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BY EMAIL

23 November 2011

RE: Erlotinib for the first line treatment of EGFR-TK mutation positive mNSCLC

Dear Kate,

Please find below our responses to the clarification questions for the above mentioned appraisal.

If any further clarification or analyses are required we would be more than happy to oblige.

Yours Sincerely,

[redacted]

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Section A: Clarification on effectiveness data

Section 2.4 – Issues relating to clinical pathway of care

A1. **Priority Request:** Please clarify, and if possible state the source of, the stated second-line treatment options for the patients who currently receive first-line gefitinib.

In the last 12 months Roche have held 8 advanced NSCLC advisory board meetings at various locations across the UK. These meetings (one national and seven regional) were designed to inform us of the current treatment of advanced NSCLC in the UK and help us to understand where and how erlotinib would likely be positioned in the treatment pathway if it were to be approved by NICE for the first line treatment of EGFR M+ patients.

In total over 70 clinicians who treat advanced NSCLC on a daily basis have attended this series of meetings. The clear feedback from these clinicians was that following first line use of gefitinib in EGFR M+ patients it is standard clinical practice to treat patients with pemetrexed/cisplatin doublet chemotherapy (as EGFR M+ patients are almost exclusively of non-squamous histology (Shigematsu et al, Mitsudomi et al)).

When assessing the next course of action for a patient with advanced NSCLC a clinician will typically consider a patient's biomarker status, disease histology, previous treatments, the availability of technologies within their centre and the patient's ability to tolerate further treatment. In this case this leaves a clinician with the opportunity of treating a patient progressing on gefitinib with either erlotinib, doublet chemotherapy (i.e. pemetrexed/cisplatin) or single agent chemotherapy (i.e. docetaxel).

If a patient has previously progressed on an EGFR TKI clinicians indicated they would not utilise another EGFR TKI post-progression (i.e. you wouldn't expect erlotinib to be followed by gefitinib or visa-versa). This leaves a clinician with the opportunity of treating a patient progressing on gefitinib with either doublet chemotherapy (of which pemetrexed/cisplatin has been established as the most efficacious combination in non-squamous patients), docetaxel monotherapy or best supportive care alone if the patient is unable to tolerate further treatment.

The NICE guidance for the use of pemetrexed/cisplatin (NICE TA181) states that:

'Pemetrexed in combination with cisplatin is recommended as an option for the first-line treatment of patients with locally advanced or metastatic non-small-cell lung cancer (NSCLC) only if the histology of the tumour has been confirmed as adenocarcinoma or large-cell carcinoma.'

TA181 Guidance Section 1.1.

Clinicians at our advisory boards noted that as EGFR M+ patients progressing on either erlotinib or gefitinib would not yet have received doublet chemotherapy for their mNSCLC, therefore they would consider pemetrexed/cisplatin as their 'first-line' chemotherapy and so would administer pemetrexed/cisplatin combination rather than docetaxel monotherapy, which they perceive as being less effective and more toxic. Although it is true that no treatment has been systematically evaluated after a first-line EGFR TKi, clinicians do not believe that prior exposure to a TKI alters chemotherapy responsiveness, so that the best chemotherapy combination for this group remains pemetrexed/cisplatin.

In terms of the decision problem, the utilisation of erlotinib rather than gefitinib in the first line treatment of EGFR M+ patients would not impact the treatment options available post-progression, as outlined above. In terms of the economic evaluation, the costs and benefits associated with second line treatment 'cancel-out' when comparing erlotinib and gefitinib as there is no evidence, or hypothesis, which suggests that what happens post-progression in terms of costs and clinical outcomes is not altered by which of these agents is used first-line.

Section 5.3 – Issues relating to methodology of relevant RCTs

A2. **Priority Request:** Please provide copies of the protocols and clinical study reports for the two primary studies (EURTAC and OPTIMAL).

As OPTIMAL was not a Roche led-study we do not have access to a completed OPTIMAL clinical study report (CSR). To our knowledge a CSR has not yet been completed for the study. OPTIMAL has however been published in the Lancet Oncology (see Zhou 2011c publication provided previously) in which details on the study design/conduct/results are provided.

Please find attached two CSRs for the EURTAC RCT (one based upon the 02/10/2010 data-cut and one based upon the 26/01/2011 data-cut) and the protocols for the EURTAC and OPTIMAL studies.

Please note that the CSRs provided should be regarded as commercial in confidence and are not to be circulated amongst consultees or commentators.

Section 5.7 – Indirect and mixed treatment comparisons

A3. **Priority Request:** Please provide the rationale for including only the third generation doublet chemotherapies in the evidence network and excluding pemetrexed in combination with cisplatin or carboplatin.

As stated in our letter on the 4th November pemetrexed/cisplatin was not considered a valid comparator to erlotinib in the first line treatment of EGFR M+ patients for the following reasons:

1. Gefitinib was determined to be cost-effective compared to pemetrexed/cisplatin in NICE TA192 (and therefore if erlotinib is found to be cost-effective compared to gefitinib logic holds it must be cost-effective compared to pemetrexed
2. Pemetrexed/Cisplatin is utilized in less than 5% of EGFR M+ patients (with an EGFR TKI used in over 95% of patients)
3. There is no evidence on the efficacy of pemetrexed/cisplatin in EGFR M+ patients

Given the minimal use of pemetrexed/cisplatin in this patient population, understanding whether erlotinib is cost effective compared to pemetrexed/cisplatin is of no practical relevance to the NHS. The management of EGFR M+ patients has moved on in light of the recent NICE guidance supporting the use of gefitinib and so a comparison of erlotinib to pemetrexed/cisplatin no longer represents the reality of the decision faced by the NHS (i.e. should we utilize erlotinib or gefitinib in the first line treatment of EGFR M+ patients?).

Due to the above we believe pemetrexed/cisplatin is not a relevant comparator to erlotinib in real-world NHS practice, could not be robustly incorporated into an analysis even if felt to be appropriate (as there are no data on the efficacy of pemetrexed/cisplatin in this group) and is redundant as a comparator given that gefitinib has been previously found to be cost-effective compared to pemetrexed/cisplatin (which is included in the analysis undertaken).

Given the omission of pemetrexed/cisplatin as a comparator there is only one reason why one may wish to include pemetrexed/cisplatin (or carboplatin) in an evidence network relevant to a comparison of erlotinib and gefitinib.

If one wished to claim that the 3rd generation chemotherapies were of differential efficacy then evidence on the relative efficacy of pemetrexed/cisplatin or pemetrexed/carboplatin to the different 3rd generation doublet chemotherapies (if available) could potentially be utilized to inform the

assessment of the relative efficacy of the 3rd generation doublet chemotherapies (and the subsequent evaluation of the relative efficacy of erlotinib and gefitinib).

Prior to building a model in support of this submission we reviewed the NICE appraisal of gefitinib for the first line treatment of EGFR M+ mNSCLC in order to understand how best to approach an indirect comparison of erlotinib and gefitinib.

The following statements were noted in the guidance:

Section 3.34 of the TA192 Guidance:

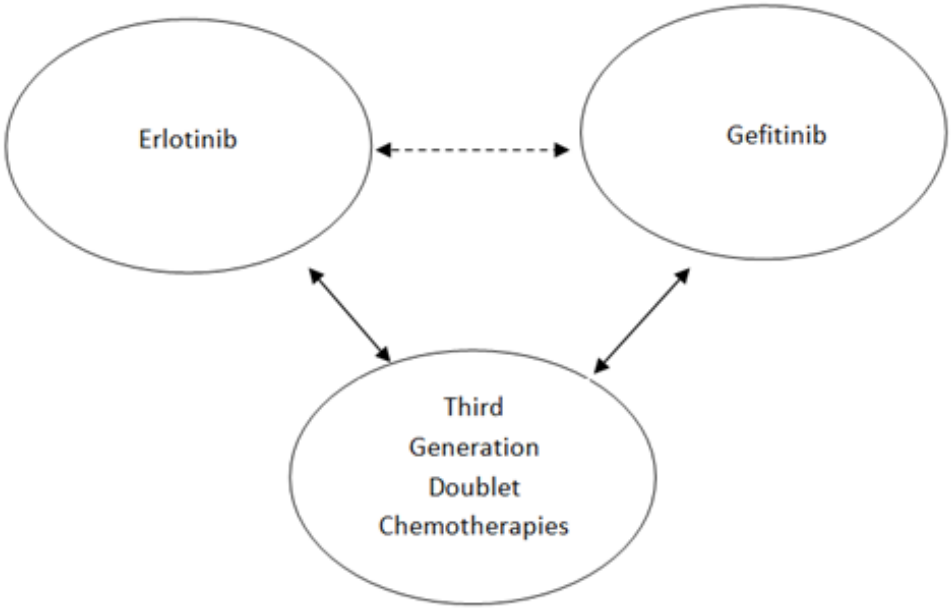
> "The ERG noted that the manufacturer's economic analysis used differential hazard ratios for the four chemotherapy regimens derived from the mixed-treatment comparison. However, the ERG felt that the four chemotherapy regimens were equally clinically effective."

Section 4.2 of the TA192 Guidance:

> "The Committee heard from clinical specialists that up to the end of 2009 UK clinical practice was to combine gemcitabine with a platinum drug, usually cisplatin or carboplatin, but that no particular regimen of combination chemotherapy was considered more effective than another. The regimen chosen for an individual patient depended on the ease of administration and the associated adverse effects."

In light of the above statements (and the fact the same ERG as featured in TA192 were assigned to this appraisal) it was determined that any indirect comparison of erlotinib and gefitinib undertaken should utilise the assumption that the third generation doublet chemotherapy combinations were equally clinically effective (i.e. see below).

Figure 1. Schema of evidence network utilised



Attempting to derive and utilise point estimates of the relative efficacy of the 3rd generation doublet chemotherapies based upon a complete evidence of network of these agents (including direct evidence and indirect evidence via any pemetrexed/cisplatin trials) would have been in contradiction to the point made by LR*i*G in Section 3.34 of the TA192 guidance and so was not thought to be appropriate. Moreover, the view that the 3rd generation chemotherapies are of equivalent efficacy was strongly supported by the clinical advisors we consulted in developing our evidence submission, strongly supported by the clinical experts consulted in the development of TA192 (as described in Section 4.2 of the TA192 guidance) and is supported by a wealth of RCT/Meta-analytic evidence (such as Schiller 2002, Scagliotti 2002, Kelly 2001 and the MTC conducted by AstraZeneca in TA192).

If it is assumed that the 3rd generation doublet chemotherapies are of equivalent efficacy then the inclusion of pemetrexed/cisplatin (or carboplatin) in a network will have no impact upon the estimated relative efficacy of erlotinib and gefitinib in EGFR M+ patients as neither agent has been compared to anything other than 3rd generation doublet chemotherapy.

In light of the statements relating to the relative efficacy of the 3rd generation doublet chemotherapies made in the TA192 guidance, the views of our clinical experts and the omission of pemetrexed/cisplatin as a comparator, the inclusion of these regimens was felt to be of limited relevance to the indirect comparison of relevance to this appraisal.

Section B: Clarification on cost-effectiveness data

Section 6.2 – De novo analysis

A4. **Priority Request:** Please provide the rationale for not considering trial overall survival results in the de novo economic model. What are the assumptions regarding the relationship between pre-progression survival and overall survival used in the economic model? Please provide a scenario analysis based on the overall survival results from the trials.

A4.1. Please provide the rationale for not considering trial overall survival results in the de novo economic model

Overall survival data is available for 5 of the RCTs identified (all studies except OPTIMAL which has yet to report overall survival data). In each study cross-over from doublet chemotherapy was a substantial confounding factor in the overall survival results observed (with varying levels of cross-over observed in each study –ranging from 59% to 95% cross-over). This OS data is summarised briefly in appendix 1 below.

The overall survival hazard ratios derived from these studies are not the product of a simple comparison of EGFR TKIs with Doublet Chemotherapy but a comparison of EGFR TKIs given pre-progression compared to Doublet Chemotherapy given pre-progression followed by the use of EGFR TKIs post-progression. This confounds the assessment of the relative impact of the use of first line erlotinib or gefitinib on the overall survival experienced by patients and makes an indirect comparison based upon unadjusted data inadvisable (particularly as the rates of cross-over observed varied between studies).

Given the level of crossover in these studies it does not seem valid to compare the outcomes observed and suggest that these are in anyway due to the choice of first line therapy.

Whilst there are a growing range of techniques that may be utilised to adjust for crossover in RCTs (i.e. rank preserving structural failure time models, the Branson and Whitehead approach etc) it is not possible to apply these methods to the data available for gefitinib. The information required to do this is not in the public domain.

We therefore took the decision that it was not possible to utilise the comparative overall survival data from the RCT evidence available in assessing the clinical and cost-effectiveness of erlotinib compared to gefitinib. We did however utilise the rate of post-progression death observed in the erlotinib arm of the study in the manner described below.

A4.2. What are the assumptions regarding the relationship between pre-progression survival and overall survival used in the economic model?

Due the absence of non-confounded randomised data that could be utilised to reliably inform the assessment of the relative overall survival gain offered by erlotinib over gefitinib, in the base-case it was assumed that the post-progression rate of death observed in the erlotinib arm of the EURTAC RCT was representative of the rate of post-progression death that would be experienced in English/Welsh patients given either erlotinib or gefitinib as a first line treatment.

This assumption of an equivalent rate of death post-progression for both erlotinib and gefitinib was strongly supported by clinicians at a national advisory board held in July 2011. These clinicians noted that as both agents are EGFR tyrosine kinase inhibitors there is no reason to believe that patients given erlotinib first line would experience a rate of post-progression death any different to that experienced by patients receiving gefitinib first line.

In the absence of evidence or a hypothesis to suggest that after completing treatment erlotinib patients would die any quicker or slower than patients given gefitinib an assumption of equal rates of post treatment progression with both drugs was made in the base-case.

We believe this is the fairest and most reasonable and appropriate assumption to make given the evidence available.

A4.3. Please provide a scenario analysis based on the overall survival results from the trials.

As stated above we believe this is statistically inappropriate and amounts to the pooling of non-randomised data which is subject to clear known differences between the post-progression treatments received between studies. Attempting such analyses will result in the mistaken misattribution of the impact of crossover (of varying levels between studies) to first line treatments and as a result highly flawed estimates of cost-effectiveness.

The relative efficacy of erlotinib and gefitinib in terms of overall survival cannot be robustly estimated given the raw OS data from the RCTs available and so we utilised the simple assumption that patients receiving erlotinib or gefitinib would die at the same rate post disease-progression in order to model what the relative overall survival offered by the agents would be based upon the progression free survival data available.

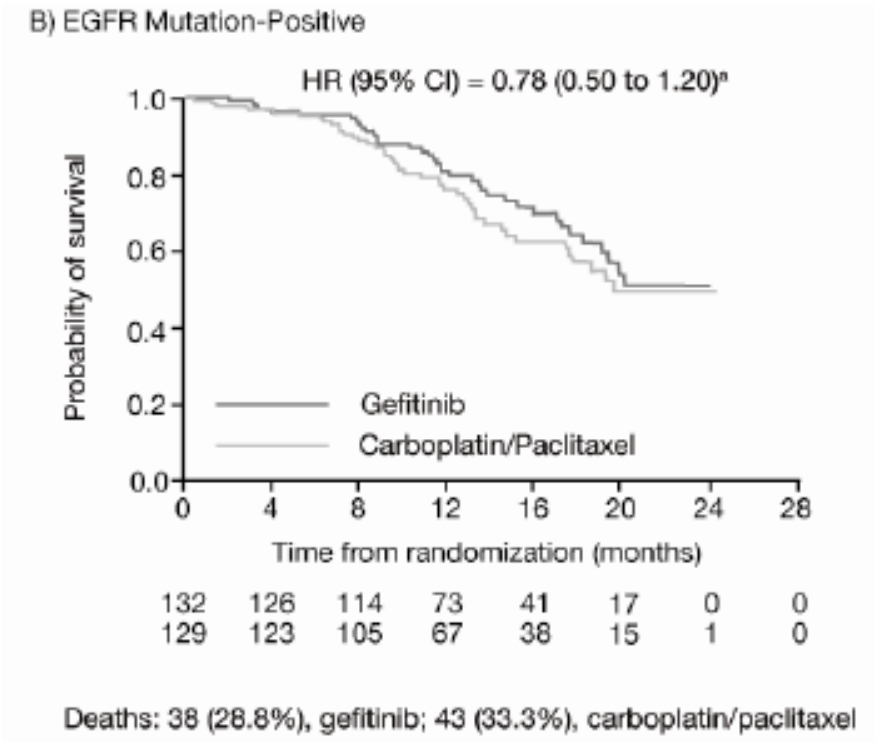
However if one were to pool the first cut of the IPASS data (the one subject to the lowest level of cross-over of the two data cuts) with the WJTOG3405 and First-SIGNAL data (note OS HRs not reported for the NEJSG study) and compare that to the first cut of the EURTAC data (with a lower rate of cross-over than observed in the 2nd data cut) and utilise this information in the model the base-case ICER with PAS would drop to £19,376/QALY gained (see appendix 2 for details).

It should be noted that we believe that any analysis attempting to utilise the raw overall survival data from the studies identified is highly flawed for the reasons identified above and should not be relied up by the Committee. Whilst we have reported the above analysis on request we do not believe it is appropriate.

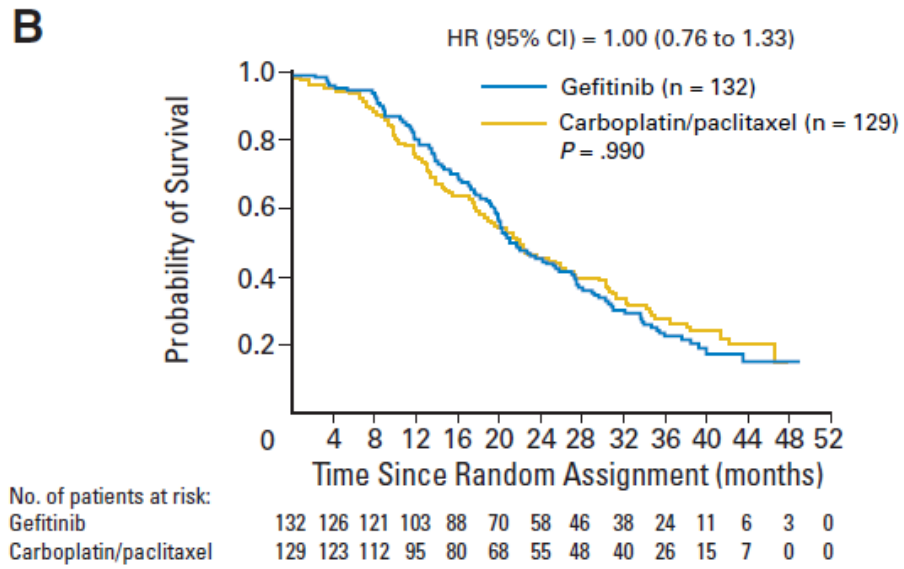
Appendix 1 – Overall Survival Data

IPASS (1st and 2nd data-cuts) – Gefitinib

Mok 2009: HR = 0.78 {0.50, 1.20} - Unreported cross-over in EGFR M+ group

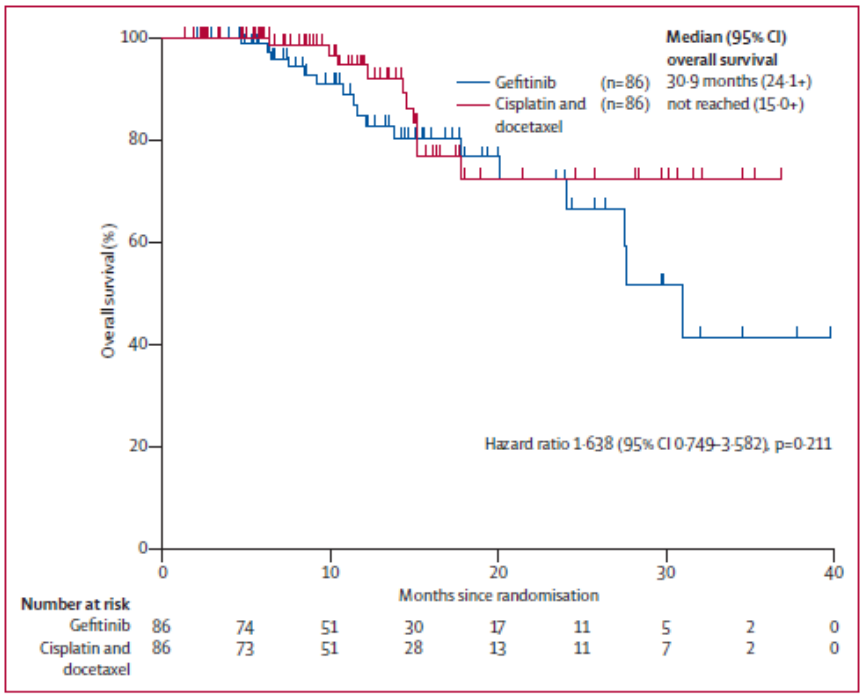


Fukoka 2011: HR = 1.00 {0.76, 1.33} - **63.4% cross-over** in EGFR M+ group



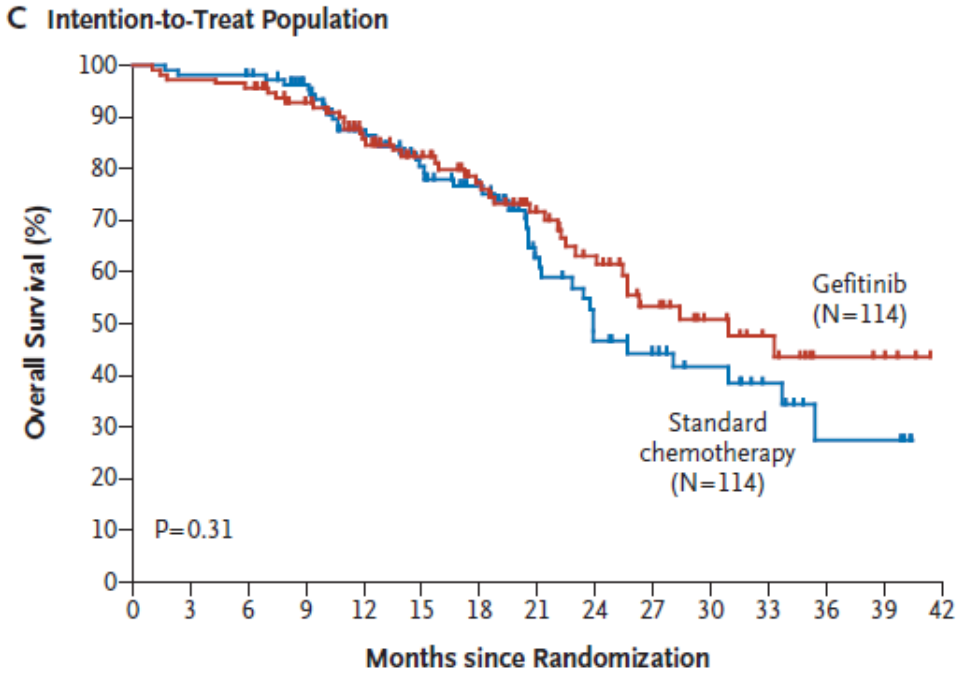
WJTOG3405 – Gefitinib

Mitsudomi 2010: HR = 1.638 {0.749-3.582} – **59.3% cross-over** in EGFR M+ group



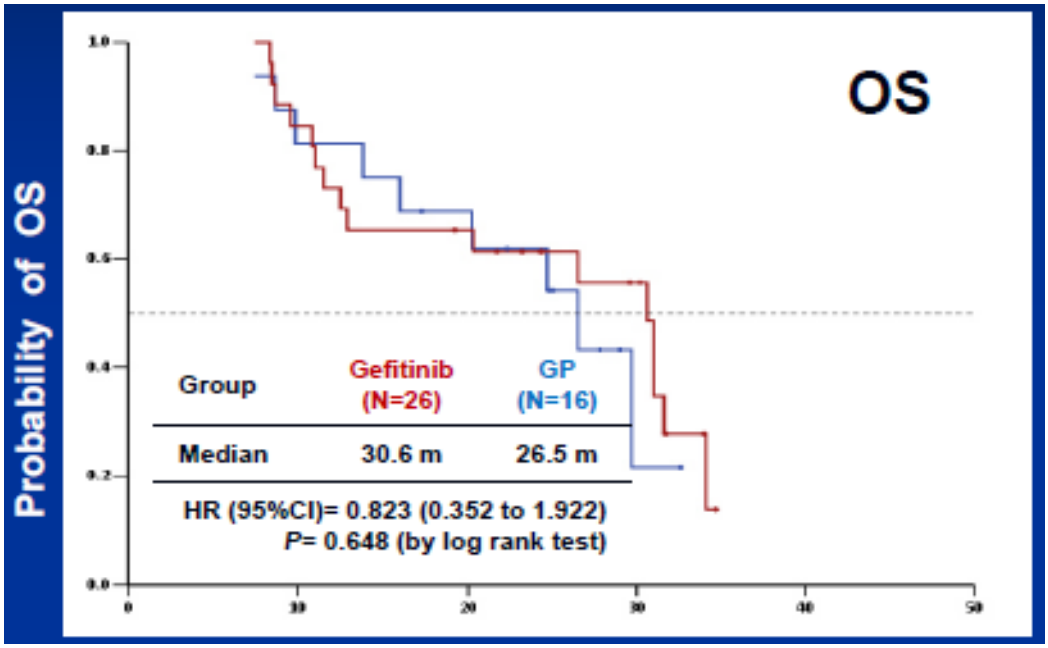
NEJSG – Gefitinib

Maemondo 2010: HR = Not reported – **94.6% cross-over** in EGFR M+ group



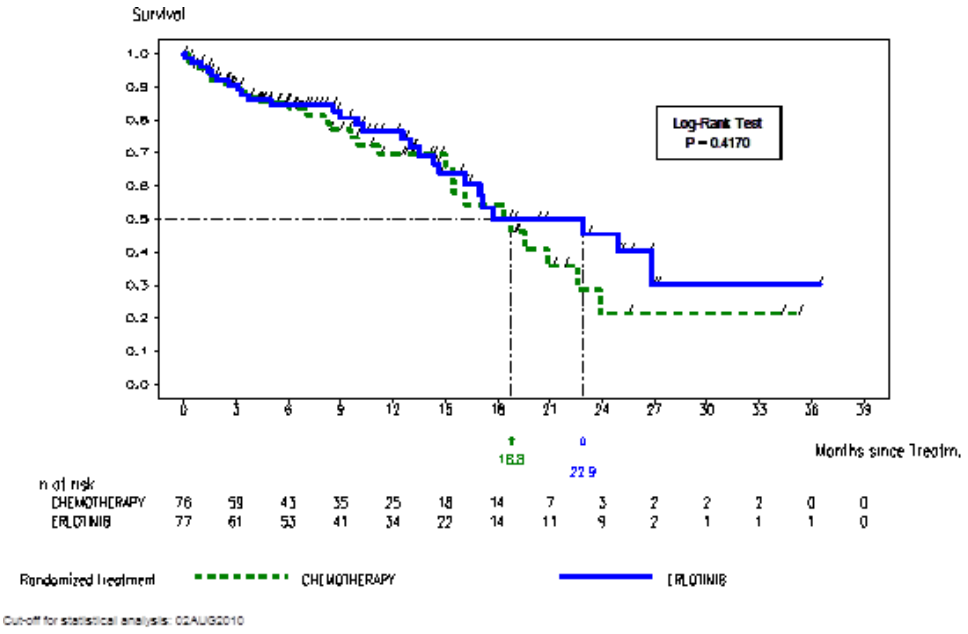
First-SIGNAL – Gefitinib

Lee 2009: HR = 0.823 {0.352, 1.922} – **80.7 % crossover** in ITT population

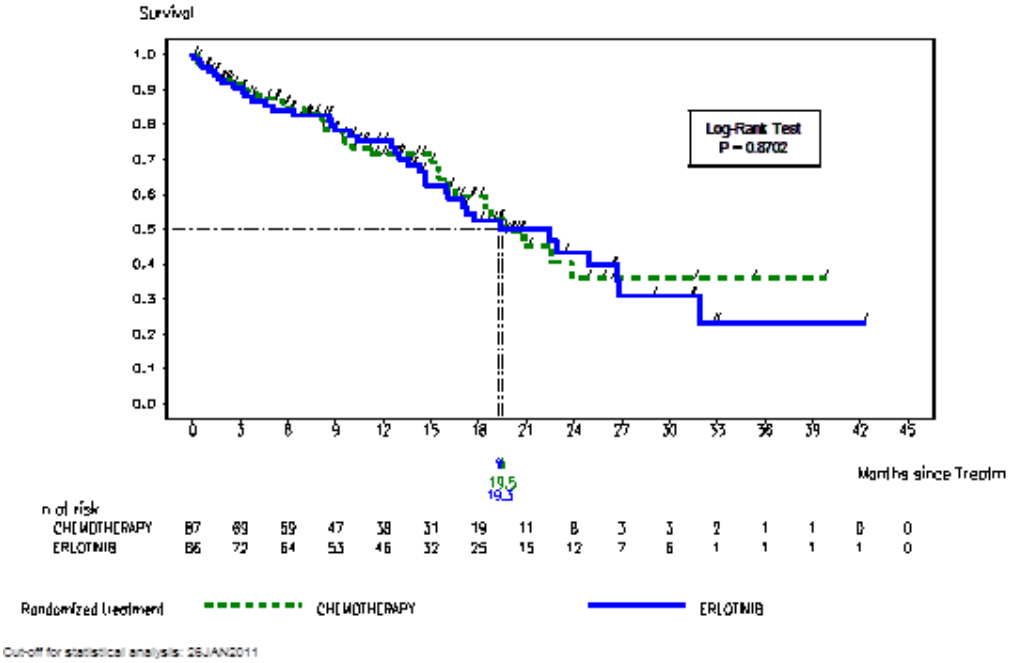


EURTAC (1st and 2nd data-cuts) – Gefitinib

2nd August 2010 Cut: HR = 0.80 {0.47, 1.37} – **66% crossover** of chemo randomised population



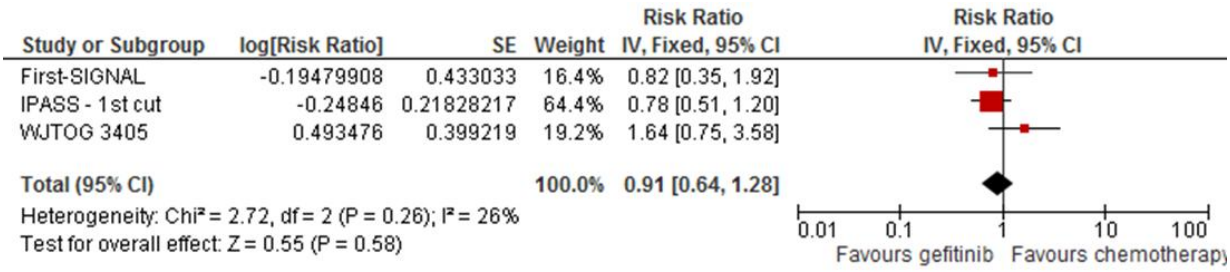
26th January 2011 Cut: HR = 1.04 {0.65, 1.68} – **76% crossover** of chemo randomised population



Appendix 2 – Overall Survival Sensitivity Analysis

NOTE: We do not believe it is appropriate to pool studies on an endpoint which is subject to heavy, and differential, confounding. We believe this analysis is inappropriate and will lead to highly erroneous, biased results. However we have conducted it as requested.

In order to facilitate the requested sensitivity analysis the First-SIGNAL, WJTOG3405 and IPASS 1st data cut OS HRs were pooled using a fixed effects model in RevMan 5.1 (see forest plot below).



Whilst a 2nd data cut of the IPASS study is available, as the 1st cut is less confounded by crossover it was assumed that this cut would provide a more accurate estimate of the relative impact of gefitinib upon overall survival than the later cut.

The resultant pooled OS HR (0.91 {0.64, 1.28} p =0.58) was then compared to the OS HR from the first data cut of the EURTAC RCT (0.80 {0.47, 1.37}) using the Bucher method in order to derive an estimate of the relative OS HR of erlotinib vs gefitinib.

$$\text{EXP (LN(0.8) - LN(0.91))} = 0.88$$

The log standard error of the indirect HR was derived by estimating the log standard error for the 1st EURTAC data cut and the pooling of gefitinib studies, by squaring these estimated standard errors, by summing the results, and then taking the square root of the resultant figure. This log standard error was then applied to the indirect OS HR on the log scale in order to estimate confidence intervals on the log scale. The results were then converted back into the normal scale to estimate an indirect OS HR of erlotinib vs gefitinib of 0.88 {0.46, 1.66}.

In order to allow this indirect HR to be applied within the model the structure of the comparator arm was changed slightly. Instead of deriving a gefitinib OS curve based upon the use of the gefitinib PFS curve with an exponential transition to death applied, the gefitinib OS curve was estimated by applying the above indirect comparison to the OS curve estimated for erlotinib (see below).

$$\text{EXP}((1/0.88) * \text{LN}(S_{erlotinib}(t)) = S_{gefitinib}(t))$$

The proportion of gefitinib patients in the PD health state in each month was then derived as the difference between the PS and PFS curves (i.e. a ‘partitioned survival’ approach).

The application of this method caused the base-case ICER to fall to £19,376/QALY gained.

We do not believe this, or any other, pooling or indirect comparison of the raw OS data from the studies identified is appropriate. We strongly believe that the use of the same rate of death post-progression for both EGFR TKIs is the only reasonable assumption that can be made in order to model overall survival given the data available.

References

Schiller et al. (2002). Comparison of Four Chemotherapy Regimens for Advanced Non–Small-Cell Lung Cancer. N Engl J Med 2002; 346:92-98.

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.*

Kelly K, Crowley J, Bunn PA Jr, et al: Randomized phase III trial of paclitaxel plus carboplatin versus vinorelbine plus cisplatin in the treatment of patients with advanced non–small-cell lung cancer: A Southwest Oncology Group trial. J Clin Oncol19:3210-3218, 2001

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 23/11/2011)