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

ERG Addendum

Produced by: *Liverpool Reviews and Implementation Group*
University of Liverpool
Room B05
Whelan Building
The Quadrangle
Brownlow Hill
Liverpool
L69 3GB
Tel: +44 (0) 151 794 5682/5541/5067
Fax: +44 (0) 151 794 5585
Email: LRiG@liv.ac.uk

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CONTENTS:

1 BACKGROUND

On 19th March 2009, the National Institute for Health and Clinical Excellence (NICE) Appraisal Committee considered the evidence for use of pemetrexed in the first-line treatment of non-small cell lung cancer (NSCLC.) Given the concerns expressed by the evidence review group (ERG) regarding the final economic model submitted by the manufacturer, it was concluded that the cost effectiveness of pemetrexed in combination with cisplatin (pemetrexed/cisplatin) had not been proven. However, given the evidence for the clinical effectiveness of pemetrexed/cisplatin from the phase III JMDB trial, the Committee considered that pemetrexed was potentially an important treatment for certain subgroups of NSCLC patients and therefore requested the following additional analyses from the manufacturer:

(1) A cost effectiveness analysis comparing pemetrexed/cisplatin with gemcitabine/cisplatin which accurately represents the outcomes of the JMDB trial ('in-trial' analysis)
(2) A separate analysis based on the JMDB clinical trial where event data from the clinical trial should be used to estimate its cost effectiveness

The Committee stated that all new analyses should be comprehensively quality assured.

In addition, the manufacturer was invited to comment on the NICE appraisal committee document (ACD) and to comment on the ERG evaluation report.

Box 1-1 Concerns raised by the Committee to be addressed by the manufacturer

- The JMDB trial data suggested that all the reported survival gain occurred after disease progression, with progression-free survival effectively identical between the pemetrexed/cisplatin and gemcitabine/cisplatin arms; it was not clear whether objective response determined the extent of health gain and whether the survival gain was restricted to only those patients whose disease had responded to treatment, or to all patients who had treatment
- All transition probabilities during the trial period were assumed to arise from constant risk processes (that is, exponential survival distributions), without any justification
- A half-cycle correction appeared to have been disabled for costs and used incorrectly for outcomes
- Cumulative costs and outcome effects of patients having more than one adverse event at any given time (for example, within a single hospital admission) were not taken into account. This omission could have led to over-estimation of the costs and harms attributable to treatment
- Use of febrile neutropenia mortality risk was questionable

On 6th May 2009, the manufacturer submitted its response to the NICE ACD for the appraisal of pemetrexed in the first-line treatment of NSCLC. This response included evidence in the form of three cost effectiveness analyses:

(1) 'in-trial' cost effectiveness analysis using the individual patient survival outcomes (censored) and resource use events from the JMDB clinical trial database (''in-trial' analysis)
(2) The original submitted Markov model was modified to more accurately represent the outcomes of the JMDB trial using Weibull distributions, and to take into account concerns raised by the Committee (see Box 1-1) in order to re-estimate the incremental cost-effectiveness of pemetrexed/cisplatin when compared to gemcitabine/cisplatin (modified Markov model)
(3) Findings from the economic model used for the Pharmaceutical Benefits Advisory Committee (PBAC) HTA submission in Australia, which was based upon the patient level data from the JMDB trial and used Weibull distributions to extrapolate survival

The manufacturer stated that a thorough validation process was followed according to the NICE request such as double build for the 'in-trial' cost effectiveness analyses, and internal and independent external reviews for both the 'in-trial' analysis and modified Markov model.

No other responses were made by the manufacturer with regard to the ACD or the ERG evaluation report.

The following sections of this report briefly summarise the manufacturer's response to the ACD before going on to describe the findings of a careful examination by the ERG of the 'in-trial' cost-effectiveness analysis and modified Markov model submitted by the manufacturer of pemetrexed, discussing the strengths and robustness of the available evidence in favour of pemetrexed/cisplatin compared to existing comparators. As the manufacturer also submitted findings from the economic model used for the PBAC HTA submission, the ERG has also commented on this model in Appendix 1.

2 'IN-TRIAL' COST-EFFECTIVENESS ANALYSIS

2.1 Summary of evidence submitted

The manufacturer of pemetrexed has provided a cost-effectiveness analysis based on the JMDB trial patient level data without use of projection techniques as requested by NICE. The data were largely processed using SPSS syntax, but the source data and calculated fields are presented in the form of an Excel workbook. The analysis adheres closely to the approach taken in the previous cost-effectiveness models, and uses the same unit cost and state utility parameter values. Economic results are presented for six scenarios:

(a) Licensed population of patients with non-squamous NSCLC receiving a maximum of four cycles chemotherapy, using differential utility values between trial arms

(b) Licensed population of patients with non-squamous NSCLC receiving up to six cycles chemotherapy, using differential utility values between trial arms

(c) Licensed population of patients with non-squamous NSCLC receiving a maximum of four cycles chemotherapy, using the same utility value in both trial arms

(d) Manufacturer's target population of patients receiving a maximum of four cycles chemotherapy, using differential utility values between trial arms

(e) Manufacturer's target population of patients with adenocarcinoma and large cell carcinoma receiving up to six cycles chemotherapy, using differential utility values between trial arms

(f) Manufacturer's target population of patients with adenocarcinoma and large cell carcinoma receiving a maximum of four cycles chemotherapy, using the same utility value in both trial arms

The cost-effectiveness results obtained (Table 2-1) range from an incremental cost effectiveness ratio (ICER) of £24,224 per quality adjusted life year (QALY) gained to £45,156 per QALY gained.

Table 2-1 Results of manufacturer's 'in-trial' cost-effectiveness analysis

Scenario	Patient population	Cycles of CTX	Utilities	Incremental cost	Incremental QALYs	ICER
a	Non-squamous	4	Different	£1,752	0.0562	£31,158
b	**Non-squamous**	**6**	**Different**	**£2,379**	**0.0562**	**£42,306**
c	Non-squamous	4	Same	£1,752	0.0388	£45,156
d	Adenocarcinoma + Large cell	4	Different	£1,774	0.0732	£24,224
e	**Adenocarcinoma + Large cell**	**6**	**Different**	**£2,470**	**0.0732**	**£33,730**
f	Adenocarcinoma + Large cell	4	Same	£1,774	0.0555	£31,972

CTX=chemotherapy; ICER=incremental cost effectiveness ratio; QALY=quality adjusted life year

2.2 Critique of manufacturer's approach

Scenarios: The principle underlying an 'in-trial' cost-effectiveness analysis is that the observed activity and resource use data are preserved, and only valuation parameters are determined in relation to the chosen national setting. Thus it is appropriate to use UK unit costs and utility values, but not to alter important trial data. On this basis, the reduction of treatment costs by limiting the number of cycles of chemotherapy is inappropriate given the JMDB trial not only included patients who had received more than four cycles but also because it involves the implicit assumption that no commensurate alteration in effectiveness is required. Therefore the ERG considers that only scenarios (b) and (e) should be considered true 'in-trial' analyses.

Utility values: In all versions of the manufacturer's full Markov model three utility values have been employed for the main health states in both treatment arms: 0.65 for "Stable", 0.67 for "Responding" and 0.47 for "Progressive Disease". In addition, a variety of utility decrements are applied to various adverse events associated with chemotherapy. However, for the 'in-trial' analysis two new values are adopted without explanation: 0.65 for patients in the pemetrexed arm, and 0.63 for patients receiving gemcitabine.

This appears to be inappropriate on two grounds. Firstly, it uses values very close to those previously applied for pre-progression health states and does not recognise that a large proportion of patients in both arms suffer disease progression leading to death within the trial period, suggesting that the appropriate values should be far lower. Secondly, it may be that the apparent differences from the previously used parameter values are intended to reflect differential AE experience, but this is not stated and it is not clear whether the size of difference in mean utility values is appropriate.

A further difficulty involves the implications of these new values for the calculation of ICERs. As previously noted by the ERG, almost all the survival benefit observed for pemetrexed in the JMDB trial occurred *after* disease progression. It therefore follows that the correct utility parameter value for use with the incremental survival is that of the "Progressive Disease" state (i.e. 0.47) not that of the pre-progression states (0.65 / 0.67).

Adjusting the incremental QALYs in the reported results in Table 2-1 to reflect this revision increases the ICER by 19-21% - to £52,000/QALY for scenario (b), and £43,000/QALY for scenario (e).

Drug acquisition costs: The ERG report highlighted the inadequacy of estimating the cost of chemotherapy agent acquisition without regard to the population variability of body surface area, and without allowing for wastage of part-used vials. It was shown that this increases the cost per cycle of

pemetrexed/cisplatin chemotherapy by £81.63 and decreases that of gemcitabine/cisplatin by £3.80. Substituting these more accurate costs into the 'in-trial' analysis has the effect of increasing the incremental cost of pemetrexed relative to gemcitabine (and therefore the ICER) by about 15% - to £49,000/QALY for scenario (b) and £39,000/QALY for scenario (e).

Discounting outcomes: The 'in-trial' analysis does not perform discounting on either costs or outcomes, despite trial follow-up extending to more than two years for some patients. This is an important omission, since much of the survival gain occurs after the first 12 months and is therefore liable for discounting. The effect of applying a discount rate of 3.5% pa to incremental survival is to increase the ICER by a small amount (2-4%).

With regard to the effect on costs, the situation is mixed. All first-line chemotherapy acquisition, administration and associated AE costs will fall within the first year and therefore do not require discounting. However, other long-term costs occurring beyond 12 months follow-up should be discounted. This is discussed in more detail below.

Terminal care, best supportive care (BSC) and second-line chemotherapy costs: The authors of the 'in-trial' analysis have used differential costs per patient for terminal care and for BSC (see Table 12 of the 'Lilly UK response to NICE Appraisal Consultation Document 6 May 2009'). However, these figures are not derived from an analysis of the trial IPD, but are mean results calculated in the manufacturer's full Markov model. This creates a confusion between observation and modelling, which may distort the results of the 'in-trial' analysis. However, restricting consideration only to patients who die within the trial period generates a bias in favour of the arm with better survival, since terminal care costs which will certainly be incurred at some time are omitted altogether. Including such costs even for patients still alive at the end of the trial is also problematic since estimating the timing of those costs would only be possible on the basis of modelling. As a compromise the ERG prefers to include terminal care and BSC costs for all patients, but discounted for a nominal period beyond the recorded survival date for patients censored in the trial.

The combined effect of amending the costs of BSC and terminal care, and applying discounting to all long-term care is to reduce the incremental cost per patient of using pemetrexed, leading to a reduction in the ICER of 4.5-5.0%.

2.3 New findings based on the ERG suggested amendments

The impact of the above changes to the submitted 'in-trial' economic analysis are detailed in Table 2-2. The net effect is a substantial increase in the estimated ICER for both scenarios, confirming that

pemetrexed/cisplatin cannot be considered a cost-effective alternative to gemcitabine/cisplatin without consideration of additional patient benefit based on projective modelling beyond the trial period.

Table 2-2 Separate and combined effects of ERG recommended amendments to manufacturer's 'in-trial' cost-effectiveness analysis

	Scenario (b)*			Scenario (e)**		
Analysis / change	**Incremental cost**	**Incremental QALY**	**ICER £/QALY**	**Incremental cost**	**Incremental QALY**	**ICER £/QALY**
Submitted analysis	**£2379**	**0.0562**	**£42,306**	**£2470**	**0.0732**	**£33,730**
Use post-progression utility value	£2379	0.0455	£52,299	£2470	0.0579	£42,686
Recalculate drug costs	£2744	0.0562	£48,797	£2839	0.0732	£38,768
Discount outcomes	£2379	0.0540	£44,026	£2470	0.0719	£34,384
Amend/discount long-term costs	£2263	0.0562	£40,248	£2359	0.0732	£32,213
Combined ERG changes	**£2683**	**0.0437**	**£60,130**	**£2728**	**0.0568**	**£48,055**

ERG=evidence review group; ICER=incremental cost effectiveness ratio; QALY=quality adjusted life year

* scenario (b) = licensed population of patients with non-squamous NSCLC receiving up to six cycles chemotherapy, using differential utility values between trial arms

** scenario (e) = manufacturer's target population of patients with adenocarcinoma and large cell carcinoma receiving up to six cycles chemotherapy, using differential utility values between trial arms

3 MANUFACTURER'S MODIFIED MARKOV MODEL

3.1 Summary of evidence submitted

A number of specific and detailed problems were identified with all three previous versions of the economic model submitted to NICE by the manufacturer. In the latest revision (dated 6th May 2009), a number of alterations have been made by the manufacturer which are intended to address many of the problems described by the ERG. New base case cost-effectiveness results from the modified Markov model were presented in Table 15 of the manufacturer's response to the ACD, reproduced here as Table 3-1.

Table 3-1 Results for base case from the manufacturer's modified Markov model

Patient population	ICER	Incremental cost	Incremental QALY
Six cycles: Non-squamous	£37,398	£2,705	0.072
Four cycles: Non-squamous Adeno/large cell	 £25,967 £24,224	 £1,994 £2,071	 0.072 0.093

ICER=incremental cost effectiveness ratio; QALY=quality adjusted life year

In this section, the ERG considers each issue in turn and assesses the adequacy of the changes which have been implemented by the manufacturer.

3.2 Critique of manufacturer's approach

3.2.1 Issues relating to model structure and assumptions

Pathways to death:

The ERG previously noted that:

> "...the manufacturer's model assumes that death only occurs from the progressive disease state, and this dictates that no patients can die within the first cycle, and very few in the second cycle (about 1%). By contrast, the trial data indicate that 4-5% of patients were dead by the end of cycle 2." (p52)

In response the manufacturer states:

> "The model structure is largely unchanged, with the exception of risk of death which is now possible from any state, not just from the Progression state." (p11)

The adequacy of this revision is assessed below when considering overall survival.

Fixed inter-state transition rates:

The ERG also commented that:

> "...all transition probabilities during the trial period are assumed to arise from constant risk processes (i.e. exponential survival distributions), without any justification. It is therefore unsurprising that the submitted model is unable to generate results consistent with the trial evidence, especially with respect to three primary clinical outcomes (OS [overall survival], PFS [progression free survival] and response rate...)." (p52)

The manufacturer describes the use of Weibull models to generate time-varying transition rates between health states, leading to better estimates of OS and PFS. A different method was used to reproduce the response rates observed in the trial; this involves partitioning patients between responders and non-responders, and then distributing the actual number of responses between the cycles in which they occurred. This guarantees that the model correctly reproduces the trial response rate profiles.

Long-term projection rates:

The ERG further observed that:

"The use of fixed transition probabilities following the end of trial medication presupposes that all subsequent events are drawn from exponential distributions, imposing a serious limitation which is difficult to justify from the trial results, and can seriously influence long-term estimated outcomes which are based on projecting outcomes beyond the observed trial evidence." (p53)

Within the latest model the manufacturer has replaced exponential functions with Weibull functions as the basis for long-term projection. This gives a more explicit basis for the method of projection, but does not necessarily ensure that the new approach represents the most appropriate or credible means of estimation, since fitting a Weibull model to data for the whole trial period places most weight on early and intermediate period events, and much less weight on the sparser events towards the end of the trial, potentially leading to systematic over- or under-estimation of survival towards the end of the trial.

Repeated and multiple concurrent adverse events:

The ERG commented that:

> "The model logic implies that all AEs occur independently, and no account is taken of cumulative cost or outcome effects of patients suffering multiple concurrent AEs (e.g. within a single hospital admission). This is a frequent occurrence in late-stage cancer, and its omission can lead to over-estimation of the costs and disbenefits attributable to treatment. However, the issue can only be resolved by careful re-analysis of IPD from the clinical trial." (p53)

No attempt appears to have been made by the manufacturer to address this issue. However, the ERG is of the view that in terms of potential magnitude, any such errors still present are likely to be of minor importance and unlikely to be decisive in assessing cost effectiveness.

3.2.2 Major errors and omissions previously identified by the ERG

Reproducing trial response rate:

The ERG report drew attention to persistent problems in the submitted models which meant that the correct rates of response to chemotherapy could not be reproduced. The newly implemented model logic should guarantee accuracy. However, an error has been identified by the ERG; in the new model, the response rates appropriate to the licensed population of patients with non-squamous NSCLC have also been attributed to all the other four trial populations. This impacts differently on each population - the ICER increases sharply in the overall trial population (by £9,000 to £11,000/QALY), but generates only small changes for patients with adenocarcinoma and/or large cell carcinoma.

Reproducing trial overall survival experience:

In the ERG report it was observed that:

> "The manufacturer's model appears to over-estimate OS in both arms and almost all patient subgroups." (p55)

In the manufacturer's modified Markov model a graphical comparison can be used to assess the performance of the model using the new Weibull survival model. Figure 3-1 and Figure 3-2 show trial data together with model results in respect of the licensed population and the manufacturer's target population of patients with adenocarcinoma and large cell carcinoma. In both cases it can be seen that there is now a systematic over-estimation of survival by the model at around 12-30 weeks, and a trend towards under-estimation in the longer term. This suggests that, although somewhat better

than the earlier versions of the model, the new Weibull formulation is still not well suited to these trial data.

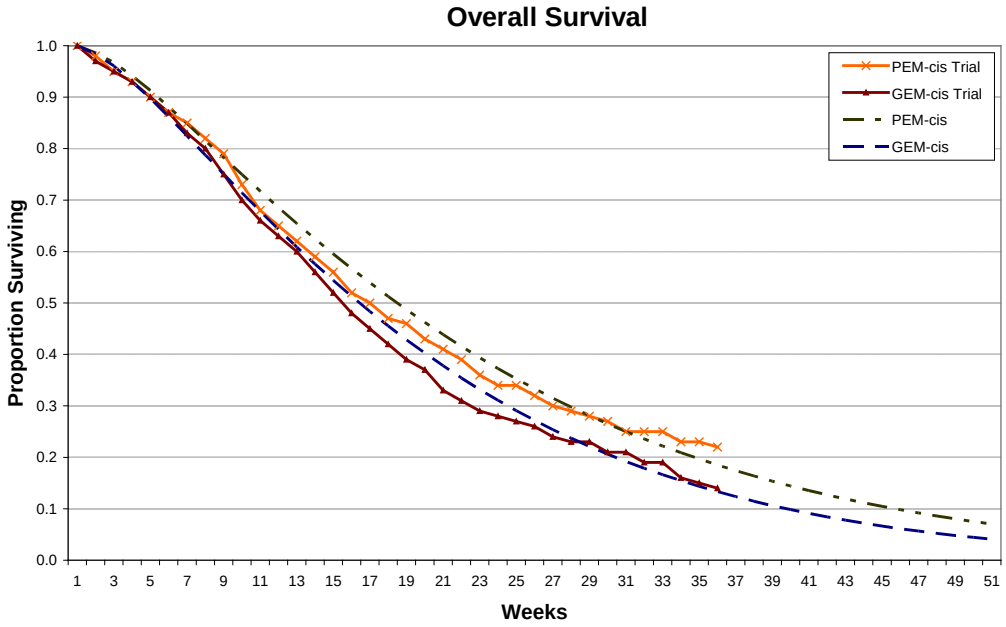

Figure 3-1 Comparison of JMDB trial results for overall survival and model estimates – patients with non-squamous NSCLC

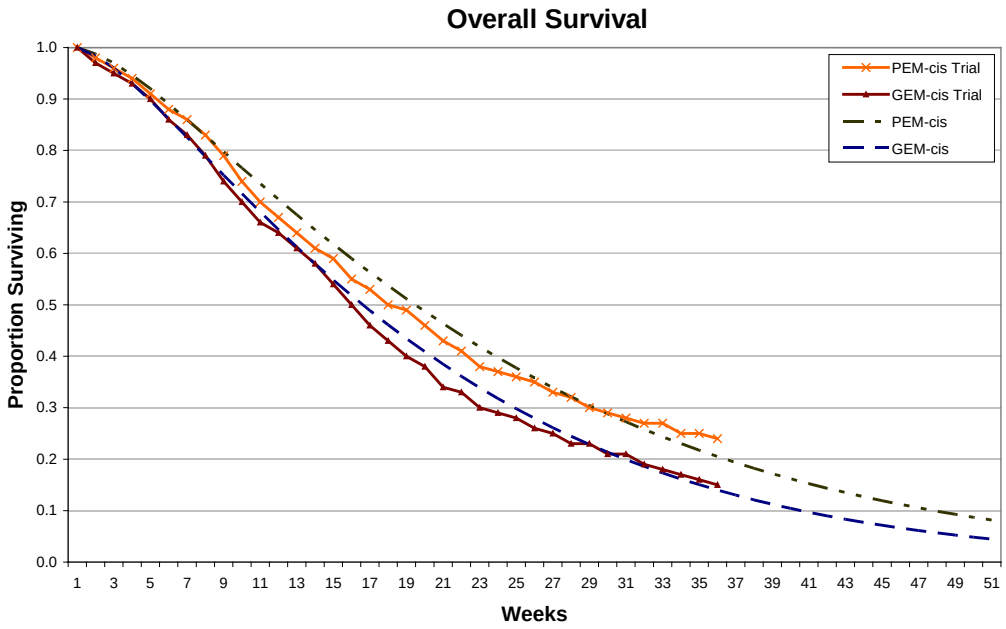

Figure 3-2 Comparison of JMDB trial results for overall survival and model estimates - manufacturer's target population of patients with adenocarcinoma and large cell carcinoma

Reproducing trial progression free survival experience:

The ERG commented in relation to the modelling of PFS:

> "For PFS, the model tends to produce under-estimates in the first six months and to over-estimate thereafter." (p55)

A direct comparison of trial versus model estimates is only accommodated in the latest model for patients with non-squamous NSCLC (Figure 3-3) and not for patients with adenocarcinoma and large cell carcinoma. Although the Weibull formulation is an improvement on the previous approach, it is still evident that there is an under-estimation of PFS by the model at around 10-30 weeks.

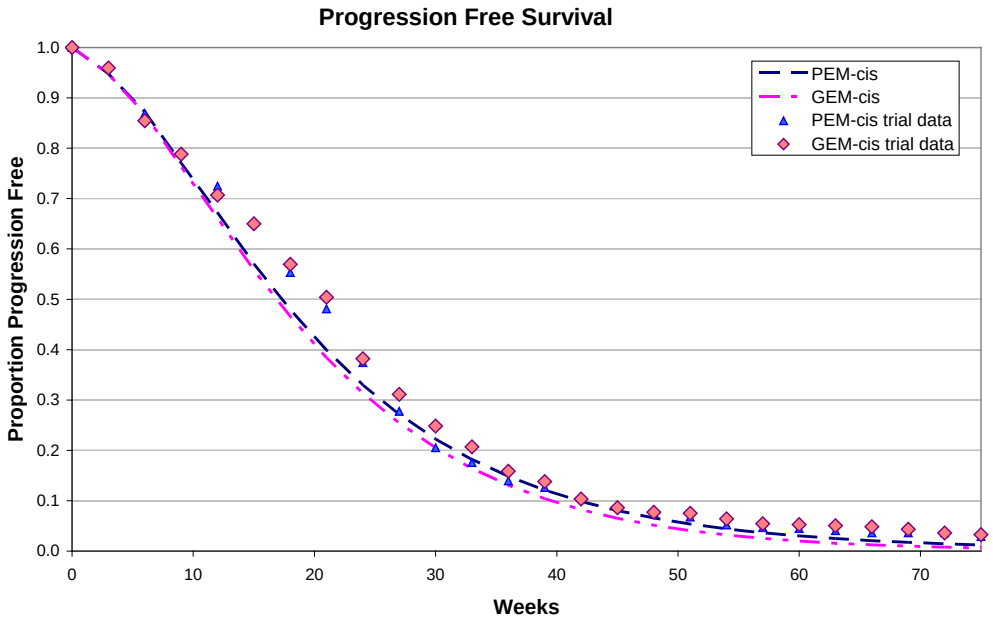

Figure 3-3 Comparison of JMDB trial results for progression-free survival and model estimates – patients with non-squamous NSCLC

Other comparators:

The ERG previously commented that the manufacturer had only partially addressed the defined scope of the assessment exercise, choosing only to consider gemcitabine and docetaxel as comparators to pemetrexed and omitting paclitaxel and vinorelbine from their model. The latest version of the model now considers only gemcitabine as a comparator, and therefore does not offer a comprehensive assessment of the merits of pemetrexed as first-line treatment of NSCLC. It may be that this decision was necessary in view of time constraints, but the manufacturer did not give any indication of this in their submission.

Price sensitivity:

The ERG also noted:

> "Furthermore, the ERG notes that gemcitabine will be off patent in the UK from March 2009. If the price of gemcitabine falls as a result, this will increase the magnitude of the pemetrexed/cisplatin versus gemcitabine/cisplatin and pemetrexed/cisplatin versus gemcitabine/carboplatin ICERs." (p56)

The manufacturer did not respond to this comment, nor did they include the results of any sensitivity analyses relating to the prices of comparator drugs.

3.2.3 Other model errors and issues previously identified by the ERG

Chemotherapy costs:

The ERG noted the inadequacy of estimates for acquisition costs of chemotherapy drugs:

> "All the chemotherapy treatments currently recommended for first-line treatment of NSCLC are dosed on the basis of the body surface area (BSA) of the individual patient. The submitted model does not take account of BSA differences between patients, including those due to gender." (p57)

A full set of revised costs taking full account of the UK distribution of BSA in lung cancer patients, and taking account of wastage of part-used vials was provided in the ERG report. The manufacturer chose not to use these values and instead substituted estimates based on vial recorded usage in the JMDB trial. Though this is clearly an improvement on early versions of the model, it does not reflect the characteristics of the UK population. The ERG considers that its previously reported cost figures are more likely to be representative of NHS experience, and can be expected to lead to important increases in the ICER in all patient populations.

Mid-cycle correction:

The ERG previously commented that:

> "The submitted model includes an optional feature to apply a half-cycle correction to the model results. However, this has been disabled for costs, and is used incorrectly for

> outcomes, where it has the effect of reducing the estimated number of QALYs in cycle 1 by a half, but does not alter anything in subsequent cycles." (p56)

In response the manufacturer states:

> "The half-cycle correction has been applied by halving the non-treatment related costs and QALYs in cycle zero. Treatment costs and treatment administration costs are not included in the half-cycle correction." (p16)

This is an improvement on the previous unsatisfactory and confusing situation. However, it still falls short of best practice since the use of a 'half-cycle' adjustment rather than a full mid-cycle adjustment (averaging separately over each cycle) is liable to bias where the time horizon of the analysis is truncated and discounting is required. Nonetheless, in this case the ERG is not of the opinion that altering the model logic would have a substantial effect on the results of the economic evaluation.

Reducing cycles of chemotherapy:

A very serious issue raised by the ERG report concerns the manner in which changes in the number of chemotherapy cycles is applied in the model:

> "The submitted model includes a facility for reducing the maximum number of chemotherapy treatment cycles offered to patients... This reduces the costs for pemetrexed but with no corresponding loss of benefits." (p56)

The assumption that additional chemotherapy after the fourth cycle has no prognostic effect at all is difficult to justify without clear clinical evidence. It seems plausible that some loss of late response and of long-term survival gain may be expected if the trial treatment protocol is truncated, though the magnitude of such a difference is uncertain. This is a key issue in the assessment of pemetrexed, and has not been addressed at all by the manufacturer. This issue is considered further in Section 4.

Febrile neutropenia and adverse event costs:

The ERG commented on the inappropriate assumption of important mortality risk associated with febrile neutropenia in the submitted model. The manufacturer has accepted this point and set the relevant parameter value to zero.

The ERG also noted logic problems with estimating the incidence rates for adverse events, especially when the number of cycles of chemotherapy is changed. New logic has been introduced into the model for all adverse events, but still exhibits unexpected behaviour. In all cases the model generates far fewer AE totals when the duration of chemotherapy is increased from four to six cycles. This is counterintuitive, since most AEs can be expected to either continue throughout chemotherapy, or to be experienced in the early cycles but not recur later - in either case reduction in overall rates seems to be unreasonable. The same logic applies to the rate of treatment discontinuation due to AEs, where higher rates apply when treatment is restricted to fewer cycles. Fortunately, the costs and utility effects of AEs are minor contributors to the incremental costs and outcomes so this persistent anomaly may not seriously affect the cost-effectiveness results.

4 ADDITIONAL EXPLORATORY ANALYSIS UNDERTAKEN BY THE ERG

A limited extract of IPD from the JMDB trial was included by the manufacturer within the 'in-trial' cost-effectiveness analysis. This is restricted to the population of patients with NSCLC and includes only information relating to chemotherapy treatment cycles and to OS i.e. the timing of death or censoring. No information was provided concerning response to treatment or the time of confirmed disease progression.

These data made it possible for the ERG to consider two important issues, independent of any of the manufacturer's models:

(1) What is the most appropriate estimate of survival gain and utility gain attributable to pemetrexed within the clinical trial?
(2) Is it possible to estimate the likely change in patient outcomes when treatment is limited to a maximum of four cycles instead of the six cycles used in the trial?

The ERG classified patients according to the last cycle in which they received a dose of pemetrexed or gemcitabine. Initial examination of Kaplan-Meier survival charts by the ERG indicated that patients could be classified into three groups which are broadly homogeneous with respect to prognosis - up to two cycles, three to four cycles and five to six cycles of chemotherapy. In the absence of specific information of disease progression or discontinuation of treatment, these divisions should reflect the approximate time when patients leave the stable or response states. In addition, they provide a basis for considering the possible effects of limiting treatment duration.

4.1 Exploratory survival analysis undertaken by the ERG

4.1.1 Analytical approach

The approach taken by the ERG to survival estimation was designed to make full use of the trial data and to minimise the contribution of trend projection beyond the available IPD. The area under the curve (AUC) was calculated from a Kaplan-Meier analysis from the start of the trial until the time when the last recorded event (death) occurred. Beyond that time, expected mean survival for patients still alive was estimated using a fitted survival model, calibrated from long-term trial data.

The approach taken to projection was based on examination of the cumulative hazard function for each treatment duration subgroup. It was observed that standard survival functions (e.g. exponential,

Weibull, Log normal, etc) were not generally compatible with the trial data across the whole range of observation. This is not unusual when treatment is of limited duration and would be expected to have a short-term effect of altering/delaying the normal course of the disease, after which the long-term progression pathway resumes. It was observed that in all cases at some time following the end of treatment the cumulative hazard function assumed a steady linear increase, indicative of a constant risk per unit of time. Therefore, for each patient subgroup an exponential function was fitted to the data from the point at which the long-term linear trend in the cumulative hazard became established. This survival function was then used to estimate the likely additional mean survival from the time of the last recorded death until the time horizon of the cost-effectiveness analysis.

4.1.2 Early treatment failures

The Kaplan-Meier survival curves for patients receiving two or less and three or four cycles of chemotherapy in the JMDB trial are shown in Figure 4-1. The close correspondence between treatment arms is apparent for both subgroups, and is confirmed by the log-rank test (p [redacted] for two or less cycles and p = [redacted] for three to four cycles). In the absence of meaningful differences in estimated survival, it was appropriate to undertake a combined analysis to estimate a common value for mean survival across both treatment arms for each subgroup. The resulting combined subgroup analysis with projection models are displayed in Figure 4-2.

It is instructive to compare the results of these analyses with those previously described in the ERG report (reproduced here as Figure 4-3), which show the close correspondence of survival curves for PFS. This suggests that the dominant cause of early cessation of chemotherapy in the JMDB trial is disease progression.

[redacted]

[redacted]

Figure 4-1 Separate Kaplan-Meier survival curves for patients receiving up to four cycles of pemetrexed or gemcitabine chemotherapy

[redacted]

Figure 4-2 Combined Kaplan-Meier survival curves for patients receiving up to four cycles of either pemetrexed or gemcitabine chemotherapy, with long-term projection models

[redacted]

[redacted]

Figure 4-3 Progression free survival for patients with non-squamous NSCLC: Kaplan-Meier analyses from JMDB trial data. (Figure 5-2 of original ERG report)

[redacted]

Figure 4-4 Kaplan-Meier survival curves for patients receiving five or more cycles of chemotherapy, with long-term projection models

4.1.3 Treatment beyond four cycles

A similar model-fitting exercise was carried out for patients receiving five or more cycles of chemotherapy, using a two-part offset exponential spline function (see Figure 4-4). As before, the estimated mean survival for each treatment was obtained by adding the AUC up until the last recorded event to the area under the projected model as far as the time horizon of the cost-effectiveness analysis (six years).

4.1.4 Summary of mean survival estimates

These results are summarised in Table 4-1 below. The benefit attributable to pemetrexed amounts to [redacted] years (undiscounted) or [redacted] years (discounted). Assuming that all this gain arises following disease progression, the ERG estimates the QALY gain to be [redacted] (undiscounted) or [redacted] (discounted) based on the utility value used in the manufacturer's submission.

Table 4-1 Estimated mean overall survival (months) in JMDB trial projected to six years

xx	Number of cycles of pemetrexed				Number of cycles of gemcitabine			
	0-2	3-4	5-6	Total	0-2	3-4	5-6	Total
Patients	[redacted]							
%								
AUC 'in-trial'								
Projected								
Total undiscounted								
discounted								
Months gained undiscounted								
discounted								

[redacted]

4.2 Impact of treatment duration limit on outcomes

The JMDB trial protocol specified that chemotherapy should be continued for a maximum of six cycles or until disease progression was confirmed. However, normal clinical practice in the UK is to restrict chemotherapy to no more than four cycles, on the grounds that very few patients show evidence of clinically significant response in later cycles. Estimating the reduced costs of treatment in the UK is relatively straightforward, but there is no obvious method for deriving the extent of any reduced effectiveness from the trial data if exposure to chemotherapy is truncated early.

At least two alternative approaches can be adopted besides that proposed by the manufacturer, depending on whether or not the clinical effectiveness gains for pemetrexed over gemcitabine are

believed to be determined by confirmed response. As previously discussed in the ERG report, the role of response to chemotherapy is not clear-cut in this trial since unusually the whole survival gain is restricted to the period after disease progression, rather than as a result of delaying disease progression.

Option 1 - No loss

The manufacturer holds that there is no loss of effectiveness when only four cycles of pemetrexed/gemcitabine are used, appealing to the small number of late responders as justification. However, the presence of *any* late responders calls that assertion into question if clinical response is held to be instrumental in determining the benefit of chemotherapy. Thus the ERG considers this position to be the most optimistic, and to be difficult to justify without additional evidence.

Option 2 - Response-based loss

The response advantage after six cycles of chemotherapy amounts to 6.85% in favour of pemetrexed (Table 4-2). However after four cycles there was only a differential of 5.54%. If it is assumed that terminating treatment after four cycles eliminates all later responses, and that long-term survival gain (which is confined to patients receiving more than four cycles of treatment as shown above) is proportionate to the response rate differential, then the ERG estimates that the likely reduction in effectiveness will amount to (6.85 - 5.54) / 6.85 = 19.1%. Applying this factor to the estimates obtained in Section 4.1.4, indicates a survival gain of [redacted] months ([redacted] months discounted) and a utility gain of [redacted] QALYs ([redacted] QALYs discounted).

Table 4-2 Response rates by treatment cycle in JMDB trial – patients with non-squamous NSCLC (adapted from Table 5-14 of original ERG report)

	Pemetrexed			**Gemcitabine**		
Cycle	**Responders**		**Cumulative**	**Responders**		**Cumulative**
1	0	0.00%	0.0%	0	0.00%	0.00%
2	99	16.02%	16.02%	89	14.04%	14.04%
3	8	1.29%	17.31%	2	0.32%	14.36%
4	53	8.58%	**25.89%**	38	5.99%	**20.35%**
5	3	0.49%	26.38%	1	0.16%	20.51%
6	14	2.24%	**28.62%**	8	1.26%	**21.77%**

Option 3 - Exposure-based loss

If it is considered that long-term survival gain was not limited to those achieving a confirmed response, but was shared by all patients in the trial receiving more than four cycles of chemotherapy

(about twice as many as those with a reported response), then it would be reasonable to relate the extent of benefit to the duration of exposure to chemotherapy. The trial individual patient data (IPD) show that [redacted] patients received five cycles of pemetrexed and [redacted] received six cycles, amounting to a total of [redacted] patient-cycles exposure. If all these patients had been limited to four cycles only, then the overall exposure would be reduced to [redacted] patient cycles, a reduction of [redacted] Similarly, [redacted] gemcitabine patients received five cycles and [redacted] received six cycles of treatment ([redacted] in total). With only four cycles per patient the exposure is reduced to [redacted] patient-cycles, a reduction of [redacted] Applying these factors to the estimates obtained in Section 4.1.4, indicates a net survival gain of [redacted] months ([redacted] months discounted) and a net utility gain of [redacted] QALYs ([redacted] QALYs discounted).

4.3 ERG revised cost-effectiveness estimates

The time available to the ERG to review the new evidence submitted by the manufacturer did not permit detailed modifications to be made to the modified Markov model, as were performed on the earlier versions of the Markov model. Instead the ERG has used the information contained in the 'in-trial' analysis, together with the findings of the exploratory survival analysis to generate modified cost-effectiveness results without recourse to a new model. The details of the data sources and assumptions made by the ERG are shown in Appendix 2, and indicate that, with the exception of the issues discussed above, this analysis is broadly consistent with the methods and parameter values used by the manufacturer.

A series of tables have been constructed to compare cost-effectiveness results under a variety of scenarios, and to highlight the individual and combined effects of the main issues for consideration. Table 4-3 allows combinations of patient population, maximum duration of chemotherapy and options for adjusting outcome benefits upon reduction of chemotherapy cycles to be considered. In all cases it is assumed that gemcitabine (at current prices) is the comparator for pemetrexed. Table 4-4 explores alternate comparators (all at current prices) in the context of reduced outcome gains assessed by treatment response (Option 2). Table 4-5 and Table 4-6 further consider the sensitivity of cost effectiveness to the likely price reductions from availability of generic gemcitabine and paclitaxel, assuming outcome gains are reduced by treatment response (Option 2) and by exposure (Option 3) respectively, when the maximum number of treatment cycles is restricted.

In comparison to the manufacturer's modified Markov model, the ERG estimates show improved survival gains arising from analysis of the patient-level trial data, offset by using the utility value appropriate to post-progression survival when estimating incremental outcome gains (Table 4-3). In

addition, the use of more accurate chemotherapy costs further increases the incremental costs and ICERs, but this is offset by the reduced number of cycles of chemotherapy recorded in the trial IPD. When a correction for loss of efficacy is introduced to match fewer cycles of treatment, the outcome gains are reduced and ICERs are increased accordingly.

In Table 4-4, the other available comparators are presented on the assumption that they give the same net outcome effects as gemcitabine. The differences are therefore predominantly driven by the relative drug costs. It appears that docetaxel is the least competitive, that paclitaxel and oral vinorelbine are roughly equivalent, but that pemetrexed is not cost-effective when measured against intravenous vinorelbine.

Table 4-5 and Table 4-6 indicate that price reductions due to the availability of generic versions of gemcitabine and paclitaxel may render pemetrexed cost ineffective for treating either patient population.

Table 4-3: Comparison of cost-effectiveness results for manufacturer's modified model with ERG estimates

Scenario	Patient population	Maximum CTX cycles	Cycle-based efficacy adjustment	Comparator	Incremental costs			Incremental outcomes		ICER
					CTX drugs, admin, AEs	Long-term care	Total	Life-years	QALYs	per QALY gained
Lilly A	Non-squamous	6	N/A	Gemcitabine	+£2,681	+£25	+£2,705	+0.1495	+0.0723	£37,398
ERG A	Non-squamous	6	N/A	Gemcitabine	+£2,605	-£139	+£2,465	+0.1857	+0.0873	£28,241
Lilly B	Non- squamous	4	None	Gemcitabine	+£1,969	+£25	+£1,994	+0.1495	+0.0723	£27,565
ERG B1	Non- squamous	4	None	Gemcitabine	+£1,929	-£139	+£1,789	+0.1857	+0.0873	£20,497
ERG B2	Non- squamous	4	19% (by response)	Gemcitabine	+£1,929	-£139	+£1,789	+0.1503	+0.0706	£25,336
ERG B3	Non- squamous	4	32% (by exposure)	Gemcitabine	+£1,929	-£139	+£1,789	+0.1263	+0.0594	£30,142
Lilly C	Adeno/large cell	6	N/A	Gemcitabine	+£2,750	+£69	+£2,819	+0.1935	+0.0933	£30,219
ERG C	Adeno/large cell	6	N/A	Gemcitabine	+£2,702	-£111	+£2,591	+0.2336	+0.1098	£23,598
Lilly D	Adeno/large cell	4	None	Gemcitabine	+£2,002	+£69	+£2,071	+0.1935	+0.0933	£22,202
ERG D1	Adeno/large cell	4	None	Gemcitabine	+£1,995	-£111	+£1,884	+0.2336	+0.1098	£17,162
ERG D2	Adeno/large cell	4	19% (by response)	Gemcitabine	+£1,995	-£111	+£1,884	+0.1890	+0.0888	£21,214
ERG D3	Adeno/large cell	4	32% (by exposure)	Gemcitabine	+£1,995	-£111	+£1,884	+0.1589	+0.0747	£25,239

AE=adverse event; CTX=chemotherapy; ICER=incremental cost effectiveness ratio; QALY=quality adjusted life year; costs and outcomes discounted at 3.5% per annum

Table 4-4: Sensitivity of ERG cost-effectiveness results to choice of comparator

Scenario	Patient population	Max. CTX cycles	Cycle-based efficacy adjustment	Comparator	Incremental costs			Incremental outcomes		ICER
					CTX drugs, admin, AEs	Long-term care	Total	Life-years	QALYs	per QALY gained
ERG B2	Non- squamous	4	19% (by response)	Gemcitabine	+£1,929	-£139	+£1,789	+0.1503	+0.0706	£25,336
ERG B2-D	Non-squamous	4	19% (by response)	Docetaxel	+£1,722	-£139	+£1,583	+0.1503	+0.0706	£22,411
ERG B2-P	Non- squamous	4	19% (by response)	Paclitaxel	+£2,245	-£139	+£2,106	+0.1503	+0.0706	£29,818
ERG B2-VO	Non- squamous	4	19% (by response)	Vinorelbine (oral)	+£2,094	-£139	+£1,955	+0.1503	+0.0706	£27,676
ERG B2-VI	Non- squamous	4	19% (by response)	Vinorelbine (IV)	+£4,316	-£139	+£4,177	+0.1503	+0.0706	£59,146
ERG D2	Adeno/large cell	4	19% (by response)	Gemcitabine	+£1,929	-£111	+£1,884	+0.1890	+0.0888	£21,214
ERG D2-D	Adeno/large cell	4	19% (by response)	Docetaxel	+£1,788	-£111	+£1,678	+0.1890	+0.0888	£18,886
ERG D2-P	Adeno/large cell	4	19% (by response)	Paclitaxel	+£2,312	-£111	+£2,201	+0.1890	+0.0888	£24,783
ERG D2-VO	Adeno/large cell	4	19% (by response)	Vinorelbine (oral)	+£2,161	-£111	+£2,050	+0.1890	+0.0888	£23,078
ERG D2-VI	Adeno/large cell	4	19% (by response)	Vinorelbine (IV)	+£4,386	-£111	+£4,276	+0.1890	+0.0888	£48,133

AE=adverse event; CTX=chemotherapy; ICER=incremental cost effectiveness ratio; QALY=quality adjusted life year; IV= intravenous; costs and outcomes discounted at 3.5% per annum

Table 4-5: Sensitivity of ERG cost-effectiveness results to chemotherapy acquisition price of gemcitabine and paclitaxel (with efficacy adjusted by response)

Scenario	Patient population	Max. CTX cycles	Cycle-based efficacy adjustment	Comparator (% of full list price)	Incremental costs			Incremental outcomes		ICER
					CTX drugs, admin, AEs	Long-term care	Total	Life-years	QALYs	per QALY gained
ERG B2	Non- squamous	4	19% (by response)	Gemcitabine (100%)	+£1,929	-£139	+£1,789	+0.1503	+0.0706	£25,336
ERG B2-G90	Non-squamous	4	19% (by response)	Gemcitabine (90%)	+£2,167	-£139	+£2,028	+0.1503	+0.0706	£28,712
ERG B2-G75	Non- squamous	4	19% (by response)	Gemcitabine (75%)	+£2,525	-£139	+£2,385	+0.1503	+0.0706	£33,776
ERG B2-G50	Non- squamous	4	19% (by response)	Gemcitabine (50%)	+£3,121	-£139	+£2,981	+0.1503	+0.0706	£42,216
ERG-B2-P	Non- squamous	4	19% (by response)	Paclitaxel (100%)	+£2,245	-£139	+£2,106	+0.1503	+0.0706	£29,818
ERG-B2-P90	Non- squamous	4	19% (by response)	Paclitaxel (90%)	+£2,510	-£139	+£2,371	+0.1503	+0.0706	£33,572
ERG B2-P75	Non- squamous	4	19% (by response)	Paclitaxel (75%)	+£2,908	-£139	+£2,769	+0.1503	+0.0706	£39,203
ERG B2-P50	Non- squamous	4	19% (by response)	Paclitaxel (50%)	+£3,431	-£139	+£3,431	+0.1503	+0.0706	£48,587
ERG D2	Adeno/large cell	4	19% (by response)	Gemcitabine (100%)	+£1,995	-£111	+£1,884	+0.1890	+0.0888	£21,214
ERG D2-G90	Adeno/large cell	4	19% (by response)	Gemcitabine (90%)	+£2,234	-£111	+£2,123	+0.1890	+0.0888	£23,902
ERG-D2-G75	Adeno/large cell	4	19% (by response)	Gemcitabine (75%)	+£2,592	-£111	+£2,481	+0.1890	+0.0888	£27,934
ERG-D2-G50	Adeno/large cell	4	19% (by response)	Gemcitabine (50%)	+£3,189	-£111	+£3,078	+0.1890	+0.0888	£34,654
ERG D2-P	Adeno/large cell	4	19% (by response)	Paclitaxel (100%)	+£2,312	-£111	+£2,201	+0.1890	+0.0888	£24,783
ERG D2-P90	Adeno/large cell	4	19% (by response)	Paclitaxel (90%)	+£2,578	-£111	+£2,467	+0.1890	+0.0888	£27,772
ERG D2-P75	Adeno/large cell	4	19% (by response)	Paclitaxel (75%)	+£2,976	-£111	+£2,865	+0.1890	+0.0888	£32,255
ERG D2-P50	Adeno/large cell	4	19% (by response)	Paclitaxel (50%)	+£3,640	-£111	+£3,529	+0.1890	+0.0888	£39,727

AE=adverse event; CTX=chemotherapy; ICER=incremental cost effectiveness ratio; QALY=quality adjusted life year; costs and outcomes discounted at 3.5% per annum

Table 4-6: Sensitivity of ERG cost-effectiveness results to the price of generic gemcitabine and paclitaxel (with efficacy adjusted by exposure)

Scenario	Patient population	Max. CTX cycles	Cycle-based efficacy adjustment	Comparator (% of full list price)	Incremental costs			Incremental outcomes		ICER
					CTX drugs, admin, AEs	Long-term care	Total	Life-years	QALYs	per QALY gained
ERG B3	Non- squamous	4	32% (by exposure)	Gemcitabine (100%)	+£1,929	-£139	+£1,789	+0.1263	+0.0594	£30,142
ERG B3-G90	Non-squamous	4	32% (by exposure)	Gemcitabine (90%)	+£2,167	-£139	+£2,028	+0.1263	+0.0594	£34,159
ERG B3-G75	Non- squamous	4	32% (by exposure)	Gemcitabine (75%)	+£2,525	-£139	+£2,385	+0.1263	+0.0594	£40,183
ERG B3-G50	Non- squamous	4	32% (by exposure)	Gemcitabine (50%)	+£3,121	-£139	+£2,981	+0.1263	+0.0594	£50,224
ERG-B3-P	Non- squamous	4	32% (by exposure)	Paclitaxel (100%)	+£2,245	-£139	+£2,106	+0.1263	+0.0594	£35,475
ERG-B3-P90	Non- squamous	4	32% (by exposure)	Paclitaxel (90%)	+£2,510	-£139	+£2,371	+0.1263	+0.0594	£39,941
ERG B3-P75	Non- squamous	4	32% (by exposure)	Paclitaxel (75%)	+£2,908	-£139	+£2,769	+0.1263	+0.0594	£46,640
ERG B3-P50	Non- squamous	4	32% (by exposure)	Paclitaxel (50%)	+£3,571	-£139	+£3,431	+0.1263	+0.0594	£57,804
ERG D3	Adeno/large cell	4	32% (by exposure)	Gemcitabine (100%)	+£1,995	-£111	+£1,884	+0.1589	+0.0747	£25,239
ERG D3-G90	Adeno/large cell	4	32% (by exposure)	Gemcitabine (90%)	+£2,234	-£111	+£2,123	+0.1589	+0.0747	£28,436
ERG-D3-G75	Adeno/large cell	4	32% (by exposure)	Gemcitabine (75%)	+£2,592	-£111	+£2,481	+0.1589	+0.0747	£33,233
ERG-D3-G50	Adeno/large cell	4	32% (by exposure)	Gemcitabine (50%)	+£3,189	-£111	+£3,078	+0.1589	+0.0747	£41,228
ERG D3-P	Adeno/large cell	4	32% (by exposure)	Paclitaxel (100%)	+£2,312	-£111	+£2,201	+0.1589	+0.0747	£29,485
ERG D3-P90	Adeno/large cell	4	32% (by exposure)	Paclitaxel (90%)	+£2,578	-£111	+£2,467	+0.1589	+0.0747	£33,040
ERG D3-P75	Adeno/large cell	4	32% (by exposure)	Paclitaxel (75%)	+£2,976	-£111	+£2,865	+0.1589	+0.0747	£38,374
ERG D3-P50	Adeno/large cell	4	32% (by exposure)	Paclitaxel (50%)	+£3,640	-£111	+£3,529	+0.1589	+0.0747	£47,263

AE=adverse event; CTX=chemotherapy; ICER=incremental cost effectiveness ratio; QALY=quality adjusted life year; costs and outcomes discounted at 3.5% per annum

5 DISCUSSION

The manufacturer of pemetrexed was asked to provide two new economic analyses for consideration by the Appraisal Committee; an 'in-trial' analysis restricted to the evidence available directly from the JMDB trial, and an analysis based on a modified Markov model, taking account of the issues identified by the ERG.

The 'in-trial' analysis has demonstrated clearly that pemetrexed/cisplatin is unlikely to be considered cost-effective as first-line chemotherapy for non-squamous NSCLC compared to gemcitabine/cisplatin without recourse to the projection of patient outcomes beyond the trial period. This is not unexpected, but confirms the critical importance of the assumptions and methods underlying projected benefits in determining the outcome of this appraisal.

The modified Markov model provided by the manufacturer includes several important changes which have succeeded in overcoming the discrepancies previously apparent in reproducing trial data for OS and response rates. These alterations are welcome, but do not overcome all the difficulties pointed out by the ERG. In particular, the manufacturer has not fully addressed other important issues relating to changing the duration of therapy, adequacy of long-term survival modelling, choice of comparators, method of costing chemotherapy, as well as utility parameter values and sensitivity of cost effectiveness to price changes in comparators. It is therefore not surprising that new economic results generated by the modified model are not much different from those previously submitted. Moreover, the adapted Australian model provided by the manufacturer is based on the same set of assumptions and parameter values and so adds little or nothing new.

There are five key areas of uncertainty which should be considered:

1) Survival modelling – the original Markov model employed a rigid structure to represent patient experience which failed to reflect trial data. The modified Markov model now assumes that a Weibull process is appropriate to represent all phases of remaining patient lifetimes, which is also quite a strong assumption (albeit rather less restrictive than before). Nonetheless, the ERG is concerned that this may not be a sufficiently robust basis for estimating long-term survival. The ERG has examined the JMDB trial IPD and employed a pragmatic approach based on hazard rate profiles which seems to offer greater compatibility with the trial evidence and therefore a more secure foundation for estimation of future benefits. If the ERG approach is accepted, it implies that the manufacturer has significantly under-estimated the likely survival gains that could be expected from the use of pemetrexed.

2) Treatment cycles and effectiveness – the manufacturer continues to contend that limiting chemotherapy to four cycles, rather than the six available in the JMDB trial, will not compromise the relative outcome gains from use of pemetrexed. The ERG believes that this is a questionable assertion which lacks supporting evidence. Access to additional IPD information concerning the timing of response to treatment and of disease progression would have allowed this issue to be considered thoroughly and very likely to be resolved. However, only information relating to OS was made available in the manufacturer's 'in-trial' analysis. Nonetheless the ERG has proposed two plausible methods of estimating the loss of effectiveness which may be anticipated from limiting the duration of chemotherapy, and these lead to less favourable cost-effectiveness estimates than those presented by the manufacturer.

3) Comparators - as noted in the ERG report, the manufacturer initially chose to model only a limited selection of the comparators specified in the appraisal scope. In their modified model they consider only one comparator (gemcitabine/cisplatin). However, gemcitabine appears to be a less challenging competitor to pemetrexed than some of those currently recommended in NICE guidance, and it may be appropriate to consider the cost effectiveness of the full range of other candidate agents as exemplified in this addendum.

4) Utility values – in the ERG report it was highlighted that all the survival gain reported in the JMDB trial occurred in the period after disease progression. This implies that such survival gain must be subject to the utility value appropriate to the progressive disease state. However, this is not the approach taken in the various analyses provided by the manufacturer. As a consequence, the ERG is of the opinion that the manufacturer overstates the QALY value of the survival gain attributable to the use of pemetrexed.

5) Market context – the ERG notes that two of the specified comparators (gemcitabine and paclitaxel) will be off patent this year, and that generic versions of gemcitabine are already being marketed internationally at substantially discounted prices. The potential impact of such market changes on the cost effectiveness of pemetrexed has been explored by the ERG, and this information may have relevance to the timing of any appraisal review if not to the current process.

The very short time available to the ERG to consider the new evidence (two models and an 'in-trial' analysis) has provided particular difficulties, and precluded a comprehensive assessment. A further in-depth critique and amendment of the modified Markov model was not feasible, and would probably not have yielded sufficient new information to justify the human input that would have been required. Instead, the ERG chose to present a simple analysis combining its own survival projections with key cost estimates obtained from the trial IPD as a decision support tool to aid the Committee in its deliberations. It has not been possible to carry out full quantitative uncertainty assessment, beyond the limited sensitivity analyses of selected factors shown above.

APPENDIX 1: ECONOMIC MODEL USED FOR THE PBAC HTA SUBMISSION IN AUSTRALIA

Summary of evidence submitted

The manufacturer of pemetrexed provided a version of a model previously submitted to the PBAC for reimbursement in Australia.

Critique of manufacturer's approach

The model was adapted for use in a UK context, by substitution of UK unit costs. It is a well constructed, clearly labelled and therefore easy to understand model. In most other respects the model uses similar assumptions to those underlying the manufacturer's economic models submitted to NICE (see below). Thus it is unsurprising that the final cost-effectiveness results for the manufacturer's target population of patients with adenocarcinoma and large cell carcinoma are very similar to those obtained with the various models submitted to NICE. This serves merely to demonstrate that the same assumptions modelled in a similar manner give consistent outcomes. However, it does nothing to address the important questions that have been raised about the manufacturer's most important assumptions.

Comparison of the Model assumptions used for the PBAC HTA submission in Australia with the model assumptions used in submissions to NICE

Population: The PBAC model considers only the populations of patients with adenocarcinoma and large cell carcinoma from the JMDB trial. The models submitted to NICE also feature the wider licensed population of patients with non-squamous NSCLC.

Duration: Results are generated for the original trial period and also modelled extensions for an additional two or three years (equivalent to time horizons of 4.5 and 5.5 years). The models submitted to NICE use a time horizon of six years.

Drugs used for adverse events: Costs are explicitly included in the analysis for erythropoietin, and G-CSF for treatment of chemotherapy-induced anaemia and neutropenia. As the use of these agents is not widespread in UK practice, some or all of these costs may be inappropriate in this analysis. They are not explicitly included in the models submitted to NICE.

Discounting: Discounting of costs and outcomes are not carried out annually after the first year as is normal practice in the UK but are carried out continuously from randomisation.

Continuity correction: This is carried out by use of a first-period half cycle adjustment. This is inaccurate when an analysis is truncated by a fixed time horizon, and in the presence of discounting. A mid-cycle adjustment (averaging over the cycle) is preferred where analytical estimation is not possible.

Chemotherapy costs: A fixed average BSA of $1.8m^2$ is assumed, with no adjustment for population variability, in the same manner as used in models submitted to NICE. This often leads to inaccurate estimates of chemotherapy costs, which tend to have a proportionate effect so that more expensive drugs suffer larger costing errors.

Cycles of chemotherapy: Chemotherapy is truncated at a maximum of four cycles per patient, but no corresponding adjustment to other costs (e.g. AEs), or to patient outcomes is applied. This is also the approach used in models submitted to NICE.

Patient utilities: The same patient utility parameter values are used as in the 'in-trial' analysis discussed in Section 2 (0.65 / 0.63). In the PBAC model the difference between these two values is justified by an enigmatic note ("PC arm utility weight -0.01") which lacks explanatory detail and arithmetic precision. The ERG's comments on this issue made in Section 2 are equally relevant for the Australian model.

Overall survival: Overall patient survival is modelled beyond the trial period using a fitted Weibull model. It is clear from two worksheets in the model ('Raw data' and 'Hazards') that the model authors experimented with a two-phase exponential formulation, based on cumulative hazards, but rejected this in favour of the Weibull function. However, the survival graphs indicate that there is a systematic under-estimation of long-term survival trends in both arms of the trial suggesting that the fitted Weibull models are inadequate for the purpose of projecting long-term survival. In the original models submitted to NICE, a sequence of exponential transition functions was employed which the ERG considered inappropriate in light of the trial evidence. The latest revision of the manufacturer's model now adopts a Weibull formulation.

APPENDIX 2: DETAILS OF ERG REVISED COST-EFFECTIVENESS ESTIMATES

Model item	Source / Assumptions	Details
Chemotherapy drug acquisition costs	Dosing by BSA based on UK lung cancer patient population from recent survey, including wastage of part-used vials	Cost per cycle values used are those detailed in Table 5-15 of the ERG report. The mean number of cycles of chemotherapy calculated from JMDB trial IPD
Chemotherapy administration costs	Mode and cost of administration the same as used in manufacturer's model	Calculation based on the mean number of cycles of chemotherapy calculated from JMDB trial IPD
Chemotherapy related adverse event costs	Costs are based on the AE costs calculated in the manufacturer's 'in-trial' analysis. ERG assumes that AE costs only apply to the period until the end of last cycle of chemotherapy received	AE costs when chemotherapy is limited to four cycles are reduced pro-rata to the mean number of cycles of chemotherapy received
Second-line chemotherapy costs	Costs are based on the second-line costs calculated in the manufacturer's 'in-trial' analysis	Second-line chemotherapy costs are discounted assuming that those patients living longer than 1 year and receiving second-line treatment do so on average 12 months prior to death
Best supportive care costs	Costs of BSC are based on those used in manufacturer's 'in-trial' analysis	BSC costs occur between 12 months and three months prior to time of death, unless death occurs prior to 12 months, in which case BSC costs are reduced pro-rata to the time alive more than three months before death
Terminal care costs	Costs of terminal care are based on those used in the manufacturer's 'in-trial' analysis	Terminal care costs are assumed to occur in the 3 months prior to death
Incremental life years gained	Exploratory survival analysis was carried out as described above, stratifying according to the number of cycles of chemotherapy received	Long-term projection on the basis of fitted late stage exponential functions was truncated at six years to conform to the manufacturer's base case time horizon
Incremental QALYs gained	In view of the equivalence of PFS experience between the JMDB trial arms, it is assumed that all survival gain occurs following disease progression	The utility value used by the manufacturer for post-progression survival (0.47) is used to convert survival gain into QALYs gained
Patient population	The full IPD data set used in the manufacturer's 'in-trial' analysis is used for the population of patients with non-squamous NSCLC; those indicated as having a histology of adenocarcinoma or large cell carcinoma are used for the population of patients with adenocarcinoma and large cell carcinoma	-

Model item	Source / Assumptions	Details
Efficacy loss due to maximum cycles limit	Adjustments related to response rates are based on details in the manufacturer's submission and model of the numbers of responses reported per cycle. Adjustments related to chemotherapy exposure time are based on the number of courses of chemotherapy recorded in the IPD within the manufacturer's 'in-trial' analysis	Pro-rata adjustments are made to the incremental life-years gained and incremental QALYs gained based on the proportion of responses/exposure falling within cycles 1-4 compared to the full trial
Chemotherapy price sensitivity	Two chemotherapy are now or soon to be 'off patent' (gemcitabine and paclitaxel). A range of potential price reductions are considered to allow exploration of the importance of possible price reductions to cost-effectiveness results	Generic versions of gemcitabine are already available internationally. Based on a Canadian pharmacy source (www.canada-pharmacy.com accessed 3/06/2009), it appears that generic pricing is only 60-70% that of the local branded product, and about 85% of the 'world' branded product. Therefore options are considered covering this range (90%, 75% and 50%)

AE=adverse events; BSA=body surface area; BSC=best supportive care; ERG=evidence review group; IPD=individual patient data; NSCLC=non-small cell lung cancer; PFS=progression free survival; QALY=quality adjusted life year