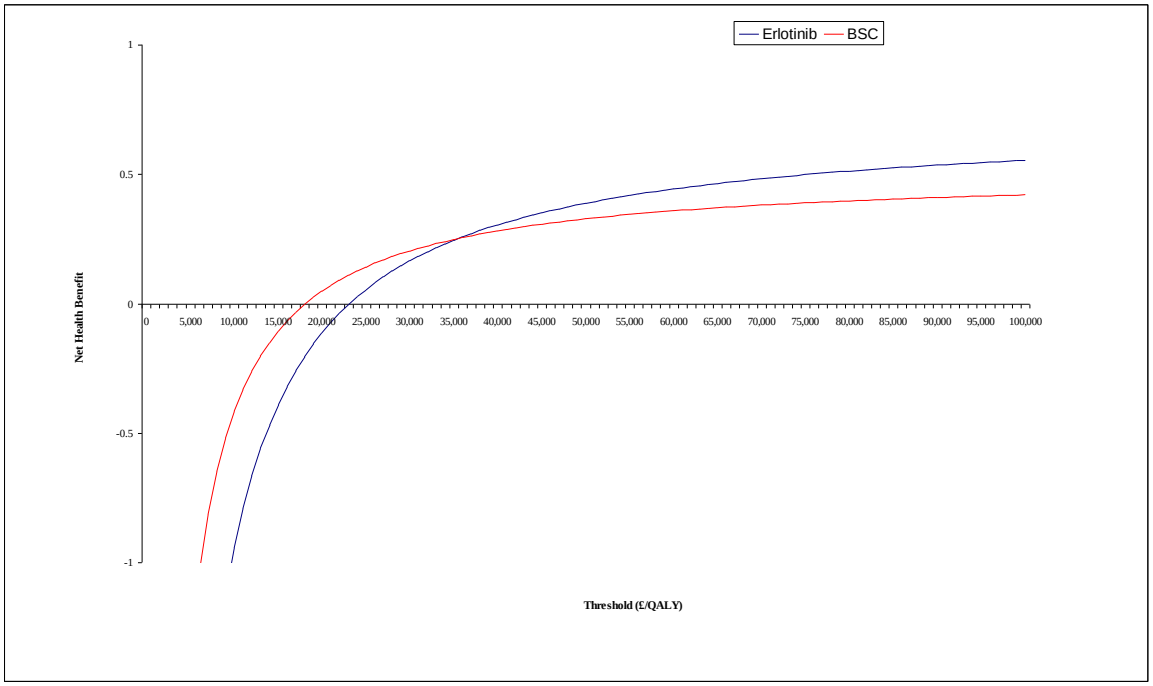


Figure 35. Squamous Histology Stable Disease Net Health Benefit Threshold Analysis



4.2.4 Sensitivity Analysis

4.2.4.1 Deterministic Sensitivity Analysis

The results of the deterministic sensitivity analyses conducted are presented overleaf. PSA was not conducted due to time constraints. The SQ SDs model sensitivities were found to be the same as those for the whole SD population.

The highest ICER produced in sensitivity analysis of parameters subject to uncertainty (i.e. excluding the analysis in which the erlotinib PAS was removed) was produced via the use of the TA181 PFS BSC values for the BSC cost in the model. This analysis produced an ICER of £40,599.

Table 20. Squamous Histology Stable Disease Deterministic Sensitivity Analysis Results - **UPDATE**

Parameter Modified	Base Parameter Value	Low Parameter Value	High Parameter Value	Base Case ICER	Low Parameter Value ICER	High Parameter Value ICER
Utilities						
PFS	Erlotinib = 0.6732 BSC = 0.6628	Erlotinib = 0.6059 BSC = 0.5965	Erlotinib = 0.7405 BSC = 0.7291	£35,491	£36,889	£34,264
PD	0.53	0.48	0.58	£35,491	£37,777	£33,465
Both utilities	As above	-	1	£35,491	-	£20,433
Costs						
Monthly PFS BSC and Monitoring Costs	£181.46	£108.88	£411.67	£35,491	£35,031	£36,943
Monthly PD BSC Cost	£160.06	£115.69	£411.67	£35,491	£34,846	£39,146
Both Monthly PFS BSC and Monitoring Costs and Monthly PD BSC Cost	As above	Both the above sensitivity analyses combined	Both the above sensitivity analyses combined	£35,491	£34,387	£40,599
Cost of 2nd Line	£6,800	£4,080	£9,520	£35,491	£35,680	£35,301

Cost of a pack of Erlotinib	£1,394.96	-	£1,631.53	£35,491	-	£40,939
Cost of Terminal Care	£2,588.25	£1,552.95	£3,623.55	£35,491	£35,491	£35,490
Clinical Practice/Patient Assumptions						
Time in PFS on treatment	Based upon SATURN time to complete treatment cessation data	85% of time in PFS	100% of time in PFS on treatment	£35,491	£34,830	£40,437
Proportion of patients receiving 2nd Line	73%	28%	100%	£35,491	£35,317	£35,782
Proportion of packs dispensed that are 150 mg / 100mg	100% 150 mg	90% 150 mg 10% 100 mg	-	£35,491	£34,885	-
Model Parameters						
Time Horizon	15 years	10 years	-	£35,491	£35,500	-
Health Discount rate	3.5%	0%	6%	£35,491	£33,711	£36,733

Costs Discount rate	3.5%	0%	6%	£35,491	£36,207	£35,031
Both Discount rates	3.5%	0%	6%	£35,491	£34,393	£36,258

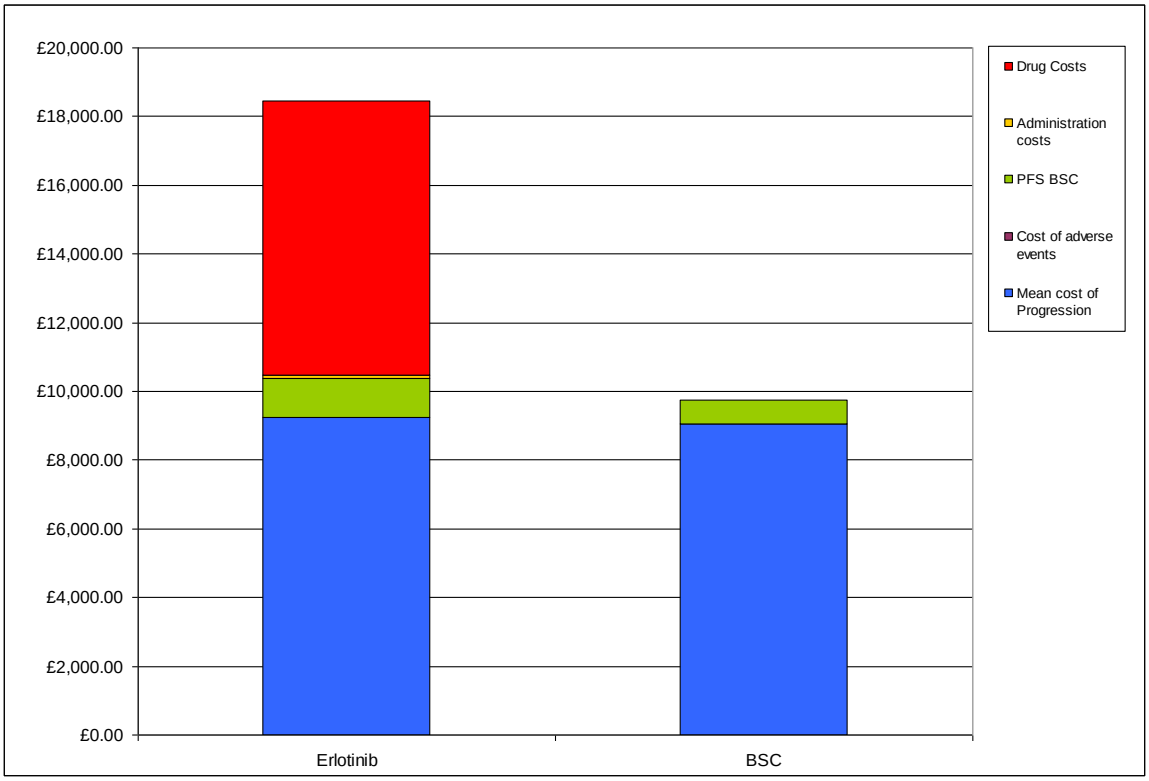
4.3 Erlotinib compared to best supportive care in Non-Squamous histology patients with stable disease as best response induction for whom maintenance with pemetrexed is unsuitable

4.3.1 Costs

Table 21. Non-squamous Stable Disease Costs

Cost Element	Erlotinib	BSC	Incremental (Erlotinib – BSC)
Cost of Erlotinib	£7,975.97	£0.00	£7,975.97
Total Drug Cost	**£7,975.97**	**£0.00**	**£7,975.97**
Cost of Erlotinib Admin	£77.19	£0.00	£77.19
Total Admin Cost	**£77.19**	**£0.00**	**£77.19**
Cost of PFS BSC	£1,143.82	£684.17	£459.65
Cost of PD BSC, 2nd line treatment and EOL	£9,233.10	£9,061.27	£171.83
Adverse events costs	£11.00	£0.00	£11.00
Total 'Other' Costs	**£10,387.92**	**£9,745.44**	**£642.48**
Total Cost	**£18,441.09**	**£9,745.44**	**£8,695.64**

Figure 36. Non-squamous Stable Disease Costs



4.3.2 Health Outcomes

Table 22. Non-squamous Stable Disease Health Outcomes

	Erlotinib	BSC	Incremental (Erlotinib – BSC)
Time in PFS (Years)	0.525	0.314	0.211
Time in PD (Years)	0.999	0.863	0.136
Total time alive (Years)	**1.523**	**1.177**	**0.347 (4.2 months)**
QALYs in PFS	0.353	0.208	0.145
QALYs in PD	0.529	0.457	0.072
Total QALYs	**0.883**	**0.665**	**0.217**

Figure 37. Squamous Histology Stable Disease QALYs

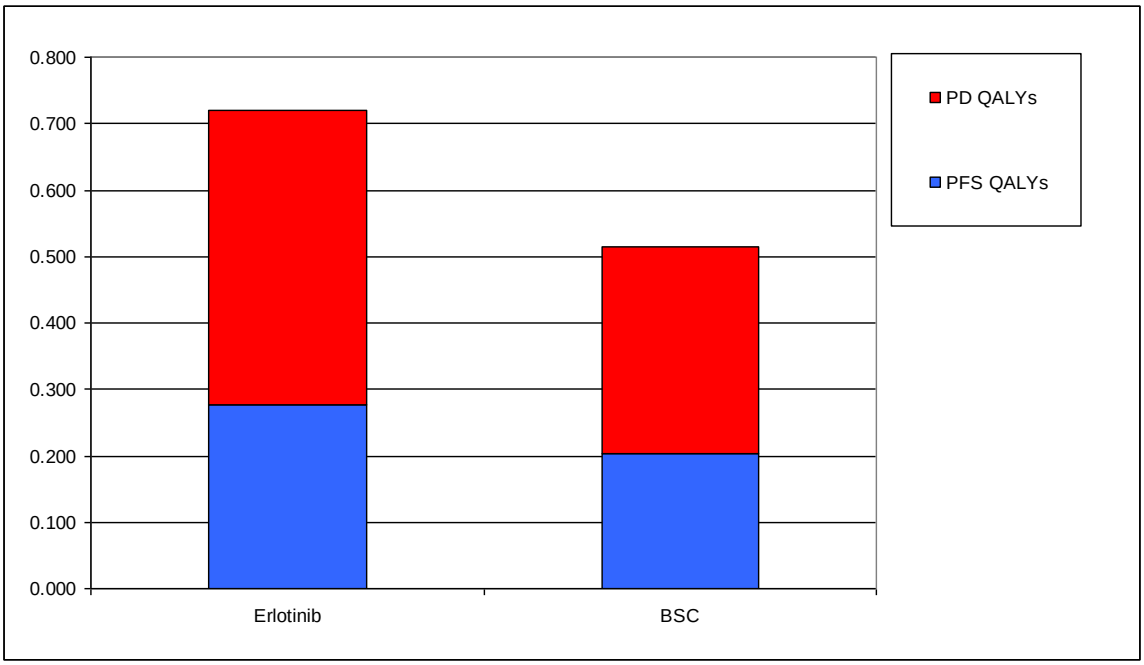
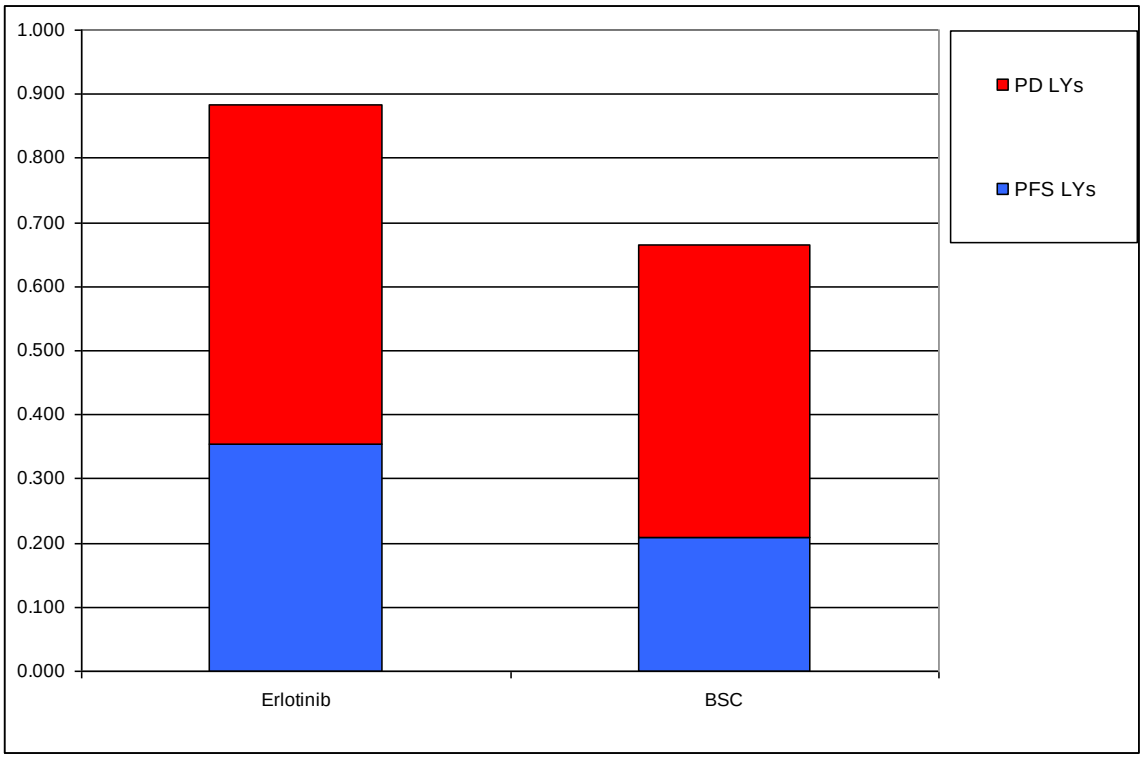


Figure 38. Squamous Histology Stable Disease Life Years



4.3.3 ICERs

Table 23. Squamous Histology Stable Disease cost per QALY gained

Regimen	Cost	QALYs	Cost per QALY gained
Erlotinib	£18,441.09	0.883	£40,020
BSC	£9,745.44	0.665	

Table 24. Squamous Histology Stable Disease cost per life year gained

Regimen	Cost	Lys	Cost per Life Year gained
Erlotinib	£18,441.09	1.523	£25,073
BSC	£9,745.44	1.177	

Figure 39. Squamous Histology Stable Disease Cost Effectiveness Plane

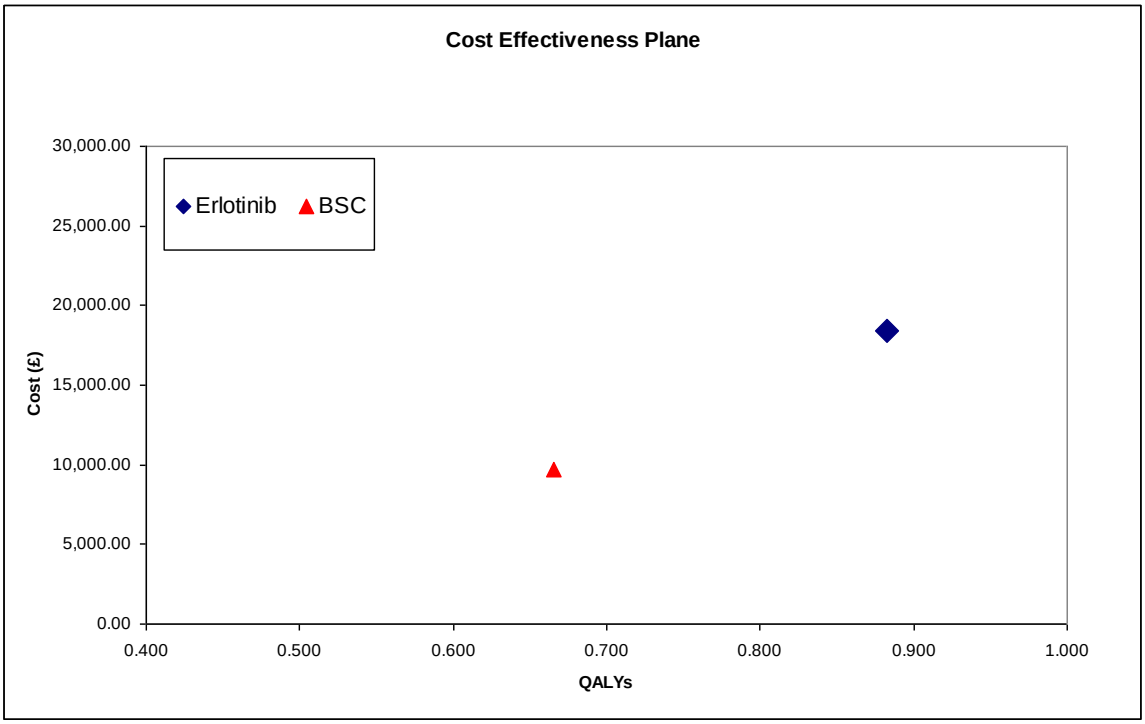
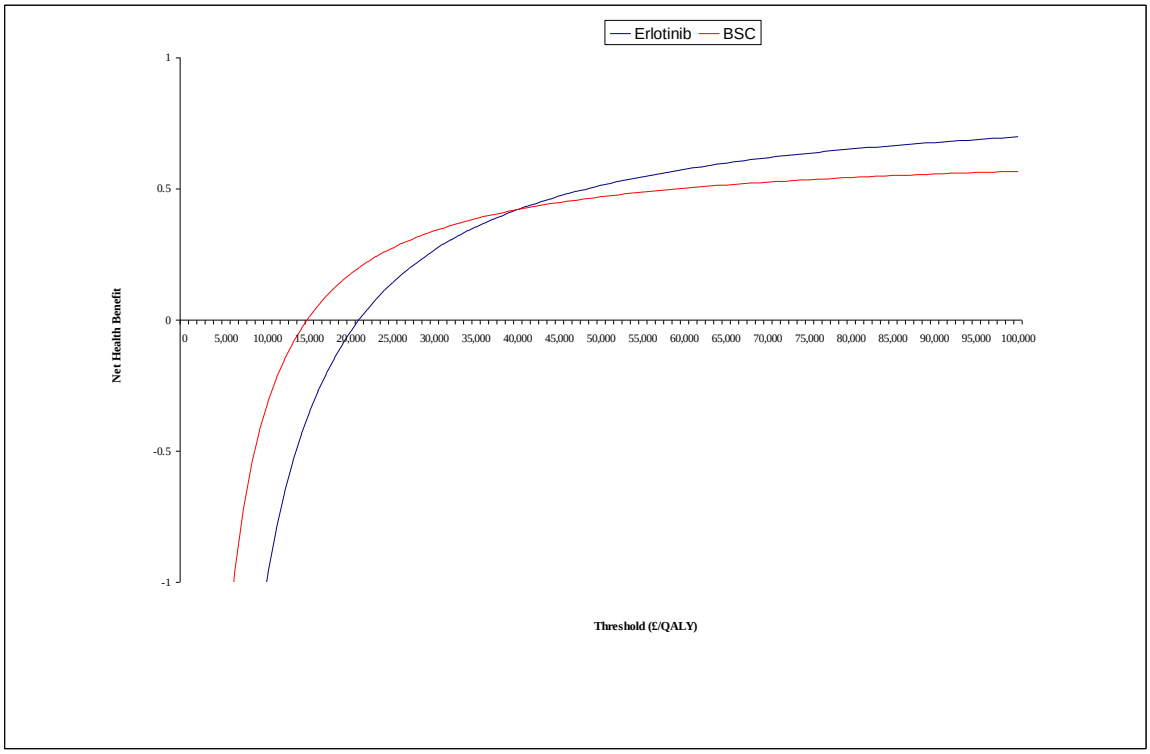


Figure 40. Squamous Histology Stable Disease Net Health Benefit Threshold Analysis



4.3.4 Sensitivity Analysis

Results provided in the table below. The NSQ SDs model sensitivities were found to be the same as those for the whole SD population and the SQ SD population (assumed BSC costs and the use of the ERG's PFS based dosing compared to the more accurate time to complete treatment cessation based dosing).

The use of the ERG's dosing method increased the base-case to £43,865 whilst the use of the TA181 PFS BSC value for the BSC within the model increased the base-case to £44,589.

Table 25. Squamous Histology Stable Disease Deterministic Sensitivity Analysis Results

Parameter Modified	Base Parameter Value	Low Parameter Value	High Parameter Value	Base Case ICER	Low Parameter Value ICER	High Parameter Value ICER
Utilities						
PFS	Erlotinib = 0.6732 BSC = 0.6628	Erlotinib = 0.6059 BSC = 0.5965	Erlotinib = 0.7405 BSC = 0.7291	£40,020	£42,884	£37,515
PD	0.53	0.48	0.58	£40,020	£41,312	£38,807
Both utilities	As above	-	1	£40,020	-	£25,073
Costs						
Monthly PFS BSC and Monitoring Costs	£181.46	£108.88	£411.67	£40,020	£39,173	£42,701
Monthly PD BSC Cost	£160.06	£115.69	£411.67	£40,020	£39,658	£41,909
Both Monthly PFS BSC and Monitoring Costs and Monthly PD BSC Cost	As above	Both the above sensitivity analyses combined	Both the above sensitivity analyses combined	£40,020	£38,840	£44,589
Cost of 2nd Line	£6,800	£4,080	£9,520	£40,020	£40,184	£39, 857
Cost of a pack of Erlotinib	£1,394.96	-	£1,631.53	£40,020	-	£46,246

Cost of Terminal Care	£2,588.25	£1,552.95	£3,623.55	£40,020	£40,021	£40,020
Clinical Practice/Patient Assumptions						
Time in PFS on treatment	Based upon SATURN time to complete treatment cessation data	85% of time in PFS	100% of time in PFS on treatment	£40,020	£37,728	£43,865
Proportion of patients receiving 2nd Line	73%	28%	100%	£40,020	£40,273	£35,317
Proportion of packs dispensed that are 150 mg / 100mg	100% 150 mg	90% 150 mg 10% 100 mg	-	£40,020	£39,329	-
Model Parameters						
Time Horizon	15 years	10 years	-	£40,020	£40,230	-
Health Discount rate	3.5%	0%	6%	£40,020	£36,998	£42,148
Costs Discount rate	3.5%	0%	6%	£40,020	£40,882	£39,488

Both Discount rates	3.5%	0%	6%	£40,020	£37,795	£41,587

4.4 Erlotinib compared to pemetrexed in Non-Squamous Stable Disease Patients for whom treatment with pemetrexed is suitable

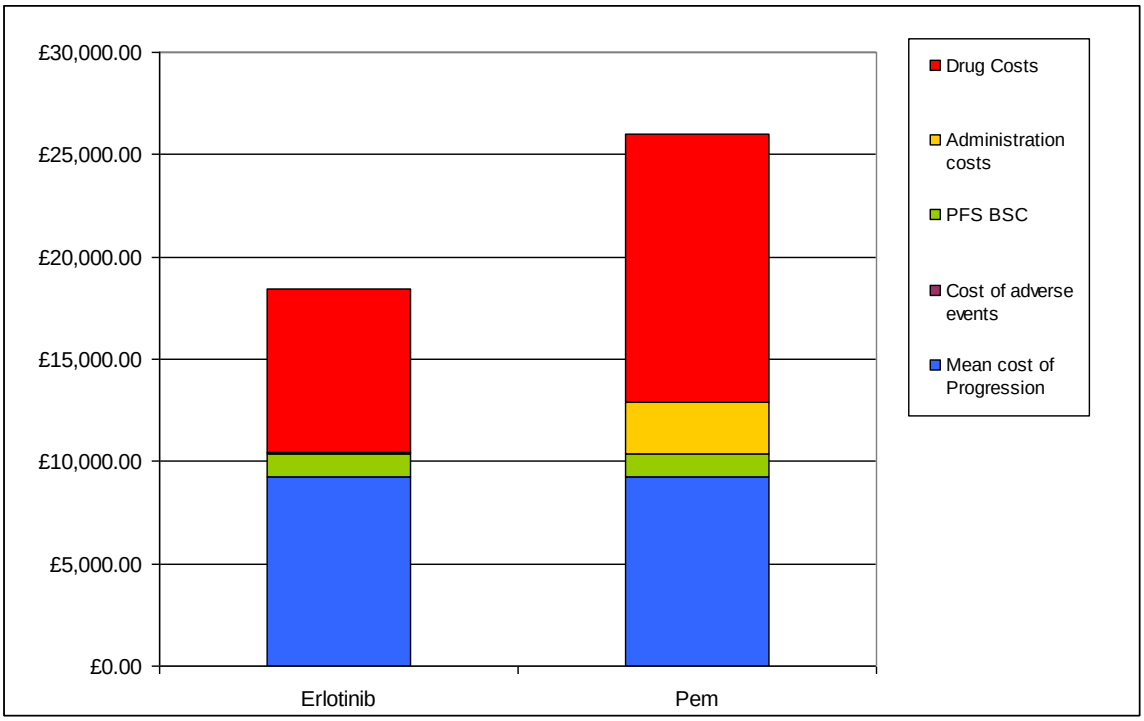
4.4.1. Costs

NOTE: Numbers in blue denote cost savings due to erlotinib

Table 26. Non Squamous Stable Disease (Pemetrexed Suitable) Costs

Cost Element	Erlotinib	Pemetrexed	Incremental (Erlotinib –Pemetrexed)
Cost of Erlotinib	£7,975.97	£0.00	£7,975.97
Cost of Pemetrexed	£0.00	£13,062.17	-£13,062.17
Total Drug Cost	**£7,975.97**	**£13,062.17**	**-£5,086.20**
Cost of Erlotinib Admin	£77.19	£0.00	£77.19
Cost of Pemetrexed Admin	£0.00	£2,508.15	-£2,508.15
Total Admin Cost	**£77.19**	**£2,508.15**	**-£2,430.96**
Cost of PFS BSC	£1,143.82	£1,143.82	£0.00
Cost of PD BSC, 2nd line treatment and EOL	£9,233.10	£9,233.10	£0.00
Adverse events costs	£11.00	£24.64	-£13.64
Total 'Other' Costs	**£10,387.92**	**£10,401.56**	**-£13.64**
Total Cost	**£18,441.09**	**£25,971.89**	**-£7,530.80**

Figure 41. Non-Squamous Stable Disease (Pemetrexed suitable) Costs



4.4.2 Health Outcomes – Scenario 1

Table 27. Squamous Stable Disease (Pemetrexed Unsuitable) Health Outcomes

	Erlotinib	**BSC**	**Incremental (Erlotinib – BSC)**
Time in PFS (Years)	0.525	0.525	0.000
Time in PD (Years)	0.999	0.999	0.000
Total time alive (Years)	**1.523**	**1.523**	**0.000**
QALYs in PFS	0.353	0.352	0.001
QALYs in PD	0.529	0.529	0.000
Total QALYs	**0.883**	**0.881**	**0.001**

Figure 42. Non-Squamous Stable Disease (Pemetrexed suitable) QALYs

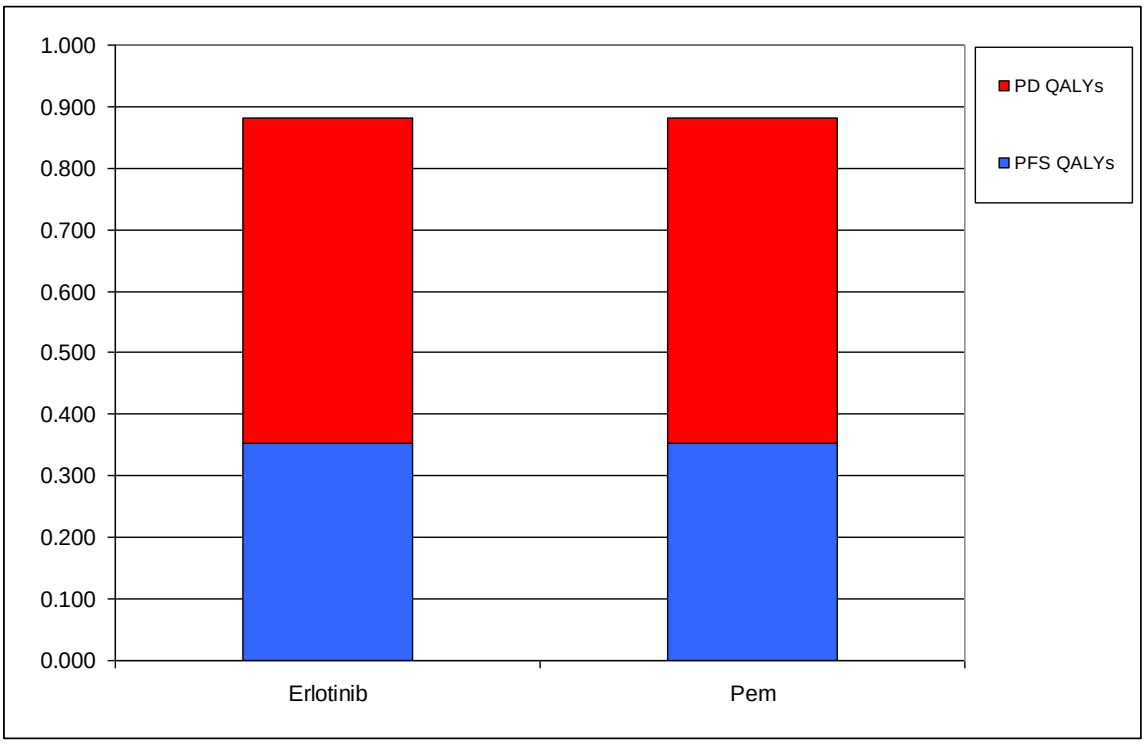
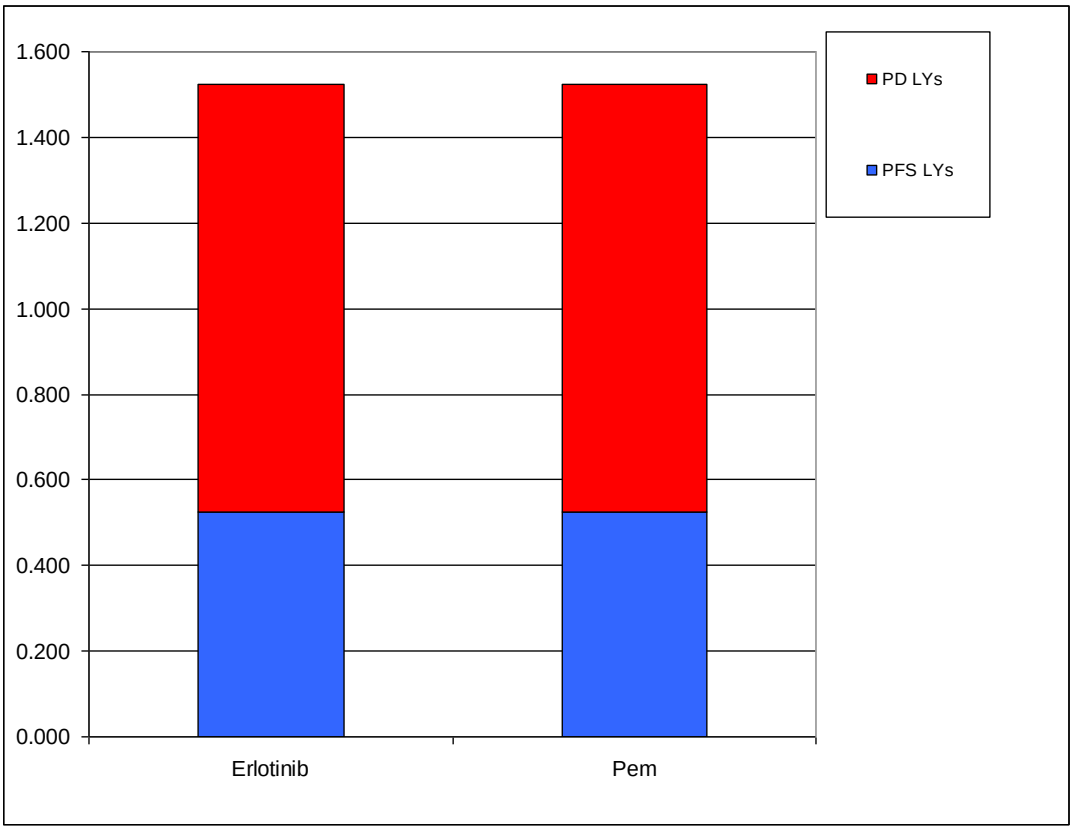


Figure 43. Non-Squamous Stable Disease (Pemetrexed suitable) Life Years



4.4.3 ICERs – Scenario 1

Table 28. Non-Squamous stable disease (Pemetrexed unsuitable) cost per QALY gained

Regimen	Cost	QALYs	Cost per QALY gained
Erlotinib	£18,441.09	0.883	Erlotinib Dominates Pemetrexed
BSC	£25,971.89	0.881	

Table 29. Squamous stable disease cost (pemetrexed unsuitable) per LY gained

Regimen	Cost	LYs	Cost per Life Year gained
Erlotinib	£18,441.09	1.523	Erlotinib Dominates Pemetrexed
BSC	£25,971.89	1.523	

Figure 44. Stable Disease Non-Squamous (Pemetrexed Suitable) Cost Effectiveness Plane

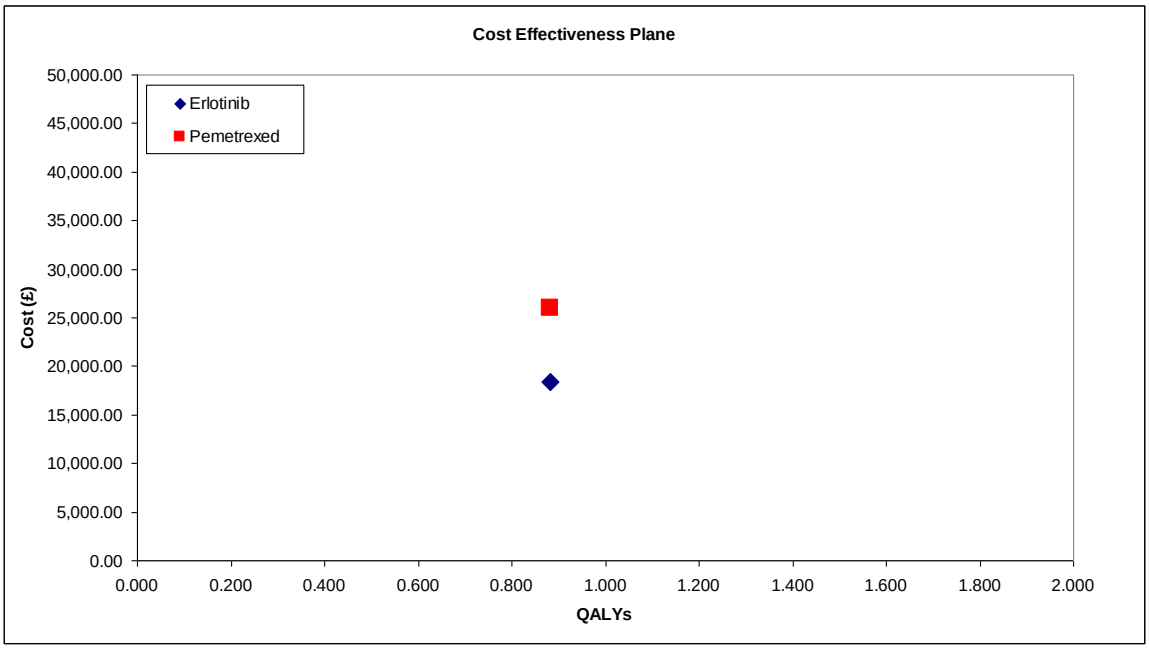
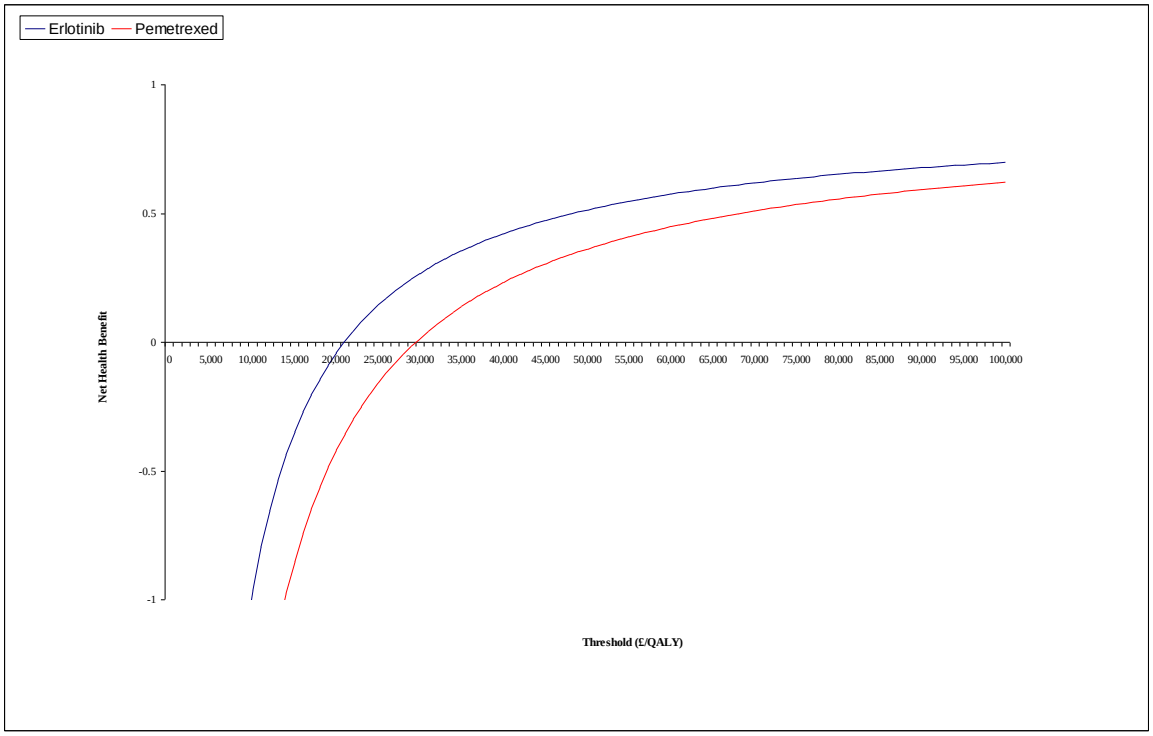


Figure 45. Stable Disease Non-Squamous (Pemetrexed Suitable) NHB Threshold Analysis



4.4.4 Sensitivity Analysis

As there is clearly uncertainty surrounding the relative efficacy of erlotinib and pemetrexed in NSQ SD patients. This uncertainty was addressed through the use of various possible HRs of the relative efficacy of the two treatment options.

The results of this analysis are provided below:

Figure 46. Pemetrexed vs Erlotinib relative efficacy scenario analyses undertaken

PFS \ OS	0.9	1.0	1.1
0.9	£105,959*	£511,351*	Erlotinib Dominates
1.0	£91,789*	Erlotinib Dominates	Erlotinib Dominates
1.1	£77,598*	Erlotinib Dominates	Erlotinib Dominates

* Note: The starred ICERs in this table are those when erlotinib is in the south west corner of an incremental cot-effectiveness plane (i.e. it is significantly cheaper but marginally less effective) and so whilst they look high these values actually demonstrate that erlotinib is extremely cost effective compared to pemetrexed. In effect the ICERs demonstrate that if this relative efficacy scenarios displayed above were true switching a patient who would have received pemetrexed to erlotinib may produce less QALYs for that patient (in those cases in which erlotinib is not dominating pemetrexed) but would come at a significant cost saving. The £511,351 ICER for example demonstrates that if this scenario were true for every QALY lost by switching to erlotinib the NHS would save over £500,000. If this cost-saving were re-invested in more efficient technologies elsewhere in the NHS (such as erlotinib in SQ SD patients) it is clear that the net health impact of a wholesale switch to erlotinib could be significantly positive.

The above analyses demonstrate conclusively that erlotinib is cost-effective compared to pemetrexed no matter which of the plausible efficacy scenarios conducted. The model provided is fully adjustable so that the ERG may implement a range of other PFS and OS HRs as they see fit.

5. Conclusions

5.1 Pemetrexed Unsuitable Patients (i.e. the stable disease group not split by histology)

The base-case ICER of erlotinib compared to best supportive care in those patients unsuitable for pemetrexed (either due to histology or due to pemetrexed based induction) is £39,936. This equates to a cost per life year gained of £24,029 with a 3.9 month expected life extension in a patient population with a typical prognosis of around 12 months. In total there are around 4,000 patients eligible to receive erlotinib in England and Wales each year (including the 1LM, 2L and metastatic pancreatic licenses) (see the attached ACD response for further detail).

This ICER is robust to sensitivity analysis across a wide range of plausible parameter variations with the most sensitive parameters being the assumed cost of BSC, the proportion of a patients time in PFS they are actually on dose and the PFS utility values used. At no point did the base-case ICER exceed £50,000 per QALY with the only analysis pushing the base-case above £45,000 being the removal of the erlotinib PAS (clearly not subject to uncertainty and only incorporated into sensitivity analysis to determine the impact of the PAS upon the cost-effectiveness estimates produced) .

Clearly this revised base case ICER is significantly lower than that originally submitting to NICE and that arrived at by the ERG through the erroneous utilisation of the extremely expensive terminal phase cost associated with progression on 2nd line for the whole period post-first-line maintenance progression. The revised analysis more accurately portrays the true cost to the NHS of the significant life-extension provided by erlotinib and is therefore the analysis that should form the cornerstone of any guidance decision made.

If granted consideration under NICE's supplementary end of life guidance erlotinib appears to be cost-effective in this group.

5.2 Patients with squamous histology with stable disease as best response to induction

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

This ICER was robust to sensitivity analysis with the use of the TA181 PFS BSC values for the BSC in the model increasing the base case to just over £40,000 per QALY gained.

5.3 Patients with non-squamous histology with stable disease as best response to induction for whom maintenance with pemetrexed is unsuitable

The base case ICER of erlotinib compared to best supportive care in patients with non-squamous histology and stable disease as best response following induction is £40,020. This ICER is robust to sensitivity analysis with the use of the TA181 PFS BSC values for the BSC in the model increasing the base-case ICER to just under £45,000 per QALY gained.

5.4 Patients with non-squamous histology with stable disease as best response to induction for whom maintenance with pemetrexed is suitable

The NSQ SD analysis demonstrates conclusively that despite the uncertainty surrounding the relative efficacy of pemetrexed compared to erlotinib in this specific population erlotinib is cost effective compared to pemetrexed (NICE approved in TA190).

The total cost of pemetrexed maintenance is around double the cost of erlotinib maintenance. Base-case results varied from erlotinib being more effective and less costly than pemetrexed to pemetrexed being more effective and more costly than erlotinib.

In the scenarios in which erlotinib was assumed to be equally as effective as pemetrexed and more efficacious than pemetrexed erlotinib dominated pemetrexed.

In the scenarios in which it was assumed pemetrexed was more effective than erlotinib the base-case ICERs ranged from £91,789 to £511,351. Whilst these ICER suggest that erlotinib is not cost-effective compared to pemetrexed it is important to note that these ICERs in fact denote that erlotinib is cost-effective compared to pemetrexed as the ICERs are generated in scenarios in which erlotinib is effectively in the south-west quadrant of a cost-effectiveness plane (i.e. erlotinib is less costly and less effective).

The £511,351 ICER for example demonstrates that if this scenario were true for every QALY lost by switching to erlotinib the NHS would save over £500,000. If this cost-saving were re-invested in more efficient technologies elsewhere in the NHS (such as erlotinib in SQ SD patients) it is clear that the net health impact of a wholesale switch to erlotinib could be significantly positive.

Irrespective of erlotinib's applicability to NICE supplementary EOL criteria erlotinib is cost-effective compared to pemetrexed in this group and should be made available as a treatment option within the NHS.

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Appendix 1

Characteristics of the SD patient population in the SATURN study

A summary of the distribution between treatment arms of the main clinical and molecular characteristic in the SD population that may have prognostic or predictive value is given in Table 1.1 and Table 1.2. In addition, a summary of the geographical distribution according to treatment arm in this subgroup is given in Table 1.3. The data show that the clinical, molecular and geographical characteristics were well balanced between the placebo and erlotinib arm in patients with SD as best response to first-line chemotherapy. In particular, the two arms were well balanced with respect to known prognostic factors of gender, age, race, stage, mutations status, and histology.

Table 1.1 Summ of clinical characteristics in patients with SD as best response to first-line chemotherapy

		Placebo N = 235	**Erlotinib N = 252**
Gender	Female	63 (27%)	62 (25%)
	Male	172 (73%)	190 (75%)
Age	Median	58.0	61.0
	Min-Max	30 – 81	33 - 82
Race	Oriental	35 (15%)	34 (13%)
	Non-Oriental	200 (85%)	218 (87%)
ECOG PS at Baseline	0	77 (33%)	70 (28%)
	1	158 (67%)	182 (72%)
Smoking Status	Current	125 (53%)	132 (52%)
	Past	62 (26%)	73 (29%)
	Never	48 (20%)	47 (19%)
Histology	Adenocarcinoma	112 (48%)	123 (49%)
	Squamous	93 (40%)	97 (38%)
	Large Cell	13 (6%)	6 (2%)
	Other	17 (7%)	26 (10%)
Stage	IV	182 (77%)	182 (72%)
	IIIB	53 (23%)	70 (28%)

Table 1.2 Summary of biomarker analysis in patients with SD as best response to first-line chemotherapy

		Placebo N = 235	Erlotinib N = 252
Tumor Site	Metastasis	57 (24%)	57 (23%)
	Primary Tumor	178 (76%)	195 (77%)
EGFR IHC	Positive	164 (70%)	182 (72%)
	Negative	34 (14%)	36 (14%)
	Indet/Missing	37 (16%)	34 (14%)
EGFR FISH	Positive	54 (23%)	68 (27%)
	Negative	71 (30%)	84 (33%)
	Indet/Missing	110 (47%)	100 (39%)
EGFR Mutation Status	Activating Mutations	15 (6%)	15 (6%)
	Wild-Type	103 (44%)	114 (45%)
	Other/Indet/Missing	117 (50%)	123 (49%)
KRAS Mutation Status	Mutations	19 (8%)	30 (12%)
	Wild-Type	109 (46%)	118 (47%)
	Indet/Missing	106 (45%)	104 (41%)
EGFR Polymorphism	High	104 (45%)	104 (42%)
	Low	105 (45%)	115 (46%)
	Indet/Missing	22 (9%)	29 (12%)

Table 1.3 Summary of geographical distribution in patients with SD as best response to first-line chemotherapy

	Placebo N = 235	Erlotinib N = 252
Africa	4 (2%)	6 (2%)
Eastern Europe	115 (49%)	119 (47%)
North America	12 (5%)	12 (5%)
South East Asia	50 (21%)	54 (21%)
Western Europe	54 (23%)	61 (24%)

Use of previous radiotherapy, time to start of investigational treatment and use of further lines of systemic therapies were also analyzed by treatment arm. The data are summarized in Table , Table , and Table 30 respectively. Factors are well balanced between the placebo and erlotinib arm.

Table 1.4 Summary of previous radiotherapy for NSCLC – response to previous chemotherapy SD

	Placebo N=235	Erlotinib N=252
Radiotherapy	9 (4%)	11 (4%)
Radiotherapy to Bone	15 (6%)	4 (2%)
Radiotherapy to Brain	2 (<1%)	9 (4%)
Radiotherapy to Lung	1 (<1%)	5 (2%)
Radiotherapy to Lymph nodes	1 (<1%)	1 (<1%)
Gamma Radiation Therapy	1 (<1%)	-
Total number of treatments*	29 (12.3%)	30 (12.0%)

*Multiple occurances of the same treatment in one individual counted only once.

Table 1.5 Summary of time between last chemotherapy and start of trial treatment – response to previous chemotherapy SD

	Placebo N=235	Erlotinib N=252
Time Between CT and TT (days)		
Mean	25.5	25.1
SD	7.99	7.45
SEM	0.52	0.47
Median	24.0	24.0
Min-Max	8-60	4-49
n	234	250

Table 30 Summary of 2nd and subsequent systemic treatments in patients with SD as best response to first-line chemotherapy

	Placebo N = 235	Erlotinib N = 252
All Therapies (excluding surgical and medical procedures)	148 (63%)	153 (61%)
Docetaxel**	67 (29%)	72 (29%)
Pemetrexed**	49 (21%)	45 (18%)
Vinorelbine**	20 (9%)	17 (7%)
Erlotinib**	35 (15%)	18 (7%)
Gefitinib**	13 (6%)	6 (2%)

* Patients receiving at least one subsequent therapy

** Patients may have received more than one subsequent therapy

In conclusion, no imbalances were found between treatment arms when clinical, molecular, geographical, prior radiotherapy, subsequent systemic treatments and time to start of investigational treatment parameters were analyzed. Furthermore, the distribution of these parameters in the two treatment arms is in line with that observed in the ITT population. This demonstrates that the efficacy observed in the SD population is not driven by imbalances in potential prognostic and predictive factors or by qualitative and quantitative differences in previous and subsequent treatments between the placebo and erlotinib arm, and thus represents a robust subgroup.