

# Appraisal Consultation Document

## Gefitinib for the first-line treatment of locally advanced or metastatic non-small-cell lung cancer

### Additional Information:

#### 1. Proposed amendment to Gefitinib Single Payment Access (SPA) scheme

AstraZeneca is minded that although the Committee agreed the gefitinib SPA scheme would be relatively simple for the NHS to administer, concerns were raised that although the scheme may be beneficial across the whole NHS, there may be occasion when a patient only receives a short course of treatment. Under this circumstance, the cost of gefitinib may be greater with the scheme than without it (see 4.17).

AstraZeneca proposes to delay the invoicing of the Single Payment Access scheme registration fee until the supply of the third monthly pack of gefitinib to the named NHS organisation. [REDACTED]

[REDACTED] However, patients who discontinue gefitinib will be followed up by AstraZeneca's Patient Safety Team to assess whether an adverse event needs to be reported. This information will add to the understanding of gefitinib's tolerability profile in a UK population, and help inform appropriate future use of gefitinib.

The consequence of this change to the SPA scheme has been factored into the gefitinib cost-effectiveness evaluation (see 1.8) using treatment duration data from IPASS (Appendix G). The treatment benefit for gefitinib, however, is still based on the overall gefitinib EGFR mutation positive population rather than the population that received  $\geq 3$  months of treatment. The gefitinib incremental cost-effectiveness ratios should therefore be considered conservative estimates.

#### 2. End of Life Criteria

[REDACTED]

### NICE Requests for Further Information

#### 1.3 to 1.6

1.3 NICE requests an exploration of alternative probability distributions for the extrapolation of progression-free survival and overall survival beyond the timeframe of the Iressa Pan Asian Study (IPASS)<sup>1</sup>. This should include the following:

1.4 Independent survival curves (overall survival and progression-free survival) for both gefitinib and paclitaxel/carboplatin based on the IPASS data and extrapolation of different approaches to applying the hazard ratio to incorporate other comparators. The different approaches to applying the hazard ratio should consider using either gefitinib or paclitaxel/carboplatin as the baseline.

1.5 Examination of alternative probability distribution and consideration of model fit to early trial data and the shape of the curves at the tail of the distribution.

1.6 Observational or epidemiological evidence of long-term survival in patients with locally advanced or metastatic NSCLC and how this relates to the most plausible model fit.

*AstraZeneca's response:*

#### **A. Examination of alternative probability distributions**

The following commonly used probability distributions for time to event data were examined to assess their goodness of fit to the PFS and OS data from the IPASS EGFR M+ subgroup: Weibull, lognormal (LogN), log-logistic (Log-log), Gompertz (Gompz) and exponential (Exp).

The models were fitted in 3 different ways:

1. To each treatment arm separately
2. To the whole dataset using a stratified model (same as 1 in the absence of other covariates)
3. To the whole dataset using an unstratified model (this assumes proportional hazards (PH) between treatments for distributions with the PH property, i.e. Weibull, exponential, Gompertz)

#### **Evaluation of goodness of fit of alternative probability distributions**

- **Akaike's Information Criterion (AIC)**

The Akaike's Information Criterion (AIC) is a statistic that can be used to compare the viability of different parametric models. The AIC of a model is defined as:

$$AIC = -2LL + 2(c + a)$$

Where LL is the logarithm of the model likelihood (log-likelihood) "c" is the number of covariates and "a" the number of ancillary parameters (e.g. 2 in the case of Weibull;  $\lambda$  the scale parameter and  $\alpha$  the shape). When comparing two parametric models fitted to the same dataset, the model with the lowest AIC is the best fit.

The AICs for the 5 selected probability distributions were determined for the PFS and OS models for the individual IPASS treatment arms<sup>1</sup> and the stratified and unstratified models (table 1 and 2).

The Weibull models were consistently the best fit (lowest AIC) for the IPASS EGFR M+ PFS data, regardless of how the model was fitted.

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<sup>1</sup> The models for the individual treatment arms are not fitted to the same data as the stratified and unstratified models. AICs determined for models based on individual treatment arms are not comparable with those generated for the stratified and unstratified models.

Weibull models were also the best fit to the OS data; however, it could be argued that the Log-logistic probability distribution also provides a good fit to the IPASS OS data.

**Table 1: Goodness of fit of probability distributions to IPASS EGFR M+ PFS data**

	Rank (AIC)				
	1	2	3	4	5
Paclitaxel/carboplatin EGFR M+	Weibull (262.9)	Log-log (272.2)	Gompz (278.9)	LogN (283.4)	Exp (313.0)
Gefitinib EGFR M+	Weibull (281.6)	Gompz (287.4)	LogN (288.4)	Log-log (289.6)	Exp (314.5)
Both arms, stratified	Weibull (539.3)	Log-log (555.6)	Gompz (560.8)	LogN (565.1)	Exp (623.1)
Both arms, unstratified	Weibull (539.7)	Log-Log (557.6)	Gompz (561.4)	LogN (565.5)	Exp (623.1)

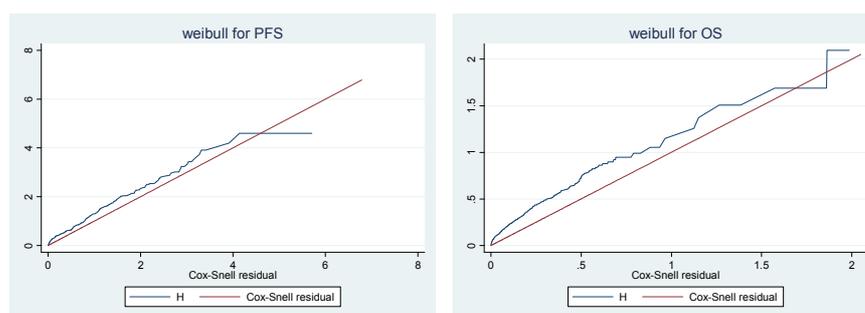
**Table 2: Goodness of fit of probability distributions to IPASS EGFR M+ OS data**

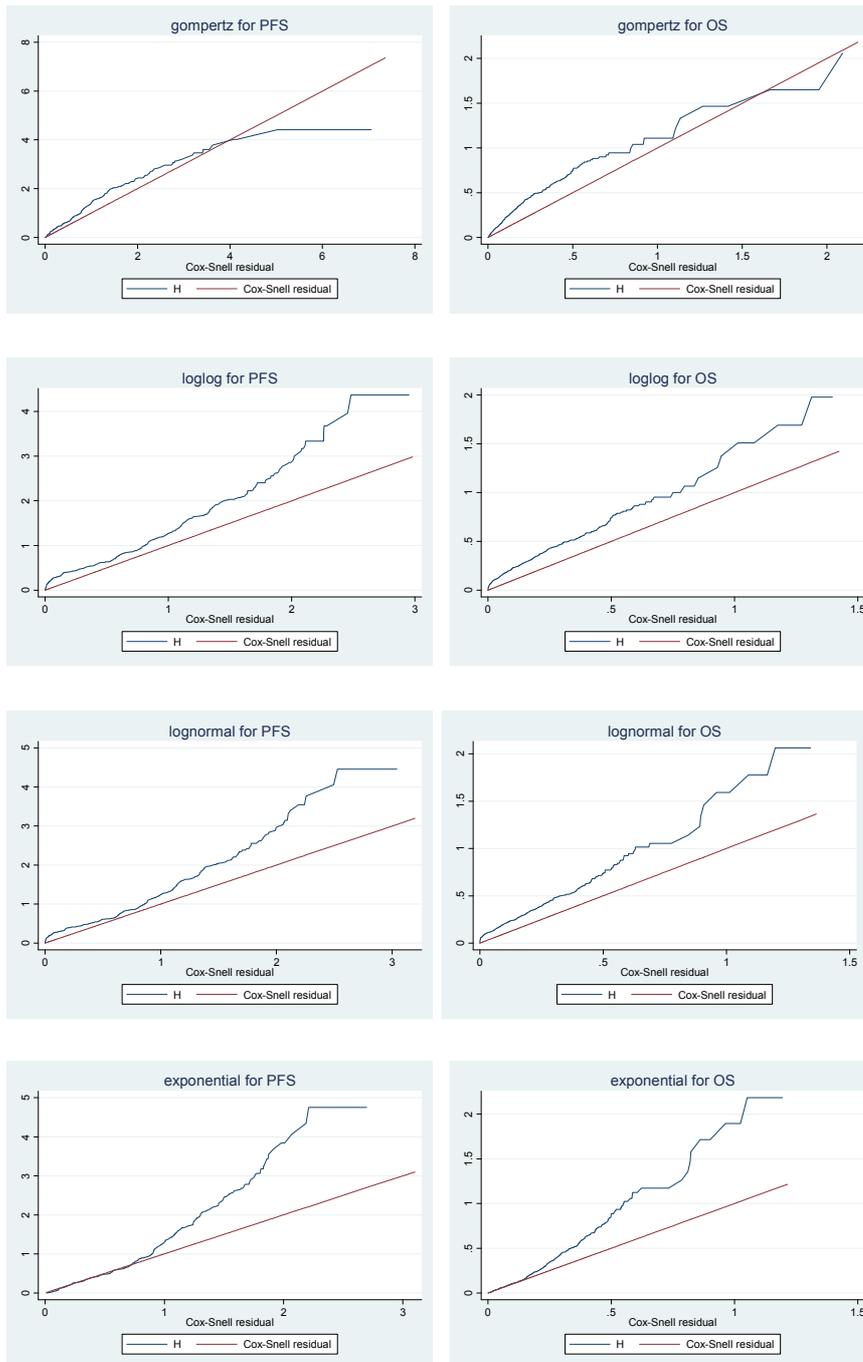
	Rank (AIC)				
	1	2	3	4	5
Paclitaxel/carboplatin EGFR M+	Weibull (204.9)	Log-log (206.0)	Gompz (207.1)	LogN (211.1)	Exp (218.2)
Gefitinib EGFR M+	Weibull (174.6)	Log-log (175.0)	LogN (175.7)	Gompz (177.8)	Exp (195.1)
Both arms, stratified	Weibull (373.1)	Log-log (374.5)	Gompz (378.7)	LogN (380.2)	Exp (409.0)
Both arms, unstratified	Weibull (374.1)	Log-log (375.5)	Gompz (379.2)	LogN (382.3)	Exp (409.0)

- **Evaluation of model residuals**

A further examination of the goodness of fit of the alternative distributions in the unstratified models was made using Cox-Snell residuals. Here the estimated cumulative hazard function of the Cox-Snell residuals (H) is plotted against the Cox-Snell residual (error or unexplained variation after fitting the regression model). If the resulting plot is linear through the origin with a slope of 1 the model can be considered a good fit with the data. Visual inspection of these plots confirmed that the Weibull model was the best fitting model for the IPASS EGFR M + PFS data (figure 7). The Cox-Snell residual plots were less conclusive for the OS data with both the Weibull and Gompertz probability distributions appearing good fits (figure 7).

**Figure 1: Cox-Snell residual plots of the IPASS EGFR M+ PFS and OS models**



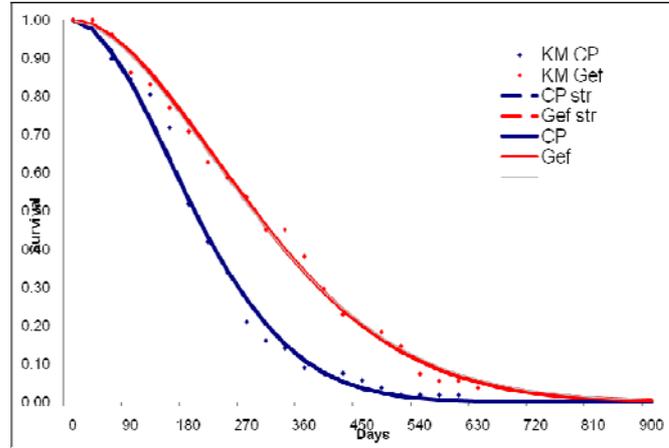


- **Graphical overlay of fitted and observed data**

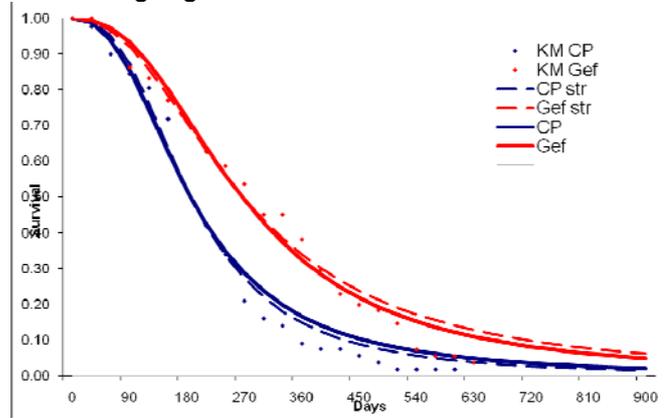
Graphical overlays of the fitted and observed data for the three distributions that appear to be the best fit to the data from the AIC and residual plots (Weibull, log-logistic and Gompertz) are shown below (stratified and unstratified models).

**Figure 2: Fitted probability distributions (unstratified and stratified) and observed data (Kaplan Meier) - PFS**

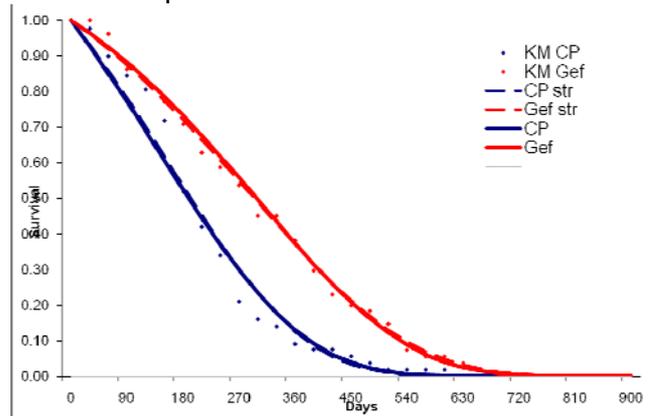
**PFS - Weibull**



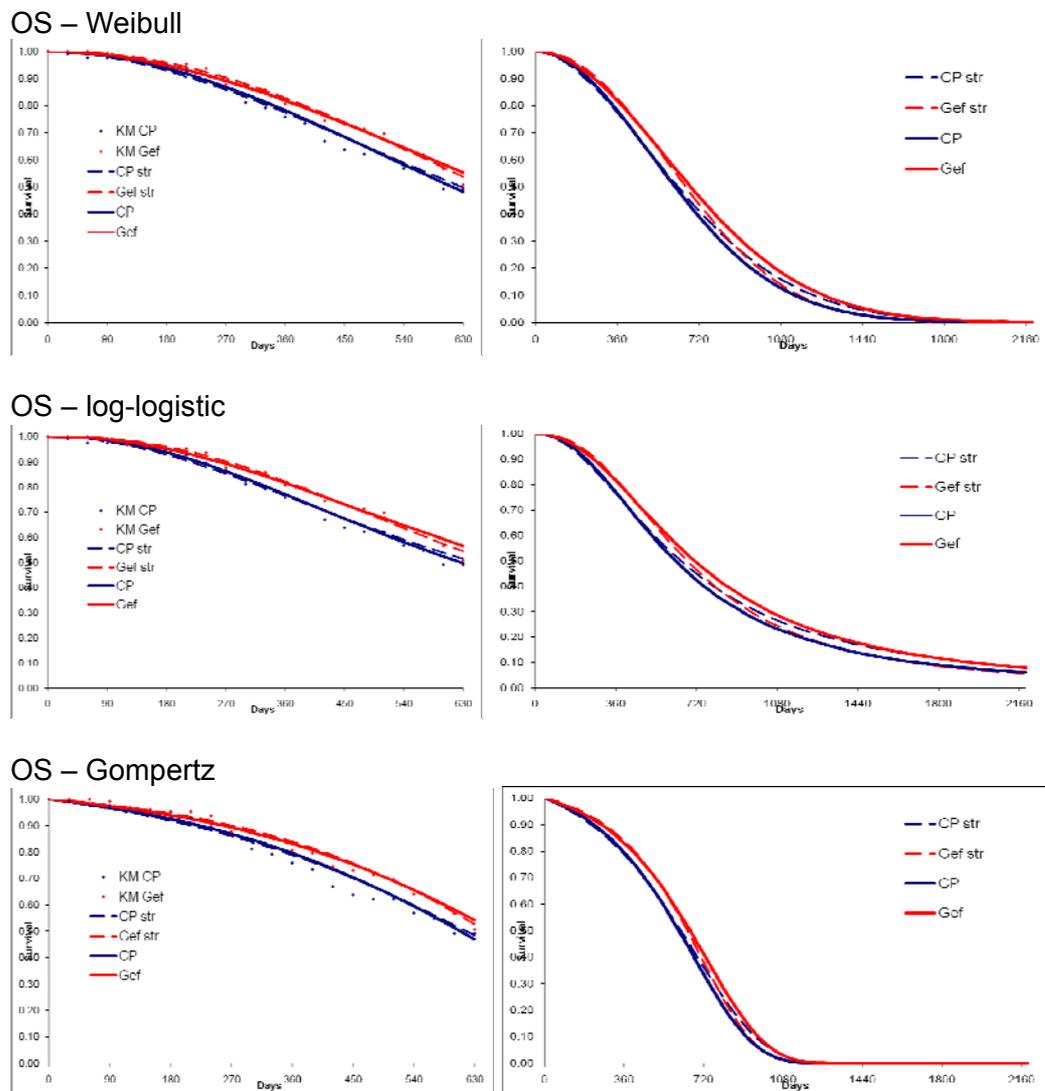
**PFS - Log-logistic**



**PFS - Gompertz**



**Figure 3: Fitted probability distributions (unstratified and stratified) and observed data (Kaplan Meier) during period of observed data (left) and long term extrapolation (right) - OS**



For PFS, the Weibull distribution looks to be the best fit considering both the early data and the tails.

For OS, during the early period of data observation, the Weibull and log-logistic distributions appear to fit the data better than the Gompertz model. In terms of long term survival extrapolation, there are no observed data beyond about 2 years to enable evaluation of the fit of the distributions to the tails. The Gompertz model has a more rapid decline in survival rates than the Weibull model, and the log-logistic has a slower decline than the Weibull model. This is consistent with the known properties of these distributions.

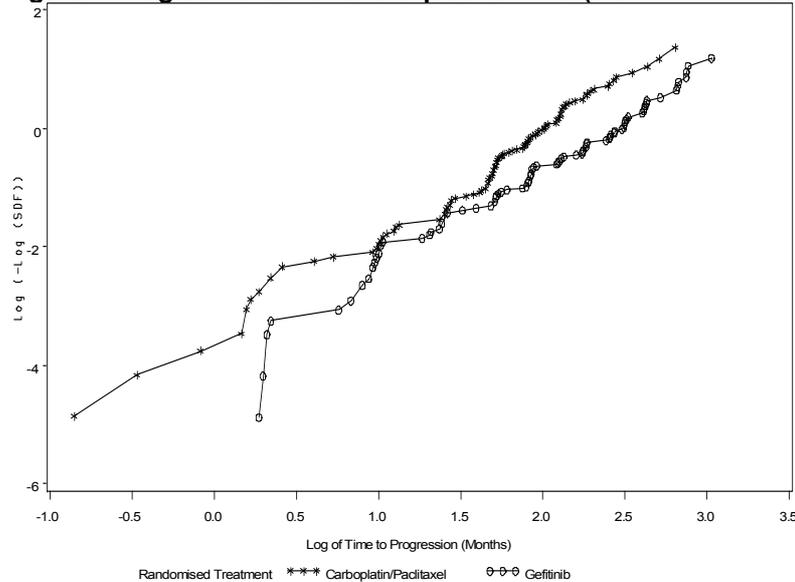
### Suitability of the Proportional Hazards Assumption

Information is presented to address the ERG's concern that the PH assumption (i.e. constant ratio of the hazards between the two treatments across all points in time) may not be applicable to the IPASS EGFR M+ data, and also to evaluate the

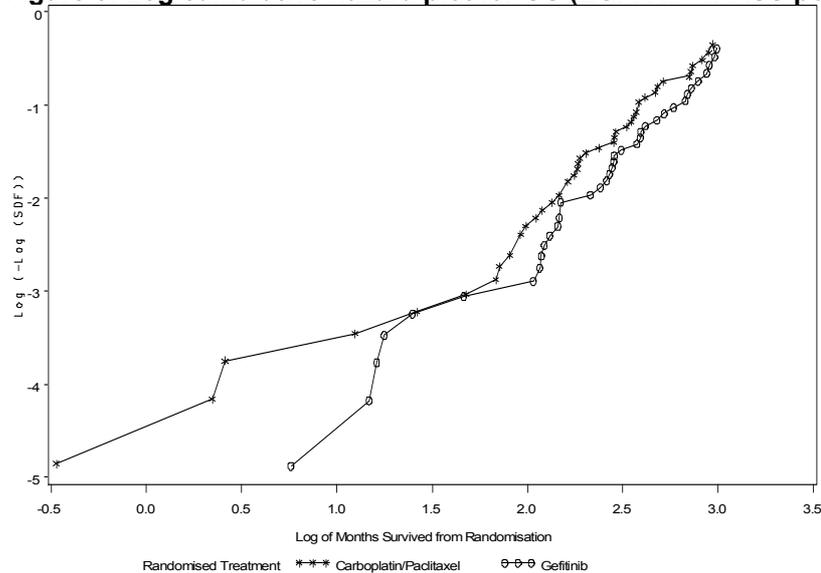
suitability of certain probability distributions and the unstratified model for fitting to the IPASS data.

If the OS and PFS EGFR M+ data from the two treatments in IPASS were to satisfy the PH assumption then the graphs of the log(-log (survival function)) versus log survival time graphs should appear as two parallel lines. As can be seen in figures 4 and 5, the lines of the gefitinib EGFR M+ and paclitaxel/carboplatin EGFR M+ treatment arms do appear approximately parallel, indicating that the PH assumption is likely to be satisfied. Additionally, the lines appear to be quite straight, which is an indication that a Weibull probability distribution may be a good fit to the data.

**Figure 4: Log cumulative hazard plot for PFS (EGFR M+ IPASS population)**



**Figure 5: Log cumulative hazard plot for OS (EGFR M+ IPASS population)**



To investigate this further, formal tests of non-proportionality have also been performed using different methods (see table 6). All the tests produce a non-significant p-value ( $p \geq 0.05$ ) – so the null hypothesis “PH assumption is valid” is not rejected.

**Table 3: Formal tests of the PH assumption for the IPASS EGFR M+ data**

Variable	Test for non PH in the Cox model (likelihood ratio test in SAS) <sup>†</sup>	Test for non PH (whether the independent shape parameters for each treatment are better than a common shape parameter) in the Weibull model	STATA test for non-PH in Cox model <sup>‡</sup>
Overall Survival	P=0.39	P=0.62	P=0.42
Progression-Free Survival	P=0.93	P=0.36	P=0.86

<sup>†</sup>This calculates the difference between  $-2\log L$  from a model with and without a treatment-by-time interaction, and compares this to a chi-square distribution, <sup>‡</sup>This tests the relationship of the hazard function's residual with time.

The above results confirm that it is reasonable to assume proportional hazards in modelling the IPASS EGFR M+ PFS and OS data. This suggests that probability distributions that make the PH assumption (Weibull, exponential, Gompertz) and unstratified models may be appropriate.

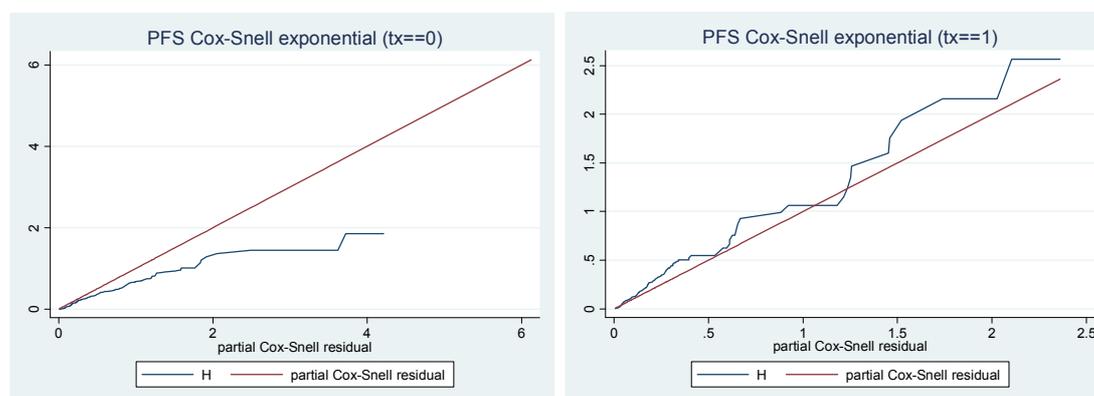
### Exponential “spline” model proposed by ERG

As a standard Weibull model appears to fit the data well and there are no concerns with violation of the PH assumption in the M+ group, AZ do not believe that the less standard exponential “spline” model proposed by ERG is necessary.

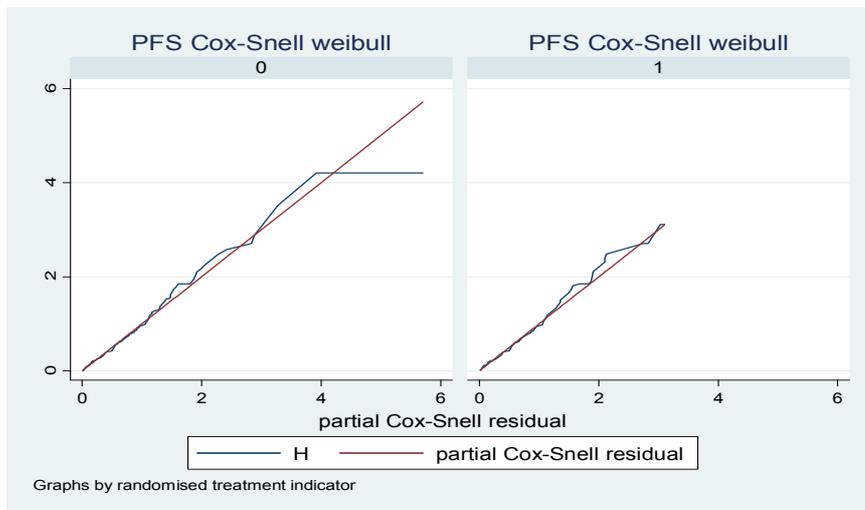
It should also be noted that the ERG analysis was based on digitised Kaplan-Meier graphs rather than individual patient data, and does not reflect the censoring pattern seen in the data, relying as it does on the point estimates of the Kaplan-Meier survival function. Given the apparent concern of the ERG with the shape of the cumulative hazards functions based on the digitised Kaplan-Meiers, we undertook a comparison of exponential models using spline points to the proportional hazards Weibull model (note that the exact same spline analysis as ERG could not be replicated as insufficient details were provided in their report), using Cox-snell residuals. This comparative analysis shows that the Weibull model is a better fit to the data than separate exponential models for each arm with these spline points.

**Figure 6 Comparison of Cox-Snell residuals from exponential models with ‘spline’ points versus proportional hazards Weibull models**

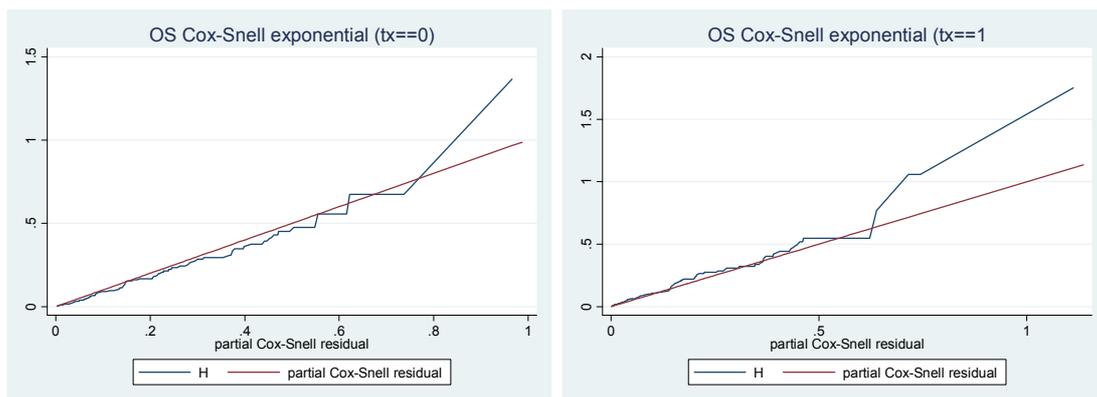
### Progression free survival – exponential spline model



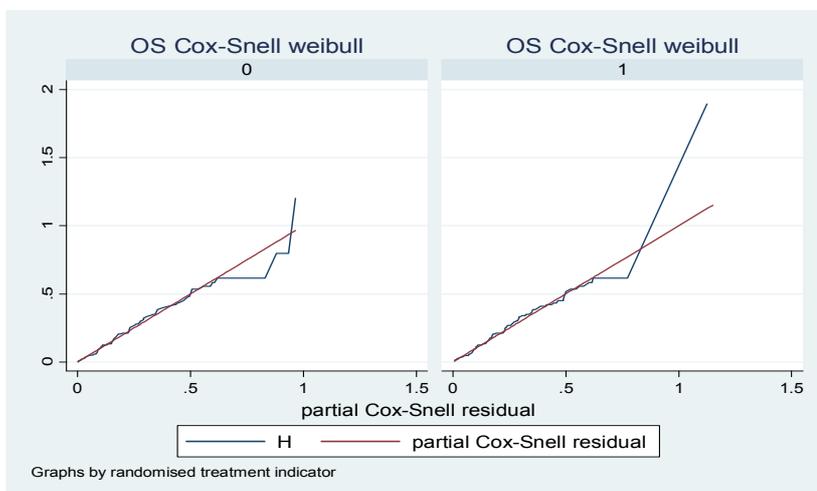
## Progression free survival – Weibull model



## Overall survival – exponential spline model



## Overall survival – Weibull model



**B. Observational evidence on long term survival in aNSCLC and relationship to plausible model fit**

The prognosis of patients with aNSCLC is poor with 2-year survival rates of only 4 to 6% being reported in the literature<sup>2</sup>. However, there is evidence that selected patients may achieve more prolonged survival.

Long-term data on overall survival (approx 10 years of follow up) for a large cohort of NSCLC patients across various disease stages are available from the publication of the IASLC Lung Cancer Staging Project<sup>3</sup>.

Considering the 2,458 disease stage Stage IV patients (IPASS is approx 75% Stage IV) and overlaying fitted curves by eye, all of the 5 probability distributions seem to fit the data well.

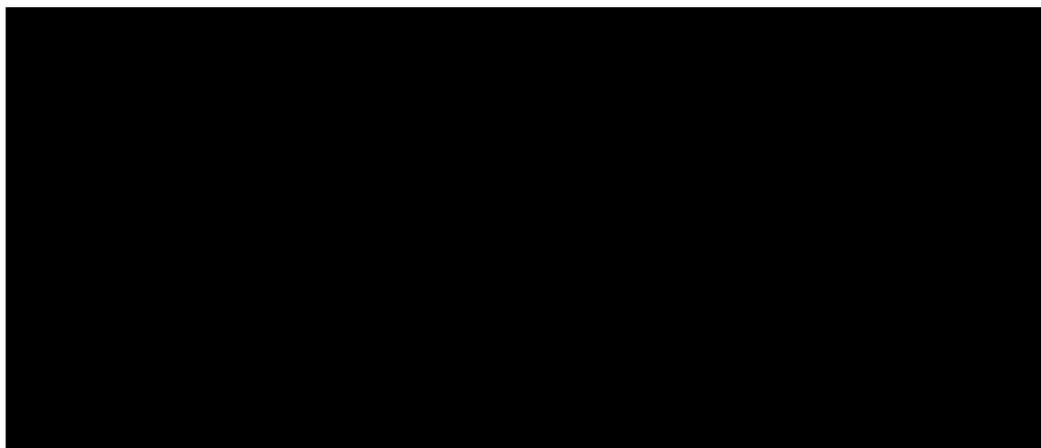
Considering the 1,224 Stage IIIB data in the same manner, it is more difficult to find a distribution that fits well to both the early data and the tails, with long-term survival tending to be under-estimated. The log-logistic distribution appears to best fit the data. However, this dataset is for unselected patients that receive a range of treatments including best supportive care.

Published data on the long-term survival of EGFR M+ patients with aNSCLC receiving 1<sup>st</sup> line therapy is limited (see Appendix E).

The North East Japan Study Group (NEJSG) has provided AstraZeneca with results of their final OS analyses of trial NEJ002<sup>4</sup> (figure 7) [see manufacturer's submission P34 for further details of this trial].

Fitting curves by eye to these data suggests that the Weibull, log-logistic and Gompertz models are all a good fit.

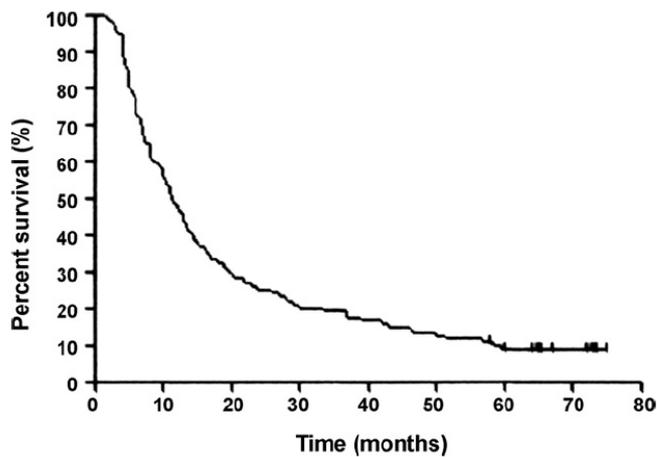
**Figure 7**



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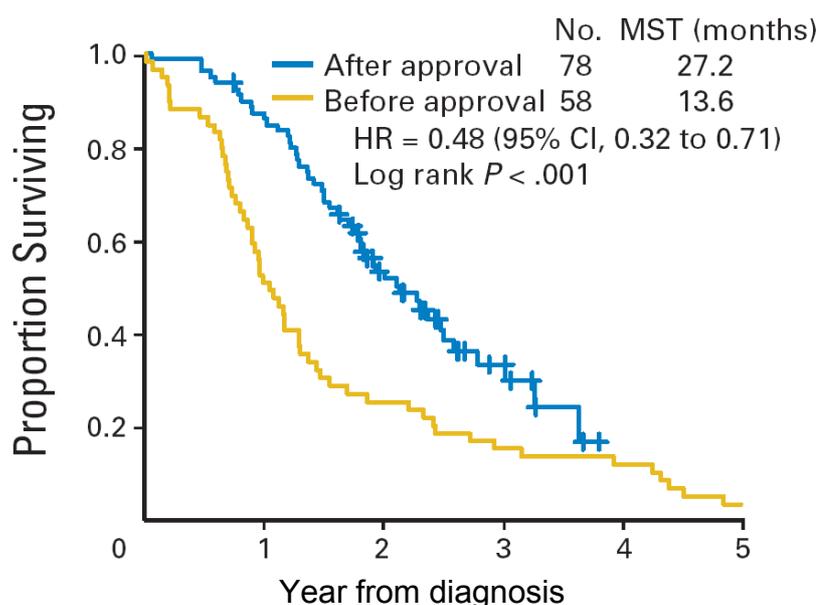
A Japanese study <sup>2</sup> has been reported that was designed to evaluate long-term survival in aNSCLC. One hundred and twenty four patients with aNSCLC that had been treated with chemotherapy were reviewed from September 2002 to October 2003. Ten patients (8%) survived for  $\geq 5$  years (figure 8). Eight of the 10 patients were treated with gefitinib as 2<sup>nd</sup> or 3<sup>rd</sup> line therapy. Fitting distributions by eye to these data suggest that all tend to underestimate long-term survival but the log-logistic distribution appears to be the best fit.

**Figure 8: Long-term survival for all 124 patients with aNSCLC (Kaira 2010)<sup>2</sup>**



A retrospective observational study by Takano et al (2008)<sup>5</sup> sheds some light onto the long-term survival in a EGFR M+ aNSCLC population. In this study, EGFR M+ patients in Japan treated with first line systemic therapy after gefitinib approval were shown to have a significant improvement in OS versus EGFR M+ that had received 1<sup>st</sup> line systemic therapy prior to the approval of gefitinib (MST 27.2 months versus 13.6 months, respectively) (see Figure 9).

**Figure 9: Overall survival in EGFR M+ patients before and after approval of gefitinib.**



It should be noted that the study was limited by being a retrospective historical comparison conducted only in East Asian patients.

In summary, the historical literature supports that for an IPASS type population of predominantly Stage IV EGFR mutation positive patients given active treatment, a Weibull or log-logistic distribution may be a good fit to the long-term survival data.

**C. Independent survival curves and different approaches to applying the hazard ratio**

**Choice of stratified or unstratified models**

The examination of alternative probability distributions indicated that the Weibull model provided the best fit to estimate progression-free survival (PFS) from IPASS EGFR M+ trial data. The graphical overlay shows that the fitted distribution looks very similar for the stratified and unstratified models. As the proportional hazards assumption appears to hold, an unstratified model is suitable.

Consistent with the similarity in the fitted distributions, both the stratified and unstratified Weibull independent survival models estimated a mean difference in PFS in favour of gefitinib of 3.35 months (see table 4). The mean PFS for gefitinib EGFR M+ was 10.1 months (95% CI: 10.0 to 10.3) versus 6.8 months (95% CI: 6.7 to 6.9) for paclitaxel/carboplatin EGFR M+.

**Table 4: Mean PFS estimated for IPASS EGFR M+ population using the Weibull model (STATA)**

	Mean (mth)	Std. Err	95% Conf. Interval	
Weibull Stratified				
Gefitinib EGFR M+	10.1385	0.0743	9.9920	10.2847
Pac/carb EGFR M+	6.7891	0.0367	6.7175	6.8622
$\Delta$ PFS	3.3494	-	-	-

	Mean (mth)	Std. Err	95% Conf. Interval	
Weibull Unstratified				
Gefitinib EGFR M+	10.1267	0.0722	9.9843	10.2687
Pac/carb EGFR M+	6.7775	0.0375	6.7038	6.8514
ΔPFS	3.3492	-	-	-

The Weibull and log-logistic probability distributions appeared to be the best fitting models for the IPASS EGFRM+ overall survival (OS) data. In the short term when data was observed from the IPASS study, the fitted distributions for both the stratified and unstratified models appeared similar. Since the proportional hazards assumptions seem to hold, an unstratified Weibull model would be appropriate.

However, the long-term survival extrapolations looked quite different for the stratified and unstratified models. Visual inspection of the plots showed the tails of the stratified Weibull and log-logistic models crossed after day 930 (2.5 years) and 840 (2.3 years), respectively. We are unable to explain this occurrence but believe it may be partly due to greater variability in one group than other. There is no clinical reason why the survival rates in the gefitinib arm would initially be greater than chemotherapy and then later decline more rapidly and fall below the chemotherapy arm. This finding also conflicts with the conclusion that the proportional hazards assumption is satisfied.

Due to these different long-term extrapolations, there was wide variation in the mean OS estimates produced by the different models, which is in part a reflection of the immaturity of the IPASS OS data (see tables 5 and 6).

**Table 5: Mean OS estimated using the Weibull model (STATA)**

	Mean (mth)	Std. Err	95% Conf. Interval	
Weibull Stratified				
Gefitinib EGFR M+	23.1590	0.2606	22.6458	23.6721
Pac/carb EGFR M+	22.7272	0.2314	22.2715	23.1829
ΔOS	0.4318	-	-	-
Weibull Unstratified				
Gefitinib EGFR M+	24.3867	0.2957	23.8045	24.9689
Pac/carb EGFR M+	21.8077	0.2094	21.3954	22.2352
ΔOS	2.5790	-	-	-

**Table 6: Mean OS estimated using the Log-logistic model (STATA)**

	Mean (mth)	Std. Err	95% Conf. Interval	
Log logistic Stratified				
Gefitinib EGFR M+	30.4328	0.3663	29.7115	31.1540
Pac/carb EGFR M+	33.7426	0.3339	33.0850	34.4002
ΔOS	-3.3098	-	-	-
Log logistic Unstratified				
Gefitinib EGFR M+	34.3205	0.4074	33.5184	35.1227
Pac/carb EGFR M+	30.1027	0.2865	29.5385	30.6669
ΔOS	4.2178	-	-	-

The unstratified Weibull and Log-logistic probability distributions produced mean OS differences in favour of gefitinib of 2.58 months and 4.22 months, respectively. In

contrast, the stratified Weibull model estimated a mean OS difference of just 0.43 months versus pac/carb EGFR M+ and the stratified log-logistic model a mean OS difference of 3.31 months in favour pac/carb EGFR M+.

For the reasons given above and since the proportional hazards assumption appears reasonable, the stratified Weibull and log-logistic OS models were therefore excluded from further analyses and unstratified models are used.

### **Summary – choice of probability distribution**

The unstratified Weibull model appears to be the most appropriate probability distribution for modelling the PFS and OS data in EGFR mutation positive patients in the IPASS trial, for the following reasons:

- It is the best fit to the data, as indicated by the lowest AIC and examination of residual plots
- The proportional hazards assumption appears to be satisfied
- It is a reasonable fit to historical long term survival data in similar populations
- It is a conventional approach used in health economic evaluation
- It provides a conservative estimate of the OS advantage of gefitinib versus doublet chemotherapy

### **Different approaches to applying the hazard ratio**

The mixed treatment comparison (MTC) has been reconfigured to incorporate the three gefitinib randomised controlled trials for the treatment of EGFR mutation positive patients with locally advanced or metastatic NSCLC (IPASS, NEJSG, First-SIGNAL)<sup>1,4,6</sup>. It has also been adjusted to use gefitinib as the “baseline” treatment so that the calculated hazard ratios for OS and PFS can be applied to the gefitinib treatment arm from IPASS. The results are presented in Appendix A.

The amended MTC produces a similar hazard ratio (HR) for gefitinib and pemetrexed/cisplatin for OS and demonstrates a significant advantage, at the 5% significance level, for gefitinib over all of the other doublet chemotherapies included in the network (including pemetrexed/cisplatin) for PFS.

As an alternative approach to calculating hazard ratios for OS and PFS, it could be assumed that for efficacy all standard doublet chemotherapies are equivalent with the exception of pemetrexed/cisplatin. In this case the best available evidence for gefitinib compared to all doublet chemotherapies (except pemetrexed/cisplatin) would be from a meta-analysis of IPASS, NEJSG, and First-SIGNAL (Appendix B).

Under this gross assumption of equivalence, an adjusted indirect comparison of gefitinib compared to pemetrexed/cisplatin could also be conducted using the results from the previous meta-analysis (Appendix B) and the results from the non-squamous sub-group from Scagliotti 2008<sup>7</sup> using the method described by Bucher and colleagues<sup>8</sup>. The results from this analysis are consistent with the results from the amended MTC (Appendix C).

### *Results*

Mean PFS and OS estimates derived using the economic model and applying HRs (see Appendix A) for the indirect comparators to the paclitaxel/carboplatin EGFR M+ or gefitinib EGFR M+ baselines are presented in tables 7a/7b and 8a/8b respectively.

**Table 7a: Mean PFS and OS estimates using pac/carb EGFR M+ baseline (Weibull unstratified model) [Economic Model]**

	Mean PFS (months)	Mean OS (months)
Gefitinib EGFR M+ (IPASS)	10.22	24.08
Gem/carb EGFR M+	5.98	22.11
Gem/cis EGFR M+	7.09	22.60
Pem/cis EGFR M+	7.77	24.60

**Table 7b: Pairwise comparison of mean PFS and OS using pac/carb EGFR M+ baseline (Weibull unstratified model) [Economic Model]**

	$\Delta$ PFS (months)	$\Delta$ OS (months)
Gefitinib EGFR M+ (IPASS) <i>versus</i> :	-	-
Gem/carb EGFR M+	4.24	1.98
Gem/cis EGFR M+	3.13	1.49
Pem/cis EGFR M+	2.45	-0.51

**Table 8a: Mean PFS and OS estimates using gefitinib EGFR M+ baseline (Weibull unstratified model) [Economic Model]**

	Mean PFS (months)	Mean OS (months)
Gefitinib EGFR M+ (IPASS) <i>versus</i> :	10.22	24.08
Gem/carb EGFR M+	5.45	21.56
Gem/cis EGFR M+	6.41	21.93
Pem/cis EGFR M+	6.79	24.46

**Table 8b: Pairwise comparison of mean PFS and OS using gefitinib EGFR M+ baseline (Weibull unstratified model) [Economic Model]**

	$\Delta$ PFS (months)	$\Delta$ OS (months)
Gefitinib EGFR M+ (IPASS) <i>versus</i> :	-	-
Gem/carb EGFR M+	4.77	2.52
Gem/cis EGFR M+	3.81	2.16
Pem/cis EGFR M+	3.43	-0.38

1.7 The provision of individual patient level data from IPASS to enable the Evidence Review Group (ERG) to validate key aspects of the submitted model, including the modelling of overall survival and progression-free survival, the choice of parameter values and structural assumptions.

*AstraZeneca's response:*

AstraZeneca have considered the request to provide individual patient level data from IPASS to the Liverpool ERG. This dataset forms the core of gefitinib's intellectual property and is rarely shared outside of clinical development. Therefore AstraZeneca is unable to supply this requested dataset.

1.8 An analysis to determine the robustness of the incremental cost-effectiveness ratio (ICER) to alternative survival distributions for progression-free survival and overall survival curves for gefitinib and paclitaxel/carboplatin from the IPASS data. The analysis should also provide evidence on the alternative approaches to applying the hazard ratio to link to other comparators. These cost-effectiveness analyses should include amended costs for first-line chemotherapy to account for a lower level of dosing in female patients and varying the number of first-line chemotherapy cycles between four and six.

*AstraZeneca's response:*

*AstraZeneca maintain their opinion that the base case analysis should reflect the maximum number of chemotherapy (CTX) cycles used in RCT (IPASS) on which the economic model is based. In IPASS, patients randomised to paclitaxel/carboplatin received a maximum of 6 cycles of chemotherapy (median number of cycles = 6). To draw conclusions on the cost-effectiveness of gefitinib based on a maximum of 4 cycles of CTX without accounting for any loss in treatment benefit introduces bias and is methodologically unsound.*

Two sets of tables of cost-effectiveness results have been presented. The first provides the ICERs for gefitinib at the original SPA price and the second (highlighted in red) illustrates the impact of the delayed invoicing proposal on the ICER.

The variables used in the base case analysis are presented in Appendix F. Costs for 1<sup>st</sup> line chemotherapy, average BSA (to account for lower CTX dosing used for female patients), time horizon (6 years), discounting method, costs of 2<sup>nd</sup> line therapy followed by chemotherapy have all been amended as outlined in the ERG report.

The Weibull (unstratified) model for the independent arms in IPASS were used to model PFS and OS (see 1.4 and 1.5 for rationale).

A. The Appraisal Committee requested a comparison of gefitinib versus gemcitabine/carboplatin and gemcitabine/cisplatin using two alternative approaches:

Scenario a) assuming the same PFS and OS as estimated for paclitaxel/carboplatin through independent survival curve fitting from IPASS using gemcitabine related costs and adverse events

Scenario b) applying the HR from the MTC of gemcitabine regimens to the independent curves for paclitaxel/carboplatin from IPASS, and using gemcitabine related costs and adverse events (see Appraisal Committee Document 4.11 P28)

Scenario a: Markov model base case results (discounted) [same PFS and OS as estimated for paclitaxel/carboplatin]:

**Table 9a: Maximum 6 cycles (mean # cycles gem/carb (cis) = 5.2). Modelled with original gefitinib SPA scheme.**

Scenario a	Mean Costs	Mean QALYs	Δ mean Costs	Δ mean QALYs	ICER (£/QALY)
Gefitinib EGFR M+ versus	£27,599 £31,992	1.058 1.226	-	-	-
Gem/carb EGFR M+	£22,390 £26,357	0.903 1.057	£5,209 £5,565	0.155 0.170	£33,610 £32,839
Gem/cis EGFR M+	£22,793 £26,760	0.905 1.059	£4,806 £5,162	0.153 0.164	£31,426 £30,834

Black text = base case Weibull (unstratified mode) for PFS OS. Blue = Weibull (unstratified) PFS model and Log-logistic (unstratified) OS model

**Table 9b: Maximum 6 cycles (mean # cycles gem/carb (cis) = 5.2). Modelled with amended gefitinib SPA scheme to incorporate the delayed invoicing proposal**

Scenario a	Mean Costs	Mean QALYs	Δ mean Costs	Δ mean QALYs	ICER (£/QALY)
Gefitinib EGFR M+ versus	£26,489 <b>£30,811</b>	1.058 <b>1.226</b>	-	-	-
Gem/carb EGFR M+	£22,390 <b>£26,357</b>	0.903 <b>1.057</b>	£4,099 <b>£4,455</b>	0.155 <b>0.170</b>	£26,448 <b>£26,288</b>
Gem/cis EGFR M+	£22,793 <b>£26,760</b>	0.905 <b>1.059</b>	£3,696 <b>£4,052</b>	0.153 <b>0.164</b>	£24,167 <b>£24,202</b>

Red (bold) = Weibull (unstratified) PFS model and Log-logistic (unstratified) OS model

**Table 10a: Maximum 5 cycles (mean # cycles gem/carb (cis) = 4.5). Modelled with original gefitinib SPA scheme.**

Scenario a	Mean Costs	Mean QALYs	Δ mean Costs	Δ mean QALYs	ICER (£/QALY)
Gefitinib EGFR M+ versus	£27,599 £31,922	1.058 1.226	-	-	-
Gem/carb EGFR M+	£21,499 £25,466	0.904 1.059	£6,100 £6,456	0.153 0.168	£39,785 £38,474
Gem/cis EGFR M+	£21,830 £25,797	0.906 1.061	£5,769 £6,124	0.151 0.166	£38,132 £36,949

Black text = base case Weibull (unstratified model) for PFS OS. Blue = Weibull (unstratified) PFS model and Log-logistic (unstratified) OS model

**Table 10b: Maximum 5 cycles (mean # cycles gem/carb (cis) = 4.5). Modelled with amended gefitinib SPA scheme to incorporate the delayed invoicing proposal.**

Scenario a	Mean Costs	Mean QALYs	Δ mean Costs	Δ mean QALYs	ICER (£/QALY)
Gefitinib EGFR M+ versus	£26,489 £30,811	1.058 1.226	-	-	-
Gem/carb EGFR M+	£21,499 £25,466	0.904 1.059	£4,990 £5,346	0.153 0.168	£32,544 £31,857
Gem/cis EGFR M+	£21,038 £25,797	0.906 1.061	£4,658 £5,014	0.151 0.166	£30,793 £30,251

Red (bold) = Weibull (unstratified) PFS model and Log-logistic (unstratified) OS model

**Table 11a: Maximum 4 cycles (mean # cycles gem/carb (cis) = 3.7). Modelled with original gefitinib SPA scheme.**

Scenario a	Mean Costs	Mean QALYs	Δ mean Costs	Δ mean QALYs	ICER (£/QALY)
Gefitinib EGFR M+ versus	£27,599 £31,922	1.058 1.226	-	-	-
Gem/carb EGFR M+	£20,520 £24,487	0.906 1.060	£7,079 £7,434	0.152 0.166	£46,725 £44,794
Gem/cis EGFR M+	£20,774 £24,741	0.908 1.063	£6,825 £7,181	0.149 0.164	£45,672 £43,810

Black text = base case Weibull (unstratified mode) for PFS OS. Blue = Weibull (unstratified) PFS model and Log-logistic (unstratified) OS model

**Table 11b: Maximum 4 cycles (mean # cycles gem/carb (cis) = 3.7). Modelled with amended gefitinib SPA scheme to incorporate the delayed invoicing proposal.**

Scenario a	Mean Costs	Mean QALYs	Δ mean Costs	Δ mean QALYs	ICER (£/QALY)
Gefitinib EGFR M+ versus	£26,489 <b>£30,811</b>	1.058 <b>1.226</b>	-	-	-
Gem/carb EGFR M+	£20,520 <b>£24,487</b>	0.906 <b>1.060</b>	£5,968 <b>£6,324</b>	0.152 <b>0.166</b>	£39,397 <b>£38,105</b>
Gem/cis EGFR M+	£20,774 <b>£24,741</b>	0.908 <b>1.063</b>	£5,715 <b>£6,071</b>	0.149 <b>0.164</b>	£38,243 <b>£37,036</b>

Red (bold) = Weibull (unstratified) PFS model and Log-logistic (unstratified) OS model

Scenario b: Markov model base case results (discounted) [PFS and OS estimated using HRs from MTC]:

Paclitaxel/carboplatin EGFR M+ used a baseline for the indirect comparators (tables 12a – 14b).

**Table 12a: Maximum 6 cycles (mean # cycles gem/carb = 5.0, gem/cis = 5.3). Modelled with original gefitinib SPA scheme**

Scenario b	Mean Costs	Mean QALYs	Δ mean Costs	Δ mean QALYs	ICER (£/QALY)
Gefitinib EGFR M+ <i>versus</i>	£27,599	1.058	-	-	-
Gem/carb EGFR M+	£23,343	0.908	£4,256	0.150	£28,429
Gem/cis EGFR M+	£23,480	0.945	£4,119	0.113	£36,487

**Table 12b: Maximum 6 cycles (mean # cycles gem/carb = 5.0, gem/cis = 5.3). Modelled with amended gefitinib SPA scheme to incorporate the delayed invoicing proposal.**

Scenario b	Mean Costs	Mean QALYs	Δ mean Costs	Δ mean QALYs	ICER (£/QALY)
Gefitinib EGFR M+ <i>versus</i>	£26,489	1.058	-	-	-
Gem/carb EGFR M+	£23,343	0.908	£3,146	0.150	£21,014
Gem/cis EGFR M+	£23,480	0.945	£3,009	0.113	£26,652

**Table 13a: Maximum 5 cycles (mean # cycles gem/carb = 4.4, gem/cis = 4.5). Modelled with original gefitinib SPA scheme.**

Scenario b	Mean Costs	Mean QALYs	Δ mean Costs	Δ mean QALYs	ICER (£/QALY)
Gefitinib EGFR M+ <i>versus</i>	£27,599	1.058	-	-	-
Gem/carb EGFR M+	£22,523	0.909	£5,076	0.148	£34,249
Gem/cis EGFR M+	£22,492	0.946	£5,107	0.111	£45,940

**Table 13b: Maximum 5 cycles (mean # cycles gem/carb = 4.4, gem/cis = 4.5). Modelled with amended gefitinib SPA scheme to incorporate the delayed invoicing proposal.**

Scenario b	Mean Costs	Mean QALYs	Δ mean Costs	Δ mean QALYs	ICER (£/QALY)
Gefitinib EGFR M+ versus	£26,489	1.058	-	-	-
Gem/carb EGFR M+	£22,523	0.909	£4,046	0.148	£26,758
Gem/cis EGFR M+	£22,492	0.946	£3,997	0.111	£35,954

**Table 14a: Maximum 4 cycles (mean # cycles gem/carb = 3.6, gem/cis = 3.7). Modelled with the original gefitinib SPA scheme.**

Scenario b	Mean Costs	Mean QALYs	Δ mean Costs	Δ mean QALYs	ICER (£/QALY)
Gefitinib EGFR M+ versus	£27,599	1.058	-	-	-
Gem/carb EGFR M+	£21,602	0.911	£5,997	0.147	£40,938
Gem/cis EGFR M+	£21,414	0.948	£6,184	0.109	£56,586

**Table 14b: Maximum 4 cycles (mean # cycles gem/carb = 3.6, gem/cis = 3.7). Modelled with amended gefitinib SPA scheme to incorporate the delayed invoicing proposal.**

Scenario b	Mean Costs	Mean QALYs	Δ mean Costs	Δ mean QALYs	ICER (£/QALY)
Gefitinib EGFR M+ versus	£26,489	1.058	-	-	-
Gem/carb EGFR M+	£21,602	0.911	£4,887	0.147	£33,359
Gem/cis EGFR M+	£21,414	0.948	£5,074	0.109	£46,428

B. The Appraisal Committee requested an exploration of different approaches to applying the HR for the comparison of gefitinib with pemetrexed as follows:

Scenario a) applying the HR from the MTC for pemetrexed/cisplatin to the independent survival curves for paclitaxel/carboplatin from IPASS, and using pemetrexed-related costs and adverse events

Scenario b) applying an indirectly derived HR for pemetrexed/cisplatin compared to gefitinib to the independent survival curve for gefitinib from IPASS, and using pemetrexed related costs and adverse events

Scenario a: Markov model base case results (discounted)

**Table 15: Maximum # chemotherapy cycles varied from 6 to 4 (paclitaxel/carboplatin EGFR M+ used as a baseline).**

Scenario a	Mean Costs	Mean QALYs	Δ mean Costs	Δ mean QALYs	ICER (£/QALY)
Gefitinib EGFR M+ <i>versus</i>	£27,599 £26,489	1.058 1.058	-	-	-
Pem/cis EGFR M+ Max 6 cycles, mean = 5.4	£27,436 £27,436	1.029 1.029	£163 -£947	0.029 0.029	£5,667 Dominant*
Pem/cis EGFR M+ Max 5 cycles, mean = 4.6	£26,038 £26,038	1.031 1.031	£1,561 £451	0.027 0.027	£57,918 £16,727
Pem/cis EGFR M+ Max 4 cycles, mean = 3.8	£24,534 £24,534	1.033 1.033	£3,065 £1,955	0.025 0.025	£122,615 £78,200

Red text = Modelled with amended gefitinib SPA scheme to incorporate the delayed invoicing proposal.

\* Dominant = gefitinib is less expensive and more effective than pemetrexed/cisplatin

Scenario b: Markov model base case results (discounted)

**Table 16: Maximum # chemotherapy cycles varied from 6 to 4 (gefitinib EGFR M+ used as a baseline).**

Scenario a	Mean Costs	Mean QALYs	Δ mean Costs	Δ mean QALYs	ICER (£/QALY)
Gefitinib EGFR M+ <i>versus</i> :	£27,599 £26,489	1.058 1.058	-	-	-
Pem/cis EGFR M+ Max 6 cycles, mean = 5.2	£27,926 £27,926	1.009 1.009	-£327 -£1,438	0.049 0.049	Dominant* Dominant*
Pem/cis EGFR M+ Max 5 cycles, mean = 4.5	£26,625 £26,625	1.011 1.011	£755 -£136	0.047 0.047	£29,637 Dominant*
Pem/cis EGFR M+ Max 4 cycles, mean = 3.7	£25,196 £25,196	1.013 1.013	£2,403 £1,293	0.045 0.045	£53,366 £28,710

Red text = Modelled with amended gefitinib SPA scheme to incorporate the delayed invoicing proposal.

\* Dominant = gefitinib is less expensive and more effective than pemetrexed/cisplatin

1.9 Further analysis to explore the sensitivity of the ICER to:

1.10 varying the prevalence of EGFR-TK mutations between 5% and 17%, taking into account different scenario costs, comorbidities and the probability of obtaining a specimen suitable for testing (including possible repeat biopsy and the possibility of not obtaining a useful result).

1.11 alternative assumptions about the volume, and hence cost, of the EGFR-TK mutation tests carried out.

*AstraZeneca's response:*

AstraZeneca has been funding the cost of EGFR test in NHS and commercial diagnostic laboratories following the approval gefitinib in June 2009. The results of the EGFR-TK tests on the lung cancer tissue samples that has been sent to these laboratories since this arrangement has been in place is presented in Table 17.

The average EGFR-TK rate in the UK currently is 17.25% (range 5.3% to 21.1%). It is important to note that no stipulation has been made for pre-selection based on patient characteristics.

An EGFR-TK testing failure rate of 5.3% (range 0% to 11.76%) has been reported to date. It could be expected that this failure rate will improve further as tissue sample quality and testing techniques are refined. Feedback AstraZeneca received from lung cancer specialists attending an advisory panel in January 2010 suggest the possibility of conducting a repeat biopsy in patients with aNSCLC is remote.

In light of the above information, EGFR-TK testing costs have been increased by 5% to account for test failures (table 18).

**Table 17: UK Mutation Data to February 10<sup>th</sup> 2010**

Variable	Lab21 N (%)	Cardiff N (%)	Birmingham N (%)	Manchester N (%)	Aberdeen N (%)	Marsden N (%)	Sheffield N (%)	Total N (%)
Tests reported	90	39	73	41	63	17	19	342
Males	50	19	NR	15	19	NR	12	115 (46%)
Females	40	20	NR	26	41	NR	7	134 (54%)
Gender Not Reported	0	0	73	0	3	17	0	–
Non Squamous	56	18	32	7	62	NR	5	180 (52.6%)
Squamous	5	4	NA	0	1	NR	12	22 (6.4%)
Histology NR	29	17	41	34	0	17	2	140 (41%)
EGFR mutation rate	19 (21.1%)	5 (12.8%)	15 (19.18%)	5 (12.2%)	12 (19.0%)	2 (11.76%)	1 (5.3%)	<b>59</b> <b>(17.25%)</b>
Failed Tests	9 (10.0%)	1 (2.6%)	2 (2.7%)	0 (0%)	2 (3.1%)	2 (11.76%)	2 (10.5%)	18 (5.3%)
Male EGFR mutation rate	6 (8.3%)	1 (5.2%)	NR	2 (13.3%)	4 (21%)	NR	1 (5.2%)	14 (12.1%)

Variable	Lab21 N (%)	Cardiff N (%)	Birmingham N (%)	Manchester N (%)	Aberdeen N (%)	Marsden N (%)	Sheffield N (%)	Total N (%)
Female EGFR mutation rate	13 (32.5%)	4 (20%)	NR	3 (11.5%)	8 (19.5%)	NR	0	28 (20.9%)

NR = not reported, NA = not available

Pemetrexed is recommended for restricted use by NICE for the 1<sup>st</sup> line treatment in a subgroup of patients with aNSCLC with adenocarcinoma [and large cell carcinoma]. Data from a large Spanish screening study<sup>9</sup> has reported an EGFR mutation rate of 17% in lung cancer patients with adenocarcinoma. Given the NICE restriction, gefitinib would only displace pemetrexed as a 1<sup>st</sup> line treatment for patients with adenocarcinoma. It would not be appropriate to conduct sensitivity analyses using the EGFR-TK mutation rate of 5% to 17% for this comparator.

Two-way sensitivity analyses have been conducted to examine the ICER of gefitinib versus gemcitabine/carboplatin taking into account variations of EGFR-TK mutation rate (5% to 17%) and EGFR testing costs (£210 per test to £157.5 per test) (Table 18). The Weibull (unstratified) models for PFS and OS, a maximum of 6 CTX cycles and the PFS and OS HRs from the MTC were used to generate the ICERs in the economic model. Paclitaxel/carboplatin EGFR mutation positive was used as the baseline.

Results are presented with the original gefitinib SPA scheme and the amended scheme (red text).

**Table 18: Two-way sensitivity analysis varying EGFR-TK mutation rate and testing costs**

Cost EGFR-TK Test EGFR-TK Mutation Rate	ICER (£/QALY)		
	5%	10%	17%
<b>£210.00</b>	£49,643 <b>£42,227</b>	£35,616 <b>£28,200</b>	£29,840 <b>£22,424</b>
<b>£178.50</b>	£45,435 <b>£38,019</b>	£33,512 <b>£26,096</b>	£28,602 <b>£21,187</b>
<b>£157.50</b>	£42,629 <b>£35,214</b>	£32,109 <b>£24,694</b>	£27,777 <b>£20,362</b>

Black text = original gefitinib SPA scheme. Red text = amended gefitinib SPA scheme incorporating the delayed invoicing proposal

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(4)

(Academic-in-confidence)

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## Appendix A:

Results of the updated mixed treatment comparison incorporating gefitinib within the network and adjusted to set gefitinib as the baseline treatment.

### Overall Survival

Treatment	Mean	95% Credible Interval	
		Lower	Upper
Gefitinib	1.00	-	-
Docetaxel/Carboplatin	1.34	0.90	1.93
Docetaxel/Cisplatin	1.23	0.86	1.70
Gemcitabine/Carboplatin	1.24	0.81	1.82
Gemcitabine/Cisplatin	1.20	0.86	1.61
Paclitaxel/Carboplatin	1.29	0.95	1.71
Paclitaxel/Cisplatin	1.16	0.83	1.58
Pemetrexed/Cisplatin	0.97	0.68	1.35
Vinorelbine/Carboplatin	ND	ND	ND
Vinorelbine/Cisplatin	1.40	0.98	1.93

ND = no data

### Progression-Free Survival

Treatment	Mean	95% Credible Interval	
		Lower	Upper
Gefitinib	1.00	-	-
Docetaxel/Carboplatin	ND	ND	ND
Docetaxel/Cisplatin	2.67	1.96	3.55
Gemcitabine/Carboplatin	3.11	1.63	5.39
Gemcitabine/Cisplatin	2.32	1.81	2.91
Pemetrexed/Cisplatin	2.09	1.58	2.69
Paclitaxel/Carboplatin	2.53	2.05	3.08
Paclitaxel/Cisplatin	2.86	2.12	3.74
Vinorelbine/Carboplatin	ND	ND	ND
Vinorelbine/Cisplatin	2.48	1.84	3.27

ND = no data

Results of the original mixed treatment using paclitaxel/carboplatin as the baseline treatment.

### Overall Survival

Treatment	Mean	95% Credible Interval	
		Lower	Upper
Paclitaxel/Carboplatin	1.00	-	-
Paclitaxel/Cisplatin	0.91	0.80	1.04
Docetaxel/Carboplatin	1.03	0.80	1.33
Docetaxel/Cisplatin	0.94	0.78	1.14
Gemcitabine/Carboplatin	0.96	0.73	1.23
Gemcitabine/Cisplatin	0.92	0.81	1.04
Pemetrexed/Cisplatin	0.78	0.65	0.93
Vinorelbine/Carboplatin	ND	ND	ND
Vinorelbine/Cisplatin	1.08	0.90	1.28

ND = no data

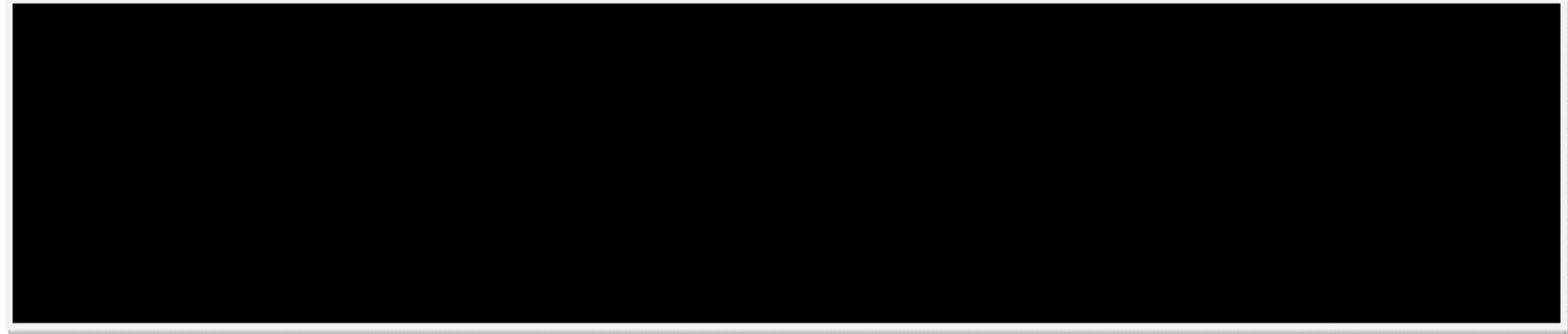
### Progression-Free Survival

Treatment	Mean	95% Credible Interval	
		Lower	Upper
Paclitaxel/Carboplatin	1.00	-	-
Paclitaxel/Cisplatin	1.14	0.93	1.39
Docetaxel/Carboplatin	ND	ND	ND
Docetaxel/Cisplatin	1.06	0.85	1.33
Gemcitabine/Carboplatin	1.25	0.69	2.08
Gemcitabine/Cisplatin	0.92	0.81	1.06
Pemetrexed/Cisplatin	0.88	0.74	1.05
Vinorelbine/Carboplatin	ND	ND	ND
Vinorelbine/Cisplatin	0.99	0.80	1.21

ND = no data

**Appendix B:**

*Figure 1.*



*Figure 2.*



Figure 3.



Figure 4.



## Appendix C:

Comparison of the results of different methods for conducting an adjusted indirect comparison of gefitinib vs pemetrexed/cisplatin

Indirect comparison	Outcome	Hazard Ratio	95% Confidence/Credible Interval	
			Lower	Upper
Bucher method <sup>8</sup>	OS	0.98	0.71	1.36
	PFS	2.24	1.76	2.84
Mixed treatment comparison	OS	0.97	0.68	1.35
	PFS	2.09	1.58	2.69

OS = overall survival; PFS = progression-free survival

HR>1 favours gefitinib, HR<1 favours pemetrexed/cisplatin

Appendix D:

Figure 5.



Figure 6.





## Appendix E:

Epidemiological or observational trials reporting long-term survival in EGFR mutation positive patients with aNSCLC receiving 1<sup>st</sup> line therapy.

### Methods:

A systematic search of the literature was conducted (29/01/2010) to identify publications that had reported long-term survival in chemotherapy naive EGFR mutation positive patients with locally advanced or metastatic NSCLC that had been treated with gefitinib or doublet chemotherapy.

The bibliographic databases that were searched in OVID included:

- Excerpta Medica Database (EMBASE)
- Index Medicus (MEDLINE)
- Biology Abstracts (BIOSIS)

Observation or epidemiological studies were considered of potential relevance to this search enquiry. Case reports were considered to offer insufficient information to help address the question raised by the Appraisal Committee and were therefore excluded.

The search was limited to English language articles that had been published from 2000 to date. Reference lists of potentially relevant articles were also reviewed to capture any articles that may have been missed.

In addition, long-term survival data for EGFR mutation positive aNSCLC that had been presented at internal conferences was requested from clinical experts within AstraZeneca.

### Search strategy:

Ovid Technologies, Inc. Email Service

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Search for: 12 and 13

Results: 1-190

Database: BIOSIS Previews, EMBASE, Ovid MEDLINE(R)

Search Strategy:

- 
- 1 ((epidermal adj growth adj factor adj receptor\$1) or EGFR\$3).mp. [mp=ab, bc, bo, bt, cb, cc, ds, ge, gn, mc, mi, mq, or, ps, sq, st, ti, tm, tn, sh, hw, ot, dm, mf, nm, ui] (73777)
  - 2 ((advanced or metastatic) and lung and (cancer\$3 or carcinoma\$1 or adenocarcinoma\$1)).ti. (10012)
  - 3 1 and 2 (595)
  - 4 (surviv\$2 or mortalit\$3).mp. [mp=ab, bc, bo, bt, cb, cc, ds, ge, gn, mc, mi, mq, or, ps, sq, st, ti, tm, tn, sh, hw, ot, dm, mf, nm, ui] (2126593)
  - 5 3 and 4 (435)
  - 6 limit 5 to english language (399)
  - 7 limit 6 to human (399)
  - 8 limit 7 to yr="2000 - 2010" (396)
  - 9 remove duplicates from 8 (234)
  - 10 from 9 keep 1-30 (30)

- 11 from 9 keep 1-234 (234)
  - 12 from 11 keep 1-234 (234)
  - 13 (gefitinib or Iressa or (EGFR \$3 adj inhibitor\$1)).mp. [mp=ab, bc, bo, bt, cb, cc, ds, ge, gn, mc, mi, mq, or, ps, sq, st, ti, tm, tn, sh, hw, ot, dm, mf, nm, an, ui] (2121801)
  - 14 12 and 13 (190)
  - 15 from 14 keep 1-190 (190)
  - 16 from 14 keep 1-190 (190)
  - 17 from 14 keep 1-190 (190)
  - 18 from 14 keep 1-190 (190)
- 

Conducted: 29/01/10

### **Results:**

The literature search retrieved 190 references to articles of potential relevance to the search enquiry. Five of these references (5/190) specially referred to long-term survival (5/190) in their abstracts. These articles were ordered for further review.

In addition, an abstract (Morita 2008) reporting a combined survival analysis of mutation positive patients from gefitinib phase II trials was found when checking the reference lists.

A summary of 4 studies (4/6) that had reported long-term survival in an EGFR mutation positive aNSCLC population is presented in table X.

Two articles (2/5)<sup>10,11</sup> were excluded because they were case reports describing long-term survival in aNSCLC patients with EGFR mutations that had been treated with gefitinib.

**Table 19.** Long-term survival in patients with aNSCLC harbouring EGFR mutations treated with gefitinib and/or CTX

Study ID	Location	Study size (n)	Characteristics	Results																								
Kaira 2010 <sup>2</sup>	Japan	124 patients who had received chemotherapy as initial treatment.	<table border="0"> <tr> <td>Age ≤65/&gt;65</td> <td>67/57</td> </tr> <tr> <td>Male/Female</td> <td>79/45</td> </tr> <tr> <td>PS 0-1/2-3</td> <td>113/11</td> </tr> <tr> <td>Smoking Y/N</td> <td>76/48</td> </tr> <tr> <td>Histology AC/non-AC</td> <td>94/30</td> </tr> <tr> <td>Stage IIIB/IV</td> <td>27/97</td> </tr> <tr> <td>Gefitinib Y/N</td> <td>67/57</td> </tr> </table> <p>EGFR mutation status was not included in the table of clinical characteristics.</p>	Age ≤65/>65	67/57	Male/Female	79/45	PS 0-1/2-3	113/11	Smoking Y/N	76/48	Histology AC/non-AC	94/30	Stage IIIB/IV	27/97	Gefitinib Y/N	67/57	<p>Median survival time (MST) 11.3 months</p> <table border="0"> <tr> <td>1 year survival</td> <td>45%</td> </tr> <tr> <td>2 year survival</td> <td>24%</td> </tr> <tr> <td>3 year survival</td> <td>17%</td> </tr> <tr> <td>4 year survival</td> <td>12%</td> </tr> <tr> <td>5 year survival</td> <td>8%</td> </tr> </table> <p>10 patients survived for more than 5 years. EGFR mutation status was unknown for 8 of the 10 patients. MST for these patients was 61.5 months (range 60.1 months to 81.0 months)</p> <p>Good performance status, adenocarcinoma and gefitinib therapy were shown to be favourable prognostic factors by univariate analysis. Cox's proportional hazard model was used to identify independent prognostic factors. The multivariate analysis demonstrated that these three variables were a significant independent factor to predict a favourable response.</p>	1 year survival	45%	2 year survival	24%	3 year survival	17%	4 year survival	12%	5 year survival	8%
Age ≤65/>65	67/57																											
Male/Female	79/45																											
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Morita 2008 <sup>12</sup>	Japan	Combined analysis of 7 phase II Japanese trials examining the efficacy of gefitinib in 148 EGFR mutation positive patients with aNSCLC.	<table border="0"> <tr> <td>Mean age</td> <td>64 (33 to 89)</td> </tr> <tr> <td>Female</td> <td>69%</td> </tr> <tr> <td>Stage IIIB/IV</td> <td>73%</td> </tr> <tr> <td>Adenocarcinoma</td> <td>97%</td> </tr> <tr> <td>PS 0-1</td> <td>86%</td> </tr> <tr> <td>Non Smoker</td> <td>57%</td> </tr> </table>	Mean age	64 (33 to 89)	Female	69%	Stage IIIB/IV	73%	Adenocarcinoma	97%	PS 0-1	86%	Non Smoker	57%	MST for patients with EGFR mutations treated with gefitinib in the aNSCLC population studied was 24.3 months (95% CI: 19.8 to 28.2).												
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Takano 2008 <sup>5</sup>	Japan	330 patients were included in this study. Consecutive patients with aNSCLC who had received 1 <sup>st</sup> line CTX after the approval of gefitinib – July 2002 to Dec 2004 (Group A) and $\geq$ 1 year before gefitinib approval – Jan 1999 to July 2001 (Group B) were identified.	<table border="1"> <thead> <tr> <th></th> <th>Group A (n=200)</th> <th>Group B (n=130)</th> </tr> </thead> <tbody> <tr> <td>Median age</td> <td>62</td> <td>62</td> </tr> <tr> <td>Female</td> <td>42%</td> <td>38%</td> </tr> <tr> <td>Never smoker</td> <td>46%</td> <td>44%</td> </tr> <tr> <td>Adenocarcinoma</td> <td>100%</td> <td>100%</td> </tr> <tr> <td>PS 0-1</td> <td>92%</td> <td>95%</td> </tr> <tr> <td>Stage IIIB/IV</td> <td>59%</td> <td>76%</td> </tr> <tr> <td>EGFR-TKI (Y)</td> <td>88%</td> <td>15%</td> </tr> <tr> <td>EGFR M+ (Y)</td> <td>39%</td> <td>42%</td> </tr> </tbody> </table>		Group A (n=200)	Group B (n=130)	Median age	62	62	Female	42%	38%	Never smoker	46%	44%	Adenocarcinoma	100%	100%	PS 0-1	92%	95%	Stage IIIB/IV	59%	76%	EGFR-TKI (Y)	88%	15%	EGFR M+ (Y)	39%	42%	MST in EGFR M+ patients was significantly longer after gefitinib approval 27.2 months than before approval 13.6 months, $p < 0.01$ (HR 0.48 95% CI: 0.32 to 0.71), whereas no significant survival improvement was seen in patients without mutations.
	Group A (n=200)	Group B (n=130)																													
Median age	62	62																													
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Takano 2007 <sup>13</sup>	Japan	212 <sup>†</sup> out of 364 consecutive patients with NSCLC who had received gefitinib (250mg/day) were retrospectively analysed using High Resolution Melting Analysis (HRMA).	<table border="1"> <tbody> <tr> <td>Female</td> <td>43%</td> </tr> <tr> <td>Never Smoker</td> <td>45%</td> </tr> <tr> <td>Adenocarcinoma</td> <td>91%</td> </tr> </tbody> </table>	Female	43%	Never Smoker	45%	Adenocarcinoma	91%	MST was significantly longer in patients with EGFR mutations than those with wild type EGFR, 21.7 months versus 8.7 months, respectively $p < 0.0001$ (HR 0.54 (95% CI: 0.39 to 0.73).																					
Female	43%																														
Never Smoker	45%																														
Adenocarcinoma	91%																														

<sup>†</sup> 152 patients were excluded from the analysis because tumour samples were unavailable or informed consent to the genetic analysis was not obtained

## Appendix F:

**Table 20: Model variables and their source used in the base case analyses.**

<b>Model Variable</b>	<b>Value</b>	<b>Source</b>
<b>Discount rates</b>		
Costs	3.5%	NICE reference case
Benefits	3.5%	NICE reference case
<b>Time horizon (years)</b>	6	ERG gefitinib report (2010)
<b>Patient characteristics</b>		
EGFR M+ (overall population)	16.6%	Rosell (2009) <sup>9</sup>
Post-progression active treatment	61%	IPASS <sup>1</sup>
Mean Body Surface Area (m <sup>2</sup> )	1.762	ERG gefitinib report (2010)
G-CSF use of prophylaxis of neutropenia	21.7%	IPASS (2009) <sup>1</sup>
<b>Treatment Response:</b>		
Gefitinib EGFR M+	71.2%	IPASS <sup>1</sup>
Gem/carb EGFR M+	43.3%	AZ MTC (updated)
Gem/cis EGFR M+	50.8%	AZ MTC (updated)
Pem/cis EGFR M+	59.5%	AZ MTC (updated)
<b>Hazard Ratio PFS (pac/carb baseline):</b>		
Gem/carb EGFR M+	1.25	AZ MTC (updated)
Gem/cis EGFR M+	0.92	AZ MTC (updated)
Pem/cis EGFR M+	0.88	AZ MTC (updated)
<b>Hazard Ratio OS (pac/carb baseline):</b>		
Gem/carb EGFR M+	0.96	AZ MTC (Appendix A)
Gem/cis EGFR M+	0.92	AZ MTC (Appendix A)
Pem/cis EGFR M+	0.78	AZ MTC (Appendix A)
<b>Hazard Ratio PFS (gefitinib baseline):</b>		
Gem/carb EGFR M+	3.11	AZ MTC (Appendix A)
Gem/cis EGFR M+	2.32	AZ MTC (Appendix A)
Pem/cis EGFR M+	2.09	AZ MTC (Appendix A)
<b>Hazard Ratio OS (gefitinib baseline):</b>		
Gem/carb EGFR M+	1.24	AZ MTC (Appendix A)
Gem/cis EGFR M+	1.20	AZ MTC (Appendix A)
Pem/cis EGFR M+	0.97	AZ MTC (Appendix A)
<b>Mean Utility Values</b>		
Baseline utility (stable disease no AEs)	0.6532	Nafees (2008) <sup>14</sup>
Treatment response (increment)	0.0193	Nafees (2008) <sup>14</sup>
<b>Utility Decrements</b>		
- Disease progression	-0.1798	Nafees (2008) <sup>14</sup>
- Progression-free iv therapy	-0.0425	ERG report (2006) <sup>15</sup>

