NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Erlotinib for the first line treatment of EGFR-TK mutation positive non-small-cell lung cancer

STA Submission

10th October 2011

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Abbreviations

AE	Adverse Event
BSC	Best Supportive Care
CEAC	Cost Effectiveness Acceptability Curve
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
CR	Complete Response
CRUK	Cancer Research UK
CSR	Clinical Study Report
EGFR	Epidermal Growth Factor Receptor
EGFR M+	Epidermal Growth Factor Receptor mutation positive
EMYY	Embase
EMA	European Medicines Agency
FAS	Full Analysis Set
HR	Hazard Ratio
ICER	Incremental Cost Effectiveness Ratio
ITT	Intention to Treat
KM	Kaplan-Meier
LRiG	Liverpool Reviews and Implementation Group
LYG	Life Years Gained
MEIP	Medline in Process
mNSCLC	Metastatic Non-Small Cell Lung Cancer
OS	Overall Survival
PAS	Patient Access Scheme
PD	Progressed Disease
PFS	Progression Free Survival
PR	Partial Response
PSA	Probabilistic Sensitivity Analysis
PSS	Personal Social Services
QALY	Quality Adjusted Life Year
RCT	Randomised Controlled Trial
RR	Response Rate
SD	Stable Disease
SMC	Scottish Medicines Consortium
TA	Technology Appraisal
TKI	Tyrosine Kinase Inhibitor

Executive summary

Erlotinib

Erlotinib (Tarceva) is an oral tyrosine kinase inhibitor (TKI) of the human epidermal growth factor receptor (EGFR, HER1).

Erlotinib is available in three tablet sizes (150 mg, 100 mg and 25 mg) and three pack variants (30 x 150 mg tablets, 30 x 100 mg tablets and 30 x 25 mg tablets). With the 14.5% discount on the list price of erlotinib agreed in NICE TA162 (erlotinib for the second line treatment of mNSCLC) the effective net price of erlotinib to the NHS will be £1,394.96 for a pack 150 mg tablets, £1,132.16 for a pack of 100 mg tablets and £323.47 and for a pack of 25 mg tablets. Whilst a new patient access scheme (PAS) has been proposed in support of this appraisal it has not yet received ministerial ratification and so is not included within this submission.

Erlotinib is typically given at a dose of 150 mg (one tablet) per day until disease progression although ‘down-dosing’ and cessation prior to disease progression are possible if a clinician deems it appropriate.

In erlotinib’s clinical development programme, it was noted that certain patients appeared to be ‘super-responsive’ to treatment. These patients were later identified as being those whose tumours harboured an activating mutation of EGFR (EGFR M+). It was therefore hypothesised that the efficacy of erlotinib should be assessed according to whether or not a patient’s tumour was EGFR M+ or EGFR wild-type (EGFR WT).

In response to this hypothesis erlotinib was studied as a second line treatment in EGFR WT patients (the TITAN study). This RCT demonstrated that, even in the absence of an EGFR mutation, erlotinib is of equivalent efficacy to docetaxel and pemetrexed monotherapy in the second line treatment of

mNSCLC (the assumption underlying NICE TA162 (the NICE appraisal of erlotinib as a second line treatment for mNSCLC)).

Following the observation that EGFR M+ patients appeared to be extremely responsive to erlotinib it was hypothesised that erlotinib monotherapy may be more effective than doublet chemotherapy in the first line treatment of EGFR M+ mNSCLC.

In order to assess this hypothesis two RCTs were conducted (the European 'EURTAC' study and the Chinese 'OPTIMAL' study). Both these studies met their primary endpoints and demonstrated convincingly the superiority of erlotinib to doublet chemotherapy in this patient population (OPTIMAL progression free survival (PFS) HR = 0.16 {0.10, 0.26}, EURTAC PFS HR = 0.37 {0.25, 0.54}).

In light of these results the EMA granted erlotinib a marketing authorisation for use in the 'first-line treatment of patients with locally advanced or metastatic non-small cell lung cancer with EGFR activating mutations' (EGFR M+ mNSCLC) in September 2011. This is the indication upon which this submission is based.

Current Practice

mNSCLC is an extremely poor prognosis condition with historical median survival of somewhere in the region of 10-11 months (Schiller et al 2002, Scagliotti et al 2002). Whilst traditionally first line treatment of mNSCLC has been based on the broad use of doublet cytotoxic chemotherapy, as understanding of the disease has evolved a range of 'personalised medicines' are now in development, or available in clinical practice. These treatments are designed to target specific genetic abnormalities driving a patients tumour (such as activating EGFR mutations and ALK translocations etc) in an attempt to improve efficacy of treatment whilst reducing the toxicity associated with untargeted treatment.

Around 10% of all UK mNSCLC patients have tumours harbouring an activating EGFR mutations. It is estimated that around 400 patients with EGFR M+ NSCLC per annum will be eligible for erlotinib as first line therapy.

Following NICE TA192 (gefitinib for the first line treatment of EGFR M+ mNSCLC) it is now standard practice to assess a patient's EGFR mutation status prior to commencing first line treatment for mNSCLC. If a patient is found to be EGFR M+, gefitinib (an oral EGFR TKI) is given as first line treatment (with the potential to use docetaxel or pemetrexed/cisplatin second line). If a patient does not have activating EGFR mutations, platinum doublet chemotherapy is typically given (with the potential to give erlotinib or docetaxel second line).

Gefitinib was NICE approved in TA192 under the condition that the manufacturer of gefitinib agreed to provide the NHS with a patient access scheme (PAS). This complex PAS consists of a fixed payment of £12,200 paid upon the dispensing of a patients third pack of gefitinib (day 60 of their treatment). If a patient experiences disease progression prior to this third pack the NHS is not charged for the gefitinib received. If a patient has not experienced disease progression at day 60 the £12,200 fixed payment is made. For those patients not progressed at day 60 (around 95% in the IPASS RCT) the NHS must assess a patient every 30 days, and confirm to the manufacturer of gefitinib that a patient has not experienced disease progression so that a new pack of gefitinib may be authorised for use. This PAS was submitted to NICE prior to introduction of PASLU.

The erlotinib scheme proposed is a simple discount. Unlike the gefitinib PAS, it requires no active registration (limiting the NHS administrative burden and financial risk due to potential PAS compliance issues) and no patient tracking.

Roche propose that, if found to be sufficiently clinically and cost-effective, erlotinib should being recommended as an option for the first line treatment of

EGFR M+ mNSCLC patients (i.e. erlotinib will be available as an option in the current positioning of gefitinib).

The efficacy of erlotinib in EGFR M+ mNSCLC

Phase II studies with erlotinib in EGFR M+ NSCLC demonstrated consistently high response rates (around 70-80%) and relatively long median progression free survival (around 14 months) compared to what had been achieved in unselected patients with standard platinum doublet chemotherapy (Rosell et al 2009, Janne et al 2010, De Greve et al 2011).

The excellent clinical outcomes with erlotinib in EGFR M+ NSCLC from the phase II studies has been affirmed by two phase III erlotinib RCTs.

EURTAC is a phase III RCT designed to compare the efficacy and safety of erlotinib to standard platinum doublet chemotherapy regimens as first line treatment of Caucasian NSCLC patients with activating EGFR mutations. EURTAC met its primary endpoint by demonstrating a highly statistically significant and clinically meaningful improvement in investigator assessed PFS, more than halving the risk of progression for patients on erlotinib compared to those receiving standard platinum doublet chemotherapy (HR 0.42; 95% CI, 0.27-0.64; $p < 0.0001$). The updated analysis of PFS confirmed the results observed at the primary analysis where the median PFS for patients in the erlotinib arm increased to 9.7 months from 9.4 months at the primary analysis and the risk of having a PFS event for erlotinib-treated patients was reduced from 42% (HR 0.42; 95% CI: 0.27; 0.64) to 37% (HR 0.37; 95% CI: 0.25; 0.54; $p < 0.0001$). Patients on erlotinib were thus two thirds less likely to have a progression event compared to those receiving standard platinum doublet chemotherapy.

Patients on erlotinib were nearly 4 times more likely to have a response to treatment compared to those receiving platinum doublet chemotherapy. The response rate was significantly greater in the erlotinib arm than in the platinum

doublet chemotherapy arm (58.1% [95% CIs: 47.0% to 68.7%] and 14.9% [95% CIs: 8.2% to 24.2%], respectively $p < 0.0001$) at the updated analysis.

EURTAC is currently the only phase III RCT to demonstrate the superiority of an EGFR TKI to platinum doublet chemotherapy as first line treatment of Caucasian NSCLC patients with activating EGFR mutations.

OPTIMAL is another phase III RCT comparing the efficacy and safety of erlotinib to standard platinum doublet chemotherapy as first line treatment of NSCLC patients with activating EGFR mutations.

OPTIMAL met its primary endpoint by demonstrating a highly statistically significant and clinically important improvement in PFS when Chinese patients with NSCLC having activating EGFR mutations were treated with 1st line erlotinib compared to platinum doublet chemotherapy. Patients on erlotinib were 84% less likely to progress compared to those receiving platinum doublet chemotherapy (HR 0.164, 95% CI 0.105-0.256, log-rank p-value < 0.0001) compared with the gemcitabine + carboplatin arm).The median PFS was three times greater in the erlotinib arm (13.7 months) compared to the platinum doublet chemotherapy arm (4.6 months).

Patients on erlotinib were more than twice as likely to respond to treatment with erlotinib compared to those receiving platinum doublet chemotherapy. The response rate was significantly greater in the erlotinib arm than in the gemcitabine + carboplatin arm (82.9% *vs* 36.1% respectively, $p < 0.0001$) and the disease control rate was also significantly greater in the erlotinib arm than in the gemcitabine + carboplatin arm (96.3% *vs* 81.9% respectively, $p = 0.0022$).

First line erlotinib treatment also produced significantly greater clinically relevant improvements in patient QoL compared to standard platinum doublet chemotherapy in patients with NSCLC having activating EGFR mutations. More than double the number of patients receiving erlotinib had clinically

relevant improvements in QoL compared to those receiving platinum double chemotherapy (~70% vs ~30% respectively) across all FACT-L scales measured.

Overall, the safety profile of erlotinib in EURTAC and OPTIMAL as first line treatment of patients with NSCLC having activating EGFR mutations was consistent with previously collected data for erlotinib in its earlier indications in the first-line maintenance and relapsed NSCLC settings. Low grade skin toxicities and diarrhoea were amongst the most commonly reported AEs in patients that received erlotinib. Haematological toxicities were infrequent with erlotinib and no grade 3/4 haematological toxicities were reported for erlotinib in EURTAC (except for 1.3% reporting of anaemia) and OPTIMAL. Overall the tolerability profile for erlotinib was significantly more acceptable than that of platinum doublet chemotherapy.

Relative effectiveness

Whilst both EURTAC and OPTIMAL compared erlotinib to doublet chemotherapy current UK clinical practice is to treat EGFR M+ patients with gefitinib (unlicensed at the point the EURTAC and OPTIMAL studies were initiated). Therefore an indirect comparison is required in order to assess the relative effectiveness of erlotinib and gefitinib. Two systematic reviews were undertaken with the objective of identifying randomised evidence on the efficacy of erlotinib or gefitinib in EGFR M+ patients that could be used for this purpose.

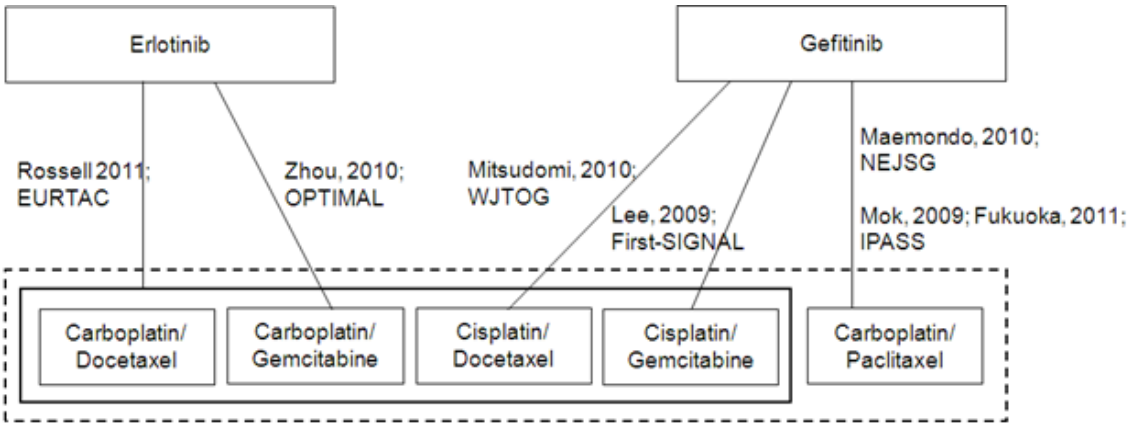
This search identified four RCTs featuring gefitinib comparing gefitinib to ‘doublet chemotherapy’ (IPASS, First-SIGNAL, WJTOG3405, NEJGSG002) in addition to the two erlotinib RCTs detailed above (EURTAC and OPTIMAL).

In EURTAC four different chemotherapy combinations (generally acknowledged as being of equivalent efficacy (Schiller et al 2002, Scagliotti et al 2002) featured in the comparator arm (carboplatin-docetaxel, carboplatin-

gemcitabine, cisplatin-docetaxel, and cisplatin-gemcitabine). In the OPTIMAL and the First-SIGNAL study, doublet chemotherapy consisted of carboplatin-gemcitabine. In the WJTOG3405 study cisplatin-docetaxel was the comparator and in NEJGSG002 and IPASS the comparator was carboplatin-paclitaxel. All of the gefitinib studies were conducted in an East Asian population. No randomized evidence on the efficacy of gefitinib in a Caucasian EGFR M+ population was identified.

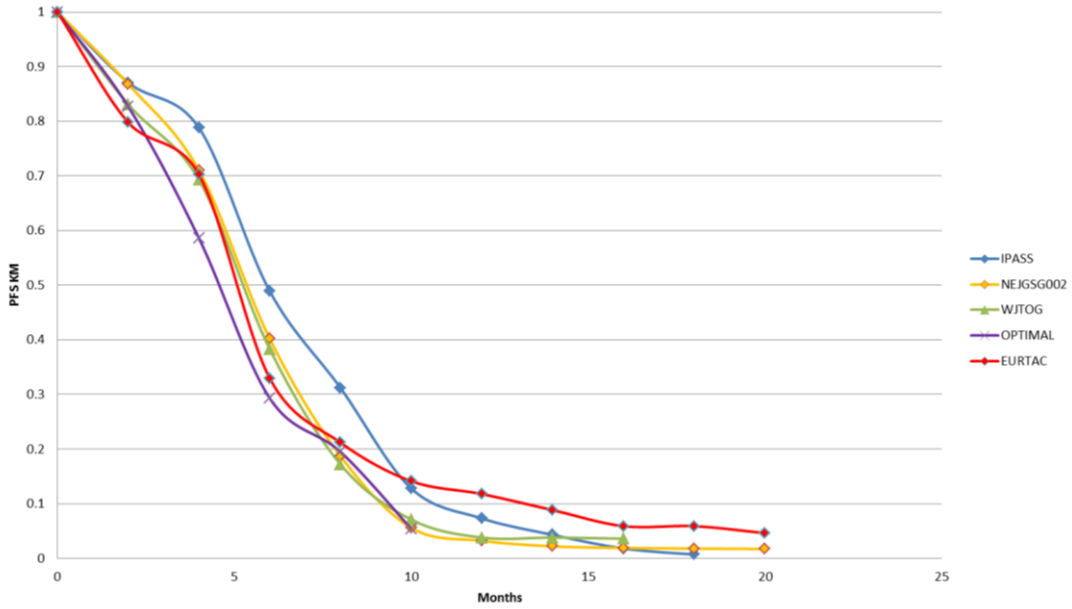
In NICE TA192 (gefitinib for the first line treatment of EGFR M+ mNSCLC) the ERG (LRiG) suggested that it would be reasonable to pool the four gefitinib studies under the assumption that their 'doublet chemotherapy' comparator arms were of equivalent efficacy (an analysis that has recently been conducted by Ku *et al* 2011). If this assumption is extended to the comparator arms of EURTAC and OPTIMAL then these six studies can (if suitably homogeneous) be linked using 'doublet chemotherapy' as an anchor point for the network (see Figure 1 below).

Figure 1: Evidence Network Identified



The assumption that the doublet chemotherapies are of equivalent efficacy appears to be supported by a naïve comparison of the reference arms of the studies identified (see Figure 2 below).

Figure 2: Comparison of RCT 'doublet chemotherapy' PFS curves



The PFS results of the two erlotinib studies and the pooled results of the gefitinib studies identified (Ku et al 2011) are summarised in below:

Table 1: PFS HRs for EURTAC, OPTIMAL and Ku et al

Study	PFS HR
EURTAC	0.37 {0.25, 0.54}
OPTIMAL	0.16 {0.10, 0.26}
Ku et al (IPASS, First-SIGNAL, WJTOG3405, NEJGSG002)	0.45 {0.38, 0.55}

The feasibility of conducting a formal meta-analysis of the two erlotinib studies was assessed and considered inappropriate due to the heterogeneity observed between the PFS treatment effects estimated in the two studies (Chi^2 p-value = 0.007, I^2 value = 86%). Whilst both studies were positive the PFS treatment effect observed in each appears to be somewhat heterogeneous.

In order to understand the cause of this heterogeneity the EURTAC and OPTIMAL studies were assessed using the PICO criteria. This exercise identified that the key differentiators between EURTAC and OPTIMAL appear to be the ethnicity of patients recruited (Caucasian in the case of EURTAC and East Asian in the case of OPTIMAL) and the level of compliance observed in the two studies (1.2% discontinuation rate in OPTIMAL compared to 13.1% in EURTAC).

In light of this it was felt that any indirect comparison of EURTAC (Caucasian patients) and the four gefitinib RCTs (which featured solely East Asian patients) should be treated with caution as if ethnicity is a treatment effect modifier for erlotinib (with East Asian patients experiencing more impressive treatment effects than Caucasian patients) then it may also be an effect modifier for gefitinib.

An indirect comparison of erlotinib and gefitinib in a Caucasian population is therefore inherently limited by the fact that gefitinib has never been studied in a Caucasian EGFR M+ population.

The only indirect comparison of erlotinib and gefitinib that can be robustly conducted is one in an Asian population comparing OPTIMAL to IPASS/First-SIGNAL/WJTOG3405/NEJGSG002. These are the only RCTs in which the patients included in each study (and centres involved) are sufficiently similar

to allow robust estimation of the relative efficacy of erlotinib and gefitinib in any population (so similar that the OPTIMAL study was largely conducted in centres that had previously participated in the IPASS RCT).

However, the current decision problem requires that the relative effectiveness of erlotinib and gefitinib in an English/Welsh population be assessed.

There are four potential quantitative indirect comparisons that could conducted to inform this comparison given the data available and the recommendation of LRiG in TA192 that IPASS/First SIGNAL/WJTOG3405/NEJGSG002 be pooled (as conducted by Ku et al).

Whilst none of these four comparisons answer the precise question at hand (and are likely biased due to heterogeneity between studies) they are nevertheless the best available evidence upon which to assess the relative effectiveness of erlotinib and gefitinib in a European population.

The results of these analyses are presented below:

1. If OPTIMAL is compared to Ku et al (i.e. a comparison of erlotinib and gefitinib in patients of similar ethnicity) the indirect PFS HR of erlotinib vs gefitinib is **0.36 {0.22, 0.59}.**

2. If the fixed effects pooled estimate of EURTAC/OPTIMAL is compared to Ku et al the PFS HR is **0.58 {0.41, 0.81}.**

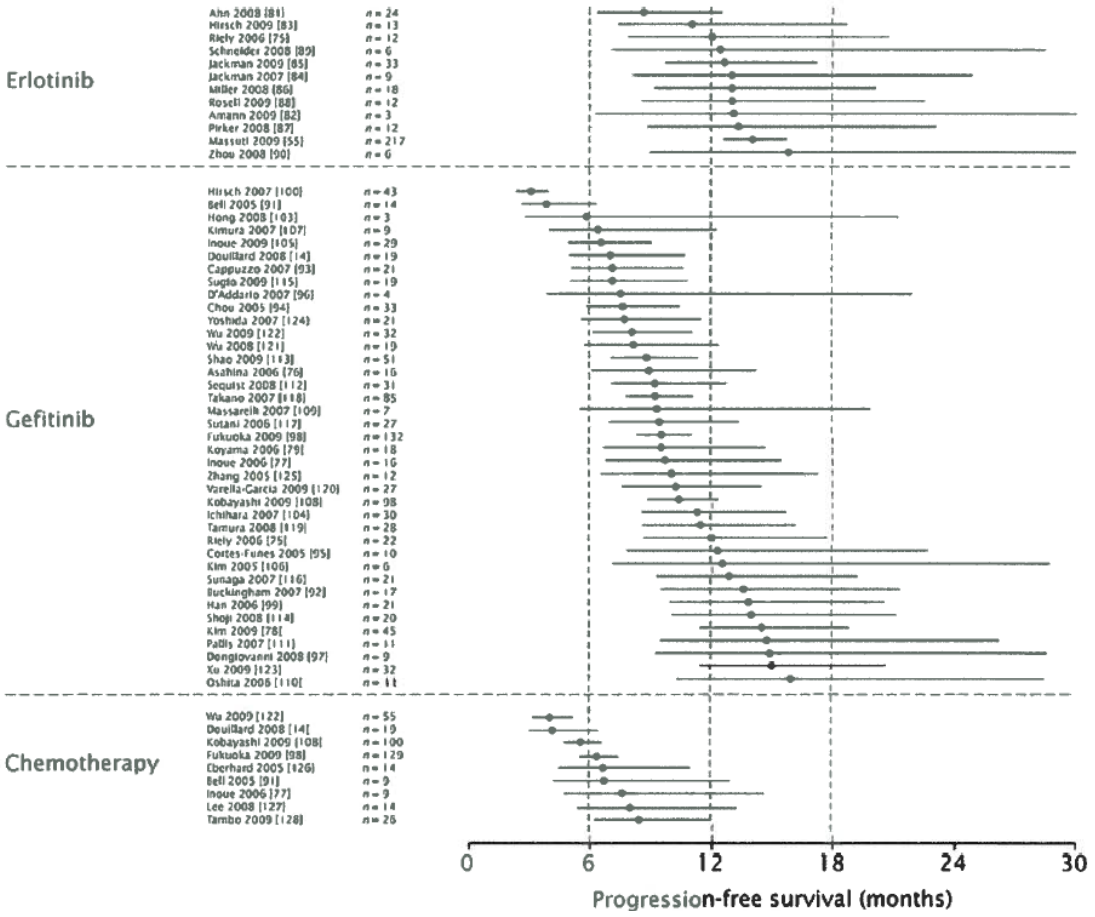
3. If the random effects pooled estimate of EURTAC/OPTIMAL is compared to Ku et al the PFS HR is **0.56 {0.24, 1.28}.**

4. The indirect PFS HR of erlotinib vs gefitinib based upon the comparison of EURTAC and Ku et al is **0.82 {0.54, 1.26}.**

Irrespective of which of the four indirect comparison approaches is undertaken erlotinib is superior (or has a trend to superiority) compared to gefitinib. This

finding is consistent with the pooled analysis of gefitinib and erlotinib observational data conducted by Paz-Ares et al 2010 in which the outcomes of 1,434 gefitinib and erlotinib EGFR M+ patients were compared. This analysis demonstrated a trend for superiority of erlotinib (albeit with the caveat that this was a pooling of observational data and may be subject to cross-trial differences). Figure 3 below demonstrates the results of the Paz-Ares pooling.

Figure 3: Paz-Ares Pooled PFS Analysis Results



In light of the above it was considered that whilst an unbiased quantitative indirect comparison of erlotinib and gefitinib could not be conducted in a Caucasian population, it may be possible to utilise the four quantitative scenarios above in an economic model if appropriate consideration is given to the bias associated with each analysis.

In order to remain as conservative as possible in the base-case economic analysis a comparison of EURTAC and Ku et al was used. If it is true that Asian patients experience larger treatment effects when treated with an EGFR TKI than Europeans (as suggested in NICE TA227 (erlotinib for the maintenance treatment of mNSCLC) and indicated by the more impressive results in OPTIMAL than EURTAC) this analysis will be biased against erlotinib (as this approach compares erlotinib's European data to gefitinib's Asian data).

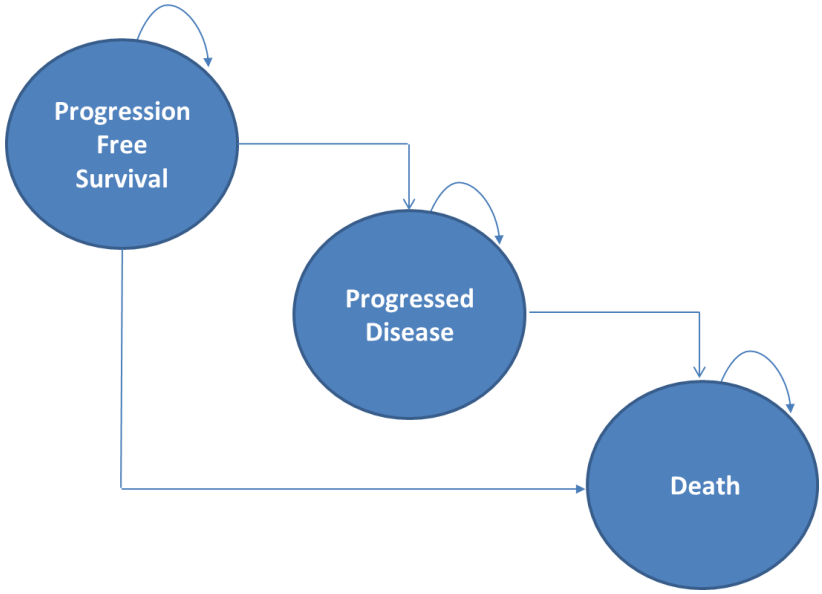
The use of the alternative quantitative indirect comparison approaches was tested in sensitivity analysis.

Cost-effectiveness

A 3 state semi-markov model (Progression Free Survival, Progressed Disease and Death) was developed in Microsoft Excel utilising the latest available data-cut of the EURTAC RCT (26/01/1986). As the EURTAC RCT was conducted in Western Europe it was assumed that it, rather than the Chinese OPTIMAL study formed the most appropriate basis for developing an economic model relevant to the current decision problem.

The model employed an NHS PSS perspective, non-differential discounting at 3.5% per annum, had a one month cycle length and featured a half-cycle correction where appropriate. A time horizon of 10 years was used in the base-case.

Figure 4: Model Structure



The utilities, PFS BSC costs, PD BSC costs, terminal care costs, pharmacy costs and AE costs used within the model were taken from recent NICE appraisals of mNSCLC technologies (NICE TA227, TA192, TA190, TA181).

The model used as much of the EURTAC PFS data as could be relied upon prior to transitioning to an extrapolated 'tail'. Liverpool Review and Implementation Group's (LRiG's) preferred approach to oncology survival curve fitting was followed throughout all modelling undertaken (i.e. an assessment of the requirement for extrapolation, an examination the relevant cumulative hazard plots, an assessment of the stability and consistency of the hazards observed and, if appropriate, extrapolation based upon the stabilised hazard trend) (NICE TA226, NICE TA227, STA on the use of Eribulin for the treatment of metastatic breast cancer (ongoing)). The indirect PFS HR for erlotinib vs gefitinib described above was applied to this erlotinib PFS baseline in order to simulate a gefitinib PFS curve under the assumption of proportional hazards between the two agents.

The monthly probability of dying in PFS if treated with erlotinib was derived from EURTAC and applied a monthly basis within the model. As there is no reason to believe the rate of death in PFS if treated with gefitinib is any

different to that if treated with erlotinib, it was assumed that this rate would apply in each arm of the model (i.e. the erlotinib rate would apply for gefitinib).

The proportion of patients experiencing disease progression in each month was defined as the residual of the above two transitions.

The monthly probability of dying in PD if treated with erlotinib first line was derived from EURTAC and applied to the proportion of patients in the PD state in a given month. As the use of erlotinib rather than gefitinib as a first line agent will have no impact upon the second line treatments received by EGFR M+ patients in England/Wales it was assumed that this rate would similarly apply for patients who received gefitinib first-line.

The cost of erlotinib was integrated into the model utilising the EURTAC RCT dosing data and the assumption that a patient would be dispensed a pack of erlotinib every 30 days (every ‘dispensing date’) until they cease treatment for any reason (i.e. disease progression, cessation due to AE etc). When implemented as described in section 6.5.5.1.1. this method incorporates both the cost of erlotinib purchased but not used (i.e. wastage) and the reduced cost associated with ‘down-dosing’ to lower dose (and less costly) doses of erlotinib.

The cost of gefitinib was estimated by applying the indirect PFS HR of erlotinib vs gefitinib detailed above to the proportion of patients in EURTAC who had yet to cease treatment by day 60 of the study (80% In EURTAC, 76% modelled value for gefitinib). This proportion was then multiplied by the £12,200 fixed cost in order to derive the expected cost of gefitinib to the NHS.

Whilst real-world data on the proportion of gefitinib patients for whom the ‘PAS payment’ is required may well be available to the NHS and the manufacturer of gefitinib this information is currently not publically available and so cannot be integrated in the modelling undertaken. This impact of utilising the indirect

gefitinib PFS curve rather than a modification of the EURTAC dosing data was tested in sensitivity analysis.

The results of the base-case analysis are presented below. These results demonstrate that at the current base-case assumptions, current agreed discount on the BNF62 price of erlotinib, and when the considering the gefitinib PAS, erlotinib is unlikely to be considered as being a cost-effective use of NHS resources.

Table 2: Base-case cost-effectiveness results

	Erlotinib	Gefitinib
Technology acquisition cost	[redacted]	£9,300
Other costs	[redacted]	£6,746
Total costs	[redacted]	£16,046
Difference in total costs	[redacted]	
LYG	[redacted]	1.80
LYG difference	[redacted]	
QALYs	[redacted]	1.02
QALY difference	[redacted]	
ICER	£48,961	

LYG, life years gained; QALY(s), quality-adjusted life year(s); ICER, incremental cost-effectiveness ratio

A wide range of sensitivity analyses were conducted in order to assess the impact of plausible variation in parameters subject to uncertainty upon the ICERs estimated.

Particular focus was paid to utilising the alternative indirect PFS HRs of erlotinib vs gefitinib (see below). The use of these alternative indirect comparisons caused the base-case ICER to fallto between £23,952 and £27,362/QALY.

Table 3: Relative efficacy of erlotinib and gefitinib ICERs

Scenario	Description	PFS HR (erlotinib vs gefitinib)	ICER
1	Base-case (EURTAC vs Ku et al)	0.82	£48,961
2	OPTIMAL vs Ku et al	0.36	£23,952
3	Random Effects (RE) pooling (EURTAC/OPTIMAL RE pooling vs Ku et al)	0.56	£26,686
4	Fixed Effects (FE) pooling (EURTAC/OPTIMAL FE pooling vs Ku et al)	0.58	£27,362

In addition the estimation of the proportion of gefitinib patients for whom the fixed PAS payment would be required for via the gefitinib PFS curve (80%) , rather than a modified version of the erlotinib 'time to last dose' curve (76%), was tested.

This analysis resulted in the ICER dropping to around £37,000/QALY.

Table 4: Proportion of patients 'activating' gefitinib PAS ICERs

Scenario	Description	ICER
1	EURTAC erlotinib 'time to last dose' curve 3 month value with indirect PFS HR applied (0.82)	£48,961
2	EURTAC erlotinib PFS curve 3 month value with indirect PFS HR applied (0.82)	£37,152
3	IPASS gefitinib PFS curve 3 month value (95%)	£24,599
4	100% of patients 'activate' the PAS	£18,109

When the comparison of OPTIMAL vs Ku et al was combined with using the indirect gefitinib PFS curve to determine the proportion of gefitinib patients the PAS payment was required for (compared to the use of the indirect 'time to last dose curve' used in the base-case) this ICER fell to £18,291.

A 2,500 simulation PSA was conducted on the base-case model (scatterplot and CEACs presented below).

At a threshold of £20,000/QALY erlotinib would be considered cost-effective in 0% of simulations conducted (with gefitinib cost-effective in 100%).

At a threshold of £25,000/QALY erlotinib would be considered cost-effective in 1.28% of simulations (with gefitinib cost-effective in 98.72%).

At a threshold of £30,000/QALY erlotinib would be considered cost-effective in 10.72% of simulations (with gefitinib cost-effective in 89.28%).

Figure 5: PSA Scatter-plot erlotinib vs gefitinib (red line = £30k/QALY)

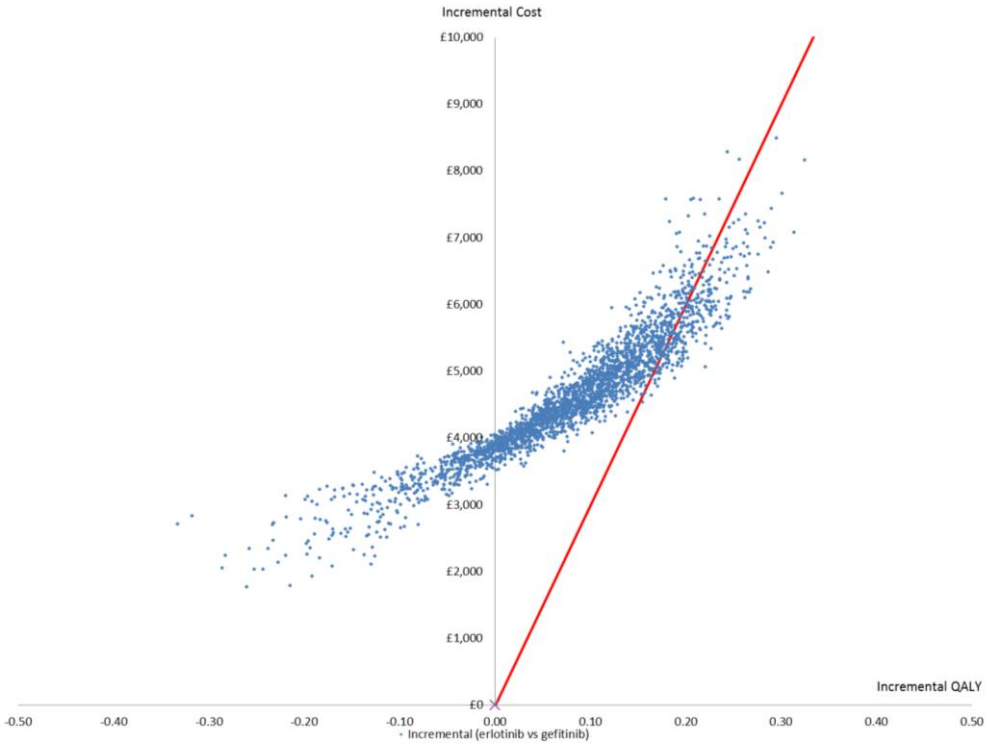
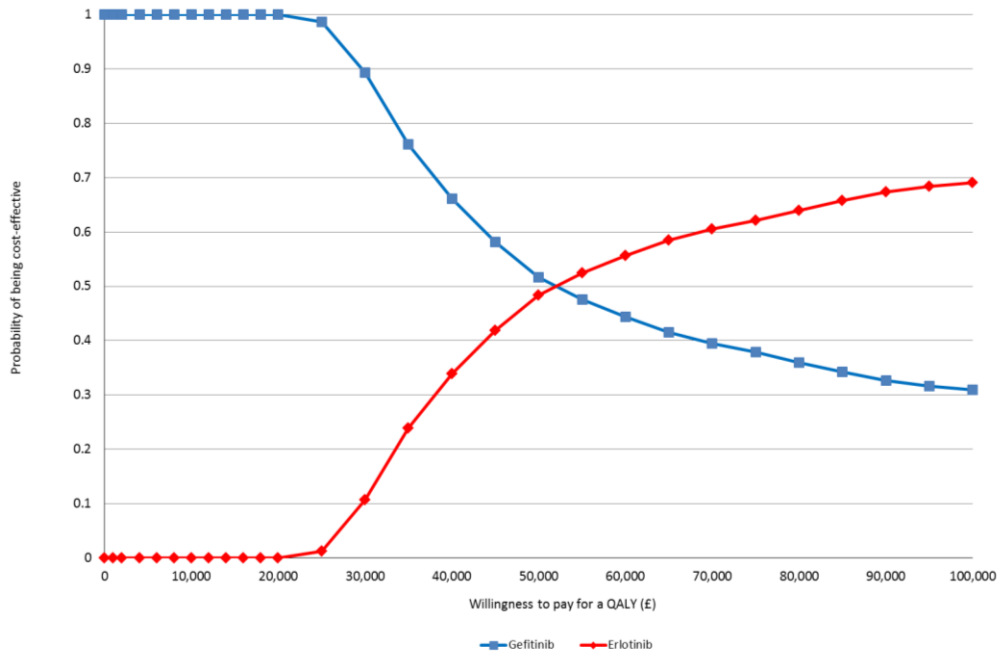


Figure 6: Cost Effectiveness Acceptability Curves



The modeling undertaken indicates that with a discount 14.5% below the BNF62 list price of erlotinib the ICER of erlotinib vs gefitinib is likely to be in the region of £24,000 (the OPTIMAL vs Ku et al analysis) to £ 49,000 (the EURTAC vs Ku et al analysis)

Budget Impact

Table 5 (below) demonstrates the expected budget impact of NICE approval of erlotinib with a 14.5% discount on the BNF62 list price.

Table 5: Budget Impact of approval

Year	2012	2013	2014	2015	2016
Eligible Population	418	420	422	424	426
Erlotinib Market Share	30%	50%	60%	70%	75%
Patients Receiving Erlotinib	125.4	210	253	297	320
Budget Impact	£577,066	£966,585	£1,165,701	£1,366,785	£1,471,734

Section A – Decision problem

Manufacturers and sponsors will be requested to submit section A in advance of the full submission (for details on timelines, see the NICE document 'Guide to the single technology appraisal (STA) process' – www.nice.org.uk). A (draft) summary of product characteristics (SPC) for pharmaceuticals or information for use (IFU) for devices, a (draft) assessment report produced by the regulatory authorities (for example, the European Public Assessment Report (EPAR)), and a (draft) technical manual for devices should be provided (see section 9.1, appendix 1).

1 Description of technology under assessment

1.1 Give the brand name, approved name and, when appropriate, therapeutic class. For devices, provide details of any different versions of the same device.

Brand Name: Tarceva

Approved Name: Erlotinib Hydrochloride

Therapeutic class: Anti-neoplastic; Epidermal Growth Factor Receptor (EGFR; HER1) tyrosine kinase inhibitor (EGFR TKI).

1.2 What is the principal mechanism of action of the technology?

Erlotinib is an orally administered inhibitor of EGFR which is dysregulated in various solid tumours including NSCLC leading to tumourogenesis.

1.3 Does the technology have a UK marketing authorisation/CE marking for the indications detailed in this submission? If so, give the date on which authorisation was received. If not, state current UK regulatory status, with relevant dates (for example, date of application and/or expected approval dates).

The European CHMP adopted a positive opinion on the application for license extension of erlotinib as first line treatment of NSCLC with EGFR activating

mutations in July 2011 and an EU Marketing Authorisation was granted on the 24th August 2011.

1.4 Describe the main issues discussed by the regulatory organisation (preferably by referring to the [draft] assessment report [for example, the EPAR]). If appropriate, state any special conditions attached to the marketing authorisation (for example, exceptional circumstances/conditions to the licence).

The main issues discussed by the CHMP were erlotinib's clinical efficacy and clinical safety in the population of patients with NSCLC having EGFR activating mutations.

The phase III RCT EURTAC provided the main evidence for the Marketing Authorisation application with supporting evidence being provided by an additional two phase III studies, three phase II studies and a pooled analysis. The CHMP considered EURTAC providing a "***highly clinically relevant gain in PFS***" adding that "***the robustness of the result was confirmed in a number of sensitivity analysis and consistent results were found in subgroups with an acceptable sample size***".

Whilst concerns were expressed over the lack of CSRs for some of the supporting studies, the CHMP none the less considered all of the efficacy data as clinically relevant stating that the "***results consistently show median PFS advantages with erlotinib in first line treatment of NSCLC patients with EGFR activating mutations ranging from 12.5 up to 16.4 months. Such results are unprecedented in this patient population***".

Taking the clinical efficacy and safety into consideration the CHMP issued the following statement in respect of the benefit-risk balance for erlotinib:-

"The benefit of erlotinib to patients with activating EGFR mutations in the 1st line setting associated with erlotinib in terms of PFS is considered to be clinically relevant compared to standard chemotherapy regimens and is significant and well documented.

The safety profile of erlotinib is considered acceptable, well-characterized and distinct from the well-known safety profile of standard chemotherapies. The oral administration of erlotinib provides convenience to the patient."

1.5 What are the (anticipated) indication(s) in the UK? For devices, provide the (anticipated) CE marking, including the indication for use.

First-line treatment of patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with EGFR activating mutations

1.6 Please provide details of all completed and ongoing studies from which additional evidence is likely to be available in the next 12 months for the indication being appraised.

EURTAC is a phase III randomised controlled trial comparing erlotinib to platinum-doublet chemotherapy in Caucasian advanced non-small-cell lung cancer (NSCLC) patients with epidermal growth factor receptor (EGFR) activating mutations. EURTAC randomised 174 patients with EGFR activating mutations to receive either erlotinib (150mg o.d) or standard platinum-doublet chemotherapy (q3weeks up to a maximum of 4 cycles). The primary endpoint of EURTAC was to demonstrate superior progression free survival and secondary endpoints included objective response rate, overall survival and safety. Interim analysis was planned when 88 events were observed. The study was formerly stopped at interim analysis when the primary endpoint had been achieved. The most recent analysis of EURTAC demonstrated superior progression free survival in favour of erlotinib compared to platinum-doublet chemotherapy (median PFS 9.7 months vs 5.2 months respectively, HR 0.37 (95% CI 0.25-0.54), $p<0.0001$). Objective response rates were also greater for the patients that received erlotinib (58%) compared to those receiving platinum-doublet chemotherapy (15%). Overall survival data are still immature and is expected to be confounded by the high level of cross-over from the platinum-doublet chemotherapy arm to an EGFR TKI (77% of patients went

on to receive a second or further-line treatment of which 99% received an EGFR TKI). No new safety issues were demonstrated in this group; patients with both treatments exhibiting the toxicity profile expected from their use in clinical practice and erlotinib demonstrating a more acceptable safety profile than standard platinum-doublet chemotherapy.

OPTIMAL is a phase III randomised controlled trial comparing erlotinib to platinum-doublet chemotherapy (gemcitabine/carboplatin) in Chinese advanced NSCLC patients with EGFR activating mutations. OPTIMAL randomised 165 patients with EGFR activating mutations to receive either erlotinib (150mg o.d) or gemcitabine/carboplatin (q3weeks up to a maximum of 4 cycles). The primary endpoint of OPTIMAL was to demonstrate superior progression free survival and secondary endpoints included objective response rate, overall survival, safety and quality of life. The most recent analysis of OPTIMAL demonstrated superior progression free survival in favour of erlotinib compared to gemcitabine/carboplatin (median PFS 13.7 months vs 4.6 months respectively, HR 0.164 (95% CI 0.105-0.256), p<0.0001). Objective response rates were also greater for the patients that received erlotinib (83%) compared to those receiving gemcitabine/carboplatin (36%). Overall survival data are still immature and have not been presented to date, but are expected to be confounded by the high level of cross-over from the gemcitabine/carboplatin arm to an EGFR TKI at disease progression. No new safety issues were identified in this group of patients with both treatments exhibiting the toxicity profile expected from their use in clinical practice and erlotinib demonstrating a more acceptable safety profile than gemcitabine/carboplatin. OPTIMAL also demonstrated that approximately 70% of patients receiving erlotinib gained clinically relevant improvements in quality of life (as measured by the FACT-L questionnaire) compared to only about 30% of patients receiving gemcitabine/carboplatin.

1.7 If the technology has not been launched, please supply the anticipated date of availability in the UK.

Erlotinib was launched in this indication in September 2011 and has been available in the UK since September 2005 since its first launch for the indication of second line mNSCLC.

1.8 Does the technology have regulatory approval outside the UK? If so, please provide details.

At the time of writing, erlotinib has regulatory approval in over 90 countries world-wide as a treatment for relapsed NSCLC. The first approval, in 2004 was in the USA. Other countries include all European Countries governed by the EMEA, the USA, Canada and Australia. Erlotinib is also approved in many countries for the first line-maintenance treatment of NSCLC either in all patients (e.g. USA) or in patients with stable disease following first-line chemotherapy (in European Countries governed by the EMEA). Further details can be supplied if these are required.

For the indication currently under consideration erlotinib received a marketing authorisation on the 24th August 2011 and was subsequently launched in the UK in September 2011.

1.9 Is the technology subject to any other form of health technology assessment in the UK? If so, what is the timescale for completion?

A submission in support of this indication was made to the Scottish Medicines Consortium (SMC) on the 5th September 2011. Advice is scheduled to be issued to NHS Scotland on the 9th December 2011. This advice will be published on the SMC website on the 17th January 2012.

1.10 For pharmaceuticals, please complete the table below. If the unit cost of the pharmaceutical is not yet known, provide details of the anticipated unit cost, including the range of possible unit costs.

Table 6: Unit costs of technology being appraised

Pharmaceutical formulation	Erlotinib (as the hydrochloride salt) is supplied in an oral (tablet) formulation. It is available for purchase in 3 different doses. The packs available are: 30 x 150 mg tablets 30 x 100 mg tablets 30 x 25 mg tablets
Acquisition cost (excluding VAT)	The BNF 62 list price of erlotinib is: 30 x 150 mg = £1,631.53 30 x 100 mg - £1,324.14 30 x 25 mg = £378.33 With this 14.5% discount utilised in this submission the effective NHS net price of erlotinib will be: 30 x 150 mg = £1,394.96 30 x 100 mg = £1,132.14 30 x 25 mg = £323.47
Method of administration	Erlotinib is an oral (tablet) formulation.
Doses	Erlotinib is typically administered at a dose of 150 mg (one 150 mg tablet) per day until disease progression. Dose reductions (typically to 100 mg or 50 mg per day) or cessation prior to progression are also possible if a clinician deems it appropriate.
Dosing frequency	See above
Average length of a course of treatment	This will be evaluated formally in economic modelling. As an approximation, it can be noted that the median PFS in the EURTAC RCT was 9.7 months.
Average cost of a course of treatment	This will be evaluated formally in economic modelling.
Anticipated average interval between courses of treatments	Patients will only receive one course of erlotinib.
Anticipated number of repeat courses of treatments	Patients will only receive one course of erlotinib.
Dose adjustments	As erlotinib is available in three different dosage strengths (150mg, 100mg, 25mg tablets) it thus offers flexible dosing allowing for dose adjustments where necessary.

1.11 For devices, please provide the list price and average selling price. If the unit cost of the device is not yet known, provide details of the anticipated unit cost, including the range of possible unit costs.

Not applicable.

1.12 Are there additional tests or investigations needed for selection, or particular administration requirements for this technology?

For the indication currently under consideration patients need to be routinely tested for the presence of EGFR activating mutations. EGFR mutation testing of chemo-naïve patients has become routine clinical practice in the UK over the last two years.

1.13 Is there a need for monitoring of patients over and above usual clinical practice for this technology?

No.

1.14 What other therapies, if any, are likely to be administered at the same time as the intervention as part of a course of treatment?

None.

2 Context

In this background section the manufacturer or sponsor should contextualise the evidence relating to the decision problem.

2.1 Please provide a brief overview of the disease or condition for which the technology is being used. Include details of the underlying course of the disease.

The public health burden of non-small cell lung cancer (NSCLC)

NSCLC accounts for about 85% (National Lung Cancer Audit, 2009) of the approximately 33,500 new cases of lung cancer which occur each year in England and Wales (CRUK, 2009).

Most cases of lung cancer prove rapidly fatal, with 1 year and 5 year survival rates of around 30% and less than 10%, respectively, so that in 2007 there were 29,660 deaths from the disease in the England and Wales, making it the biggest cause of cancer deaths in the country (CRUK, 2009) and a major public health issue.

Current treatments for NSCLC.

The dismal prognosis for patients with NSCLC is a reflection of the fact that most patients present with advanced disease where the efficacy of current treatments is modest.

According to the most recent UK Lung Cancer Audit data, 67% of lung cancer patients in this country present with tumours which have either spread within the chest (Stage IIIB, locally advanced disease) or to distant organs (Stage 4, metastatic disease) to an extent where cure is not a realistic prospect.

For these patients the treatment of choice – as recommended by NICE in its 2011 guidance on the management of lung cancer- is combination chemotherapy with a platinum-based drug (cisplatin plus carboplatin) plus a second active cytotoxic drug (gemcitabine, paclitaxel, docetaxel, vinorelbine

or pemetrexed) administered with a view to extending survival by a few months whilst palliating the debilitating symptoms of advanced NSCLC (cough, pain and dyspnoea in particular). Platinum-based doublet chemotherapy is aggressive and requires patients to be reasonably fit (NICE recommends it only for patients with a “Performance Status” of 0-1); this rules out almost half of UK patients with stage IIIB/IV disease. Combined with other factors this has historically led to low treatment rates in the UK so that only about 6,250 NSCLC patients in England and Wales receive platinum-based doublet chemotherapy each year.

Of these around half achieve a reduction in their tumour burden or stabilisation of their disease following chemotherapy and may be eligible for further maintenance treatment either with single agent chemotherapy (NICE recommends pemetrexed) or erlotinib.

For those that do not respond or relapse following their first line treatment, second line treatment may be considered (NICE recommends docetaxel and erlotinib as options), but there is a high attrition rate with only about 30% of patients treated with first-line chemotherapy receiving second-line systemic therapy.

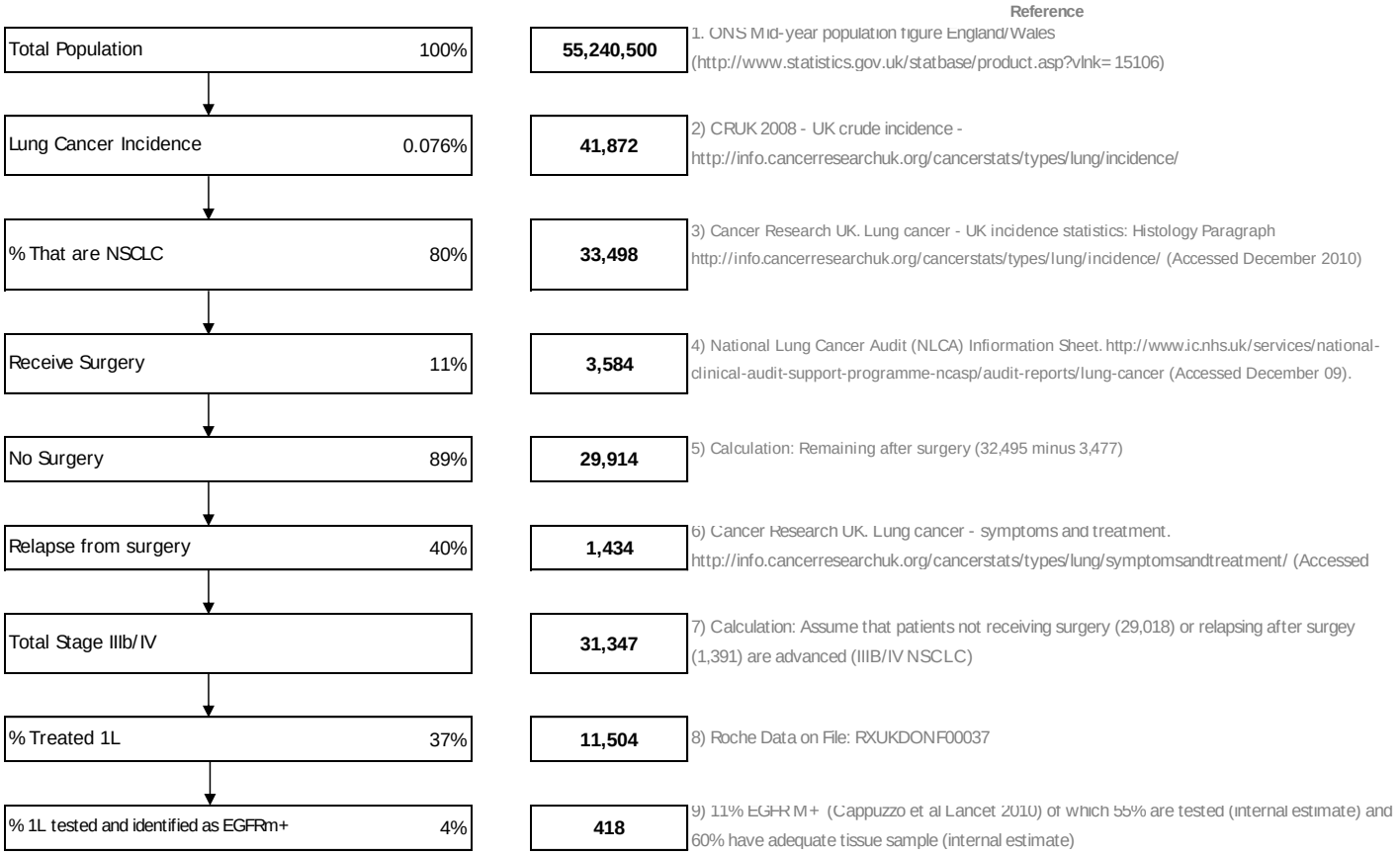
Personalised healthcare in treating NSCLC.

Recent advances in both technology (including access) and new data have led to a more personalised approach to treating chemo-naïve NSCLC patients in turn leading to better clinical outcomes and better quality of life for the patient depending on the therapy they are receiving. EGFR mutation testing has become the standard of care in the UK over the last two years and NICE has recommended gefitinib (an EGFR TKI) for patients that are chemo-naïve and EGFR mutation positive.

2.2 How many patients are assumed to be eligible? How is this figure derived?

It is estimated that around 400 patients a year are eligible for 1st line treatment with erlotinib. The derivation of this figure is shown below.

Figure 7: First line EGFR M+ mNSCLC eligible patient population algorithm



2.3 Please give details of any relevant NICE guidance or protocols for the condition for which the technology is being used. Specify whether any specific subgroups were addressed.

To date there has been only one NICE appraisal of a technology used in the first line treatment of EGFR M+ patients (the STA on the use of gefitinib (TA192).

No subgroups were addressed within the appraisal of gefitinib.

Related Technology Appraisals:

Technology Appraisal No. 227, June 2011, 'Erlotinib monotherapy for the maintenance treatment of non-small-cell lung cancer'. Review date: April 2013.

Technology Appraisal No. 192, July 2010, 'Gefitinib for the first-line treatment of locally advanced or metastatic non-small-cell lung cancer. Review date April 2013.

Technology Appraisal No. 181, September 2009, 'Pemetrexed for the first-line treatment of non-small-cell lung cancer'. Review date mid 2011.

Technology Appraisal No.148, June 2008, 'Bevacizumab for the treatment of non-small-cell lung cancer' (terminated appraisal).

Related Guidelines:

Clinical Guideline No. 121. April 2011, 'The diagnosis and treatment of lung cancer (update of NICE clinical guideline 24)'.

Clinical Guideline No. 24. February 2005, ‘The diagnosis and treatment of lung cancer’. Replaced by CG121.

2.4 Please present the clinical pathway of care that depicts the context of the proposed use of the technology. Explain how the new technology may change the existing pathway. If a relevant NICE clinical guideline has been published, the response to this question should be consistent with the guideline and any differences should be explained.

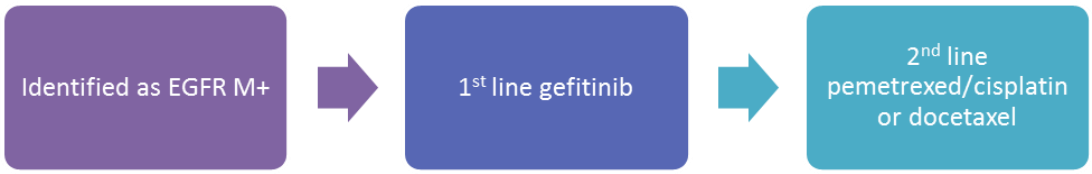
Following NICE TA192, EGFR mutation testing has now become standard clinical practice in England and Wales. For those patients whose tumours are found to harbour an activating EGFR mutation (EGFR M+) an EGFR TKI (such gefitinib or erlotinib) is now utilized as a first line agent in around 95% of all patients (Kantar Health Wave 4, May 2011– with gefitinib accounting for over 90% of all first line EGFR TKI use). In those patients whose tumours are found not to harbour an activating EGFR mutation (i.e. those who are EGFR wild-type (EGFR WT)) or whose tumours cannot be properly assessed for mutation status (perhaps due to lack of tissue for testing) it is standard practice to utilize a pemetrexed/cisplatin chemotherapy doublet (NICE TA181) As the scope of this appraisal is limited to those patients with EGFR M+ tumours this EGFR WT population is not considered within the evaluation undertaken.

Erlotinib provides an alternative first line treatment option to gefitinib for patients with EGFR activating mutations. It is the only EGFR TKI to have demonstrated efficacy in a European mNSCLC population and is the only EGFR TKI that has the ability to be dosed flexibly (with the 150 mg, 100 mg and 25 mg tablet sizes allowing physicians to tailor the dose given to each patient according to the side-effects of EGFR TKI therapy they experience).

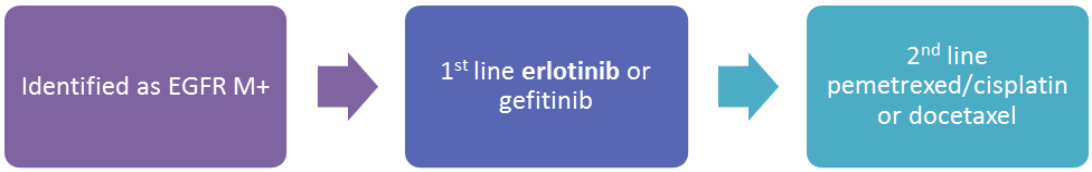
Patients that currently receive first-line gefitinib receive either platinum doublet chemotherapy or docetaxel monotherapy upon progression. NICE approval of erlotinib as an option in the first line treatment of EGFR M+ mNSCLC will

have no impact upon later lines of therapy with erlotinib simply replacing gefitinib in the treatment pathway (where a clinician deems it appropriate for their patient).

Current Treatment Pathway:



Future Treatment Pathway:



2.5 Please describe any issues relating to current clinical practice, including any variations or uncertainty about best practice.

Options for the first-line treatment of patients with EGFR activating mutations, which specifically target this oncogenic abnormality, are limited to only gefitinib which has become the standard of care since NICE issued TA192, highlighting the clinical demand for an EGR TKI for this specific group of patients. Erlotinib would not only provide an additional option for patients with EGFR activating mutations but also provide a treatment that allows the treatment dose to be adjusted according to patients' tolerability therefore allowing continued active treatment of their disease.

2.6 Please identify the main comparator(s) and justify their selection.

Following NICE TA192 gefitinib has become the standard of care in the first line treatment of EGFR M+ mNSCLC patients.

Gefitinib is an oral EGFR tyrosine kinase inhibitor. It was approved by NICE in TA192 under the condition that its manufacturer agreed to provide gefitinib at

a fixed cost of £12,200 upon the dispensing of the third pack of gefitinib to a patient.

Market research (Kantar Health Wave 4, May 2011) indicates that 86% of UK EGFR M+ patients are receiving gefitinib as a first line treatment (despite TA192 being issued less than 12 months prior to this research being conducted) whilst 9% are receiving erlotinib. The remaining 5% of patients not receiving an EGFR TKI first line are currently treated with an assortment of doublet chemotherapies (primarily pemetrexed/cisplatin). This research demonstrates that an EGFR M+ patient is nearly 20 times more likely to receive an EGFR TKI than pemetrexed/cisplatin as a first line treatment for their mNSCLC with the proportion of patients receiving pemetrexed/cisplatin declining rapidly in the year following TA192.

Market research indicates strongly that gefitinib is the appropriate comparator to erlotinib in this setting.

2.7 Please list therapies that may be prescribed to manage adverse reactions associated with the technology being appraised.

Erlotinib produces the side-effects characteristic of an EGFR inhibitor – primarily rash (in 50% of patients) and diarrhoea (in 20% of patients) when used as a maintenance therapy. Clinicians treating lung cancer are now very experienced in managing these side-effects early, utilising appropriate intervention with prophylactic/palliative measures. These are straightforward and low-cost (typically emollient creams, topical or systemic tetracyclines or steroids and loperamide or dose reduction). Both EURTAC and OPTIMAL demonstrated no new safety signals and the safety profile for erlotinib was consistent with that demonstrated in studies where erlotinib is used in later line of treatment for NSCLC.

2.8 Please identify the main resource use to the NHS associated with the technology being appraised. Describe the location of care, staff

usage, administration costs, monitoring and tests. Provide details of data sources used to inform resource estimates and values.

As erlotinib is an oral formulation it is associated with minimal use of NHS resources for supply and administration. Patients are typically dispensed a pack of 30 tablets each month and take one of these tablets a day until their pack is complete (or they cease treatment for some reason).

Following NICE TA192 the testing of mNSCLC patients for EGFR mutation status has become standard clinical practice. There is therefore no incremental cost associated with the requirement for patients to be confirmed as EGFR M+ prior to commencing treatment with erlotinib as a first line agent.

Erlotinib requires no further monitoring beyond that currently undertaken in the NHS for the routine care of patient with inoperable NSCLC undergoing active treatment.

2.9 Does the technology require additional infrastructure to be put in place?

No.

3 Equity and equality

NICE considers equity in terms of how the effects of a health technology may deliver differential benefits across the population. Evidence relevant to equity considerations may also take a variety of forms and come from different sources. These may include general-population-generated utility weightings applied in health economic analyses, societal values elicited through social survey and other methods, research into technology uptake in different population groups, evidence on differential treatment effects in different population groups, and epidemiological evidence on risks or incidence of the condition in different population groups.

3.1 Identification of equity and equalities issues

3.1.1 Please specify any issues relating to equity or equalities in NICE guidance, or protocols for the condition for which the technology is being used.

Not applicable.

3.1.2 Are there any equity or equalities issues anticipated for the appraisal of this technology (consider issues relating to current legislation and any issues identified in the scope for the appraisal)?

Not applicable.

3.1.3 How have the clinical and cost-effectiveness analyses addressed these issues?

Not applicable.

4 Statement of the decision problem

Table 7: Decision problem

	Final scope issued by NICE	Decision problem addressed in the submission	Rationale if different from the scope
Population	Adults with previously untreated EGFR-TK mutation positive locally advanced or metastatic non-small-cell lung cancer	As per scope	N/A
Intervention	Erlotinib	As per scope	N/A
Comparator (s)	• Gefitinib For people with non-squamous non-small cell lung cancer of adenocarcinoma or large cell carcinoma histology: • Pemetrexed in combination with cisplatin or carboplatin	Gefitinib	See section 2.6. Market research indicates that an EGFR TKI (either erlotinib or gefitinib) is currently used in the first line treatment of 95% of UK patients with an EGFR M+ tumour. Only around 5% of patients receive doublet chemotherapy. Whilst pemetrexed/platinum may have been an appropriate comparator to gefitinib in TA192 the sizeable uptake in first line use of an EGFR TKI in the 12 months following the issuance of that guidance indicates that this is no longer the case. A UK patient with an EGFR M+ tumour is nearly 20 times more likely to receive an EGFR TKI than doublet chemotherapy as a first line treatment (with that likelihood increasing rapidly in an extremely short period of time following approval of gefitinib). In addition it should be

			noted that in TA192 it was found that an indirect comparison of 'traditional doublet chemotherapy' and pemetrexed/cisplatin in an EGFR M+ population was not possible due to a lack of data on the efficacy of pemetrexed/cisplatin in this group. In light of this declining relevance of pemetrexed/cisplatin in this group and the difficulty/impossibility in conducting such a comparison (as concluded in TA192) the pemetrexed based doublet chemotherapy regimens detailed in the scope are not addressed as comparators within the submission.
Outcomes	The outcome measures to be considered include: • overall survival • progression-free survival • response rates • adverse effects of treatment • health-related quality of life	As per scope	N/A
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year.	As per scope	Whilst as per scope it should be noted that EGFR mutation testing is currently standard practice in the NHS. There is no additional mutational testing

	The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective. Costs of any additional mutational testing required for this treatment should be considered in the economic analysis.		associated with the first line use of erlotinib and therefore no incremental cost.
Subgroups to be considered	None	As per scope	N/A
Special considerations, including issues related to equity or equality	None	As per scope	N/A

Section B – Clinical and cost effectiveness

When estimating clinical and cost effectiveness, particular emphasis should be given to adhering to the 'reference case' (see the NICE document 'Guide to the methods of technology appraisal' – www.nice.org.uk). Reasons for deviating from the reference case should be clearly explained. Particularly important features of the reference case include those listed in the table below.

Element of health technology assessment	**Reference case**	**Section in 'Guide to the methods of technology appraisal'**
Defining the decision problem	The scope developed by NICE	5.2.5 and 5.2.6
Comparator(s)	Therapies routinely used in the NHS, including technologies regarded as current best practice	5.2.5 and 5.2.6
Perspective costs	NHS and PSS	5.2.7 to 5.2.10
Perspective benefits	All health effects on individuals	5.2.7 to 5.2.10
Type of economic evaluation	Cost-effectiveness analysis	5.2.11 and 5.2.12
Synthesis of evidence on outcomes	Based on a systematic review	5.3
Measure of health effects	QALYs	5.4
Source of data for measurement of HRQL	Reported directly by patients and carers	5.4
Source of preference data for valuation of changes in HRQL	Representative sample of the public	5.4
Discount rate	An annual rate of 3.5% on both costs and health effects	5.6
Equity weighting	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	5.12

HRQL, health-related quality of life; NHS, National Health Service; PSS, Personal Social Services; QALY(s), quality-adjusted life year(s)

5 Clinical evidence

Manufacturers and sponsors are requested to present clinical evidence for their technology in the following sections. This section should be read in conjunction with NICE's 'Guide to the methods of technology appraisal', sections 3 and 5.3.1 to 5.3.8.

5.1 Identification of studies

5.1.1 Describe the strategies used to retrieve relevant clinical data, both from the published literature and from unpublished data that may be held by the manufacturer or sponsor. The methods used should be justified with reference to the decision problem. Sufficient detail should be provided to enable the methods to be reproduced, and the rationale for any inclusion and exclusion criteria used should be provided. Exact details of the search strategy used should be provided in section 9.2, appendix 2.

Medline (MEYY), Embase (EMYY), Medline in Process (MEIP) and the Cochrane Library were searched for randomised evidence on the efficacy of erlotinib in the first line treatment of patients with activating mutations of the EGFR tyrosine kinase. MEYY, EMYY and MEIP were searched using Dialogue DataStar whilst the Cochrane Library was searched via the Cochrane Library website. The search strategies used are provided in section 9.2, appendix 2. In addition to these databases internal experts on the clinical trial program for erlotinib were consulted in order to ensure all relevant studies were identified.

Each database was searched individually for potentially relevant records. The duplicates from these records were then removed and the remaining individual studies' titles/abstracts assessed against the pre-defined inclusion/exclusion criteria by a single reviewer (see section 5.2.1.). Where a record was found to be irrelevant the reason for its exclusion was detailed. Where a record was identified as being potentially relevant based upon the title/abstract it was retrieved in full for an assessment against the inclusion/exclusion criteria.

5.2 Study selection

5.2.1 Describe the inclusion and exclusion selection criteria, language restrictions and the study selection process. A justification should be provided to ensure that the rationale is transparent. A suggested format is provided below.

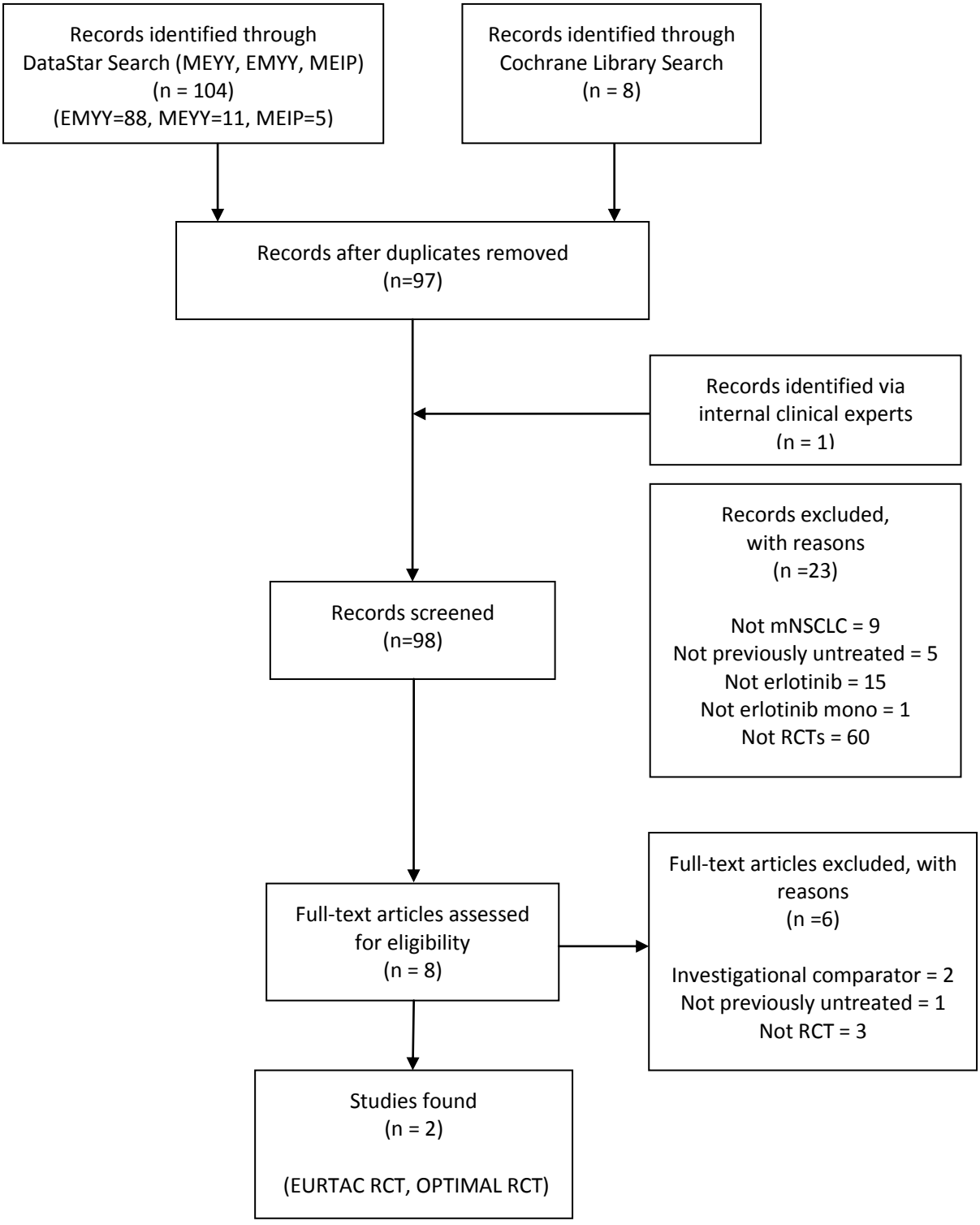
The inclusion/exclusion criteria used are presented below. Both criteria were designed to identify randomized evidence relative to the decision problem.

Table 8: Eligibility criteria used in search strategy

	Inclusion Criteria	Exclusion Criteria
Population	Previously untreated mNSCLC patients whose tumours harbour an activating mutation of the EGFR tyrosine kinase	Early NSCLC patients, SCLC patients, patients previously treated for their mNSCLC (i.e. maintenance treatment, second and later line treatment), patients with tumours that do not contain a mutation of the EGFR tyrosine kinase or have unknown EGFR mutation status non-mNSCLC
Interventions	Erlotinib monotherapy	Erlotinib combination therapy, non-erlotinib therapy
Comparators	Any comparator capable of informing the relative efficacy of erlotinib to gefitinib	Investigational Agents
Outcomes	Progression Free Survival, Overall Survival, Adverse Events	-
Study Design	Randomised controlled trials	Observational data, registry analyses, single arm studies, meta-analyses

5.2.2 A flow diagram of the numbers of studies included and excluded at each stage should be provided using a validated statement for reporting systematic reviews and meta-analyses such as the QUOROM statement flow diagram (www.consort-statement.org/?o=1065).

Figure 8: PRISMA Flow-chart of erlotinib RCT search



5.2.3 When data from a single RCT have been drawn from more than one source (for example, a poster and a published report) and/or when trials

are linked (for example, an open-label extension to an RCT), this should be made clear.

Two RCTs were identified. One based upon a single publication (the OPTIMAL RCT) and one based upon unpublished data identified internally which was not found by the search (the EURTAC RCT).

Complete list of relevant RCTs

5.2.4 Provide details of all RCTs that compare the intervention with other therapies (including placebo) in the relevant patient group. The list must be complete and will be validated by independent searches conducted by the Evidence Review Group. This should be presented in tabular form. A suggested format is presented below.

Using the search strategies outlined in section 5.1.1, two RCTs were identified comparing erlotinib with platinum doublet chemotherapy as first-line treatment of patients with NSCLC having activating EGFR mutations.

- **EURTAC:** Erlotinib vs chemotherapy (CT) in advanced non-small-cell lung cancer (NSCLC) patients (p) with epidermal growth factor receptor (EGFR) activating mutations: Interim results of the European Tarceva® vs Chemotherapy (EURTAC) phase III randomized trial (in Caucasian patients).

- **OPTIMAL:** Erlotinib versus chemotherapy as first-line treatment for patients with advanced EGFR mutation-positive non-small-cell lung cancer (OPTIMAL, CTONG-0802): a multicentre, open-label, randomised, phase 3 study (in East Asian patients)

Table 9: List of relevant RCTs

Trial no. (acronym)	Intervention	Comparator	Population	Primary study ref.
EURTAC	Erlotinib 150mg o.d until PD	Cisplatin 75 mg/m^2 i.v. Day 1 and docetaxel 75 mg/m^2 i.v. Day 1. Repeat cycles every 3 weeks or Cisplatin 75 mg/m^2 i.v. on Day 1 and gemcitabine 1250 mg/m^2 on Days 1 and 8. Repeat cycles every 3 weeks or Docetaxel 75 mg/m^2 Day 1 and carboplatin AUC = 6 Day 1, every 21 days or Gemcitabine 1000 mg/m^2 Days 1 and 8 and carboplatin AUC = 5 Day 1, every 21 days	Caucasian patients with advanced non-small-cell carcinoma of the lung whose tumours have activating mutations in the TK domain of EGFR	Rosell et al 2011 Gervais et al 2011
OPTIMAL	Erlotinib 150mg o.d until PD	Gemcitabine 1000 mg/m^2; Day 1 and Day 8 and carboplatin AUC = 5, Day 1 every 21 days	East Asian patients with advanced non-small-cell carcinoma of the lung whose tumours have activating mutations in the TK domain of EGFR	Zhou et al 2010 Zhou et al. 2011a Zhou et al. 2011b Zhou et al. 2011c

5.2.5 Please highlight which of the RCTs identified above compares the intervention directly with the appropriate comparator(s) with reference to the decision problem. If there are none, please state this.

The regulatory submission which formed the basis of the EMEA's regulatory approval for erlotinib as 1st line treatment for NSCLC in patients with activating EGFR mutations was based primarily on a phase III randomised controlled trial (RCT) conducted in a Caucasian population – EURTAC (Rosell et al.2011, Gervais

et al 2011). Supportive evidence for the efficacy of erlotinib in patients with Activating EGFR mutations was provided through another phase III RCT conducted in Chinese patients – OPTIMAL (Zhou et al 2010, 2011a, 2011b, 2011c) and phase II data in Caucasian patients from the Spanish Lung Cancer Screening study (Rosell et al 2009), CLAGB 3405 study (Janne et al 2010) and the FIELT study (De Greve et al 2011).

EURTAC will form the basis of this submission as it is the only phase III randomised controlled trial to compare an EGFR TKI to standard platinum doublet chemotherapy in a Caucasian population according to EMEA standards. Supportive evidence from the other studies (mainly OPTIMAL) will be provided where appropriate.

5.2.6 When studies identified above have been excluded from further discussion, a justification should be provided to ensure that the rationale for doing so is transparent. For example, when studies have been identified but there is no access to the level of trial data required, this should be indicated.

Not applicable.

List of relevant non-RCTs

5.2.7 Please provide details of any non-RCTs (for example experimental and observational data) that are considered relevant to the decision problem and a justification for their inclusion. Full details should be provided in section 5.8 and key details should be presented in a table; the following is a suggested format.

No relevant non-RCT data has been submitted as part of this application as we have provided evidence from two RCTs. However if the committee would like Roche to submit any further evidence, we would be willing to do so.

5.3 Summary of methodology of relevant RCTs

5.3.1 As a minimum, the summary should include information on the RCT(s) under the subheadings listed in this section. Items 2 to 14 of the CONSORT checklist should be provided, as well as a CONSORT flow diagram of patient numbers (www.consort-statement.org). It is expected that all key aspects of methodology will be in the public domain; if a manufacturer or sponsor wishes to submit aspects of the methodology in confidence, prior agreement must be requested from NICE. When there is more than one RCT, **the information should be tabulated**.

Trial no. (acronym)	**EURTAC**	**OPTIMAL**
Scientific background rationale (2a)	EGFR is important in multiple signal transduction pathways and appears to play a critical role in both tumourigenesis and tumour growth. It appears to play an important role in epithelial malignancies including NSCLC where EGFR expression correlates with aggressive morphology, poor outcome and poor response to treatment. This made it a relevant target for anti-cancer treatments and led to the development of erlotinib, a small-molecule inhibitor of the tyrosine kinase function of EGFR. Erlotinib has been shown to significantly improve survival when used as a first line maintenance treatment and as a second- or third-line treatment for NSCLC (and is widely used in this setting). Earlier clinical trials showed that it had no significant effect on outcomes when used concomitantly with first-line platinum-based chemotherapy in unselected patients. Analysis of the clinical trials with erlotinib and other EGFR antagonists in unselected patients with advanced NSCLC demonstrated striking activity in a subset of patients who were of Asian descent, predominantly female with no (or very limited) smoking history. Seminal research demonstrated that the compelling clinical benefit was related to activating mutations of the EGF receptor. The most significant of these mutations are deletions in exon 19 and a point mutation (L858R) in exon 21. The importance of these EGFR-activating mutations in the management of NSCLC has been confirmed in many studies with EGFR tyrosine kinase inhibitors (TKIs) given as monotherapy. Results from these trials, some in the first-line setting, have consistently shown that EGFR TKIs confer greater progression-free survival (PFS) and response rates benefit compared to chemotherapy in patients harbouring EGFR activating mutations. Erlotinib's oral route of administration and generally favourable toxicity profile make it a good candidate as a first line treatment.	
Study Objectives (2a)	EURTAC was a phase III RCT conducted in Caucasian patients designed to determine whether erlotinib as oral monotherapy improved clinical outcomes in patients with advanced Stage IIIB/IV NSCLC with activating EGFR mutations compared to standard platinum doublet chemotherapy.	The objective of OPTIMAL was to verify the efficacy of erlotinib *vs* gemcitabine + carboplatin (G+C) in the first line treatment of unresectable stage IIIB (T4 effusion) or stage IV NSCLC patients with EGFR mutations.
Study Objectives/Hypothesis (2b)	**Objectives** The primary objective of EURTAC was to compare investigator-assessed PFS in the two treatment arms (standard platinum doublet chemotherapy *vs*. erlotinib) in patients with advanced NSCLC with Activating EGFR mutations who have not received previous systemic anti-tumour therapy for their disease.	**Objectives** The primary objective of OPTIMAL was to compare the efficacy of erlotinib *vs* gemcitabine + carboplatin chemotherapy with respect to PFS. Secondary objectives were to compare the efficacy of erlotinib *vs* gemcitabine + carboplatin chemotherapy with respect to:

	Since cross-over was allowed at disease progression improvement in Overall Survival (OS) within the study was not expected. The secondary objectives included: • Investigator-assessed objective response • Overall survival (including 1- and 2-year survival rates) • Safety profile • Quality of life (lung cancer symptom scale [LCSS]) PFS and overall response was also assessed by independent central review (by an Independent Review Committee – IRC) and served as a sensitivity analysis of EURTACs' primary endpoint of investigator assessed PFS as well as to corroborate response/non-response/progression (complete response, partial response, stable disease or progressive disease) according to Response Evaluation Criteria in Solid Tumours [RECIST] V1.0 criteria) during the study **Hypothesis** A 2-sided log-rank test was used for testing the difference in PFS between the erlotinib and platinum doublet chemotherapy arms. The hypothesis tested was: H_0: "There is no difference in the survival distribution of the parameter PFS between the erlotinib and platinum doublet chemotherapy arms." *vs* H_1: "There is a difference in the survival distribution of the parameter PFS between the erlotinib and platinum doublet chemotherapy arms." A 2-sided log-rank test was used for OS. For the other secondary parameters further tests between the 2 treatment arms were performed. All tests were 2-sided at	• Overall Survival (OS); • Objective Response Rate (ORR); • Time to Progression (TTP); • Duration of Response; • Health Related Quality of Life; • Investigation of biomarkers (in tumour tissues). **Hypothesis** A median PFS of approximately 6 months in the platinum doublet chemotherapy arm (based on historical data) and 11 months in the erlotinib arm (a conservative estimate based on the results from the SLCG Phase II study - Rosell et al.2009) provided a Hazard Ratio of 0.54 for the erlotinib arm *vs* the platinum doublet chemotherapy arm. Using a two-sided log-rank test with an overall alpha level of 5% (alpha-spending for an interim analysis), 103 PFS events were estimated to be required for the present study with a confidence level of 80% to detect a HR of 0.54 in the erlotinib arm versus the chemotherapy arm. Assuming a 12 month accrual period, with a 24-month follow-up for the last patient, the sample size was estimated to be 69 pairs. Taking into consideration a drop-out rate of 10%, a total sample size of 152 patients was required. Note: As no interim analysis was performed for this study, a bilateral α of 0.05 was used for the hypothetic analysis of PFS.

	a 5% significance level.	

Methods

5.3.2 Describe the RCT(s) design (for example, duration, degree and method of blinding, and randomisation) and interventions. Include details of length of follow-up and timing of assessments. The following tables provide a suggested format for when there is more than one RCT.

Table 10: Comparative summary of methodology of the RCTs

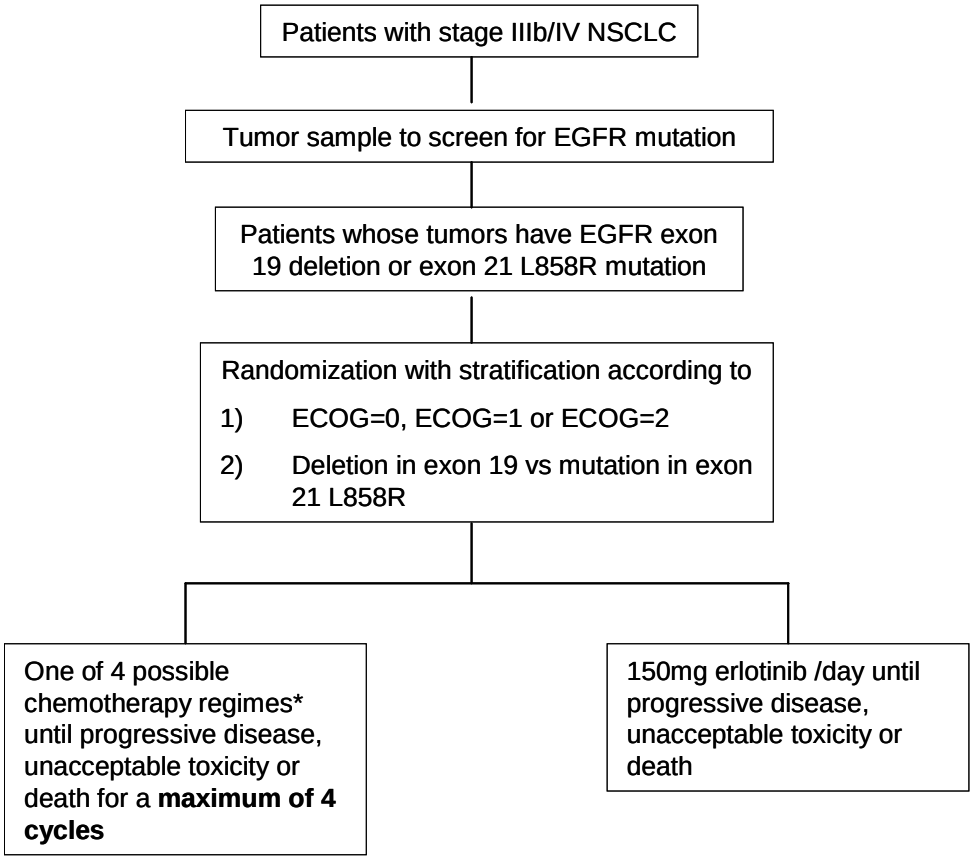
Trial no. (acronym)	**EURTAC**	**OPITMAL**
Location (4b)	Spain, France, Italy	China
Design (3a and 3b))	A phase III, multicentre, open-label, randomised study of first line erlotinib treatment versus platinum doublet chemotherapy in patients with advanced non-small-cell carcinoma of the lung whose tumours have activating mutations in the TK domain of EGFR. The study design for EURTAC is illustrated in Figure 9 (below this table).	A multicentre, randomized, open-label, controlled phase III study comparing the efficacy of first line erlotinib monotherapy versus gemcitabine + carboplatin chemotherapy in chemo-naïve stage IIIB or stage IV NSCLC patients with activating EGFR mutations. The study design for OPTIMAL is illustrated in Figure 10 (below this table).
Duration of study	2007-2011	2008-2010
Method of randomisation (8a, 8b, 9, 10)	Patients were randomized by means of fax to receive either erlotinib or platinum doublet chemotherapy. The choice of platinum doublet chemotherapy was at the discretion of the investigator and was selected according to what was in the patients' best interest. A block randomization with a block size of 2 was used. Randomisation was stratified by the following factors: • According to ECOG performance status three different groups were established: ECOG = 0, ECOG = 1 and ECOG = 2 • Deletion in exon 19 vs. mutation in exon 21 L858R	Patients were randomized by e-mail or telephone in a 1:1 ratio to receive erlotinib monotherapy or gemcitabine + carboplatin combination chemotherapy. Randomisation was stratified according to the following factors: • Mutation type (exon 19 deletion vs exon 21 L858R mutation) • Histology (adenocarcinoma vs non-adenocarcinoma) • Smoking status (smokers vs non-smokers)
Method of blinding (care provider, patient and outcome assessor) (11a, 11b)	Open-label study	Open-label study
Intervention(s) (n =) and comparator(s) (n =) (5)	**Intervention (n=86)** Erlotinib 150mg o.d. until PD **Comparator (n=87)** Cisplatin 75 mg/m^2 i.v. Day 1 and docetaxel 75 mg/m^2 i.v. Day 1. Repeat cycles every 3 weeks or Cisplatin 75 mg/m^2 i.v. on Day 1 and gemcitabine 1250 mg/m^2 on Days 1 and 8. Repeat cycles every 3 weeks or Docetaxel 75 mg/m^2 Day 1 and carboplatin AUC = 6 Day 1, every 21	**Intervention (n=82)** Erlotinib 150mg o.d. until PD **Comparator (n=72)** Gemcitabine 1000 mg/m^2; Day 1 and Day 8 and carboplatin AUC = 5, Day 1 every 21 days Platinum doublet chemotherapy was administered for a maximum of 4 cycles (3 months)

	days or Gemcitabine 1000 mg/m^2 Days 1 and 8 and carboplatin AUC = 5 Day 1, every 21 days Platinum doublet chemotherapy was administered for a maximum of 4 cycles (3 months)	

Primary outcomes (including scoring methods and timings of assessments) (6a, 6b)	**Progression Free Survival** The primary efficacy parameter was progression-free survival, defined as the time between randomisation and the first occurrence of progressive disease (both radiological and clinical progression) or death from any cause, whichever occurred first. Patients who had neither progressed nor died at the time of analysis were censored at the date of the last tumour assessment where non-progression was documented (i.e., CR, PR or SD). If a patient received a second anti-cancer therapy without prior documentation of disease progression, the patient was censored at the date of last tumour assessment before starting the new anti-cancer therapy. Patients without any valid post-baseline tumour assessments were censored at the date of randomization, unless they died within the first 49 days after randomization, in which case they were not censored and their death was counted as a PFS event. Plots of the Kaplan-Meier estimates for each treatment group were produced. Estimates of the median, HR and event-free rate in each treatment group were calculated.	**Progression Free Survival** The primary efficacy parameter was duration of PFS, defined as the time from date of randomisation to the date of first documented disease progression or death due to any cause (whichever occurred first). Disease progression was defined according to the RECIST 1.0 criteria. Patients who had neither progressed nor died at the time of study completion (or data cut-off) or who were lost to follow-up were censored at the date of the last tumour assessment where non-progression was documented or the last date of follow-up for progression of disease, whichever occurred later. Patients with symptomatic deterioration were not considered as having disease progression without evidence of progressive disease.
Secondary outcomes (including scoring methods and timings of assessments) (6a, 6b)	**Overall Survival** Overall survival (OS) was defined as the time between randomisation and the date of death, irrespective of the cause of death. Patients still alive at the time of analysis were censored at the date they were last known to be alive. **Objective Response – Best Overall Response** A patient was considered to be a responder if their best overall response was either CR or PR. Patients with a best overall response of SD, PD or missing were considered to be non-responders. Objective response analysis was performed according to the investigator's assessment of tumour response.	**Tumour Response and Time to Progression** Tumour response and disease progression were assessed by the investigator according to the RECIST 1.0 criteria. **Overall Survival** Overall survival (OS) was defined as the time from date of randomization to date of death due to any cause. If a patient was known to be alive up to the cut-off date, survival was censored at the last date the patient was known to be alive. **Quality of Life** The Quality of Life assessment was based on the Functional Assessment of Cancer Therapy–Lung (FACT–L) questionnaire (in which scores range from 0 to

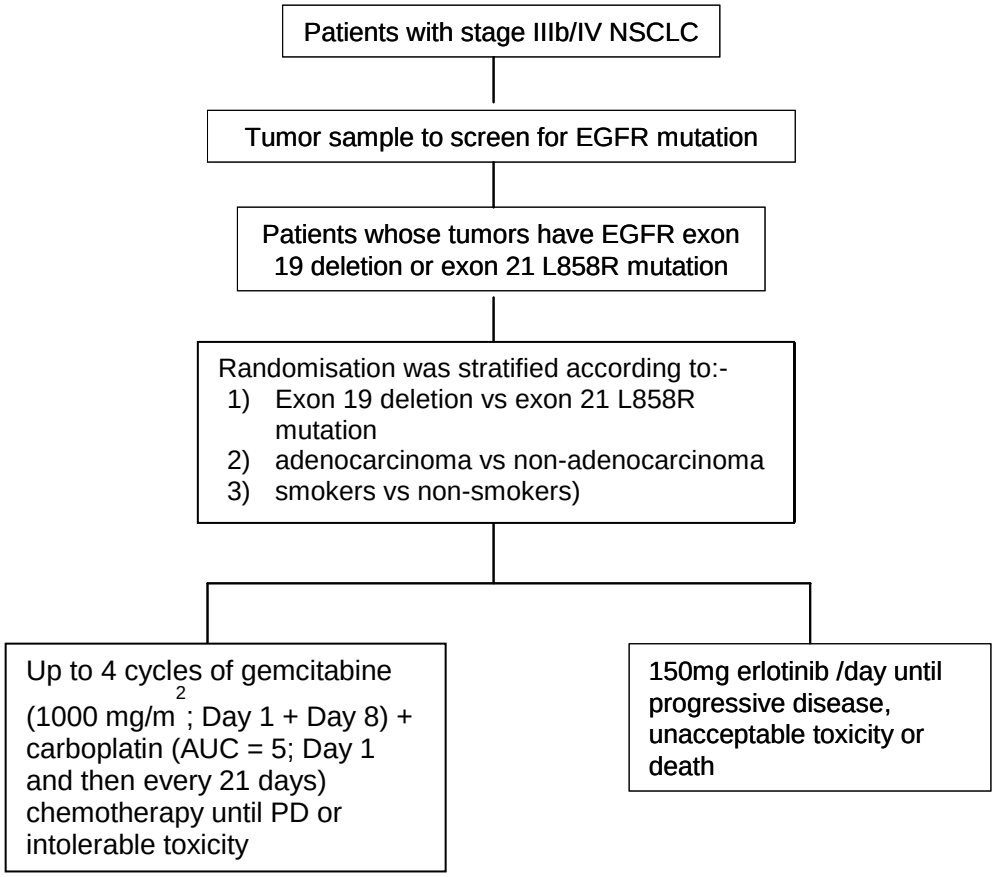
	Disease Control Disease control was defined either as response (CR, PR) or maintained disease stabilisation (SD for at least 6 weeks). **Quality of Life** The protocol requested that QoL assessments be completed every 3 weeks until disease progression on both treatment arms. **Safety Reporting and Analysis** Adverse events were recorded as they were encountered during the study and up until 28 days after administration of last dose of study treatment and classified according to the NCI-CTC AE v3.0 (http://ctep.cancer.gov/reporting/ctc.html). It is important to note that, due to the nature of the treatments, the duration of therapy differed in the 2 arms. Platinum doublet chemotherapy was administered to patients for a maximum of 4 cycles (approximately 3 months) whereas erlotinib was administered until PD or unacceptable toxicity. The causality relationship of study drug to the AE was assessed by the investigator as unrelated, remote, possible and probable. For reporting purposes, all AEs assessed by the investigator as remotely, possibly or probably related to study drug were considered as AEs related to study drug. If multiple occurrences of the same AE in the same patient were reported, the most extreme intensity was used for summarising AEs. Special AEs of interest include rash, interstitial lung disease (ILD)-like events and diarrhoea.	136, with higher scores indicating better quality of life) and the Trial Outcome Index (TOI, which is the sum of the physical well-being, functional well-being, and lung-cancer subscale [LCSS] scores of FACT-L; scores range from 0 to 84, with higher scores indicating better quality of life), and symptoms were assessed with the use of the LCSS score (scores range from 0 to 100, with higher scores indicating fewer symptoms). The FACT-L questionnaire was completed at randomisation, once every 6 weeks until week 12, and also when study drug was discontinued. Clinically relevant improvement was predefined as an improvement of six points or more in the FACT-L and TOI scores or an improvement of two points or more in LCSS scores, with the higher scores maintained for at least 21 days.
Duration of follow-up	At the interim analysis (data cut-off date of August 2, 2010) median follow-up was 10.7 months in the platinum doublet chemotherapy arm and 14.3 months in the erlotinib arm.	The primary cut-off date for PFS was July 16, 2010; an updated PFS analysis was performed on January 7, 2011 after a median follow-up of 19.8 months

Figure 9: EURTAC Study Design



*Patients in the platinum doublet chemotherapy arm received one of the following standard platinum doublet chemotherapy regimens: (Cisplatin plus docetaxel: cisplatin 75 mg/m^2 intravenous (i.v.) Day 1 and docetaxel 75 mg/m^2 i.v. Day 1. Repeat cycles every 3 weeks; Cisplatin plus gemcitabine: cisplatin 75 mg/m^2 i.v. on Day 1 and gemcitabine 1250 mg/m^2 on Days 1 and 8. Repeat cycles every 3 weeks; Docetaxel 75 mg/m^2 Day 1 and carboplatin area under the plasma concentration curve (AUC) = 6 Day 1, every 21 days; Gemcitabine 1000 mg/m^2 Days 1 and 8 and carboplatin AUC = 5 Day 1, every 21 days.

Figure 10: OPTIMAL Study Design



Participants

5.3.3 Provide details of the eligibility criteria (inclusion and exclusion) for the trial. The following table provides a suggested format for the eligibility criteria for when there is more than one RCT. Highlight any difference between the trials.

Table 11: Eligibility criteria in the RCTs (4a)

Trial no. (acronym)	Inclusion criteria	Exclusion criteria

EURTAC	• Informed consent was obtained in writing from the patient and documented before witnesses.
	• Histologic diagnosis of NSCLC, stage IV or stage IIIB with malignant pleural effusion or N3 tumours, not candidates for thoracic irradiation who present exon 19 deletions or an exon 21 L858R mutation in the TK domain of EGFR (histology was performed locally)
	• Measurable or evaluable disease
	• Patients over 18 years
	• Performance status ≤ 2 on the ECOG scale
	• Adequate bone marrow reserve:
	  • haemoglobin ≥ 9 g/dl
	  • absolute neutrophil count > 1500/µl
	  • platelet count > 100,000/µl
	• Adequate kidney function: serum creatinine ≤ 1.5 x upper limit of normality (ULN) or calculated creatinine clearance (CrCl) > 60 ml/min using the Cockcroft-Gault formula:
	• If the patient was not eligible for cisplatin treatment, carboplatin was administered and the Calvert formula for dose calculation was used
	• Adequate liver function:
		• Women who were pregnant or in the period of lactation.
		• Women of childbearing age who presented a positive pregnancy test result in the baseline evaluation or who did not undergo this test.
		• Sexually active men and women (of childbearing age) who were not willing to use contraceptive methods during the study.
		• Previous treatment with chemotherapy for metastatic disease. The administration of neoadjuvant or adjuvant chemotherapy was allowed as long as it was completed ≥ 6 months before entering the study.
		• Previous treatment with therapeutic agents targeting EGFR.
		• Patients could have received radiotherapy as long as the irradiated lesion was not the only target lesion for evaluating response and as long as radiotherapy had been completed before initiating the study treatment (a 2-week period was recommended).
		• Treatment with an investigational drug agent during the 3 weeks before enrolment in the study.
		• Any known significant ophthalmologic anomaly of the ocular surface. The use of contact lenses was not recommended.
		• Pre-existent motor or sensory neurotoxicity grade ≥ 2

	• total bilirubin ≤ ULN • serum aspartate aminotransferase/ glutamic oxaloacetic transaminase (ASP/SGOT) and/or serum alanine aminotransferase/ glutamic pyruvic transaminase (ALT/SGPT) ≤ 2.5 × ULN. • alkaline phosphatase ≤ 5 ULN, except in the presence of exclusive bone metastases and in the absence of any liver disorder. • Patients must be accessible for treatment and follow-up. • Women of childbearing age must have a negative serum or urine pregnancy test within 7 days before beginning treatment. • Patients of both sexes of childbearing age, including women who had their last menstrual period in the last 2 years, must use an effective contraceptive method. • Oral swallowing capability. • Patients with asymptomatic and stable cerebral metastases receiving medical treatment were eligible for the study. Patients who received radiation therapy for their cerebral metastases before the initiation of systemic treatment for NSCLC were also eligible. • Absence of intestinal transit problems, such as malabsorption syndrome,	according to the National Cancer Institute – Common Toxicity Criteria (NCI-CTC) AE scale. • Evidence of spinal cord compression. • Incapacity to take oral medication or previous surgical procedures that affect absorption and imply the need for intravenous or parenteral feeding. • Other serious diseases or clinical conditions, including, but not limited to: • Unstable heart disease despite treatment; myocardial infarction in the 6 months preceding enrolment in the study. • History of significant neurologic or psychiatric disorders, including dementia and epileptic seizures. • Uncontrolled active infection. • Uncontrolled active peptic ulcer. • Unstable diabetes mellitus or any other contraindication to corticoid use. • ASP/SGOT and/or ALT/SGPT > 1.5 × ULN associated to alkaline phosphatase > 2.5 × ULN. • Other serious underlying medical processes that could affect the patient's capacity to participate in the study. • Absolute contraindication for steroid use.

	chronic intestinal inflammatory disease, or other pathologies that, in the judgment of the investigator, can alter absorption of the medication.	• Dementia or significantly disturbed mental state that could interfere with the patient's understanding and granting of informed consent. • History of another neoplasm other than carcinoma *in situ* of the uterine cervix, basal cell skin carcinoma treated adequately, or prostate carcinoma with a good prognosis (Gleason ≤ 6) treated radically. History of another neoplasm treated curatively and without evidence of disease in the last 5 years.

OPTIMAL	• Stage IIIB (cytologically confirmed with malignant pleural effusion or pericardial effusion) or histologically or cytologically documented stage IV NSCLC or postoperatively recurrent NSCLC. • EGFR exon19 deletion or exon 21 L858R mutation determined by PCR-DNA direct sequencing of fresh or paraffin-embedded tumour samples • Measurable disease, according to the Response Evaluation Criteria in Solid Tumours (RECIST). • Local radiotherapy was permitted if completed 3 weeks prior to the first drug administration, but the lesions in the radiotherapy field were not to be included in the RECIST assessment. • Prior surgery was permitted if the operation was performed 4 weeks before the first drug administration. • Age > 18 years. • ECOG Performance Status 0-2 • Life expectancy of at least 12 weeks. • Adequate bone marrow and hepatic and renal function confirmed by routine laboratory examination 7 days before the first drug administration: - Haemoglobin ≥ 9.0 g/dL - Absolute neutrophil count (ANC) ≥ $1500/mm^3$	• Patients with any systemic anti-cancer therapy (e.g. cytotoxic drugs, monoclonal antibody therapy, experimental treatment, adjuvant or neoadjuvant chemotherapy) for current or previously diagnosed NSCLC. (Post-surgical recurrent patients could be included if treatment had been discontinued for ≥ 6 months). • Patients with wild type EGFR. • Uncontrolled pericardial or pleural effusions. • History of cardiovascular disease: Congestive Heart Failure > NYHA grade II. Unstable angina (with symptoms at rest) or new occurrence of angina (onset within the last 3 months) or myocardial infarction in the last 6 months. • Brain metastases (patients were permitted if the metastases were under control and did not require hormone therapy). • Known infection with HIV. • Active serious clinical infection > CTCAE grade 2. • A history of major operation or serious trauma within 3 weeks before the first drug administration. • A history of non-NSCLC cancer within 5 years before initiation of study treatment (patients with carcinoma in-situ of the cervix, cured basal cell carcinoma, or bladder epithelial tumour including Ta and Tis could be enrolled). • Mixed with small cell lung

	- Platelets ≥ 100,000/mm^3 - Total bilirubin ≤ 1.5 × ULN - Aspartate transaminase (AST) and alanine transaminase (ALT) ≤ 2.5 × ULN in the absence of liver metastases (AST, ALT ≤ 5 × ULN in case of liver metastases). - INR ≤ 1.5, APTT in the normal range (1.2 × LLN to 1.2 × ULN) - Serum creatinine ≤ 1.5 × ULN • Ability to understand and voluntarily sign informed Consent.	cancer; • Inability to take oral medication. • Any condition leading to malabsorption. • Women of childbearing age with positive pregnancy test within 7 days before start of study treatment. • Male or female patients of child bearing potential were to use a reliable method of contraception prior to and during the study and for 30 days after discontinuation of the study. Reliable contraceptive methods were determined by the principal investigator or a designee.

5.3.4 Describe the patient characteristics at baseline. Highlight any differences between study groups. The following table provides a suggested format for the presentation of baseline patient characteristics for when there is more than one RCT.

Table 12: Characteristics of participants in the RCTs across randomised groups

EURTAC STUDY	**Initial Interim Analysis (Cut-off for Statistical Analysis 2nd August 2010)**		**Updated Analysis (Cut-off for Statistical Analysis 26th January 2011)**	
	Platinum Doublet Chemotherapy (n= 76)	**Erlotinib (n= 77)**	**Platinum Doublet Chemotherapy (n= 87)**	**Erlotinib (n= 86)**
Age (years)				
Median	64.0	65.0	65.0	65.0
Min-Max	29-82	24-82	29-82	24-82
Sex				
Female	60 (79%)	52 (68%)	68 (78%)	58 (67%)
Male	16 (21%)	25 (32%)	19 (22%)	28 (33%)

Race (White vs. Other)	76 (100%)	77 (100%)	85 (98%)	86 (100%)
White	-	-	2 (2%)	-
Other				
Country	15 (20%)	20 (26%)	18 (21%)	21 (24%)
France	6 (8%)	10 (13%)	8 (9%)	11 (13%)
Italy	55 (72%)	47 (61%)	61 (70%)	54 (63%)
Spain				
Smoking Status (derived)	10 (13%)	3 (4%)	12 (14%)	7 (8%)
Current Smoker	56 (74%)	54 (70%)	63 (72%)	57 (66%)
Never Smoker	10 (13%)	20 (26%)	12 (14%)	22 (26%)
Past Smoker				
ECOG PS Score at Baseline	26 (34%)	23 (30%)	30 (24%)	27 (31%)
0	41 (54%)	44 (57%)	45 (52%)	47 (45%)
1	9 (12%)	10 (13%)	12 (14%)	12 (14%)
2				
Location and type of activating mutation	48 (63%)	49 (64%)	58 (67%)	57 (66%)
Exon 19 deletion	28 (37%)	28 (36%)	29 (33%)	29 (34%)
Exon 21 mutations	-	1 (1%)	-	-
Histology of NSCLC	67 (88%)	73 (95%)	-	-
Squamous cell carcinoma	1 (1%)	3 (4%)	-	-
Adenocarcinoma	6 (8%)	-	-	-
Large cell carcinoma	2 (3%)	-	-	-
Other				
Bronchioalveolar carcinoma	-	1 (1%)	-	-
Stage of NSCLC at Baseline	5 (7%)	6 (8%)	-	-
N3 (not candidate for thoracic radiotherapy)	71 (93%)	69 (91%)	-	-
Stage IIIB (with pleural effusion)				
Stage IV (metastatic)	5.00	5.29	-	-

Weeks since First Diagnosis of NSCLC Median Min-Max	0.9 - 727.9	1.6 - 211.3	-	-
OPTIMAL STUDY	**Gemcitabibine + carboplatin (n= 72)**	**Erlotinib (n= 82)**		
Age				
Mean (SD)	58.65 (9.600)	56.36 (10.017)		
Median	58.8	56.5		
Min, Max	35.6, 78.0	30.6, 73.9		
Sex				
M	29 (40.3%)	34 (41.5%)		
F	43 (59.7%)	48 (58.5%)		
Total	72 (100.0%)	82 (100.0%)		
Smoking Status				
Non-smoker	50 (69.4%)	59 (72.0%)		
Smoker	22 (30.6%)	23 (28.0%)		
Total	72 (100.0%)	82 (100.0%)		
ECOG PS				
0	23 (31.9%)	30 (36.6%)		
1	46 (63.9%)	45 (54.9%)		
2	3 (4.2%)	7 (8.5%)		
Exon 19 de;letion				
Yes	33 (45.8%)	39 (47.6%)		
No	39 (54.2%)	43 (52.4%)		
Total	72 (100.0%)	82 (100.0%)		
L858R mutation				
Yes	39 (54.2%)	43 (52.4%)		
No	33 (45.8%)	39 (47.6%)		
Total	72 (100.0%)	82 (100.0%)		
Histology				
Non-adenocarcinoma	10 (13.9%)	10 (12.2%)		
Adenocarcinoma	62 (86.1%)	72 (87.8%)		
Total	72 (100.0%)	82 (100.0%)		
Clinical Stage				
IIIB	5 (6.9%)	11 (13.4%)		
IV	67 (93.1%)	71 (86.6%)		
Total	72 (100.0%)	82 (100.0%)		

Outcomes

5.3.5 Provide details of the outcomes investigated and the measures used to assess those outcomes. Indicate which outcomes were specified in the trial protocol as primary or secondary, and whether they are relevant with reference to the decision problem. This should include therapeutic outcomes, as well as patient-related outcomes such as assessment of health-related quality of life, and any arrangements to measure compliance. Data provided should be from pre-specified outcomes rather than post-hoc analyses. When appropriate, also provide evidence of reliability or validity, and current status of the measure (such as use within UK clinical practice). The following table provides a suggested format for presenting primary and secondary outcomes when there is more than one RCT.

Table 13: Primary and secondary outcomes of the RCTs

Trial no. (acronym)	Primary outcome(s) and measures	Reliability/ validity/ current use in clinical practice	Secondary outcome(s) and measures	Reliability/ validity/ current use in clinical practice
EURTAC	**Progression Free Survival** The primary efficacy parameter was progression-free survival, defined as the time between randomisation and the first occurrence of progressive disease (both radiological and clinical progression) or death from any cause, whichever occurred first. Patients who had neither progressed nor died at the time of analysis were censored at the date of the last tumour assessment where non-progression was documented (i.e., CR, PR or SD). If a patient received a second anti-cancer therapy without prior documentation of disease progression, the patient was censored at the date of last tumour assessment before starting the new anti-cancer therapy. Patients without any valid post-baseline tumour assessments were censored at the date of randomization, unless they died within the first 49 days after randomization, in which case they were not censored and their death was counted as a PFS event. Plots of the Kaplan-Meier estimates for each treatment group were produced. Estimates of the median, HR and	Progression free survival is accepted as a reliable endpoint and is widely used as a primary endpoint/outcome measure in clinical trials when investigating a treatment effect in the early treatment of advanced NSCLC. It is also "cleaner" endpoint that is not subject to the diluting effects of subsequent treatments given off protocol after the end of the study treatment, particularly in studies where there is likely to be a high degree of post-discontinuation cross-over of treatments. In EURTAC PFS was measured according the internationally recognised RECIST criteria by study investigators and also by validated further by independent review.	**Overall Survival** Overall survival (OS) was defined as the time between randomisation and the date of death, irrespective of the cause of death. Patients still alive at the time of analysis were censored at the date they were last known to be alive. **Objective Response – Best Overall Response** A patient was considered to be a responder if their best overall response was either CR or PR. Patients with a best overall response of SD, PD or missing were considered to be non-responders. Objective response analysis was performed according to the investigator's assessment of tumour response. **Disease Control** Disease control was defined either as response (CR, PR) or maintained disease stabilisation (SD for at least 6 weeks). **Quality of Life** The protocol requested that QoL assessments be completed every 3 weeks until disease progression on both treatment arms. **Safety Reporting and Analysis** Adverse events were	Overall survival has long been established as a standard endpoint/outcome measure used in oncology clinical trials and has been used as a primary or secondary endpoint/outcome measure depending on the stage of advanced NSCLC under investigation. Similarly, objective response and disease control have been utilised as secondary endpoints/outcome measures extensively and considered robust supportive evidence for PFS and OS outcomes in evaluating a treatment effect in patients. Both are considered by the oncology clinical community to be important when trying to assess the impact of a treatment on a patients' tumour and the longevity of disease control Quality of life has become increasingly important in assessing the patients' treatment experience, particularly as there has been a need to find not only more effective treatments for treating advanced NSCLC but also better tolerated treatments which together would considerably improve a

	event-free rate in each treatment group were calculated.		recorded as they were encountered during the study and up until 28 days after administration of last dose of study treatment and classified according to the NCI-CTC AE v3.0 (http://ctep.cancer.gov/reporting/ctc.html). It is important to note that, due to the nature of the treatments, the duration of therapy differed in the 2 arms. Platinum doublet chemotherapy was administered to patients for a maximum of 4 cycles (approximately 3 months) whereas erlotinib was administered until PD or unacceptable toxicity. The causality relationship of study drug to the AE was assessed by the investigator as unrelated, remote, possible and probable. For reporting purposes, all AEs assessed by the investigator as remotely, possibly or probably related to study drug were considered as AEs related to study drug. If multiple occurrences of the same AE in the same patient were reported, the most extreme intensity was used for summarising AEs. Special AEs of interest include rash, interstitial lung disease (ILD)-like events and diarrhoea.	patients' day to day activities. The Lung Cancer Sub-Scale (LCSS) of the FACT-L questionnaire was used to assess quality of life in EURTAC which is a well validated and internationally recognised tool to measure quality of life in lung cancer clinical trials. Safety reporting is also a well-established standard outcome measure within oncology clinical trials owing to the nature of the condition and sometimes the toxicity of the treatments to treat the disease (e.g. haematological toxicities associated with chemotherapies). In EURTAC safety reporting was conducted in accordance with the National Cancer Institute – Common Toxicity Criteria (NCI-CTC) which is an internationally recognised set of guidelines for the reporting of adverse events in oncology clinical trials.

OPTIMAL	**Progression Free Survival** The primary efficacy parameter was duration of PFS, defined as the time from date of randomisation to the date of first documented disease progression or death due to any cause (whichever occurred first). Disease progression was defined according to the RECIST 1.0 criteria. Patients who had neither progressed nor died at the time of study completion (or data cut-off) or who were lost to follow-up were censored at the date of the last tumour assessment where non-progression was documented or the last date of follow-up for progression of disease, whichever occurred later. Patients with symptomatic deterioration were not considered as having disease progression without evidence of progressive disease.	As for EURTAC above.	**Tumour Response and Time to Progression** Tumour response and disease progression were assessed by the investigator according to the RECIST 1.0 criteria. **Overall Survival** Overall survival (OS) was defined as the time from date of randomization to date of death due to any cause. If a patient was known to be alive up to the cut-off date, survival was censored at the last date the patient was known to be alive. **Quality of Life** The Quality of Life assessment was based on the Functional Assessment of Cancer Therapy–Lung (FACT–L) questionnaire (in which scores range from 0 to 136, with higher scores indicating better quality of life) and the Trial Outcome Index (TOI, which is the sum of the physical well-being, functional well-being, and lung-cancer subscale [LCSS] scores of FACT-L; scores range from 0 to 84, with higher scores indicating better quality of life), and symptoms were assessed with the use of the LCSS score (scores range from 0 to 100, with higher scores indicating fewer symptoms). The FACT-L questionnaire was completed at randomisation, once every 6 weeks until week 12, and also when study drug was discontinued.	As for EURTAC above.

			Clinically relevant improvement was predefined as an improvement of six points or more in the FACT-L and TOI scores or an improvement of two points or more in LCSS scores, with the higher scores maintained for at least 21 days.	

Statistical analysis and definition of study groups

5.3.6 State the primary hypothesis or hypotheses under consideration and the statistical analysis used for testing hypotheses. Also provide details of the power of the study and a description of sample size calculation, including rationale and assumptions. Provide details of how the analysis took account of patients who withdrew (for example, a description of the intention-to-treat analysis undertaken, including censoring methods; whether a per-protocol analysis was undertaken). The following table provides a suggested format for presenting the statistical analyses in the trials when there is more than one RCT.

Table 14: Summary of statistical analyses in RCTs

Trial no. (acronym)	Hypothesis objective	Statistical analysis	Sample size, power calculation	Data management, patient withdrawals
EURTAC	**Primary Endpoint** The Data Reporting and Management Manual (DRAM) for EURTAC specified the following hypothesis and approach to testing it: **Hypothesis** A 2-sided log-rank test was used for testing the difference in PFS between the erlotinib and platinum doublet chemotherapy arms. The hypothesis tested was: H_0: "There is no difference in the survival distribution of the parameter PFS between the erlotinib and platinum doublet chemotherapy arms." *vs* H_1: "There is a difference in the survival distribution of the parameter PFS between the erlotinib and platinum doublet chemotherapy arms."	**Analysis** All randomised patients were included in the full analysis set (FAS) analysis and presented according to the therapy that they were randomised to receive. The FAS is equivalent to the commonly used term "intent-to-treat" (ITT) population. **Timing of Analyses** An interim analysis was planned after 88 PFS events were observed across both arms. If the interim analysis was positive, recruitment into EURTAC was planned to be stopped at the time interim analysis results were made public. Otherwise, recruitment into EURTAC was to continue until 174 patients were recruited and the final analysis was to be performed when a total of 135 events had occurred across	The planned sample size in EURTAC was 174 patients which was based on the following assumptions: • A median PFS of 10 months in the erlotinib arm and of 6 months in the platinum doublet chemotherapy arm, corresponding to a hazard ratio (HR) of 0.6. • A 2-sided log-rank test at 5% significance level for testing the hypothesis of equality of survival distribution of the parameter PFS. • An interim analysis after 65% of the PFS events had occurred in this study • A Lan-DeMets alpha-spending function with a Pocock stopping boundary • A 5% yearly dropout rate.	**Data Management** Study data were collected on case report forms (CRFs) and entered into Oracle Clinical at the Contract Research Organization (CRO) in charge of the clinical operations and data management of the study. The data were transferred from the CRO to Roche Biostatistics Department (PDBB) in SAS format. These data were mapped into a Generic Data Model (GDM) structure as specified in the annotated CRF and the Data Delivery Specifications (DDS) document prepared by PDBB. The GDM database was stored on the UNIX environment. The GDM was the basis for all analyses and reporting. Standard safety

	A 2-sided log-rank test was used for OS. For the other secondary parameters further tests between the 2 treatment arms were performed. All tests were 2-sided at a 5% significance level.	both arms. A Lan-DeMets alpha-spending function with a Pocock boundary was used to maintain the significance level at 5%. The following significance levels were used to evaluate PFS at the interim analysis (based on 88 events) and the final analysis (based on 135 events): • Interim analysis: 0.037 • Final analysis: 0.025. Deviations from this plan in terms of the exact number of events were allowed, and new boundaries could be calculated using the same methods in this case. A stricter stopping boundary for the interim analysis was defined in the IDMC charter. This stricter stopping boundary took precedence over the interim analysis boundary defined in the DRAM. The		analysis was performed using the Management, Analysis and Reporting of Safety Data (MARS) system. **Patient Withdrawals** All patients who had received at least one dose of trial medication and had at least one safety follow-up, whether withdrawn prematurely or not, were included in the safety analysis. Withdrawals were presented in a listing and summary table in the CSR.

		IDMC could recommend recruitment stop, full evaluation of study data and release of study results due to a clinical benefit of erlotinib over platinum doublet chemotherapy if, among several other conditions, results of primary efficacy analysis of investigator-assessed PFS were statistically significant and in favour of erlotinib (e.g. HR ~ 0.50 or lower). Under these circumstances, the p-value of the primary efficacy analysis at interim analysis was likely to be around 0.001 and, therefore smaller than both the above Pocock p-value cut-off of 0.037 and the O'Brien & Fleming p-value cut-off of 0.016. This stopping boundary was conservative and strongly preserved the overall significance level.		

Trial no. (acronym)	Hypothesis objective	Statistical analysis	Sample size, power calculation	Data management, patient withdrawals
OPTIMAL	The primary endpoint was progression free survival. No interim analysis was performed for this study. A bilateral α of 0.05 was used for the hypothetic analysis of PFS.	The primary analyses of efficacy and safety were conducted on all patients who received at least one dose of study treatment. An additional population was defined for the analysis of tumour response which included all patients who experienced a partial or complete response as defined by RECIST criteria. The population defined for the safety analysis included all patients who received at least one dose of the study drug. The primary analysis was to be performed when 103 PFS events had occurred. Progression free survival was compared between the erlotinib and platinum doublet chemotherapy arms using a two-sided log-rank test at the alpha level of	A median PFS of approximately 6 months in the platinum doublet chemotherapy arm (based on historical data) and 11 months in the erlotinib arm (a conservative estimate based on the results from the SLCG Phase II study - Rosell et al.2009) provided a Hazard Ratio of 0.54 for the erlotinib arm *vs* the platinum doublet chemotherapy arm. Using a two-sided log-rank test with an overall alpha level of 5% (alpha-spending for an interim analysis), 103 PFS events were estimated to be required for the present study with a confidence level of 80% to detect a HR of 0.54 in the erlotinib arm *vs* the platinum doublet chemotherapy arm. Assuming a 12 month accrual period, with a 24-month follow-up for the last patient, the sample size was estimated to be 69 pairs. Taking	This was a phase III clinical trial initiated by Tongji University Affiliated Shanghai Pulmonary Hospital in China. **Data Management** Study monitoring of the data recorded on CRFs was performed by a CRO. Data management was the responsibility the CRO which ensured the accuracy, integrity and privacy of data. The data management process complied with the regulations (ICH, GCP and FDA 21 CFR Part 11) ensuring that the clinical study data was traceable. The database was established and managed by the CRO in compliance with FDA 21 CFR Part 11. **Patient Withdrawals**.

		0.05. The stratification factors included exon 19 mutation *vs* exon 21 mutation, adenocarcinoma *vs* non-adenocarcinoma and smokers *vs* non-smokers. For PFS, Kaplan-Meier survival curves, estimated median and 95% CI were presented. The hazard ratio of PFS endpoint events (disease progression or death) between the erlotinib arm and the platinum doublet chemotherapy group was calculated together with a 95% CI. The calculation of hazard ratios were based on a Cox regression model.	into consideration a drop-out rate of 10%, a total sample size of 152 patients was required.	Patients could withdraw from the study at any time for any reason. The reason for withdrawal and medical history were recorded in the CRF and presented as listings and narratives in the CSR.

5.3.7 Provide details of any subgroup analyses that were undertaken and specify the rationale and whether they were pre-planned or post-hoc.

In EURTAC Cox-regression analyses including solely treatment allocation as an explanatory variable were performed for certain subgroups of patients (i.e. univariate analyses). These analyses were conducted based upon the baseline characteristics recorded within the study and the stratification factors detailed previously.

In OPTIMAL, pre-planned analysis in terms of PFS and ORR was performed for subgroups of patients based on demographic or baseline disease characteristics. Subgroups included:

- exon 19 deletion vs exon 21 mutation
- adenocarcinoma vs non-adenocarcinoma subtype
- squamous carcinoma vs non-squamous carcinoma histology
- smoker vs non-smoker
- age < 65 years vs age ≥ 65 years
- male vs female
- NSCLC chemo-naïve vs not chemo- naïve

A Cox's proportional hazard model was used for subgroup analysis of PFS and OS, with hazard ratios (HR) and bilateral 95% CIs. A logistic regression model was used for subgroup analysis of ORR, and odds ratio with bilateral 95% CI presented for estimated efficacy.

Participant flow

5.3.8 Provide details of the numbers of patients who were eligible to enter the RCT(s), randomised, and allocated to each treatment. Provide details of and the rationale for, patients who crossed over treatment groups and/or were lost to follow-up or withdrew from the RCT. This information should be presented as a CONSORT flow chart.

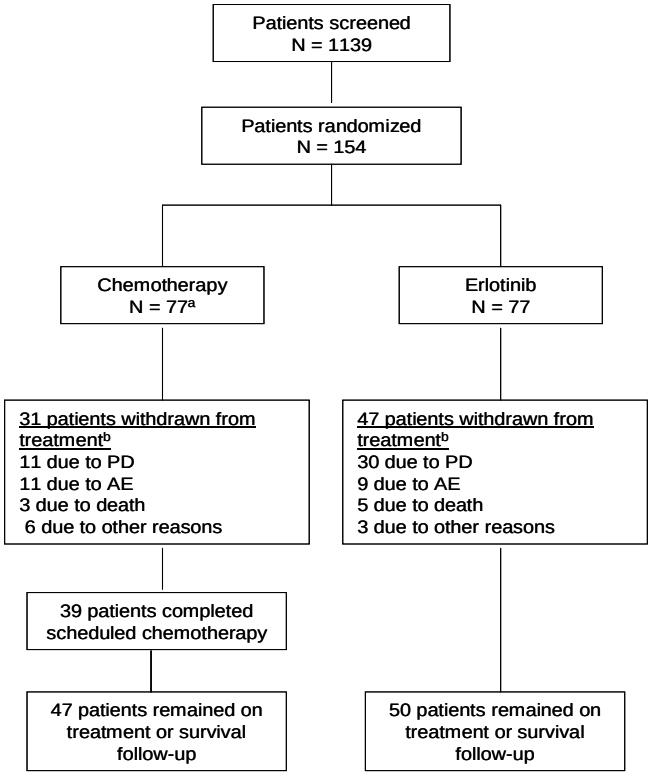
5.3.8.1 Patient Disposition in EURTAC

For the interim analysis 1139 patients were screened across 42 centres in 3 countries (Spain, France and Italy) for activating EGFR mutations between 15th February 2007 and 30th July 2010. 154 patients with activating EGFR mutations were randomised to receive either erlotinib or standard platinum doublet chemotherapy (77 in each arm). The database was locked on the 2nd August 2010 for the interim analysis of PFS.

For the updated analysis (January 26, 2011), a total of 1275 patients had been screened for EURTAC and 174 patients had been randomised (88 to the platinum doublet chemotherapy arm and 86 to the erlotinib arm). Patient 174 was randomised into EURTAC on January 03, 2011.

The disposition of patients recruited into EURTAC is shown below in Figure 11.

Figure 11: Patient Disposition in the EURTAC Study



[a]One patient received chemotherapy prior to randomization

[b] The imbalance in the number of treatment discontinuations due to PD or death is due to the fact that chemotherapy was administered for a maximum of 4 cycles (12-week treatment) and erlotinib was administered until disease progression. At the time of cut-off for interim analysis, 27 patients had died in each arm and 47 and 45 PFS events were observed in the chemotherapy and erlotinib arm, respectively.

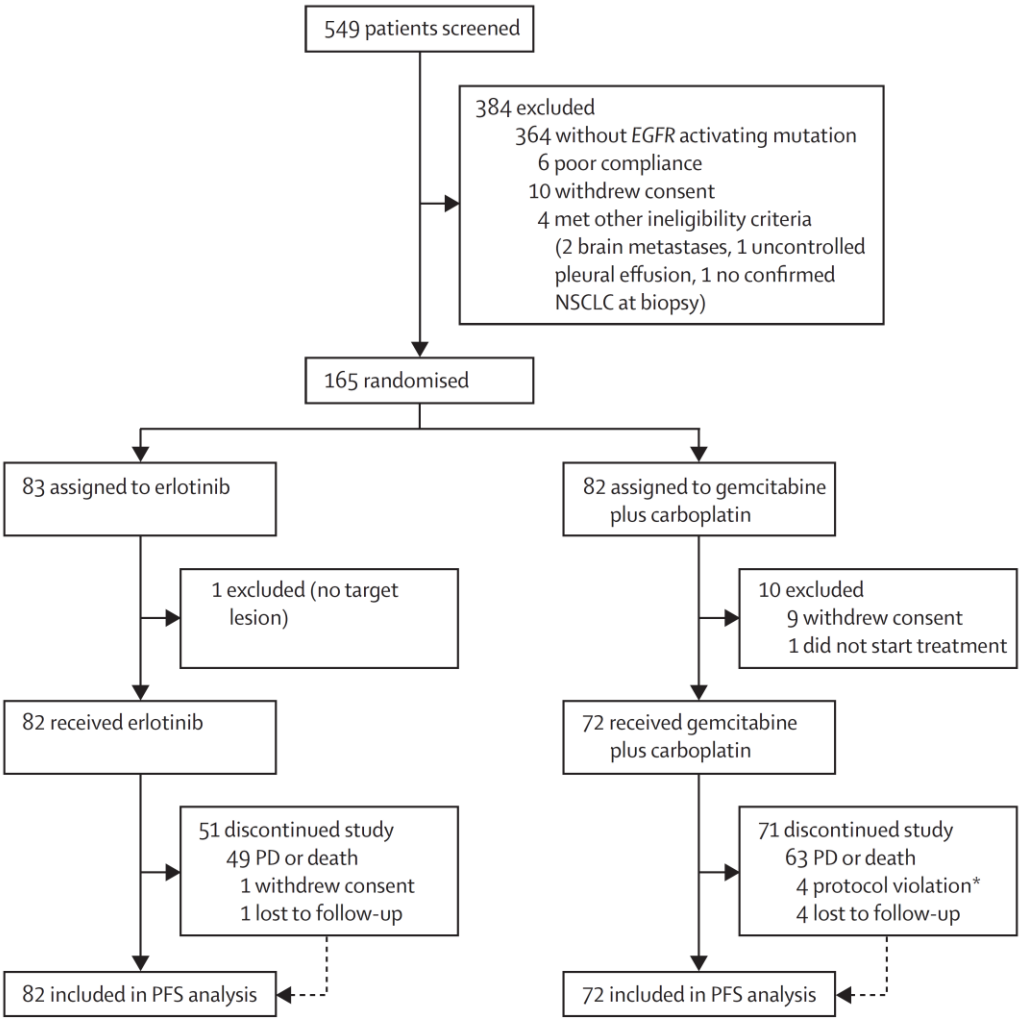
5.3.8.2 Patient Disposition in OPTIMAL

Eighty three patients were randomised to receive erlotinib 150 mg/day and 82 patients were randomised to receive up to 4 cycles of gemcitabine (1000 mg/m^2) + carboplatin (AUC = 5) chemotherapy in the absence of unacceptable toxicity and/or PD.

Nine patients refused platinum doublet chemotherapy after being randomised to the gemcitabine + carboplatin arm (all 9 patients stated a preference to receive TKI treatment) and one patient was discontinued by the investigator due to their unsuitability for platinum doublet chemotherapy as a result of a rapid progression of

malignant pleural effusion. These 10 patients were excluded from all efficacy and safety analyses. An additional patient was excluded from the efficacy (ITT population) analysis due to a major protocol violation (patient had no measurable lesions at baseline).

Figure 12: Patient Disposition in the OPTIMAL Study



5.4 Critical appraisal of relevant RCTs

5.4.1 The validity of the results of an individual study will depend on the robustness of its overall design and execution, and its relevance to the decision problem. Each study that meets the criteria for inclusion should therefore be critically appraised. Whenever possible, the criteria for

assessing published studies should be used to assess the validity of unpublished and part-published studies. The critical appraisal will be validated by the ERG. The following are the minimum criteria for assessment of risk of bias in RCTs, but the list is not exhaustive.

- Was the method used to generate random allocations adequate?
- Was the allocation adequately concealed?
- Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?
- Were the care providers, participants and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?
- Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?
- Is there any evidence to suggest that the authors measured more outcomes than they reported?
- Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?

Table 15: Quality assessment results for RCTs

	EURTAC	**OPTIMAL**
Was the method used to generate random allocations adequate?	Yes. Patients were randomized by means of fax to the CRO to receive either erlotinib or platinum doublet chemotherapy. The randomisation list was kept by the CRO. In order to minimize the bias introduced by knowledge of treatment group assignment, the treatment code was not be available to any person from Roche Biostatistics involved in the study prior to database closure.	Yes. Patients were randomized by e-mail or telephone in a 1:1 ratio to receive erlotinib monotherapy or gemcitabine + carboplatin combination chemotherapy.

Was allocation adequately concealed?	Not applicable as EURTAC was an open-label study	Not applicable as OPTIMAL was an open-label study
What randomisation technique was used?	Randomisation was conducted through a computing application (ACCESS) called "randomizer". The randomization list that supported this application was done according to the protocol using SAS statistical software.	Patients were randomly assigned (1:1) to either erlotinib or chemotherapy by dynamic minimisation procedure with Mini Randomisation software (version 1·5).
Were the care providers, participants and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?	No – see above for details of blinding.	No – see above for details of blinding
Was a justification for sample size provided?	Yes, based on the statistical requirement to demonstrate a predetermined treatment effect with a specified degree of statistical certainty. The sample size calculation was based on explicit assumptions about the clinical behaviour of the patient group in question and the impact of treatment	Yes, based on the statistical requirement to demonstrate a predetermined treatment effect with a specified degree of statistical certainty. The sample size calculation was based on explicit assumptions about the clinical behaviour of the patient group in question and the impact of treatment
Were the groups similar at the outset of the study in terms of prognostic factors, for example severity of disease?	Yes – see Table 12, Baseline characteristics	Yes – see Table 12, Baseline characteristics
Was follow-up adequate?	Yes – analyses were event driven and conducted after sufficient events to demonstrate unequivocally the impact on highly relevant clinical end-point of PFS. At the	Yes – analyses was event driven and conducted after sufficient events to demonstrate unequivocally the impact on a relevant clinical end-point of PFS.

	time of analysis for the primary PFS end-point there had been 111 progression or death events across the erlotinib and chemotherapy arms (52 and 59 respectively).	
Was the design parallel group or cross-over?	The study was a parallel group design and the primary end-point (PFS) would not have been influenced by cross-over. However, cross-over was possible at disease progression and this could have reduced the impact of the trial intervention on the secondary end-point of OS	The study was a parallel group design and the primary end-point (PFS) would not have been influenced by cross-over. However, cross-over was possible at disease progression and this could have reduced the impact of the trial intervention on the secondary end-point of OS
Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?	No.	No.
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No.	No.
Was the RCT conducted in the UK?	No. EURTAC was conducted in entirely Caucasian patients with NSCLC having activating EGFR mutations and therefore would be highly representative of NSCLC patients in the UK	No. OPTIMAL was conducted in 22 centres in China
How do RCT participants compare with the clinical population of patients within the UK?	UK lung oncologists see patients with inoperable NSCLC who have reasonable PS for whom they prescribe platinum doublet chemotherapy. These patients represent a discrete sub-population of patients presenting with inoperable NSCLC (many	UK lung oncologists see patients with inoperable NSCLC who have reasonable PS for whom they prescribe platinum doublet chemotherapy. These patients represent a discrete sub-population of patients presenting with inoperable NSCLC (many

	of whom are deemed too unfit for systemic chemotherapy). There is no reason to suppose that patients recruited into this study are not representative of the population of NSCLC patients receiving chemotherapy in routine clinical practice in the UK Currently, patients with advanced NSCLC with activating EGFR mutations are being treated with an EGFR TKI recommended by NICE based on RCT evidence entirely in patients from East Asia, which have a starkly different demographic and prognostic profile than patients in the UK. EURTAC recruited only Caucasian patients and therefore provides evidence of the efficacy of erlotinib in patients that are more representative of UK patients.	of whom are deemed too unfit for systemic chemotherapy. There is no reason to suppose that patients recruited into this study are not representative of the population of NSCLC patients receiving chemotherapy in routine clinical practice in the UK.
Were the study groups comparable?	Table 12 shows that patients in the control and experimental arms of EURTAC were well matched in terms of demographic, disease and treatment characteristics.	Table 5 shows that patients in the control and experimental arms of OPTIMAL were well matched in terms of demographic, disease and treatment characteristics.
Were the statistical analyses undertaken appropriate?	Yes. The manipulation of data from the study was undertaken according to a clear plan (the DRAM) finalised with expert statistician input prior to the availability of study data	Yes. The manipulation of data from the study was undertaken according to a clear plan finalised with expert statistician input prior to the availability of study data
Did the analysis include an intention to treat analysis?	Yes. This was the primary	No. The main analysis population defined for the

If so, was this appropriate and were appropriate methods used to account for missing data?	analysis.	efficacy included all randomised patients who received at least one dose of study drug (the CSR stated that this was the intent-to-treat (ITT) population).
Are there any other confounding factors that may attenuate the interpretation of the results of the RCTs?	Patients were allowed to cross-over post-progression. This would be likely to attenuate any impact of study treatment on the secondary end-point of OS but not the primary PFS endpoint.	Patients were allowed to cross-over post-progression. This would be likely to attenuate any impact of study treatment on the secondary end-point of OS but not the primary PFS endpoint.

5.4.2 Please provide as an appendix a complete quality assessment for each RCT. See section 9.3, appendix 3 for a suggested format.

See Appendix 3.

5.4.3 If there is more than one RCT, tabulate a summary of the responses applied to each of the critical appraisal criteria. A suggested format for the quality assessment results is shown below.

Table 16: Quality assessment results for RCTs

Trial no. (acronym)	EURTAC	OPTIMAL
Was randomisation carried out appropriately?	(yes)	(yes)
Was the concealment of treatment allocation adequate?	(N/A)	(N/A)
Were the groups similar at the outset of the study in terms of prognostic factors?	(yes)	(yes)
Were the care providers, participants and outcome assessors blind to treatment allocation?	(no)	(no)
Were there any unexpected imbalances in drop-outs between groups?	(no)	(no)
Is there any evidence to suggest that the authors measured more outcomes than they reported?	(no)	(no)
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	(yes)	(yes)

5.5 Results of the relevant RCTs

5.5.1 Provide the results for all relevant outcome measure(s) pertinent to the decision problem. Data from intention-to-treat analyses should be presented whenever possible and a definition of the included patients provided. If patients have been excluded from the analysis, the rationale for this should be given. **If there is more than one RCT, tabulate the responses.**

5.5.1.1 Summary of Key Outcomes from EURTAC

The primary and key secondary efficacy results are summarised in Table 17.

Table 17: Summary of Overall Efficacy Results in EURTAC – Interim Analysis

Parameter	Platinum Doublet Chemotherapy Arm	Erlotinib Arm
Progression Free Survival in FAS (Investigator assessment)		
Patients with event	47 (61.8 %)	45 (58.4 %)
Patients without event	29 (38.2 %	32 (41.6 %)
median (months)	**5.2**	**9.4**
p-value (Log-Rank test)	**< 0.0001**	
HR (95% CI):		
Non-stratified	0.42 [95% CI 0.27 to 0.64]	
Stratified	0.39 [95% CI 0.25 to 0.61]	
Progression Free Survival in FAS (IRC assessment)		
Patients with event	30 (39.5%)	31 (40.3%)
Patients without event	46 (60.5%)	46 (59.7%)
median (months)	**5.4**	**10.4**
p-value (Log-Rank test)	**0.0030**	
HR (95% CI):		
Non-stratified	0.47 [95% CI 0.28 to 0.78]	
Stratified	0.55 [95% CI 0.32 to 0.94]	
Overall Survival in FAS		
Patients with event	27 (35.5%)	27 (35.1%)
Patients without event	49 (64.5%)	50 (64.9%)
median (months)	**18.8**	**22.9**
p-value (Log-Rank test)	**0.4170**	
COX regression HR (95% CI);		
Non-stratified	0.80 [95% CI 0.47 to 1.37]	
Stratified	0.88 [95% CI 0.51 to 1.52]	
Best Overall Response (Investigator Assessment)		
Responders	**8 (10.5%)**	**42 (54.5%)**
Non-responders	68 (89.5%)	35 (45.5%)
difference in response rate [approx 95% CI, Hauck-Anderson]	**44.02 [30.2 to 57.9]**	
p-value (Chi-squared test)	**< 0.0001**	
Complete response	0 (0%)	2 (2.6%)
Partial response	8 (10.5%)	40 (51.9%)
Stable disease	42 (55.3%)	18 (23.4%)
Progressive disease	10 (13.2%)	6 (7.8%)
Missing	16 (21.1%)	11 (14.3%)
Best Overall Response (IRC Assessment)		
Responders	**7 (9.2%)**	**32 (41.6%)**
non-responders	69 (90.8%)	45 (58.4%)
difference in response rate [approx 95% CI, Hauck-Anderson]	**32.35 [18.8 to 45.9]**	
p-value (Chi-squared test)	**< 0.0001**	
Complete response	0 (0%)	1 (1.3%)
Partial response	7 (9.2%)	31 (40.3%)
Stable disease	29 (38.2%)	23 (29.9%)
Progressive disease	4 (5.3%)	3 (3.9%)
Missing	36 (47.4%)	19 (24.7%)

Note: p-values are based on non-stratified analysis

The updated analysis of PFS confirmed the results observed at the primary analysis. The median PFS for patients in the erlotinib arm increased to 9.7 months from 9.4 months at the primary analysis and the relative risk of having a PFS event for erlotinib-treated patients was reduced from 0.42 (95% CI : 0.27; 0.64) to 0.37 (95% CI: 0.25; 0.54). The independent central review was not updated for the updated analysis.

Table 18: Summary of Overall Efficacy Results in EURTAC – Updated Analysis

Parameter	Platinum Doublet Chemotherapy Arm	Erlotinib Arm
Progression Free Survival in FAS (Investigator assessment)		
Patients with event	59(67.8 %)	52 (60.5 %)
Patients without event	28(32.2 %)	34 (39.5 %)
median (months)	**5.2**	**9.7**
p-value (Log-Rank test)	**<0.0001**	
HR (95% CI)	0.37 [0.25;0.54]	
Overall Survival in FAS		
Patients with event	31 (35.6%)	38 (44.2%)
Patients without event	56 (64.4%)	48 (55.8%)
median (months)	**19.5**	**19.3**
p-value (Log-Rank test)	**0.8702**	
HR (95% CI)	1.04 [0.65; 1.68]	
Best Overall Response (Investigator Assessment)		
Responders	**13 (14.9%)**	**50 (58.1%)**
Non-responders	74 (85.1%)	36 (41.9%)
difference in response rate [approx 95% CI, Hauck-Anderson]	**43.20 [29.7 to 56.7]**	
p-value (Chi-squared test)	**< 0.0001**	
Complete response	0 (0%)	2 (2.3%)
Partial response	13 (14.9%)	48 (55.8%)
Stable disease	44 (50.6%)	18 (20.9%)
Progressive disease	11 (12.6%)	6 (7.0%)
Missing	19 (21.8%)	12 (14.0%)

5.5.1.2 Summary of Key Outcomes from OPTIMAL

.

Table 19: Summary of Overall Efficacy Results in OPTIMAL

Parameter	Gemcitabine + Carboplatin Arm (n=72)	Erlotinib Arm (n=82)
Progression Free Survival		
Patients with event	64(88.9 %)	58 (70.7 %)
Patients without event	8(11.1 %)	24 (29.3 %)
median (months)	**4.6**	**13.7**
p-value (Log-Rank test)	**<0.0001**	
HR (95% CI)	0.164 [0.105;0.256]	
Best Overall Response (Investigator Assessment)		
CR	-	2 (2.4%)
PR	26 (36.1%)	66 (80.5%)
SD	33 (45.8%)	11 (13.4%)
PD	12 (16.7%)	3 (3.7%)
NE	1 (1.4%)	-
ORR (%)	**26 (36.1%)**	**68 (82.9%)**
95% CI	25.1%, 48.3%	73.0%, 90.3%
OR	8.96 (4.29, 19.81)	
p	**<0.0001**	
DCR (%)	**59 (81.9%)**	**79 (96.3%)**
95% CI	71.1%, 90.0%	89.7%, 99.2%
OR	6.22 (1.86, 28.58)	
p	**0.0022**	
Lung Cancer Symptoms and Health-related Quality of Life (HRQoL)	**Patients with Clinically Relevant Improvements in QoL During the Study**	
PS, smoking history and gender as covariates	**Gemcitabine + Carboplatin Arm (n=54)**	**Erlotinib Arm (n=74)**
TOTAL FACT-L	**29.6%**	**73.0%**
OR (95% CI)	6.90 (3.07-15.48)	
p	**<0.0001**	
TOI	**24.1%**	**71.6%**
OR (95% CI)	7.79 (3.44-17.66)	
p	**<0.0001**	
LCSS	**31.5%**	**75.6%**
OR (95% CI)	6.77 (3.04-15.05	
p	**<0.0001**	
Exon mutation type, , smoking history and histologic type as covariates	**Gemcitabine + Carboplatin Arm (n=54)**	**Erlotinib Arm (n=74)**
TOTAL FACT-L	**29.6%**	**73.0%**
OR (95% CI)	6.93 (3.10-15.47)	
p	**<0.0001**	
TOI	**24.1%**	**71.6%**
OR (95% CI)	8.63 (3.75-19.85)	
p	**<0.0001**	
LCSS	**31.5%**	**75.7%**
OR (95% CI)	7.05 (3.18-15.64)	
p	**<0.0001**	

5.5.2 The information may be presented graphically to supplement text and tabulated data. If appropriate, please present graphs such as Kaplan-Meier plots.

See section 5.5.3 below.

5.5.3 For each outcome for each included RCT, the following information should be provided.

- The unit of measurement.
- The size of the effect; for dichotomous outcomes, the results ideally should be expressed as both relative risks (or odds ratios) and risk (or rate) differences. For time-to-event analysis, the hazard ratio is an equivalent statistic. Both absolute and relative data should be presented.
- A 95% confidence interval.
- Number of participants in each group included in each analysis and whether the analysis was by ‘intention to treat’. State the results in absolute numbers when feasible.
- When interim RCT data are quoted, this should be clearly stated, along with the point at which data were taken and the time remaining until completion of that RCT. Analytical adjustments should be described to cater for the interim nature of the data.
- Other relevant data that may assist in interpretation of the results may be included, such as adherence to medication and/or study protocol.
- Discuss and justify definitions of any clinically important differences.
- Report any other analyses performed, including subgroup analysis and adjusted analyses, indicating those pre-specified and those exploratory.

5.5.3.1 Efficacy Outcomes in EURTAC

5.5.3.1.1 Primary Endpoint: Progression-Free Survival in EURTAC

The primary efficacy end-point was PFS as assessed by the investigator in the FAS. Progression-free survival was also assessed by an IRC.

At the interim analysis patients treated with erlotinib had significantly prolonged PFS when compared to patients treated with platinum doublet chemotherapy (p-value < 0.0001, log-rank test), Table 20. The median PFS in the platinum doublet chemotherapy arm was 5.2 months compared to 9.4 months in the erlotinib arm and the risk of having a PFS event (progression or death, whichever occurs first) was significantly reduced by 58% (HR 0.42; [95% CI 0.27 to 0.64]) for patients in the erlotinib arm. Twelve percent of patients in the platinum doublet chemotherapy arm and 37% of patients in the erlotinib arm were event-free, 1 year after randomisation.

In the updated analysis, patients treated with erlotinib still had significantly prolonged PFS when compared to patients treated with platinum doublet chemotherapy (p-value < 0.0001, log-rank test). The median PFS in the platinum doublet chemotherapy arm was 5.2 months compared to 9.7 months in the erlotinib arm and the risk of having a PFS event (progression or death, whichever occurs first) was significantly reduced by 63% (HR 0.37; [95% CI 0.25 to 0.54]) for patients in the erlotinib arm. Eleven percent of patients in the platinum doublet chemotherapy arm and 40% of patients in the erlotinib arm were event-free, 1 year after randomization.

Table 20: Summary of the Primary PFS Endpoint in EURTAC

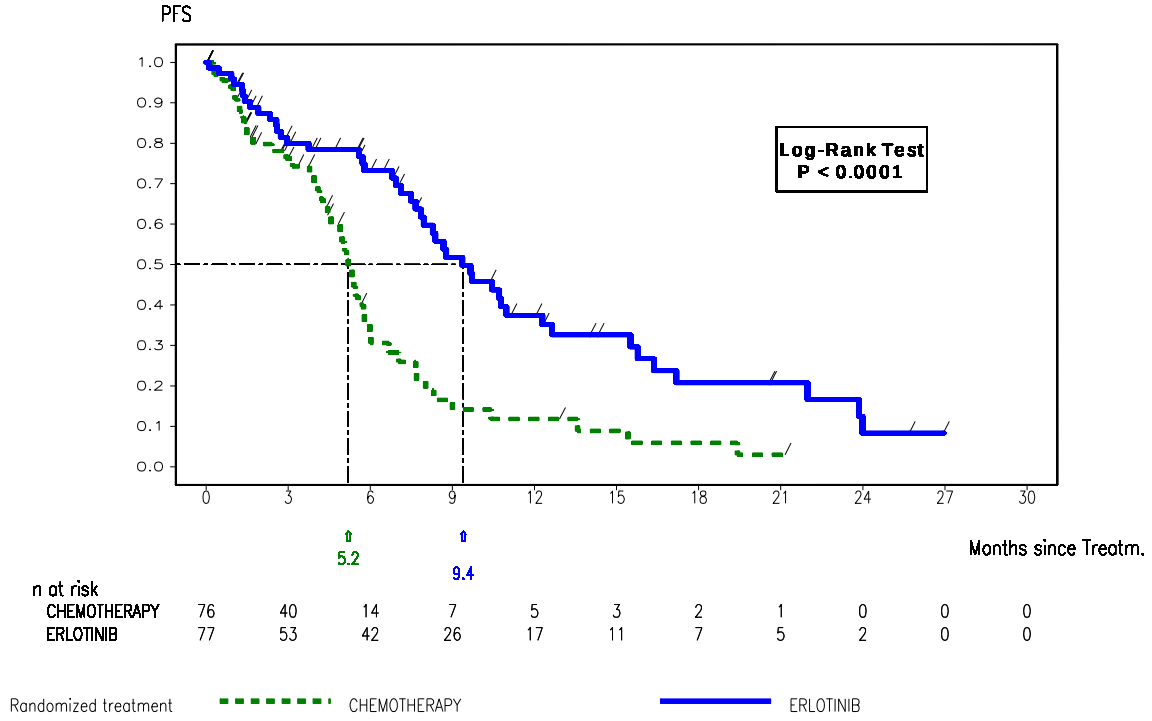
	Interim Analysis (Data Cut-off 2nd August 2010)		**Updated Analysis (Data Cut-off 26th January 2011)**	
	Platinum Doublet Chemotherapy (n=76)	**Erlotinib (n=77)**	**Platinum Doublet Chemotherapy (n=76)**	**Erlotinib (n=77)**
Patients with Event	47 (61.8%)	45 (58.4%)	59 (67.8%)	52 (60.5%)
Patients Without Event[Δ]	29 (38.2%)	32 (41.6%)	28 (32.2%)	34 (39.5%)
Time to Event (months)				
Median[♯]	**5.2**	**9.4**	**5.2**	**9.7**
95% CI for Median[♯]	**(4.4-5.8)**	**(7.9-12.3)**	**(4.5-6.0)**	**(8.4-12.6)**
25% and 75%-ile	3.2 ; 7.7	5.7 ; 16.4	3.8 ; 7.0	5.8 ; 17.2
Range[▲]	0.0-21.2	0.0-26.9	0.0-23.5	0.0-32.5
p-value (Log-Rank Test)	**<0.0001**		**<0.0001**	
Hazard Ratio	**0.42**		**0.37**	
95% CI	**(0.27-0.64)**		**(0.25-0.54)**	
1-year estimate				

Patients remaining at risk	5	17	5	21
Event-free Rate[#]	0.12	0.37	0.11	0.40
95% CI for Rate[#]	(0.02-0.21)	(0.24-0.51)	(0.02-0.19)	(0.28-0.52)

PFS [months] (TTPFS M) - Censoring: PFS Censoring (1=PD/death) (CSPFS)
[Δ]censored
[#]Kaplan-Meier estimates
[▲]including censored observations

For the initial interim analysis of the primary PFS endpoint, the Kaplan-Meier curves for PFS begin to separate at around 6 weeks and remain well separated over the course of the observation period.

Figure 13: Kaplan-Meier Curve of PFS (FAS) – Interim Analysis

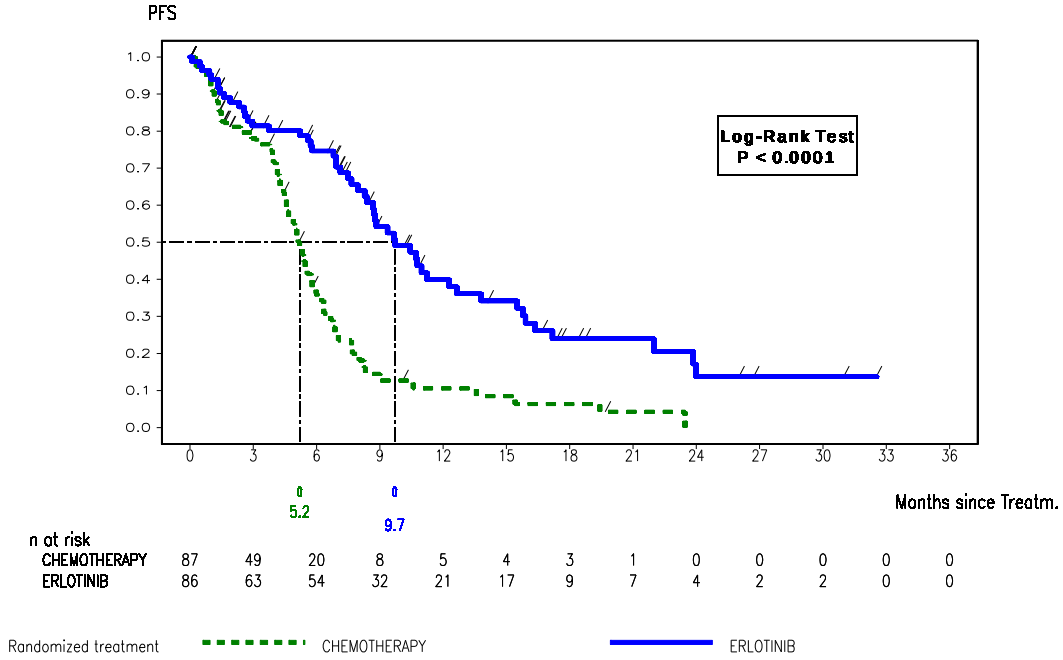


Cut-off for statistical analysis: 02AUG2010

Outcomes for the primary efficacy analysis of PFS as assessed by the IRC were consistent with the primary PFS analysis based on the investigator's assessment. The median PFS was 5.4 months in the platinum doublet chemotherapy arm compared to 10.4 months in the erlotinib arm (p = 0.0030, log-rank test, HR: 0.47 [95% CI 0.28 to 0.78]). Twenty-five percent of patients in the platinum doublet chemotherapy arm and 41% of patients in the erlotinib arm were event free at 1 year.

In the updated analysis for the primary PFS endpoint, the Kaplan-Meier curves for PFS begin to separate at around 6 weeks and remain well separated over the course of the observation period.

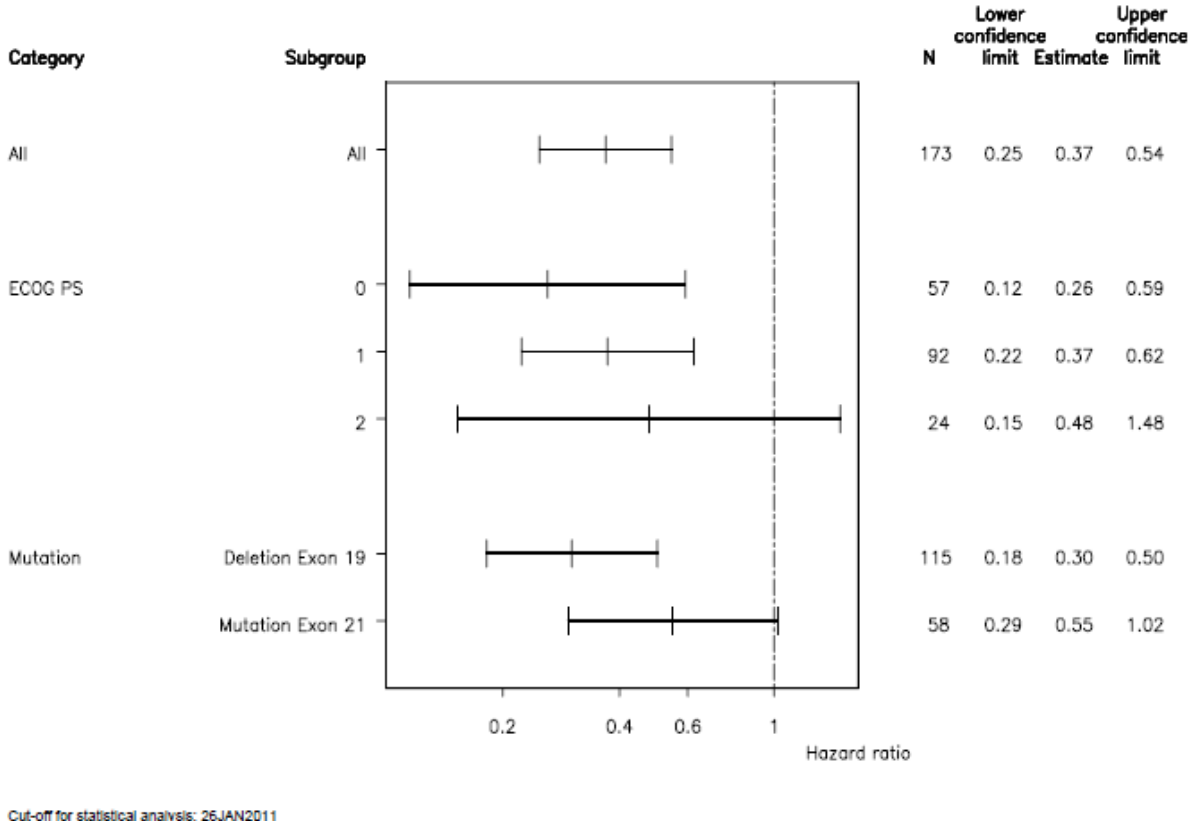
Figure 14: **Kaplan-Meier Curve of PFS (FAS) – Updated Analysis**



Cut-off for statistical analysis: 26JAN2011

The results of the analyses of PFS by stratification factors were also consistent with those of the FAS

Figure 15: Forest Plot of Hazard Ratios and 95% CIs for PFS by Subgroup (Stratification Factors)



Cut-off for statistical analysis: 26JAN2011

5.5.3.1.2 Secondary Endpoints in EURTAC

Best Overall Response

The proportion of responders (patients having a confirmed CR or PR after randomisation) was significantly greater in the erlotinib arm than in the platinum doublet chemotherapy arm (54.5% [95% CIs: 42.8% and 65.9%] and 10.5% [95% CIs: 4.7% to 19.7%], respectively $p < 0.0001$). Sixteen patients (21.1%) in the platinum doublet chemotherapy arm and 11 patients (14.3%) in the erlotinib arm had a missing best overall response. These patients were counted as non-responders.

The results of the analysis of best overall response as assessed by the IRC were consistent with those as assessed by the investigator (difference in response rate between treatment arms 32.4%, $p < 0.0001$ in favour of erlotinib).

At the updated analysis, there was a similar difference in response rates in the erlotinib and platinum doublet chemotherapy arms (58.1% [95% CIs: 47.0% to

68.7%] and 14.9% [95% CIs: 8.2% to 24.2%], respectively p < 0.0001). Nineteen patients (21.8%) in the platinum doublet chemotherapy arm and 12 patients (14.0%) in the erlotinib arm had a missing best overall response. These patients were counted as non-responders.

Table 21: Summary of Best Overall Response (FAS)

	Interim Analysis (Data Cut-off 2nd August 2010)		Updated Analysis (Data Cut-off 26th January 2011)	
	Platinum Doublet Chemotherapy (n=76)	Erlotinib (n=77)	Platinum Doublet Chemotherapy (n=76)	Erlotinib (n=77)
Responders$	**8 (10.5%)**	**42 (54.5%)**	**13 (14.9 %)**	**50 (58.1%)**
Non-Responders	68 (89.5%)	35 (45.5%)	74 (85.1%)	36 (41.9%)
95% CI for Response Rates*	**[4.7-19.7]**	**[42.8-65.9]**	**[8.2-24.2]**	**[47.0-68.7]**
Difference in Response Rates	44.02		43.20	
95% CI for Difference in Response Rates#	[30.2-57.9]		[29.7-56.7]	
p-Value (Chi-squared Test)	**<.0.0001**		**<0.0001**	
Odds Ratio	10.20		7.90	
95% CI for Odds Ratio	[4.32-24.08]		[3.8-16.38]	
Complete Response (CR)	0 (0.0%)	2 (2.6%)	0 (0.0%)	2 (2.3%)
95% CI for CR Rates*	[0.0-4.7]	[0.3-9.1]	[0.0-4.2]	[0.3-8.1]
Partial Response (PR)	8 (10.5%)	40 (51.9%)	13 14.9%)	48 (55.8%)
95% CI for PR Rates*	[4.7-19.7]	[40.3-63.5]	[8.2-24.2]	[44.7-66.5]
Stable Disease (SD)	42 55.3%)	18 (23.4%)	44 (50.6%)	18 (20.9%)
95% CI for SD Rates*	[43.4-66.7]	[14.5-34.4]	[39.6-61.5]	[12.9-31.0]
Progressive Disease (PD)	10 (13.2%)	6 (7.8%)	11 (12.6%)	6 (7.0%)
95% CI for PD Rates*	[6.5-22.9]	[2.9-16.2]	[6.5-21.5]	[2.6-14.6]
Missing (No Response Assessment)	16 (21.1%)	11 (14.3%)	19 (21.8%)	12 (14.0%)

Best Overall Response (BRESP)
* 95% CI for one sample binomial using Pearson-Clopper method
# Approximate 95% CI for difference of two rates using Hauck-Anderson method
$ Patients with best overall response of confirmed CR or PR
Non-Responder is SD, PD or missing.

Disease Control

Disease control was greater for patients receiving erlotinib (77.9%) compared to those receiving platinum doublet chemotherapy (65.8%) as assessed by the investigator but this was not statistically significant (p = 0.0951, chi-squared test).

In contrast to the investigator assessment, the IRC assessment revealed a statistically significant difference in disease control rate between the treatment arms,

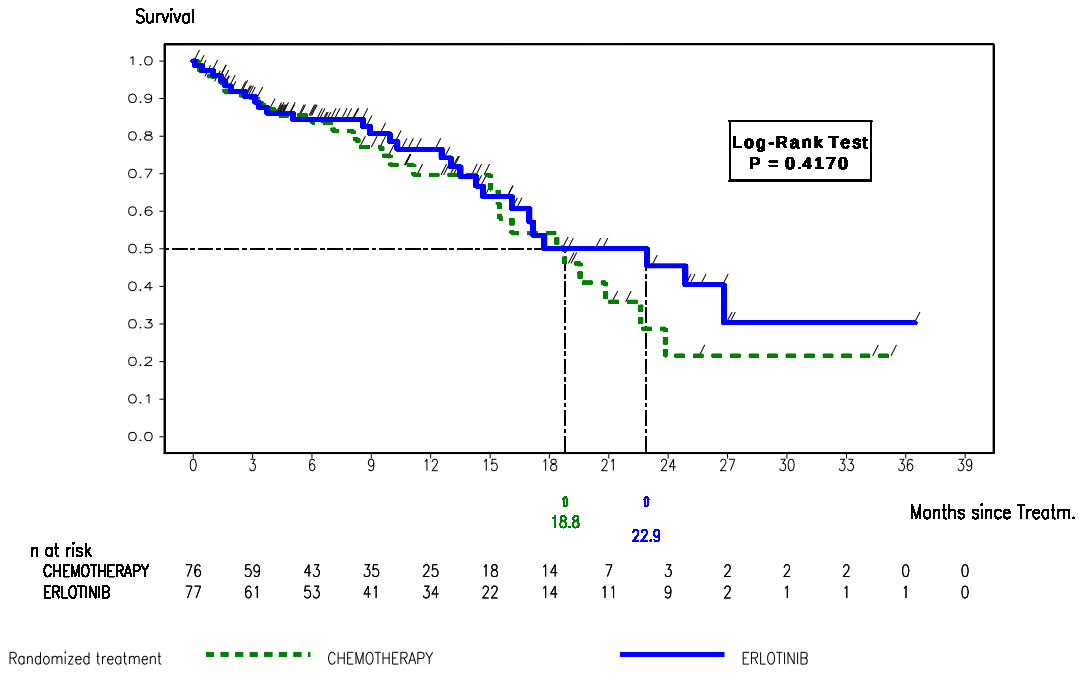
47.4% and 71.4% in the platinum doublet chemotherapy and erlotinib arms, respectively, (p = 0.0024, chi-squared test).

Overall Survival

The OS data were immature at the interim analysis cut-off date of 2nd August 2010, when 54 patients (35%) had died. The median time to death was 18.8 and 22.9 months in the platinum doublet chemotherapy and erlotinib arms respectively. The HR was 0.80 (95% CI 0.47 to 1.37, p-value of log-rank test 0.42). The 1-year event free rate was 0.70 in the platinum doublet chemotherapy arm compared to 0.77 in the erlotinib arm.

The Kaplan-Meier curves broadly overlap for approximately 19 months before they start to separate in favour of erlotinib. The 2-year event free rate was 22% in the platinum doublet chemotherapy arm compared to 45% in the erlotinib arm.

Figure 16: **Kaplan-Meier Curve of Overall Survival (FAS) – Interim Analysis**

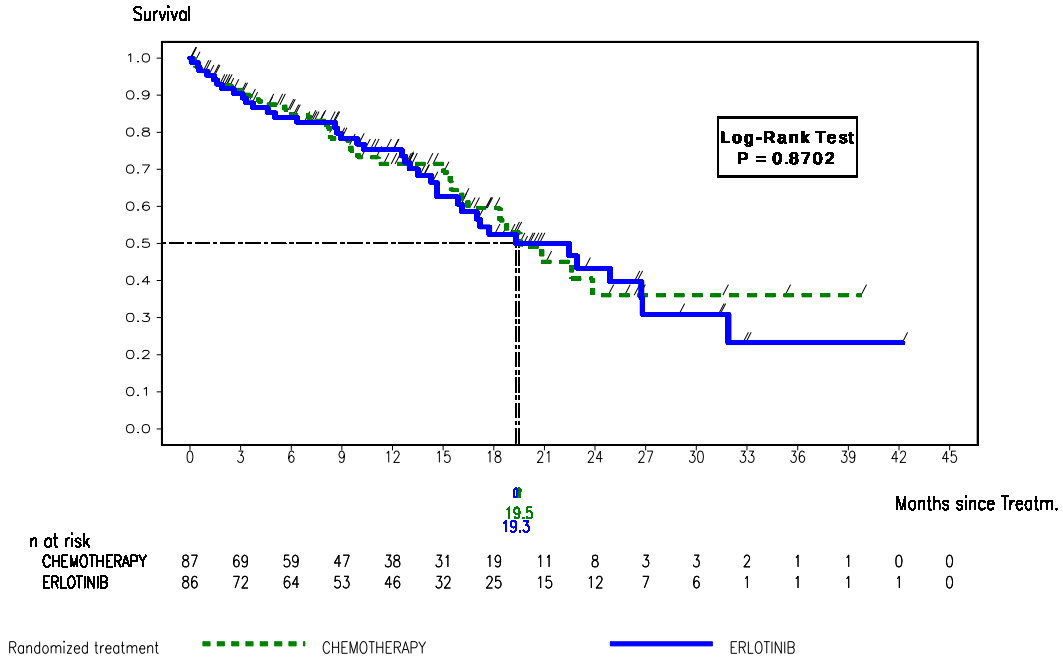


Cut-off for statistical analysis: 02AUG2010

The OS data were still immature at the updated analysis cut-off date of January 26th, 2011, when 69 patients (40%) had died (compared to 54 patients [35%] at primary

analysis). The median time to death was 19.5 months in the platinum doublet chemotherapy arm and 19.3 months in the erlotinib arm. The HR was 1.04 (95% CI 0.65 to 1.68, p-value of log-rank test 0.8702). The 1-year event free rate was 71% in the platinum doublet chemotherapy arm and 75% in the erlotinib arm. The 2-year event free rate was 36% in the platinum doublet chemotherapy arm and 43% in the erlotinib arm.

Figure 17: **Kaplan-Meier Curve of Overall Survival (FAS) – Updated Analysis**



Cut-off for statistical analysis: 26JAN2011

The OS data is still maturing. However, due to the high level of cross-over from platinum doublet chemotherapy to an EGFR TKI post-progression, it is unlikely to reach statistical significance. In addition, EURTAC was not powered to show a difference in OS.

Second- and Further-Line Treatments for NSCLC in EURTAC

More patients in the platinum doublet chemotherapy arm received second- and further-line treatments compared to the erlotinib arm, 77% and 45%, respectively. This is a similar trend to that observed at the primary analysis where 67% and 36% of patients received a second- and further-line treatment, in the platinum doublet

chemotherapy and erlotinib arms, respectively. This is in part due to the fact that more patients in the erlotinib arm were still on treatment at the cut-off for the updated analysis due to the longer PFS compared to the platinum doublet chemotherapy arm. In addition, more patients in the platinum doublet chemotherapy arm compared to the erlotinib arm crossed over to receive another treatment after withdrawing from EURTAC due to an AE, investigator's criterion or other reasons.

Sixty-seven patients in the platinum doublet chemotherapy arm received a second- or further-line treatment of whom 66 (99%) received at least one treatment with a tyrosine kinase inhibitor (TKI) (65 patients received erlotinib: 2 patients received gefitinib).

Anti-metabolites (mainly pemetrexed) were administered as treatments to 30 of the 39 patients (77%) who received a second- or further-line treatment in the erlotinib arm compared to 13/67 (19.4%) patients in the platinum doublet chemotherapy arm.

Platinum-based compounds were administered to 27 of 39 patients (69%) who received a second- or further-line treatment in the erlotinib arm compared to 5 of 67 patients (7%) in the platinum doublet chemotherapy arm.

Quality of Life (Lung Cancer Symptom Scale) in EURTAC

The completion rate of the LCSS questionnaire was low across both treatment arms. Completion rates were lower in the platinum doublet chemotherapy arm than in the erlotinib arm (at baseline 63% and 70% in the platinum doublet chemotherapy and erlotinib arms, respectively). At visit 1, only 23% and 28% patients in the platinum doublet chemotherapy and erlotinib arms, respectively, completed the questionnaire. On visit 2, completion rates had increased to 56% and 82% of patients in the platinum doublet chemotherapy and erlotinib arms, respectively. The majority of platinum doublet chemotherapy patients did not complete the questionnaire after

completing platinum doublet chemotherapy. The completion rate for the observer scale questionnaire (optional) was lower than that of the patient scale questionnaire.

In light of the low completion rates of the LCSS questionnaire observed at the primary analysis, the data on QoL are considered inconclusive and therefore have not been included for EURTAC within this application. Quality of life data has however been presented for OPTIMAL which was more complete and sufficient for adequate analysis of the impact of the two treatment arms on patients QoL.

5.5.3.1.3 Summary of Efficacy in EURTAC

EURTAC met its primary endpoint by demonstrating a highly statistically significant and clinically meaningful improvement in investigator assessed PFS, more than halving the risk of progression for patients on erlotinib compared to those receiving standard platinum doublet chemotherapy. The updated analysis of PFS confirmed the results observed at the primary analysis where the median PFS for patients in the erlotinib arm increased to 9.7 months from 9.4 months at the primary analysis and the risk of having a PFS event for erlotinib-treated patients was reduced from 42% (95% CI: 0.27; 0.64) to 37% (95% CI: 0.25; 0.54). Patients on erlotinib were thus two thirds less likely to have a progression event compared to those receiving standard platinum doublet chemotherapy.

Patients on erlotinib were nearly 4 times more likely to have a response to treatment compared to those receiving platinum doublet chemotherapy. The response rate was significantly greater in the erlotinib arm than in the platinum doublet chemotherapy arm (58.1% [95% CIs: 47.0% to 68.7%] and 14.9% [95% CIs: 8.2% to 24.2%], respectively $p < 0.0001$) at the updated analysis.

The OS remained immature and high levels of cross-over were observed in the platinum doublet chemotherapy arm.

5.5.3.2 Efficacy Outcomes in OPTIMAL

As EURTAC was a study conducted in a Caucasian population, the data is likely to be more representative of the efficacy observed in the UK population.

The superior efficacy outcomes of erlotinib over platinum doublet platinum doublet chemotherapy demonstrated in EURTAC are further supported by another phase III RCT conducted in Chinese patients, namely the OPTIMAL study.

OPTIMAL was a multicentre, randomised, open-label, controlled phase III study comparing the efficacy of erlotinib monotherapy *vs* gemcitabine + carboplatin chemotherapy in chemo-naïve stage IIIB or stage IV NSCLC patients with activating EGFR mutations.

The target population for this study comprised chemo-naïve patients with pathologically confirmed unresectable stage IIIB or stage IV NSCLC and tumours with activating EGFR mutations (exon 19 deletion or exon 21 L858R mutation).

5.5.3.2.1 Primary Endpoint: Progression-Free Survival in OPTIMAL

As shown in EURTAC, OPTIMAL demonstrated that 1st line treatment with erlotinib significantly improved the primary outcome measure of PFS compared to platinum doublet chemotherapy (gemcitabine + carboplatin).

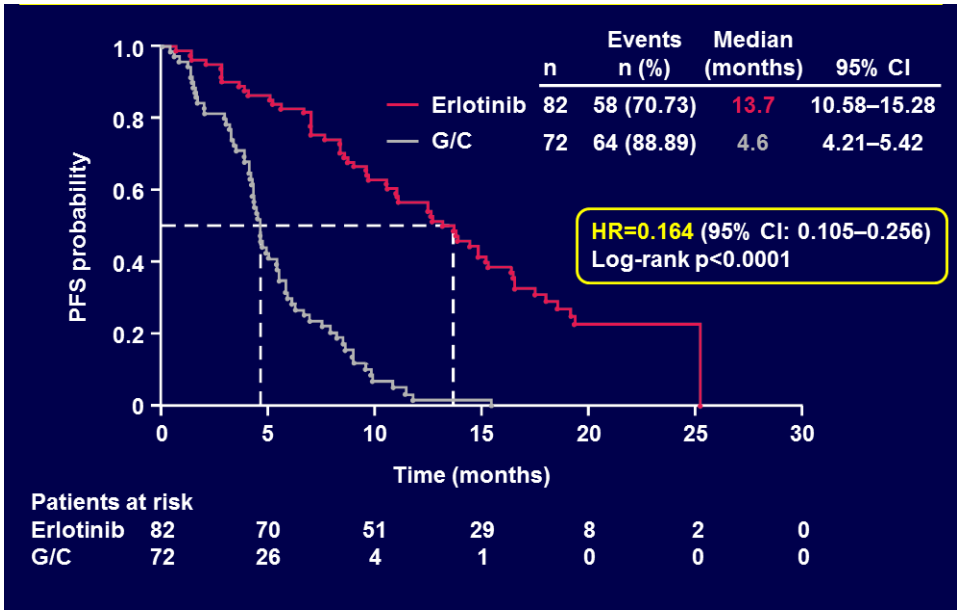
At the time of the data cut-off for the most recent analysis of PFS (7th January 2011), 122 events of progression or death had occurred, 58 events had occurred in the erlotinib arm and 64 events in the gemcitabine + carboplatin arm.

The results demonstrate that compared with gemcitabine + carboplatin, erlotinib monotherapy significantly prolonged PFS and reduced the risk of progression or death in NSCLC patients with EGFR mutations. The hazard ratio (HR) indicated an

83.6% reduction in the risk of progression or death in the erlotinib arm (HR 0.164, 95% CI 0.105-0.256, log-rank p-value < 0.0001) compared with the gemcitabine + carboplatin arm. The median time to progression or death was 13.7 months (95% CI 10.58-15.28 months) for patients in the erlotinib arm and 4.6 months (95% CI 4.21-5.42 months) for patients in the gemcitabine + carboplatin arm.

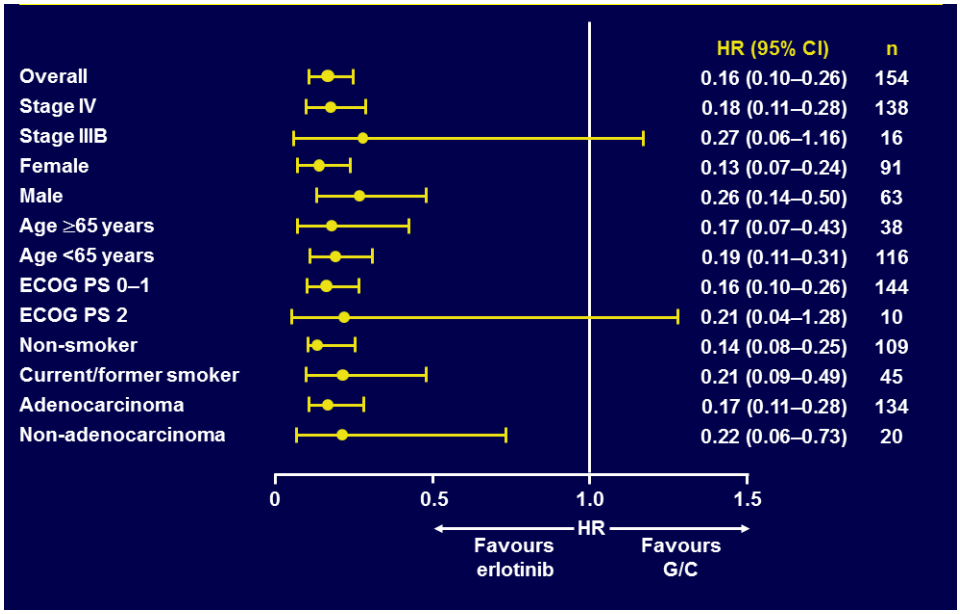
The Kaplan-Meier curves presented below demonstrates separation of the curves in favour of the erlotinib arm as early as 1 month after initiation of treatment.

Figure 18: **Kaplan-Meier Curve of PFS**



The results of each of the subgroup analyses for PFS were consistent with those seen for all patients and showed at least a 70% reduction in the risk of progression or death with erlotinib compared with chemotherapy for all groups examined.

Figure 19: Forest Plot of Hazard Ratios and 95% CIs for PFS by Subgroup (Baseline Demographic Characteristics and Stratification Factors)



5.5.3.2.2 Secondary Endpoints in OPTIMAL

Objective Response Rate (ORR)

The percentage of patients with a best objective response of CR + PR was higher in the erlotinib arm (68/82 patients; 82.9%) compared with the gemcitabine + carboplatin arm (26/72 patients; 36.1%). Logistic regression analysis revealed a highly statistically significant between-group difference, $p < 0.0001$. The efficacy odds ratio (OR) for objective response rate between the two groups was 8.96 (95% CI 4.29-19.81).

Disease Control Rate (DCR)

The disease control rate (CR + PR + SD) was 96.3% (95% CI 89.7%-99.2%) in the erlotinib arm and 81.9% (95% CI 71.1%-90.0%) in the gemcitabine + carboplatin arm. The Log-rank test revealed a highly statistically significant difference between the two treatment arms in favour of erlotinib treatment ($p = 0.0022$). The efficacy odds ratio (OR) for disease control rate between the two groups was 6.22 (95% CI 1.86-28.58).

Table 22: Logistic Regression Analysis of the Response and Objective Response Rate (ORR)

	Treatment Arm		
Response	**Erlotinib**	**gemcitabine + carboplatin**	**P**
	n=82	**n=72**	
CR	2 (2.4%)	-	<0.0001
PR	66 (80.5%)	26 (36.1%)	
SD	11 (13.4%)	33 (45.8%)	
PD	3 (3.7%)	12 (16.7%)	
NE	-	1 (1.4%)	
ORR (%)	**68 (82.9%)**	**26 (36.1%)**	**<0.0001**
95% CI	73.0%, 90.3%	25.1%, 48.3%	.
OR	8.96 (4.29, 19.81)		
DCR (%)	**79 (96.3%)**	**59 (81.9%)**	**0.0022**
95% CI	89.7%, 99.2%	71.1%, 90.0%	.
OR	6.22 (1.86, 28.58)		

ORR = CR + PR; DCR = CR + PR + SD

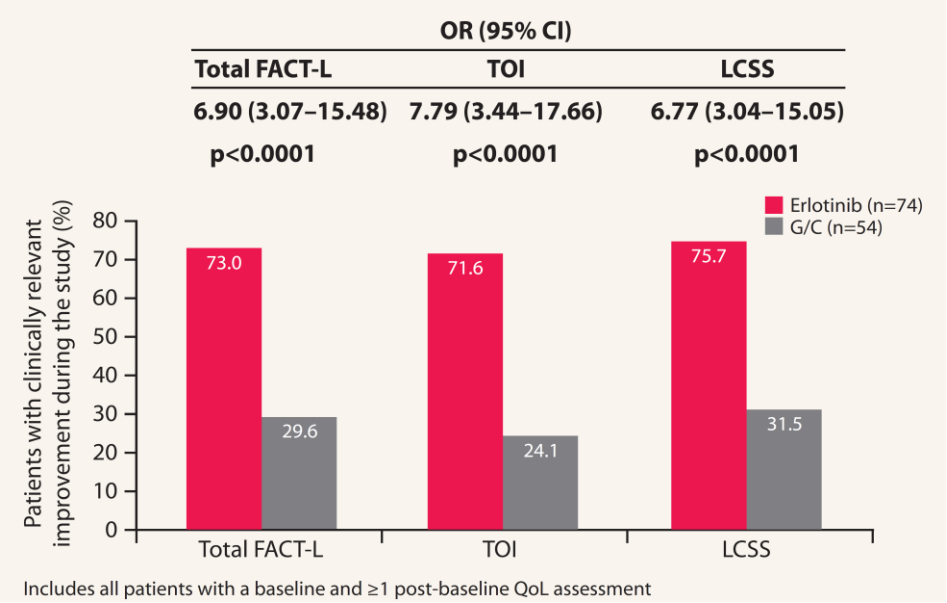
Overall Survival (OS)

At data cut-off overall survival data remain immature, median duration of overall survival could not be determined.

Lung Cancer Symptoms and Health-related Quality of Life (HRQoL)

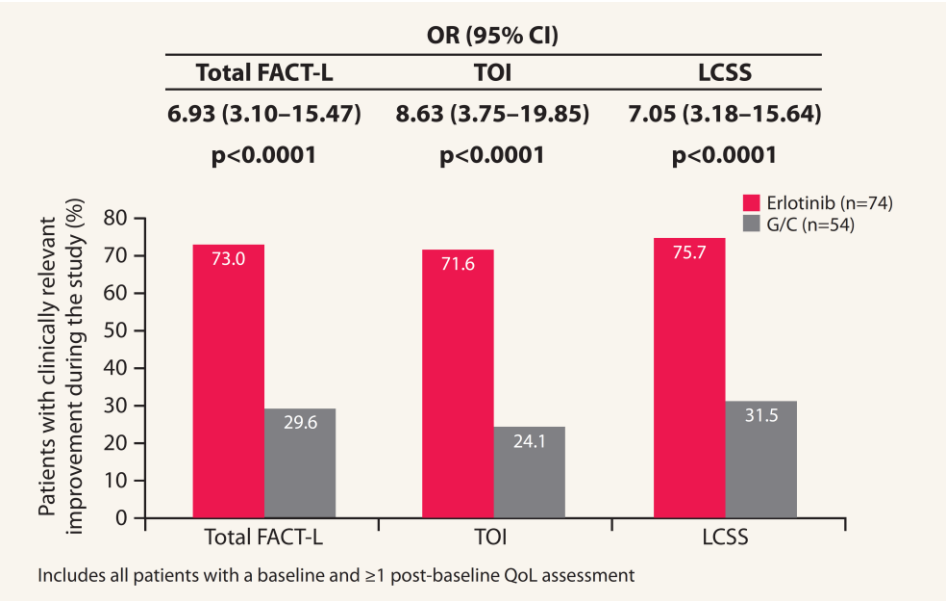
Pre-planned QoL analyses conducted in 128 patients (83.2%) demonstrated that patients receiving first-line erlotinib experienced significantly greater clinically relevant improvements in QoL compared with patients receiving gemcitabine + carboplatin on all QoL scales, using PS, smoking history and gender as covariates.

Figure 20: **Clinically relevant improvement in QoL scores and symptoms during the study with PS, smoking history and gender as covariates**



Greater significant improvements in QoL were also observed in favour of erlotinib using mutation type, smoking history and histological type as covariates on all QoL scales.

Figure 21: **Clinically relevant improvement in QoL scores and symptoms during the study with exon mutation type, smoking history and histologic type as covariates**



5.5.3.2.3 Summary of Outcomes in OPTIMAL

OPTIMAL met its primary endpoint by demonstrating a highly statistically significant and clinically important improvement in PFS when Chinese patients with NSCLC having activating EGFR mutations were treated with 1st line erlotinib compared to platinum doublet chemotherapy. Patients on erlotinib were 84% less likely to progress compared to those receiving platinum doublet chemotherapy (HR 0.164, 95% CI 0.105-0.256, log-rank p-value < 0.0001) compared with the gemcitabine + carboplatin arm).The median PFS was three times greater in the erlotinib arm (13.7 months) compared to the platinum doublet chemotherapy arm (4.6 months).

Patients on erlotinib were more than twice as likely to respond to treatment with erlotinib compared to those receiving platinum doublet chemotherapy. The response rate was significantly greater in the erlotinib arm than in the gemcitabine + carboplatin arm (82.9% *vs* 36.1% respectively, p < 0.0001) and the disease control rate was also significantly greater in the erlotinib arm than in the gemcitabine + carboplatin arm (96.3% *vs* 81.9% respectively, p = 0.0022).

The OS data remains immature and has not been presented yet.

First line erlotinib treatment also produced significantly greater clinically relevant improvements in patient QoL compared to standard platinum doublet chemotherapy in patients with NSCLC having activating EGFR mutations. More than double the number of patients receiving erlotinib had clinical relevant improvements in QoL compared to those receiving platinum double chemotherapy (~70% vs ~30% respectively) across all FACT-L scales measured.

The clinical efficacy results of OPTIMAL are consistent with the results of EURTAC in demonstrating the superiority of erlotinib over standard platinum doublet chemotherapy. OPTIMAL also demonstrated that more significantly patients

receiving erlotinib gained meaningful improvements in QOL compared to those receiving platinum doublet chemotherapy.

5.6 Meta-analysis

When more than one study is available and the methodology is comparable, a meta-analysis should be undertaken. This section should be read in conjunction with NICE's 'Guide to the methods of technology appraisal', sections 5.3.9 to 5.3.12.

5.6.1 The following steps should be used as a minimum when presenting a meta-analysis.

- Perform a statistical assessment of heterogeneity. If the visual presentation and/or the statistical test indicate that the RCT results are heterogeneous, try to provide an explanation for the heterogeneity.
- Statistically combine (pool) the results for both relative risk reduction and absolute risk reduction using both the fixed effects and random effects models (giving four combinations in all).
- Provide an adequate description of the methods of statistical combination and justify their choice.
- Undertake sensitivity analysis when appropriate.
- Tabulate and/or graphically display the individual and combined results (such as through the use of forest plots).

Assessment of Heterogeneity

According to the Cochrane Collaboration, when considering conducting a meta-analysis it is:

"… important to consider to what extent the results of studies are consistent. If confidence intervals for the results of individual studies (generally depicted graphically using horizontal lines) have poor overlap, this generally indicates the presence of statistical heterogeneity. More formally, a statistical test for

heterogeneity is available. This chi-squared (χ^2, or Chi^2) test is included in the forest plots in Cochrane reviews" (Cochrane Handbook, Chapter 9.5.2. – Higgins, 2011)

Whilst the EURTAC and OPTIMAL studies were both unquestionably positive in favour of erlotinib and both compared against 'doublet chemotherapy', the precise magnitude of the treatment effect observed in each study was not consistent.

In the EURTAC RCT a PFS HR of 0.37 {0.25, 0.54} was estimated with a median PFS of 9.7 months and 5.2 months for erlotinib and chemotherapy respectively. In the OPTIMAL study a PFS HR of 0.16 {0.11, 0.26} was observed with associated median PFS values of 13.7 for erlotinib and 4.6 months for chemotherapy. Whilst both studies demonstrate the efficacy of erlotinib it is notable that the magnitude of the treatment effect observed in the Asian OPTIMAL study is greater than that of the European EURTAC study (both in terms of the PFS HR and the median PFS).

The extent of this diversity means that if one were to conduct an indirect comparison of erlotinib in OPTIMAL and erlotinib in EURTAC as if they were different treatments a point estimate PFS hazard ratio of 0.44 (EXP(LN(0.162)-LN(0.37)) = 0.44) (Bucher et al 1997) would be estimated. Clearly this suggests that there is heterogeneity between studies and brings into doubt the pooling of the treatment effects observed in each study. Furthermore when the confidence intervals of the two estimates are compared (as suggested by the Cochrane Collaboration) it is apparent that there is minimal overlap between the two estimates (suggesting heterogeneity).

This hypothesis of heterogeneity was tested statistically via a Chi^2 test and the generation of an I^2 statistic (derived using the Cochrane collaboration's RevMan 5.1 software). As suggested by a simple comparison of the results of the two studies these analyses demonstrates that there is considerable heterogeneity between the studies (Chi^2 p-value = 0.007, I^2 value = 86%).

Explanation of Heterogeneity

In order to ensure all potential causes of heterogeneity between EURTAC and OPTIMAL were captured, the two studies were systematically described and

compared using a PICOS (population, intervention, comparators, outcomes, study design) framework. This comparison was designed to evaluate any meaningful differences between the two studies and discern why the OPTIMAL study suggests a higher treatment effect for erlotinib than the EURTAC RCT.

Population (P)

The characteristics of patients in the EURTAC and OPTIMAL RCTs are presented in Table 12 above. In general these populations appear broadly comparable in terms of the proportion of patients who were 'never-smokers', the proportion of patients with stage IV disease and the proportion of patients with a performance status of 0-1 (although as data from OPTIMAL is not split by PS 0 and 1 it is possible there may an imbalance in the proportion of patients in each of the individual PS categories). There is however, some heterogeneity in terms of the age of patients in each of the studies (median age of patients in EURTAC of 65 compared to 57 and 59 the two arms of OPTIMAL) slightly favouring OPTIMAL although the extent to which being younger results in a patient diagnosed with mNSCLC living longer is debatable. There was also a slightly greater proportion of female patients enrolled in the EURTAC RCT compared to OPTIMAL (an imbalance potentially favouring EURTAC if female patients have better prognosis than males). Similarly there was a higher proportion of Exon 19 deletions compared to L858R point mutations in EURTAC than OPTIMAL (modestly favouring EURTAC).

The most evident differentiator between the populations of OPTIMAL and EURTAC appears to be the race of the participants enrolled. EURTAC was conducted in entirely European centres using patients broadly representative of those expected in English/Welsh practice whilst OPTIMAL was conducted in entirely Chinese centres.

In the NICE appraisal of erlotinib as a maintenance treatment for mNSCLC (NICE TA227) one of the key objections of the Appraisal Committee to the SATURN RCT data presented was that this study featured a 'high' proportion of Asian patients and that Asian patients were *'known to respond better to lung cancer treatments than patients of other races'* (TA227 FAD, Section 4.5).

If this hypothesis of a differential treatment effect for EGFR TKIs in European and Asian patients is true (perhaps due to the presence/absence of some unknown or unobserved race related covariate) this may be the reason for the heterogeneity observed between the EURTAC and OPTIMAL studies.

Whilst there are other differences in the characteristics of patients included in each study none of these differences appear particularly sizeable or likely to bias the results unduly towards OPTIMAL (indeed they appear to 'cancel each other out' or perhaps even slightly favour the EURTAC RCT).

Given the opinion expressed by the Appraisal Committee in NICE TA227 and the clear ethnic differences between patients in EURTAC and OPTIMAL it appears possible that ethnicity may be responsible, at least in part, for the heterogeneity in treatment effects observed.

Interventions (I)

Both EURTAC and OPTIMAL studied erlotinib at a protocol dose of 150mg (one tablet) per day until disease progression or unacceptable toxicity (with the potential for down-dosing to a smaller tablet size where required).

However, there does appear to be some differences in how the intervention was actually administered in each RCT between the two studies which may explain the heterogeneity observed. The OPTIMAL RCT featured a much lower rate of down-dosing due to AEs (4.8% in OPTIMAL compared to 13.1% in EURTAC) and a much lower rate of discontinuation (1.2% discontinuation rate in OPTIMAL compared to 13.1% in EURTAC).

This issue of compliance is perhaps one of the clearest differentiators between EURTAC and OPTIMAL. It appears logical that better compliance would result in a greater treatment effect, and therefore heterogeneity in outcomes in studies with differing levels of compliance. In effect whilst both RCTs studied 'erlotinib' within its SPC specified dose the OPTIMAL study featured erlotinib given, on average, at a higher dose and for a longer proportion of a patient's time in PFS than in EURTAC.

Comparators (C)

The EURTAC RCT allowed clinicians to utilize a choice of 4 chemotherapy regimens (accepted to be of broadly equivalent efficacy – NICE TA192, Schiller et al 2002, Scagliotti et al 2002) whilst OPTIMAL restricted clinicians to solely gemcitabine/carboplatin doublet chemotherapy (one of the doublet chemotherapy regimens generally accepted as being of the same efficacy). A simple naïve cross-trial comparison of the PFS medians of patients receiving doublet chemotherapy in EURTAC and OPTIMAL indicates that the median PFS of patients given gemcitabine/carboplatin in OPTIMAL was slightly lower than that for EURTAC (4.6 months in OPTIMAL compared to 5.2 months in EURTAC)

Whilst it may be hypothesised that this modestly 'under-performing' comparator arm could lead to the heterogeneity in PFS hazard ratios observed in EURTAC and OPTIMAL it does not explain the difference in erlotinib PFS medians between studies. Median PFS in the chemotherapy arm in OPTIMAL was lower than that in EURTAC yet median PFS in the erlotinib arm was substantially higher in OPTIMAL than EURTAC (around 4 months higher). This suggests that whilst this apparent under-performance may (in part) contribute to the heterogeneity in HR observed it is likely that there is some heterogeneity associated with erlotinib between the studies that is driving the heterogeneity observed.

Outcomes (O)

Both studies utilised 'progression free survival' as their primary endpoint. Both studies utilised the same definition of progression (via the use of the RECIST criteria) and considered deaths due to any cause as PFS events. There therefore does not appear to be considerable heterogeneity between the ways outcomes were defined in EURTAC and OPTIMAL that may have led to the observation of different treatment effects in each study.

Study Design (S)

Both studies were RCTs of comparable size that featured 1:1 randomisation to either erlotinib or doublet chemotherapy. Both were open-label. Both utilised the RECIST criteria to define progression. There therefore does not appear to be significant heterogeneity between the design of EURTAC and OPTIMAL.

Conclusion:

Whilst there is sizeable heterogeneity between the treatment effects observed in EURTAC and OPTIMAL it is difficult to target precisely what the cause of this heterogeneity is. The heterogeneity in treatment effect observed:

- *may* be due to a slightly underperforming comparator arm in OPTIMAL (at least in terms of the PFS HR observed – clearly this does not explain the 4 month difference in the median PFS of patients given erlotinib in OPTIMAL compared to EURTAC).

- *may* be a product of differences in the ethnic mix of the patients included in each study (if Asians do indeed perform better in response to EGFR TKIs than their European counterparts)

- *may* be a product of the better compliance and more aggressive adherence to the maximum possible dose of erlotinib treatment in OPTIMAL than in EURTAC

Whilst it is not possible to identify the precise cause of the heterogeneity observed, given the magnitude of heterogeneity present it appears inappropriate to rely upon an estimate of the pooled efficacy of erlotinib vs doublet chemotherapy based upon the EURTAC and OPTIMAL studies.

As EURTAC is the more relevant of the two studies to English/Welsh clinical practice and was conducted as per EMA regulatory requirements we believe that it, rather than the OPTIMAL RCT or a pooling of the EURTAC and OPTIMAL RCTs, is likely

to offer the best basis on which to assess the clinical and cost-effectiveness of erlotinib in the first line treatment of a Caucasian population.

Despite the reservations stated above the EURTAC and OPTIMAL studies were pooled using RevMan 5.1 in order to determine what the pooled PFS HR of erlotinib vs doublet chemotherapy *would* be if it was assumed the heterogeneity observed was not of consequence. Both Random and Fixed Effects analyses were conducted based upon generic inverse variance weighting of the two studies.

The results of these analyses are presented in the forest plots below:

Figure 22: **Random Effects EURTAC/OPTIMAL Pooling Forest Plot**

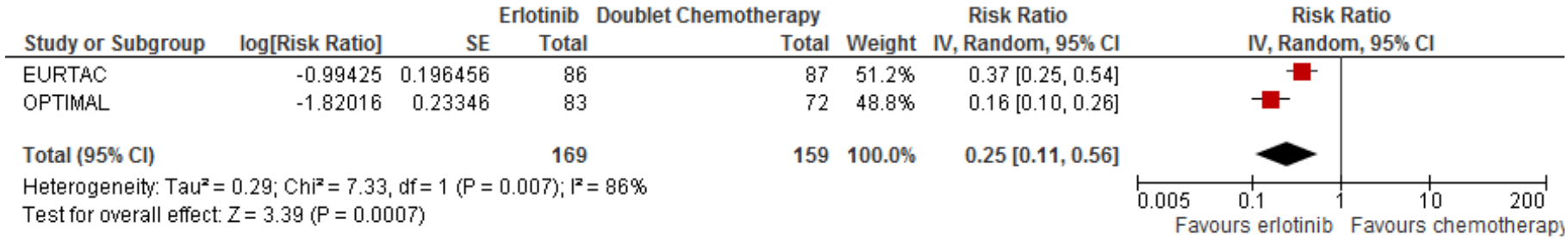
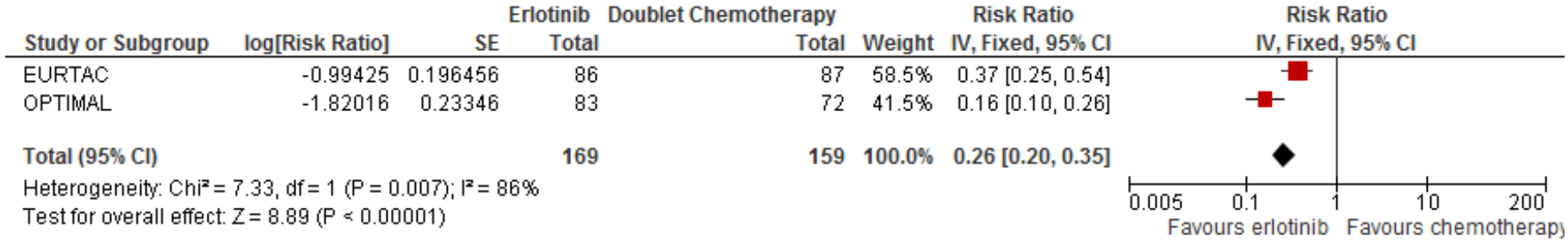


Figure 23: Fixed Effect: EURTAC/OPTIMAL Pooling Forest Plot



Both the random and fixed approaches produced broadly consistent, and highly significant, point estimates of the pooled HR of erlotinib vs doublet chemotherapy (PFS HR = 0.25 for RE and 0.26 for FE). Given the heterogeneity between the two studies the confidence intervals surrounding the RE estimate were wider than the FE estimates (although still extremely significant with an upper confidence interval of 0.56).

5.6.2 If a meta-analysis is not considered appropriate, a rationale should be given and a qualitative overview provided. The overview should summarise the overall results of the individual studies with reference to their critical appraisal.

See above.

5.6.3 If any of the relevant RCTs listed in response to section 5.2.4 (Complete list of relevant RCTs) are excluded from the meta-analysis, the reasons for doing so should be explained. The impact that each exclusion has on the overall meta-analysis should be explored.

See above.

5.7 Indirect and mixed treatment comparisons

Data from head-to-head RCTs should be presented in the reference-case analysis, if available. If data from head-to-head RCTs are not available, indirect treatment comparison methods should be used. This section should be read in conjunction with NICE's 'Guide to the methods of technology appraisal', sections 5.3.13 to 5.3.22.

5.7.1 Describe the strategies used to retrieve relevant clinical data on the comparators and common references both from the published literature and from unpublished data. The methods used should be justified with reference to the decision problem. Sufficient detail should be provided to enable the methods to be reproduced, and the rationale for any inclusion

and exclusion criteria used should be provided. Exact details of the search strategy used should be provided in section 9.4, appendix 4.

The search conducted in order to identify RCTs on the efficacy of erlotinib described in section 5.1 was repeated for gefitinib (with the ‘erlotinib OR Tarceva’ search term simply replaced with ‘gefitinib OR Iressa’). The conduct of the gefitinib RCT search was as described previously for the erlotinib search.

The inclusion/exclusion criteria were as follows:

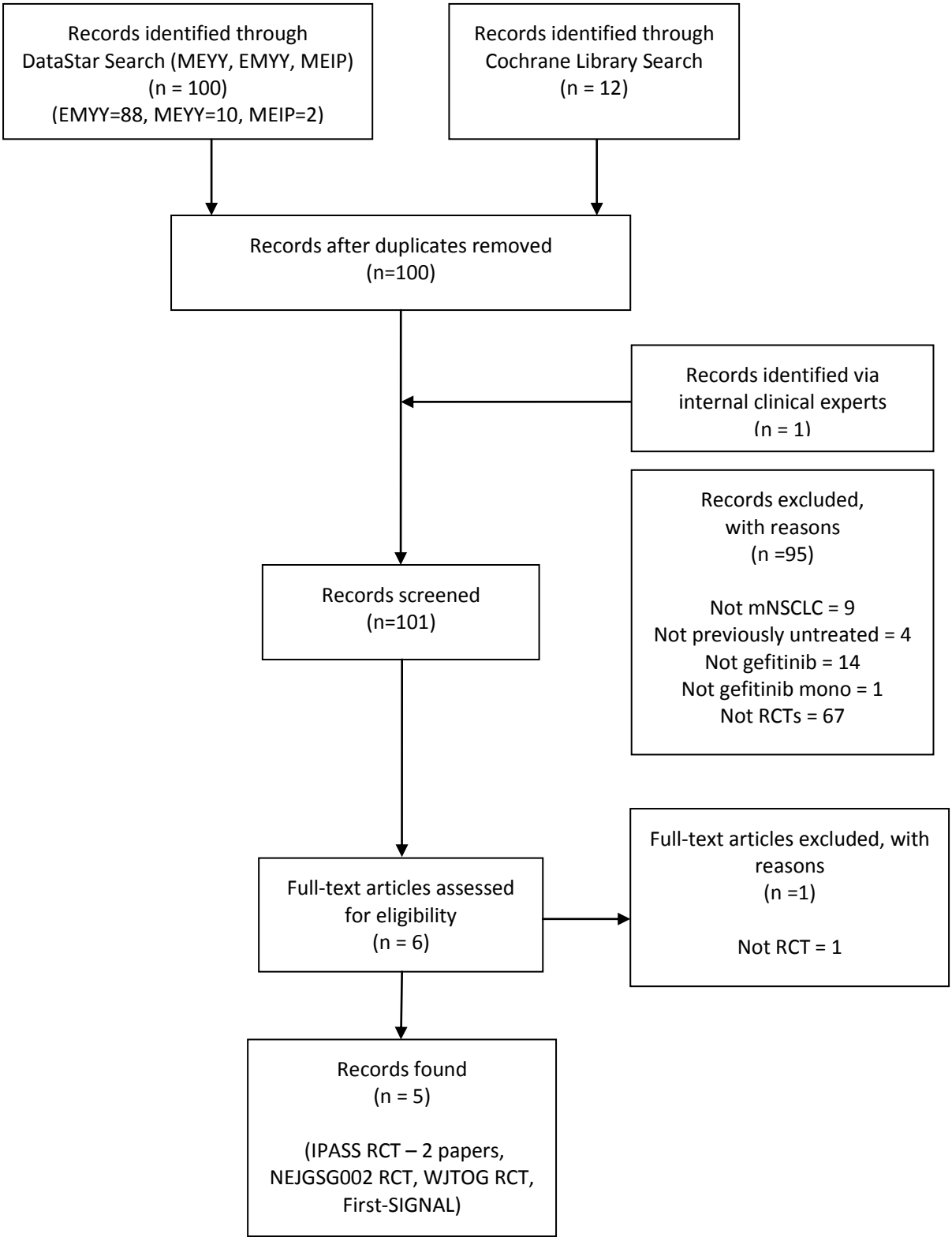
Table 23: Eligibility criteria used in search strategy (gefitinib search)

	Inclusion Criteria	Exclusion Criteria
Population	Previously untreated mNSCLC patients whose tumours harbour an activating mutation of the EGFR tyrosine kinase	Early NSCLC patients, SCLC patients, patients previously treated for their mNSCLC (i.e. maintenance treatment, second and later line treatment), patients with tumours that do not contain a mutation of the EGFR tyrosine kinase or have unknown EGFR mutation status non-mNSCLC
Interventions	Gefitinib monotherapy	Gefitinib combination therapy, non-gefitinib therapy
Comparators	Any comparator capable of informing the relative efficacy of erlotinib to gefitinib	Investigational Agents
Outcomes	Progression Free Survival, Overall Survival, Adverse Events	-
Study Design	Randomised controlled trials	Observational data, registry analyses, single arm studies, meta-analyses

5.7.2 Please follow the instructions specified in sections 5.1 to 5.5 for the identification, selection and methodology of the trials, quality assessment and the presentation of results. Provide in section 9.5, appendix 5, a complete quality assessment for each comparator RCT identified.

The conduct of the search is presented in the PRISMA flow-chart below.

Figure 24: PRISMA Flow-chart of gefitinib RCT search



Following the initial search the results identified were shared with internal clinical experts in the gefitinib clinical trial program and compared to those studies identified in NICE TA192. This validation step revealed that the First-SIGNAL RCT (Lee et al 2009) was absent from the initial results. This record was therefore added to those identified via searching and screened with all records identified.

In total 4 RCTs were identified. Two of the records found were associated with the IPASS RCT (Mok *et al* 2009, Fukoka *et al* 2011).

5.7.2.1 Gefitinib RCT Study Selection

Complete List of Gefitinib RCTs

Using the search strategies outlined in section 5.7.1 and 5.7.2, four RCTs were identified comparing gefitinib with platinum doublet chemotherapy as first-line treatment of patients with NSCLC having activating EGFR mutations.

IPASS: Mok *et al*. *2009.* Gefitinib or Carboplatin–Paclitaxel in Pulmonary Adenocarcinoma*.*

WJTOG3405: Mitsudomi *et al 2010*. Gefitinib versus cisplatin plus docetaxel in patients with non-small-cell lung cancer harbouring mutations of the epidermal growth factor receptor (WJTOG3405): an open label, randomised phase 3 trial. *Lancet Oncology. 2010: 11; 121-128.*

NEJGSG002: Maemondo *et al.2010.* Gefitinib or Chemotherapy for Non–Small-Cell Lung Cancer with Mutated EGFR.

First SIGNAL: Lee *et al. 2009.* A randomized phase III study of gefitinib (IRESSA) versus standard chemotherapy (gemcitabine plus cisplatin) as a first-line treatment for never-smokers with advanced or metastatic adenocarcinoma of the lung.

Table 24: List of Relevant Gefitinib RCTs

Trial no. (acronym)	Intervention	Comparator	Population	Primary study ref.
IPASS	Gefitinib 250mg o.d. until progression	Paclitaxel (200 mg/m^2) and carboplatin (AUC 5.0 or 6.0),i.v once every 3 weeks for up to 6 cycles	Clinically selected (adenocarcinoma, never/ex-light smokers) East Asian patients with advanced non-small-cell carcinoma of the lung (sub-group analysis of patients based on EGFR mutation status)	Mok et al. 2009 Fukuoka et al. 2011
WJTOG3405	Gefitinib 250mg o.d. until progression	Docetaxel (60 mg/m^2) and cisplatin (80 mg/m^2), i.v once every 21 days for 3-6 cycles.	East Asian patients with advanced non-small-cell carcinoma of the lung whose tumours have activating mutations in the TK domain of EGFR	Mitsudomi et al. 2010
NEJGSG002	Gefitinib 250mg o.d. until progression	Paclitaxel (200 mg/m2) and carboplatin (AUC 6), i.v, both administered on the first day of every 3-week cycle for at least 3 cycles	East Asian patients with advanced non-small-cell carcinoma of the lung whose tumours have activating mutations in the TK domain of EGFR	Maemondo et al. 2010
First-SIGNAL	Gefitinib 250mg o.d. until progression	Gemcitabine (1250 mg/m^2)on days 1 and 8 and cisplatin (80mg/m2) on day 1,i.v once every 3 weeks for up to 9 cycles	Clinically selected (adenocarcinoma, never/ex-light smokers) East Asian patients with advanced non-small-cell carcinoma of the lung (sub-group analysis of patients based on EGFR mutation status)	Lee et al. 2009

Appropriateness of Gefitinib RCTs

The gefitinib RCTs listed in the above table are appropriate for inclusion based on the fact that IPASS formed the basis of the EMEA submission and subsequent NICE STA application (NICE TA 192) for gefitinib as first line treatment of advanced NSCLC harbouring activating EGFR mutations. The data package for both submissions was supported by the inclusion of NEJSG002 and First-SIGNAL. Results of the WJTOG3405 trial emerged once the initial applications had been

submitted and are still relevant. This in turn led to the EU approval of gefitinib in 2009 and NICE recommendation in 2010.

The four gefitinib RCTs identified are detailed below. Given the randomised data available no search for observational evidence on the efficacy of gefitinib was conducted.

5.7.2.2 Gefitinib RCT Methodology

Methods

Table 25: Comparative summary of methodology of the Gefitinib RCTs

Trial no. (acronym)	**IPASS**	**WJTOG3405**	**NEJGSG002**	**First SIGNAL**
Location (4b)	China, Hong Kong, Indonesia, Japan, Malaysia, Philippines, Singapore, Taiwan, Thailand	Japan	Japan	Korea
Design (3a and 3b)	An open-label, randomised, parallel-group, multicentre, Phase III study to assess efficacy, safety and tolerability of gefitinib (Iressa (250 mg tablet) vs carboplatin / paclitaxel doublet chemotherapy as first-line treatment in selected patients with advanced (Stage IIIB or IV) non-small-cell lung cancer (NSCLC) in Asia	Gefitinib versus cisplatin plus docetaxel in patients with non-small-cell lung cancer harbouring mutations of the epidermal growth factor receptor (WJTOG3405): an open label, randomised phase 3 trial	First-line gefitinib versus first-line chemotherapy by carboplatin (CBDCA) plus paclitaxel (TXL) in non-small cell lung cancer (NSCLC) patients (pts) with EGFR mutations: A phase III study (002) by North East Japan Gefitinib Study Group	A Randomized Phase III Study of Gefitinib (IRESSATM) versus Standard Chemotherapy (Gemcitabine plus Cisplatin) as a First-line Treatment for Never-smokers with Advanced or Metastatic Adenocarcinoma of the Lung
Duration of study	March 2006-October 2007	March 2006-June 2009	March 2006-May 2009	October 2005-November 2007
Method of randomisation (8a, 8b, 9, 10)	-	-	-	-
Method of blinding (care provider, patient and outcome assessor) (11a, 11b)	Not applicable	Not applicable	Not applicable	Not applicable
Intervention(s) (n =) and comparator(s) (n =) (5)	**Intervention (n=609)** Geftinib 250mg o.d. until PD **Comparator (n=608)** Paclitaxel (200 mg/m^2) and carboplatin (AUC 5.0 or 6.0),i.v once every 3 weeks for up to 6 cycles **For efficacy analysis based**	**Intervention (n=88)** Geftinib 250mg o.d. until PD **Comparator (n=89)** Docetaxel (60 mg/m^2) and cisplatin (80 mg/m^2), i.v once every 21 days for 3-6 cycles	**Intervention (n=114)** Geftinib 250mg o.d. until PD **Comparator (n=114)** Paclitaxel (200 mg/m2) and carboplatin (AUC 6), i.v. both administered on the first day of every 3-week cycle for at least 3 cycles	**Intervention (n=159)** Geftinib 250mg o.d. until PD **Comparator (n=150)** Gemcitabine (1250 mg/m^2)on days 1 and 8 and cisplatin (80mg/m2) on day 1,i.v once every 3 weeks for up to 9 cycles

	EGFR Mutation Positive Status **Intervention (n=132)** **Comparator (n=129)**			**For efficacy analysis based EGFR Mutation Positive Status** **Intervention (n=26)** **Comparator (n=16)**
Primary outcomes (including scoring methods and timings of assessments) (6a, 6b)	The primary end point (progression-free survival) was analysed with the use of a Cox proportional hazards model in the intention-to-treat population to assess non-inferiority of gefitinib to chemotherapy	The primary endpoint was progression-free survival	The primary end point was progression-free survival, as a measure of the superiority of gefitinib over carboplatin–paclitaxel	The primary endpoint was overall survival (OS)
Secondary outcomes (including scoring methods and timings of assessments) (6a, 6b)	Secondary end points included:- • overall survival • objective response rate, • quality of life, • reduction in symptoms • safety • adverse-event profile • efficacy • efficacy according to baseline biomarker status of EGFR were planned exploratory objectives	Secondary end points included:- • overall survival • response rate Tertiary endpoints were:- • disease control rate • safety • mutation-type-specific survival	Secondary end points included:- • overall survival • response rate • time to the deterioration of performance status to ECOG PS score of ≥3 • toxic effects	Secondary end points were:- • objective response rate (ORR) • progression-free survival (PFS) • toxicity
Duration of follow-up	Median follow-up was 5.6 months	Median follow-up was 81 days	Median follow-up was 527 days (>17 months)	-

Participants

Table 26: Eligibility Criteria in Geftinib RCTs

Trial no. (acronym)	Inclusion criteria	Exclusion criteria
IPASS	• ≥18 years of age • PS 0 to 2 • Histologically or cytologically confirmed stage IIIB or IV non–small-cell lung cancer with histologic features of adenocarcinoma (including bronchoalveolar carcinoma) • measurable disease according RECIST criteria with at least 1 measurable lesion not previously irradiated • non-smokers (defined as patients who had smoked <100 cigarettes in their lifetime) or former light smokers (those who had stopped smoking at least 15 years previously and had a total of ≤10 pack-years of smoking) • no previous chemotherapy or biologic or immunologic therapy • adjuvant chemotherapy permitted if not platinum-based and completed > 6 months previously • absolute neutrophil count > 2.0 x 10^9/L • adequate hepatic function	-
WJTOG3405	• histologically or cytologically confirmed NSCLC • harbouring activating *EGFR* mutations (either exon 19 deletion or L858R in exon 21) • aged 75 years or younger • PS 0–1 • measurable or non-measurable disease according to the RECIST • adequate organ function • patients with postoperative recurrence, treated with adjuvant therapy other than cisplatin plus docetaxel, were included when the interval between the end of adjuvant chemotherapy and registration exceeded 6 months for platinum-doublet therapy and more than 1 month for oral	• previous drug therapy that had targeted EGFR, • history of interstitial lung disease • severe drug allergy • active infection or other serious disease condition, • symptomatic brain metastases, poorly controlled pleural effusion, pericardial effusion or ascites necessitating drainage, active double cancer, or severe hypersensitivity to drugs containing polysolvate 80 • patients in pregnancy or lactation • patients whose participation in the trial was judged to be inappropriate by the attending doctor, were not eligible

	tegafur plus uracil therapy	

NEJGSG002	• histologically or cytologically diagnosed as having non-small cell lung cancer • stage IIIB or stage IV non-small cell lung cancer • lung cancer sample is available for the EGFR mutation test - confirmed to have sensitive EGFR mutations • the absence of the resistant EGFR mutation T790M • lesions that can be evaluated by RECIST criteria • chemotherapy-naive cases • previous treatment with UFT or OK-432 is permitted • aged between 20 years old and 75 years old • PS 0 or 1 according to the ECOG criteria • normal bone marrow, liver, and renal function	• interstitial pneumonia or pulmonary fibrosis as revealed by chest CT that is suspected to cause a serious clinical problem during the treatment • second-stage registration process: cases in which lung cancer is positive for the resistant EGFR mutation, T790M • symptomatic brain metastasis unless symptoms are resolved by radiation therapy are eligible • received radiation therapy for primary lesions • received palliative radiation therapy for their brain/or bone metastases more than two weeks previously are eligible • severe complications such as uncontrolled heart, lung, liver, or kidney diseases or diabetes mellitus • pregnant or lactating women, and women who are likely to be or want to become pregnant • severe malabsorption syndrome or with diseases affecting digestive function, as exemplified by post-total gastrectomy and active inflammatory bowel disease • received systemic administration of steroids for 4 weeks or longer • pleural effusion, pericardial effusion and/or peritoneal effusion requiring tube drainage. Cases that have been clinically stable after drainage at least for 2 weeks are eligible • considered to be contra-indicated for gefitinib, carboplatin, or paclitaxel. • active other cancers. - intramucosal carcinomas are not considered to be an independent cancer. • judged by attending physicians to be inappropriate for enrollment
First-SIGNAL	• Age 18-75 years	-

	• never-smokers • chemo-naïve • stage IIIB/IV lung adenocarcinoma • ECOG PS 0-2 • adequate organ functions	

Baseline Characteristics

Table 27: Characteristics of participants in the Gefitinib RCTs across randomised groups - IPASS

Characteristic	Gefitinib (N = 609)	Carboplatin–Paclitaxel (N = 608)
Age — yr		
Median	57	57
Range	24–84	25–84
Sex — no. (%)		
Male	125 (20.5)	127 (20.9)
Female	484 (79.5)	481 (79.1)
Ethnic group — no. (%)†		
Chinese	314 (51.6)	304 (50.0)
Japanese	114 (18.7)	119 (19.6)
Other East Asian‡	179 (29.4)	184 (30.3)
Other	2 (0.3)	1 (0.2)
Smoking history — no. (%)		
Never smoked	571 (93.8)	569 (93.6)
Former light smoker	37 (6.1)	38 (6.2)
Former non–light smoker	1 (0.2)	1 (0.2)
WHO performance status — no. (%)§		
0	157 (25.8)	161 (26.5)
1	391 (64.2)	382 (62.8)
2	61 (10.0)	65 (10.7)
Histologic feature of tumor — no. (%)		
Adenocarcinoma	581 (95.4)	591 (97.2)
Bronchoalveolar carcinoma	27 (4.4)	15 (2.5)
Unknown	1 (0.2)	2 (0.3)
Disease stage at entry — no. (%)		
IIIB	150 (24.6)	144 (23.7)
IV	459 (75.4)	463 (76.2)
Unknown	0	1 (0.2)
Time from diagnosis to randomization — no. (%)		
<6 mo	582 (95.6)	573 (94.2)
≥6 mo	27 (4.4)	34 (5.6)
Unknown	0	1 (0.2)
Disease stage at diagnosis — no. (%)¶		
IA	7 (1.1)	12 (2.0)
IB	2 (0.3)	9 (1.5)
IIA	2 (0.3)	1 (0.2)
IIB	1 (0.2)	6 (1.0)
IIIA	6 (1.0)	3 (0.5)
IIIB	166 (27.3)	163 (26.8)
IV	424 (69.6)	413 (67.9)
Unknown	1 (0.2)	1 (0.2)

Table 28: Characteristics of participants in the Gefitinib RCTs across randomised groups – WJTOG3405

	Gefitinib (N=86)	Cisplatin plus docetaxel (N=86)
Sex		
Male	27	26
Female	59	60
Age (years; median; range)	64·0 (34–74)	64·0 (41–75)
Histological type		
Adenocarcinoma	83	84
Adenosquamous carcinoma	0	1
Squamous-cell carcinoma	1	0
Non-small-cell lung cancer; not otherwise specified	2	1
Smoking history		
Never	61	57
Former/current	25	29
Performance status		
0	56	52
1	30	34
Stage		
Postoperative recurrence	35	36
With postoperative adjuvant chemotherapy	19	23
Without postoperative adjuvant chemotherapy	16	13
IIIB	10	9
IV	41	41
EGFR mutation		
Exon 19 deletion	50	37
L858R	36	49

Table 29: Characteristics of participants in the Gefitinib RCTs across randomised groups – NEJGSG002

Characteristic	Gefitinib (N=114)	Carboplatin–Paclitaxel (N=114)
Sex — no. (%)		
Male	42 (36.8)	41 (36.0)
Female	72 (63.2)	73 (64.0)
Age — yr		
Mean	63.9±7.7	62.6±8.9
Range	43–75	35–75
Smoking status — no. (%)		
Never smoked	75 (65.8)	66 (57.9)
Previous or current smoker	39 (34.2)	48 (42.1)
ECOG performance status score — no. (%)		
0	54 (47.4)	57 (50.0)
1	59 (51.8)	55 (48.2)
2	1 (0.9)	2 (1.8)
Histologic diagnosis — no. (%)		
Adenocarcinoma	103 (90.4)	110 (96.5)
Large-cell carcinoma	1 (0.9)	0
Adenosquamous carcinoma	2 (1.8)	1 (0.9)
Squamous-cell carcinoma	3 (2.6)	2 (1.8)
Other	5 (4.4)	1 (0.9)
Clinical stage — no. (%)		
IIIB	15 (13.2)	21 (18.4)
IV	88 (77.2)	84 (73.7)
Postoperative relapse	11 (9.6)	9 (7.9)
Type of EGFR mutation — no. (%)		
Exon 19 deletion	58 (50.9)	59 (51.8)
L858R	49 (43.0)	48 (42.1)
Other	7 (6.1)	7 (6.1)

As First-SIGNAL has not been published and patient baseline characteristics are not contained with the abstract or the presentation at WCLC 2009 they are not provided.

Outcomes

The primary and secondary outcomes in the gefitinib RCTs have been provided above in Table 25 (Comparative summary of methodology of the Gefitinib RCTs) and are detailed further in sections 5.7.2.4.1 to 5.7.2.4.3.

Statistics

IPASS (Mok et al 2009)

The primary end point (progression-free survival) was analysed with the use of a Cox proportional hazards model in the intention-to-treat population (all randomly assigned patients) to assess the non-inferiority of gefitinib as compared with carboplatin–paclitaxel, with the WHO performance status (0 or 1, or 2), smoking status (non-smoker or former light smoker), and sex as covariates. For non-inferiority to be demonstrated, the 95% confidence interval for the hazard ratio had to lie entirely below the predefined non-inferiority limit of 1.2. It was estimated that with a total of 944 progression events, the study would have 80% power to demonstrate non-inferiority if the treatments were truly equal, with a two-sided 5% probability of an erroneous demonstration of non-inferiority. If the 95% confidence interval for the hazard ratio was also below 1, the P value would be less than 0.05 and superiority could be concluded from the same analysis without statistical penalty (closed test procedure).

Planned subgroup analyses were performed to compare progression-free survival between treatments in groups defined according to WHO performance status (0 or 1, or 2), smoking status (non-smoker or former light smoker), sex, age at randomization (<65 years or ≥65 years), disease stage at screening (stage IIIB or IV), and presence or absence of biomarkers. Tests to determine interactions of treatment with covariates were used to identify predictive factors by assessing whether there was a significant difference in the treatment effect for progression-free survival (hazard ratio for progression or death) between subgroups.

Overall survival was analysed with the use of methods that were similar to those used for the analysis of progression-free survival. The objective response rate (in the intention-to-treat population) and quality of life and rates of symptom reduction (among all patients with a baseline and at least one post-baseline quality-of-life assessment that could be evaluated) were assessed with the use of a logistic-regression model with the same covariates as those considered for progression-free survival to calculate odds ratios and 95% confidence intervals. Planned subgroup analyses of the objective response rate were performed with the use of methods that were similar to those used for the analysis of progression-free survival.

Adverse events were summarized for all patients who received at least one dose of the assigned study treatment. The incidence rates of 10 specified safety events (5 that were possibly associated with each study treatment) were compared with the use of Fisher's exact test; adjustment for multiple comparisons was performed with the use of the method of Westfall and Young.

WJTOG3405 (Mitsudomi et al 2010)

The authors state that in previous studies the progression-free survival of patients harbouring EGFR mutations and treated with gefitinib was reported as 12.6 months compared with 6.6 months for patients harbouring EGFR mutations treated with carboplatin plus paclitaxel. They assumed a progression-free survival for gefitinib and platinum doublet chemotherapy of 12.5 and 7 months, respectively, which would yield a hazard ratio (HR) of 0.56. Taking this HR into consideration, they calculated that 146 patients would be required to achieve 90% power to show superiority with α=0.05 (two-sided). Therefore, sample size was initially set at 200 patients.

While this trial was ongoing, the results of the Iressa Pan-Asia Study (IPASS) were presented at the annual meeting of the European Society for Medical Oncology (Stockholm, Sweden, Sept 12–16, 2008), and were later published. Subgroup analysis of patients with EGFR mutations using about a third of the patients showed

that the HR of gefitinib compared with carboplatin plus paclitaxel for progression-free survival was 0.48. Similarly, the HR of gefitinib compared with carboplatin plus paclitaxel for progression-free survival in patients with EGFR mutations was 0.36 in the study done by the North East Japan (NEJ) 002 Gefitinib Study Group, which was presented at the annual meeting of the American Society of Clinical Oncology (Orlando, FL, USA, May 29–June 2, 2009). NEJ 002 was a phase 3 trial that analysed 198 patients with EGFR mutation randomised either to gefitinib or carboplatin plus paclitaxel. 177 patients had been randomised to WJTOG3405 as of June 13, 2009, and 79 events had been noted during the regular monitoring done in March, 2009. The number of events needed to detect a conservative HR of 0.48 was calculated to be 78, based on normal approximation of the logarithm of the hazard ratio under α=0.05 (two-sided) and 90% power. Therefore, further accrual of patients was considered to be futile and potentially unethical. Although interim analysis was originally planned to analyse progression-free survival, this analysis was not done. Instead, the steering committee held on June 13, 2009, proposed the amendment of the sample size and the final analyses be done using available data. This proposal was approved by the independent data and safety monitoring committee on Aug 28, 2009. The data were locked on June 30, 2009. with patient follow-up for safety and survival to be continued until 1-5 years after the last patient entry, as originally described in the study protocol.

Progression-free and overall survival were analysed for the modified intention-to-treat population as defined previously. They were analysed using the Kaplan-Meier method, and were compared using the log-rank test. Hazard ratios in the overall population and in patient subsets were calculated using the Cox proportional hazards model. The $\chi 2$ test was used to compare proportions. Differences were considered significant at a two-sided p value of 0.05 or less. All statistical analyses were done with SAS version 9.1.

NEJGSG002 (Maemondo et al 2010)

The primary end point was progression-free survival, as a measure of the superiority of gefitinib over carboplatin–paclitaxel. From previous data, it was hypothesized that the progression-free survival with gefitinib was 9.7 months and from the results of the Iressa NSCLC Trial Assessing Combination Treatment (INTACT), it was hypothesized that the progression-free survival with standard chemotherapy was 6.7 months. It was estimated that a total of 230 events would be needed for the study to have a power of 80% to confirm the superiority of gefitinib over standard chemotherapy, with the use of a log-rank test and a two-sided significance level of 5%. Setting the duration of enrolment to 2 years with a minimum follow-up period of 6 months, it was initially planned to enrol 320 patients. Kaplan–Meier survival curves were drawn for progression-free survival and were compared by means of a log-rank test. Hazard ratios (and 95% confidence intervals) were calculated with the use of a Cox proportional-hazards analysis. Pre-specified adjustment factors included sex and clinical stage.

Secondary end points included overall survival, response rate, time to the deterioration of performance status (Eastern Cooperative Oncology Group [ECOG] performance status score of ≥3, capability of only limited self-care, or confinement to a bed or chair for >50% of waking hours19), and toxic effects. Overall survival and the time to ECOG performance status score of 3 or more were analysed in the same way as progression-free survival. The response rate and rate of toxic effects were compared between the two groups with Fisher's exact test and the Wilcoxon test, respectively. Each analysis was performed with the use of a two-sided, 5% significance level and a 95% confidence interval by means of SAS for Windows software (release 9.1, SAS Institute).

One interim analysis was planned to analyse the primary end point (significance level, P = 0.003). The Lan–DeMets method was used to adjust for multiple comparisons. The O'Brien–Fleming type alpha-spending function was also used.

First-SIGNAL (Lee et al 2009)

No statistical analysis information was available for the First-SIGNAL study.

Sub-group Analysis

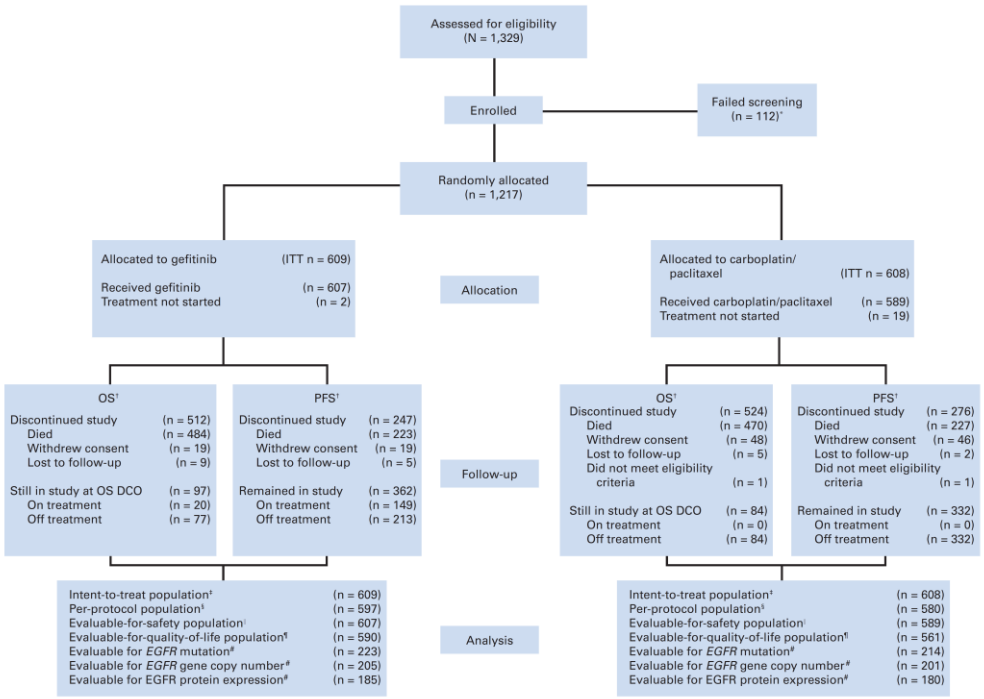
Not applicable.

Participant Flow

The flow of patients in the gefitinib RCTs are presented in the subsequent CONSORT figures below.

Patient Disposition in IPASS

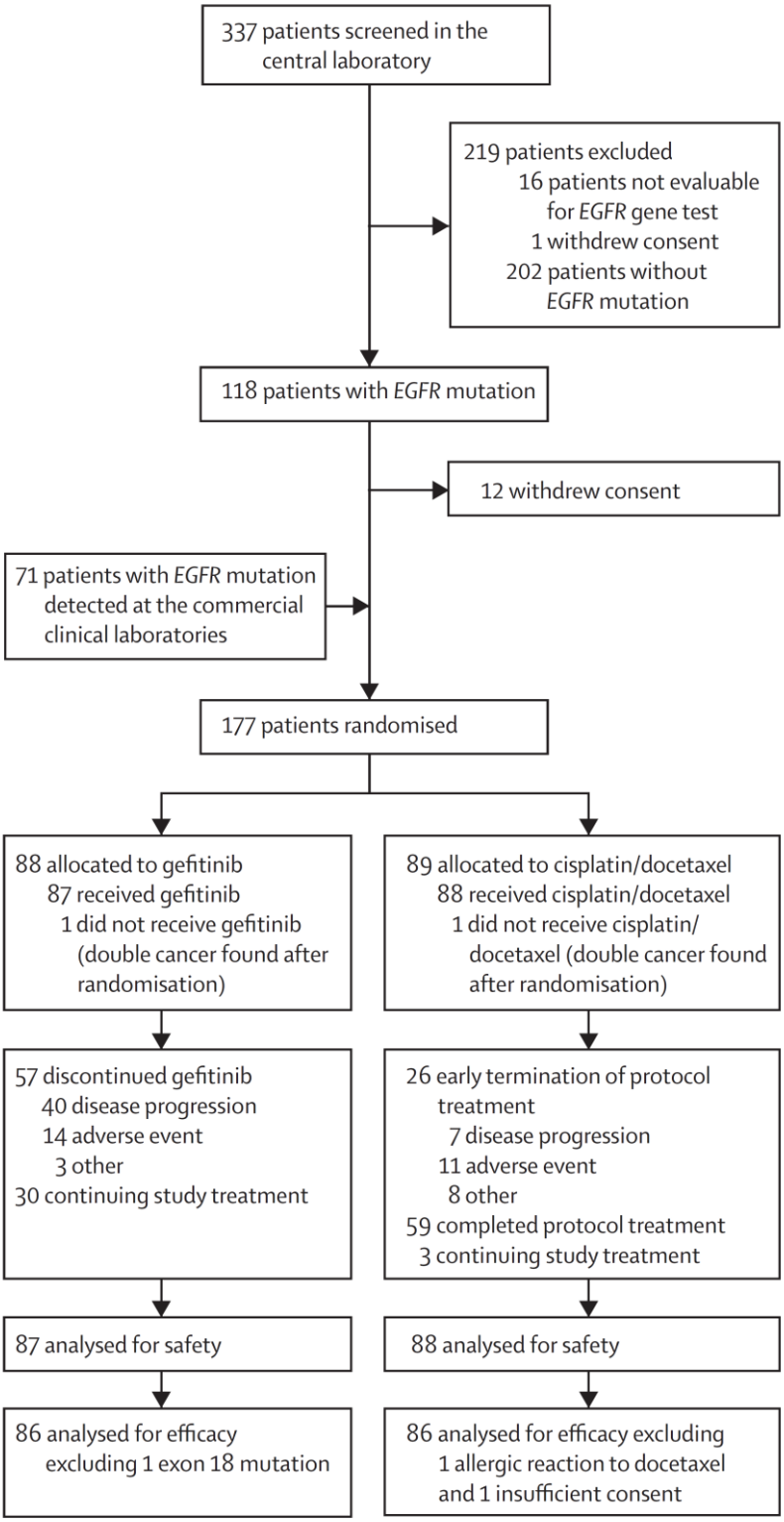
Figure 25: Patient Disposition in the IPASS Study



DCO = data cut-off; EGFR = epidermal growth factor receptor.

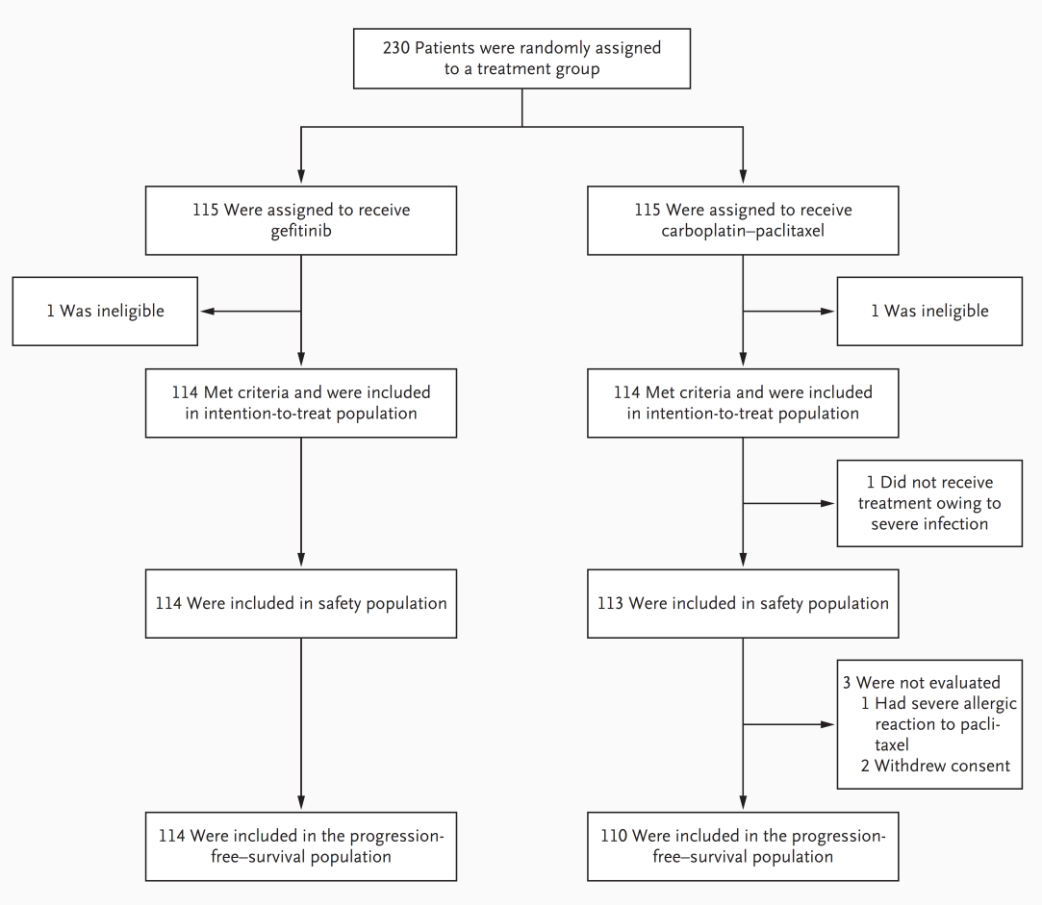
Patient Disposition in WJTOG3405

Figure 26: Patient Disposition in the WJTOG3405 Study



Patient Disposition in NEJGSG002

Figure 27: Patient Disposition in the NEJGSG002 Study



Patient Disposition in First SIGNAL

No information was available regarding the patient disposition in First-SIGNAL.

5.7.2.3 Critical appraisal of relevant Gefitinib RCTs

Table 30: Quality assessment results for Gefitinib RCTs

Trial no. (acronym)	IPASS	WJTOG3405	NEJGSG002	First-SIGNAL
Was randomisation carried out appropriately?	(yes)	(yes)	(yes)	(yes)
Was the concealment of treatment allocation adequate?	(N/A)	(N/A)	(N/A)	(N/A)
Were the groups similar at the outset of the study in terms of prognostic factors?	(yes)	(yes)	(yes)	(yes)
Were the care providers, participants and outcome assessors blind to treatment allocation?	(no)	(no)	(no)	(no)
Were there any unexpected imbalances in drop-outs between groups?	(no)	(no)	(no)	(no)
Is there any evidence to suggest that the authors measured more outcomes than they reported?	(no)	(no)	(no)	(no)
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	(yes)	(yes)	(yes)	(yes)

5.7.2.4 Results of the relevant Geftinib RCTs

Table 31: Summary of Overall Efficacy Results in Gefitinib RCTs

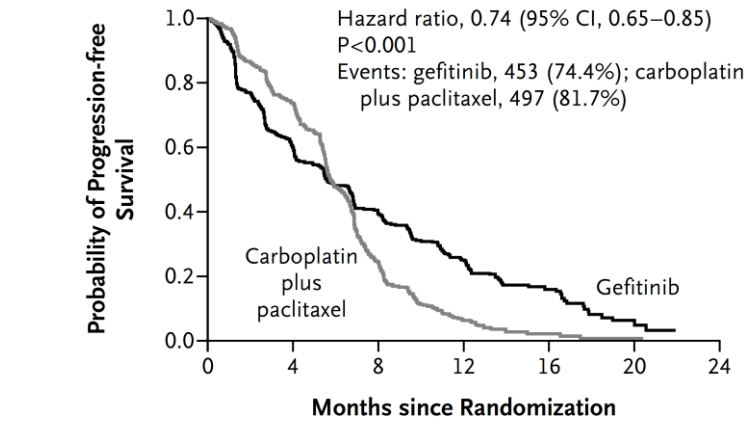
Parameter	**Platinum Doublet Chemotherapy Arm**	**Gefitinib Arm**	
	Median Progression Free Survival		**HR (95% CI)** ***p value***
IPASS	6.3 months	9.5 months	0.48 (0.36-0.64) *p < 0.0001*
WJTOG3405	6.3 months	9.2 months	0.489 (0.336-0.710) *p < 0.0001*
NEJGSG002	5.4 months	10.8 months	0.30 (0.22-0.41) *p < 0.0001*
First-SIGNAL	6.7 months	8.4 months	0.613 (0.308-1.221) *p = 0.084*
	Best Overall Response		**Odds Ratio (95% CI)** ***p value***
IPASS	47.3%	71.2%	2.75 (1.65-4.60) *p = 0.0001*
WJTOG3405	32.2%	62.1%	*(12.6-47.1)* *p < 0.0001*
NEJGSG002	30.7%	73.7%	*p < 0.0001*
First-SIGNAL	37.5%	84.6%	9.167 (2.109-39.847) *p < 0.002*
	Median Overall Survival		**HR (95% CI)** ***p value***
IPASS	21.9 months	21.6 months	0.90 (0.79-1.02) *p = 0.109*
WJTOG3405	Not reached	30.9 months	n/a
NEJGSG002	23.6 months	30.5 months	*p = 0.31*
First-SIGNAL	26.5months	30.6 months	*p = 0.648*
Lung Cancer Symptoms and Health-related Quality of Life (HRQoL)	**Patients with Clinically Relevant Improvements in QoL During the Study** **EGFR mutation patients only**		
PS, smoking history and gender as covariates	**Platinum Doublet Chemotherapy Arm**	**Gefitinib Arm**	**Odds Ratio (95% CI)** ***p value***
IPASS – Total FACT-L	44.5	70.2	3.01 (1.79-5.07) *p < 0.0001*
IPASS – TOI	38.3	70.2	3.96 (2.33-6.71) *p < 0.0001*
IPASS – LCSS	53.9	75.6	2.70 (1.58-4.62) *p = 0.0003*
WJTOG3405	Not reported		
NEJGSG002	Not reported		
First-SIGNAL	Not reported		

5.7.2.4.1 Progression Free Survival

IPASS

IPASS met its primary end point of demonstrating non-inferiority for PFS of gefitinib to paclitaxel-carboplatin and showed superiority for PFS in favour of gefitinib in the ITT population (HR 0.74; 95% CI, 0.65-0.85; p < 0.001) in patients that had been clinically selected (adenocarcinoma and never/ex-light smokers). The probability that a patient would be free of disease progression was greater with carboplatin–paclitaxel in the first 6 months and greater with gefitinib in the following 16 months (Figure 28).

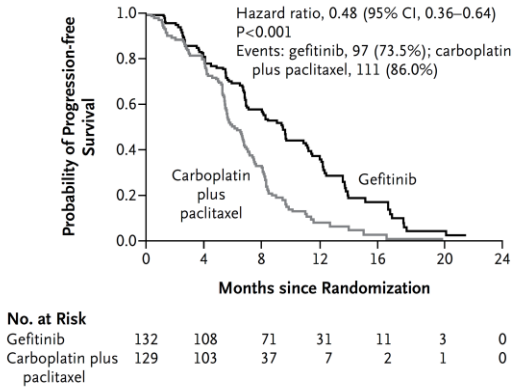
Figure 28: Progression Free Survival in IPASS (ITT)



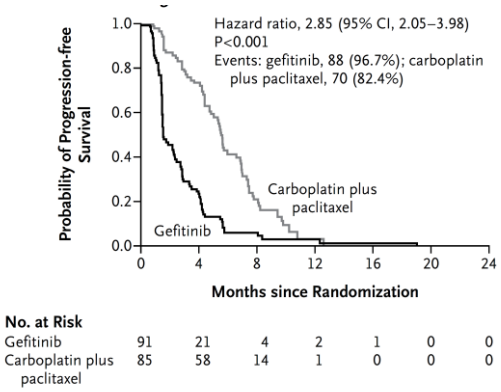
No. at Risk							
Gefitinib	609	363	212	76	24	5	0
Carboplatin plus paclitaxel	608	412	118	22	3	1	0

Progression-free survival was significantly longer among patients receiving gefitinib than among those receiving carboplatin–paclitaxel in the mutation-positive subgroup (HR 0.48; 95% CI, 0.36-0.64; P<0.001) and significantly shorter among patients receiving gefitinib than among those receiving carboplatin–paclitaxel in the mutation-negative subgroup (HR 2.85; 95% CI, 2.05-3.98; P<0.001). The median progression free survival was longer for patients receiving gefitinib (9.5 months) than those receiving carboplatin-paclitaxel (6.2 months).

Figure 29: Progression Free Survival in IPASS According to EGFR Mutation Status



EGFR Mutation Positive

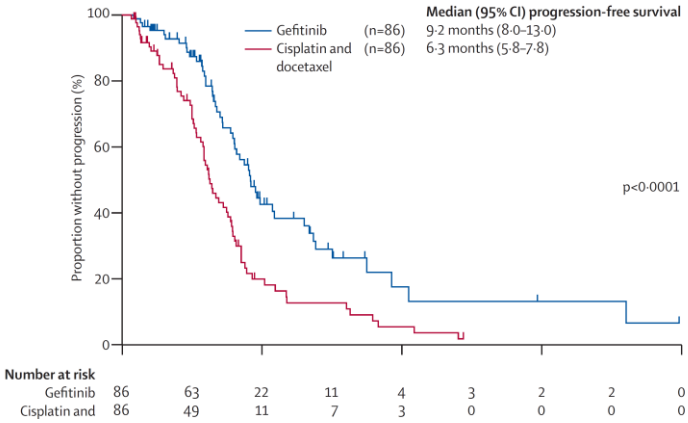


EGFR Mutation Negative

WJTOG3405

WJTOG3405 was conducted in patients specifically selected for the presence activating EGFR mutations. Median progression free survival was 9.2 months (95% CI 8.0–13.9) in the gefitinib group and 6.3 months (5.8–7.8) in the cisplatin plus docetaxel group ($p < 0.0001$). Gefitinib treatment resulted in significantly longer progression-free survival than cisplatin plus docetaxel (HR 0.489; 95% CI 0.336–0.710; $p < 0.0001$.

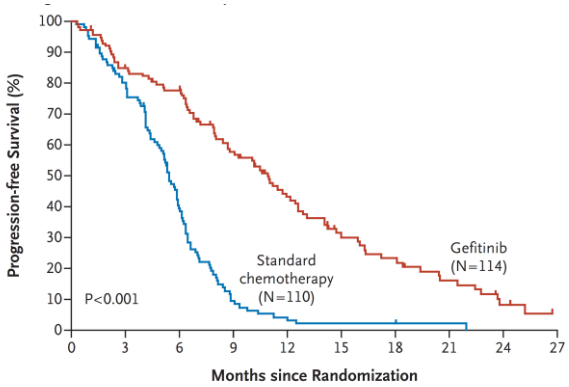
Figure 30: Progression Free Survival in WJTOG3405



NEJGSG002

Similarly to WJTOG3405, NEJSGS002 specifically recruited patients that had confirmed activating EGFR mutations. The interim analysis performed in May 2009 showed that progression-free survival was significantly longer in the gefitinib group than in the chemotherapy group (median, 10.4 months vs. 5.5 months; HR 0.36; 95% CI, 0.25-0.51; p<0.001). A significant difference was again observed in the final analysis, performed in December 2009 (median progression-free survival, 10.8 months with gefitinib vs. 5.4 months with chemotherapy; HR 0.30; 95% CI, 0.22-0.41; p<0.001.

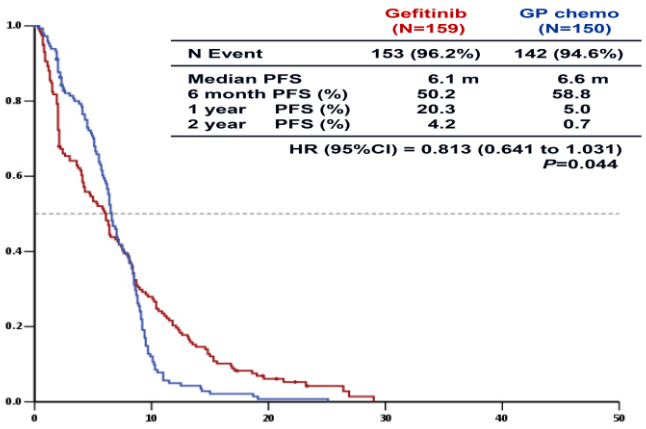
Figure 31: Progression Free Survival in NEJGSG002



First-SIGNAL

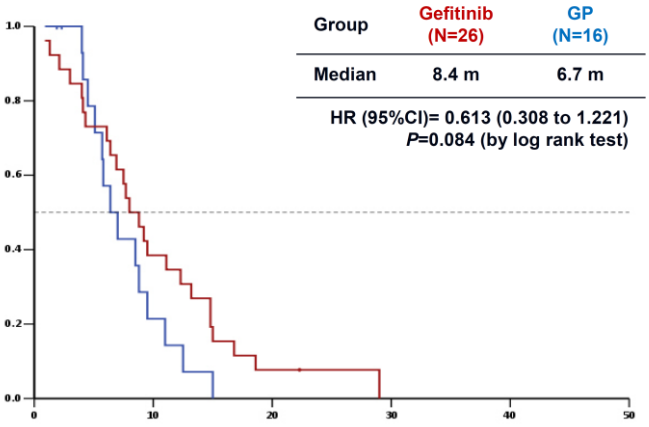
First-SIGNAL clinically selected patients that were adenocarcinoma histology and never smokers. Unlike the other gefitinib RCTs the primary endpoint of this study was overall survival (as opposed to progression free survival in the other studies).Progression free survival was significantly longer in the overall population (HR 0.813; 95% CI, 0.641-1.031; p < 0.044). Similar to the PFS Kaplain Meier curve in IPASS for the overall population there was cross-over in the PFS curves in First-SIGNAL.

Figure 32: Progression Free Survival in First-SIGNAL (ITT)



In patients that were EGFR mutation positive, progression free survival was longer in the gefitinib group than the gemcitabine-cisplatin group (median PFS 8.4 months and 6.7 months respectively). Although patients in the gefitinib group had a reduction in the risk of progression compared to those receiving platinum doublet chemotherapy, this did not reach statistical significance (HR 0.613; 95% CI, 0.308-1.221; p = 0.084).

Figure 33: Progression Free Survival in First-SIGNAL (EGFR Mutation Positive)



5.7.2.4.2 Response Rates

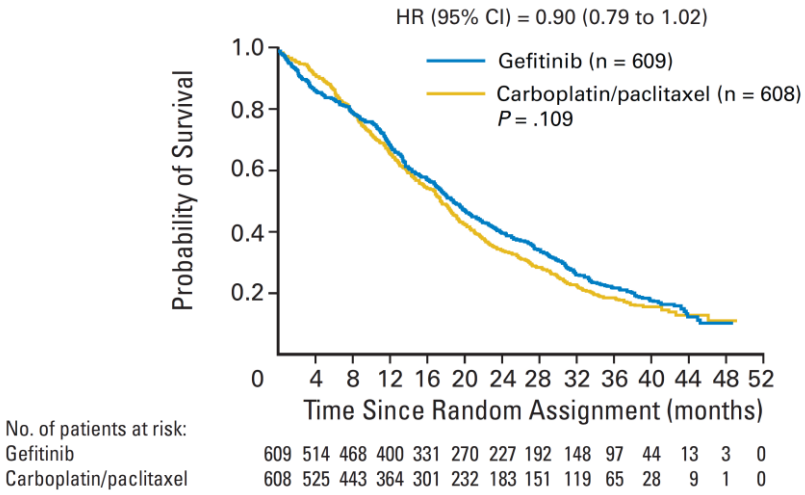
All 4 gefitinib RCTs consistently demonstrated significantly greater response rates for EGFR mutation positive patients receiving gefitinib than those receiving platinum doublet chemotherapy (Table 31 in section 5.7.2.4 above).

5.7.2.4.3 Overall Survival

IPASS

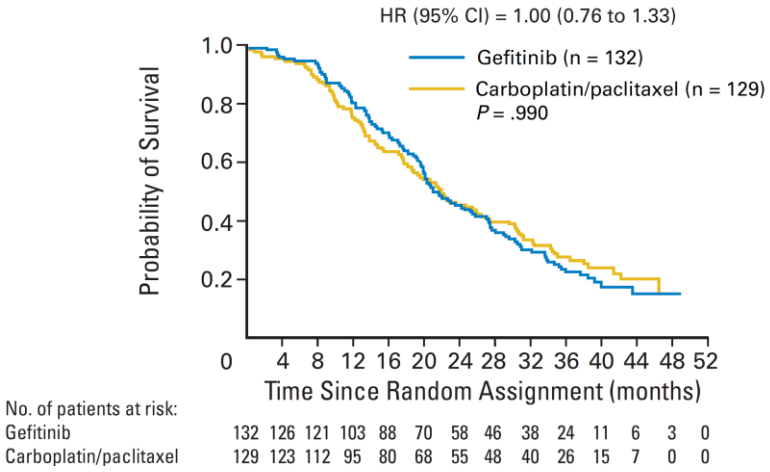
The median duration of follow-up for OS was 17.0 months. At the time of data cut-off for OS (June 14, 2010), 954 patients (78%) had died. In the overall population, OS was similar for gefitinib and carboplatin/paclitaxel with no significant difference between treatments (484 and 470 events, respectively; HR 0.90; 95%CI, 0.79-1.02; *p = 0*.109; median OS for gefitinib, 18.8 months *v* 17.4 months for carboplatin/paclitaxel).

Figure 34: Overall Survival in IPASS (ITT)



There was no significant difference in OS for gefitinib versus carboplatin/ paclitaxel in the subgroups of patients with EGFR mutation positive tumours (HR 1.00; 95% CI, 0.76-1.33; p = 0.990; median OS, 21.6 *v* 21.9 months respectively).

Figure 35: Overall Survival in IPASS (EGFR Mutation Positive)



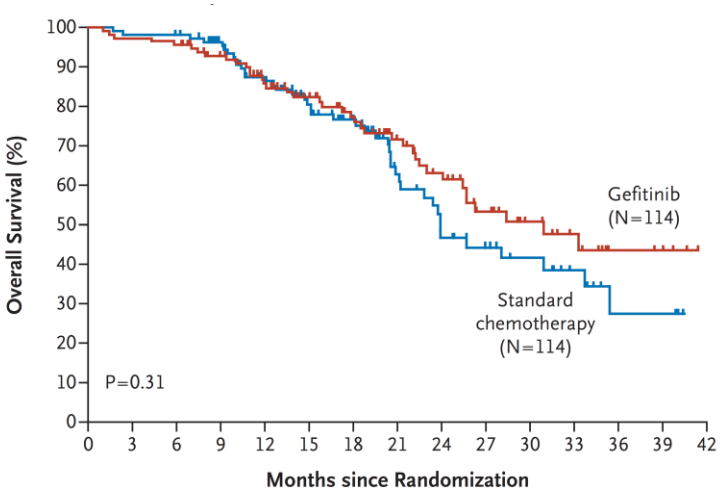
WJTOG3405

The overall survival data in the WJTOG study are immature with follow-up still ongoing.

NEJGSG002

Overall survival did not differ significantly between the two treatment groups in the NEJGSG002 study. The median survival times were 30.5 months for the gefitinib group and 23.6 months for the carboplatin–paclitaxel group (P = 0.31).

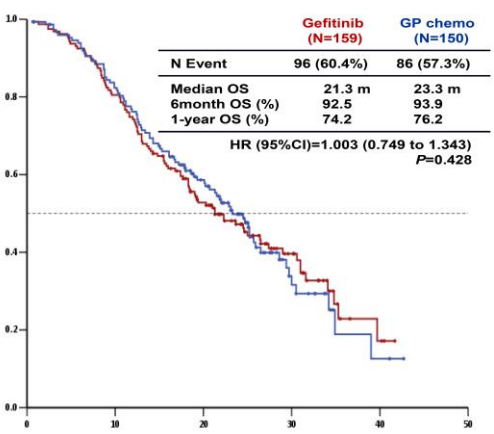
Figure 36: Overall Survival in NEJGSG002



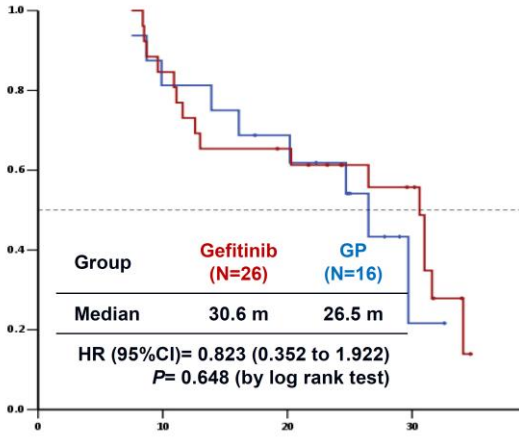
First-SIGNAL

There was no significant difference in overall survival between patients receiving gefitinib or patients receiving gemcitabine-cisplatin in either the ITT population or in patients that were EGFR mutation positive.

Figure 37: Overall Survival in First SIGNAL



ITT population



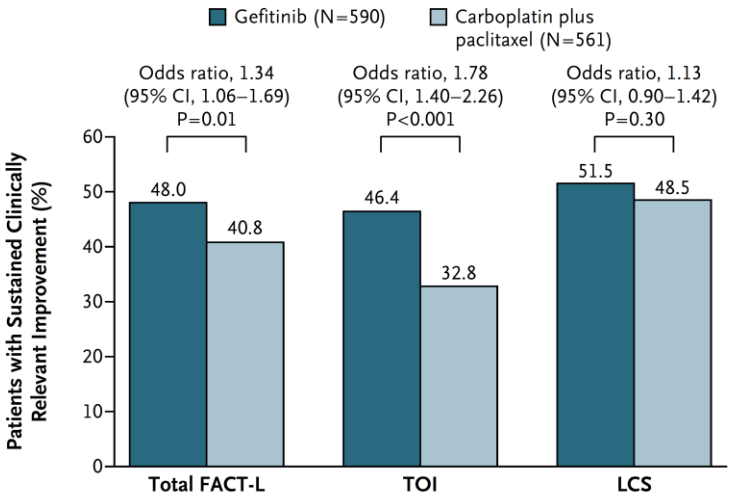
EGFR Mutation Positive

5.7.2.4.3 Quality of Life

Of the four gefitinib RCTs detailed within this application, only IPASS reported quality of life outcomes using the FACT-L questionnaire.

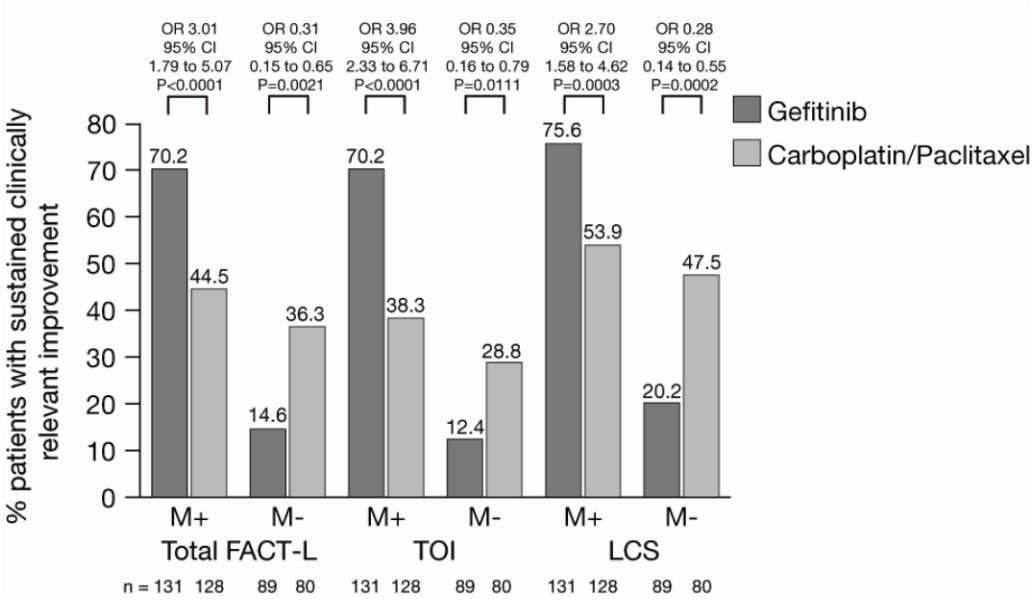
Significantly more patients in the gefitinib group than in the carboplatin–paclitaxel group had a clinically relevant improvement in quality of life, as assessed by scores on the FACT-L questionnaire (OR 1.34; 95% CI, 1.06-1.69; p = 0.01) and by scores on the TOI (OR 1.78; 95% CI, 1.40-2.26; p<0.001). Rates of reduction in symptoms, as assessed on the basis of the LCS scores, were similar between patients who received gefitinib and those who received carboplatin–paclitaxel (OR with gefitinib 1.13; 95% CI, 0.90-1.42; p = 0.30).

Figure 38: Rates of Improvement in Scores for Quality of Life and Symptoms (IPASS)



When quality of life and symptom improvement was analysed according to mutation status, amongst patients with activating EGFR mutations significantly more patients in the gefitinib group than in the carboplatin–paclitaxel group had a clinically relevant improvement in quality of life, as assessed by scores on the FACT-L questionnaire (OR 3.01; 95% CI, 1.79-5.07; p < 0.0001) and by scores on the TOI (OR 3.96; 95% CI, 2.33-6.71; p < 0.0001) and LCS (OR 2.70; 95% CI, 1.58-4.62; p < 0.0003).

Figure 39: Rates of Improvement in Scores for Quality of Life and Symptoms According to EGFFR Mutation Status (IPASS)



By contrast, in patients that were EGFR mutation negative, the carboplatin-paclitaxel group had significantly greater clinically relevant improvement in quality of life scores as assessed by the FACT-L questionnaire and by scores on the TOI and LCS.

5.7.2.4.4 Summary of Efficacy Outcomes in Gefitinib RCTs

All gefitinib RCTs were conducted in East Asian patients. Two gefitinib RCTs recruited patients based on clinical selection criteria of adenocarcinoma histology and never/ex-light smoker status (IPASS and First-SIGNAL). Efficacy in EGFR mutation positive patients in these studies was assessed by post-hoc sub-group analyses. The other two gefitinib RCTs specifically targeted patients with activating EGFR mutations (WJTOG3405 and NEJGSG002).

Across the 4 gefitinib RCTs, gefitinib demonstrated improvements in progression free survival and significantly greater response rates compared to platinum doublet chemotherapy. Median PFS ranged between 8.4-10.8 months for patients treated with gefitinib compared to medians between 5.4-6.7 months for patients treated with platinum doublet chemotherapy. Response rates were also significantly greater for

gefitinib (ranging between 62.1%-84.6%) compared to platinum doublet chemotherapy (ranging between 30.7%-47.3%). In IPASS, the improvements in PFS and response rates were reflected in statistically significant, clinically relevant improvements in quality of life in patients taking gefitinib compared to those taking carboplatin-paclitaxel.

None of the 4 gefitinib RCTs were able to demonstrate an improvement in overall survival for gefitinib compared to platinum doublet chemotherapy. The most likely explanation for this is that there was a high degree of cross-over from platinum doublet chemotherapy to an EGFR TKI (and vice-versa) upon progression, which in turn would confound any overall survival benefit in EGFR mutation positive patients. In the EGFR mutation positive group in IPASS, 64.3% of the patients receiving carboplatin-paclitaxel went on to receive an EGFR TKI. In NEJGSG and First-SIGNAL the cross-over rate from platinum doublet chemotherapy to an EGFR TKI upon discontinuation of first line treatment was even higher, 95% and 80.7% respectively; as expected there was no difference in overall survival between the two treatment arms in each study. The overall survival data in WJTOG3405 are immature at present.

5.7.3 Provide a summary of the trials used to conduct the indirect comparison. A suggested format is presented below. Network diagrams may be an additional valuable form of presentation.

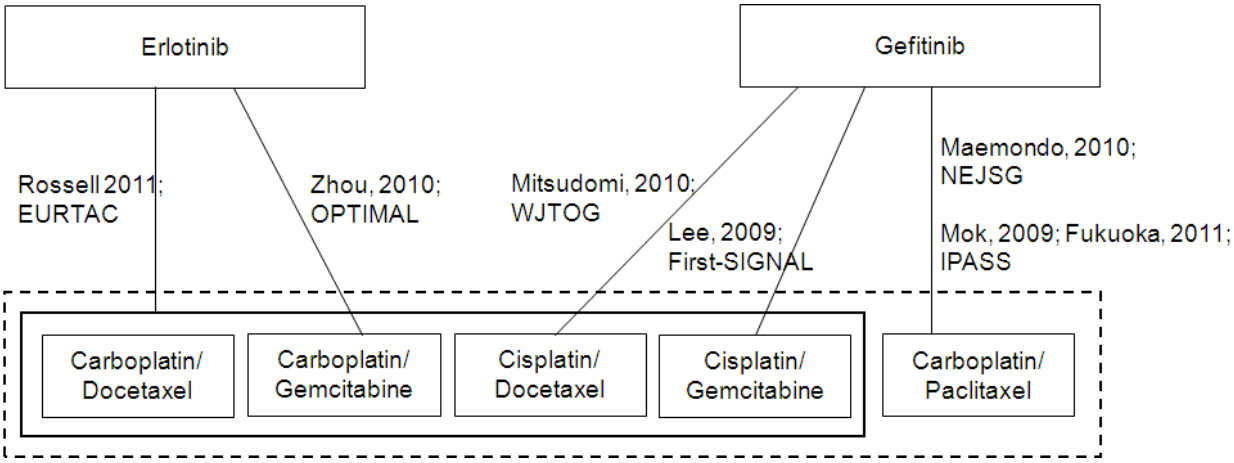
In total six relevant RCTs were identified. Each of these studies compared either gefitinib or erlotinib to some form of doublet chemotherapy in the first line treatment of EGFR M+ mNSCLC. None of these studies featured a head to head comparison of the two comparators of interest (as both agents were unlicensed in this setting at the point these trials were commenced).

Two of the RCTs found compared erlotinib to doublet chemotherapy (EURTAC, OPTIMAL) whilst four compared gefitinib to doublet chemotherapy (IPASS,

WJTOG3405, First-SIGNAL, NEJGSG002). In EURTAC four different chemotherapy combinations (generally acknowledged as being of equivalent efficacy (Schiller et al 2002, Scagliotti et al 2002) featured in the comparator arm (carboplatin-docetaxel, carboplatin-gemcitabine, cisplatin-docetaxel, and cisplatin-gemcitabine). In the OPTIMAL and the First-SIGNAL study, doublet chemotherapy consisted of carboplatin-gemcitabine. In the WJTOG3405 study cisplatin-docetaxel was the comparator and in NEJGSG002 and IPASS the comparator was carboplatin-paclitaxel.

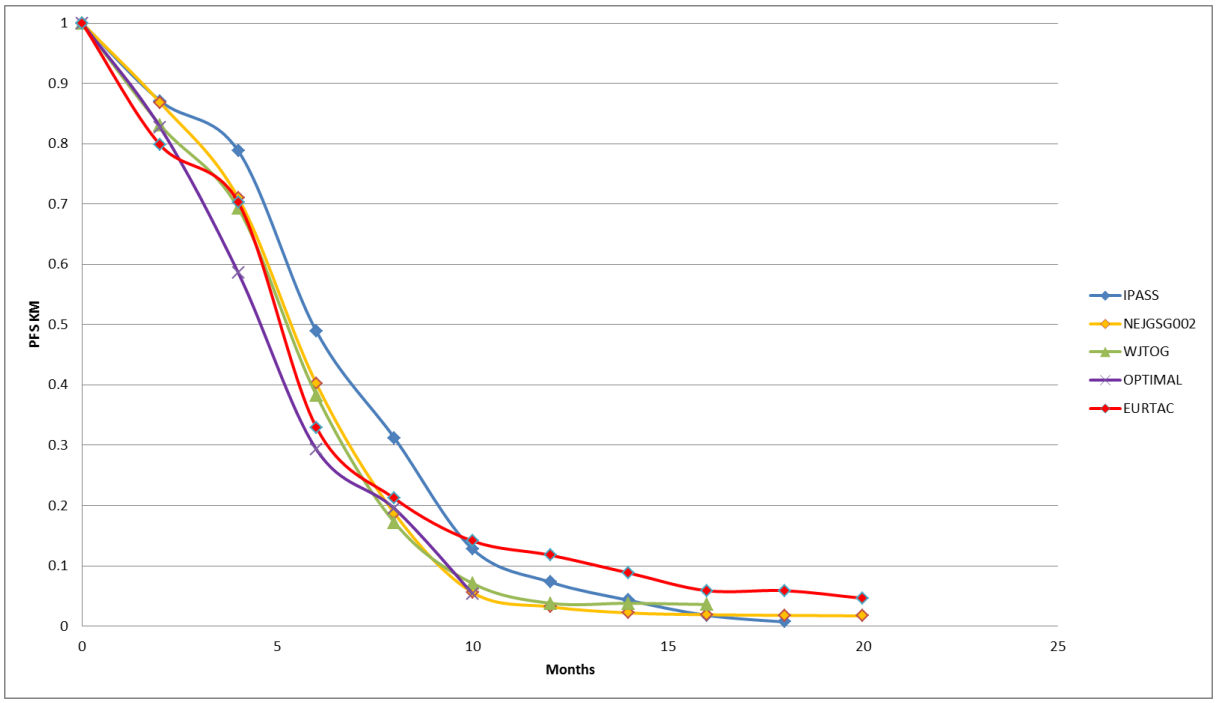
In NICE TA192 (gefitinib for the first line treatment of EGFR M+ mNSCLC) the ERG (LRiG) suggested that it would be reasonable to pool the four gefitinib studies under the assumption that their 'doublet chemotherapy' comparator arms were of equivalent efficacy (an analysis that has recently been conducted by Ku *et al* 2011). If this assumption is extended to the comparator arms of EURTAC and OPTIMAL then these six studies can (*at least in theory*) be linked using 'doublet chemotherapy' as an anchor point for the network (see Figure 40 below).

Figure 40: Network of randomized controlled trials



The notion of using the 'doublet chemotherapy' arms of EURTAC and OPTIMAL to link into a network comparing to gefitinib appears to be broadly supported by Figure 41 below. This figure demonstrates that if the comparator arms from each of the six studies are presented on the same axis they appear broadly comparable.

Figure 41: Comparability of 'Doublet Chemotherapy' control arms



Comparability of Studies

One of the pre-requisites of an indirect comparison is the assumption that the treatment effects observed in studies considered for inclusion in such an analysis are comparable and exchangeable between studies. As discussed previously this assumption appears not to apply for the OPTIMAL and EURTAC RCTs. In order to assess the differences/similarities between all the studies identified in a systematic manner the characteristics of each study (and the patients involved in each study) were tabulated and compared. Table 32 and Table 33 (below) provide the results of this tabulation.

Summary of findings

All studies enrolled chemotherapy naïve patients with Stage IIIB or IV NSCLC and a WHO/ECOG performance status of at least 0 or 1. The type of EGFR mutation (e.g. exon 19 deletion or L858R in exon 21) in the study population was specified in all studies except the First-SIGNAL study. Histological data was not consistently reported in the studies; only three studies (NEJGSG002 , WJTOG3405, OPTIMAL) described the histology of their entire study populations.

All four RCTs that compared gefitinib with chemotherapy (IPASS, First-SIGNAL, NEJGSG002 , WJTOG3405) included Asian patients. Across studies, the proportion of the study population classified as never smokers ranged from 62% (NEJGSG002) to 100% (First-SIGNAL) while two studies included patients who were current smokers (NEJGSG002 , WJTOG3405). In all studies, at least 90% of patients had a WHO/ECOG performance status of 0 or 1. The percentage of patients with stage IIIB ranged from 10%-15%, while one study (IPASS) did not report disease stage; two studies (NEJGSG002 , WJTOG3405) also included post-operative relapse patients who were therefore not classified as in stage IIIB or IV disease. Regarding the type of EGFR mutation, approximately 50% of patients had the exon 19 deletion in all studies.

The differences between the EURTAC and OPTIMAL studies (i.e. ethnicity and compliance) have been discussed previously and so are not reviewed again here.

Table 32: Study characteristics

Author	Trial	Treatment	Location	Population	Inclusion criteria	Exclusion criteria
Mok et al, 2009/Fukuoka et al, 2011	IPASS	Gefitinib vs. Carboplatin+ Paclitaxel	87 centers in Hong Kong, elsewhere in China, Indonesia, Japan, Malaysia, Phillipines, Singapore, Taiwan and Thailand	Asian	18 years of age or older, had histologically or cytologically confirmed stage IIIB or IVnon–small-cell lung cancer with histologic features of adenocarcinoma (including bronchoalveolar carcinoma), were nonsmokers (defined as patients who had smoked <100 cigarettes in their lifetime) or former light smokers (those who had stopped smoking at least 15 years previously and had a total of ≤10 pack-years of smoking), and had had no previous chemotherapy or biologic or immunologic therapy	NR
Lee et al, 2009	First-SIGNAL	Gefitinib vs. Gemcitabine + cisplatin	Korea	Korean	Age 18-75; 1.Histologically or cytologically confirmed diagnosis of adenocarcinoma; 2.Stage IIIB with malignant pleural effusion/pleural seeding or stage IV patients; no prior chemotherapy; never smoker (<100 cigarettes in lifetime); ECOG performance status of 0-2	Known severe hypersensitivity to gefitinib or any of the excipients of this product; Any evidence of clinically active interstitial lung disease; any evidence of severe or uncontrolled systemic disease; Concomitant use of phenytoin, carbamazepine, rifampicin, barbiturates, or St John's Wort; Pregnant or lactating women
Maemondo et al, 2010	NEJGSG002	Gefitinib vs. Carboplatin+ Paclitaxel	43 institutions in Japan	Japanese	Presence of advanced non–small-cell lung cancer harboring sensitive EGFR mutations, the absence of the resistant EGFR mutation T790M, no history of chemotherapy, and an age of 75 years or younger	NR

Author	Trial	Treatment	Location	Population	Inclusion criteria	Exclusion criteria
Mitsudomi et al, 2010	WJTOG 340534 05	Gefitinib vs. Cisplatin+ Docetaxel	36 centers in Japan	Japanese	Patients were eligible if they had histologically or cytologically confirmed NSCLC, harbouring activating EGFR mutations (either exon 19 deletion or L858R in exon 21), were aged 75 years or younger, had WHO performance status 0–1, had measurable or non-measurable disease according to the Response Evaluation Criteria in Solid Tumours (RECIST), and had adequate organ function. Patients with postoperative recurrence, treated with adjuvant therapy other than cisplatin plus docetaxel, were included when the interval between the end of adjuvant chemotherapy and registration exceeded 6 months for platinum-doublet chemtoerhapy	Not eligible if they had received previous drug therapy that had targeted EGFR, had a history of interstitial lung disease, severe drug allergy, active infection or other serious disease condition, symptomatic brain metastases, poorly controlled pleural effusion, pericardial effusion or ascites necessitating drainage, or severe hypersensitivity to drugs containing polysolvate 80. Patients in pregnancy or lactation, or whose participation in the trial was judged to be inappropriate by the attending doctor, werenotligible
Zhou et al, 2010	OPTIM AL	Erlotinib vs Gemcitabine + carboplatin	23 centres in China	Chinese	Age ≥ 18 years old, histology confirmed advanced or recurrent stage IIIB or IV NSCLC. EGFR exon 19 deletions or exon 21 L858R mutation detected via direct polymerase chain reaction (PCR) sequencing (all mutation testing was conducted in one central laboratory), measurable disease, according to RECIST, ECO PS 0-2, adequate hematologic, biochemical and organ function , prior systemic anticancer therapy (adjuvant or neoadjuvant allowed where relapse occurred ≥ 6 months after final treatment), uncontrolled brain metastases	NR
Rossell et al, 2011	EURTA C	Erlotinib vs Platinum based doublet chemotherapy q3wksx4 cycles	Europe	Western	Age ≥ 18 years old, histology confirmed stage IIIB or IV NSCLC. EGFR exon 19 deletions or exon 21 L858R mutation , measurable disease, ECO PS 0-2, adequate hematologic, biochemical and organ function	Prior chemotherapy for metastatic disease, adjuvant or neoadjuvant allowed if completed ≥ 6 months before entering study, uncontrolled brain metastases

Table 33: Patient characteristics in RCTs identified

Author	Trial name	Intervention	Dosage	sample size (n)	Female (%)	Age in yrs (median)	Never smoked	previous/ current smoker	Disease stage IIIB	Disease stage IV	Post operative relapse	Exon 19 deletion	L858R	Other	PS 0 (%)	PS 1 (%)	PS 2 (%)	Adenocarcinoma
Mok et al, 2009/ Fukuoka et al., 2011	IPASS	Gefitinib	250 mg/day	132	81.8%	<65: 72.0%	93.9%	NR	NR	NR	NR	50.0%	48.5%	6.1%	90.2%	NR	NR	NR
		Carboplatin/ Paclitaxel	AUC 6/ 200 mg/m^2	129	79.8%	<65: 69.8%	94.6%	NR	NR	NR	NR	57.4%	36.4%	10.1%	94.6%	NR	NR	NR
Lee et al, 2009*	First - SIGNAL	Gefitinib	250 mg/day	159	88.0%	57	100.0%	NR	10.7%	89.3%	NR	NR	NR	NR	25.8%	65.4%	8.8%	NR
		Gemcitabine + cisplatin	1250mg/m^2 dl / 200 mg/m2 dl	150	89.3%	57	100.0%	NR	9.3%	90.7%	NR	NR	NR	NR	20.7%	70.0%	9.3%	NR
Maemondo et al, 2010	NEJGSG 002	Gefitinib	250 mg/day	114	63.2%	63.9 (mean)	65.8%	34.2%	13.2%	77.2%	9.6%	50.9%	43.0%	6.1%	47.4%	51.8%	0.9%	90.4%
		Carboplatin/ Paclitaxel	AUC 6/ 200 mg/m^2	114	64.0%	62.6 (mean)	57.9%	42.1%	18.4%	73.7%	7.9%	51.8%	42.1%	6.1%	50.0%	48.2%	1.8%	96.5%
Mitsudomi et al, 2010	WJTOG3 4053405	Gefitinib	250 mg/day	86	68.6%	64	70.9%	29.1%	11.6%	47.7%	40.7%	58.1%	41.9%	NR	65.1%	34.9%	NR	96.5%
		Cisplatin+ Docetaxel	60 mg/m^2	86	69.8%	64	66.3%	33.7%	10.5%	47.7%	41.9%	43.0%	57.0%	NR	60.5%	39.5%	NR	97.7%
Zhou et al, 2010	OPTIMAL	Erlotinib	150 mg/day	82	58%	57	72%	28%	13%	87 %	NR	52%	48%	NR	92.0% PS0-1	NR	8.0%	88.0%
		Gemcitabine + carboplatin	1000mg/m^2 / AUC 5	72	60%	59	69%	31%	7%	93%	NR	54%	46%	NR	96.0% PS0-1	NR	4.0%	86.0%
Rosell et al, 2011	EURTAC	Erlotinib	150 mg/day	86	67%	65	66%	34%	NR	90.0%	NR	66%	34%	NR	31%	55%	14%	90.0%
		Platinum based CT	Platinum based CT doublet	87	78%	65	72%	28%	NR	90.0%	NR	67%	33%	NR	34%	52%	14%	90.0%

			therapy														

* Patient characteristics reflect total population and not just EGFR M+ population

Overall, the RCTs with gefitinib have a slightly higher proportion of patients classified as never smokers than those with erlotinib. The WHO/ECOG performance status is similar between these trials. As two of the RCTs with gefitinib included post-operative relapse patients, the proportion of patients with stage IV disease is higher in the erlotinib studies than in the gefitinib studies. The distribution of type of EGFR mutation is somewhat different across comparison, as well as the distribution of race: For erlotinib the evidence base consists of a Caucasian and an Asian study, whereas for gefitinib only Asian studies are available.

The question of importance to the current decision problem is whether the covariates showing a difference across comparisons are effect modifiers with sufficient impact to be a relevant source of bias in the indirect comparison of erlotinib and gefitinib. Subgroup analyses of EURTAC and OPTIMAL as well NEJGSG002 , IPASS, and WJTOG3405 do not show different hazard ratios for PFS by EGFR mutation type and as such differences in the distribution of EGFR M+ are unlikely to be a source of bias in an indirect comparison .

This leaves ethnicity as the key differentiator between the data available for erlotinib and for gefitinib. The prevalence of EGFR M+ NSCLC is appreciably higher in East Asian than in Caucasian populations. Since all studies concern EGFR M+ patients, ethnicity can only be a cause of bias in an indirect comparison of erlotinib and gefitinib if ethnicity is not a perfect proxy for the modifying effect of EGFR status on the efficacy of erlotinib and gefitinib.

Conclusion

An indirect comparison of erlotinib and gefitinib in a Caucasian population is inherently limited by the fact that gefitinib has never been studied in a phase III RCT conducted in Caucasian EGFR M+ population and the divergence between OPTIMAL and EURTAC indicates that ethnicity may be an EGFR TKI treatment effect modifier.

The only indirect comparison of erlotinib and gefitinib that can be robustly conducted is one in an East Asian population comparing OPTIMAL to IPASS/First-SIGNAL/WJTOG3405/NEJGSG002 . These are the only RCTs in which the patients included in each study (and centres involved) are sufficiently similar to allow robust estimation of the relative efficacy of erlotinib and gefitinib in any population (so similar that the OPTIMAL study was largely conducted in centres that had previously participated in the IPASS RCT).

However, the current decision problem requires that the relative effectiveness of erlotinib and gefitinib in a European population be assessed. There are four potential (albeit perhaps not unbiased) quantitative indirect comparisons that could be conducted to inform this comparison given the data available and the recommendation of LRiG in TA192 that IPASS/First-SIGNAL/WJTOG3405/NEJGSG002 be pooled (as conducted by Ku et al). The results of these analyses are presented below (derivation described in section 5.7.5. below).

1. If OPTIMAL is compared to IPASS/First-SIGNAL/WJTOG3405/NEJGSG002 (i.e. a comparison of erlotinib and gefitinib in patients of similar ethnicity) the indirect PFS HR of erlotinib vs gefitinib is **0.36 {0.22, 0.59}.**

2. If the fixed effects pooled estimate of EURTAC/OPTIMAL is compared to IPASS/First-SIGNAL/WJTOG3405/NEJGSG002 the PFS HR is **0.58 {0.41, 0.81}.**

3. If the random effects pooled estimate of EURTAC/OPTIMAL is compared to IPASS/First-SIGNAL/WJTOG3405/NEJGSG002 the PFS HR is **0.56 {0.24, 1.28}.**

4. The indirect PFS HR of erlotinib vs gefitinib based upon the comparison of EURTAC and IPASS/First-SIGNAL/WJTOG3405/NEJGSG002 is **0.82 {0.54, 1.26}.**

The above analyses demonstrate that irrespective of which indirect comparison is undertaken erlotinib is superior (or has a trend to superiority) compared to gefitinib. Whilst none of the four analyses above answer the precise question at hand they are nevertheless the best available evidence upon which to assess the relative effectiveness of erlotinib and gefitinib in a European population.

See section 6.3.1 for how this issue was dealt with in the base-case economic modelling.

5.7.4 For the selected trials, provide a summary of the data used in the analysis.

Table 34: Summary of data used in indirect comparison

	PFS HR	LCL	UCL	Scenario
OPTIMAL	0.162	0.102	0.256	1
FE Pooling EURTAC/OPTIMAL	0.26	0.2	0.35	2
RE Pooling EURTAC/OPTIMAL	0.25	0.11	0.56	3
EURTAC	0.37	0.25	0.54	4
Ku et al	0.45	0.38	0.55	1,2,3,4

As described above in the base-case economic analysis EURTAC (PFS HR = 0.37 {0.25, 0.54}) was conservatively compared to Ku et al (PFS HR 0.45 {0.38, 0.55}).

5.7.5 Please provide a clear description of the indirect/mixed treatment comparison methodology. Supply any programming language in a separate appendix.

All four indirect comparisons were conducted using the adjusted indirect comparison methodology developed by Bucher et al (2007). The Ku et al 2011 meta-analysis of IPASS/WJTOG3405/First-SIGNAL and NEJGSG002 (PFS HR = 0.45 {0.38, 0.55}) was used in all four analyses conducted (following LRiG's opinion in TA192 that it was appropriate to pool these four studies).

The Bucher method

The indirect PFS HRs were derived by first converting the hazard ratios from Ku et al, EURTAC, OPTIMAL, the Fixed Effects EURTAC/OPTIMAL pooling and Random Effects EURTAC/OPTIMAL pooling to log hazard ratios. The Log Ku et al PFS HR was then subtracted from the chosen Log erlotinib vs doublet chemotherapy PFS HR (i.e. one of the four detailed above). The resultant indirect log hazard ratio was then exponentiated in order to derive the indirect PFS on the non-log scale.

This calculation is demonstrated for the EURTAC vs Ku et al below:

EXP(LN(0.37) – LN(0.45)) = 0.82

The confidence intervals for each indirect estimate were derived by:

1) Converting the PFS HRs and confidence intervals from each of the four erlotinib vs doublet chemotherapy scenarios and the Ku et al meta-analysis into Log HRs and Log confidence intervals

2) Estimating the log standard error for each of these estimates by dividing the difference between the log lower and log higher confidence interval for each estimate by 1.96*2

3) By squaring each log standard error and summing those relevant to the comparison being undertaken (i.e. the Ku et al figure and that relevant to whichever of the erlotinib scenarios being undertaken)

4) By taking the square root of the result and applying it to the log indirect HR estimate (i.e. log indirect HR estimate +/- 1.96 * log indirect

standard error) in order to derive the log confidence intervals of the indirect estimate

5) By taking the exponential of the resultant confidence intervals in order to convert them back from the log scale.

5.7.6 Please present the results of the analysis.

The indirect PFS HR of erlotinib vs gefitinib based upon the comparison of EURTAC and Ku et al is 0.82 {0.54, 1.26}.

If OPTIMAL is compared to Ku et al (i.e. a comparison of erlotinib and gefitinib in patients of similar ethnicity) the indirect PFS HR of erlotinib vs gefitinib is 0.36 {0.22, 0.59}.

If the fixed effected pooled estimate of EURTAC/OPTIMAL is compared to Ku et al the PFS HR is 0.58 {0.41, 0.81}.

If the random effects pooled estimate of EURTAC/OPTIMAL is compared to Ku et al the PFS HR is 0.56 {0.24, 1.28}.

5.7.7 Please provide the statistical assessment of heterogeneity undertaken. The degree of, and the reasons for, heterogeneity should be explored as fully as possible.

The only tests for heterogeneity conducted were those described for the pooling of EURTAC and OPTIMAL described previously (i.e. the Chi^2 test and the generation of an I^2 statistics). No statistical test for heterogeneity was undertaken for the gefitinib data included in the Ku et al meta-analysis. As LRiG had recommended the pooling of the four studies in the Ku et al 2011 analysis it was assumed that the studies would be sufficiently homogeneous to allow pooling and integration into the indirect comparison undertaken.

5.7.8 If there is doubt about the relevance of a particular trial, please present separate sensitivity analyses in which these trials are excluded.

See above.

5.7.9 Please discuss any heterogeneity between results of pairwise comparisons and inconsistencies between the direct and indirect evidence on the technologies.

Not applicable.

5.8 Non-RCT evidence

Non-RCT, both experimental and observational, evidence will be required, not just for those situations in which RCTs are unavailable, but also to supplement information from RCTs when they are available. This section should be read in conjunction with NICE's 'Guide to the methods of technology appraisal', sections 3.2.8 to 3.2.10.

5.8.1 If non-RCT evidence is considered (see section 5.2.7), please repeat the instructions specified in sections 5.1 to 5.5 for the identification, selection and methodology of the trials, and the presentation of results. For the quality assessments of non-RCTs, use an appropriate and validated quality assessment instrument. Key aspects of quality to be considered can be found in 'Systematic

reviews: CRD's guidance for undertaking reviews in health care' (www.york.ac.uk/inst/crd). Exact details of the search strategy used and a complete quality assessment for each trial should be provided in sections 9.6 and 9.7, appendices 6 and 7.

Due the current length of this submission (>300 pages, 62,000 words) and RCT evidence available, extensive amounts of observational data have not been provided within this submission. If it is felt to be of use to the Committee we can provide this information on request.

In place of a comprehensive review we would point the Committee to the pooled analysis of erlotinib and gefitinib observational data published by Paz-Ares et al in 2010. This analysis pooled the outcomes of 1,434 EGFR M+ patients treated with erlotinib or gefitinib in studies up to June 2009

This analysis demonstrated median PFS outcomes of 13.2 months for erlotinib, 9.8 months for gefitinib and 5.9 months for chemotherapy across multiple lines of treatment. A similar trend in PFS outcomes was observed when the analysis included predominantly first line treatment with median PFS outcomes of 12.5 months for erlotinib, 9.9 months for gefitinib and 6.0 months for chemotherapy.

Whilst this analysis is subject to the usual biases of observational data it is nevertheless supportive of the efficacy of erlotinib in the first line treatment of EGFR M+ patients

Figure 42 and Figure 43 below demonstrate the results of the Paz-Ares pooling.

Figure 42: Paz-Ares Pooled PFS Analysis Results

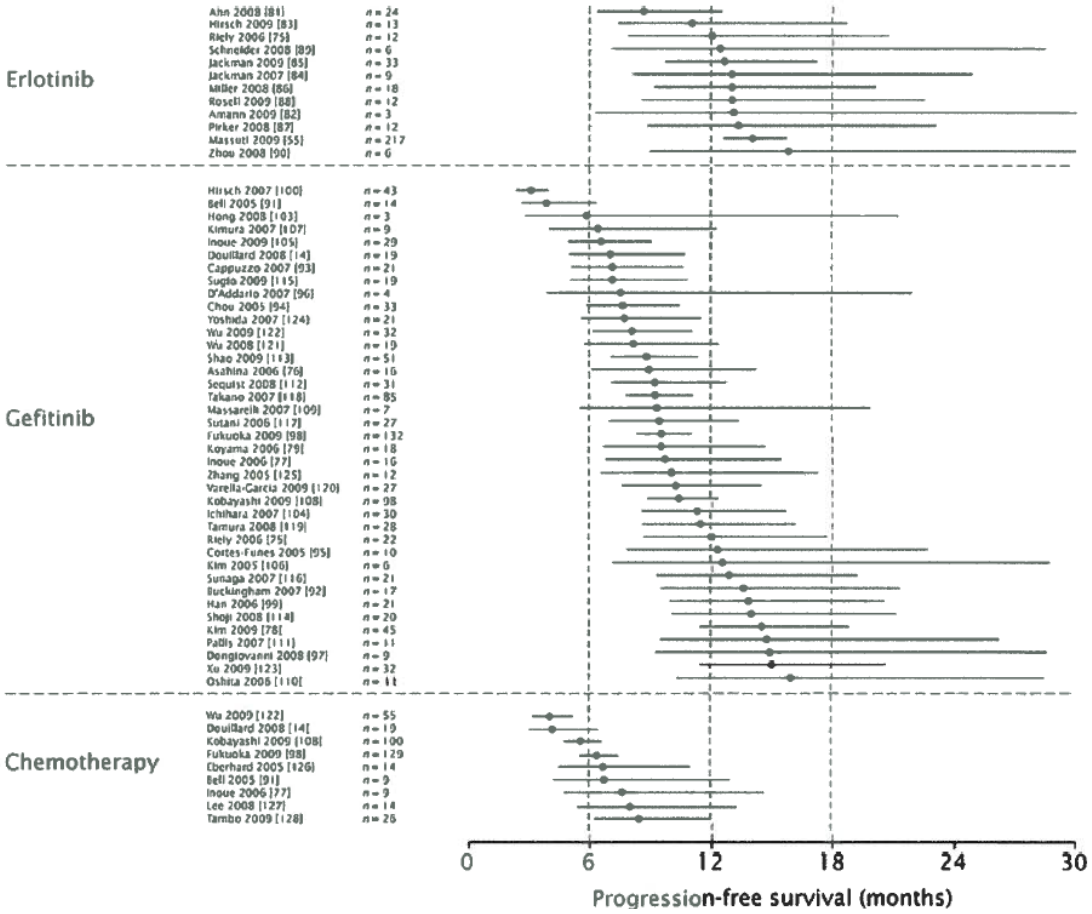
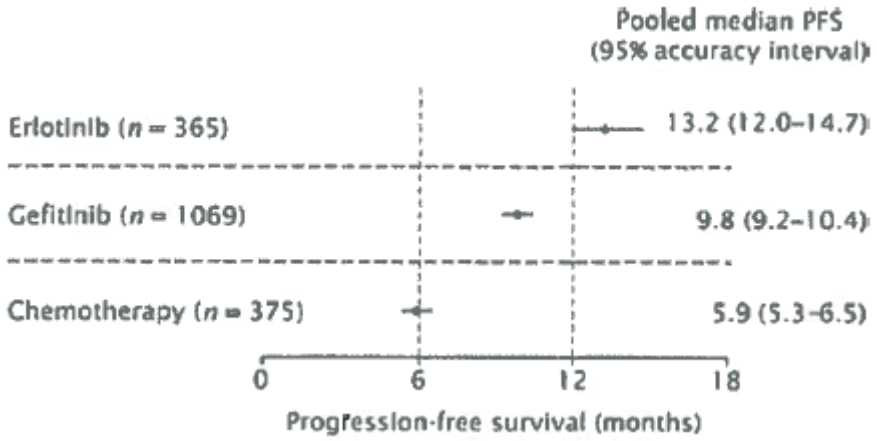


Figure 43: Paz-Ares Pooled PFS Analysis Results



Adverse events

This section should provide information on the adverse events experienced with the technology in relation to the decision problem. Evidence from comparative RCTs and regulatory summaries is preferred; however, findings from non-comparative trials may sometimes be relevant. For example, post-marketing surveillance data may demonstrate that the technology shows a relative lack of adverse events commonly associated with the comparator, or the occurrence of adverse events is not significantly associated with other treatments.

5.8.2 If any of the main trials are designed primarily to assess safety outcomes (for example, they are powered to detect significant differences between treatments with respect to the incidence of an adverse event), please repeat the instructions specified in sections 5.1 to 5.5 for the identification, selection, methodology and quality of the trials, and the presentation of results. Examples for search strategies for specific adverse effects and/or generic adverse-effect terms and key aspects of quality criteria for adverse-effects data can found in 'Systematic reviews: CRD's guidance for undertaking reviews in health care' (www.york.ac.uk/inst/crd). Exact details of the search strategy used and a complete quality assessment for each trial should be provided in sections 9.8 and 9.9, appendices 8 and 9.

Not applicable

5.8.3 Please provide details of all important adverse events for each intervention group. For each group, give the number with the adverse event, the number in the group and the percentage with the event. Then present the relative risk and risk difference and associated 95% confidence intervals for each adverse event. A suggested format is shown below.

5.8.3.1 Safety and Tolerability of erlotinib in EURTAC

Overall, the safety profile of erlotinib in EURTAC as 1st line treatment of patients with NSCLC having activating EGFR mutations was consistent with previously collected data for erlotinib in its earlier indications in the first-line maintenance and relapsed NSCLC settings (summarised in Table 35).

It is important to note that the duration of therapy differed in the treatment arms. Platinum doublet chemotherapy was administered for a maximum of 4 cycles (approximately 3 months) whereas erlotinib was administered until PD or unacceptable toxicity typically for 9-10 months. This largely reflects the difference in the nature of the two treatments in terms of patient tolerability where erlotinib provides patients the opportunity to continue active treatment for their disease for considerably longer than with platinum doublet chemotherapy, in turn achieving significantly improved efficacy and QoL outcomes. However the longer period of treatment, inevitably results in more AEs being reported during the treatment period, especially in a condition like NSCLC where patients experience a variety of disease symptoms and complications which will be registered as AEs and often be treated symptomatically with drugs that may, in themselves, result in further AE's. Many of these AE's will be disease- and not treatment-related.

The majority of AEs reported in EURTAC were NCI-CTC grade 1 or grade 2 (432/527 events [82.0%] in the platinum doublet chemotherapy arm and 621/681 events [91.2%] in the erlotinib arm).

More patients experienced grade 3 and grade 4 AEs in the platinum doublet chemotherapy arm than in the erlotinib arm. More patients in the platinum doublet chemotherapy arm experienced severe events (NCI-CTC grade ≥ 3) (49 patients [66.2%]) compared to 31 patients [41.3%] in the erlotinib arm).

Skin toxicities were more frequently observed in the erlotinib arm (82.7%) compared to the platinum doublet chemotherapy arm (23.0%) and included rash (49.3% vs 1.4%), dry skin (17.3% *vs* 2.7%), acne (12.0% *vs* 0%) and pruritus (10.7% *vs* 1.4%).

Diarrhoea was also more commonly reported in the erlotinib arm (57.3% patients) than in the platinum doublet chemotherapy arm (18.9% patients).

Haematological toxicities were more frequently reported by patients in the platinum doublet chemotherapy arm than in the erlotinib arm (anaemia: 45.9% *vs* 10.7%, neutropenia: 36.5% *vs* 0%, febrile neutropenia: 4.1% vs 0%, leukopenia: 13.5% *vs* 2.7% and thrombocytopenia: 12.2% *vs* 1.3%).

Gastrointestinal disorders were reported to a similar extent across both treatment arms (67.6% and 69.3% in the platinum doublet chemotherapy and erlotinib arms, respectively), but nausea (40.5% *vs* 22.7%), vomiting (21.6% *vs* 13.3%) and constipation (21.6% *vs* 8.0%) were more frequently reported in the platinum doublet chemotherapy arm.

More patients receiving platinum doublet chemotherapy experienced asthenia (68.9% *vs* 53.3% in the erlotinib arm).

The incidence of infections and infestations was higher in the erlotinib arm (49.3% *vs* 16.2% in the platinum doublet chemotherapy arm), due mainly to the occurrence of paronychia and folliculitis which were reported exclusively in the erlotinib arm by 16.0% patients and 8.0% patients, respectively. However, these generally represent only modest inconvenience and discomfort to patients and are not life-threatening, unlike the infections that can accompany periods of chemotherapy-induced immunosuppression.

Most other AEs within this category were isolated single occurrences. Eye disorders were reported exclusively in the erlotinib arm (26.7% patients),

particularly conjunctivitis (12% patients). Other eye disorders included blepharitis (2/75 patients, 2.7%), dry eye (2.7%), growth of eyelashes (2.7%), increased lacrimation (2.7%), and single incidents of eyelid oedema, ocular hyperaemia, ocular toxicity, photopsia and vitreous floaters. More patients treated with erlotinib experienced cough (45.3% *vs* 35.1% in platinum doublet chemotherapy) and dyspnoea (41.3% *vs* 25.7% in platinum doublet chemotherapy). However, more patients in the erlotinib arm experienced mucosal inflammation compared to the platinum doublet chemotherapy arm (17.3% and 5.4%, for erlotinib and platinum doublet chemotherapy arms, respectively).

Table 35: Summary of Adverse Events with an Incidence Rate of at Least 10% in EURTAC

Parameter	Platinum Doublet Chemotherapy Arm (n=74) Number (%)			Erlotinib Arm (n=75) Number (%)		
	All Grades	Grade 3	Grade 4	All Grades	Grade 3	Grade 4
Gastrointestinal Disorders						
Diarrhoea	14 (18.9)	-	-	43 (57.3)	3 (4.0)	-
Nausea	30 (40.5)	4 (5.4)	-	17 (22.7)	1 (1.3)	-
Vomiting	16 (21.6)	3 (4.1)	-	10 (13.3)	-	-
Constipation	16 (21.6)	-	-	6 (8.0)	-	-
Stomatitis	7 (9.5)	-	-	8 (10.7)	-	-
General Disorders and Administration Site Conditions						
Asthenia	51 (68.9)	13 (17.6)	-	40 (53.3)	5 (6.7)	-
Chest Pain	10 (13.5)	-	-	13 (17.3)	1 (1.3)	-
Pyrexia	10 (13.5)	-	-	8 (10.7)	-	-
Mucosal Inflammation	4 (5.4)	-	-	13 (17.3)	1 (1.3)	-
Respiratory, Thoracic and Mediastinal Disorders						
Cough	26 (35.1)	-	-	34 (45.3)	1 (1.3)	-
Dyspnoea	19 (25.7)	1 (1.4)	-	31 (41.3)	6 (8.0)	-
Skin and Subcutaneous Tissue Disorders						
Rash	1 (1.4)	-	-	37 (49.3)	4 (5.3)	-
Alopecia	13 (17.6)	2 (2.7)	-	11 (14.7)	-	-
Dry Skin	2 (2.7)	-	-	13 (17.3)	1 (1.3)	-
Acne	-	-	-	9 (12.0)	-	-
Pruritus	1 (1.4)	-	-	8 (10.7)	-	-
Blood and Lymphatic System Disorders						
Anaemia	34 (45.9)	3 (4.1)	-	8 (10.7)	-	1 (1.3)
Neutropenia	27 (36.5)	11 (14.9)	5 (6.8)	-	-	-
Febrile Neutropenia	3 (4.1)	1 (1.4)	2 (2.7)	-	-	-
Leukopenia	10 (13.5)	4 (5.4)	-	2 (2.7)	-	-
Thrombocytopenia	9 (12.2)	4 (5.4)	5 (6.8)	1 (1.3)	-	-
Metabolism and Nutrition Disorders						
Decreased Appetite	25 (33.8)	-	-	21 (28.0)	-	-
Musculoskeletal and Connective Tissue Disorders						
Back Pain	4 (5.4)	-	-	12 (16.0)	-	-
Infections and Infestations						
Paronychia	-	-	-	12 (16.0)	-	-
Ear and Labyrinth Disorders						
Tinnitus	8 (10.8)	-	-	1 (1.3)	-	-
Eye Disorders						
Conjunctivitis	-	-	-	9 (12.0)	-	-

Multiple occurrences of the same adverse event in one individual counted only once.
Cut-off for statistical analysis: 02AUG2010

Consistent with the known toxicity profile of erlotinib, low grade skin toxicities and diarrhoea were amongst the most commonly reported AEs in patients that received erlotinib.

Key erlotinib toxicities: rash and diarrhoea

Skin toxicities were mainly mild to moderate in nature and never life-threatening, with only 5% and 1% of patients experiencing grade 3 rash and dry skin respectively. No grade 4 skin toxicities were reported for erlotinib in EURTAC, which is consistent with previously published data (Shepherd et al. 2005, Capuzzo et al. 2010). Since 2005 when erlotinib received its first Marketing Authorization, considerable expertise has developed amongst the UK clinical community in the management of erlotinib-related skin toxicities due to their extensive use of erlotinib as the standard of care in relapsed NSCLC. Consensus guidelines have been produced for the management of rash (Thatcher et al. 2009) detailing prophylactic and reactive measures that can be undertaken to prevent or reduce the severity of skin toxicities experienced by patients. These are in most cases relatively inexpensive and do not place too much of a burden on either the patients or associated healthcare professionals taking care of the patient.

Diarrhoea was also mainly mild to moderate in nature in patients on erlotinib, with only 4% of patients experiencing grade 3 diarrhoea and no reports of grade 4 diarrhoea. Effective control of diarrhoea symptoms is often achieved with the use of simple readily available and relatively inexpensive medications such as loperamide (Tarceva SmPC 2010) and symptoms are usually quick to resolve following the cessation of treatment with no long term debilitating impact on patients' QoL.

Key chemotherapy toxicities: myelotoxicity, nausea and vomiting

As expected, the most common and severely reported AEs for platinum doublet chemotherapy in EURTAC were haematological toxicities and

asthenia, which would inevitably have considerable impact on a patient's well-being and QoL.

Patients on platinum doublet chemotherapy experienced grade 3 anaemia (4.1%), neutropenia (14.9%), febrile neutropenia (1.4%), leukopenia (5.4%), and thrombocytopenia (5.4%); and grade 4 neutropenia (6.8%), febrile neutropenia (2.7%) and thrombocytopenia (6.8%). These AEs can be life-threatening pre-disposing patients to severe infection which would in turn lead to urgent, unplanned, hospital admission and institution of IV antibiotics. As these AEs are hard to predict, there is the inherent requirement for routine blood monitoring during treatment - which can place an additional burden on both the patients and associated healthcare professionals in terms of time and resource requirement. In contrast, haematological toxicities overall were reported less frequently by patients on erlotinib with no grade 3 and 4 haematological toxicities being reported (except for 1 patient reporting grade 3 anaemia).

Grade 3 nausea (5.4%) and vomiting (4.1%) was reported more frequently for patients receiving platinum doublet chemotherapy than those receiving erlotinib (1.3% and 0% respectively). These AEs are not always easy to treat and can have considerable impact on a patients' QoL.

Impact of toxicity on patients

Due to the contrasting nature of the safety profiles of erlotinib and platinum doublet chemotherapy, it is helpful to take a broad view of the impact of toxicity on patients as well as comparing the frequency of specific adverse events, as is done in Table 36. In summary:

- more patients experienced severe AEs (NCI-CTC grade ≥ 3) in the platinum doublet chemotherapy arm (66.2%) compared to the erlotinib arm (41.3%)

- a higher proportion of patients in the platinum doublet chemotherapy arm experienced a treatment related SAE (16.2% *vs* 6.7% in the erlotinib arm)
- more patients in the platinum doublet chemotherapy arm (52.7%) had AEs leading to dose alterations compared to the erlotinib arm (26.7%)
- a higher proportion of patients in the platinum doublet chemotherapy arm were withdrawn due to an AE (17.6%) compared to the erlotinib arm (13.3%)
- in the platinum doublet chemotherapy arm, most patients (25/39) had dose delays / reductions due to haematological toxicity.

Table 36: Summary of Adverse events, Withdrawals and Deaths in EURTAC

Parameter	Platinum Doublet Chemotherapy Arm (n=74) Number (%)	Erlotinib Arm (n=75) Number (%)
Total Patients with at Least one AE	73 (98.6)	72 (96.0)
Total Number of AEs	527	681
Deaths #	5 (6.8)	10 (13.3)
Study withdrawals due to an AE #	11 (14.9)	9 (12.0)
Patients with at least one		
AE leading to Death	4 (5.4)	7 (9.3)
Serious AE	19 (25.7)	20 (26.7)
Related serious AE	12 (16.2)	5 (6.7)
AE leading to withdrawal from treatment	13 (17.6)	10 (13.3)
AE leading to dose modification/interruption	39 (52.7)	20 (26.7)
Related AE	70 (94.6)	69 (92.0)
Related AE leading to withdrawal from treatment	11 (14.9)	5 (6.7)
Severe AE	49 (66.2)	31 (41.3)

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.
Cut-off for statistical analysis: 02AUG2010

5.8.3.2 Safety and Tolerability of erlotinib in OPTIMAL

The safety profile of erlotinib compared to platinum doublet chemotherapy in OPTIMAL was consistent what has been reported for EURTAC and in line with previously collected data (Table 37).

Compared with the gemcitabine + carboplatin arm, erlotinib treatment was associated with a lower rate of NCI-CTC grade III-IV adverse events, adverse events leading to discontinuation and dose modifications due to toxicity.

The most common AEs in the erlotinib arm were rash, elevated ALT level and diarrhoea, the incidence of which were higher than in the gemcitabine + carboplatin arm.

The most common AEs in the gemcitabine + carboplatin arm were haematological or gastrointestinal events all of which were reported with a markedly higher frequency in the platinum doublet chemotherapy arm than the erlotinib arm. These events included decreased neutrophil count, platelet count, haemoglobin and nausea/ vomiting.

Table 37: Summary of Adverse Events with an Incidence Rate of at Least 5% in OPTIMAL

	Erlotinib Arm (N=83) Number (%)		**Gemcitabine + Carboplatin Arm (N=72) Number (%)**	
	All AEs	**CTC Grades III~IV**	**All AEs**	**CTC Grades III~IV**
At least one AE	77 (92.8%)	14 (16.9%)	69 (95.8%)	47 (65.3%)
Blood and lymphatic system disorders	14 (16.9%)	0 (0.0%)	64 (88.9%)	44 (61.1%)
Haemoglobin decreased	4 (4.8%)	0 (0.0%)	52 (72.2%)	9 (12.5%)
Neutrophil count decreased	5 (6.0%)	0 (0.0%)	50 (69.4%)	30 (41.7%)
Platelet count decreased	3 (3.6%)	0 (0.0%)	46 (63.9%)	29 (40.3%)
White blood cell count decreased	10 (12.0%)	0 (0.0%)	49 (68.1%)	17 (23.6%)
Cardiac disorders	8 (9.6%)	1 (1.2%)	3 (4.2%)	0 (0.0%)
Gastrointestinal disorders	29 (34.9%)	2 (2.4%)	35 (48.6%)	1 (1.4%)
Constipation	0 (0.0%)	0 (0.0%)	11 (15.3%)	0 (0.0%)
Diarrhoea	21 (25.3%)	1 (1.2%)	4 (5.6%)	0 (0.0%)
Nausea	0 (0.0%)	0 (0.0%)	21 (29.2%)	1 (1.4%)
Stomatitis	11 (13.3%)	1 (1.2%)	1 (1.4%)	0 (0.0%)

	Erlotinib Arm (N=83) Number (%)		Gemcitabine + Carboplatin Arm (N=72) Number (%)	
	All AEs	**CTC Grades III~IV**	**All AEs**	**CTC Grades III~IV**
Vomiting	1 (1.2%)	0 (0.0%)	12 (16.7%)	0 (0.0%)
General disorders and administration site condition	11 (13.3%)	0 (0.0%)	32 (44.4%)	5 (6.9%)
Chest discomfort	5 (6.0%)	0 (0.0%)	3 (4.2%)	0 (0.0%)
Chest pain	1 (1.2%)	0 (0.0%)	8 (11.1%)	0 (0.0%)
Fatigue	4 (4.8%)	0 (0.0%)	17 (23.6%)	1 (1.4%)
Pain	2 (2.4%)	0 (0.0%)	4 (5.6%)	2 (2.8%)
Pyrexia	0 (0.0%)	0 (0.0%)	11 (15.3%)	2 (2.8%)
Hepatobiliary disorders	45 (54.2%)	5 (6.0%)	26 (36.1%)	1 (1.4%)
Alanine aminotransferase increased	31 (37.3%)	3 (3.6%)	24 (33.3%)	1 (1.4%)
Aspartate aminotransferase increased	17 (20.5%)	2 (2.4%)	10 (13.9%)	0 (0.0%)
Blood alkaline phosphatase increased	5 (6.0%)	2 (2.4%)	1 (1.4%)	0 (0.0%)
Blood bilirubin increased	24 (28.9%)	2 (2.4%)	1 (1.4%)	0 (0.0%)
Infections and infestations	14 (16.9%)	1 (1.2%)	7 (9.7%)	0 (0.0%)
Lung infection	6 (7.2%)	1 (1.2%)	4 (5.6%)	0 (0.0%)
Upper respiratory tract infection	5 (6.0%)	0 (0.0%)	2 (2.8%)	0 (0.0%)
Injury, poisoning and procedural complications	0 (0.0%)	0 (0.0%)	5 (6.9%)	0 (0.0%)
Investigations	15 (18.1%)	0 (0.0%)	9 (12.5%)	1 (1.4%)
White blood cells urine positive	5 (6.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Metabolism and nutrition disorders	12 (14.5%)	0 (0.0%)	28 (38.9%)	1 (1.4%)
Anorexia	5 (6.0%)	0 (0.0%)	23 (31.9%)	1 (1.4%)
Hypokalaemia	6 (7.2%)	0 (0.0%)	1 (1.4%)	0 (0.0%)
Musculoskeletal and connective tissue disorders	5 (6.0%)	0 (0.0%)	5 (6.9%)	1 (1.4%)
Back pain	1 (1.2%)	0 (0.0%)	4 (5.6%)	1 (1.4%)
Nervous system disorders	4 (4.8%)	0 (0.0%)	6 (8.3%)	2 (2.8%)
Renal and urinary disorders	9 (10.8%)	1 (1.2%)	6 (8.3%)	0 (0.0%)
Proteinuria	5 (6.0%)	0 (0.0%)	1 (1.4%)	0 (0.0%)
Respiratory, thoracic and mediastinal disorders	19 (22.9%)	1 (1.2%)	18 (25.0%)	1 (1.4%)
Cough	10 (12.0%)	1 (1.2%)	8 (11.1%)	0 (0.0%)
Respiratory depth decreased	1 (1.2%)	0 (0.0%)	6 (8.3%)	0 (0.0%)
Skin and subcutaneous tissue disorders	65 (78.3%)	2 (2.4%)	19 (26.4%)	0 (0.0%)
Pruritus	1 (1.2%)	0 (0.0%)	4 (5.6%)	0 (0.0%)
Rash	61 (73.5%)	2 (2.4%)	14 (19.4%)	0 (0.0%)

A similar incidence of SAEs was reported in the erlotinib and gemcitabine + carboplatin arms. However, SAEs considered treatment-related were reported in only 2 patients in the erlotinib arm (both elevated ALT) compared with 13.9% of patients in the gemcitabine + carboplatin arm, where treatment-related SAEs were mostly haematological toxicities such as platelet count decrease and decreased neutrophil count.

5.8.3.3 Safety and Tolerability of Gefitinib in Gefitinib RCTs

An overview of the toxicity profiles of gefitinib and platinum doublet chemotherapy in the gefitinib RCTs is provided in tabular form in Appendix 14.

The safety profile of gefitinib across all 4 RCTs is characteristic of the toxicity profile of EGFR TKIs across multiple studies in NSCLC.

The most prominent side effects of gefitinib are skin-related conditions (including rash, acne, dry skin etc.) and diarrhoea. The majority of the adverse events reported across the gefitinib RCTs were mild to moderate.

Similarly to erlotinib, patients receiving gefitinib in the RCTs experienced considerably less haematological toxicities compared those patients receiving platinum doublet chemotherapy.

5.9.2.4 Summary

Both erlotinib and gefitinib demonstrate broadly similar safety profiles characteristic of inhibitors of the EGFR pathway.

Looking across the six RCTs contained within this submission (2 RCTs for erlotinib and 4 RCTs for gefitinib) the rates of reporting for majority of the defined toxicities appeared to be broadly similar with a few exceptions. In particular, the reporting rate was higher in gefitinib RCTs for pruritus (in IPASS), anaemia and dry skin (in WJTOG34053405) and thrombocytopenia (in WJTOG34053405 and NEJGSG002) compared to the rates reported for the respective AEs in either of the erlotinib RCTs (EURTAC and OPTIMAL).

Both WJTOG34053405 and EURTAC reported higher rates of asthenic conditions than the rates reported in IPASS, NEJGSG002 and OPTIMAL.

5.8.4 Give a brief overview of the safety of the technology in relation to the decision problem.

In the absence of a head to head RCT between erlotinib and gefitinib, analysis of the two erlotinib RCTs contained within this application demonstrate that erlotinib does not add any additional significant toxicities either by way of type of toxicities or reported incidence rates of toxicities as first line treatment for NSCLC patients with activating EGFR mutations.

Erlotinib has been available to UK oncologists since 2005 and recommended by NICE since 2008 for the treatment of relapsed NSCLC. Over that time UK healthcare professionals have gained considerable experience in the administration of erlotinib and the management of any side effects. It is anticipated that making erlotinib available as a first line treatment for NSCLC patients with activating EGFR mutations would conform to existing management strategies currently in place for relapsed patients being treated with erlotinib. Furthermore, at present the only first line treatment for NSCLC patients with activating EGFR mutations specifically recommended by NICE is gefitinib (which is only available at a fixed dose of 250mg o.d.). Consequently, patients experiencing unmanageable toxicities on gefitinib have no other option but to discontinue treatment. Erlotinib on the other hand is available at three different dosage strengths and therefore offers flexible dosing for patients in order to continue to manage control of their disease.

5.9 Interpretation of clinical evidence

5.9.1 Please provide a statement of principal findings from the clinical evidence highlighting the clinical benefit and harms from the technology.

EURTAC and OPTIMAL phase III RCTs met their primary endpoints and clearly demonstrated that erlotinib significantly improves PFS compared to platinum doublet chemotherapy (EURTAC: median PFS 9.7 months vs 5.2 months respectively (HR 0.37; 95% CI 0.25 to 0.54, $p < 0.0001$); OPTIMAL:

median PFS 13.7 months vs 4.6 months respectively (HR 0.164; 95% CI 0.105-0.256, p < 0.0001).

EURTAC is the only phase III RCT to demonstrate the superiority of an EGFR TKI in Caucasian NSCLC patients with activating EGFR mutations. OPTIMAL is the only phase III RCT to demonstrate the extension of median PFS to over a year (13.7 months) in NSCLC patients with activating EGFR mutations.

EURTAC and OPTIMAL also demonstrate that erlotinib significantly improves tumour response rates and disease control rates compared to platinum doublet chemotherapy.

OPTIMAL demonstrated that the improvements in clinical outcomes highlighted above also translated to significant improvements in patient's quality of life when receiving erlotinib compared to those receiving platinum doublet chemotherapy. More than double the number of patients receiving erlotinib had clinical relevant improvements in QoL compared to those receiving platinum double chemotherapy (~70% vs ~30% respectively) across all FACT-L scales measured.

Overall, the safety profile of erlotinib in EURTAC and OPTIMAL as first line treatment of patients with NSCLC having activating EGFR mutations was consistent with previously collected data for erlotinib in its earlier indications in the first-line maintenance and relapsed NSCLC settings. Low grade skin toxicities and diarrhoea were amongst the most commonly reported AEs in patients that received erlotinib. Haematological toxicities were infrequent with erlotinib and no grade 3/4 haematological toxicities were reported for erlotinib in EURTAC (except for 1.3% reporting of anaemia) and OPTIMAL. Overall the tolerability profile for erlotinib was significantly more acceptable than that of platinum doublet chemotherapy.

5.9.2 Please provide a summary of the strengths and limitations of the clinical-evidence base of the intervention.

Two robust well-designed phase III RCTs have been submitted as evidence to support the case for erlotinib to be made available for NSCLC patients with activating EGFR mutations in the UK.

The clinical evidence provided is primarily derived from the phase III RCT EURTAC which has been conducted entirely in Caucasian patients and therefore is more representative of the NSCLC population with activating EGFR mutations in the UK. EURTAC is the only phase III RCT to demonstrate the superiority of an EGFR TKI in Caucasian NSCLC patients with activating EGFR mutations.

The relevance of the OPTIMAL data to a UK population could be argued. However, NICE has already recommended the use of gefitinib as first line treatment for NSCLC having activating EGFR mutations (NICE TA 192 2010) based on data from the IPASS study (and supported by NEJGSG002 and First-SIGNAL studies) which were RCTs comprising entirely of East Asian patients. OPTIMAL is the only phase III RCT to demonstrate the extension of median PFS to over a year (13.7 months) in NSCLC patients with activating EGFR mutations.

5.9.3 Please provide a brief statement of the relevance of the evidence base to the decision problem. Include a discussion of the relevance of the outcomes assessed in clinical trials to the clinical benefits experienced by patients in practice.

Chemotherapy naïve NSCLC patients in the UK are currently being routinely tested for the presence of activating EGFR mutations. Patients that are identified as having activating EGFR mutations have only gefitinib as a treatment option which has been recommended by NICE since 2010 (NICE TA 192 2010). The evidence base upon which NICE recommended gefitinib as a first line treatment in NSCLC patients was based on RCTs conducted in East Asian patients with median PFS outcomes ranging between 8.4 and 10.8 months (Mok et al. 2009, Lee et al. 2009, Maemondo et al. 2010). To date there has not been any published data to demonstrate that similar outcomes

for gefitinib can be achieved in a Caucasian population which would be more representative of NSCLC patients in the UK.

Evidence from OPTIMAL (a phase III RCT conducted in Chinese patients) provides assurance of the efficacy of erlotinib in East Asian NSCLC patients with activating EGFR mutations and is the only phase III RCT to extend median PFS to over a year (13.7 months), longer than that reported for any of the gefitinib phase III RCTs.

EURTAC provides the only evidence for the superiority of an EGFR TKI (erlotinib in this case) to platinum doublet chemotherapy in the form of a phase III RCT in Caucasian patients and is currently the most robust evidence base to demonstrate the efficacy of an EGFR TKI (erlotinib) in Caucasian NSCLC patients with activating EGFR mutations. As such, EURTAC represents the most relevant evidence base when considering the use of an EGFR TKI in UK NSCLC patients with activating EGFR mutations.

5.9.4 Identify any factors that may influence the external validity of study results to patients in routine clinical practice; for example, how the technology was used in the trial, issues relating to the conduct of the trial compared with clinical practice, or the choice of eligible patients. State any criteria that would be used in clinical practice to select patients for whom treatment would be suitable based on the evidence submitted. What proportion of the evidence base is for the dose(s) given in the SPC?

Erlotinib is currently licenced as oral therapy to be taken once daily at a dose of 150mg per day for the first line maintenance treatment of patients with stable disease following first line chemotherapy and in patients with relapsed NSCLC. Both EURTAC and OPTIMAL utilised the licenced dose of erlotinib in accordance with what is stipulated in the erlotinib SPC and in accordance with procedures that are used in routine clinical practice in the UK.

EURTAC recruited only Caucasian patients and as such these patients are a good representation of the majority of the NSCLC population in the UK.

Both EURTAC and OPTIMAL were seeking to compare the efficacy of erlotinib to standard platinum doublet chemotherapy, both studies recruited patients that were predominantly performance status 0-1. Doublet chemotherapy is not generally recommended as first line treatment of patients with performance status of two and above (NICE CG 121 2011). In order for erlotinib to be a treatment option for chemotherapy naïve NSCLC patients in the UK it is mandatory that patients are tested for the presence of activating EGFR mutations. Over the last two years EGFR mutation testing has become routine practice in the UK with over 90% of UK clinicians having access to EGFR mutation testing (Roche Market Research). Therefore identification of an eligible population for treatment with first line erlotinib would not be an issue in routine UK clinical practice.

6 Cost-effectiveness

6.1 Published cost-effectiveness evaluations

Identification of studies

6.1.1 Describe the strategies used to retrieve relevant cost-effectiveness studies from the published literature and from unpublished data held by the manufacturer or sponsor. The methods used should be justified with reference to the decision problem. Sufficient detail should be provided to enable the methods to be reproduced, and the rationale for any inclusion and exclusion criteria used should be provided. The search strategy used should be provided as in section 9.10, appendix 10.

Embase (EMYY), Medline (MEYY), Medline in Process (MEIP) and NHS EED were searched for studies assessing the cost-effectiveness of erlotinib compared to gefitinib in the first line treatment of EGFR M+ mNSCLC. The search was designed to evaluate whether de novo modelling was necessary in order to answer the decision problem set. The complete search strategy is provided in section 9.10. The methodology used was based upon on the methods outlined in the CRD's 'Guidance for undertaking reviews in health care' (2008).

Keyword strategies were developed using key references retrieved through initial scoping searches. No date limit was placed on the search undertaken. Dialogue DataStar was used to search EMYY, MEYY and MEIP whilst NHS EED was searched using the University of York's 'Centre for Reviews and Dissemination' (CRD) website (http://www.crd.york.ac.uk/crdweb/SearchPage.asp - accessed on 13/09/2011). Each search result's title and abstract were assessed for relevance according to the pre-defined inclusion and exclusion criteria (see Table 38 below). If a record was deemed potentially relevant it was retrieved in full and re-assessed against the inclusion/exclusion criteria.

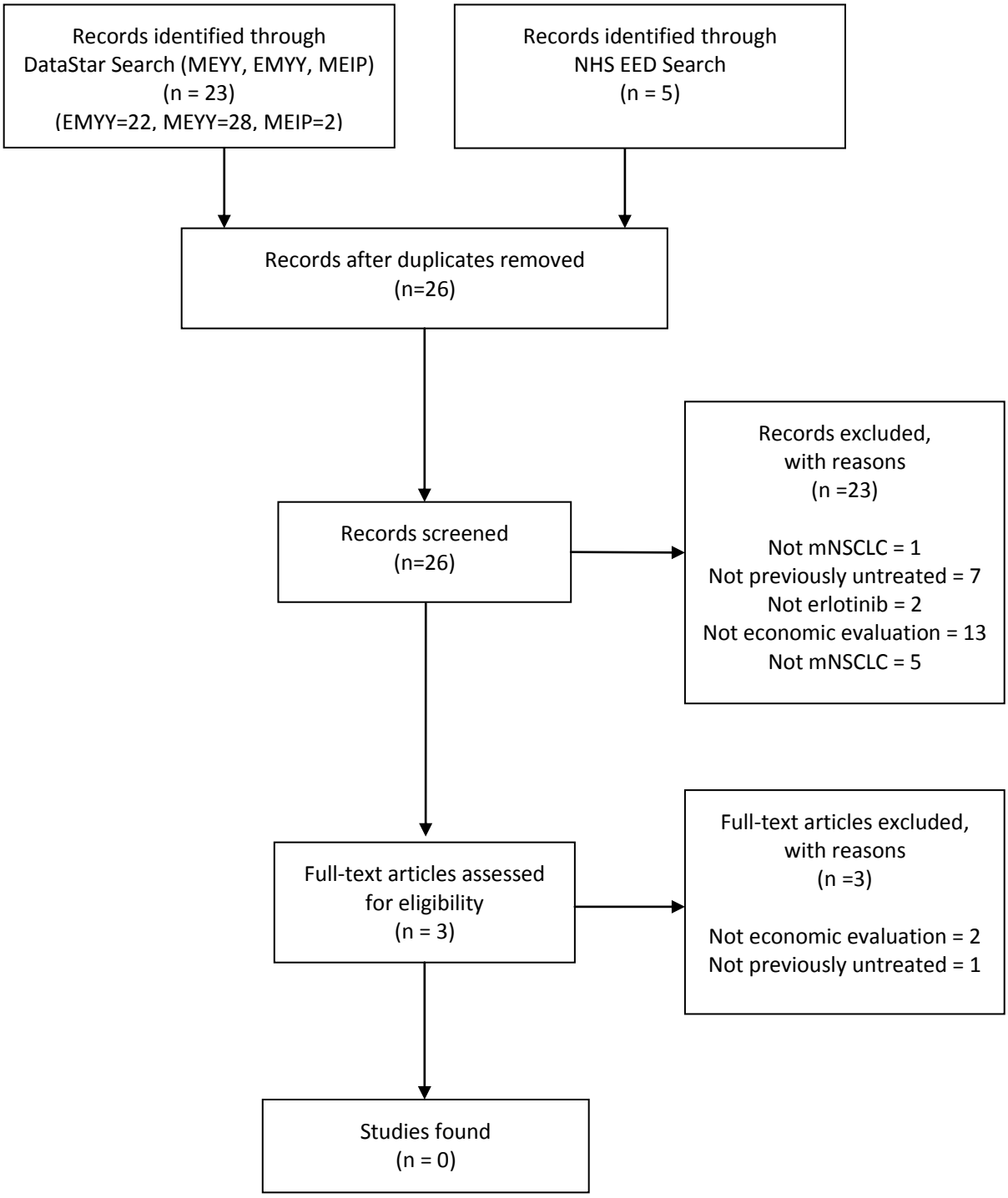
Table 38: Economic Evaluation Search Inclusion/Exclusion Criteria

Parameter	Inclusion Criteria	Exclusion Criteria
Population	Previously untreated mNSCLC patients with an activating mutation of the EGFR tyrosine kinase	Small cell lung cancer patients, Non-lung cancer patients (i.e. mesothelioma), previously treated patients, patients without a confirmed EGFR mutation
Intervention	Erlotinib monotherapy	-
Comparator	Gefitinib monotherapy	-
Outcome	Cost per QALY gained, Cost per LY gained,	-
Study Design	Economic Evaluations (cost effectiveness analyses, cost utility analyses, cost minimisation analyses)	RCTs, Observational Data, Budget Impact Assessments

In total 26 individual records were identified via the four databases. Of these 23 studies were excluded upon initial screening of title and abstract (see the PRISMA diagram below for the rationale for these exclusions) and four were deemed potentially relevant. These three results were then retrieved and assessed more comprehensively against the inclusion/exclusion criteria with all three found to be of no relevance to the decision problem.

The conduct of the search is presented in the PRISMA flow-chart below.

Figure 44: PRISMA Flow-chart of economic evaluation search



Description of identified studies

6.1.2 Provide a brief overview of each study, stating the aims, methods, results and relevance to decision-making in England and Wales. Each study's results should be interpreted in light of a critical appraisal of its methodology. When studies have been identified and not included, justification for this should be provided. If more than one study is identified, please present in a table as suggested below.

No relevant studies were identified. As erlotinib has only recently been EMA approved for use in the first line treatment of EGFR M+ mNSCLC the lack of economic evaluations of relevance to the decision problem is expected.

6.1.3 Please provide a complete quality assessment for each cost-effectiveness study identified. Use an appropriate and validated instrument, such as those of Drummond and Jefferson (1996) or Philips et al. (2004). For a suggested format based on Drummond and Jefferson (1996), please see section 9.11, appendix 11.

No relevant studies were identified.

6.2 De novo analysis

Patients

6.2.1 What patient group(s) is (are) included in the economic evaluation? Do they reflect the licensed indication/CE marking or the population from the trials in sections 1.4 and 5.3.3, respectively? If not, how and why are there differences? What are the implications of this for the relevance of the evidence base to the specification of the decision problem? For example, the population in the economic model is more restrictive than that described in the (draft) SPC/IFU and included in the trials.

The population considered in the economic evaluation is as per the scope of this appraisal (i.e. previously untreated English and Welsh mNSCLC patients

with tumours harbouring an activating mutation of the EGFR tyrosine kinase for whom erlotinib is a potential treatment option). This population is consistent with the marketing authorisation for erlotinib.

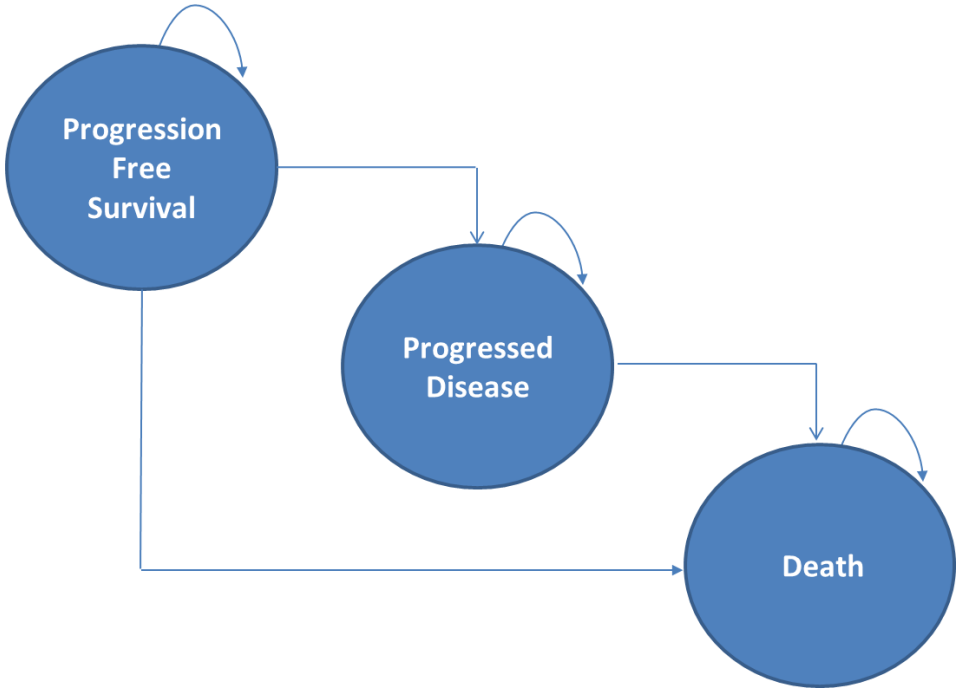
Model structure

6.2.2 Please provide a diagrammatical representation of the model you have chosen.

Three health states were utilised to model the disease progression of EGFR M+ mNSCLC patients given the two comparators of interest (i.e. erlotinib monotherapy or gefitinib monotherapy).

All patients enter the model in the progression free survival (PFS) health state and in each month can either progress to a 'worse' health state (i.e. from PFS to progressed disease (PD) or from PD to Death) or remain in the same health state. Figure 45 below demonstrates this model structure.

Figure 45: Model Structure



6.2.3 Please justify the chosen structure in line with the clinical pathway of care identified in section 2.4.

The model structure is fully aligned with two of the primary objectives of treatment in mNSCLC; namely:

- Prolonging life
- Delaying disease progression

This model structure and the health states utilised are typical of modelling in metastatic oncology and have been utilised in numerous NICE STAs and MTAs previously (NICE TA227, NICE TA212, Fleeman et al 2010, Hoyle et al 2011).

6.2.4 Please define what the health states in the model are meant to capture.

The PFS health state is designed to capture a patient's relatively high quality of life period prior to their disease progression. The PD state is designed to capture the relatively poor quality of life phase post disease progression and prior to death. These health states are those typically utilised in the modelling of metastatic oncology.

6.2.5 How does the model structure capture the main aspects of the condition for patients and clinicians as identified in section 2 (Context)? What was the underlying disease progression implemented in the model? Or what treatment was assumed to reflect underlying disease progression? Please cross-reference to section 2.1.

The model is a 3 state model typically utilised in the modelling of metastatic cancer (NICE TA227, NICE TA34, McNamara et al 2010). As noted previously this structure captures both the length and quality of a patient's life via the dichotomisation of their time alive into a relatively high quality of life 'pre-progression' phase and a lower quality of life post-progression phase.

The EURTAC study was utilised as the baseline in all modelling undertaken as it was assumed that this study would be more representative of the outcomes expected in UK clinical practice than the OPTIMAL study.

6.2.6 Please provide a table containing the following information and any additional features of the model not previously reported. A suggested format is presented below.

Table 39: Key features of analysis

Factor	Chosen values	Justification	Reference
Time horizon	10 years	Sufficient to capture all meaningful differences in technologies compared	NICE Guide to Methods
Cycle length	One month	Sufficient resolution to capture all meaningful differences in technologies compared	NICE Guide to Methods
Half-cycle correction	Yes – Where appropriate (i.e. not when assessing the cost of an oral therapy)	NICE reference case	NICE Guide to Methods
Were health effects measured in QALYs; if not, what was used?	Yes	NICE reference case	NICE Guide to Methods
Discount of 3.5% for utilities and costs	Yes	NICE reference case	NICE Guide to Methods
Perspective (NHS/PSS)	Yes	NICE reference case	NICE Guide to Methods

Technology

6.2.7 Are the intervention and comparator(s) implemented in the model as per their marketing authorisations/CE marking and doses as stated in sections 1.3 and 1.5? If not, how and why are there differences? What are the implications of this for the relevance of the evidence base to the specified decision problem?

Each intervention (erlotinib monotherapy or gefitinib monotherapy) is modelled within the restrictions set by their respective SPC's and as observed in the RCTs conducted for each agent.

In the case of erlotinib that was a maximum of one 150 mg tablet per day until disease progression (as per EURTAC and OPTIMAL – with EURTAC used in the base-case modelling) whilst in the case of gefitinib it was a maximum of one 250 mg per day until disease progression (as per IPASS, NEJGSG002, WJTOG3405 and First-SIGNAL).

6.2.8 Please note that the following question refers to clinical continuation rules and not patient access schemes. Has a treatment continuation rule been assumed? If the rule is not stated in the (draft) SPC/IFU, this should be presented as a separate scenario by considering it as an additional treatment strategy alongside the base-case interventions and comparators.

The model assumes patients receive a pack of erlotinib or gefitinib tablets every 30 days until disease progression or early cessation for any reason (as observed in EURTAC). Disease progression is typically assessed by CT scan every 3 months. This cost is considered in the economic evaluation undertaken.

6.3 Clinical parameters and variables

6.3.1 Please demonstrate how the clinical data were implemented into the model.

Data Used

The most recent data-cut of the EURTAC RCT (26/01/2011) was used in the model. This study was conducted in an entirely European Caucasian population (Spain, Italy and France) at the standard required by the EMA in order to gain a marketing authorisation. It can therefore be regarded as being representative of the outcomes expected for Caucasian EGFR M+ patients given treatment with erlotinib in English/Welsh clinical practice.

Model Structure/Method of implementation of EURTAC data

The model developed was a semi-markov model.

An extrapolated 'Area under the curve' approach was used in order to determine the proportion of patients in PFS at each month of the model. All other transitions in the model were estimated using a markov model (i.e via transition probabilities).

Only the probability of remaining in PFS each month or experiencing disease progression in each month was treatment specific (i.e. erlotinib was assumed to have no more treatment effect post-progression). Common transition probabilities were used for death in PFS, death in PD and not dying in PD.

The source of each transition is summarised in Table 40 and discussed in more detail in the sections below.

Table 40: Model Transitions

Monthly Transition	Erlotinib	Gefitinib
PFS to PFS (i.e. Don't progress or die)	Derived directly from EURTAC RCT erlotinib PFS curve with exponential 'tail' fitted in order to allow estimation of the mean time in PFS	As per erlotinib with indirect PFS HR applied (as discussed in below)
PFS to Death (i.e. Die before progression)	Derived directly from EURTAC RCT erlotinib arm and applied within the model on a monthly basis	Assumed to be the same as for erlotinib.

PFS to PD (i.e. Progress)	Derived as the difference between the two transitions above (as a patient who was previously in PFS who is no longer in PFS and has not died must have progressed)	Derived as the difference between the two transitions above (as a patient who was previously in PFS who is no longer in PFS and has not died must have progressed)
PD to Death (i.e. Die after progression)	Monthly probability of death in PD observed for erlotinib arm in EURTAC applied to the proportion of patients in PD in each month.	Assumed to be the same as for erlotinib.
PD to PD (i.e. Don't die after progression)	1 minus the probability of death in PD. If a patient was in PD and hasn't died they must still be in PD (as patients cannot 'un-progress' after moving from PFS to PD). =1 - TP[PD to Death]	1 minus the probability of death in PD. If a patient was in PD and hasn't died they must still be in PD (as patients cannot 'un-progress' after moving from PFS to PD). =1 - TP[PD to Death]

Indirect Comparison

As noted in section 5.7.3. above, as gefitinib has never been studied in a Caucasian EGFR M+ population and the divergence between the EURTAC and OPTIMAL RCTs appears to indicate that ethnicity may be a treatment effect modifier for EGFR TKIs (with East Asian patients experiencing a larger treatment effect than Caucasians) an indirect comparison of erlotinib and gefitinib in a Caucasian population is difficult.

In order to remain as conservative as possible when assessing the cost-effectiveness of erlotinib in this setting we propose to utilise the most conservative of the scenarios discussed in section 5.7.3. in the base-case economic modelling (i.e. a comparison of EURTAC and IPASS/First-SIGNAL/WJTOG3405/NEJSG002 - (erlotinib vs gefitinib PFS HR = 0.82 {0.54, 1.26}).

Whilst this comparison will not produce an unbiased estimate of the relative efficacy of erlotinib and gefitinib it should be noted that all the evidence available suggests that this analysis will be biased against erlotinib (and that therefore the ICER of erlotinib in this setting is likely to have been overestimated).

If it is true that Asian patients experience larger treatment effects when treated with an EGFR TKI than Europeans (be that due to ethnicity or due to differing attitudes towards compliance between differing parts of the world) this analysis will be biased against erlotinib (as this approach compares erlotinib's European data to gefitinib's Asian data).

The use of OPTIMAL, and a pooling of EURTAC/OPTIMAL, rather than EURTAC alone will be tested in sensitivity analysis.

6.3.2 Demonstrate how the transition probabilities were calculated from the clinical data. If appropriate, provide the transition matrix, details of the transformation of clinical outcomes or other details here.

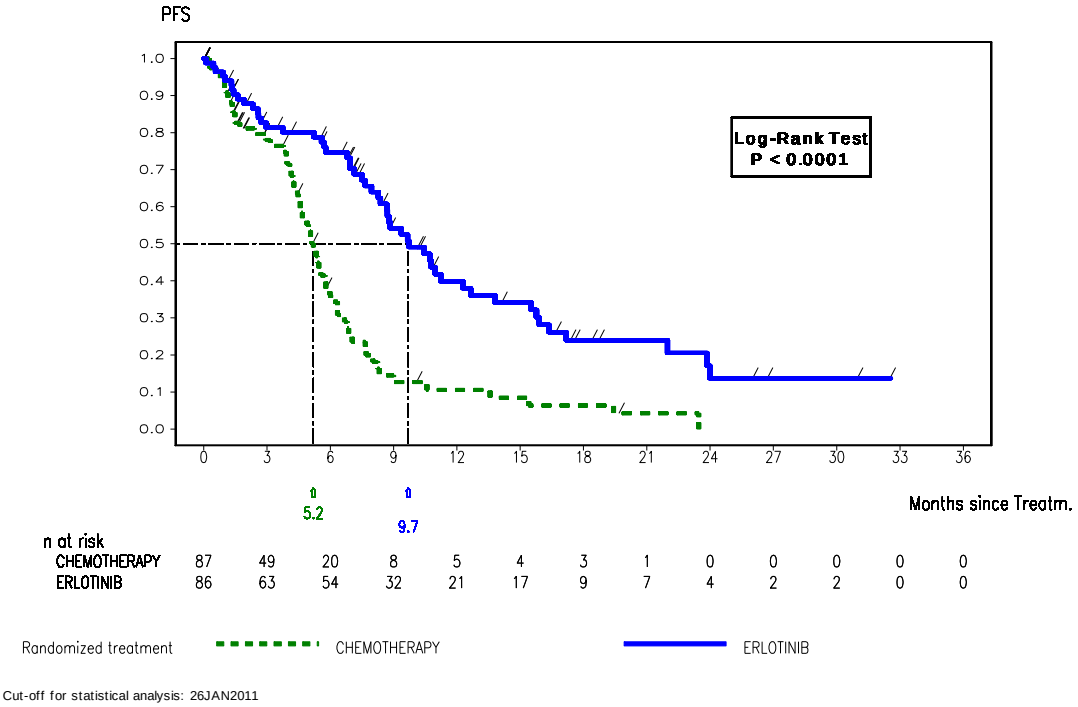
Each of the 5 transitions described in section 6.3.1 above are discussed individually below.

6.3.2.1 Probability of Remaining in PFS

Erlotinib

The proportion of patients in in the erlotinib arm of the model in PFS in each month was derived using an 'area under the curve' approach. As the erlotinib KM data was not complete (see Figure 46 below) it was necessary to apply extrapolation to the observed data in order to derive the mean time a patient spent in the PFS health state.

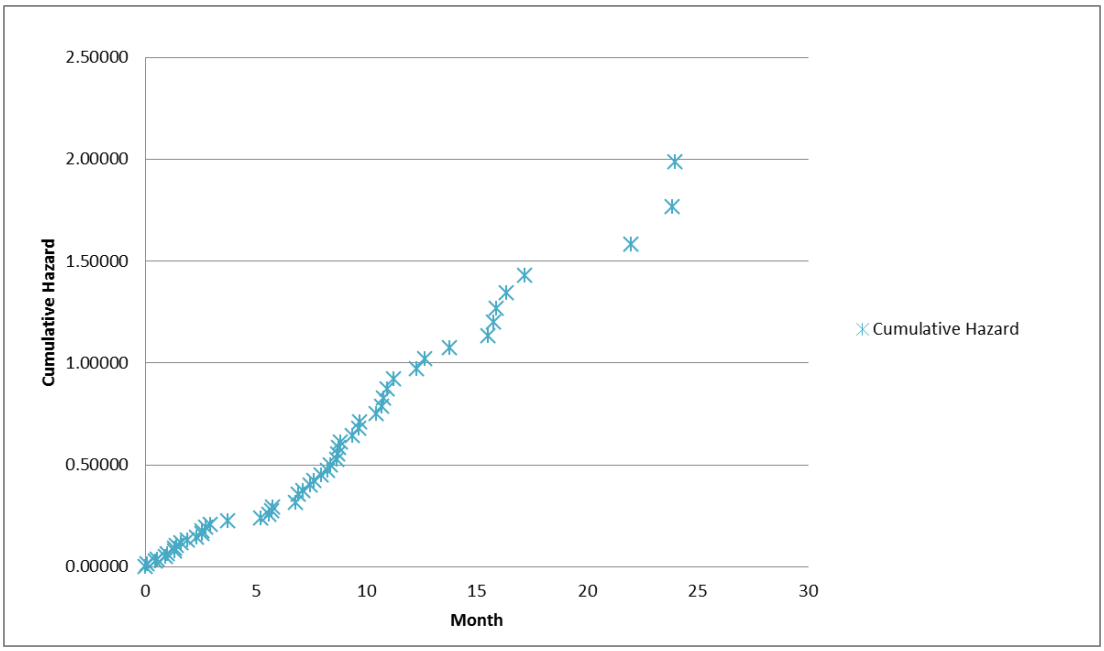
Figure 46: EURTAC PFS KMs



Cut-off for statistical analysis: 26JAN2011

In order to determine the most appropriate form of extrapolation of the observed erlotinib PFS Kaplan-Meier data a PFS cumulative hazard plot was generated (via a negative log transformation of the KM data) and assessed for consistency and linearity.

Figure 47: EURTAC PFS Cumulative Hazard Plot



This plot indicates that after a period of initial volatility (up to around 5 months) the hazard (the slope of the cumulative hazard plot) of experiencing a PFS event appears to stabilize and thereafter remain fairly constant.

It was therefore hypothesized that any extrapolation of the erlotinib PFS curve should be based upon an exponential function (due to the apparently linear nature of the curve) derived based upon the data from month 5 onwards (due to stabilization of the hazard from this point onward).

Linear regression was used in order to derive the hazard from month 5 onwards.

Figure 48: Post-5 month EURTAC PFS Cumulative Hazard Plot with exponential fit

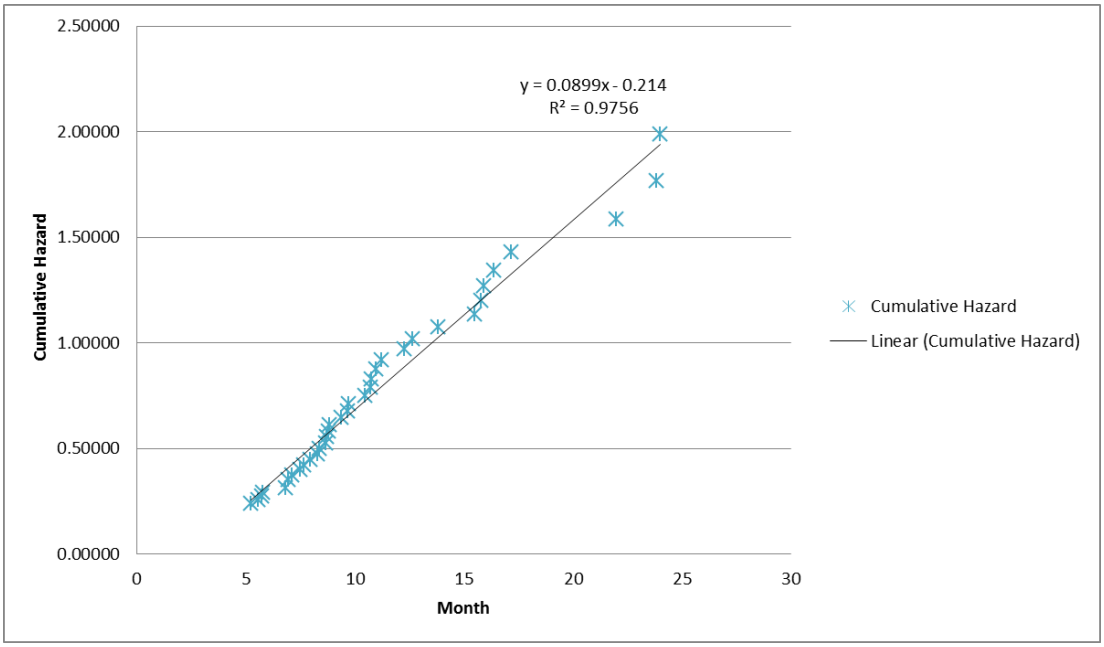


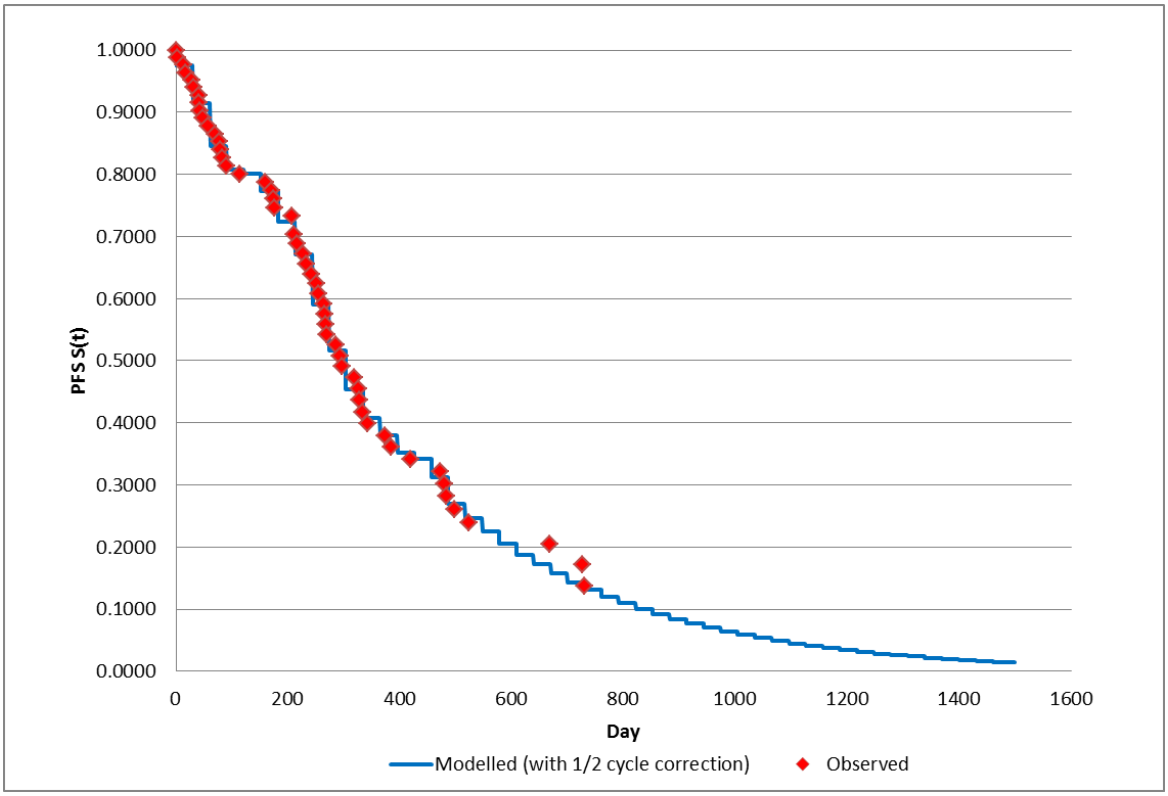
Figure 5 (above) demonstrates the function fitted using this method and the resultant monthly hazard (the first differential of the function (0.0899)). The R^2 value estimated for this function was extremely high (0.9756) indicating a good fit to the observed data.

This hazard was then converted into a monthly probability (Briggs et al 2006) in order to allow application within the model.

Examination of the cumulative hazard plot indicated that Month 16 appeared to be one of the last months in which the hazard plot and KM curve could be relied upon (with the modeled hazard/KM having reasonably good concordance with the observed hazard up to this point - and the observed hazard/KM becoming more volatile from this point onwards due to decreasing patient numbers (as shown by the sudden flattening at month 16 in Figure 46).

Therefore the use of the Month 16 as a transition point between the observed KM and the extrapolated tail was tested and assessed for face-validity.

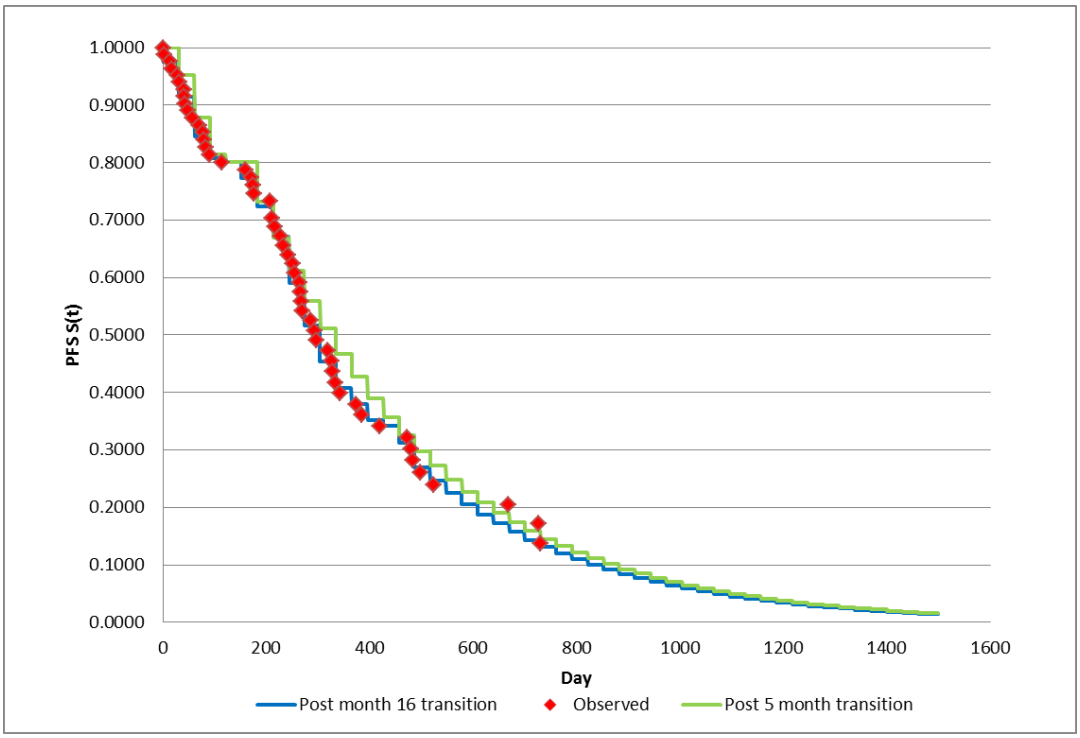
Figure 49: Modeled PFS - Post month 16 transition



Note: The 'steps' in the above figure are a product of the use of a monthly cycle length.

In order to ensure the transition point used was not unduly biased towards/against erlotinib the use of a post-5 month transition was tested (another potentially legitimate transition point given the stabilization of the hazard from this point in time onwards). See Figure 50 below for a demonstration of the face validity of this extrapolation compared to the observed clinical data and the post month 16 extrapolation.

Figure 50: Modeled PFS - Post month 5 transition



The use of a transition point of month 5 rather than month 16 changed the mean time in PFS by 8 days indicating that the precise transition point used was unlikely to have a substantial impact upon the model's results (at least when considering solely those points prior to the KM curve becoming erratic as potential transition points). This is perhaps unsurprising given the strong concordance between the observed KM and modeled curve between these two points of time.

In the base-case it was determined that as much of the observed KM data as could be relied upon should be used (i.e. up to month 16) with the remainder of the curve extrapolated using the exponential function described above. This is the more conservative of the two approaches presented in Figure 50 above. The impact of utilizing earlier/later transitions was tested in sensitivity analysis.

This approach to extrapolation is consistent with that utilized by LRiG in many recent NICE oncology technology appraisals (TA226, TA227).

Gefitinib

The proportion of patients in the gefitinib arm of the model in PFS each month was estimated using a transformed version of that used for erlotinib (i.e. an area under the curve approach with the indirect PFS HR of EURTAC vs Ku et al applied to the 'curve' utilized for erlotinib).

This was done under the assumption of proportional hazards between erlotinib and gefitinib. The potential for integrating gefitinib into the model via the use of the EURTAC doublet chemotherapy arm as a baseline was considered, but dismissed as it was felt that the hazard trend associated with gefitinib was more likely to be proportional to erlotinib than doublet chemotherapy.

Mechanically this was applied within the model using the following methods:

Adjusting the KM curve:

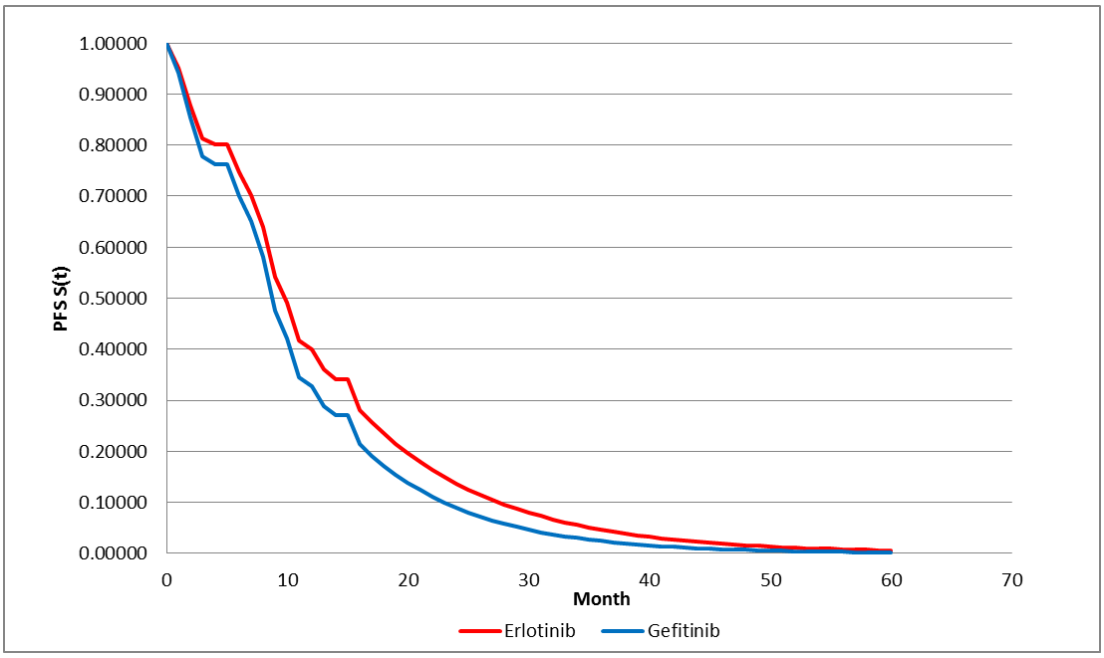
gefitinib S(t)=EXP(Indirect PFS HR gefitinib vs erlotinib*LN(erlotinib S(t))

Adjusting the hazard applied in the 'tail':

gefitinib hazard = Erlotinib hazard * Indirect PFS HR gefitinib vs erlotinib

The base-case gefitinib PFS curve derived via this method is presented next to that for erlotinib in Figure 51 below. The modeled median PFS advantage offered by erlotinib over gefitinib was estimated to be one month.

Figure 51: Modeled PFS curves



6.3.2.2 Die in PFS

The monthly probability of death in PFS for an EGFR M+ receiving erlotinib was estimated using the EURTAC RCT data.

In order to do this the number of PFS deaths observed in the erlotinib arm of EURTAC was first divided by the number of PFS months experienced by erlotinib randomized patients. This resulted in the monthly rate of death in PFS. This value was then converted from a rate to a probability so that it could be applied within each cycle of the model (Briggs et al 2006).

Table 41: Monthly probability of dying in PFS

Monthly Probability of Dying in PFS	
No. of PFS Deaths	11
PFS Person Months	768.788501
Monthly Rate of Death*	0.014308226
Monthly Probability of Dying in PFS	0.01420635

As there is no reason to believe the rate of death in PFS for gefitinib is any different to that for erlotinib it was assumed that the monthly probability of

death in PFS derived for erlotinib based upon EURTAC would similarly apply for gefitinib.

6.3.2.3 Transition from PFS to PD

This transition was estimated as the residual of the above two transitions.

6.3.2.4 Transition from PD to Death

In order to model patients' transitions from the 'progression' state to death an exponential model was fitted to the post-progression survival data of patients randomized to erlotinib in EURTAC. A monthly hazard of 0.078739474 was estimated which resulted in a monthly probability of death of 0.075719 (i.e. around 7.57% of patients in PD each month will die in that month).

As there is no reason to believe, or evidence to support, the notion that the choice of erlotinib or gefitinib as a first line therapy will have any influence upon a patient's rate of death post-progression it was assumed that this rate would similarly apply for gefitinib.

The use of time-variant probabilities was considered but dismissed as this would add substantial complexity to the model (as it would require the use of tunnel states) with no incremental advantage to either modeled arm (as the post-progression rates used in the model apply equally to patients who received erlotinib or gefitinib first line).

6.3.2.5 Remain in PD

This transition was estimated as the residual of the above transition.

6.3.3 Is there evidence that (transition) probabilities should vary over time for the condition or disease? If so, has this been included in the evaluation? If there is evidence that this is the case, but it has not been included, provide an explanation of why it has been excluded.

The PFS cumulative hazard plot indicates that the monthly hazard of experiencing a PFS event is relatively volatile before month 5 and linear from month 5 onwards. This was incorporated into the model as described in section 6.3.2.

6.3.4 Were intermediate outcome measures linked to final outcomes (for example, was a change in a surrogate outcome linked to a final clinical outcome)? If so, how was this relationship estimated, what sources of evidence were used, and what other evidence is there to support it?

No surrogate markers were used.

6.3.5 If clinical experts assessed the applicability of values available or estimated any values, please provide the following details

All clinical data incorporated in the model was based upon the clinical trial evidence base available. No clinical expert elicitation of efficacy parameters was required.

Summary of selected values

6.3.6 Please provide a list of all variables included in the cost-effectiveness analysis, detailing the values used, range (distribution) and source. Provide cross-references to other parts of the submission. Please present in a table, as suggested below.

Table 42: Summary of variables applied in the economic model

Variable	Value	CI (distribution)	Reference to section in submission
Transition Probabilities			
Monthly probability of disease progression after month 16 (erlotinib) – note: KM used before this point in time.	0.085977	PSA of relative efficacy undertaken using indirect PFS HR confidence intervals rather than shifting of erlotinib baseline	Section 6.3.2.
Monthly probability of disease progression after month 16 (gefitinib) - note: indirect PFS HR adjusted KM used before this point in time.	0.104567	0.0682,0.159 (log normal)	Section 6.3.2.
Monthly probability of death in PFS (both erlotinib and gefitinib)	0.014206	-	Section 6.3.2.
Monthly probability of death in PD (both erlotinib and gefitinib)	0.075719	-	Section 6.3.2.
Indirect PFS HR of erlotinib vs gefitinib	0.82	0.54, 1.26 (log normal)	Section 5.7.3.
Utility Values			
PFS (Stable Disease)	0.6532	0.6096, 0.6968 (normal)	Section 6.4.9.
		0.0065, 0.0321	Section

PFS (Response dummy variable)	0.0193	(normal – PSA applied as a transformation of the above to ensure the mean produced by PSA was not distorted by the normal distribution's bottom limit)	6.4.9.
Disutility of Rash	-0.0325	-0.0554, -0.0095 (normal: applied via transformation)	Section 6.4.9.
Disutility of Diarrhoea	-0.0468	-0.0772, -0.0164 (normal: applied via transformation)	Section 6.4.9.
PD (progression dummy variable disutility relative to PFS SD baseline)	-0.1798	-0.2223, -0.1373 (normal: applied via transformation)	Section 6.4.9.
Costs			
Pharmacy costs per pack of erlotinib/gefitinib dispensed	£13	£6.63, £19.37 Gamma distribution applied under assumption standard error (SE) was a quarter of base-case value	Section 6.5.5.2.
Monthly PFS BSC Cost (including monitoring)	£181.46	£92.54, £270.38 Gamma distribution applied under assumption SE was a quarter of base-case value	Section 6.5.6.

Monthly PD BSC Cost	£160.06	£81.63, £238.49 Gamma distribution applied under assumption SE was a quarter of base-case value	Section 6.5.6.
Terminal Care Cost	£2,588.25	£1,320.01, £3,856.49 Gamma distribution applied under assumption SE was a quarter of base-case value	Section 6.5.6.
Gefitinib PAS fixed cost payment	£12,200	N/A	Section 6.5.5.1.2.
Gefitinib PAS administration cost	£70 set up cost per patient, £35 per month on-going cost	Gamma distribution applied under assumption standard error (SE) was a quarter of base-case value for each component of PAS administration	Section 6.5.5.3
General Parameters			
Age	63.4	-	EURTAC
Gender Mix (Female/Male)	73.2% / 26.8%	-	EURTAC
CI, confidence interval			

6.3.7 Are costs and clinical outcomes extrapolated beyond the trial follow-up period(s)? If so, what are the assumptions that underpin this extrapolation and how are they justified? In particular, what assumption was used about the longer term difference in effectiveness between the intervention and its comparator? For the extrapolation of clinical outcomes, please present graphs of any curve fittings to Kaplan-Meier plots.

As mNSCLC is a relatively poor prognosis disease only minor extrapolation of the observed clinical data was required. This is detailed in section 6.3.2.

6.3.8 Provide a list of all assumptions in the de novo economic model and a justification for each assumption.

Table 43: List of assumptions in economic model

Assumption	Justification
The clinical outcomes observed in the EURTAC study are representative of what would be observed if erlotinib was given first line in England/Welsh clinical practice	EURTAC was conducted entirely in Caucasian patients in Europe (Spain, France and Italy) and at the standards expected for an EMA regulatory submission. It therefore appears reasonable to assume that this data is representative of the outcomes in Caucasian patients expected in England/Wales.
If a patient has yet to have receive their last dose of erlotinib at each 'dispensing date' (i.e. every 30 days) they will be administered a new pack of erlotinib	This method considers the cost of all erlotinib dispensed by the NHS rather than solely those tablets taken by patients (i.e. it includes wastage). This method is as per that used in Roche's supplementary evidence submission in NICE TA227.
For parameters without a standard error (SE) it was assumed that the SE would be one quarter of the base-case parameter value	Allows plausible variation in parameters subject to uncertainty when conducting PSA. Whilst clearly inferior to actual SEs this approach offers a pragmatic solution which

	enables PSA to be conducted. Approach is a slight modification of that presented in Briggs et al 2006.
The indirect PFS HR of erlotinib compared to gefitinib in a European population is (conservatively) 0.82 – value based upon an indirect comparison of EURTAC and the four Asian gefitinib RCTs (biased against erlotinib for the reasons detailed in section 5.7.3. previously)	As noted in section 5.7.3. previously the use of an indirect comparison founded upon EURTAC and the four Asian gefitinib studies is highly likely to be biased against erlotinib and so this assumption can be regarded as conservative. The true HR is likely lower than this value.
If the PFS HR for erlotinib vs gefitinib is applied to the erlotinib 'time to last dose' KM curve from EURTAC the resultant curve is representative of that which would be observed for gefitinib had it featured in EURTAC	This information is required in order to estimate the proportion of gefitinib patients for whom the PAS fixed cost payment is required and in order to estimate the pharmacy administration costs of gefitinib. Whilst this assumption is clearly inferior to availability of real world data on the use of gefitinib in UK clinical practice or to RCT data on the use of gefitinib in Caucasian patients this information is either not publicly available (in the case of real-world data on the proportion of patients 'activating' the gefitinib PAS payment) or non-existent (in the case of the RCT evidence). This approach is consistent with that used for erlotinib and therefore appears reasonable although imperfect.

6.4 Measurement and valuation of health effects

This section should be read in conjunction with NICE's 'Guide to the methods of technology appraisal', section 5.4.

The HRQL impact of adverse events should still be explored regardless of whether they are included in cost-effectiveness analysis.

All parameters used to estimate cost effectiveness should be presented clearly in tabular form and include details of data sources. For continuous

variables, mean values should be presented and used in the analyses. For all variables, measures of precision should be detailed.

Patient experience

6.4.1 Please outline the aspects of the condition that most affect patients' quality of life.

Patients diagnosed with NSCLC have a considerable impact on their quality of life either directly as a result of their disease or indirectly due to the treatments they receive (including tolerating the side effects of treatment and the accommodation of time and effort for the administration of the treatment). Taken together this places a significant burden on the patient's daily living and treatments addressing both of these aspects which impact a patient's quality of life would be welcomed.

At diagnosis, due to the nature of NSCLC, it is likely that a patient may be suffering from any number of problems including breathing problems, persistent cough, shortness of breath, wheezing, chest pain and haemoptysis (coughing up blood). Other associated symptoms include shoulder pain, hoarseness and dysphagia. The patient may also be pre-disposed to infection (abscesses or pneumonia) if there is collapse of a portion of the lung. Depending where the lung has spread a patient may experience excruciating bone pain, headaches, blurred vision, seizures, strokes and general weakness. In addition to these symptoms a patient may experience general symptoms related to cancer including weight loss, weakness, fatigue and psychological disorders. As a result of these symptoms there is a huge impact on the ability of patients to conduct aspects of their daily activities in turn affecting greatly their quality of life.

It is also clear that with the existing co-morbidities associated with NSCLC, the treatment options available will be greatly restricted as a patient may not be able to tolerate cytotoxic chemotherapy (mainly due to the extensive and often life threatening hematological toxicities that these treatments are associated with). Patients receiving cytotoxic chemotherapies often require

frequent monitoring of blood counts and interventions such as blood transfusion or the administration of concomitant medications such as steroids, antibiotics or anti-emetics etc. Furthermore, as cytotoxic chemotherapies require administration in a hospital environment at usually 3-weekly intervals, it places an additional burden on the patient in terms of time and effort to receive the treatment. The latter has considerable impact on carers also.

It is therefore important that any treatment that this administered for NSCLC addresses both the clinical condition directly (i.e. that produces good response rates and prolonged progression free survival) but is also better tolerated and easier to administer. As demonstrated in OPITMAL and EURTAC, erlotinib produced significant tumour shrinkage in patients and prolonged the patients' progression free survival compared to platinum doublet chemotherapy. Erlotinib also was better tolerated than platinum doublet chemotherapy in both studies and offers itself as an oral therapy that can be taken at home on a daily basis. OPTIMAL further demonstrated that more patients receiving erlotinib had clinically relevant improvements in quality of life compared to those receiving platinum doublet chemotherapy.

6.4.2 Please describe how a patient's HRQL is likely to change over the course of the condition.

As Stage IIIb and IV NSCLC is an aggressive disease, it has a huge impact on a patient and the overall prognosis is poor with 5 year survival rates typically around 10%. Due to its aggressive nature the onset of the symptoms described above is usually quite rapid and there is a rapid decline in the performance status of the patient. This in turn affects the patient's daily living quite dramatically leading to a bleak outlook without appropriate intervention. Providing an effective, well tolerated and easily administered treatment such as erlotinib has demonstrated significant clinically relevant improvements in quality of life of patients in the OPTIMAL study.

HRQL data derived from clinical trials

6.4.3 If HRQL data were collected in the clinical trials identified in section 5 (Clinical evidence), please comment on whether the HRQL data are consistent with the reference case.

No health utility instruments (i.e. EQ-5D, HUI3 or SF-6D) were included in either the OPTIMAL or EURTAC RCTs.

Mapping

6.4.4 If mapping was used to transform any of the utilities or quality-of-life data in clinical trials, please provide the following information.

Mapping was not conducted.

HRQL studies

6.4.5 Please provide a systematic search of HRQL data. Consider published and unpublished studies, including any original research commissioned for this technology. Provide the rationale for terms used in the search strategy and any inclusion and exclusion criteria used. The search strategy used should be provided in section 9.12, appendix 12.

Embase (EMYY), Medline (MEYY), Medline in Process (MEIP), NHS EED and ECON LIT were searched for studies assessing utility values for different health states in mNSCLC. The search was designed to evaluate all potentially relevant utility scores that have been used in lung cancer health technology evaluations. The complete search strategy is provided in section 9.10. The methodology used was based upon on the methods outlined in the CRD's 'Guidance for undertaking reviews in health care' (2008).

Keyword strategies were developed using key references retrieved through initial scoping searches. No date limit was placed on the search undertaken. Dialogue DataStar was used to search EMYY, MEYY and MEIP whilst NHS EED was searched using The Cochrane Library

http://www.thecochranelibrary.com/view/0/index.html and ECON LIT was searched using: http://www.aeaweb.org/econlit/index.php

Each search result's title and abstract were assessed for relevance according to the pre-defined inclusion and exclusion criteria (see Table 44 below).

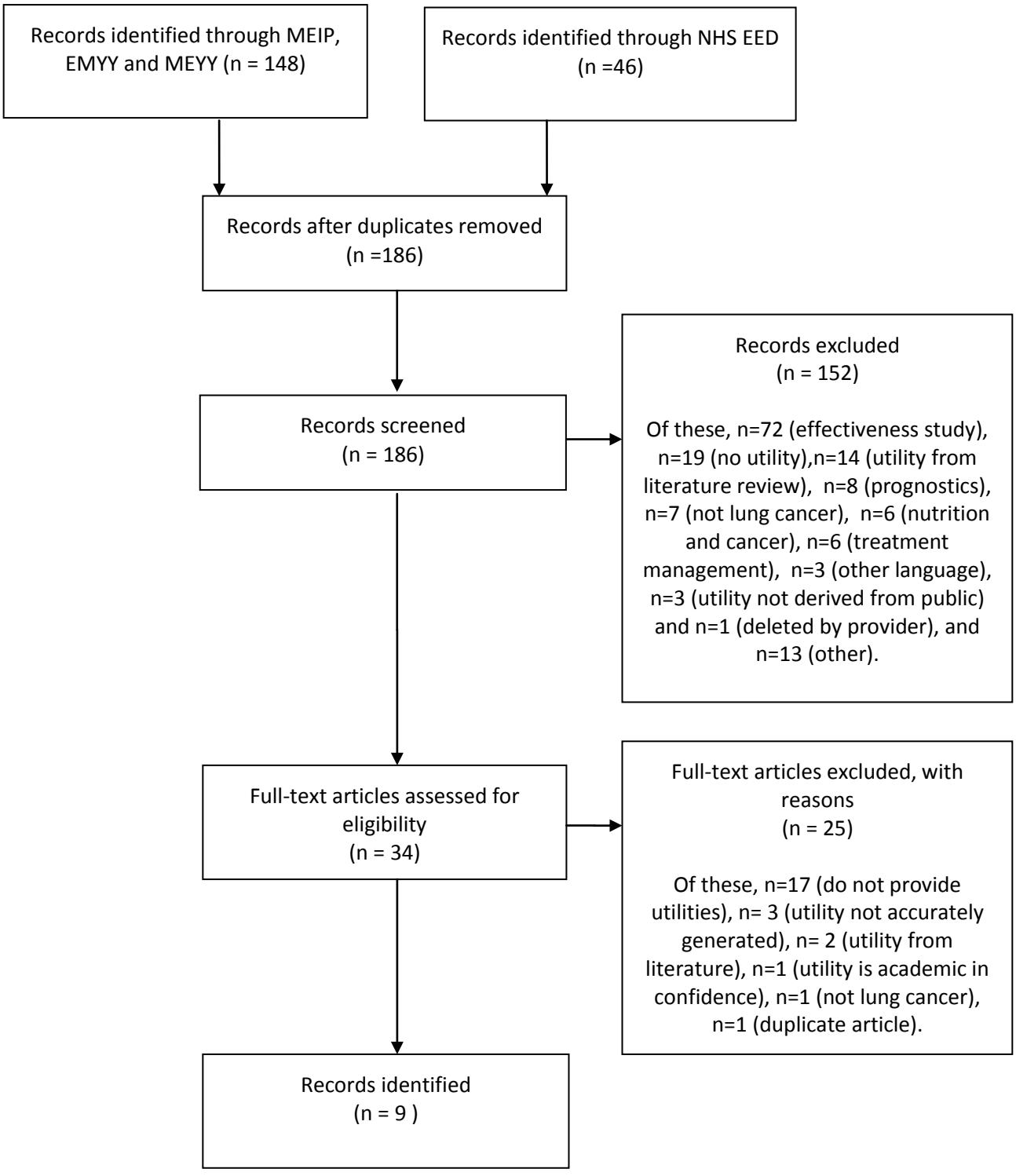
If a record was deemed potentially relevant it was retrieved in full and re-assessed against the inclusion/exclusion criteria.

Table 44: QoL Search Inclusion/Exclusion Criteria

Inclusion Criteria	Exclusion Criteria
Metastatic or advanced lung cancer Health related quality of life QALY or quality adjusted life year SF-36 OR SF-12 OR EQ-5D OR EQ-5D-5L OR EUROQOL Utilities Time Trade Off or Standard Gamble	Review of studies already included Not QoL studies No useful HRQoL/Utility values Not in metastatic/advanced setting

In total 186 individual records were identified via the five databases (no results were found from ECON LIT). Of these, 152 studies were excluded upon initial screening of title and abstract (see the PRISMA diagram below for the rationale for these exclusions) and 34 were deemed potentially relevant. These 34 results were then retrieved and assessed more comprehensively against the inclusion/exclusion criteria, 9 were found to be relevant.

Figure 52: QoL Search PRISMA Flow diagram



These 9 records were Nafees et al.(2006), Lloyd et al. (2008), Dooms et al. (2006), Lee L. J-H., et al. (2011), Lewis et al. (2010) and 3 ERG reports (Pemetrexed for the first-line treatment of locally advanced or metastatic non-

small cell lung cancer (TA190), Pemetrexed for the maintenance treatment of locally advanced or metastatic non-small cell lung cancer (TA181) and Gefitinib for the first-line treatment of locally advanced non-small cell lung cancer (TA192). These 9 records were associated with four utility studies – Nafees et al 2006, Lloyd et al 2006, Dooms et al 2006 and Lee et al 2006.

Following review of the above search it was noted that two relevant records had been omitted (NICE TA227 – the STA on the use of erlotinib as a maintenance treatment for mNSCLC and NICE TA162 the STA on the use of erlotinib in the second line treatment of mNSCLC). In order to ensure all potentially relevant information was considered these two appraisals were evaluated for utility values relevant to the current decision problem. These two appraisals identified no new utility values (with the Lloyd ones used in TA162 (prior to use of a cost-minimisation approach vs docetaxel) and the Nafees values used in TA227 (following first ERG report)).

4 of the NICE STAs identified (NICE TA181, TA190, TA192, TA227) and the Lewis et al. (2010) publication utilised utility values from Nafees et al. (2006). The Lloyd et al values were used in the manufacturer's submission in TA162 (although were not relied upon when determining the cost-effectiveness of erlotinib in the second line treatment of mNSCLC) whilst the Dooms et al and Lee et al values were identified solely in their source publications.

6.4.6 Provide details of the studies in which HRQL is measured.

Dooms et al. (2006) derived utility values directly, but in their derivation the author utilise the Visual Analogue Scale (VAS) which is not in keeping with NICE Guide to Methods.

Lee L. J-H. et al. (2011) derived utilities directly using the Standard Gamble method. However, they only report one overall utility value for NSCLC patients, whereas to capture the subtleties and sensitivities of the economic modeling in metastatic lung cancer, utility values for health states within the model are required.

Nafees et al. (2006) derived utilities directly using Standard Gamble and VAS on 100 members of the UK general public. This study was designed to provide utility values for different mNSCLC health states and adverse events associated with mNSCLC treatment. This study was used in NICE TA181, NICE TA190, NICE TA192 and NICE TA227.

Lloyd et al. (2006) derived utility values directly, but the legitimacy of these values has been questioned previously (see NICE TA162).

In light of the fact that the Nafees values were estimated in a UK population using the standard gamble approach, have been used in four previous NICE technology appraisals and allow the incorporation of the disutility of adverse events into an economic model it was determined that these values would be the most appropriate to use in this economic evaluation.

6.4.7 Please highlight any key differences between the values derived from the literature search and those reported in or mapped from the clinical trials.

Not applicable. Mapping was not conducted.

Adverse events

6.4.8 Please describe how adverse events have an impact on HRQL.

The incidence of grade 3/4 adverse events associated with erlotinib and gefitinib is much lower than that associated with the doublet chemotherapies traditionally utilised in first line mNSCLC. AEs commonly associated with each agent include diarrhoea and rash. These AEs are associated with a disutility (as investigated by Nafees et al 2008) and this disutility is considered within the economic evaluation conducted.

Quality-of-life data used in cost-effectiveness analysis

6.4.9 Please summarise the values you have chosen for your cost-effectiveness analysis in the following table, referencing values obtained in sections 6.4.3 to 6.4.8. Justify the choice of utility values, giving consideration to the reference case.

Table 45: Summary of quality-of-life values for cost-effectiveness analysis

State	Utility value	CI	Justification
PFS (Stable Disease)	0.6532	0.6096, 0.6968	Nafees et al values used in NICE TA227, TA192, TA190 and TA181.
PFS (Response dummy variable)	0.0193	0.0065, 0.0321	
Disutility of Rash	-0.0325	-0.0554, -0.0095	
Disutility of Diarrhoea	-0.0468	-0.0772, -0.0164	
PD (dummy variable disutility relative to PFS SD baseline)	-0.1798	-0.2223, -0.1373	
Resultant erlotinib PFS	0.661	Not derived explicitly	See below. Erlotinib PFS utility value 0.87% higher than gefitinib PFS utility value due to AE profile and response rate.
Resultant gefitinib PFS	0.656	Not derived explicitly	

The PFS utility value for erlotinib was derived by combining the Nafees et al values with the response rate observed in EURTAC (58.10%) and the grade 3/4 incidence of diarrhoea (4%) and rash (5.3%) (the AEs most commonly associated with erlotinib) as demonstrated below:

Erlotinib PFS Utility = 0.661

= ((0.6725)*0.581)+(0.6532*(1-0.581))+(-0.03248*0.053)+(-0.0468*0.04)

An indirect comparison of the response rate in the EURTAC study and the pooled gefitinib relative response rate derived by Ku et al 2011 was conducted (see below) in order to estimate what the response rate of gefitinib would have been had it featured in EURTAC.

EURTAC Erlotinib Response Rate = 58.10%

EURTAC Chemotherapy Response Rate = 14.90%

Ku et al 2011 relative response rate (gefitinib vs chemotherapy) = 1.895

Indirect gefitinib EURTAC response rate = 14.90% * 1.895 = 28.23%

This indirect response rate analysis was conducted in order to inform the PFS utility of gefitinib as using solely the absolute, rather than relative, response rates from each study would violate randomisation and equate to a naïve cross-trial comparison.

The EURTAC RCT response rates were used as a baseline with which to estimate those for gefitinib in English/Welsh practice as it was assumed that EURTAC would be more representative of England/Wales than the other available studies (all of which were conducted in East Asia). The EURTAC RCT chemotherapy arm response rate is relatively low compared to that observed in other studies and so it is possible that the decision problem may be better modelled by increasing this response rate in order to more accurately model the expected response rate with gefitinib (requiring a similar

increase in the erlotinib response rate if the evaluation is not to be biased against erlotinib).

This indirect response rate was then combined with the incidence of grade 3/4 diarrhoea (3.8%) and rash (2.3%) in the IPASS RCT in order to estimate the PFS utility value of gefitinib.

Gefitinib PFS Utility = 0.65612

= ((0.6725)*0.2823)+(0.6532*(1-0.2823))+(-0.03248*0.0229)+(-0.0468*0.038)

The IPASS study AEs were used as this was the largest of the gefitinib RCTs. The influence of using alternative AE sources was tested in sensitivity analysis via deviation in the gefitinib PFS utility value used in the model.

The PD utility value used in the model was that derived by Nafees et al 2008. It was assumed that the choice of first line treatment had no influence upon the utility patients experienced post-progression.

This approach is consistent with that taken in other NICE mNSCLC technology appraisals (NICE TA227, NICE TA192, NICE TA190 and NICE TA181).

The use of non-treatment differential PFS utility values was tested in sensitivity analysis.

6.4.10 If clinical experts assessed the applicability of values available or estimated any values, please provide the following details:

These utility values have been used in numerous recent NICE technology appraisals in mNSCLC and so it was felt that further clinical validation was not required.

6.4.11 Please define what a patient experiences in the health states in terms of HRQL. Is it constant or does it cover potential variances?

The ‘progression free survival’ health state is designed to capture patients’ relatively high quality of life prior to disease progression whilst the ‘progressed disease’ state is designed to represent a patients relatively low quality of life prior to their death.

6.4.12 Were any health effects identified in the literature or clinical trials excluded from the analysis? If so, why were they excluded?

The evaluation incorporated the utility associated with PFS (in terms of both response and lack of response to treatment), the disutility associated with grade 3 and 4 rash and diarrhoea (the adverse events most commonly associated with gefitinib and erlotinib) and the utility associated with the ‘progressed disease’ health state. These health states capture the health effects most commonly associated with mNSCLC and treatment with erlotinib or gefitinib.

6.4.13 If appropriate, what was the baseline quality of life assumed in the analysis if different from health states? Were quality-of-life events taken from this baseline?

Not applicable.

6.4.14 Please clarify whether HRQL is assumed to be constant over time. If not, provide details of how HRQL changes with time.

Average HRQoL is assumed to be constant within each health state for each model arm but vary between health states.

6.4.15 Have the values in sections 6.4.3 to 6.4.8 been amended? If so, please describe how and why they have been altered and the methodology.

See above.

6.5 Resource identification, measurement and valuation

In line with recent NICE technology appraisals of mNSCLC technologies (TA227, TA192, TA190, TA181) the following range of cost inputs were considered in the modeling undertaken.

These included:

- The cost of erlotinib (including drug wastage and a 14.5% discount on the BNF62 list price of erlotinib)
- The cost of gefitinib (incorporating the PAS proposed in NICE TA192)
- The cost of adverse events
- The cost of administering the erlotinib and gefitinib patient access schemes
- The cost of dispensing erlotinib and gefitinib
- The cost of PFS Best Supportive Care (BSC)
- The cost of post-progression BSC
- The cost of monitoring
- The cost of terminal care

The PFS BSC costs, PD BSC costs, terminal care costs, monitoring costs, pharmacy costs and adverse events costs used in the model were those used, and accepted by the Committee and ERG, in the recent (2011) NICE appraisal of erlotinib for the maintenance treatment of mNSCLC (NICE TA227).

The cost of EGFR mutation testing was not considered in the modeling undertaken. It is current NHS practice to undertake EGFR mutation testing of mNSCLC patients and this will remain the case whether or not erlotinib is NICE recommended as a first line treatment option (and so there is no

incremental testing cost associated with the use of erlotinib).

Similarly second line treatment costs were not considered in the model. As the choice of erlotinib or gefitinib as a first line treatment will have no impact upon the choice of second line treatment given, or the duration of that second line treatment, the cost of second line treatment in each arm of the model would be the same and would therefore be 'cancelled out' when estimating the relative cost of the two comparators.

NHS costs

6.5.1 Please describe how the clinical management of the condition is currently costed in the NHS in terms of reference costs and the payment by results (PbR) tariff. Provide the relevant Healthcare Resource Groups (HRG) and PbR codes and justify their selection. Please consider in reference to section 2.

As both erlotinib and gefitinib are oral technologies they do not require extensive NHS administration/management resources (simply pharmacy dispensing every 30 days and monitoring/best-supportive care typically associated with mNSCLC patients). These costs were incorporated into the model using the same approach used in NICE TA227, TA181 and TA190 (i.e. the use of BSC costs based upon a 2004 University of Sheffield report on the cost of palliative care for cancer patients, via the use of dispensing costs based upon PSSRU 2010 and a time and motion study (Millar 2008) and via the application of the cost of a CT scan every 3 months in active treatment).

6.5.2 Please describe whether NHS reference costs or PbR tariffs are appropriate for costing the intervention being appraised.

See above. The approach followed in NICE TA227, TA181 and TA190 was followed when costing both interventions.

Resource identification, measurement and valuation studies

6.5.3 Please provide a systematic search of relevant resource data for the UK.

Embase (EMYY), Medline (MEYY), Medline in Process (MEIP), NHS EED and ECON LIT were searched for studies assessing resource utilisation of patients with advanced lung cancer. The search was designed to evaluate potentially relevant BSC and adverse event costs that have been used in lung cancer health technology evaluations, within the United Kingdom. The complete search strategy is provided in section 9.10. The methodology used was based upon on the methods outlined in the CRD's 'Guidance for undertaking reviews in health care' (2008).

Keyword strategies were developed using key references retrieved through initial scoping searches. No date limit was placed on the search undertaken. Dialogue DataStar was used to search EMYY, MEYY and MEIP whilst NHS EED was searched using The Cochrane Library http://www.thecochranelibrary.com/view/0/index.html and ECON LIT was searched using: http://www.aeaweb.org/econlit/index.php

Each search result's title and abstract were assessed for relevance according to the pre-defined inclusion and exclusion criteria (see Table 46 below).

If a record was deemed potentially relevant it was retrieved in full and re-assessed against the inclusion/exclusion criteria.

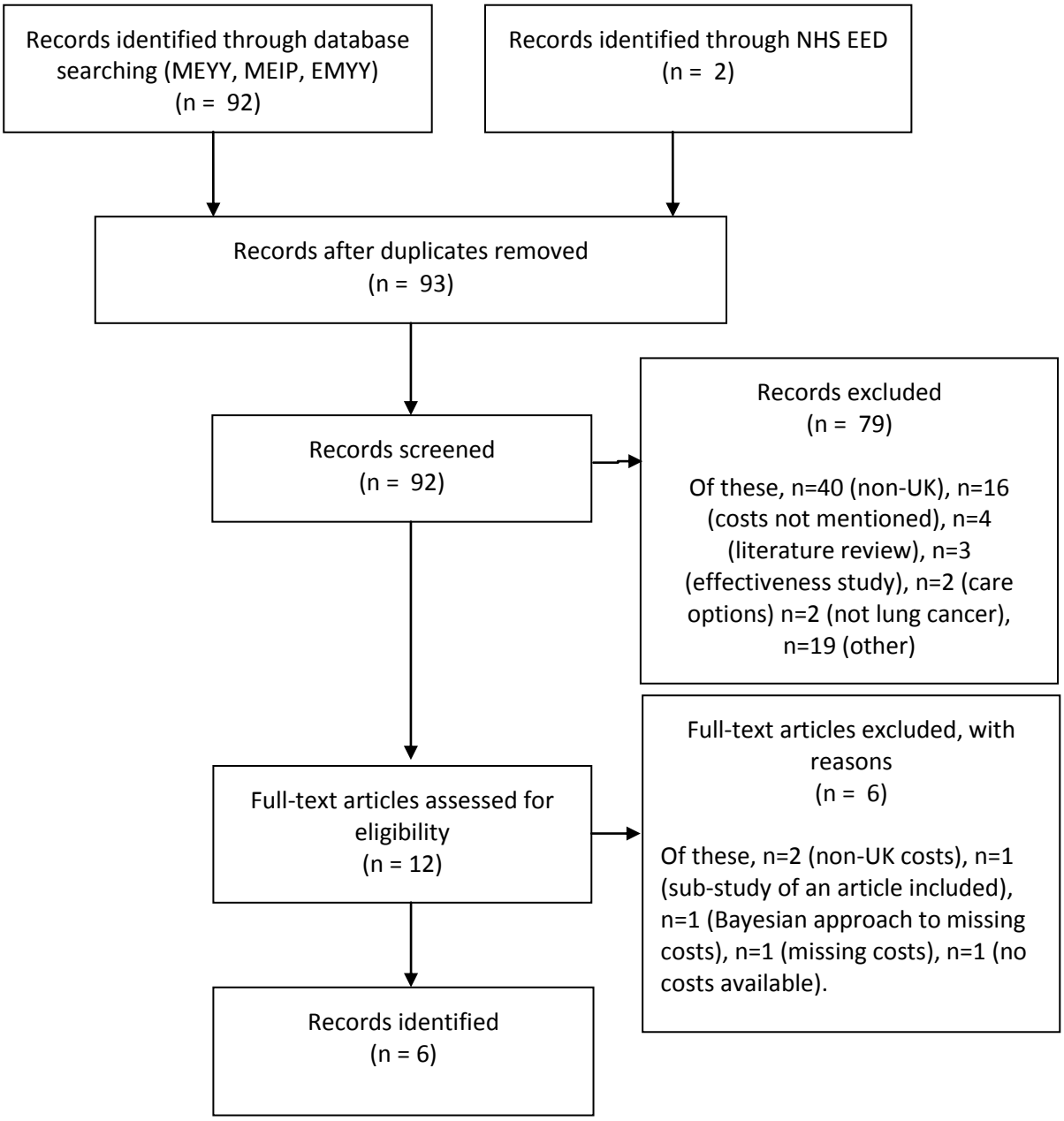
Table 46: Cost Studies Search Inclusion/Exclusion Criteria

Inclusion criteria	Exclusion criteria
Advanced or metastatic lung cancer Resource utilisation from an NHS perspective	Early lung cancer Resource utilisation from any non-UK country.

In total 93 individual records were identified via the five databases (no results were found from ECON LIT). Of these, 79 studies were excluded upon initial screening of title and abstract (see the PRISMA diagram below for the rationale for these exclusions) and 12 were deemed potentially relevant.

These 12 results were then retrieved and assessed more comprehensively against the inclusion/exclusion criteria, 6 were found to be relevant.

Figure 53: Cost Search PRISMA flow diagram



Following review of these records it was noted that NICE TA227 (the NICE STA on the use of erlotinib for the maintenance treatment of mNSCLC) had

not been identified by the search. This was then added to the 76 identified in order to ensure all potentially relevant costs were considered (7 records identified in total).

The 7 records were, Lewis et al. (2010), 4 ERG Reports (Erlotinib for the treatment of relapsed non-small cell lung cancer (NICE TA162), Pemetrexed for the first-line treatment of non-small cell lung cancer (NICE TA190), Pemetrexed for the maintenance treatment of locally advance or metastatic non-small cell lung cancer (NICE TA181) and Gefitinib for the first-line treatment of locally advance or metastatic non-small cell lung cancer (NICE TA192), Maslove et al. (2005), and the previously mentioned NICE TA227 (erlotinib for the maintenance treatment of mNSCLC).

The Lewis et al publication related to the use of erlotinib in a second line setting and was based upon NICE TA162. Lewis et al include a range of BSC and adverse events costs derived via an expert panel advisory board. However as patients in a second line setting have more advanced disease than those in a first line setting the relevance of these BSC costs is doubtful (although the adverse events costs still potentially relevant).

The Maslove et al publication recorded real world data associated with chemotherapy administration which is of limited relevance to this appraisal (in which no chemotherapy regimen is considered as a comparator or an intervention).

In NICE TA181, TA190 and TA227 (first ERG report onwards) the best-supportive care costs incorporated into the model were based upon a 2004 publication by the University of Sheffield which reported the average cost of Specialist Palliative Care per cancer death per year. These were incorporated for both the PFS and PD health states and in a patient's terminal phase with cost of monitoring (via 3 monthly CT scan) applied in combination.

In TA192 (gefitinib first line NICE STA) the manufacturer utilised the BSC costs derived by Clegg et al. 2002 and applied these solely in the PD health

state of their model (i.e. PFS included monitoring and dispensing costs but no other BSC costs).

See section 6.5.6 for a description of the BSC/monitoring costs applied within the model. See section 6.5.7 for a description of the AE costs applied within the model.

6.5.4 If clinical experts assessed the applicability of values available or estimated any values, please provide the following details:

The resource use figures used in the model are those that have been used in numerous recent mNSCLC appraisals (TA227, TA190, TA181) and so it was felt that further expert validation for the purpose of this appraisal was not warranted.

Intervention and comparators' costs

6.5.5 Please summarise the cost of each treatment

The individual components associated with each comparator (in terms of drug cost, administration/pharmacy cost and PAS administration costs) are detailed individually below.

6.5.5.1 Drug Costs

6.5.5.1.1. Drug Costs - Erlotinib

The cost of erlotinib was incorporated into the model using a slightly modified version of the method developed by LRiG in NICE TA227.

This was done by:

1. Generating a 'time to last dose' Kaplan Meier curve for erlotinib based upon the EURTAC RCT.

2. Extrapolating that curve beyond the period of trial follow-up (following assessment of the need for extrapolation and examination of the relevant cumulative hazard plot - see below).

3. Recording the proportion of patients yet to cease treatment at the start of each 30 day period (i.e. the 'dispensing dates').

4. Deriving the expected cost of a pack of erlotinib dispensed on each of the dispensing dates (an average of the cost of the three pack variants available for purchase, weighted by the proportion of tablets of each type dispensed in each 30 day period in EURTAC)

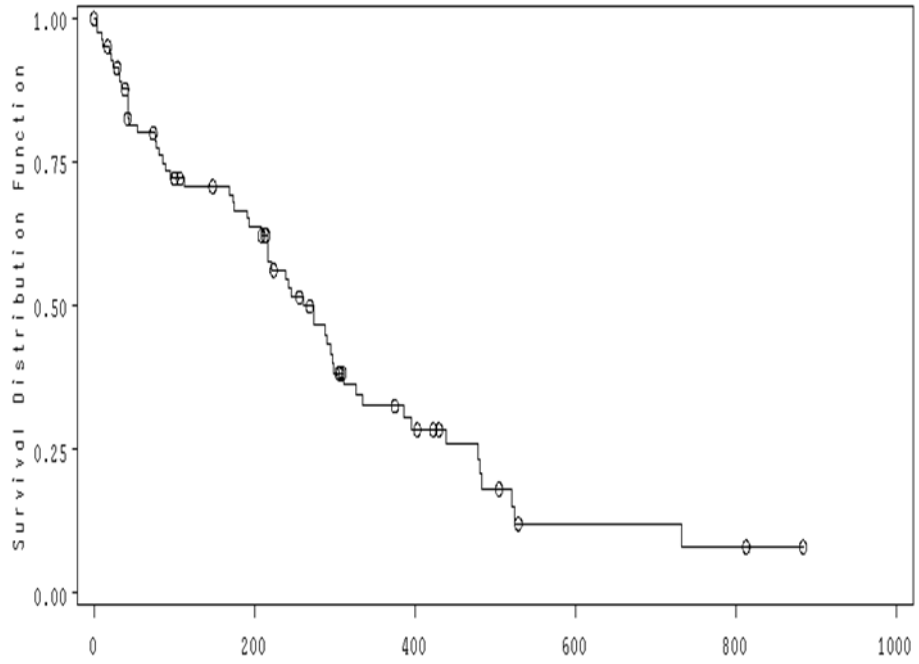
5. Multiplying the proportion of patients yet to receive their last dose at each dispensing date by the expected cost per pack dispensed at that date (under the assumption that a patient yet to cease treatment at a dispensing date would be dispensed another pack of erlotinib) in order to derive the expected cost of erlotinib every 30 days

6. Discounting and summing the above.

This method is applied transparently within the 'Erlotinib Drug Cost' worksheet of the supplied economic model. As it operates on the basis of 'dispensing dates' and does not incorporate a half-cycle correction the method incorporates the cost of all erlotinib dispensed rather than simply those tablets taken (i.e. it includes drug wastage).

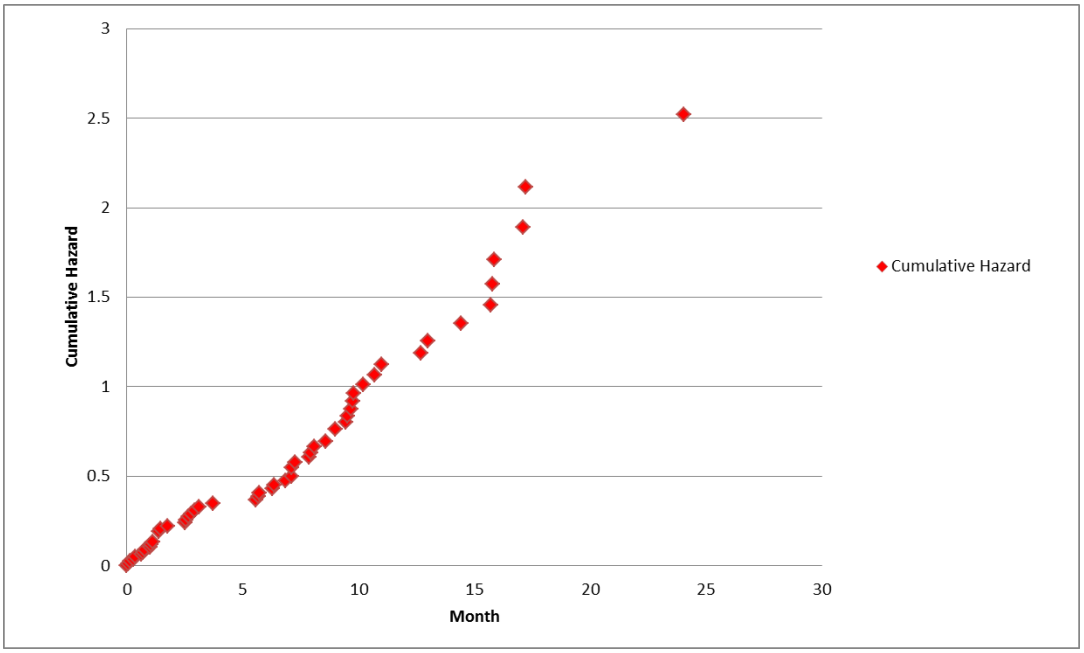
Figure 54 below demonstrates the erlotinib 'time to last dose' KM curve generated based upon the data observed in the EURTAC RCT. As this curve was not complete it was necessary to extrapolate the data observed in order to estimate the expected cost of erlotinib treatment to the NHS.

Figure 54: EURTAC erlotinib time to last dose KM



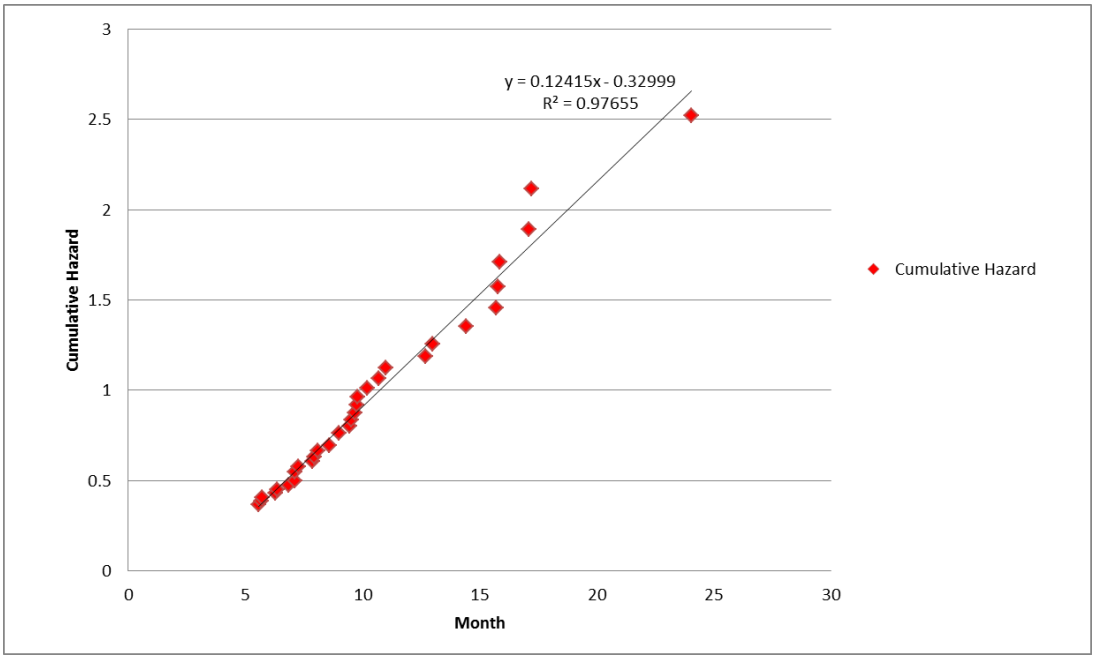
In order to determine the most appropriate form of extrapolation for this curve the cumulative hazard plot for this 'time to last dose' curve was generated and assessed for consistency and linearity (Figure 55 below).

Figure 55: EURTAC erlotinib time to last dose cumulative hazard plot



As was the case for PFS this curve appeared to indicate an initial period of volatility (up to around month 5) followed by a period in which the hazard became more linear. It was therefore hypothesized that any extrapolation of this curve should be based upon an exponential function derived from the period after 5 months (consistent with PFS). The hazard of this function was estimated using linear regression excluding those events that occurred before month 5. The function fitted using this method is presented in Figure 56 below.

Figure 56: EURTAC post-month 5 erlotinib time to last dose cumulative hazard plot with exponential model fitted



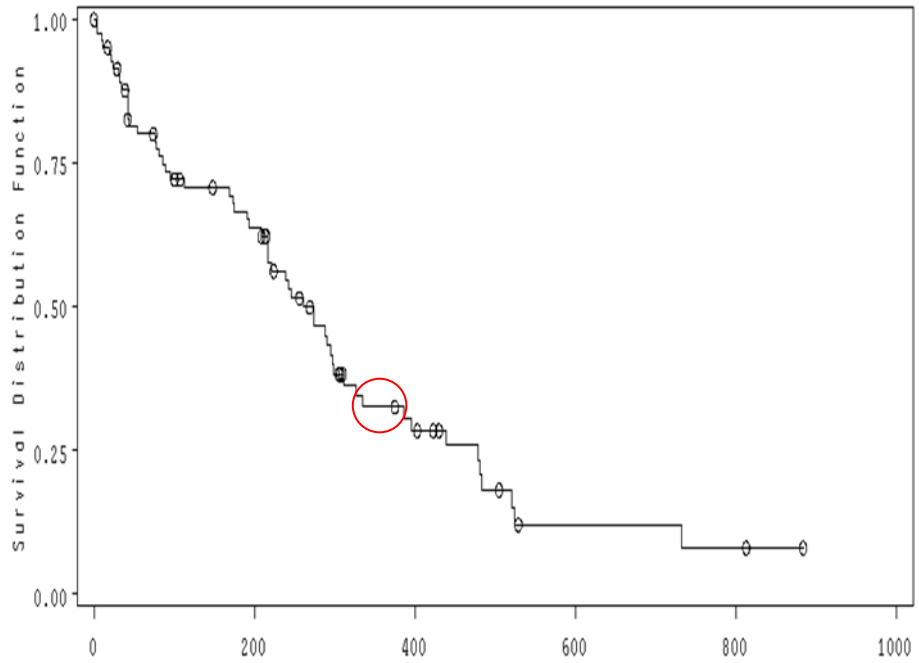
This regression estimated a monthly hazard of 0.12415 with an R^2 value of 0.97655 suggesting the function fitted the observed data well.

Whilst a monthly cycle length was used to model health outcomes and the majority of costs within the model a 30 day cycle length was used to estimate the cost of erlotinib (in order to allow the use of the 'dispensing date' approach to estimating the cost of erlotinib). In order to allow the hazard estimated to be applied within the model the monthly rate shown above was converted into a 30 day rate and then converted into a probability (Briggs *et al* 2006).

The cumulative hazard plot and KM curve were then re-assessed in order to determine where to transition from the observed KM data to the exponential tail. The objective of this evaluation was to determine the point of transition at which as much observed data as possible could be used in the model without incorporating potential spurious ‘jumps’ in the KM curve (a product of small numbers towards the tail).

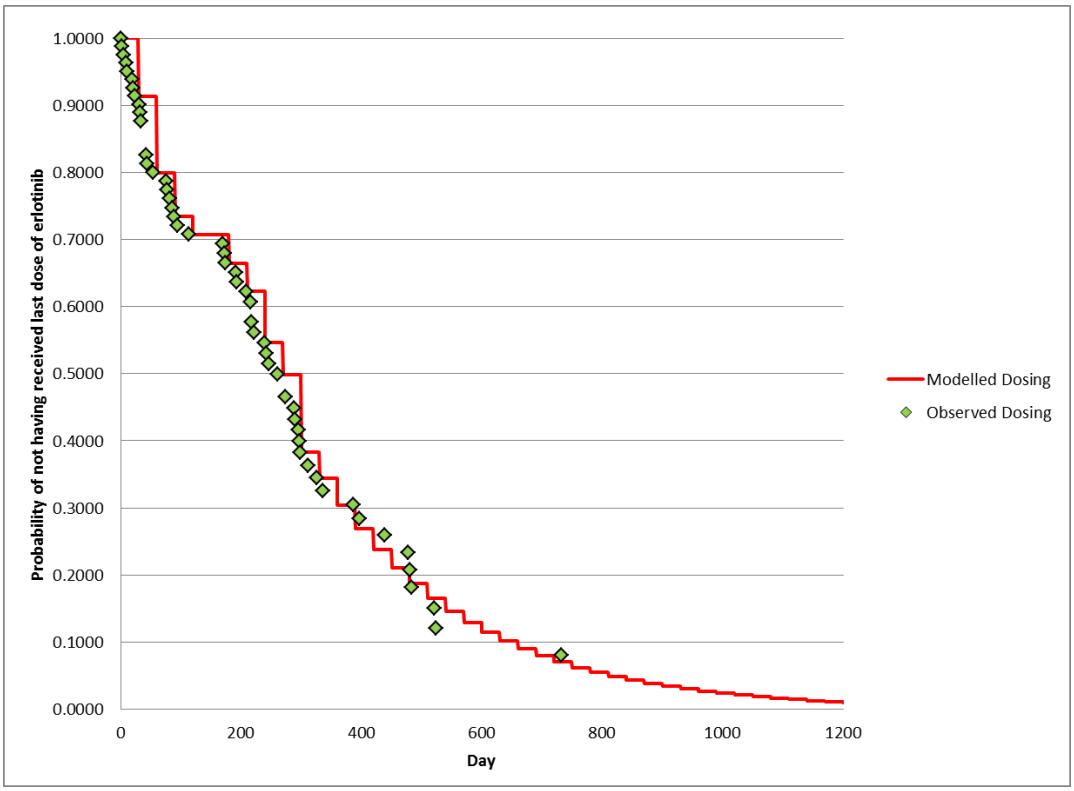
Both plots suggested that the hazard was fairly consistent between 5 months and 12 months and that after month 12 the hazard became slightly more erratic. It was felt that beginning extrapolation at one of these more erratic points would result in the tail of the curve being unfairly biased (either in favor of erlotinib or against erlotinib depending upon whether the point chosen was following a (potentially spurious) sudden flattening or drop in the KM). It was therefore determined that beginning extrapolation prior to month 12 would be most appropriate. The beginning of this more erratic ‘jagged KM’ phase can be observed in Figure 57 below with the sudden flattening of the KM curve at around 350 days (circled in red).

Figure 57: EURTAC erlotinib time to last dose KM with beginning of 'erratic' phase circled



In light of this observation and the desire to utilize as much observed, rather than modeled, data as possible a transition point of day 330 (around month 11 – Just before the flattening highlighted above) was tested and assessed for face-validity (see Figure 58 below – note that the 'steps' are a product of the fact that a half cycle correction has not been applied in order to consider the cost of all erlotinib dispensed by the NHS).

Figure 58: Modeled erlotinib time to last dose KM with day 330 transition



This transition point offered strong face validity and appeared to allow maximum use of the observed data for as long as it appeared reliable. Therefore it was used in the base-case. Alternative transition points were tested in sensitivity analysis.

6.5.5.1.2. Drug Costs - Gefitinib

In NICE TA192 gefitinib was approved as an option for the first line treatment of EGFR M+ mNSCLC patients. This approval was gained under the condition that the manufacturer of gefitinib agreed to provide gefitinib at a fixed cost of £12,200 per patient (paid upon the dispensing of a patients third pack of gefitinib). Under the terms of this PAS if a patient experiences disease progression prior to the dispensing of this 3rd pack (before day 60 of their treatment) the NHS is not charged for the gefitinib that patient has received.

The expected cost of gefitinib to the NHS can therefore be derived by multiplying the £12,200 fixed cost by the proportion of patients for whom the PAS payment is required for.

Whilst ideally real-world data on the precise proportion of patients registered on the gefitinib scheme for whom the fixed payment was required, or 'time to last dose' KM information for gefitinib, would be available this information is not publicly available and so we cannot incorporate it into this submission. This information may be available to the NHS and to the manufacturer of gefitinib (AstraZeneca).

In the base case the indirect comparison PFS HR of erlotinib vs gefitinib (based upon the comparison of EURTAC and Ku et al 2011 (0.82) – see section 5.7.3) was applied to the 'time to last dose' curve generated for erlotinib in order to estimate the proportion of patients initiated on gefitinib who are yet to have received their last dose of treatment at day 60 of the model. This proportion was then multiplied by the fixed cost payment in order to estimate the expected cost of gefitinib to the NHS. Whilst this approach is clearly inferior to the availability of real-world data on the gefitinib PAS it is nevertheless consistent with the approach taken to costing erlotinib.

The impact of assuming different proportions of patients 'activating' the gefitinib PAS payment was considered in sensitivity analysis.

6.5.5.2 Administration/Pharmacy costs

As erlotinib and gefitinib are oral products they do not require administration in a hospital chemotherapy suite nor do they require reconstitution in a pharmacy asceptic unit. Both simply require a pharmacist to dispense and check a prescription every 30 days with no further cost to the NHS. They are therefore relatively cheap treatments to administer compared to the doublet chemotherapies currently given to non-EGFR mutated mNSCLC patients.

In 2008 a prospective time-and-motion study was conducted in two UK secondary care NHS Trusts to quantify, in terms of time, the secondary care NHS resource use associated with the preparation and administration of XELOX (capecitabine in combination with oxaliplatin) and FOLFOX-6 (5-FU in combination with folinic acid and oxaliplatin) in metastatic colorectal cancer (Millar 2008). The results of the study indicated that dispensing of capecitabine (an oral agent) required an average of 12 minutes. Therefore for the base-case it was assumed that the dispensing of erlotinib and gefitinib would similarly take 12 minutes.

One hour of a pharmacist time performing patient related activities (accounting for overheads, qualifications, and salary on costs) costs £65 (PSSRU, 2010). It was therefore estimated in the base case that the cost of dispensing erlotinib or gefitinib (not including the cost of PAS) was £13 (65*12/60).

For erlotinib this was applied within the model using the same ‘time to last dose’ curve and dispensing dates methodology described for drug costs in section 6.5.5.1.2. (i.e. at each dispensing date if a patient was yet to have received their last dose of erlotinib it was assumed a pack would be dispensed). For gefitinib this same approach was followed with the PFS HR estimate described in section 5.7.3. (EURTAC vs Ku et al) applied to erlotinib ‘time to last dose’ curve.

6.5.5.3 PAS administration costs

Both the PAS included within this submission and that proposed for future consideration by the Committee consist of a simple discount on all erlotinib purchased by the NHS. The PAS is therefore not associated with an administration cost to the NHS.

The gefitinib PAS is not a simple discount. It is a complex scheme submitted to NICE prior to the introduction of PASLU that requires considerable NHS

resources to administer relative to the PAS proposed for erlotinib. The gefitinib PAS requires initial patient registration by a pharmacist, the monthly completion of a request form to confirm a patient has not yet progressed on their disease so that another pack of gefitinib may be sent by the manufacturer, and it requires NHS trust finance to track the operation of the scheme (in order to ensure all invoicing and payments are correct – with the potential for query management where discrepancies/errors are identified) (expert opinion).

The activities associated with administering the gefitinib PAS are displayed in Table 47 below. The type, length, and frequency of the activities displayed below were estimated by an expert in the administration of patient access schemes within the NHS. The costs associated with each activity were estimated based upon the below activities and the 'Pay Circular (AforC) 1/2009' (Pay and conditions for NHS Staff covered by the Agenda for Change agreement) document which can be viewed on the NHS Employers website (www.nhsemployers.org)).

Table 47: Gefitinib PAS administration costs

What	Who	Grade	How Long	Frequency	Cost per activity
Patient Registration	Pharmacist	6	1 hour	Once per patient	£32
Completion of Form to Request Pack	Pharmacist	6	0.5 hours	Once per patient every 30 days	£16
Invoicing	Trust Finance	6	0.5 hours	Once per patient	£19
Payment Reconciliation	Trust Finance	6	0.5 hours	Once per patient every 30 days	£19
Query Management	Trust Finance	6	0.5 hours	Once per patient	£19

These costs were applied as a one off cost of £70 (patient registration, invoicing and query management) and at an ongoing cost of £35 (completion of request pack and payment reconciliation) every 30 days (applied to the gefitinib 'time to last dose' curve in the same manner in which pharmacy costs were estimated).

6.5.5.4 Summary of technology associated costs

Table 48: Unit costs associated with the technology in the economic model

Items	Erlotinib	Gefitinib	Ref. in submission
Drug Costs	Proportion of patients yet to cease treatment each 'dispensing date' multiplied by expected cost of pack (including PAS) dispensed at each dispensing date (weighted average of different tablet sizes dispensed in EURTAC in each 30 day period)	£12,200 * proportion not yet ceased treatment at month 3	Section 6.5.5.1.2.
Per patient PAS administration cost	£0	£70 one off cost + £35 per pack administered	Section 6.5.5.3.
Administration / Pharmacy cost every 30 days	£13 per pack dispensed	£13 per pack dispensed	Section 6.5.5.2.

Health-state costs

6.5.6 Please summarise, if appropriate, the costs included in each health state. Cross-reference to other sections of the submission for the resource costs. Provide a rationale for the choice of values used in the cost-effectiveness model. The health states should refer to the states in section 6.2.4.

The health state costs used in the model were as per those used, and accepted by the Committee and ERG, in NICE TA227 (erlotinib for the maintenance treatment of mNSCLC), NICE TA181 (pemetrexed for the maintenance treatment of mNSCLC) and NICE TA190 (pemetrexed for the first line treatment of mNSCLC).

As described in Roche's supplementary evidence submission in NICE TA227 these health state costs include the cost of best supportive care (derived from a 2004 report by the University of Sheffield on the cost of palliative care in Cancer) and the cost of 3 monthly CT scan response assessment (for the whole period of PFS and throughout the expected period of second line treatment for PD).

Table 49: List of health states and associated costs in the economic model

Health states	Items	Value	Reference in submission
PFS Best Supportive Care and Monitoring	Supportive care + CT assessment of response every 3 months	£181.46	6.5.6.
PFS Best Supportive Care and Monitoring	Supportive care + CT assessment of response every 3 months whilst on 2nd line treatment (estimate based upon the SATURN RCT in NICE TA227)	£160.06	6.5.6.
Terminal Phase Best Supportive Care Costs	Supportive care	£2,588.25	6.5.6.

Adverse-event costs

6.5.7 Please summarise the costs for each adverse event listed in section 5.9 (Adverse events). These should include the costs of therapies identified in section 2.7. Cross-reference to other sections of the submission for the resource costs. Provide a rationale for the choice of values used in the cost-effectiveness model discussed in section 6.2.2.

Table 50: List of adverse events and summary of costs included in the economic model

Adverse events	Value	Reference
Rash	£116	Roche 2006 cited in Brown et al 2009 (NICE TA192 ERG Report)
Diarrhoea	£867	Eli Lilly 2009 cited in Brown et al 2009 (NICE TA192 ERG Report)

The cost of managing grade 3/4 Rash and Diarrhoea was incorporated into the model using the same values as were used in NICE TA192 (the STA of gefitinib). These AEs are those most commonly associated with erlotinib and gefitinib (which both have comparably 'clean' toxicity profiles relative to the chemotherapy utilised in this patient group prior to the advent of EGFR targeted therapies). These were applied in the first cycle of the model and so are not subject to discounting. The incidence of grade 3/4 Rash and Diarrhoea was taken from EURTAC for erlotinib and from IPASS for gefitinib. The impact of utilising other gefitinib RCTs to inform this parameter was tested in sensitivity analysis.

Miscellaneous costs

6.5.8 Please describe any additional costs that have not been covered anywhere else (for example, PSS costs). If none, please state.

All cost incorporated into the model are presented in the above sections.

6.6 Sensitivity analysis

6.6.1 Has the uncertainty around structural assumptions been investigated? Provide details of how this was investigated, including a description of the alternative scenarios in the analysis.

Structural sensitivity analysis was focused upon understanding the cost-effectiveness implications of choosing alternative points to transition from the observed KM curves for PFS and 'time to last dose' to the extrapolated 'tails'. These are detailed in Table 54 and Table 55 below.

6.6.2 Which variables were subject to deterministic sensitivity analysis? How were they varied and what was the rationale for this? If any parameters or variables listed in section 6.3.6 (Summary of selected values) were omitted from sensitivity analysis, please provide the rationale.

6.6.2.1. Univariate sensitivity analyses

Table 51 (below) details the univariate sensitivity analyses undertaken with the objective of determining the sensitivities of the model. Table 52, Table 53, (below) present the range of values used for two parameters felt to be important to the estimated cost-effectiveness of erlotinib (the relative efficacy of erlotinib and gefitinib, and the proportion of gefitinib patients for whom the PAS fixed cost payment is required.) Table Table 54Table 55 present the sensitivity analyses undertaken to investigate the impact of choosing different transition points from the observed KM data to the modelled 'tails' for both PFS and the 'time to last dose' curve.

Table 51: Parameters varied in deterministic sensitivity analysis

Parameter	Base-Case Value	Low Value	High Value
Transition Probabilities			
Monthly probability of disease progression after month 16 (erlotinib) – note: KM used before this point in time.	0.085977	-10%	+10%
Monthly probability of disease progression after month 16 (gefitinib) - note: indirect PFS HR adjusted KM used before this point in time.	0.104567	-10%	+10%
Monthly probability of death in PFS (both erlotinib and gefitinib)	0.014206	-10%	+10%
Monthly probability of death in PD (both erlotinib and gefitinib)	0.075719	-10%	+10%
Utility Values			
PFS (Stable Disease)	0.6532	0.6096 (Lower confidence interval)	0.6968 (Upper confidence interval)
PFS (Response dummy variable)	0.0193	0.0065 (Lower confidence interval)	0.0321 (Upper confidence

			interval)
Disutility of Rash	-0.0325	-0.0554 (Lower confidence interval)	-0.0095 (Upper confidence interval)
Disutility of Diarrhoea	-0.0468	-0.0772, (Lower confidence interval)	-0.0164 (Upper confidence interval)
PD (progression dummy variable disutility relative to PFS SD baseline)	-0.1798	-0.2223 (Lower confidence interval)	-0.1373 (Upper confidence interval)
Resultant PFS Values	PFS erlotinib = 0.661 PFS gefitinib = 0.656	Gefitinib PFS utility (0.656) applied for gefitinib and erlotinib	Erlotinib PFS utility (0.661) applied for gefitinib and erlotinib
Costs			
Pharmacy costs per pack of erlotinib/gefitinib dispensed	£13	£6.63 (Lower confidence interval if standard error = 1/4 base case value (assumption))	£19.37 (Upper confidence interval if standard error = 1/4 base case value (assumption))
Monthly PFS BSC Cost (including monitoring)	£181.46	£92.54 (Lower confidence	£270.38 (Upper confidence

		interval if standard error = 1/4 base case value (assumption))	interval if standard error = 1/4 base case value (assumption))

Monthly PD BSC Cost	£160.06	£81.63 (Lower confidence interval if standard error = 1/4 base case value (assumption))	£238.49 (Upper confidence interval if standard error = 1/4 base case value (assumption))
Terminal Care Cost	£2,588.25	£1,320.01 (Lower confidence interval if standard error = 1/4 base case value (assumption))	£3,856.49 (Upper confidence interval if standard error = 1/4 base case value (assumption))
Gefitinib per patient PAS administration cost	£70 one off cost, £35 per month on-going costs	£35 one off cost, £17.50 per month on-going costs (i.e. -50%)	£140 one off cost, £70 per month on-going costs (i.e. +50%)
General Parameters			
Time Horizon	10 years	5 years	20 years
Costs Discount Rate	3.5%	0%	6%
Health Outcomes Discount Rate	3.5%	0%	6%
Both Discount Rates	3.5%	0%	6%

Table 52: Relative efficacy of erlotinib and gefitinib sensitivity analyses

Scenario	Description	PFS HR (erlotinib vs gefitinib)
1	Base-case (EURTAC vs Ku et al)	0.82
2	'Asian Only' analysis (OPTIMAL vs Ku et al)	0.36
3	Random Effects (RE) pooling (EURTAC/OPTIMAL RE pooling vs Ku et al)	0.56
4	Fixed Effects (FE) pooling (EURTAC/OPTIMAL FE pooling vs Ku et al)	0.58

Table 53: Proportion of patients 'activating' gefitinib PAS payment sensitivity analyses

Scenario	Description
1	EURTAC erlotinib 'time to last dose' curve 3 month value with indirect PFS HR applied (0.82)
2	EURTAC erlotinib PFS curve 3 month value with indirect PFS HR applied (0.82)
3	IPASS gefitinib PFS curve 3 month value (95%)
4	100% of patients 'activate' the PAS

Table 54: Point of transition from erlotinib PFS KM to modeled 'tail' sensitivity analyses

Scenario	Description
1	Base-Case (After Month 16)
2	After Month 5
3	After Month 21
4	After Month 30

Table 55: Point of transition from observed 'Time to last dose' erlotinib KM Curve to modeled 'tail' sensitivity analyses

Scenario	Description
1	Base-Case (After Day 300)
2	After Day 150
3	After Day 540
4	After Day 600

6.6.3 Was PSA undertaken? If not, why not? If it was, the distributions and their sources should be clearly stated if different from those in section 6.3.6, including the derivation and value of ‘priors’. If any parameters or variables were omitted from sensitivity analysis, please provide the rationale for the omission(s).

PSA was undertaken. This was conducted as per section 6.3.6.

Whilst the individual costs associated with the administration of the gefitinib PAS are not presented in section 6.3.6. (see section 6.5.5.3) these were considered in the PSA undertaken. The approach taken for these PAS administration costs was the same as applied for other costs in the model where the standard error required to conduct PSA was unknown (i.e. via the use of a gamma function and the assumption that the standard error of the parameter was a quarter of the base-case value used).

6.7 Results

Clinical outcomes from the model

6.7.1 For the outcomes highlighted in the decision problem (see section 4), please provide the corresponding outcomes from the model and compare them with clinically important outcomes such as those reported in clinical trials. Discuss reasons for any differences between modelled and observed results (for example, adjustment for cross-over). Please use the following table format for each comparator with relevant outcomes included.

Table B19 below presents a comparison of the median PFS and OS values for erlotinib in EURTAC compared to the model results (with half cycle correction). These demonstrate that the model results are comparable to the clinical trial results observed. It should be noted that as the model has a one month cycle length the median estimate of both OS and PFS must fall on a whole month rather than part-way through a month.

Table 56: Summary of model results compared with clinical data

Outcome	Clinical trial result	Model result
Progression-free survival	9.7 month (median)	10 month (median)
Overall survival	19.3 month (median)	20 month (median)
Response Rate	58.10%	58.10%

As an indirect comparison of gefitinib was conducted it is not possible to compare the modelled outcomes to those observed in four gefitinib trials identified (as this would equate to naïve comparison).

6.7.2 Please provide (if appropriate) the proportion of the cohort in the health state over time (Markov trace) for each state, supplying one for each comparator.

Table 57 below presents the markov trace for both erlotinib and gefitinib (without half cycle correction).

Table 57: Markov Trace (without half-cycle correction)

	Erlotinib			Gefitinib		
Month	PFS	PD	Death	PFS	PD	Death
0	1.000	0.000	0.000	1.000	0.000	0.000
1	0.952	0.034	0.014	0.942	0.044	0.014
2	0.878	0.092	0.030	0.853	0.116	0.031
3	0.814	0.136	0.050	0.778	0.170	0.052
4	0.801	0.128	0.072	0.763	0.161	0.076
5	0.801	0.118	0.081	0.763	0.149	0.088
6	0.746	0.152	0.102	0.700	0.190	0.110
7	0.703	0.173	0.124	0.651	0.214	0.134
8	0.640	0.214	0.147	0.581	0.259	0.160
9	0.542	0.286	0.172	0.475	0.338	0.188
10	0.491	0.307	0.201	0.421	0.359	0.220
11	0.418	0.351	0.232	0.346	0.401	0.253
12	0.399	0.337	0.264	0.327	0.385	0.288
13	0.361	0.344	0.295	0.289	0.389	0.322
14	0.342	0.332	0.327	0.271	0.373	0.356
15	0.342	0.307	0.352	0.271	0.345	0.384
16	0.281	0.339	0.380	0.214	0.372	0.414
17	0.257	0.333	0.409	0.192	0.363	0.445
18	0.235	0.327	0.438	0.172	0.353	0.475
19	0.215	0.319	0.466	0.154	0.341	0.505
20	0.196	0.310	0.494	0.138	0.329	0.533
21	0.180	0.301	0.520	0.124	0.317	0.560
22	0.164	0.291	0.545	0.111	0.304	0.585

23	0.150	0.281	0.569	0.100	0.291	0.610
24	0.137	0.270	0.593	0.089	0.278	0.633
25	0.125	0.259	0.615	0.080	0.265	0.656
26	0.115	0.249	0.637	0.072	0.252	0.677
27	0.105	0.238	0.657	0.064	0.239	0.697
28	0.096	0.228	0.677	0.058	0.227	0.716
29	0.087	0.217	0.695	0.052	0.215	0.734
30	0.080	0.207	0.713	0.046	0.203	0.751
31	0.073	0.197	0.730	0.041	0.192	0.767
32	0.067	0.187	0.746	0.037	0.181	0.782
33	0.061	0.178	0.761	0.033	0.171	0.796
34	0.056	0.169	0.775	0.030	0.161	0.809
35	0.051	0.160	0.789	0.027	0.151	0.822
36	0.047	0.152	0.802	0.024	0.142	0.834
37	0.043	0.144	0.814	0.022	0.133	0.845
38	0.039	0.136	0.825	0.019	0.125	0.855
39	0.036	0.128	0.836	0.017	0.118	0.865
40	0.033	0.121	0.846	0.016	0.110	0.874
41	0.030	0.114	0.856	0.014	0.103	0.883
42	0.027	0.108	0.865	0.012	0.097	0.891
43	0.025	0.102	0.874	0.011	0.090	0.898
44	0.023	0.096	0.882	0.010	0.085	0.905
45	0.021	0.090	0.889	0.009	0.079	0.912
46	0.019	0.085	0.896	0.008	0.074	0.918
47	0.017	0.080	0.903	0.007	0.069	0.924
48	0.016	0.075	0.909	0.006	0.064	0.929
49	0.014	0.070	0.915	0.006	0.060	0.934
50	0.013	0.066	0.921	0.005	0.056	0.939
51	0.012	0.062	0.926	0.005	0.052	0.943
52	0.011	0.058	0.931	0.004	0.049	0.947
53	0.010	0.055	0.935	0.004	0.045	0.951
54	0.009	0.051	0.940	0.003	0.042	0.954
55	0.008	0.048	0.944	0.003	0.039	0.958
56	0.008	0.045	0.947	0.003	0.037	0.961
57	0.007	0.042	0.951	0.002	0.034	0.963
58	0.006	0.039	0.954	0.002	0.032	0.966
59	0.006	0.037	0.957	0.002	0.030	0.968
60	0.005	0.035	0.960	0.002	0.028	0.971
61	0.005	0.032	0.963	0.002	0.026	0.973
62	0.005	0.030	0.965	0.001	0.024	0.975
63	0.004	0.028	0.968	0.001	0.022	0.977
64	0.004	0.026	0.970	0.001	0.021	0.978
65	0.003	0.025	0.972	0.001	0.019	0.980
66	0.003	0.023	0.974	0.001	0.018	0.981
67	0.003	0.022	0.976	0.001	0.016	0.983
68	0.003	0.020	0.977	0.001	0.015	0.984
69	0.002	0.019	0.979	0.001	0.014	0.985
70	0.002	0.018	0.980	0.001	0.013	0.986
71	0.002	0.016	0.982	0.001	0.012	0.987
72	0.002	0.015	0.983	0.000	0.011	0.988

73	0.002	0.014	0.984	0.000	0.011	0.989
74	0.002	0.013	0.985	0.000	0.010	0.990
75	0.001	0.012	0.986	0.000	0.009	0.991
76	0.001	0.012	0.987	0.000	0.008	0.991
77	0.001	0.011	0.988	0.000	0.008	0.992
78	0.001	0.010	0.989	0.000	0.007	0.993
79	0.001	0.009	0.990	0.000	0.007	0.993
80	0.001	0.009	0.990	0.000	0.006	0.994
81	0.001	0.008	0.991	0.000	0.006	0.994
82	0.001	0.008	0.992	0.000	0.005	0.994
83	0.001	0.007	0.992	0.000	0.005	0.995
84	0.001	0.007	0.993	0.000	0.005	0.995
85	0.001	0.006	0.993	0.000	0.004	0.996
86	0.001	0.006	0.994	0.000	0.004	0.996
87	0.000	0.005	0.994	0.000	0.004	0.996
88	0.000	0.005	0.995	0.000	0.003	0.997
89	0.000	0.005	0.995	0.000	0.003	0.997
90	0.000	0.004	0.995	0.000	0.003	0.997
91	0.000	0.004	0.996	0.000	0.003	0.997
92	0.000	0.004	0.996	0.000	0.002	0.997
93	0.000	0.003	0.996	0.000	0.002	0.998
94	0.000	0.003	0.997	0.000	0.002	0.998
95	0.000	0.003	0.997	0.000	0.002	0.998
96	0.000	0.003	0.997	0.000	0.002	0.998
97	0.000	0.003	0.997	0.000	0.002	0.998
98	0.000	0.002	0.997	0.000	0.002	0.998
99	0.000	0.002	0.998	0.000	0.001	0.999
100	0.000	0.002	0.998	0.000	0.001	0.999
101	0.000	0.002	0.998	0.000	0.001	0.999
102	0.000	0.002	0.998	0.000	0.001	0.999
103	0.000	0.002	0.998	0.000	0.001	0.999
104	0.000	0.002	0.998	0.000	0.001	0.999
105	0.000	0.001	0.998	0.000	0.001	0.999
106	0.000	0.001	0.999	0.000	0.001	0.999
107	0.000	0.001	0.999	0.000	0.001	0.999
108	0.000	0.001	0.999	0.000	0.001	0.999
109	0.000	0.001	0.999	0.000	0.001	0.999
110	0.000	0.001	0.999	0.000	0.001	0.999
111	0.000	0.001	0.999	0.000	0.001	0.999
112	0.000	0.001	0.999	0.000	0.001	0.999
113	0.000	0.001	0.999	0.000	0.000	1.000
114	0.000	0.001	0.999	0.000	0.000	1.000
115	0.000	0.001	0.999	0.000	0.000	1.000
116	0.000	0.001	0.999	0.000	0.000	1.000
117	0.000	0.001	0.999	0.000	0.000	1.000
118	0.000	0.001	0.999	0.000	0.000	1.000
119	0.000	0.001	0.999	0.000	0.000	1.000
120	0.000	0.000	1.000	0.000	0.000	1.000

6.7.3 Please provide details of how the model assumes QALYs accrued over time. For example, Markov traces can be used to demonstrate QALYs accrued in each health state over time.

Table 58 below demonstrates the way in which QALYs are accumulated over time for both erlotinib and gefitinib (results with half cycle correction and discounting).

Table 58: QALY accumulation 'trace' (with discounting and half cycle correction)

	Erlotinib			Gefitinib		
Month	PFS	PD	Total	PFS	PD	Total
0	[redacted]	[redacted]	[redacted]	0.053	0.001	0.054
1				0.102	0.004	0.106
2				0.147	0.010	0.156
3				0.189	0.016	0.205
4				0.231	0.022	0.253
5				0.271	0.029	0.300
6				0.308	0.037	0.345
7				0.341	0.046	0.388
8				0.370	0.058	0.428
9				0.395	0.072	0.466
10				0.416	0.087	0.502
11				0.434	0.102	0.536
12				0.450	0.117	0.567
13				0.465	0.132	0.597
14				0.479	0.145	0.625
15				0.492	0.159	0.651
16				0.503	0.173	0.676
17				0.512	0.187	0.699
18				0.521	0.200	0.721
19				0.529	0.213	0.741
20				0.536	0.225	0.761
21				0.542	0.237	0.779
22				0.548	0.248	0.796
23				0.552	0.259	0.811
24				0.557	0.269	0.826
25				0.561	0.278	0.839
26				0.564	0.287	0.852
27				0.567	0.296	0.863
28				0.570	0.304	0.874
29				0.573	0.312	0.884
30				0.575	0.319	0.894
31				0.577	0.326	0.903

32		[redacted]			[redacted]			[redacted]		0.579	0.332	0.911
33										0.580	0.338	0.919
34										0.582	0.344	0.926
35										0.583	0.350	0.933
36										0.584	0.354	0.939
37										0.585	0.359	0.944
38										0.586	0.363	0.949
39										0.587	0.367	0.954
40										0.588	0.371	0.959
41										0.588	0.375	0.963
42										0.589	0.378	0.967
43										0.589	0.381	0.971
44										0.590	0.384	0.974
45										0.590	0.387	0.977
46										0.591	0.389	0.980
47										0.591	0.392	0.983
48										0.591	0.394	0.985
49										0.591	0.396	0.987
50										0.592	0.398	0.989
51										0.592	0.400	0.991
52										0.592	0.401	0.993
53										0.592	0.403	0.995
54										0.592	0.404	0.996
55										0.593	0.405	0.998
56										0.593	0.407	0.999
57										0.593	0.408	1.001
58										0.593	0.409	1.002
59										0.593	0.410	1.003
60										0.593	0.411	1.004
61										0.593	0.411	1.005
62										0.593	0.412	1.005
63										0.593	0.413	1.006
64										0.593	0.414	1.007
65										0.593	0.414	1.008
66										0.593	0.415	1.008
67										0.593	0.415	1.009
68										0.593	0.416	1.009
69										0.593	0.416	1.010
70										0.593	0.417	1.010
71										0.593	0.417	1.011
72										0.593	0.417	1.011
73										0.594	0.418	1.011
74										0.594	0.418	1.012
75										0.594	0.418	1.012
76										0.594	0.419	1.012
77										0.594	0.419	1.012
78										0.594	0.419	1.013
79										0.594	0.419	1.013
80										0.594	0.419	1.013
81										0.594	0.420	1.013

82		[redacted]			[redacted]			[redacted]		0.594	0.420	1.013
83										0.594	0.420	1.014
84										0.594	0.420	1.014
85										0.594	0.420	1.014
86										0.594	0.420	1.014
87										0.594	0.420	1.014
88										0.594	0.421	1.014
89										0.594	0.421	1.014
90										0.594	0.421	1.014
91										0.594	0.421	1.014
92										0.594	0.421	1.015
93										0.594	0.421	1.015
94										0.594	0.421	1.015
95										0.594	0.421	1.015
96										0.594	0.421	1.015
97										0.594	0.421	1.015
98										0.594	0.421	1.015
99										0.594	0.421	1.015
100										0.594	0.421	1.015
101										0.594	0.421	1.015
102										0.594	0.421	1.015
103										0.594	0.421	1.015
104										0.594	0.421	1.015
105										0.594	0.421	1.015
106										0.594	0.422	1.015
107										0.594	0.422	1.015
108										0.594	0.422	1.015
109										0.594	0.422	1.015
110										0.594	0.422	1.015
111										0.594	0.422	1.015
112										0.594	0.422	1.015
113										0.594	0.422	1.015
114										0.594	0.422	1.015
115										0.594	0.422	1.015
116										0.594	0.422	1.015
117										0.594	0.422	1.015
118										0.594	0.422	1.015
119										0.594	0.422	1.015
120										0.594	0.422	1.015

6.7.4 Please indicate the life years and QALYs accrued for each clinical outcome listed for each comparator. For outcomes that are a combination of other states, please present disaggregated results.

Table 59: Model outputs by clinical outcomes - erlotinib

Outcome	LY	QALY	Cost (£)

Progression-free survival	[redacted]	[redacted]	[redacted]
Post-progression survival	[redacted]	[redacted]	[redacted]
Overall survival	[redacted]	[redacted]	[redacted]
LY, life years; QALY, quality-adjusted life year			

Table 60: Model outputs by clinical outcomes – gefitinib

Outcome	LY	QALY	Cost (£)
Progression-free survival	0.905	0.594	£11,860
Post-progression survival	0.891	0.422	£4,186
Overall survival	1.796	1.015	£16,046
LY, life years; QALY, quality-adjusted life year			

6.7.5 Please provide details of the disaggregated incremental QALYs and costs by health state, and of resource use predicted by the model by category of cost. Suggested formats are presented below.

Table 61: Summary of QALY gain by health state

Health state	QALY (erlotinib)	QALY (gefitinib)	Increment	Absolute increment	% absolute increment
PFS	[redacted]	0.59	[redacted]	[redacted]	[redacted]
PD	[redacted]	0.42	[redacted]	[redacted]	[redacted]
Total	[redacted]	1.02	[redacted]	[redacted]	[redacted]
QALY, quality-adjusted life year Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee					

Table 62: Summary of costs by health state

Health state	Cost (erlotinib)	Cost (gefitinib)	Increment	Absolute increment	% absolute increment
PFS	[redacted]	11,860.26	[redacted]	[redacted]	[redacted]
PD	[redacted]	4,185.75	[redacted]	[redacted]	[redacted]
Total	[redacted]	16,046.01	[redacted]	[redacted]	[redacted]
Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee					

Table 63: Summary of predicted resource use by category of cost

Unit Cost	Cost (erlotinib)	Cost (gefitinib)	Increment	Absolute increment	% absolute increment
Drug	[redacted]	£9,300	[redacted]	[redacted]	[redacted]

Pharmacy		[redacted]		£116		[redacted]			[redacted]			[redacted]	
AEs		[redacted]		£36		[redacted]			[redacted]			[redacted]	
PAS admin		[redacted]		£438		[redacted]			[redacted]			[redacted]	
PFS BSC		[redacted]		£1,970		[redacted]			[redacted]			[redacted]	
PD BSC		[redacted]		£1,711		[redacted]			[redacted]			[redacted]	
Terminal BSC		[redacted]		£2,475		[redacted]			[redacted]			[redacted]	
Total		[redacted]		£16,046		[redacted]			[redacted]			[redacted]	
Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee													

Base-case analysis

6.7.6 Please present your results in the following table. List interventions and comparator(s) from least to most expensive and present ICERs in comparison with baseline (usually standard care) and then incremental analysis ranking technologies in terms of dominance and extended dominance.

Table 64: Base-case results

Technologies	Total costs (£)	Total LYG	Total QALYs	Inc. costs (£)	Inc. LYG	Inc. QALYs	ICER (£) versus baseline (QALYs)	ICER (£) incremental (QALYs)
Gefitinib	£16,046	1.796	1.015					
Erlotinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£48,961	£48,961
ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years								

Cost per LYG = £36,410.

Sensitivity analyses

6.7.7 Please present results of deterministic sensitivity analysis. Consider the use of tornado diagrams.

See the tables and figures below.

Table 65: The impact of the PAS upon the ICER

Scenario	Description	ICER
1	BNF62 List Price	£74,300

2	14.5% discount (i.e. discount agreed in NICE TA162)	£48,961

Table 66: Parameters varied in deterministic sensitivity analysis

Parameter	Base-Case Value	Low Value	High Value		Base-Case ICER	Low Value ICER	High Value ICER
Transition Probabilities							
Monthly probability of disease progression after month 16 (erlotinib) – note: KM used before this point in time.	0.085977	-10%	+10%		£48,961	£42,527	£56,090
Monthly probability of disease progression after month 16 (gefitinib) - note: indirect PFS HR adjusted KM used before this point in time.	0.104567	-10%	+10%		£48,961	£54,253	£45,360
Monthly probability of death in PFS (both erlotinib and gefitinib)	0.014206	-10%	+10%		£48,961	£48,351	£49,587
Monthly probability of death in PD (both erlotinib and gefitinib)	0.075719	-10%	+10%		£48,961	£49,794	£48,300
Utility Values							

PFS (Stable Disease)	0.6532	0.6096 (Lower confidence interval)	0.6968 (Upper confidence interval)	£48,961	£52,008	£46,251
PFS (Response dummy variable)	0.0193	0.0065 (Lower confidence interval)	0.0321 (Upper confidence interval)	£48,961	£51,517	£46,646
Disutility of Rash	-0.0325	-0.0554 (Lower confidence interval)	-0.0095 (Upper confidence interval)	£48,961	£49,391	£48,537
Disutility of Diarrhoea	-0.0468	-0.0772, (Lower confidence interval)	-0.0164 (Upper confidence interval)	£48,961	£49,091	£48,831

PD (progression dummy variable disutility relative to PFS SD baseline)	-0.1798	-0.2223 (Lower confidence interval)	-0.1373 (Upper confidence interval)	£48,961	£48,236	£49,707
Resultant PFS Values	PFS erlotinib = 0.661 PFS gefitinib = 0.656	Gefitinib PFS utility (0.656) applied for gefitinib and erlotinib	Erlotinib PFS utility (0.661) applied for gefitinib and erlotinib	£48,961	£51,709	£51,277
Costs						
Pharmacy costs per pack of erlotinib/gefitinib dispensed	£13	£6.63 (Lower confidence interval if standard error = 1/4 base case value (assumption))	£19.37 (Upper confidence interval if standard error = 1/4 base case value	£48,961	£48,860	£49,091

			(assumption))			
Monthly PFS BSC Cost (including monitoring)	£181.46	£92.54 (Lower confidence interval if standard error = 1/4 base case value (assumption))	£270.38 (Upper confidence interval if standard error = 1/4 base case value (assumption))	£48,961	£47,149	£50,772
Monthly PD BSC Cost	£160.06	£81.63 (Lower confidence interval if standard error = 1/4 base case value (assumption))	£238.49 (Upper confidence interval if standard error = 1/4 base case value (assumption))	£48,961	£49,239	£48,628

Terminal Care Cost	£2,588.25	£1,320.01 (Lower confidence interval if standard error = 1/4 base case value (assumption))	£3,856.49 (Upper confidence interval if standard error = 1/4 base case value (assumption))		£48,961	£49,021	£48,900
Gefitinib per patient PAS administration cost	£70 one off cost, £35 per month on-going costs	£35 one off cost, £17.50 per month on-going costs	£140 one off cost, £70 per month on-going costs		£48,961	£51,291	£44,299
Cost of grade 3/4 Rash	£116	£59.16	£172.84		£48,961	£48,942	£48,979
Cost of grade 3/4 Diarrhoea	£867	£442.17	£1,291.83		£48,961	£48,951	£48,970
General Parameters							

Time Horizon	10 years	5 years	20 years	£48,961	£51,812	£49,926
Costs Discount Rate	3.5%	0%	6%	£48,961	£50,759	£47,784
Health Outcomes Discount Rate	3.5%	0%	6%	£48,961	£45,810	£51,188
Both Discount Rates	3.5%	0%	6%	£48,961	£47,493	£49,957

Figure 59: Tornado Diagram

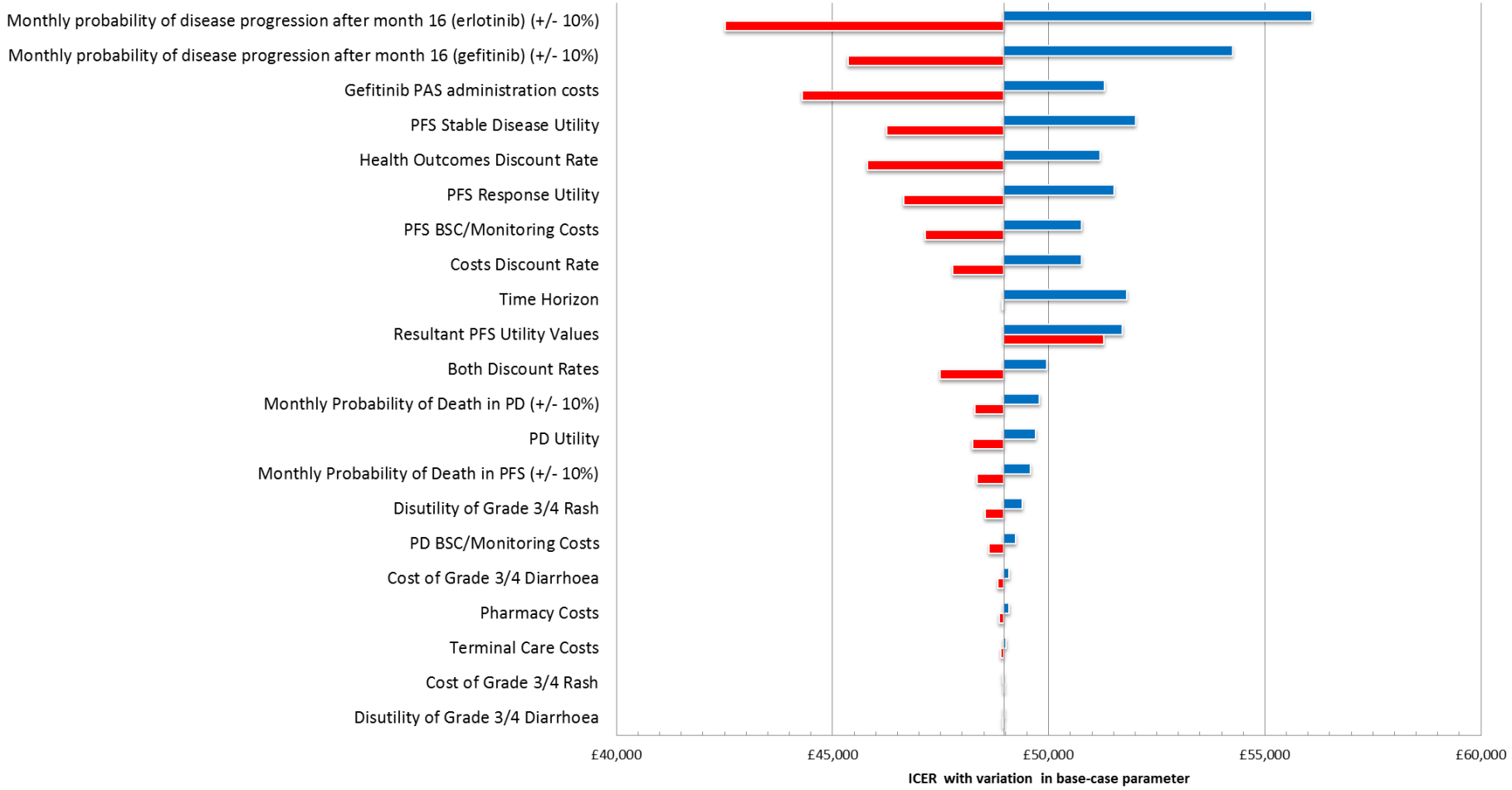


Table 67: Relative efficacy of erlotinib and gefitinib ICERs

Scenario	Description	PFS HR (erlotinib vs gefitinib)	ICER
1	Base-case (EURTAC vs Ku et al)	0.82	£48,961
2	OPTIMAL vs Ku et al	0.36	£23,952
3	Random Effects (RE) pooling (EURTAC/OPTIMAL RE pooling vs Ku et al)	0.56	£26,686
4	Fixed Effects (FE) pooling (EURTAC/OPTIMAL FE pooling vs Ku et al)	0.58	£27,362

Table 68: Proportion of patients 'activating' gefitinib PAS ICERs

Scenario	Description	ICER
1	EURTAC erlotinib 'time to last dose' curve 3 month value with indirect PFS HR applied (0.82)	£48,961
2	EURTAC erlotinib PFS curve 3 month value with indirect PFS HR applied (0.82)	£37,152
3	IPASS gefitinib PFS curve 3 month value (95%)	£24,599
4	100% of patients 'activate' the PAS	£18,109

Table 69: Point of transition from observed PFS KM Curve to modeled 'tail' ICERs

Scenario	Description	ICER
1	Base-Case (After Month 16)	£48,961
2	After Month 5	£48,119
3	After Month 21	£35,646
4	After Month 30	£31,694

Table 70: Point of transition from observed 'Time to last dose' erlotinib KM Curve to modeled 'tail'

Scenario	Description	ICER
1	Base-Case (After Day 300)	£48,961
2	After Day 150	£45,156
3	After Day 540	£48,677
4	After Day 600	£51,839

When the comparison of OPTIMAL vs IPASS/First-SIGNAL/WJTOG3405/NEJGSG002 was combined with using the indirect gefitinib PFS curve to determine the proportion of gefitinib patients the PAS payment was required for (compared to the use of the indirect 'time to last dose curve' used in the base-case) this ICER fell to £18,291.

6.7.8 Please present the results of a PSA, and include scatter plots and cost-effectiveness acceptability curves.

2,500 simulations were conducted in order to derive the mean ICER of erlotinib vs gefitinib in this setting. These simulations were utilised to produce the scatter-plot and cost-effectiveness acceptability curves presented below.

Table 71: Probabilistic mean results

Technologies	Total costs (£)	Total LYG	Total QALYs	Inc. costs (£)	Inc. LYG	Inc. QALYs	ICER (£) versus baseline (QALYs)	ICER (£) incremental (QALYs)
Gefitinib	[redacted]	[redacted]	[redacted]					
Erlotinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£57,850	£57,850
ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years								

Figure 60: PSA Scatter-plot erlotinib vs gefitinib (red line = £30k/QALY)

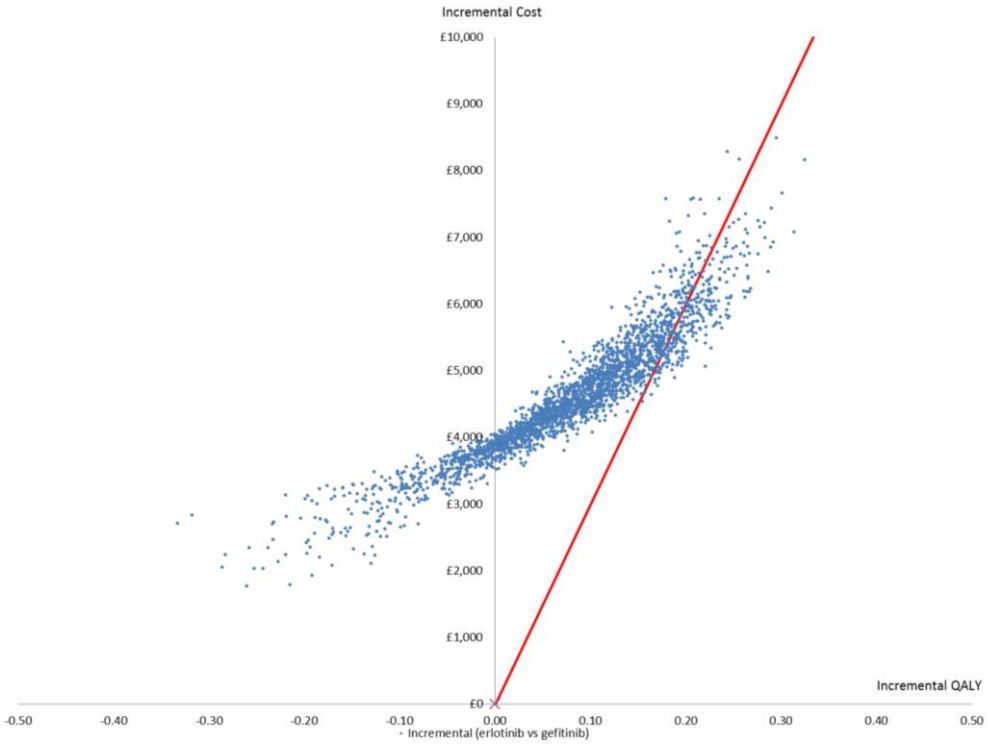
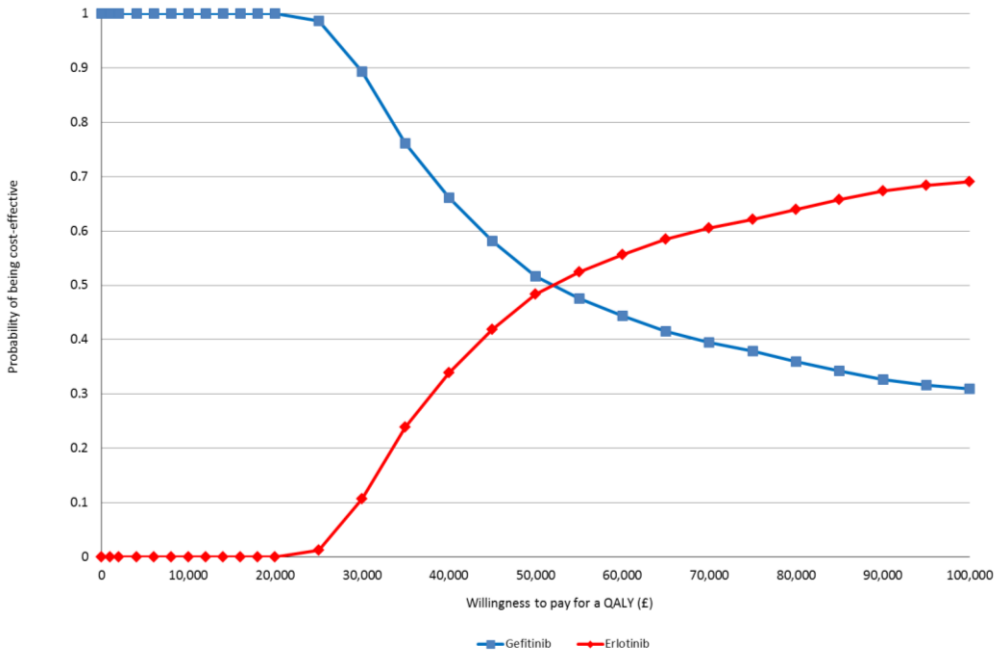


Figure 61: Cost Effectiveness Acceptability Curves



At a threshold of £20,000/QALY erlotinib would be considered cost-effective in 0% of simulations conducted (with gefitinib cost-effective in 100%).

At a threshold of £25,000/QALY erlotinib would be considered cost-effective in 1.28% of simulations (with gefitinib cost-effective in 98.72%).

At a threshold of £30,000/QALY erlotinib would be considered cost-effective in 10.72% of simulations (with gefitinib cost-effective in 89.28%).

6.7.9 Please present the results of scenario analysis. Include details of structural sensitivity analysis.

See above.

6.7.10 What were the main findings of each of the sensitivity analyses?

The sensitivity analyses undertaken indicate that:

- The ICER is sensitive to the indirect comparison of erlotinib and gefitinib used in the model. The use of a comparison of OPTIMAL vs the four gefitinib studies or a pooling of EURTAC/OPTIMAL (either random or fixed effects) vs the four gefitinib studies resulted in the base case ICER falling from £48,961 to around £25,000/QALY gained.

- The more of the observed PFS data that is used in the model the lower the ICER becomes. If the transition from the observed PFS KM data to the modelled tail is moved from after month 16 (as in the base-case) to after month 30 the base-case ICER drops to around £31,000/QALY

- The model is extremely sensitive to the assumed proportion of patients for whom the gefitinib PAS payment is required. Whilst the base-case utilises dosing data from EURTAC (with the indirect PFS HR applied to PFS applied to the EURTAC dosing data) if alternative methods are used (i.e. using the indirect PFS curve directly, or using the IPASS PFS curve) the ICER drops sizeably to £37,152 and £24,599 respectively.

- Despite the use of the most-conservative of the quantitative indirect comparisons possible given the data available (PFS HR of 0.82 {0.45, 1.26}) erlotinib produced more QALYs than gefitinib in 83% of simulations

In light of the above it appears that the current base-case ICER should be regarded as conservative. If the use of EURTAC vs Ku et al is biased against erlotinib then the base-case ICER will be lower than £48,961.

However given the results produced it appears unlikely that, without modification to the base-case assumptions, or an alteration of the 14.5% discount PAS included in this submission, erlotinib will be considered a cost-effective use of NHS resources in the first line treatment of EGFR M+ patients.

6.7.11 What are the key drivers of the cost-effectiveness results?

The key drivers of the cost-effectiveness results are the indirect comparison of erlotinib and gefitinib and the proportion of patients for whom the gefitinib fixed PAS payment is required.

6.8 Validation

6.8.1 Please describe the methods used to validate and quality assure the model. Provide references to the results produced and cross-reference to evidence identified in the clinical, quality of life and resources sections.

The model was validated by a Health Economist not directly involved in the development of this submission. They reviewed the face validity of the model's response to changes in parameter inputs, compared the modelled erlotinib PFS survival curves with those observed in the EURTAC RCT and assessed the model for logical errors.

Following review it was found that the cost of pharmacy dispensing of erlotinib had erroneously been converted to a monthly cost (rather than 30 day cost) prior to application using the 'time to last dose' curve (i.e. £13.90 rather than £13 had been applied). This was amended prior to the finalisation of the submission.

In addition it was noted that the monthly post-progression to death hazard derived from the EURTAC RCT had been applied directly in the model as if it were a probability. Following this review the hazard was converted into probability and then applied correctly within the model.

6.9 Subgroup analysis

For many technologies, the capacity to benefit from treatment will differ for patients with differing characteristics. This should be explored as part of the reference-case analysis by providing separate estimates of clinical and cost effectiveness for each relevant subgroup of patients.

This section should be read in conjunction with NICE's 'Guide to the methods of technology appraisal', section 5.10.

Types of subgroups that are not considered relevant are those based solely on the following factors.

- Individual utilities for health states and patient preference.
- Subgroups based solely on differential treatment costs for individuals according to their social characteristics.
- Subgroups specified in relation to the costs of providing treatment in different geographical locations within the UK (for example, when the costs of facilities available for providing the technology vary according to location).

6.9.1 Please specify whether analysis of subgroups was undertaken and how these subgroups were identified. Were they identified on the basis of an a priori expectation of differential clinical or cost effectiveness due to known, biologically plausible, mechanisms, social characteristics or other clearly justified factors? Cross-reference the response to section 5.3.7.

No subgroups were considered (as per the scope of this appraisal).

6.9.2 Please clearly define the characteristics of patients in the subgroup.

N/A.

6.9.3 Please describe how the statistical analysis was undertaken.

N/A.

6.9.4 What were the results of the subgroup analysis/analyses, if conducted? Please present results in a similar table as in section 6.7.6 (Base-case analysis).

N/A.

6.9.5 Were any obvious subgroups not considered? If so, which ones, and why were they not considered? Please refer to the subgroups identified in the decision problem in section 4.

N/A.

6.10 Interpretation of economic evidence

6.10.1 Are the results from this economic evaluation consistent with the published economic literature? If not, why do the results from this evaluation differ, and why should the results in the submission be given more credence than those in the published literature?

There is currently no published literature on the cost effectiveness of erlotinib in the first line treatment of EGFR M+ mNSCLC patients.

6.10.2 Is the economic evaluation relevant to all groups of patients who could potentially use the technology as identified in the decision problem in section 4?

Yes.

6.10.3 What are the main strengths and weaknesses of the evaluation? How might these affect the interpretation of the results?

Strengths

1. The model is based upon a high quality RCT conducted in a population representative of Caucasian patients in England and Wales (the EURTAC RCT)

2. All extrapolation within the model is based upon assessment of the cumulative hazard plots associated with each time to event curve and utilises as much of the reliable observed data as possible (as per the method followed by LRiG is many recent NICE oncology technology appraisals)

3. The model inputs have (almost entirely) been utilised in previous NICE appraisals of mNSCLC technologies (NICE TA227, TA192, TA190, TA181)

4. The model includes the cost of erlotinib wastage

5. The base-case is based upon the most-conservative of the indirect comparisons that could be conducted given the data available and is likely to be biased against erlotinib as gefitinib has only be studied in East-Asian patients (which may perform better when treated with EGFR TKIs than Caucasian patients (as indicated by the heterogeneity observed between the EURTAC and OPTIMAL studies)

6. Extensive sensitivity analyses have been conducted across a wide range of parameters subject to uncertainty

Weaknesses

1. There is no randomised data on the efficacy of gefitinib in a Caucasian EGFR M+ mNSCLC population and there appears to be differential treatment effects for EGFR TKIs depending upon whether or not a patient is Asian or European. The model is therefore reliant upon a biased comparison of erlotinib and gefitinib (albeit biased against erlotinib)

2. The model is reliant upon a simulated estimate of the proportion of gefitinib patients for whom the PAS fixed payment is required. There is likely to be real-world data on the proportion of gefitinib patients for whom this payment is required in UK clinical practice but this information is not available to Roche.

Interpretation of the evidence

The above strengths and weaknesses indicate that the modelled base-case is likely to be conservative towards the cost-effectiveness of erlotinib in this setting.

6.10.4 What further analyses could be undertaken to enhance the robustness/completeness of the results?

Ideally real-world data on the proportion of patients ‘activating’ the gefitinib PAS fixed payment would be incorporated into the model. This information is not publically available and so cannot (currently) be included in the submission/model.

Section C – Implementation

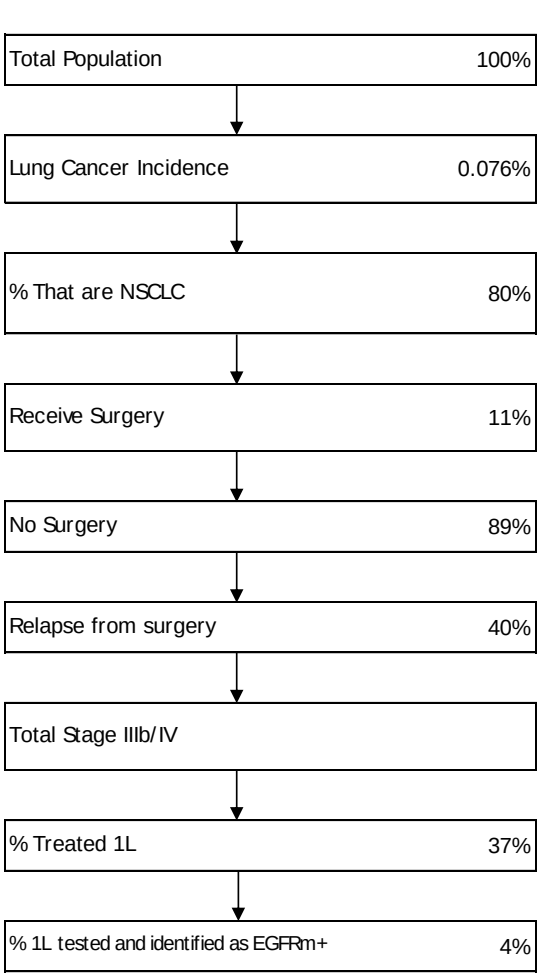
7 Assessment of factors relevant to the NHS and other parties

The purpose of this section is to provide an analysis of any factors relevant to the NHS and other parties that may fall outside the remit of the assessments of clinical effectiveness and cost effectiveness. This will allow the subsequent evaluation of the budget impact analysis. Such factors might include issues relating to service organisation and provision, resource allocation and equity, societal or ethical issues, plus any impact on patients or carers.

7.1 How many patients are eligible for treatment in England and Wales? Present results for the full marketing authorisation/CE marking and for any subgroups considered. Also present results for the subsequent 5 years.

See the algorithm below.

First line EGFR M+ mNSCLC eligible patient population algorithm:



	Reference
55,240,500	1. ONS Mid-year population figure England/Wales (http://www.statistics.gov.uk/statbase/product.asp?vlnk=15106)
41,872	2) CRUK 2008 - UK crude incidence - http://info.cancerresearchuk.org/cancerstats/types/lung/incidence/
33,498	3) Cancer Research UK. Lung cancer - UK incidence statistics: Histology Paragraph http://info.cancerresearchuk.org/cancerstats/types/lung/incidence/ (Accessed December 2010)
3,584	4) National Lung Cancer Audit (NLCA) Infiormation Sheet. http://www.ic.nhs.uk/services/national-clinical-audit-support-programme-ncasp/audit-reports/lung-cancer (Accessed December 09).
29,914	5) Calculation: Remaining after surgery (32,495 minus 3,477)
1,434	6) Cancer Research UK. Lung cancer - symptoms and treatment. http://info.cancerresearchuk.org/cancerstats/types/lung/symptomsandtreatment/ (Accessed
31,347	7) Calculation: Assume that patients not receiving surgery (29,018) or relapsing after surgey (1,391) are advanced (IIIB/IV NSCLC)
11,504	8) Roche Data on File: RXUKDONF00037
418	9) 11% EGFR M+ (Cappuzzo et al Lancet 2010) of which 55% are tested (internal estimate) and 60% have adequate tissue sample (internal estimate)

418 patients are estimated to eligible for treatment with erlotinib in year 1. Assuming a population growth of 0.5% per year, this figure grows to 420 in year 2, 422 in year 3, 424 in year 4 and 426 in year 5.

Table 72: Eligible Population Figures

Year	2012	2013	2014	2015	2016
Eligible Patient Pool	418	420	422	424	426

7.2 What assumption(s) were made about current treatment options and uptake of technologies?

It was assumed that 100% of patients are currently receiving gefitinib.

7.3 What assumption(s) were made about market share (when relevant)?

As gefitinib has not demonstrated efficacy in Caucasian EGFR M+ patients in a phase 3 RCT (which erlotinib has), cannot be down-dosed to allow a patients treatment to be tailored to their disease (which erlotinib can) and requires the use of a complex PAS in order to prescribe (which erlotinib does not) we believe upon NICE approval uptake of erlotinib in the first line treatment of EGFR M+ mNSCLC patients will be strong.

Table 73: Market Share Assumptions

Year	2012	2013	2014	2015	2016
Erlotinib Market Share	30%	50%	60%	70%	75%
Gefitinib Market Share	70%	50%	40%	30%	25%

7.4 In addition to technology costs, please consider other significant costs associated with treatment that may be of interest to commissioners (for example, procedure codes and programme budget planning).

The budget impact includes all relevant costs as submitted in the economic model.

7.5 What unit costs were assumed? How were these calculated? If unit costs used in health economic modelling were not based on national reference costs or the PbR tariff, which HRGs reflected activity?

Unit costs are calculated as per the economic model.

7.6 Were there any estimates of resource savings? If so, what were they?

The budget impact model considers the reduced administration costs associated with the erlotinib PAS (a straight discount) compared to gefitinib PAS (a complex scheme requiring registration and tracking of patients).

7.7 What is the estimated annual budget impact for the NHS in England and Wales?

Table 74: Budget Impact of approval

Year	2012	2013	2014	2015	2016
Eligible Population	418	420	422	424	426
Erlotinib Market Share	30%	50%	60%	70%	75%
Patients Receiving Erlotinib	125.4	210	253	297	320
Budget Impact	£577,066	£966,585	£1,165,701	£1,366,785	£1,471,734

7.8 Are there any other opportunities for resource savings or redirection of resources that it has not been possible to quantify?

Not that we are aware of.

8 References

Briggs et al (2006). Decision Modelling for Health Economic Evaluation. Oxford University Press

CRD (2008). Guidance for Undertaking Reviews in Healthcare. http://www.york.ac.uk/inst/crd/pdf/Systematic_Reviews.pdf (last accessed on 10/10/2011)

De Greve et al (2011). First-line erlotinib in advanced non-small cell lung cancer (NSCLC) carrying an activating EGFR mutation: A multicenter academic phase study in Caucasian patients (pts) (NCT00339586)—FIELT study group. J Clin Oncol 29: 2011 (suppl; abstr 7597

Dooms et al (2006). Cost–utility analysis of chemotherapy in symptomatic advanced non-small cell lung cancer. Eur Respir J 2006; 27: 895–901

Gervais et al (2011). The EURTAC (European Tarceva® vs chemotherapy) study: interim results of a phase III randomised trial of erlotinib vs chemotherapy (CT) in advanced non-small cell lung cancer (NSCLC) patients (p) with epidermal growth factor receptor (EGFR) activating mutations. Abstract 733. WCLC 2011 Meeting. Amsterdam. Holland.

Higgins et al. (2011) Cochrane Handbook for Systematic Reviews of Interventions. Version 5.1.0. 2011. http://www.cochrane-handbook.org/ (last accessed on 10/10/2011)

Hoyle M, Crathorne L, Peters J, Jones-Hughes T, Cooper C, Napier M, Tappenden P, Hyde C. (2011). The effectiveness and cost effectiveness of cetuxmab (mono- or combination therapy, bevacizumab (combination with non-oxaliplatin chemotherapy) and panitumumab (monotherapy) for the treatment of metastatic colorectal cancer after first-line chemotherapy (review of technology appraisal 150 and part review of technology appraisal 118): a systematic review and economic model. University of Exeter (Report).

Janne et al (2010). Randomized phase II trial of erlotinib (E) alone or in combination with carboplatin/paclitaxel (CP) in never or light former smokers with advanced lung adenocarcinoma: CALGB 30406. J Clin Oncol 28:15s, 2010 (suppl; abstr 7503)

Ku et al (2011). Gefitinib vs. chemotherapy as first-line therapy in advanced non-small cell lung cancer: Meta-analysis of phase III trials. Lung Cancer (in press). doi:10.1016/j.lungcan.2011.04.008

Lee et al (2009). A Randomized Phase III Study of Gefitinib (Iressa) versus Standard Chemotherapy (Gemcitabine plus Cisplatin) as a First-line Treatment for Never-smokers with Advanced or Metastatic Adenocarcinoma of the Lung: First-line Single Agent Iressa versus Gemcitabine and cisplatin Trial in Never-smokers with Adenocarcinoma of the Lung -First-SIGNAL. 13th World Congress in Lung Cancer. Seoul. South Korea. Journal Thoracic Oncology. 4(9). S283-S284.

Lee et al (2011). Comparison of the quality of life between patients with non-small-cell lung cancer and healthy controls. Qual Life Res (2011) 20:415–423

Lewis et al (2010). Cost-effectiveness of Erlotinib versus Docetaxel for Second-line Treatment of Advanced Non-small-cell Lung Cancer in the United Kingdom. The Journal of International Medical Research. 38: 9 – 21.

Maslove et al (2005). Estimation of the additional costs of chemotherapy for patients with advanced non-small cell lung cancer. Thorax 2005;60:564–569.

McNamara et al (2010). A Cost Utility Analysis on the use of Trastuzumab + Anastrozole compared to Lapatinib + Letrozole, Letrozole monotherapy or

Anastrozole monotherapy in the treatment of HER2+/Hormone Receptor Positive (HR+) Metastatic Breast Cancer (mBC) from the perspective of the UK National Health Service (NHS). Value in Health. Vol 13; No. 7, A269

Maemondo et al (2010). Gefitinib or Chemotherapy for Non–Small-Cell Lung Cancer with Mutated EGFR. N Engl J Med 2010;362:2380-8.

Millar et al. 'A service evaluation to compare secondary care resource use between XELOX and FOLFOX-6 regimens in the treatment of metastatic colorectal cancer from a UK National Health Service (NHS) perspective' Presented at ISPOR Athens. November 9th - 11th 2008.

Mitsudomi et al (2010). Gefi tinib versus cisplatin plus docetaxel in patients with non-small-cell lung cancer harbouring mutations of the epidermal growth factor receptor (WJTOG3405): an open label, randomised phase 3 trial. *Lancet Oncol* 2010; 11: 121–28

Mok et al (2009). Gefitinib or Carboplatin–Paclitaxel in Pulmonary Adenocarcinoma. N Engl J Med 2009;361:947-57.

Nafees et al. 'Health State Utilities for Non-Small Cell Lung Cancer' Health and Quality of Life Outcomes 2008, 6:84

NICE TA162: Erlotinib for the treatment of non-small cell lung cancer (2008). http://guidance.nice.org.uk/TA162 (last accessed on 10/10/2011)

NICE TA181: Pemetrexed for the first-line treatment of non-small-cell lung cancer (2009). http://guidance.nice.org.uk/TA181 (last accessed on 10/10/2011)

NICE TA190: Pemetrexed for the maintenance treatment of non-small-cell lung cancer (2010). http://guidance.nice.org.uk/TA190 (last accessed on 10/10/2011)

NICE TA192: Gefitinib for the first-line treatment of locally advanced or metastatic non-small-cell lung cancer (2010). http://guidance.nice.org.uk/TA192 (last accessed on 10/10/2011)

NICE TA226: Rituximab for the maintenance treatment of Non-Hodgkin's lymphoma cancer (2011). http://guidance.nice.org.uk/TA226 (last accessed on 10/10/2011)

NICE TA227: Erlotinib monotherapy for the maintenance treatment of non-small cell lung cancer (2011). http://guidance.nice.org.uk/TA227 (last accessed on 10/10/2011)

PSSRU 'Unit Costs of Health and Social Care 2010' http://www.pssru.ac.uk/uc/uc2010contents.htm (last accessed on 10/10/2011)

Paz-Ares et al (2010). Clinical outcomes in non-small-cell lung cancer patients with EGFR mutations: pooled analysis. J. Cell. Mol. Med. Vol 14, No 1-2, 2010 pp. 51-69.

Rosell et al (2009). Screening for Epidermal Growth Factor Receptor Mutations in Lung Cancer. N Engl J Med 2009;361:958-67.

Rosell et al (2011). Erlotinib versus chemotherapy (CT) in advanced non-small cell lung cancer (NSCLC) patients (p) with epidermal growth factor

receptor (EGFR) mutations: Interim results of the European Erlotinib Versus Chemotherapy (EURTAC) phase III randomised trial. Abstract 7503. ASCO 2011 Annual Meeting. Chicago. USA.

Scagliotti et al. (2002). Phase III Randomized Trial Comparing Three Platinum-Based Doublets in Advanced Non–Small-Cell Lung Cancer. *J Clin Oncol 20:4285-4291.*

Schiller et al. (2002). Comparison of Four Chemotherapy Regimens for Advanced Non–Small-Cell Lung Cancer. N Engl J Med 2002; 346:92-98.

Tarceva Summary of Product Charatieristics. Accessed 21 August 2011. http://www.medicines.org.uk/EMC/medicine/16781/SPC/Tarceva+25mg%2c+100mg+and+150mg+Film-Coated+Tablets/

Zhou et al (2010). Efficacy results from the randomised phase III OPTIMAL (CTONG 0802) study comparing first-line erlotinib versus carboplatin (CBDCA) plus gemcitabine (GEM), in Chinese advanced nonsmall-cell lung cancer (nsclc) patients (pts) with EGFR activating mutations. Abstract LBA 13. ECCO/ESMO 2010. Milan. Italy.

Zhou et al (2011a). Updated efficacy and quality-of-life (QoL) analyses in OPTIMAL, a phase III, randomised, open-label study of first-line erlotinib versus gemcitabine/carboplatin in patients with *EGFR*-activating mutation-positive (*EGFR* Act Mut+) advanced non-small cell lung cancer (NSCLC). Abstract 7520. ASCO Annual Meeting. Chicago. USA.

Zhou et al (2011b). Updated median PFS and analysis of quality of life (QOL) in OPTIMAL, a phase III, randomised, open-label, first line study of erlotinib vs carboplatin/gemcitabine in patients with advanced non-small cell lung cancer (NSCLC) with EGFR activating mutations. Abstract 777. WCLC 2011 Meeting. Amsterdam. Holland.

Zhou et al (2011c). Erlotinib versus chemotherapy as first-line treatment for patients with advanced *EGFR* mutation-positive non-small-cell lung cancer (OPTIMAL, CTONG-0802): a multicentre, open-label, randomised, phase 3 study. Lancet 2011. 12;735-742.

Appendices

8.1 Appendix 1

8.1.1 SPC/IFU, scientific discussion or drafts.

8.2 Appendix 2: Search strategy for section 5.1 (Identification of studies)

The following information should be provided.

8.2.1 The specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter), including at least:

- Medline
- Embase
- Medline (R) In-Process
- The Cochrane Library.

Medline (MEYY), Embase (EMYY) and Medline (R) In-Process (MEIP) were searched using DataStar. The Cochrane Library was searched using their website (http://www.thecochranelibrary.com/view/0/index.html).

8.2.2 The date on which the search was conducted.

The search was conducted on the 14/09/2011.

8.2.3 The date span of the search.

The search was not restricted by date.

8.2.4 The complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean).

DataStar was searched using the following search strategy.

	Database	Search term	Results
1	EMYY	LUNG ADJ (CANCER OR CARCINOMA) OR MNSCLC OR NSCLC	100114
2	EMYY	LUNG-NON-SMALL-CELL-CANCER.DE.	34233
3	EMYY	MUTATED OR MUTATION OR MUTATIONS OR EXON ADJ '19' OR EXON ADJ '21'	443344
4	EMYY	ADVANCED OR METASTATIC OR STAGE ADJ 3 OR STAGE ADJ '4' OR INOPERABLE	320350
5	EMYY	ERLOTINIB OR TARCEVA	9075
6	EMYY	RCT OR RANDOMISED OR RANDOMIZED	386378
7	EMYY	HUMAN=YES	8050652
8	EMYY	(1 OR 2) AND 3 AND 4 AND 5 AND 6 AND 7	88
9	MEYY	LUNG ADJ (CANCER OR CARCINOMA) OR MNSCLC OR NSCLC	68342
10	MEYY	CARCINOMA-NON-SMALL-CELL-LUNG.DE.	22360
11	MEYY	MUTATED OR MUTATION OR MUTATIONS OR EXON ADJ '19' OR EXON ADJ '21'	430378
12	MEYY	ADVANCED OR METASTATIC OR STAGE ADJ '3' OR STAGE ADJ '4' OR INOPERABLE	297678
13	MEYY	ERLOTINIB OR TARCEVA	2290
14	MEYY	RCT OR RANDOMISED OR RANDOMIZED	398622
15	MEYY	(CLINICAL-TRIALS# OR PT=CLINICAL-TRIAL#) AND HUMAN=YES	490070

16	**MEYY**	**(9 OR 10) AND 11 AND 12 AND 13 AND 14 AND 15**	**11**
17	**MEIP**	**LUNG ADJ (CANCER OR CARCINOMA) OR MNSCLC OR NSCLC**	**2780**
18	**MEIP**	**MUTATED OR MUTATION OR MUTATIONS OR EXON ADJ '19' OR EXON ADJ '21'**	**11524**
19	**MEIP**	**ADVANCED OR METASTATIC OR STAGE ADJ '3' OR STAGE ADJ '4' OR INOPERABLE**	**12767**
20	**MEIP**	**ERLOTINIB OR TARCEVA**	**173**
21	**MEIP**	**RCT OR RANDOMISED OR RANDOMIZED**	**11128**
22	**MEIP**	**17 AND 18 AND 19 AND 20 AND 21**	**5**
23	**EMYY MEYY MEIP** [all]	**combined sets 8, 16, 22**	**104**
24	**EMYY MEYY MEIP** [all]	**dropped duplicates from 23**	**12**
25	**EMYY MEYY MEIP** [all]	**unique records from 23**	**92**

The Cochrane Library was searched using the following strategy:

5. erlotinib OR Tarceva

6. lung cancer OR mNSCLC OR NSCLC

7. metastatic OR Locally Advanced OR Stage 3 OR Stage 4 OR Inoperable

8. Mutation OR Mutated OR Mutant OR Mutations or Exon 19 OR Exon 21

9. 1 AND 2 AND 3 AND 4 AND 5

8.2.5 Details of any additional searches, such as searches of company databases (include a description of each database).

Following the initial searches internal experts on the erlotinib clinical trial program were questioned to ensure all available data had been identified. This questioning identified that the EURTAC RCT had been not been found via searching as it has yet to published.

8.2.6 The inclusion and exclusion criteria.

The inclusion/exclusion criteria were pre-defined prior to searching. These criteria are presented below.

	Inclusion Criteria	**Exclusion Criteria**
Population	Previously untreated mNSCLC patients whose tumours harbour an activating mutation of the EGFR tyrosine kinase	Early NSCLC patients, SCLC patients, patients previously treated for their mNSCLC (i.e. maintenance treatment, second and later line treatment), patients with tumours that do not contain a mutation of the EGFR tyrosine kinase or have unknown EGFR mutation status non-mNSCLC
Interventions	Erlotinib monotherapy	Erlotinib combination therapy, non-erlotinib therapy
Outcomes	Progression Free Survival, Overall Survival, Adverse Events	-
Study Design	Randomised controlled trials	Observational data, registry analyses, single arm studies
Language Restrictions	Available in English	Not available in English

8.2.7 The data abstraction strategy.

The search was conducted using MEYY, MEIP, EMYY and the Cochrane Library using the search strategies identified above. Duplicates were then

removed and the titles/abstracts of the individual records identified assessed against the pre-defined inclusion/exclusion criteria by a single reviewer. Where a record was deemed potentially relevant it was retrieved and assessed more fully against the pre-defined inclusion/exclusion criteria. As only two RCTs were identified a formal data extraction process was not undertaken and the studies identified were simply assessed for adherence to the inclusion/exclusion criteria by a single reviewer.

8.3 Appendix 3: Quality assessment of RCT(s) (section 5.4)

8.3.1 A suggested format for the quality assessment of RCT(s) is shown below.

Study ID or acronym: EURTAC		
Study question	**How is the question addressed in the study?**	**Grade (yes/no/not clear/N/A)**
Was randomisation carried out appropriately?	Yes. Patients were randomized by means of fax to the CRO to receive either erlotinib or platinum doublet chemotherapy. The choice of platinum doublet chemotherapy was at the discretion of the investigator and was selected according to what was in the patients' best interest. A block randomization with a block size of 2 was used. The randomisation list was kept by the CRO. In order to minimize the bias introduced by knowledge of treatment group assignment, the treatment code was not be available to any person from Roche Biostatistics involved in the study prior to database closure.	Yes
Was the concealment of treatment allocation adequate?	Not applicable as EURTAC was an open-label study	N/A
Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?	Yes. Randomisation was stratified by the following factors: • According to ECOG performance status three different groups were established: ECOG = 0, ECOG = 1 and ECOG = 2 • Deletion in exon 19 vs. mutation in exon 21 L858R	Yes
Were the care providers, participants and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?	No – see above for details of blinding.	N/A
Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?	No	N/A
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No	N/A

Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes. This was the primary analysis defined within the statistical analysis plan and in the DRAM.	Yes

8.4 Appendix 4: Search strategy for section 5.7 (Indirect and mixed treatment comparisons)

The following information should be provided.

8.4.1 The specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter), including at least:

- Medline
- Embase
- Medline (R) In-Process
- The Cochrane Library.

Medline (MEYY), Embase (EMYY) and Medline (R) In-Process (MEIP) were searched using DataStar. The Cochrane Library was searched using their website (http://www.thecochranelibrary.com/view/0/index.html).

8.4.2 The date on which the search was conducted.

The search was conducted on the 15/09/2011.

8.4.3 The date span of the search.

The search was not restricted by date.

8.4.4 The complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean).

No.	Database	Search term	Results
CP		[Clipboard]	0
1	EMYY	LUNG ADJ (CANCER OR CARCINOMA) OR MNSCLC OR NSCLC	100138
2	EMYY	LUNG-NON-SMALL-CELL-CANCER.DE.	34239
3	EMYY	MUTATED OR MUTATION OR MUTATIONS OR EXON ADJ '19' OR EXON ADJ '21'	443453
4	EMYY	ADVANCED OR METASTATIC OR STAGE ADJ '3' OR STAGE ADJ '4' OR INOPERABLE	324187
5	EMYY	Gefitinib OR Iressa	10844
6	EMYY	RCT OR RANDOMISED OR RANDOMIZED	386517
7	EMYY	HUMAN=YES	8052909
8	EMYY	(1 OR 2) AND 3 AND 4 AND 5 AND 6 AND 7	88
9	MEYY	LUNG ADJ (CANCER OR CARCINOMA) OR MNSCLC OR NSCLC	68390
10	MEYY	CARCINOMA-NON-SMALL-CELL-LUNG.DE.	22367
11	MEYY	MUTATED OR MUTATION OR MUTATIONS OR EXON ADJ '19' OR EXON ADJ '21'	430498
12	MEYY	ADVANCED OR METASTATIC OR STAGE ADJ '3' OR STAGE ADJ '4' OR INOPERABLE	297799
13	MEYY	Gefitinib OR Iressa	3310
14	MEYY	RCT OR RANDOMISED OR RANDOMIZED	398676
15	MEYY	(CLINICAL-TRIALS# OR PT=CLINICAL-TRIAL#) AND HUMAN=YES	490114
16	MEYY	(9 OR 10) AND 11 AND 12 AND 13 AND 14 AND 15	10
17	MEIP	LUNG ADJ (CANCER OR CARCINOMA) OR MNSCLC OR NSCLC	2793
18	MEIP	MUTATED OR MUTATION OR MUTATIONS OR EXON ADJ '19' OR EXON ADJ '21'	11554

19	**MEIP**	**ADVANCED OR METASTATIC OR STAGE ADJ '3' OR STAGE ADJ '4' OR INOPERABLE**	**12801**
20	**MEIP**	**Gefitinib OR Iressa**	**172**
21	**MEIP**	**RCT OR RANDOMISED OR RANDOMIZED**	**11149**
22	**MEIP**	**17 AND 18 AND 19 AND 20 AND 21**	**2**
23	**EMYY MEYY MEIP** [all]	**combined sets 8, 16, 22**	**100**
24	**EMYY MEYY MEIP** [all]	**dropped duplicates from 23**	**9**
25	**EMYY MEYY MEIP** [all]	**unique records from 23**	**91**

The Cochrane Library was searched using the following strategy:

10. gefitinib OR Iressa

11. lung cancer OR mNSCLC OR NSCLC

12. metastatic OR Locally Advanced OR Stage 3 OR Stage 4 OR Inoperable

13. Mutation OR Mutated OR Mutant OR Mutations or Exon 19 OR Exon 21

14. 1 AND 2 AND 3 AND 4 AND 5

8.4.5 Details of any additional searches (for example, searches of company databases [include a description of each database]).

Not applicable.

8.4.6 The inclusion and exclusion criteria.

	Inclusion Criteria	**Exclusion Criteria**
Population	Previously untreated mNSCLC patients whose tumours harbour an activating mutation of the EGFR tyrosine kinase	Early NSCLC patients, SCLC patients, patients previously treated for their mNSCLC (i.e. maintenance treatment, second and later line treatment), patients with tumours that do not contain a mutation of the EGFR tyrosine kinase or have unknown EGFR mutation status non-mNSCLC
Interventions	Gefitinib monotherapy	Gefitinib combination therapy, non-grlotinib therapy
Outcomes	Progression Free Survival, Overall Survival, Adverse Events	-
Study Design	Randomised controlled trials	Observational data, registry analyses, single arm studies
Language Restrictions	Available in English	Not available in English

8.4.7 The data abstraction strategy.

The search was conducted using MEYY, MEIP, EMYY and the Cochrane Library using the search strategies identified above. Duplicates were then removed and the titles/abstracts of the individual records identified assessed against the pre-defined inclusion/exclusion criteria by a single reviewer.

Where a record was deemed potentially relevant it was retrieved and assessed more fully against the pre-defined inclusion/exclusion criteria. As only two RCTs were identified a formal data extraction process was not undertaken and the studies identified were simply assessed for adherence to the inclusion/exclusion criteria by a single reviewer.

8.5 Appendix 5: Quality assessment of comparator RCT(s) in section 5.7 (Indirect and mixed treatment comparisons)

8.5.1 A suggested format for the quality assessment of RCT(s) is shown below.

9 Study ID or acronym: IPASS		
Study question	**How is the question addressed in the study?**	**Grade (yes/no/not clear/N/A)**
Was randomisation carried out appropriately?	Yes. Patients were randomly assigned, in a 1:1 ratio. Randomisation was performed with the use of dynamic balancing.	(yes)
Was the concealment of treatment allocation adequate?	N/A. IPASS was an open-label study.	(N/A)
Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?	Yes. For the ITT population, randomisation was performed with the use of dynamic balancing with respect to performance status, as assessed by the World Health Organization (WHO) performance scale measuring activity (0 or 1, or 2 on a scale of 0 to 4, with lower numbers indicating a higher degree of activity); smoking status (non-smoker or former light smoker); sex; and center.	(yes)
Were the care providers, participants and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?	No. IPASS was an open label study.	(no)

Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?	No. IPASS used dynamic balancing with respect to performance status, as assessed by the World Health Organization (WHO) performance scale measuring activity (0 or 1, or 2 on a scale of 0 to 4, with lower numbers indicating a higher degree of activity); smoking status (non-smoker or former light smoker); sex; and center.	(no)
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No.	(no)
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes.	(yes)

Study ID or acronym: WJTOG3405		
Study question	**How is the question addressed in the study?**	**Grade (yes/no/not clear/N/A)**
Was randomisation carried out appropriately?	A desktop computer programmed for the minimisation method was used. Patient allocation was concealed from the investigator.	(yes)
Was the concealment of treatment allocation adequate?	Yes (for treatment allocation. WJTOG3405 was however an open-label study.	(N/A)
Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?	Yes. Stratification factors were: institution; postoperative adjuvant chemotherapy (presence *vs* absence); interval between surgery and recurrence (≥1 *vs* <1 year) for patients with postoperative recurrent disease; and institution; stage (IIIB *vs* IV); and sex (male *vs* female) for patients with stage IIIB/IV disease.	(yes)
Were the care providers, participants and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?	No. WJTOG3405 was an open-label Study.	(no)

Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?	No. Stratification factors were: institution; postoperative adjuvant chemotherapy (presence *vs* absence); interval between surgery and recurrence (≥1 *vs* <1 year) for patients with postoperative recurrent disease; and institution; stage (IIIB *vs* IV); and sex (male *vs* female) for patients with stage IIIB/IV disease.	(no)
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No.	(no)
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes.	(yes)

Study ID or acronym: NEJGSG002		
Study question	**How is the question addressed in the study?**	**Grade (yes/no/not clear/N/A)**
Was randomisation carried out appropriately?	Unable to assess as no information provided in literature.	(yes)
Was the concealment of treatment allocation adequate?	N/A. NEJGSG002 was an open-label study.	(N/A)
Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?	Yes. Patients were stratified according to sex, clinical stage of non–small-cell lung cancer (IIIB, IV, or postoperative relapse), and institution.	(yes)
Were the care providers, participants and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?	No. NEJGSG002 was an open-label study.	(no)
Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?	No. Patients were stratified according to sex, clinical stage of non–small-cell lung cancer (IIIB, IV, or postoperative relapse), and institution.	(no)
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No.	(no)
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes.	(yes)

Study ID or acronym: First-SIGNAL		
Study question	**How is the question addressed in the study?**	**Grade (yes/no/not clear/N/A)**
Was randomisation carried out appropriately?	Yes. Unable to assess as no information provided in literature.	(yes)
Was the concealment of treatment allocation adequate?	N/A. First-SIGNAL was an open-label study.	(N/A)
Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?	Yes. Stratification factors were Female vs. Male, PS 0, 1 vs. 2, Stage IIIb vs. IV.	(yes)
Were the care providers, participants and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?	No. First-SIGNAL was an open-label study.	(no)
Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?	No. Stratification factors were Female vs. Male, PS 0, 1 vs. 2, Stage IIIb vs. IV.	(no)
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No.	(no)
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes.	(yes)

Appendix 6: Search strategy for section 5.8 (Non-RCT evidence)

The following information should be provided.

9.1.1 The specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter), including at least:

- Medline
- Embase
- Medline (R) In-Process
- The Cochrane Library.

Not Applicable.

9.1.2 The date on which the search was conducted.

Not Applicable.

9.1.3 The date span of the search.

Not Applicable.

9.1.4 The complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean).

Not Applicable.

9.1.5 Details of any additional searches (for example, searches of company databases [include a description of each database]).

Not Applicable.

9.1.6 The inclusion and exclusion criteria.

Not Applicable.

9.1.7 The data abstraction strategy.

Not Applicable.

9.2 Appendix 7: Quality assessment of non-RCT(s) in section 5.8 (Non-RCT evidence)

9.2.1 Please tabulate the quality assessment of each of the non-RCTs identified.

Not applicable.

9.3 Appendix 8: Search strategy for section 5.9 (Adverse events)

The following information should be provided.

9.3.1 The specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter), including at least:

- Medline
- Embase
- Medline (R) In-Process
- The Cochrane Library.

Not Applicable.

9.3.2 The date on which the search was conducted.

Not Applicable.

9.3.3 The date span of the search.

Not Applicable.

9.3.4 The complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean).

Not Applicable.

9.3.5 Details of any additional searches (for example, searches of company databases [include a description of each database]).

Not Applicable.

9.3.6 The inclusion and exclusion criteria.

Not Applicable.

9.3.7 The data abstraction strategy.

Not Applicable.

9.4 Appendix 9: Quality assessment of adverse event data in section 5.9 (Adverse events)

9.4.1 Please tabulate the quality assessment of each of the non-RCTs identified.

Not Applicable.

9.5 Appendix 10: Search strategy for cost-effectiveness studies (section 6.1)

The following information should be provided.

9.5.1 The specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter), including at least:

- Medline
- Embase

- Medline (R) In-Process
- EconLIT
- NHS EED.

Medline (MEYY), Embase (EMYY) and Medline in Process (MEIP) were searched using Dialogue Data-Star. NHS EED was searched using the University of York's 'Centre for Reviews and Dissemination' (CRD) website.

9.5.2 The date on which the search was conducted.

The search was conducted on 13/09/2011.

9.5.3 The date span of the search.

No restrictions were placed on the date-range searched.

9.5.4 The complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean).

The Dialogue Datastar search was conducted using the below search strategy:

No.	Database	Search term	Results
1	EMYY	Cost ADJ Effectiveness OR Cost ADJ Utility OR Cost ADJ Minimisation OR CEA OR CUA	99079
2	EMYY	COST-EFFECTIVENESS-ANALYSIS.DE. OR HEALTH-ECONOMICS.DE. OR ECONOMIC-EVALUATION.DE.	83708
3	EMYY	Erlotinib OR Tarceva	9070
4	EMYY	Lung ADJ Cancer OR NSCLC OR mNSCLC	87203
5	EMYY	Muta$4 OR M+	576654
6	EMYY	(1 OR 2) AND 3 AND 4 AND 5	20
7	MEYY	Cost ADJ Effectiveness OR Cost ADJ Utility OR Cost ADJ Minimisation OR CEA OR CUA	43381
8	MEYY	Economic ADJ Evaluation OR Health ADJ Economic	14708

9	MEYY	COST-BENEFIT-ANALYSIS.DE.	41990
10	MEYY	Erlotinib OR Tarceva	2287
11	MEYY	LUNG-NEOPLASMS.DE. OR CARCINOMA-NON-SMALL-CELL-LUNG.DE.	83036
12	MEYY	Lung ADJ Cancer OR NSCLC OR mNSCLC	62405
13	MEYY	Muta$4 OR M+	526727
14	MEYY	(7 OR 8 OR 9) AND 10 AND (11 OR 12) AND 13	3
15	MEIP	Cost ADJ Effectiveness OR Cost ADJ Utility OR Cost ADJ Minimisation OR CEA OR CUA	1549
16	MEIP	Economic ADJ Evaluation OR Health ADJ Economic	675
17	MEIP	Erlotinib OR Tarceva	177
18	MEIP	Lung ADJ Cancer OR NSCLC OR mNSCLC	2675
19	MEIP	Muta$4 OR M+	14221
20	MEIP	(15 OR 16) AND 17 AND 18 AND 19	0
21	EMYY MEIP MEYY [all]	combined sets 6, 14, 20	23
22	EMYY MEIP MEYY [all]	dropped duplicates from 21	1
23	EMYY MEIP MEYY [all]	unique records from 21	22

NHS EED was searched using the terms ‘erlotinib’ and ‘Tarceva’ with a Boolean ‘OR’ operator between the two terms.

9.5.5 Details of any additional searches (for example, searches of company databases [include a description of each database]).

No further searches were undertaken.

9.6 Appendix 11: Quality assessment of cost-effectiveness studies (section 6.1)

As no cost-effectiveness studies were identified this section is redundant.

9.7 Appendix 12: Search strategy for section 6.4 (Measurement and valuation of health effects)

The following information should be provided.

9.7.1 The specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter), including at least:

- Medline
- Embase
- Medline (R) In-Process
- NHS Economic Evaluation Database (NHS EED)
- EconLIT.

Dialog DataStar was used to search

Medline

Embase

Medline (R) In-Process

The Cochrane Library was used to search

NHS Economic Evaluation Database (NHS EED)

The American Economic Association was used to search

EconLIT.

9.7.2 The date on which the search was conducted.

DataStar was searched on 20th September 2011.

The Cochrane Library and The American Economic Association were searched on 27th September 2011.

9.7.3 The date span of the search.

DataStar: 1993 – 20th September 2011.

NHS EED and ECON LIT: 1993 – 27th September 2011.

9.7.4 The complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean).

No.	Database	Search term	Results
CP		[Clipboard]	0
1	EMYY	LUNG ADJ CANCER OR NSCLC	88048
2	EMYY	ADVANCED OR METASTATIC OR STAGE ADJ '3' OR STAGE ADJ '4' OR INOPERABLE	329178
3	EMYY	1 AND 2	17149
4	EMYY	QUALITY ADJ ADJUSTED ADJ LIFE ADJ YEAR OR QALY$2 OR QALIES	8789
5	EMYY	SF-36 OR SF-12 OR EQ-5D OR EQ-5D-5L OR EUROQOL	1663
6	EMYY	TIME ADJ TRADE ADJ OFF$2 OR TTO$2 OR STANDARD ADJ GAMBLE$2 OR SG$2	58193
7	EMYY	UTILITY ADJ VALUES OR UTILITY ADJ SCORES	1076
8	EMYY	3 AND (4 OR 5 OR 6 OR 7)	124
9	MEYY	LUNG ADJ CANCER OR NSCLC	62781
10	MEYY	ADVANCED OR METASTATIC OR STAGE ADJ '3' OR STAGE ADJ '4' OR INOPERABLE	299087
11	MEYY	9 AND 10	12989
12	MEYY	QUALITY ADJ ADJUSTED ADJ LIFE ADJ YEAR OR QALY$2 OR QALIES	7346
13	MEYY	SF-36 OR SF-12 OR EQ-5D OR EQ-5D-5L OR EUROQOL	1490
14	MEYY	TIME ADJ TRADE ADJ OFF$2 OR TTO$2 OR STANDARD ADJ GAMBLE$2 OR SG$2	32115
15	MEYY	UTILITY ADJ VALUES OR UTILITY ADJ SCORES	1031
16	MEYY	11 AND (12 OR 13 OR 14 OR 15)	85
17	MEIP	LUNG ADJ CANCER OR NSCLC	2680

18	**MEIP**	**ADVANCED OR METASTATIC OR STAGE ADJ '3' OR STAGE ADJ '4' OR INOPERABLE**	**12844**
19	**MEIP**	**17 AND 18**	**555**
20	**MEIP**	**QUALITY ADJ ADJUSTED ADJ LIFE ADJ YEAR OR QALY$2 OR QALIES**	**273**
21	**MEIP**	**SF-36 OR SF-12 OR EQ-5D OR EQ-5D-5L OR EUROQOL**	**109**
22	**MEIP**	**TIME ADJ TRADE ADJ OFF$2 OR TTO$2 OR STANDARD ADJ GAMBLE$2 OR SG$2**	**1349**
23	**MEIP**	**UTILITY ADJ VALUES OR UTILITY ADJ SCORES**	**58**
24	**MEIP**	**19 AND (20 OR 21 OR 22 OR 23)**	**6**
25	**EMYY MEYY MEIP** [all]	**combined sets 8, 16, 24**	**215**
26	**EMYY MEYY MEIP** [all]	**dropped duplicates from 25**	**67**
27	**EMYY MEYY MEIP** [all]	**unique records from 25**	**148**

NHS EED and ECON LIT were search on 27th September with the following strategy:

1. Lung Cancer or NSCLC
2. Advanced or Metastatic or Stage 3 or Stage 4 or Inoperable
3. Quality adjusted life year or QALY or Qalies or SF_36 or SF-12 or EQ-5D or EQ-5D-5L or Euroqol or Time trade off or Standard Gamble or Utility value or Utility Score
4. 1 and 2 and 3.

9.7.5 Details of any additional searches (for example, searches of company databases [include a description of each database]).

None.

9.7.6 The inclusion and exclusion criteria.

Inclusion Criteria	Exclusion Criteria
Metastatic or advanced lung cancer Health related quality of life QALY or quality adjusted life year Fact-b OR SF-36 OR SF-12 OR EQ-5D OR EQ-5D-5L OR EUROQOL Utilities Time Trade Off or Standard Gamble	Review of studies already included Not QoL studies No useful HRQoL/Utility values Not in metastatic/advanced setting

9.7.7 The data abstraction strategy.

An individual extracted articles as per the inclusion and exclusion criteria above. All search terms and inclusion and exclusion criteria were agreed upon before the search was conducted. The final lists of articles selected were then reviewed by a health economist experienced in advanced non-small cell lung cancer Health Technology Appraisals.

9.8 Appendix 13: Resource identification, measurement and valuation (section 6.5)

The following information should be provided.

9.8.1 The specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter), including at least:

- Medline
- Embase
- Medline (R) In-Process
- NHS EED

- EconLIT.

Dialog DataStar was used to search for

Medline

Embase

Medline (R) In-Process

The Cochrane Library was used to search for

NHS EED

The American Economic Association was used to search for

EconLIT.

9.8.2 The date on which the search was conducted.

DataStar: 20th September 2011.NHS EED and ECON LIT: 27th September 2011.

9.8.3 The date span of the search.

1993 – 20th September 2011 for Datastar

1993 – 27th September 2011 for NHS EED and ECON LIT

9.8.4 The complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean).

No.	Database	Search term	Results
CP		[Clipboard]	0
1	EMYY	LUNG ADJ CANCER OR NSCLC	88048
2	EMYY	ADVANCED OR METASTATIC OR STAGE ADJ '3' OR STAGE ADJ '4' OR INOPERABLE	329178
3	EMYY	1 AND 2	17149
4	EMYY	RESOURCE ADJ UTILISATION OR NHS ADJ REFERENCE ADJ COSTS OR ECONOMICS OR COST ADJ CONTROL OR COST ADJ SAVING	602969

		OR PRICE$1 OR EXPENDITURE$1 OR HEALTH ADJ CARE ADJ COST$1 OR COST ADJ ALLOCATION$1	
5	EMYY	ENGLAND OR WALES OR UNITED ADJ KINGDOM	314239
6	EMYY	3 AND 4 AND 5	29
7	MEYY	LUNG ADJ CANCER OR NSCLC	62781
8	MEYY	ADVANCED OR METASTATIC OR STAGE ADJ '3' OR STAGE ADJ '4' OR INOPERABLE	299087
9	MEYY	7 AND 8	12989
10	MEYY	RESOURCE ADJ UTILISATION OR NHS ADJ REFERENCE ADJ COSTS OR ECONOMICS OR COST ADJ CONTROL OR COST ADJ SAVING OR PRICE$1 OR EXPENDITURE$1 OR HEALTH ADJ CARE ADJ COST$1 OR COST ADJ ALLOCATION$1	356528
11	MEYY	RESOURCE ADJ UTILISATION OR NHS ADJ REFERENCE ADJ COSTS OR ECONOMICS OR COST ADJ CONTROL OR COST ADJ SAVING OR PRICE$1 OR EXPENDITURE$1 OR HEALTH ADJ CARE ADJ COST$1 OR COST ADJ ALLOCATION$1	356528
12	MEYY	RESOURCE ADJ UTILISATION OR NHS ADJ REFERENCE ADJ COSTS OR ECONOMICS OR COST ADJ CONTROL OR COST ADJ SAVING OR PRICE$1 OR EXPENDITURE$1 OR HEALTH ADJ CARE ADJ COST$1 OR COST ADJ ALLOCATION$1	356528
13	MEYY	ENGLAND OR WALES OR UNITED ADJ KINGDOM	2553811
14	MEYY	9 AND 10 AND 13	73
15	MEIP	LUNG ADJ CANCER OR NSCLC	2680
16	MEIP	ADVANCED OR METASTATIC OR STAGE ADJ '3' OR STAGE ADJ '4' OR INOPERABLE	12844
17	MEIP	15 AND 16	555
18	MEIP	RESOURCE ADJ UTILISATION OR NHS ADJ REFERENCE ADJ COSTS OR ECONOMICS OR COST ADJ CONTROL OR COST ADJ SAVING OR PRICE$1 OR EXPENDITURE$1 OR HEALTH ADJ CARE ADJ COST$1 OR COST ADJ ALLOCATION$1	6284
19	MEIP	ENGLAND OR WALES OR UNITED ADJ KINGDOM	82867
20	MEIP	17 AND 18 AND 19	1
21	EMYY MEYY MEIP [all]	combined sets 6, 14, 20	103
22	EMYY MEYY MEIP [all]	dropped duplicates from 21	11
23	EMYY MEYY MEIP [all]	unique records from 21	92

NHS EED and ECON LIT were search on 27th September 2011with the following terms

1. Lung Cancer or NSCLC
2. Advanced or Metastatic or Stage 3 or Stage 4 or Inoperable
3. Resource utilisation or NHS reference costs or Health care cost
4. England and Wales or United Kingdom
5. 1 and 2 and 3 and 4

9.8.5 Details of any additional searches (for example, searches of company databases [include a description of each database]).

None.

9.8.6 The inclusion and exclusion criteria.

Inclusion criteria	Exclusion criteria
Advanced or metastatic lung cancer Resource utilisation from an NHS perspective	Early lung cancer Resource utilisation from a private/US setting – and any other non-UK country.

9.8.7 The data abstraction strategy.

An individual extracted articles as per the inclusion and exclusion criteria above. All search terms and inclusion and exclusion criteria were agreed upon before the search was conducted. The final lists of articles selected were then reviewed by a health economist experienced in advanced non-small cell lung cancer Health Technology Appraisals.

9.9 Appendix 14: Gefitinib Toxicities

IPASS	Gefitinib (N = 607)		Carboplatin–Paclitaxel (N = 589)	
Adverse Event	**All N (%)**	**CTC Grade 3, 4, or 5 N (%)**	**All N (%)**	**CTC Grade 3, 4, or 5 N (%)**
Rash or acne†	402 (66.2)	19 (3.1)	132 (22.4)	5 (0.8)
Diarrhoea	283 (46.6)	23 (3.8)	128 (21.7)	8 (1.4)
Dry skin	145 (23.9)	0	17 (2.9)	0
Anorexia†	133 (21.9)	9 (1.5)	251 (42.6)	16 (2.7)
Pruritus†	118 (19.4)	4 (0.7)	74 (12.6)	1 (0.2)
Stomatitis†	103 (17.0)	1 (0.2)	51 (8.7)	1 (0.2)
Asthenic conditions†	102 (16.8)	2 (0.3)	259 (44.0)	11 (1.9)
Nausea	101 (16.6)	2 (0.3)	261 (44.3)	9 (1.5)
Paronychia	82 (13.5)	2 (0.3)	0	0
Vomiting	78 (12.9)	1 (0.2)	196 (33.3)	16 (2.7)
Constipation	73 (12.0)	0	173 (29.4)	1 (0.2)
Alopecia	67 (11.0)	0	344 (58.4)	0
Neurotoxic effects†	66 (10.9)	2 (0.3)	412 (69.9)	29 (4.9)
Myalgia	47 (7.7)	3 (0.5)	186 (31.6)	10 (1.7)
Arthralgia	39 (6.4)	1 (0.2)	113 (19.2)	6 (1.0)
Neutropenia‡				
Any	NA	22 (3.7)	NA	387 (67.1
Febrile	1 (0.2)	1 (0.2)	17 (2.9)	17 (2.9)
Anemia‡	NA	13 (2.2)	NA	61 (10.6)
Leukopenia‡	NA	9 (1.5)	NA	202 (35.0)
WJTOG3405	**Gefitinib (n=87)**		**Cisplatin plus docetaxel (n=88)**	
Non-haematological toxicity	**All (%)**	**CTC grade ≥3 (%)**	**All (%)**	**CTC grade ≥3 (%)**
Rash*	74	2	7	0
AST*	61	14	17	1
ALT*	61	24	35	2
Dry skin*	47	0	3	0
Diarrhoea	47	1	35	0
Fatigue*	34	2	73	2
Paronychia*	28	1	1	0
Stomatitis	19	0	13	0
Nausea*	15	1	89	3
Constipation*	14	0	39	0
Alopecia*	8	0	67	0
Sensory disturbance*	7	1	23	0
Haematological toxicity				
Leucocytopenia*	13	0	82	43
Thrombocytopenia*	12	0	29	0
Neutropenia*	7	0	81	74
Anaemia*	33	0	79	15

	Gefitinib (N = 114)				No. patients (%)	Carboplatin–Paclitaxel (N = 113)				No. patients (%)	
NEJGSG002	Grd 1	Grd 2	Grd 3	Grd 4	Grade ≥ 3	Grd 1	Grd 2	Grd 3	Grd 4	Grade ≥ 3	P value
Diarrhoea	32	6	1	0	1 (0.9)	7	0	0	0	0	<0.001
Appetite loss	7	4	6	0	6 (5.3)	39	18	7	0	7 (6.2)	<0.001
Fatigue	8	1	3	0	3 (2.6)	19	11	1	0	1 (0.9)	0.002
Rash	38	37	6	0	6 (5.3)	8	14	3	0	3 (2.7)	<0.001
Neuropathy (sensory)	0	1	0	0	0	28	27	7	0	7 (6.2)	<0.001
Arthralgia	1	2	1	0	1 (0.9)	25	21	8	0	8 (7.1)	<0.001
Pneumonitis	3	0	2	1	3 (2.6)	0	0	0	0	0	<0.001
Aminotransferase elevation	20	13	29	1	30 (26.3)	31	5	0	1	1 (0.9)	<0.001
Neutropenia	5	1	0	1	1 (0.9)	4	9	37	37	74 (65.5)	0.020
Anemia	19	2	0	0	0	35	32	0	0	6 (5.3)	<0.001
Thrombocytopenia	8	0	0	0	0	25	3	1	1	4 (3.5)	<0.001
Any	17	44	43	4	47 (41.2)	4	25	40	4	81 (71.7)	<0.001

First SIGNAL: Grade 3/4 toxicity was less common in the gefitinib arm (28.3% vs.67.3%, p<0.0001) while no unusual toxicity was noted in both arms

	IPASS N (%)	WJTOG3405 (%)	NEJGSG002 (%)	EURTAC (%)	OPTIMAL (%)
Rash or acne†	402 (66.2)	74	71	49.3	73.5
Diarrhoea	283 (46.6)	47	34	57.3	25.3
Dry skin	145 (23.9)	47	-	17.3	-
Anorexia†	133 (21.9)	-	15	28.0	6.0
Pruritus†	118 (19.4)	-	-	10.7	1.2
Stomatitis†	103 (17.0)	19		10.7	13.3
Asthenic conditions†	102 (16.8)	34	11	53.3	4.8
Nausea	101 (16.6)	15		22.7	0
Paronychia	82 (13.5)	28	-	16.0	-
Vomiting	78 (12.9)	-	-	13.3	1.2
Constipation	73 (12.0)	14	-	8.0	0
Alopecia	67 (11.0)	8	-	14.7	-
Neurotoxic effects†	66 (10.9)	-	-	-	-
Myalgia	47 (7.7)	-	-	-	-
Arthralgia	39 (6.4)	-	4	-	-
Neutropenia‡					
Any	NA	7	6	0	6.0
Febrile	1 (0.2)	-	-	0	-
Anaemia‡	NA	33	18	10.7	4.8
Leukopenia‡	NA	13		2.7	12.0
Thrombocytopenia	-	12	8	1.3	3.6
ALT		61	54		37.3
AST		61			28.5