National Institute for Health and Clinical Excellence

Centre for Health Technology Evaluation

ERG Responses to manufacturers issues raised as factual inaccuracies in the ERG report 21 January 2010

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

1. Issues requiring amendment:

Description of problem raised by manufacturer	Description of proposed amendment by manufacturer	Justification for amendment by manufacturer	ERG response
Issue 26 P77 The ERG comment that "[the manufacturer's model overstates] the mean number of cycles of paclitaxel/carboplatin administered per patient – increasing from 4.83 in IPASS to 5.51 in the model" is inaccurate.	Amend the statement to read "[the manufacturer's model overstates] the mean number of cycles of paclitaxel/carboplatin administered per patient – increasing from 4.83 in IPASS to 5.20 in the model."	The model submitted to the ERG produced a mean number of cycles of paclitaxel/carboplatin administered per patient of 5.20 not 5.51.	This represents a factual inaccuracy. The mean cycles in IPASS were 5.2. The ERG acknowledges this to be a typing error. It should read "This has the effect of overstating the mean number of cycles of paclitaxel/carboplatin administered per patient – increasing from 4.83 in IPASS to 5.239. As this was a typing error it had no effect on results.

2. Issues considered interpretive matters:

Description of problem raised by manufacturer	Description of proposed amendment by manufacturer	Justification for amendment by manufacturer	ERG response
Issue 1 P16 & P30 In order to identify patients with adenocarcinoma histology, diagnostic testing is required which is currently not routinely carried out or consistently performed across regions within the NHS; in addition, it is not always possible to determine the exact cell type from pathology	Remove this statement as it contradicts previous advice that the Appraisal Committee provided during the STA process for Pemetrexed in the first line setting	The STA for pemetrexed/cisplatin in the first line setting states that identifying adenocarcinoma histology is not routinely available in the UK NHS but states that 'the Committee were satisfied that there would not be a problem with doing this in practice because pathology services across the UK can perform such histological diagnoses'. This is also in keeping with the LUCADA database finding concerning use of histology in the NHS. The impact of this statement in the ERG report would cause confusion with NHS stakeholders implementing NICE's advice for pemetrexed in the first line setting and not accurately reflect the current NHS environment as described by clinical experts at the Appraisal Committee meeting.	The wording reflects the ERGs view of the clinical situation, not a factual inaccuracy. The issue was discussed at the Appraisal Committee meeting.
Issue 2 P14 & P85.The ERG sought additional information from the manufacturer in the form of a limited extract of IPD from the IPASS trial, to enable more accurate estimation of survival	The ERG sought additional information from the manufacturer in the form of a limited extract of IPD from the IPASS trial, to enable more accurate estimation of survival models to be carried out (using trial data directly, rather than via approximations obtained by digitisation). In addition this would have allowed correlations between the new model parameters to be	The statement as it reads currently is inaccurate and does not accurately reflect the dialogue that occurred between the Manufacturer and NICE when the request for further statistical analyses was made.	The wording is not factually inaccurate. The manufacturer expressed the view that they would not provide IPD data, and were not able to provide the additional analyses in a timeframe that would enable the ERG to include it in its

models to be carried out (using trial data directly, rather than via approximations obtained by digitisation). In addition this would have allowed correlations between the new model parameters to be estimated as a basis for updating the PSA facility within the manufacturer's model. The manufacturer refused this request, and subsequently failed to provide specified statistical analyses requested by the ERG in time to assist in this investigation.	estimated as a basis for updating the PSA facility within the manufacturer's model. The manufacturer refused this request, and was only able to provide half of the specified statistical analyses in the short timeline provided by ERG. ERG refused to accept the partial statistical analyses which the Manufacturer was able to conduct in the short timeframe and therefore no further analyses was submitted.		report.
Issue 3 P95. The IPASS study has not yet reached maturity; only 450/1217 (37%) deaths have occurred. This means that there are no definitive OS data available for patients with EGFR M+ from this RCT. Consequently, there is insufficient evidence to indicate that the treatment offers an extension to life of at least an additional three months compared to current treatment	Include information about the modelled overall survival benefit.	Previous discussion with the Associate Director indicated that robust modelled OS data may suffice (please see 2.3 of the EoL supplementary advice) and that the Appraisal Committee meeting would then have to make a judgement on whether the modelled data is sufficient enough for the criteria to be applied. Therefore AstraZeneca believes it is inaccurate for the ERG to only accept definitive OS data and not discuss the modelled overall survival.	The wording reflects the ERGs interpretation of the clinical trial results and is therefore not a factual inaccuracy.
Issue 4 Page 34, section 4.1.8 In terms of statistical methodology	In terms of statistical methodology the ERG is concerned that ~~(i) the trial was not adequately powered for the subgroup analysis based on the EGFR M+ population~~, ~~(ii) measurement of the~~	i)This statement raises concern that the subgroup analyses were underpowered. Power is the chance of concluding a difference	The wording reflects the ERGs view on alternative statistical methods and does not represent a factual inaccuracy.

the ERG is concerned that (i) the trial was not adequately powered for the subgroup analysis based on the EGFR M+ population, (ii) measurement of the primary outcome (PFS) may be unreliable as it was assessed without blinding and the HRs may have been inappropriately calculated using Cox proportional hazards[27] and (iii) the analysis of OS data was immature.	~~primary outcome (PFS) may be unreliable as it was assessed without blinding and the HRs may have been inappropriately calculated using Cox proportional hazards[27] and~~ (iii) the analysis of OS data was immature.	between treatments (if one truly exists), it is not the chance of concluding a difference in error (that would be assessed by the significance level). Lack of power could potentially therefore provide no significant difference between treatments even if one exists. Therefore, if these subgroup analyses had more power, there would be an ever greater chance of detecting a significant result. The IPASS results in the subgroups by EGFR mutation status were very clear, with $p<0.0001$ for both the treatment by mutation status interaction test and the comparison of treatments within all subgroups (positive, negative, and unknown), therefore these results are highly unlikely to be due to chance. The statement as it reads is misleading to the reader and should be altered. ii) The pre-specified primary analysis of this regulatory study was using a Cox proportional hazards model. The pre-planned primary analysis of a regulatory study should always be reported for transparency. Indeed, there is no other way to compare the result to the pre-specified non-inferiority margin of 1.2 in the overall population – for consistency the	

		same method (Cox regression) was used for all subgroup analyses of PFS and OS. Sensitivity analyses were performed on the overall result including a nonparametric log rank test. All were consistent and showed p<0.0001 in favour of gefitinib, indicating that the p-value from the Cox model in the overall population is robust. Even with non-proportional hazards, the HR and 95% CI and p-value for the comparison of the treatment arms is still valid when it is interpreted as a representation of the entire study period (i.e., an average progression rate across all patients for the whole follow up period) (see Armitage and Berry 1987, Carroll 2003).	
Issue 5 ERG report states that there are differences in baseline characteristics in the IPASS and NEJGSG trials and that the best available evidence for assessing gefitinib vs paclitaxel/carboplatin is from the head-to-head comparison in IPASS (pages 45 and 46).	The meta-analysis of IPASS and NEJSGS provides the most appropriate estimate of gefitinib compared to paclitaxel/carboplatin.	The key driver of treatment effect with gefitinib is EGFR-TK mutation status. As the meta-analysis is conducted in the patient subgroups that are EGFR-TK M+ the differences in other patient characteristics are unlikely to cause significant heterogeneity. No significant heterogeneity was identified in the meta-analyses of efficacy or grade 3/4/5 adverse events. As the ERG report	The wording reflects the ERGs view of the clinical trial results and does not represent a factual inaccuracy.

		acknowledges, "*For the primary outcomes of interest (PFS), the results from the meta-analysis are consistent with the results from IPASS*." The manufacturer's submission followed the recommended approach in the NICE Single Technology Appraisal Template, "*Where more than one study is available and the methodology is comparable, a meta-analysis should be undertaken*."	
Issue 6 ERG states that the manufacturer's own MTC demonstrates that paclitaxel/carboplatin and gemcitabine/cisplatin are not substantially different in terms of clinical benefit and improved tolerability (page 45).	This statement should be removed from the ERG report. The available evidence suggests that paclitaxel/carboplatin and gemcitabine/cisplatin are not equivalent in terms of clinical benefit and tolerability.	The MTC approach used in the manufacturer's submission is based on Bayesian statistical inference which has the advantage of being able to calculate direct probability statements for which treatment is the most effective, even when standard methods might determine no significant difference between treatments (Caldwell et al. 2005); e.g. for PFS there is a 56% probability that gemcitabine/cisplatin is the most effective treatment of those assessed in the MTC while only 8% for paclitaxel/carboplatin. In addition, from a "frequentist" perspective, gemcitabine/cisplatin is associated with significantly more anaemia, fatigue, nausea and	The wording reflects the ERGs interpretation of the clinical trial results presented and does not represent a factual inaccuracy. The effectiveness of different chemotherapy regimens in the treatment of NSCLC was discussed at the Committee meeting.

		vomiting, and significantly less febrile neutropenia than paclitaxel/carboplatin, at the 5% significance level.	
Issue 7 ERG report states that the most appropriate meta-analysis to conduct is a meta-analysis of IPASS, NEJSGS and First-SIGNAL (page 46).	The meta-analysis of IPASS and NEJSGS provides the most appropriate estimate of gefitinib compared to paclitaxel/carboplatin. First-SIGNAL provides supportive evidence of the efficacy of gefitinib with an alternative doublet CTX. Performing a meta-analysis of all three trials would provide an estimated treatment effect for gefitinib over different doublet CTX and not be useful for clinical decision making or the subsequent economic evaluation.	Paclitaxel/carboplatin and gemcitabine/cisplatin have not been shown to be clinically equivalent within a randomised controlled trial. In addition the meta-analysis conducted by Le Chevalier et al. 2005 demonstrates clinical advantages of gemcitabine-platinum combinations over other platinum containing regimens and the meta-analysis conducted by Ardizzoni et al. 2007 demonstrates an advantage of cisplatin-based chemotherapy over carboplatin-based chemotherapy. The MTC conducted, as part of the manufacturer's submission, does not support the gross assumption that paclitaxel/carboplatin and gemcitabine/cisplatin have equivalent clinical benefits and tolerability (see Evidence Synthesis Issue 2).	The wording reflects the ERGs view of how to conduct a mixed treatment comparison; it does not represent a factual inaccuracy.

Issue 8 ERG report states that only an interim analysis of PFS is available from NEJGSG trial	No data on OS is available from the NEJGSG trial.	An analysis of PFS at a later date is not expected from the NEJGSG trial. Only an OS analysis will be conducted in late 2009 (Kobayashi	Whilst it is acknowledged that the wording used by the ERG implies a later analysis of PFS, this is not considered a substantive error that needs

(pages 45).		et al. 2009).	correction.
Issue 9 ERG report states that the manufacturer has assumed that the EGFR mutation status of patients has no impact on treatment outcomes if patients are receiving doublet CTX (page 47).	The manufacturer assumes that doublet CTX are all equally affected by mutation status.	As stated in the manufacturer's submission, there is reason to suspect that the efficacy of paclitaxel/carboplatin is affected by EGFR-TK mutation status (median OS in EGFR M+ patients was 19.5 months and 12.6 months in EGFR M- patients). In addition, Takano et al. 2008 have shown this is likely to be true for other CTX used for first-line aNSCLC (median OS 13.6 vs 10.4 months in EGFR-TK M+ and M-, respectively, p=0.034). In order to account of this likely increase in benefit in EGFR M+ patients, the relative treatment effects calculated in the MTC are applied to the baseline treatment response of paclitaxel/carboplatin in EGFR-TK M+ patients from IPASS in the economic model. If the manufacturer had assumed that EGFR mutation status of patients has no impact on treatment outcomes if patients are receiving doublet CTX it would have been appropriate to include the three gefitinib trials (IPASS, NEJGSG, First-SIGNAL) directly into the MTC network.	The manufacturer suggests an alternative wording but the issue is not considered a factual inaccuracy.

Issue 10 ERG report states that the approach taken to estimating the effect of doublet CTX in an EGFR M+ population is a "naïve comparison" as it breaks randomisation (page 47).	The approach taken to estimating treatment effects with doublet CTX compared to paclitaxel/carboplatin is a standard approach commonly employed with the results from standard pair-wise meta-analysis.	In a standard pair-wise meta-analysis it is common practise to apply the relative efficacy measures calculated to a baseline for economic evaluation. The approach taken with the results of the MTC is exactly the same. It does not break randomisation by applying the MTC relative estimates to a baseline treatment effect.	The wording reflects the ERGs opinion; it does not constitute a factual inaccuracy.
Issue 11 ERG states that the manufacturer should have used the Parmar approach to calculate HR from all trials and that the results of the MTC should be carefully considered due to potential selection bias regarding the studies included (page 47).	Where HR for OS and PFS were not reported in the clinical trials identified for inclusion in the MTC, the manufacturer obtained data on these outcomes from two independently published meta-analyses (Ardizzoni et al. 2007 and Le Chevalier et al. 2005). This may have introduced selection bias based on the HR for OS and PFS available in the published literature.	Independently published sources of clinical data informed the MTC, including HR calculated from individual patient-level data that would have been unavailable to the manufacturer (Ardizzoni et al. 2007).	The wording reflects the ERGs view of the manufacturers approach to calculating HRs and the results from the MTC; it does not constitute a factual inaccuracy.
Issue 12 ERG states that all patients randomised were not included for Mazzanti et al. 2003 and Schiller et al. 2002 in all of the MTC efficacy analyses (page 47).	This statement should be removed from the ERG report.	The MTC includes where possible the ITT population as defined by the individual trials in each of the efficacy analyses. In Mazzanti et al. 2003 this was the defined ITT population while in the Schiller et al. 2002 this was the eligible patients population.	The wording used by the ERG is not factually inaccurate.
Issue 13 ERG states that data from Helbekkmo et al. 2007 was not taken from the two cited meta-	This statement should be removed from the ERG report.	Helbekkmo et al. 2007 was not included in the MTC as neither the trial nor the two meta-analyses identified provided a HR for PFS.	Whilst it is acknowledged that the wording used by the ERG could be misinterpreted, this is not considered a substantive

analyses for the MTC of PFS (page 48).		This was indicated in the data tables supplied to the ERG in response to their clarification questions. The 6 trials included in data tables supplied to the ERG for the MTC of PFS were: Chang et al. 2001; Gridelli et al. 2002; Scagliotti et al. 2002; Schiller et al. 2002; Thomas et al. 2002; Van Meerbeck et al. 2001 (also published as Smit et al. 2003).	error that needs correction.
Issue 14 ERG states that they are uncertain why an indirect comparison restricted to the three trials including gefitinib was not conducted (page 48).	The small number of patients in the First-SIGNAL trial harbouring EGFR-TK M+ mutations was very small (n=42), as such any estimate of the treatment effect of gefitinib vs gemcitabine/cisplatin would be unreliable.	The manufacturer's approach to the best estimate of the treatment effect with gemcitabine/cisplatin was calculated within the MTC.	The wording reflects the ERGs viewpoint and is not a factual inaccuracy.
Issue 15 ERG states that in the updated MTC pemetrexed/cisplatin is much closer to gefitinib in terms of PFS and OS and is significantly better than other doublet CTXs (pages 46 and 49).	In the updated MTC, pemetrexed/cisplatin (non squamous) has significantly higher OS and objective response compared to paclitaxel/carboplatin, at the 5% level of significance, but would not be considered to have significantly improved OS or objective response compared to the other doublet CTX assessed in the MTC. In addition, gefitinib would appear to have significantly higher PFS and objective response	The updated MTC includes pemetrexed/cisplatin (non squamous) and reports the results using paclitaxel/carboplatin as the baseline. However, this does not preclude the comparison of all of the doublet CTX included in the network. Pemetrexed/cisplatin would not be considered to have statistically significant OS or objective response when compared	Whilst it is acknowledged that the wording used by the ERG could be misinterpreted, this is not considered a substantive error that needs correction.

	than pemetrexed/cisplatin, at the 5% level of significance.	with any other doublet CTX included in the MTC, at the 5% significance level. In addition, while the immature OS for gefitinib is similar to pemetrexed/cisplatin when compared to paclitaxel/carboplatin, the best available evidence would appear to suggest that gefitinib is significantly more effective in terms of PFS and objective response, at the 5% significance level. OS gefitinib vs paclitaxel/carboplatin (IPASS) HR 0.78, 95% CI: 0.50 to 1.20 pemetrexed/cisplatin vs paclitaxel/carboplatin (MTC) HR 0.78, 95% CrI: 0.65 to 0.93 PFS gefitinib vs paclitaxel/carboplatin (MA) HR 0.43, 95% CI: 0.34 to 0.53 pemetrexed/cisplatin vs paclitaxel/carboplatin (MTC) HR 0.88, 95% CrI: 0.74 to 1.05 Objective response gefitinib vs paclitaxel/carboplatin (MA) OR 4.04, 95% CI: 2.73 to	

		5.98 pemetrexed/cisplatin vs paclitaxel/carboplatin (MTC) OR 1.64, 95% CrI: 1.15 to 2.27	
Issue 16 ERG states that the MTC is weak as it relies on a very strong assumption that EGFR mutation status does not affect treatment outcomes if patients are receiving doublet CTX (page 49).	This statement is should be removed from the ERG report.	The MTC comparison of doublet CTX using paclitaxel/carboplatin in unselected patients does not rely on EFGR mutation status and is a robust comparison of the treatments included in the network of randomised controlled trials. The manufacturer's approach follows the methodology recommended in the NICE Single Technology Appraisal template.	The wording reflects the ERGs opinion on the MTC, it does not represent a factual inaccuracy.
Issue 17 ERG states that the manufacturer's own MTC demonstrates equivalent efficacy for the doublet CTX regimens assessed in the economic evaluation (page 65 and 84) and so all comparators for gefitinib should be based on paclitaxel/carboplatin from IPASS rather than the MTC (page 84).	This statement should be removed from the ERG report. The MTC does not demonstrate equivalence for any of the doublet CTX assessed in the MTC. The results of the MTC should be applied for each of the doublet CTX rather than a gross assumption of clinical equivalence.	Clinical equivalence is not demonstrated by lack of a statistically significant difference in treatment effects, "absence of evidence is not evidence of absence" (Altman & Bland 1995). It is well established in the health economic literature (Briggs & O'Brien 2001) that only under very particular circumstances can clinical equivalence be established and a cost-minimisation analysis performed. In all other cases parameter uncertainty needs to be assessed in sensitivity analysis. This is why the	Whilst it is acknowledged that the wording used by the ERG could be misinterpreted, this is not considered a substantive error that needs correction.

		NICE Guide to the Method of Technology Appraisal advocates probabilistic sensitivity analysis to assess the interplay of uncertainty of all parameters within an economic model and why the manufacturer submission summarises the MTC section by stating that the interplay of the different outcome (efficacy and safety) in the economic analysis would identify which treatment would offer best value to the NHS.	
Issue 18 ERG states that the manufacturer's MTC was updated to include pemetrexed/cisplatin and docetaxel/cisplatin (pages 85, 86, 89).	The MTC was updated to include pemetrexed/cisplatin.	The MTC submitted by the manufacturer included all 8 doublet CTX used in clinical practice. Pemetrexed/cisplatin was excluded from the original submission as it was undergoing NICE Single Technology Appraisal and based on the comments in the ACD it was assumed that it would not be approved by NICE for use in the UK NHS.	ERG do not accept that the statement is factually incorrect when considered in the context of the preceding sections of the report: Sections 5.7.3 and 5.7.4 relate explicitly to issues concerning the manufacturer's model. In this context, the reference to "additional CTX comparators" should be read as additional to the features included in the model, not as additional to the MTC. The extended (for pemetrexed) and updated (for all other comparators) MTC results made it possible to include both the additional comparators in a revised model analysis on the same basis.
Issue 19	Gemcitabine/carboplatin should be used as the	Of the multiple comparators	The wording reflects the ERGs

P75 It is factually inaccurate to claim that paclitaxel/carboplatin is the most relevant comparator to inform the NICE decision problem.	base case scenario.	identified in the NICE scoping exercise, gemcitabine/carboplatin is the most routinely used 1st line treatment for aNSCLC in clinical practice in England and Wales and should therefore be considered of most relevance to the NICE decision problem. Gemcitabine/carboplatin accounts for around 52% to 67% of 1st line aNSCLC patient initiations in the UK (manufacturers submission P76). Fewer than 5% of patients with aNSCLC are treated with taxane based doublet chemotherapy. The ERG comment that adopting gemcitabine/carboplatin as the most appropriate comparator requires an indirect comparison involving mixed treatment comparison (MTC) is not a strong argument for choosing paclitaxel/carboplatin as the most appropriate reference case comparator. The NICE guide to HTA recommends that in absence of data from a head-to-head RCTs evidence from a MTC should be considered.	view and does not reflect a factual inaccuracy. The NICE guide to the methods of technology appraisal states that data from head-to-head RCTs should be presented in the reference case analysis, if available. Mixed treatment comparisons can be presented in additional to the reference case analysis if considered to add information that is not available from the head to head comparison. The appropriate comparator was discussed at the Appraisal Committee meeting.
Issue 20 P76, P93 – the maximum number of CTX cycles in the UK is	ERG reference case should apply the manufacturer's assumption that CTX would be limited to a maximum of 6 cycles in all the base case analyses.	The ERG has presented no evidence to support their statement that the maximum number of CTX cycles in England and Wales is	The wording reflects the ERGs view of the number of treatment cycles based on experience in previous appraisals, it does not

typically four is factually incorrect.		usually 4. This is of concern since this parameter is a major cost driver and impacts significantly on the ICER(s). Justification for the amendment is as follows: There is evidence that a number of Cancer Networks allow the use of up to 6 cycles of CTX in their NSCLC guidelines. For example, Leicestershire, Northamptonshire & Rutland Cancer Network (www.lnrcancernetwork.nhs.uk) allow the use of up to 6 cycles of gemcitabine/(carboplatin or cisplatin). Derby and Burton Cancer Network (www.derbyhospitals.nhs.uk) permit the use of up to 6 cycles of paclitaxel/carboplatin and gemcitabine/carboplatin, Surrey, West Sussex and Hampshire CN also treat patients with aNSCLC with up to 6 cycles of gemcitabine/carboplatin www.swsh.nhs.uk. Market research data was presented in our submission (P103 4th bullet point) that reported an average of 4.8 cycles of gemcitabine/carboplatin were given as 1st line treatment to patients (n=454) with aNSCLC in England and Wales (Jan 05 to March 09).	constitute a factual inaccuracy. The issue was discussed at the Appraisal Committee meeting.

		Approximately 36% of patients in this sample received more than 4 cycles of doublet chemotherapy. Imposing a maximum of 4 cycles of CTX in the economic model submitted to the ERG reduces the mean number of gemcitabine/carboplatin to just 3.6. Whereas adopting a maximum of 6 cycles results in a mean number of gemcitabine/carboplatin of 5.0. This value is consistent with market research data presented in our submission.	
Issue 21 P76 At present the ERG is **not aware** of any convincing evidence that reducing the number of cycles of CTX will reduce the extent of benefit likely to be achieved.	ERG reference case should apply the manufacturer's assumption that CTX would be limited to a **maximum** of 6 cycles in all the base case analyses.	Liverpool ERG has recently been commissioned to review the pemetrexed maintenance STA. Pemetrexed has recently been licensed as maintenance therapy in patients with aNSCLC (non-squamous) whose disease has not progressed after 4 cycles of CTX (4CTX). This can be considered an extension of CTX beyond 4 cycles. The pivotal study on which the license was gained met its primary endpoint and showed a statistically significant improvement in PFS in the 4CTX + pemetrexed treatment arm over 4CTX; median of 4.0 months and 2.0 months, respectively) hazard ratio = 0.60,	The wording reflects the ERGs view of the effect of the number of cycles of CTX, not a factual inaccuracy.

		(95% CI: 0.49-0.73, p < 0.00001). The median OS for the overall population (N = 663) was 13.4 months for 4CTX + pemetrexed arm versus 10.6 months for the 4CTX arm, hazard ratio = 0.79 (95% CI: 0.65 to 0.95; p = 0.01192). This study demonstrates that extending CTX beyond 4 cycles can significantly improve OS and PFS. In addition, a reference was made in our submission to a recent meta-analysis (JCO 2009) that reported that extending chemotherapy for aNSCLC beyond a standard duration (4-6 cycles) substantially improves PFS (HR 0.75; 95% CI, 0.69 to 0.81; p<0.0001) and also improves OS (HR 0.92; 95% CI, 0.85 to 0.99; p=0.03). Finally, the ERG's assumption is inconsistent with their assumption made in the pemetrexed 1st line STA. Here, the ERG heavily criticised the manufacturer for failing to employ robust and defensible methods for adjusting treatment effects when a scenario is used with fewer treatment cycles than in the trial evidence, which used a maximum of 6 cycles.	
Issue 22 P79 The ERG's statement "the	Revision of text in all relevant sections to qualify that the Weibull model for OS provides as good	It is evident from Figure 5-8 (P81) that the Weibull (WB) model is as	The wording reflects the ERGs interpretation on the curve

[ERG] 'spline' models are more accurate at **all** times than the Weibull models [developed by the manufacturer]" is inaccurate. P79 and P81 Incorrect gefitinib PFS HR has been used to make a comparison of the "spline model" with the Weibull model. P94 Statement that the Weibull survival models "do not reflect the trial outcomes results accurately" is inaccurate. Table 5-9 The ERG comment that "Overall survival was not adequately modelled; poor correspondence between parametric survival models and source data" is inaccurate.	a fit for OS IPASS EGFR data as the "spline" model. It is also likely to provide a more accurate extrapolation of the OS data than the "spline" model. Table 5-11 also need to be corrected. Mean PFS for gefitinib should read 10.10 not 10.72. Figure 5-8 should be corrected using the gefitinib IPASS PFS HR of 0.48.	good a fit for OS in IPASS EGFR M+ patients as the "spline" model. In addition, the validation of the WB model (see Table 32 P103 of the manufacturer's submission) demonstrates an acceptable degree of fit between fitted and empirical OS and PFS curves. The ERG has incorrectly used the gefitinib PFS HR of 0.43 from the meta-analysis to compare their "spline model" to the Weibull model. They should have used the IPASS gefitinib PFS HR of 0.48 to generate the Weibull PFS curve. The ERG's statement that "the 'spline' models are more accurate at all times than the Weibull models" is therefore factually inaccurate. The ERG has employed an unconventional survival model to estimate transition probabilities for PFS and OS data for EGFR M+ patients. We are particularly concerned over the robustness of their approach in extrapolating the IPASS OS data. The "spline model" gives a mean OS for paclitaxel/carboplatin EGFR of 27.19 months. This may overestimate the survival benefit given the median OS for this patient	fitting, it does not represent a factual inaccuracy. The Appraisal Committee discussed the conflicting survival models in detail and has requested more analyses.

		group in IPASS was 19.5 months. The tail of the “spline” paclitaxel/carboplatin OS curve also appears to plateau. The spline model estimates a 5-year OS of > 10% in aNSCLC EGFR M+ patients treated with paclitaxel/carboplatin which is debateable. The strengths of the WB survival model over the spline model are: Individual patient level data have been used to generate the WB OS and PFS curves. This approach takes into account the numbers at risk as time progresses. In contrast, the “spline approach” uses summary data, which leads to equal weight being given to the tail of the KM curves as it is to the front of the curves. The WB model enables HRs for PFS and OS for **all** the relevant comparators to be applied to a common baseline (IPASS paclitaxel/carboplatin EGFR M+). Using this approach it is possible to incorporate differences in CTX treatment effects that were identified in the MTC into the cost-effectiveness analyses. The WB model allows uncertainty in the treatment benefits of the individual comparators to be	

		explored using PSA. It is not apparent that the “spline” approach lends itself to making cost-effectiveness comparisons for any comparator other than paclitaxel/carboplatin. There is also no evidence that the “spline” approach allows uncertainty to be examined via PSA, as per NICE guidance to manufacturers.	
Issue 23 P92 The statement that pemetrexed/cisplatin dominates gefitinib is inaccurate.	Two possible solutions: 1. Removal of this statement from section 6.3. 2. Add qualifications to the state that pemetrexed/cisplatin (non-squamous) would dominate gefitinib EGFR M+ patients only if **all** the following caveats were applied: The maximum number of cycles of pemetrexed/cisplatin was limited to 4 in routine practice in England & Wales (mean of 3.7 cycles) **and** Restricting the maximum number of cycles of pemetrexed/cisplatin to 4 as opposed to 6 has no effect on PFS or OS **and** The “spline approach” for extrapolating and modelling OS and PFS for gefitinib provides a more accurate estimates of treatment effect than the Weibull analysis developed using patient level data from IPASS **and**	It is inaccurate for the ERG to draw the conclusion that gefitinib is dominated by pemetrexed/cisplatin (non squamous) in aNSCLC EGFR M+ patients. The best available evidence demonstrates that gefitinib is significantly better than pemetrexed/cisplatin in objective response rate and PFS and comparable in OS (see Evidence Synthesis Issue 15). It is therefore implausible to assume that pemetrexed/cisplatin would be a more effective treatment for aNSCLC patients with EGFR mutations. The ERG conducted 10 one-way sensitivity analyses to examine the cost-effectiveness of gefitinib	This sentence refers to a description of ERG exploratory analysis results and as such is not factually incorrect.

	It is valid to use the “spline approach” to extrapolate and estimate mean OS for gefitinib. However, the mean OS for pemetrexed/cisplatin can legitimately be estimated by applying the HRs from the MTC produced the manufacturer to the paclitaxel/carboplatin EGFR M+ baseline **and** It is appropriate to omit the cost of g-CSF that was given to 21.7% of patients treated with paclitaxel/carboplatin in IPASS from the cost-effectiveness calculations while maintaining the same incidence of febrile neutropenia that was observed in this study.	versus pemetrexed/cisplatin (non-squamous patients) (see Table 6-3). Gefitinib dominated or was cost-effective versus pemetrexed/cisplatin in **all** but one of the scenarios they examined. The only scenario when gefitinib failed to demonstrate it was cost-effective versus pemetrexed/cisplatin (non-squamous) (ICER = £43,984) was when where the maximum number of cycles was limited to 4. Restricting the maximum number of cycles to 4 would lead to a mean of 3.7 treatment cycles of pemetrexed/cisplatin being delivered in routine practice in England & Wales. The underlying assumption that limiting the maximum number of cycles of pemetrexed/cisplatin to 4 would result in no loss of treatment efficacy has questionable validity as a base case (see Issue 20). It is only when the ERG combined all their assumptions that pemetrexed/cisplatin (non-squamous) dominated gefitinib. There are a number of inaccuracies in these assumptions that have	

		been highlighted above. We therefore challenge the ERG's decision to use the "Combined effect of all the changes" as their base case and consider that these estimates fail to accurately reflect the cost-effectiveness of gefitinib.	
Issue 24 P75 The ERG's assumption that the most appropriate dose of vinorelbine to adopt in the cost-effectiveness analysis is 25mg/m^2 is inaccurate.	The manufacturer's dose assumption for vinorelbine 30mg/m^2 should be adopted in the base case analysis.	The ERG has based their assumption on advice from a sample of 1. A more thorough review would have identified a number of NSCLC treatment protocols that have been published by Cancer Networks (CN) in England and Wales. Leicester, Northamptonshire & Rutland CN, Derby and Burton CN, Surrey, West Sussex and Hampshire CN all specify a vinorelbine dose of 30mg/m^2.	Dose of vinorelbine is an ERG assumption, rather than a factual inaccuracy. The appropriateness of vinorelbine as comparator was discussed at the Committee meeting.
Issue 25 P83 and Tables 6-1, 6-2, 6-3. The assumption that it is methodologically valid to omit g-CSF prophylaxis from the cost-effectiveness analyses is inaccurate.	Two options are available: Increase the incidence of febrile neutropenia for the paclitaxel/carboplatin treatment arm that would occur without g-CSF prophylaxis Reinstate the cost of g-CSF in the base case analysis	Although it is acknowledged that g-CSF is not routinely used in clinical practice in the UK, 21.7% of patients treated with paclitaxel/carboplatin in IPASS received g-CSF prophylaxis. This resulted in a low incidence of febrile neutropenia of 3.9% in this treatment arm. Simply removing the cost of g-CSF from the CTX comparators because it doesn't reflect UK practice, without adjusting for a higher incidence of	The wording reflects the ERGs view of what assumptions should go into the model and does not constitute a factual inaccuracy. The issue was discussed at the Appraisal Committee meeting.

		febrile neutropenia is methodologically unsound.	
Issue 27 P67 The critical appraisal that allowance was not appropriately made for uncertainty in the estimates of costs and consequences is inaccurate.	Critical appraisal should be Yes for this item.	Uncertainty was adequately addressed via PSA. PSA is the NICE preferred method for addressing parameter uncertainty.	The wording reflects the ERGs view of how uncertainty was addressed in the manufacturer's model; it does not represent a factual inaccuracy.

References in addition to the Manufacturer's Submission

Altman DG, Bland MJ. Absence of evidence is not evidence of absence. BMJ 1995; 311: 485.

Briggs AH, O'Brien BJ. The death of cost-minimization analysis? Health Econ 2001; 10: 179-84.

Takano T, Fukui T, Ohe Y, et al. EGFR mutations predict survival benefit from gefitinib in patients with advanced lung adenocarcinoma: a historical comparison of patients treated before and after gefitinib approval in Japan. J Clin Oncol 2008; 26: 5589-95.