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

ERG Report

LRiG comments on additional information provided by the manufacturer

Confidential data has been blacked out

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1 Background

Following the publication of the Appraisal Consultation Document (ACD) relating to the use of gefitinib for the first-line treatment of locally advanced or metastatic non-small cell lung cancer (NSCLC), the manufacturer (AstraZeneca) has responded to the request for additional information as outlined in the ACD.

The ERG was asked to examine and comment on the information provided by the manufacturer to assist the Appraisal Committee in its deliberations; given the timetable of the AC meeting the ERG has been afforded five days to carry out this analysis and provide this report.

2 ERG investigation and findings

The manufacturer has appropriately presented their response in a structure that appears to be a composite of the information requested in points 1.3-1.11 of the ACD and the textual comments provided primarily from points 4.11 to 4.15. In addition to this the submission provides an alternative Single Payment Access (SPA) scheme and new data from a trial that was not part of their original submission as the basis for an estimates of clinical outcomes and an argument to support approval based on end of life criteria.

This document firstly provides the results of the ERG's investigation of the presented findings with a focus on what are, in its view, the key issues to be addressed in relation to the requested additional information.

Appendix 1 provides a summary of the additional information requested by the AC from AstraZeneca, AstraZeneca's response and the ERG's comments on the information provided.

2.1 Number of cycles of first-line chemotherapy

Previous NICE appraisals of chemotherapy for NSCLC patients have accepted a general consensus within the UK of limiting first-line chemotherapy to a maximum of four cycles. In their submission the manufacturer has sought to question this standard and to suggest that up to six cycles is widely used. It should be noted that limiting treatment to four cycles is not merely a matter of clinical preference, but is based on randomised studies which have addressed this question. Most notably

Socinski (2002)[1] reported a phase III trial comparing limited (four cycles) and unlimited paclitaxel/carboplatin in terms of survival, tolerability and quality of life. The reported conclusion was:

> *"In summary, this trial has failed to show an overall clinical benefit to continuing therapy with carboplatin/paclitaxel in advanced NSCLC beyond four cycles. This finding is consistent with the previously reported experience comparing three versus six cycles of MVP showing no clinical benefit derived from extending therapy beyond three cycles and the trial comparing maintenance vinorelbine after four cycles of MIP. These three trials challenge the current standard both in practice as well as in the clinical trial setting of recommending six or more cycles of treatment in this disease setting. The use of a brief duration of first-line treatment yields equivalent survival would reduce the risk of any cumulative toxicities that may negatively impact on a patient's individual QOL, and would likely improve resource utilization."*

This is an important issue since the use of six cycles of the comparator platinum-based regimen greatly improves the cost effectiveness of gefitinib.

2.2 Estimated gain in overall survival

In Tables 5 and 6 of their response to the ACD the manufacturer has presented four different estimates for the mean gain in overall survivial (OS) attributable to treatment with gefitinib compared to paclitaxel/carboplatin (IPASS trial). These are summarised in Table 2-1 together with 95% confidence intervals for the gain in OS.

The diversity of these results in relation to the size and direction of the apparent survival differences (ranging from -3.3 months to +4.2 months advantage for gefitinib) is not encouraging. The manufacturer has dismissed the log-logistic models apparently because of the negative result in the stratified analysis. However, the choice between the two Weibull models is equally problematic, since in the stratified case there appears to be little to choose between the treatments (95% confidence interval including zero). It would require considerably greater consistency in the estimated differences for any estimate of OS gain with gefitinib therapy to be described as 'robust'.

Having opted for the unstratified Weibull model to use in the economic model, the manufacturer reports the PFS and OS estimated gains (Tables 7b and 8b in the manufacturer's response). In all modelled comparisons the estimated OS advantage for gefitinib is below 3 months (1.49 – 2.52 months compared to gemcitabine based chemotherapy). On this basis it seems clear that there is no robust evidence available directly from analysis of the IPASS data or from the economic model

[1] Socinski MA, Schell MJ, Peterman A, Bakri K, Yates S, Gitten R, Unger P, Lee J, Lee J-H, Tynan M, Moore M, Kies MS. Phase III trial comparing a defined duration of therapy versus continuous therapy followed by second-line therapy in advanced-stage IIIB/IV non-small-cell lung cancer. Journal of Clinical Oncology 2002;20(5): 1335-1343.

which indicates with any confidence a survival benefit of more than three months, as is required to satisfy the NICE 'end of life' criteria.

Table 2-1 Manufacturer's estimates of overall survival

Estimation method	Treatment	Mean OS	SE	LCL	UCL
Weibull stratified (arms modelled separately)	Gefitinib	23.16	0.26	22.65	23.67
	Paclitaxel/carboplatin	22.73	0.23	22.27	23.18
	Difference	**+0.43**	**0.35**	**-0.25**	**+0.68**
Weibull unstratified (arms modelled jointly)	Gefitinib	24.39	0.30	23.80	24.97
	Paclitaxel/carboplatin	21.81	0.21	21.40	22.24
	Difference	**+2.58**	**0.36**	**+1.87**	**+3.29**
Log-logistic stratified (arms modelled separately)	Gefitinib	30.43	0.37	29.71	31.15
	Paclitaxel/carboplatin	33.74	0.33	33.09	34.40
	Difference	**-3.31**	**0.50**	**-4.28**	**-2.34**
Log-logistic unstratified (arms modelled jointly)	Gefitinib	34.32	0.41	33.52	35.12
	Paclitaxel/carboplatin	30.10	0.29	29.54	30.67
	Difference	**+4.22**	**0.50**	**3.24**	**5.20**

Having opted for the unstratified Weibull model to use in the economic model, the manufacturer reports the PFS and OS estimated gains (Tables 7b and 8b in the manufacturer's response). In all modelled comparisons the estimated OS advantage for gefitinib is below 3 months (1.49 – 2.52 months compared to gemcitabine based chemotherapy). On this basis it seems clear that there is no robust evidence available directly from analysis of the IPASS data or from the economic model which indicates with any confidence a survival benefit of more than three months, as is required to satisfy the NICE 'end of life' criteria.

Please see section 4.2 .for comments on the information volunteered (over and above to what was requested by the AC) by the manufacturer to support its case for gefitinib as an 'end of life' treatment.

3 ERG modified economic results

The manufacturer has provided several tables of economic results in response to the issues raised in the ACD. Discussion of the specific requests is commented on below. A general comment applies to all the analyses. Overall, attempts have been made by the manufacturer to incorporate some of the modifications identified by the ERG in the ERG report; however four changes have not been made or have been implemented incorrectly. To address these problems the ERG has performed a mid-cycle correction, corrected first-line chemotherapy costs, corrected second-line chemotherapy costs and

adjusted costs to take account of patient drug exposure. The ERG has amended the new versions of the revised manufacturer's model to include these alterations, all of which affect only the costs of care, and do not impact on model estimates of health outcomes. These amended tables are provided in the appendices as noted below and it should be noted that the table numbers refer to those used in the manufacturer's post ACD submission.

3.1 Comparison of gefitinib versus gemcitabine/carboplatin and gemcitabine/cisplatin

The ERG notes that the manufacturer has argued (pg 14 of their submission) for their approach which is the use of an unstratified mode for the analysis (presented on pages 17-19 of their submission). This analysis does not meet the AC request for independent survival curve analysis and it is worth noting that analysis as requested would not have favoured the case put forward by the manufacturer.

3.2 Comparison of gefitinib with pemetrexed

Similar to the case of the previous analysis, the AC requested the application of the HR from the MTC to the independent survival curves for this analysis. The results of the analysis are presented in tables 15 and 16 of the manufacturer's submission. It is not possible to tell from the submission whether an independent survival curve analysis has been carried out but the ERG believes that it is unlikely.

In spite of these important limitations, tables in Appendix 1are provided to demonstrate the updated economic results when all ERG changes are incorporated. In most cases, these indicate rather less favourable cost-effectiveness ratios for use of gefitinib than those presented by the manufacturer of gefitinib.

3.3 Prevalence of EGFR-TK mutations and costs

The post ACD submission points out that the manufacturer has been funding the cost of EGFR tests in the NHS since June 2009. They go on to provide details of frequency of testing as well as a discussion of the problem of testing failure and a two way sensitivity analysis related to cost and frequency of the test. Appendix 3 provides the revised tables related to the resultant ICERs.

4 Additional information not requested in by the ACD

AstraZeneca volunteered additional information that was not asked for by the AC. In summary, the manufacturer proposed an amendment to the gefitinib single payment access scheme (SPA) and provided additional information to support its case for gefitinib to be treated as an end of life treatment.

4.1 Proposed amendment to gefitinib single payment access scheme

The ACD referred to concerns expressed at the first meeting of the Appraisal Committee regarding the operation of the SPA scheme which involves a fixed charge per patient receiving treatment with gefitinib regardless of the duration of that course of treatment. In particular, patients whose treatments were to be terminated in the first few weeks (due to disease progression or withdrawal for other adverse events or any other reason) would incur very high costs with no corresponding benefit.

In response to this concern the manufacturer has proposed a modified version of their scheme, which exempts from reimbursement any patient whose duration of therapy is not greater than two 30-tablet packs (60 days). On the basis of information from the IPASS trial it is estimated that this would effectively involve an additional 9.1% discount on the original SPA scheme. However, no rationale or evidence has been provided by the manufacturer to support the use of the proposed cut-off of 60 days.

The ERG has re-examined the IPASS trial results to consider how the duration of treatment may be related to the timing of accrued health benefits. By comparing the time profiles of cumulative hazard in each of the trial arms (gefitinib and paclitaxel/carboplatin) it is possible to estimate at each protocol assessment point (every 42 days) the relative advantage exhibited for patients in the gefitinib arm. Figure 4-1 shows the results of this analysis in relation to PFS as the primary trial outcome. It appears that there is no evidence of meaningful measurable outcome gains at any assessment up to and including 126 days. The first clear indication of advantage occurs at 168 days. If these analyses were considered an appropriate objective basis for defining a threshold for reimbursement related to likely patient benefit, then it would suggest that treatment for more than 120 days (four packs) may be an appropriate criterion. The IPASS data indicate that this would reduce by 18.9% the number of patients to be included in a fixed price scheme (cf. 9.1% in the manufacturer's revised SPA).

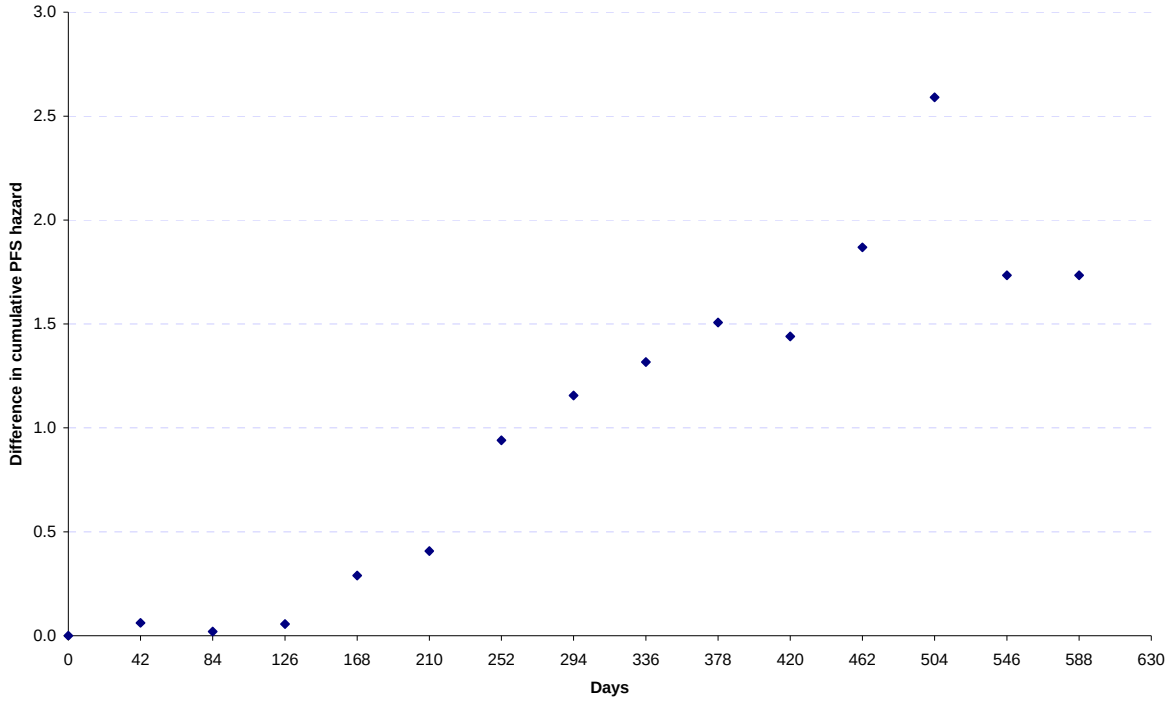

Figure 4-1 Advantage accruing over time (difference in cumulative hazard for disease progression) in IPASS trial, measured at each protocol assessment

Table 4-1 shows how sensitive the cost effectiveness of gefitinib is to different SPA schemes. The ICERs are calculated using the manufacturer's base case Weibull (unstratified model) with ERG amendments assuming a maximum of four cycles of comparator chemotherapy as in ERG amended Table 11a.

Table 4-1Impact of the changes to single payment access scheme on ICERs

			Comparator	
SPA version	**Threshold for reimbursement**	**Patients not reimbursed**	**ICERs (£/QALY) Gemcitabine / carboplatin**	**ICERS (£/QALY) Gemcitabine / cisplatin**
Original	None	0.00%	£49,661	£48,074
Revised	Tx > 60 days	9.09%	£42,341	£40,654
Alternatives	Tx > 90 days	16.67%	£36,236	£34,466
	Tx > 120 days	18.94%	£34,408	£32,613
	Tx > 150 days	23.48%	£30,752	£28,906
	Tx > 180 days	29.55%	£25,864	£23,951

ICER= incremental cost-effectiveness ratio; QALY= quality adjusted life year; SPA= single payment access

4.2 'End of life' criteria

AstraZeneca provided new preliminary OS data from the North East Japan Study Group (NEJSG) which is Academic in Confidence. AstraZeneca attempted to discuss this evidence at the first AC meeting on the 7th January 2010 but the Appraisal Committee Chair did not allow discussion of the data because the information was not included in the original manufacturer submission. The nature of the NESJG trial data is not observational or epidemiological as requested by the AC. The new data would not have been identified from any search of the literature as it is unpublished. [redacted].

5 Conclusion

Based on consideration of the additional evidence provided by the manufacturer to NICE and the extra amendments made by the ERG to the resubmitted model, the ERG is of the opinion that the revised ICERs are rather less favourable than those presented by the manufacturer of gefitinib in their original submission.

Based on the original evidence submitted, the ERG is of the opinion that in all modelled comparisons the estimated OS advantage for gefitinib is below three months. The ERG cannot comment on the manufacturer's view that unpublished new data from the NEJSG trial [redacted] should be taken into account when considering gefitinib as an 'end of life' treatment.

6 Appendices

Appendix 1 Summary of data requested, manufacturer response and LRiG's comments

	AC requested AstraZeneca to	Summary of AstraZemeca response	ERG comments
1.3 (4.11)	Explore alternative probability distributions for the extrapolation of PFS and OS beyond the timeframe of the Iressa Pan Asian Study (IPASS).	AstraZeneca provided data as requested. AstraZeneca concluded that the unstratified Weibull model appears to be the most appropriate probability distribution for modelling the PFS and OS data in EGFR M+ patients in the IPASS trial, as described in the original MS.	The manufacturer estimates survival differences using four different models. Given the range of apparent survival differences (-3.3 months to +4.2 months), the ERG is of the opinion that it would require considerably greater consistency in the estimated differences for any estimate of OS gain with gefitinib therapy to be described as 'robust'.
1.4 (4.11)	Consider independent survival curves (OS and PFS) for both gefitinib and paclitaxel/carboplatin based on the IPASS data and exploration of different approaches to applying the hazard ratio to incorporate other comparators (e.g. pemetrexed and other platinum-based regimens). The different approaches to applying the hazard ratio should consider using either gefitinib or paclitaxel/carboplatin as the baseline.		
1.5 (4.11)	Examine alternative probability distributions and give consideration of model fit to early trial data and the shape of the curves at the tail of the distribution.		
1.6 (4.11)	Identify observational or epidemiological evidence on long-term survival in patients with locally advanced or metastatic NSCLC and demonstrate how this relates to the most plausible model fit.	AstraZeneca searched for publications that had reported long-term survival in chemotherapy naive EGFR M+ patients with locally advanced or metastatic NSCLC that had been treated with gefitinib or doublet chemotherapy. AstraZeneca concludes that the historical literature supports that for an IPASS type population, a Weibull or	The ERG notes the mismatch in the request from the AC and the data submitted by the manufacturer. The manufacturer's focus is on chemotherapy naive EGFR M+ patients that had been treated with gefitinib or doublet chemotherapy. The AC did not limit its

	AC requested AstraZeneca to	Summary of AstraZemeca response	ERG comments
		log-logistic distribution may be a good fit to the long-term survival data.	request to this patient group.
1.7 (4.11)	To provide IPD from IPASS to enable the ERG to validate key aspects of the submitted model, including the modelling of OS and PFS, the choice of parameter values, and structural assumptions.	AstraZeneca did not supply IPD from IPASS	The ERG prefers to analyse IPD whenever possible. However, given that the time allotted for consideration of the manufacturer's additional data was only five days the ERG would not have had time to conduct a comprehensive analysis even if the data had been provided.
1.8 (4.11)	To determine the robustness of the ICER to alternative survival distributions for PFS and OS, based on the independent survival curves for gefitinib and paclitaxel/carboplatin from the IPASS data. The analysis should also provide evidence on 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. It is requested that for the comparison of gefitinib with gemcitabine/carboplatin and gemcitabine/cisplatin the following alternative approaches should be used: (a) assuming the same PFS and OS as established for paclitaxel/carboplatin through the independent survival curve fitting from IPASS using gemcitabine related costs and adverse events; and (b) applying the hazard ratio from the mixed-treatment comparison for the gemcitabine regimens to the independent survival curves for paclitaxel/carboplatin from IPASS, and using gemcitabine related costs and	(i) AstraZeneca did not determine the robustness of the ICER to alternative survival distributions for PFS and OS. (ii) AstraZeneca varied the number of first-line chemotherapy cycles between four and six and accounted for a lower level of dosing in female patients in their base case analysis. (iii) AstraZeneca compared gefitinib versus gemcitabine/carboplatin and gemcitabine/cisplatin using	(i) AstraZeneca discussed clinical outcomes associated with four different survival models but they did not go as far as to determine the robustness of the ICER to alternative survival distributions. (ii) In summary, four of the changes recommended by the ERG have not been made or were implemented incorrectly by the manufacturer. After correction, most of the ERG ICERs are higher than those presented by the manufacturer. The ERG notes that the manufacturer

	AC requested AstraZeneca to	Summary of AstraZemeca response	ERG comments
	adverse events. The Committee also agreed that exploration of different approaches to applying the hazard ratio should be carried out for the comparison of gefitinib with pemetrexed/cisplatin as follows: (a) applying the hazard ratio from the mixed-treatment comparison for pemetrexed/cisplatin to the independent survival curves for paclitaxel/carboplatin from IPASS, and using pemetrexed-related costs and adverse events; and (b) applying an indirectly derived hazard ratio for pemetrexed/cisplatin compared with gefitinib to the independent survival curves for gefitinib from IPASS, and using pemetrexed-related costs and adverse events.	scenarios (Aa) and (Ab) as described on page 16 of their response to NICE. (iv) AstraZeneca explored different approaches to applying the hazard ratio for key comparisons as described in scenario (Ab) (pg 16) and scenarios (Ba) and (Bb) as described on page 22 of their response to NICE.	has opted to use, without sufficient rationale, the unstratified model assumption in table 9a, 11a, 9b and 11b. The ERG is therefore of the opinion that the manufacturer has not fully delivered what was asked of them by the AC with reference to Aa. Re points Ab, Ba and Bb, the ERG comments that the methodology used to explore the different approaches to estimating hazard ratios is unclear.
1.9-1.11 (4.12)	Further explore the sensitivity of the ICER to: varying the prevalence of EGFR-TK mutations between 5% and 17%, taking into account different scenarios 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), alternative assumptions about the volume, and hence cost, of the EGFR-TK mutation tests carried out.	AstraZeneca conducted a two-way sensitivity analyses 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)	Using the additional information submitted by manufacturer, the ERG's revised ICERs are higher than the manufacturer's new ICERs.

ICER=incremental cost-effectiveness ratio; PFS= progression free survival; OS= overall survival; M+ = mutation positive; NSCLC= non-small cell lung cancer; IPD= individual patient data; EGFR= epidermal growth factor receptor

Appendix 2 *ERG modified results using original SPA scheme*

(note table numbers match those in the manufacturer's submission)

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

Scenario a (same PFS and OS	**Mean Costs**	**Mean QALYs**	**Δ mean Costs**	**Δ mean QALYs**	**ICER (£/QALY)**
Gefitinib EGFR M+ *versus*	£25,982 *£29,288*	1.0576 *1.2264*	-	-	-
Gem/carb EGFR M+	£19,958 *£23,032*	0.9026 *1.0569*	£6,023 *£6,256*	0.1550 *0.1695*	£38,861 *£36,919*
Gem/cis EGFR M+	£20,532 *£23,606*	0.9047 *1.0590*	£5,449 *£5,682*	0.1529 *0.1674*	£35,628 *£33,942*

Normal text = base case Weibull (unstratified model) for PFS/ OS. *Italic text* = Weibull (unstratified) PFS model and Log-logistic (unstratified) OS model

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

Scenario a (same PFS and OS	**Mean Costs**	**Mean QALYs**	**Δ mean Costs**	**Δ mean QALYs**	**ICER (£/QALY)**
Gefitinib EGFR M+ *versus*	£25,982 *£29,288*	1.0576 *1.2264*	-	-	-
Gem/carb EGFR M+	£18,458 *£21,531*	0.9061 *1.0604*	£7,523 *£7,757*	0.1515 *0.1660*	£49,661 *£46,737*
Gem/cis EGFR M+	£18,797 *£21,870*	0.9082 *1.0625*	£7,184 *£7,418*	0.1494 *0.1639*	£48,074 *£45,254*

Normal text = base case Weibull (unstratified model) for PFS/ OS. Italic text = Weibull (unstratified) PFS model and Log-logistic (unstratified) OS model

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

Scenario b (PFS and OS	**Mean Costs**	**Mean QALYs**	**Δ mean Costs**	**Δ mean QALYs**	**ICER (£/QALY)**
Gefitinib EGFR M+ *versus*	£25,982	1.0576	-	-	-
Gem/carb EGFR M+	£20,663	0.9079	£5,319	0.1497	£35,525
Gem/cis EGFR M+	£21,061	0.9447	£4,920	0.1129	£43,587

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

Scenario b (PFS and OS	**Mean Costs**	**Mean QALYs**	**Δ mean Costs**	**Δ mean QALYs**	**ICER (£/QALY)**
Gefitinib EGFR M+ *versus*	£25,982	1.0576	-	-	-
Gem/carb EGFR M+	£19,261	0.9111	£6,720	0.1465	£45,874
Gem/cis EGFR M+	£19,290	0.9483	£6,693	0.1093	£61,222

6.1 ERG modified results using revised SPA scheme

ERG amended 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 (same PFS and OS	**Mean Costs**	**Mean QALYs**	**Δ mean Costs**	**Δ mean QALYs**	**ICER (£/QALY)**
Gefitinib EGFR M+ *versus*	£24,871 *£28,178*	1.0576 *1.2264*	-	-	-
Gem/carb EGFR M+	£19,958 *£23,032*	0.9026 *1.0569*	£4,913 *£5,146*	0.1550 *0.1695*	£31,698 *£30,368*
Gem/cis EGFR M+	£20,532 *£23,606*	0.9047 *1.0590*	£4,339 *£4,572*	0.1529 *0.1674*	£28,369 *£27,311*

Normal text = base case Weibull (unstratified model) for PFS/ OS. Italic text = Weibull (unstratified) PFS model and Log-logistic (unstratified) OS model

ERG amended 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 (same PFS and OS	**Mean Costs**	**Mean QALYs**	**Δ mean Costs**	**Δ mean QALYs**	**ICER (£/QALY)**
Gefitinib EGFR M+ *versus*	£24,871 *£28,178*	1.0576 *1.2264*	-	-	-
Gem/carb EGFR M+	£18,458 *£21,531*	0.9061 *1.0604*	£6,413 *£6,646*	0.1515 *0.1660*	£42,333 *£40,048*
Gem/cis EGFR M+	£18,797 *£21,870*	0.9082 *1.0625*	£6,074 *£6,307*	0.1494 *0.1639*	£40,646 *£38,481*

Normal text = base case Weibull (unstratified model) for PFS/ OS. Italic text = Weibull (unstratified) PFS model and Log-logistic (unstratified) OS model

ERG amended 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 (PFS and OS	**Mean Costs**	**Mean QALYs**	**Δ mean Costs**	**Δ mean QALYs**	**ICER (£/QALY)**
Gefitinib EGFR M+ *versus*	£24,871	1.0576	-	-	-
Gem/carb EGFR M+	£20,663	0.9079	£4,208	0.1497	£28,109
Gem/cis EGFR M+	£21,061	0.9447	£3,810	0.1129	£33,753

ERG amended 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 (PFS and OS	**Mean Costs**	**Mean QALYs**	**Δ mean Costs**	**Δ mean QALYs**	**ICER (£/QALY)**
Gefitinib EGFR M+ *versus*	£24,871	1.0576	-	-	-
Gem/carb EGFR M+	£19,261	0.9111	£5,610	0.1465	£38,295
Gem/cis EGFR M+	£19,290	0.9483	£5,581	0.1093	£51,065

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

Scenario a (applying HR from the	**Mean Costs**	**Mean QALYs**	**Δ mean Costs**	**Δ mean QALYs**	**ICER (£/QALY)**
Gefitinib EGFR M+ *versus*	£25,982	1.0576	-	-	-
Pem/cis EGFR M+	£24,192 *£24,192*	1.0288 *1.0288*	£1,789 *£679*	0.0288 *0.0288*	£62,215 *£23,615*
Pem/cis EGFR M+	£23,133 *£23,133*	1.0307 *1.0307*	£2,848 *£1,738*	0.0270 *0.0270*	£105,672 *£64,481*
Pem/cis EGFR M+	£21,937 *£21,937*	1.0326 *1.0326*	£4,044 *£2,934*	0.0250 *0.0250*	£161,788 *£117,374*

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

Appendix 3 EGFR sensitivity analysis

ERG amended Table 18: Two-way sensitivity analysis varying EGFR-TK mutation rate and testing costs (ICER vs. Gemcitabine+carboplatin 6 cycles)

Cost EGFR-TK Test / **EGFR-TK Mutation Rate**	**ICER (£/QALY)**		
	5%	**10%**	**17%**
£210.00	£56,739 *£49,323*	£42,712 *£35,296*	£36,936 *£29,520*
£178.50	£52,530 *£45,115*	£40,608 *£33,192*	£35,698 *£28,283*
£157.50	£49,725 *£42,309*	£39,205 *£31,789*	£34,873 *£27,457*

Normal text = original gefitinib SPA scheme. Italic text = amended gefitinib SPA scheme incorporating the delayed invoicing proposal

ERG amended Table 18: Two-way sensitivity analysis varying EGFR-TK mutation rate and testing costs (ICER vs. Gemcitabine+carboplatin 4 cycles)

Cost EGFR-TK Test / EGFR-TK Mutation Rate	ICER (£/QALY)		
	5%	**10%**	**17%**
£210.00	£67,554 *£59,975*	£53,219 *£45,640*	£47,316 *£39,737*
£178.50	£63,253 *£55,875*	£51,068 *£43,490*	£46,051 *£38,472*
£157.50	£60,386 *£52,808*	£49,635 *£42,056*	£45,208 *£37,629*

Normal text = original gefitinib SPA scheme. Italic text = amended gefitinib SPA scheme incorporating the delayed invoicing proposal

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

Scenario b (applying an indirectly derived HR for pem/cis	**Mean Costs**	**Mean QALYs**	**Δ mean Costs**	**Δ mean QALYs**	**ICER (£/QALY)**
Gefitinib EGFR M+ *versus*:	£29,250 *£28,140*	1.0576 *1.0576*	-	-	-
Pem/cis EGFR M+ Max 6 cycles, mean = 5.2	£29,154 *£29,154*	1.0091 *1.0091*	£96 *-£1,014*	0.0485 *0.0485*	£1,982 *Dominant**
Pem/cis EGFR M+ Max 5 cycles, mean = 4.5	£28,164 *£28,164*	1.0107 *1.0107*	£1,086 *-£24*	0.0469 *0.0469*	£23,169 *Dominant**
Pem/cis EGFR M+ Max 4 cycles, mean = 3.7	£27,024 *£27,024*	1.0126 *1.0126*	£2,226 *£1,115*	0.0450 *0.0450*	£49,428 *£24,772*

Italic text = Modelled with amended gefitinib SPA scheme to incorporate the delayed invoicing proposal.* Dominant = gefitinib is less expensive and more effective than pemetrexed/cisplatin