Lilly UK response to NICE Appraisal Consultation Document for the appraisal of pemetrexed in the first-line treatment of non-small cell lung cancer

6th May 2009

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Appendices

1 Executive summary

Lilly UK appreciate the opportunity to respond to the appraisal consultation document (ACD) for pemetrexed/cisplatin in first-line other than predominantly squamous NSCLC.

The response document addresses each of the concerns raised by the appraisal committee in turn. We have provided further data to support the cost-effectiveness of pemetrexed when compared to gemcitabine, as requested by the appraisal committee.

Actions taken in response to ACD/appraisal committee concerns:

1.1 The original submitted Markov model has been modified to a) more accurately represent the outcomes of the JMDB trial using Weibull distributions and b) take into account the concerns raised by the committee in 3.17 and 3.18 of the ACD to re-estimate the incremental cost-effectiveness of pemetrexed/cisplatin when compared to gemcitabine/cisplatin.

1.2 An additional trial-based economic analysis has been conducted using the individual patient survival outcomes (censored) and resource use events from the JMDB clinical trial database.

1.3 Findings from the economic model used for the PBAC HTA submission in Australia, which was based upon the patient level data from the clinical trial and used Weibull distributions to extrapolate survival, have also been provided to further validate our submitted estimates of cost-effectiveness for pemetrexed/cisplatin compared to gemcitabine/cisplatin.

1.4 Thorough validation processes have been followed according to the NICE request such as double build for the trial-based model, and internal and independent external reviews, for both the modified and clinical trial-based models.

Summary of response to areas of concern listed in the ACD

1.5 The modified, the trial-based and the PBAC models all demonstrated consistent results to the original submitted model, with incremental cost-effectiveness ratios in the range of £22,202 to £25,967 for the adeno and large cell carcinoma patient population when pemetrexed was used for up to four cycles, in accordance with UK practice (see Table 1 below).

Table 1.Cost effectiveness estimates from a) submitted model, b) modified model c) trial-based analysis and d) model used for PBAC

Population	ICER (original)	ICER (modified)	ICER (trial-based)	ICER (PBAC)
Adenocarcinoma and large cell patients (target population)				
Max 4 cycles	£25,967*	£ 22,202	£24,224	£23,157
Licensed population				
Max 4 cycles	£33,065	£ 27,565	£31,157	_

*From the addendum, in the submission adenocarcinoma and large cell ICERs were presented separately.

1.6 *Model structure:* The submitted Markov model was a valid structure used in previous oncology models in accordance with the NICE reference case. The estimates produced by the submitted model fairly reflected the incremental cost-effectiveness of pemetrexed when compared to gemcitabine. When the model was modified to include Weibull (time dependent) distributions, the results were consistent with the submitted model.

1.7 *Overall survival*: No modelled survival distribution or 'fit', whether exponential or Weibull, is perfect. The exponential distribution is used as standard within analyses of oncology clinical trials and is commonly utilised for modelling the cost-effectiveness of oncology therapies. The use of exponential distribution led to estimates within the submitted model that were consistent with our regulatory submission and also increased the simplicity of the model. The modified model confirms that use of Weibull distribution compared to exponential has increased the complexity of the model with little impact upon the cost-effectiveness estimates (see Table 1).

1.8 *Progression-free survival and response rates:* It is agreed that PFS and tumour response are not key drivers of survival in lung cancer. However, they are health states that are of clinical importance in terms of physician decision-making and patient experience. The discrepancy in total response between the trial and model was very small and in favour of gemcitabine leading to an underestimate of the benefit of pemetrexed within the model and therefore a conservative estimate of cost-effectiveness within the original submission.

1.9 *Half-cycle correction*: The half-cycle correction was disabled for costs because the majority of costs in cancer are incurred at the beginning of the cycle at drug administration. When the half-cycle correction was adjusted as requested in the modified model, this had minimal impact on the results. Therefore, the half-cycle correction used in the original submission did not interfere with the ability of the model to produce credible results.

1.10 *Adverse event rates*: As the majority of patients within the trial (80%) experienced zero or only one adverse event and there was a very limited rate of grade 3/4 adverse events, although of great importance to patients, adverse events were not a major driver within the cost-effectiveness model. Therefore, the assumption made within the original model did not limit the model's ability to determine the cost-effectiveness of the pemetrexed compared to gemcitabine.

1.11 *Mortality risk used for febrile neutropenia:* As stated in the ERG report (pg57), the advantage conferred by the febrile neutropenia mortality rate to pemetrexed is of such small value (difference of 0.6% from baseline value) that it had no effect upon the model's ability to produce credible results.

2 Response to specific comments made within the ACD regarding the cost-effectiveness estimates for pemetrexed.

Section 3.16 "…The chosen Markov model structure does not seem to be appropriate because it does not replicate the trial data used to calibrate the model to an acceptable level of accuracy… noticeably for response and survival. …The model appears to overestimate overall survival in both arms and almost all patient groups."

2.1 The Markov model was a valid structure used in previous oncology models and designed in accordance with the NICE reference case.

2.2 The ERG's main criticism of the model structure was based on point-estimate comparisons of survival at various time points and the use of constant risk hazards (exponential distributions). The modelling decision regarding the use of an exponential distribution to extrapolate survival was made, in part, to be consistent with our regulatory submission survival estimates and also to take a pragmatic approach to reduce the complexity of the model. The decision was made deliberately after weighing the relative benefits of implementing a different distribution that would allow for time-dependent transition probabilities.

2.3 While the survival function based on the exponential distribution is a simplification of the observed survival curve, all modelling is a simplified replica of the real world. The considerations that inform the methodology should be based on whether or not the simplification leads to misleading results or significantly detracts from the modelled analysis. In this case, the simplification to a constant hazard led to overestimation of the survival at certain time points earlier in the modelled time horizon. However, the survival function was parameterised in identical manner for the comparator arms, meaning both were overestimated in equal measures. In terms of producing incremental results, the benefit of the intervention over the comparator was accurate and even underestimated.

2.4 No modelled survival distribution or 'fit', whether exponential or Weibull, is perfect. The structural decisions regarding the model were made to ensure the most robust and conservative estimates of cost effectiveness were produced whilst maintaining a relatively straightforward and easy to use model. Outputs in terms of survival from the model were compared against the trial, using both mean and

median values within the submission. While the absolute outputs were overestimated in the model, the incremental benefits were not and hence the results of the modified model are £22,202 compared to £25,967 in the original model submitted. Therefore, the estimates produced by the original model fairly reflected the incremental cost-effectiveness of pemetrexed when compared to gemcitabine.

> *Section 3.17 "…All reported survival gain occurred after disease progression … but it was not clear if Objective response determined the extent of health gain and whether the survival gain was restricted to patient who had responded to treatment … If response does not predict PFS or post progression survival, then its use as a distinct health state is … misleading."*

2.5 It is agreed that PFS and tumour response play a smaller role in determining overall survival of NSCLC patients, compared to breast cancer, for example, but as a consequence, variations in the clinical inputs for response have little effect on the cost effectiveness estimate. Not having response within the model would have ignored important elements of clinical decision-making (in terms of continuing treatment) and also in terms of patient experience that relate to clinical tumour response, so the state was retained.

2.6 The partitioning of the response rates were again a simplification of the response pattern from JMDB, keeping in mind that the majority of responders did so in the 2nd cycle. This proportion from the trial was preserved. The remaining responders were averaged among the remaining number of cycles in order to ensure that the total response of the trial was not lost. While as a simplification there was underestimation of response, it was systematic in both arms, as noted by the ERG, meaning again the incremental benefit attributable to the intervention was accurate, or even under-estimated. The discrepancy in total response between the trial and original model was very small and in favour of gemcitabine; the incremental difference was underestimated by roughly 1%.

2.7 Regarding PFS, as the ERG estimates demonstrate, the reality of the difference between arms not being modelled so closely is to underestimate the incremental benefit of pemetrexed, leading again to a conservative estimate of cost-effectiveness.

2.8 The PBAC model did not use response rate or PFS within the model structure and produced very similar results (£23,157) to both the original model (£25,967) and the modified model (£22,202).

3.18 Additional concerns with model

- *Exponential survival distribution (or constant risk processes) used without any justification*
- *Half-cycle correction 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 … not taken into account*
- *Use of febrile neutropenia mortality risk was questionable*

2.9 *Exponential survival distributions used without justification*

The decision to use exponential distributions was justified within the manufacturer's response to clarification questions. Indeed the exponential distribution is used as standard within analysis of oncology clinical trials and is commonly utilised for modelling the cost-effectiveness of oncology therapies. The use of exponential distribution led to estimates within the model that were consistent with our regulatory submission and also increased the simplicity and transparency of the model.

2.10 Our modelling based upon Weibull distributions confirms that use of Weibull compared to exponential has increased the complexity of the model with little impact upon the cost-effectiveness estimates (see Table 1). Our trial-based analyses using the per patient survival outcomes again confirm our original modelled estimates.

2.11 In addition, we have provided estimates from another Lilly model for pemetrexed in first-line NSCLC that was used for HTA submission to PBAC. This model utilised Weibull distributions for survival and individual patient data from the clinical trial. The modified model and the two additional analyses are described in more detail below (Sections 3-5), summary results are provided in Table 1.

2.12 *Half-cycle correction disabled for costs and used incorrectly for outcomes*

The half-cycle correction was disabled for costs because the majority of costs in cancer are incurred at the beginning of the cycle at drug administration. When these were adjusted in the modified model it had minimal impact on the results (£22,202 with half-cycle applied vs £21,252 without half-cycle). We do not believe a half-cycle

correction is of particular relevance when the cycle duration is of only 3 weeks. Sonnenberg and Beck (1993) suggest that a half-cycle correction is not needed if the cohort is completely absorbed at the end of the simulation (as is the case in the original submitted model with the six year time horizon). They go on to suggest that if the cycle length is very short relative to average survival then the need for a half-cycle correction is small. Similarly, Briggs et al (1994) argued that such a correction might not be so important in economic evaluations, since calculation of incremental costs and benefits would not be affected. Using a half-cycle correction, whether for costs or outcomes, has little impact on the results in the comparison between pemetrexed and gemcitabine. Therefore, the half-cycle correction used did not interfere with the ability of the model to produce credible results

2.13 *Costs and harms due to treatment may have been overestimated due to cumulative costs of >1 AE not being considered.*

The majority of patients (80%) experienced zero or one adverse event and there was a very limited rate of grade 3/4 adverse events as included in the model, based on the JMDB trial data for grade 3/4 adverse events that were statistically significantly different in each arm. Therefore the actual overlap between AEs is very small and occurred generally in patients with anaemia and fatigue. As the fatigue unit cost does not incorporate a hospital stay and is only £38.90 per episode, the assumption made that AEs were experienced separately a) greatly simplified the structure of the model and b) made little difference to the results.

2.14 The adverse events being considered as independent was a simplification deemed necessary in order to populate the model with appropriate pay-offs, as standard unit costs do not exist for combinations of AE. Also, while concurrent AEs may lead to a savings in total cost incurred, it could equally lead to more resources being needed to treat one episode as complications arise from the co-morbidities. Moreover, the overall rate of AEs in the JMDB trial was so low as to have very little impact on the results when its rates were altered. Within the trial-based model (reported in section 4) the recorded hospitalisation rates in the trial were used within the sensitivity analyses leading to a cost-effectiveness ratio of £27,234 compared with £25,967 in the original model which used NHS reference costs, in accordance with the NICE reference case. Therefore, the assumption made within the submitted model did not limit the model's ability to determine the cost-effectiveness of the intervention.

2.15 *Mortality risk used for febrile neutropenia questionable*

As stated in the ERG report (page 57), the advantage conferred by the febrile neutropenia mortality rate to pemetrexed was of such small value (difference of 0.6% from baseline value) that it did not affect the model's ability to produce credible results. The febrile neutropenia mortality was set to 0% in the modified model (see section 3) and found to have resulted in less than £100 difference in the cost-effectiveness ratio.

3 Modified version of the original Markov model, revised in accordance with the appraisal committee's requests

3.1 *Objective*

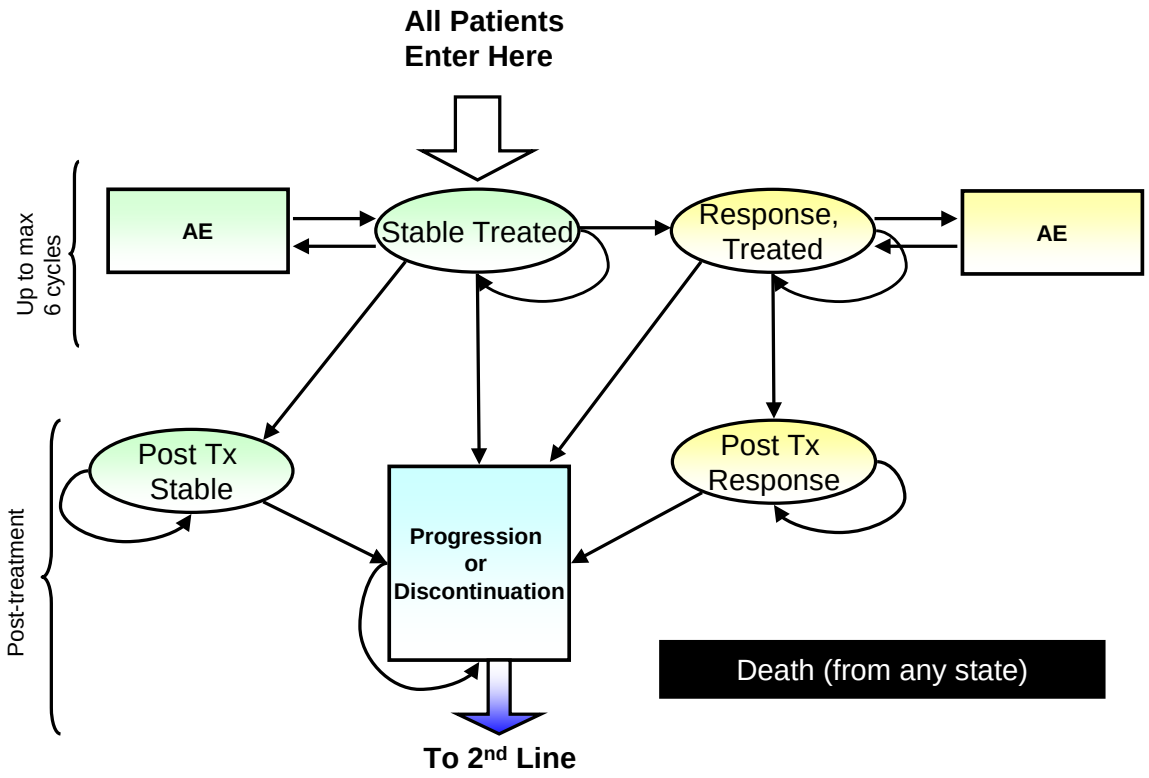
To compare pemetrexed/cisplatin with gemcitabine/cisplatin in a cost-effectiveness analysis, which accurately represents the outcomes of the JMDB trial.

Methods

3.2 *Model Structure*

The health states from the original Markov model were retained. The major change implemented was in the method of calculating transition probabilities for time-to-event variables, which are now based on a Weibull distribution and are time-dependent. Former transition matrices are no longer in use. 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. All other characteristics of the original model structure have been retained including all AE states (see figure 1).

Figure 1. Simplified Schematic of Model



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Sequencing of Health States

3.3 *First-line treatment*

Patients still enter the model at the Stable state, neither in response or progression. From that state, they can progress, respond or die. Patients can start in two types of Stable states: responders and non-responders. This division is further explained under Response Rates. Once patients respond, it is assumed that they stay there until they progress or die. While in the stable or response state they can also experience AEs.

3.4 *Transition Probabilities*

Transition probabilities to death from any state and progression from stable disease have been modified to reflect time-dependency. Progression from responding disease is based on Duration of Response and is therefore identical to the original transition probability.

Efficacy Inputs

3.5 *Time to progression for non-responders*

The time to progression data from the trial were used to fit a Weibull distribution and obtain a survival function. This was then used to calculate transition probabilities to progression based on the method described below. A Weibull model was employed to model the time to progression. Therefore, lambda (λ) and gamma (γ) parameters were applied to the following survival function:

$$S(t) = \exp\{-\lambda t^{\gamma})$$

3.6 The survival function was estimated twice to validate the findings using weeks in one method and months in the other. Translating these into curves found that that both sets of equations produced identical curves.

3.7 Once the survival function S(t), was obtained, it was possible to define the transition probability as one minus the ratio of the survival function at the end of an interval to the survival function at the beginning of the interval:

Transition probability = 1- (S(t)/S(t-1))

3.8 This calculated for each point in time gives the time-dependent probability of dying in the model. The lambda and gamma estimates for each treatment arm and histology group can be found in Appendix 1. An example of the time dependent transition probabilities of progression for stable patients on pemetrexed for the first 6 cycles are detailed in Table 2.

Table 2.Transition probabilities for time to progression by histology

Cycle	All patients	Licensed	Adeno. and large cell	Adeno.	Large cell
0	0.000	0.000	0.000	0.000	0.000
1	0.068	0.055	0.056	0.054	0.054
2	0.096	0.090	0.089	0.086	0.101
3	0.111	0.110	0.108	0.104	0.132
4	0.122	0.126	0.122	0.118	0.157
5	0.131	0.139	0.134	0.130	0.179
6	0.138	0.150	0.144	0.140	0.198

Overall Survival

3.9 The overall survival data from the trial were used to fit a Weibull distribution and obtain a survival function. This was then used to calculate transition probabilities to death based on the method described below. A Weibull model was employed to model the time to progression and overall survival estimates. Therefore, lambda (λ) and gamma (γ) parameters were applied to the following survival function.

$$S(t) = \exp\{-\lambda t^{\gamma}\}$$

3.10 The survival function was estimated twice to validate the findings using weeks in one method and months in the other. Translating these into curves found that that both sets of equations produced identical curves.

3.11 The survival function was applied in the same way as described for time to progression. The lambda and gamma estimates for each treatment arm and histology group can be found in Appendix 1. The probability of death in the model was applied to all health states except those patients in a stable health state who respond to treatment before cycle 6. An example of the time dependent transition probabilities for overall survival on pemetrexed for the first 6 cycles is detailed in Table 3.

Table 3.Transition probabilities for overall survival by histology

Cycle	All patients	Licensed	Adeno. and large cell	Adeno.	Large cell
0	0.000	0.000	0.000	0.000	0.000
1	0.022	0.020	0.018	0.017	0.025
2	0.030	0.027	0.025	0.023	0.034
3	0.034	0.031	0.028	0.027	0.038
4	0.037	0.033	0.031	0.029	0.042
5	0.039	0.036	0.033	0.031	0.044
6	0.041	0.038	0.035	0.033	0.046

Response Rates

3.12 Response rates were used in the model to generate transition probabilities for patients moving into the Response state from stable disease. Response rates from the trial were available by cycle, but applying them directly to the Stable population would result in an underestimate since the response rates are based on the ITT populations, while the Stable population decreases with time due to death and progressive disease.

3.13 In addition, the application of the Time to PD for non-responders to the entire Stable population erroneously measures the time to progression for responders, as the Stable population contains both non-responders and responders.

3.14 To ensure the response rates were used to accurately reflect the number of patients responding in the trial, the stable population was divided into those who never respond and those who respond at some point during treatment. Those who respond are not subject to progression rates, which are only applicable to the non-responders group. For responders, progression can only take place once they have responded.

3.15 The proportion of patients responding were taken from the JMDB trial and summarised below:

Table 4. Response Rates

Histology	PEM (n)	PEM (%)	GEM (n)	GEM (%)
All	234	27.1%	213	24.7%
Licensed	177	28.6%	141	22.2%
Adeno/Large	147	28.7%	110	22.5%
Adeno	126	28.9%	89	21.7%
Large	21	27.6%	21	27.3%

3.16 Of these, the licensed group's values are used to illustrate how they have been incorporated into the model.

Table 5. Probability of Responding (Licensed population)

Cycle	At Risk	Responders	Probability of Responding/Cycle
1	177	0	0.00
2	177	105	0.59
3	72	8	0.11
4	64	53	0.83
5	11	3	0.27
6	8	8	1.00

Time to progression for responders

3.17 Once responders actually enter the Response state they are subject to the transition probability of progressing, which is based on Duration of Response, as in the original model.

Adverse Events

3.18 The only change to adverse events has been to reduce the probability of death from febrile neutropenia to zero, as the mortality rate is only applicable to post-discharge patients and includes all-cause mortality, as indicated by the ERG. The JMDB trial data shows that death due to febrile neutropenia was less than 1%; the safety evaluable population shows that only two deaths due to febrile neutropenia were recorded and thus making this rate 0% would be more accurate than using the previous 3.9% death rate.

Treatment cost estimates

3.19 Treatment costs are now based on the number of vials used in the clinical trial. The previous model estimated treatment cost based on an assumption of patients mean body surface area. Therefore, the new assumptions are more reflective of the variability in dose received for different patients in the trial but potentially less reflective of the UK population. The cost per cycle for pemetrexed, gemcitabine and cisplatin are detailed in Table 6. These estimates include the cost of wastage.

Table 6. Per cycle treatment cost

	Pemetrexed	Gemcitabine	Cisplatin
Cost per cycle	£1,509.58	£755.99	£79.17

Half-cycle correction

3.20 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.

Probabilistic sensitivity analysis

3.21 Time to progression and overall survival curves were varied in the probabilistic sensitivity analysis. The correlation between the parameter estimates (lambda and gamma) was captured in the PSA using the variance-covariance matrices.

Results

Table 7. Adeno and large cell carcinoma (target population) up to four cycles

	Pemetrexed + cisplatin	Gemcitabine + cisplatin
Total Costs	£12,722	£10,651
Total QALYs	0.6793	0.5860
Total Life Years	1.2871	1.0936
Inc. QALYs		0.093
Inc. costs		£2,071
ICER (inc. cost per QALY)		£22,202

Table 8. Licensed population, up to four cycles of treatment

	Pemetrexed + cisplatin	Gemcitabine + cisplatin
Total Costs	£12,666	£10,672
Total QALYs	0.6479	0.5755
Total Life Years	1.2264	1.0770
Inc. QALYs		0.072
Inc. costs		£1,994
ICER (inc. cost per QALY)		£27,565

Table 9. Results for licensed population (6 cycles)

	Pemetrexed + cisplatin	Gemcitabine + cisplatin
Total Costs	£15,244	£12,538
Total QALYs	0.6479	0.5756
Total Life Years	1.2264	1.0770
Inc. QALYs		0.072
Inc. costs		£2,705
ICER (inc. cost per QALY)		£37,398

3.23 These results show that the total costs of pemetrexed are greater than gemcitabine. However, the life years and QALYs gained are greater in the pemetrexed arm. Patients in the pemetrexed arm gain 0.15 life years. Therefore, pemetrexed is more costly and more effective than gemcitabine. The cost per additional gain in QALY is £22,202 for the target population.

Validation – QC

See Appendix 2 for QC report and changes made to the model.

Validation – compared to trial data

3.24 A validation exercise was undertaken to compare the progression free survival and overall survival in the model to the trial observed trial data. Figure 2 illustrates how the simulated progression free survival and overall survival from the model matches to the observed trial data. A similar analysis was undertaken by the ERG in their appraisal of the original model. Figure 3 reports the analysis from the ERG. These two graphs illustrate that the changes to the model have improved the model fit to the observed trial data, although cost-effectiveness results have not changed greatly. Similar analysis on the gemcitabine arm of the model is presented in Figures 4 and 5.

Figure 2. New PFS and overall survival results

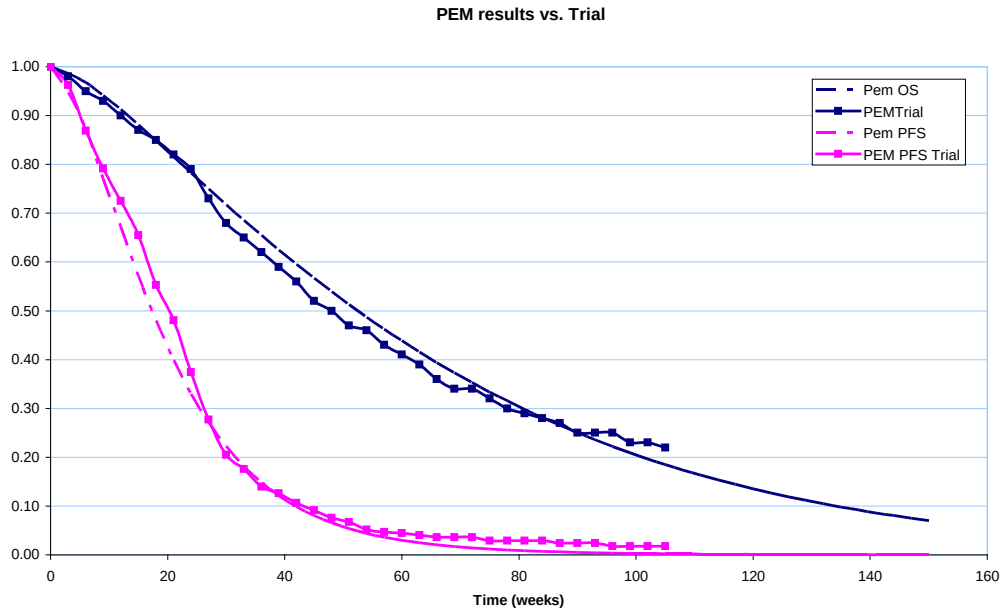


Figure 3. Previous curves by ERG

A Pemetrexed + platinum

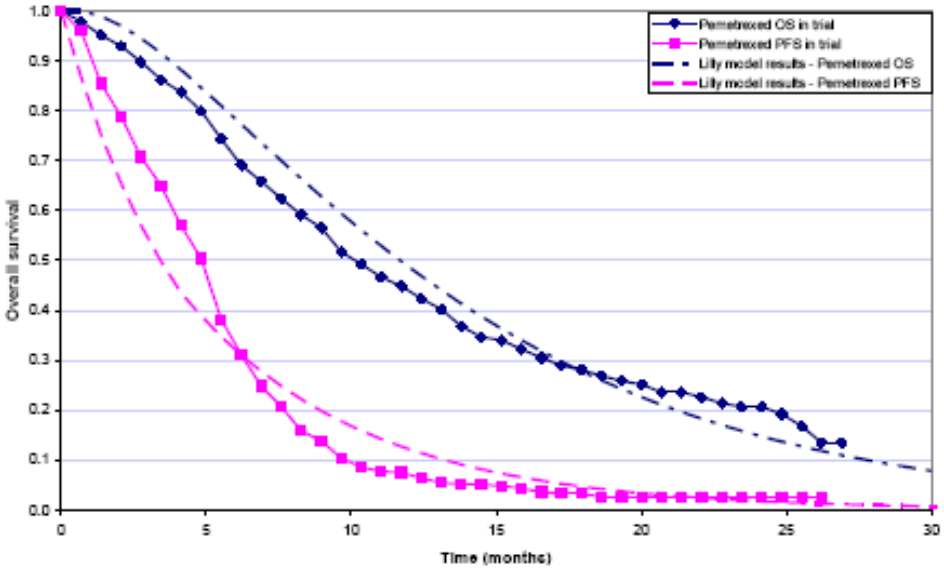


Figure 4. New PFS and overall survival results

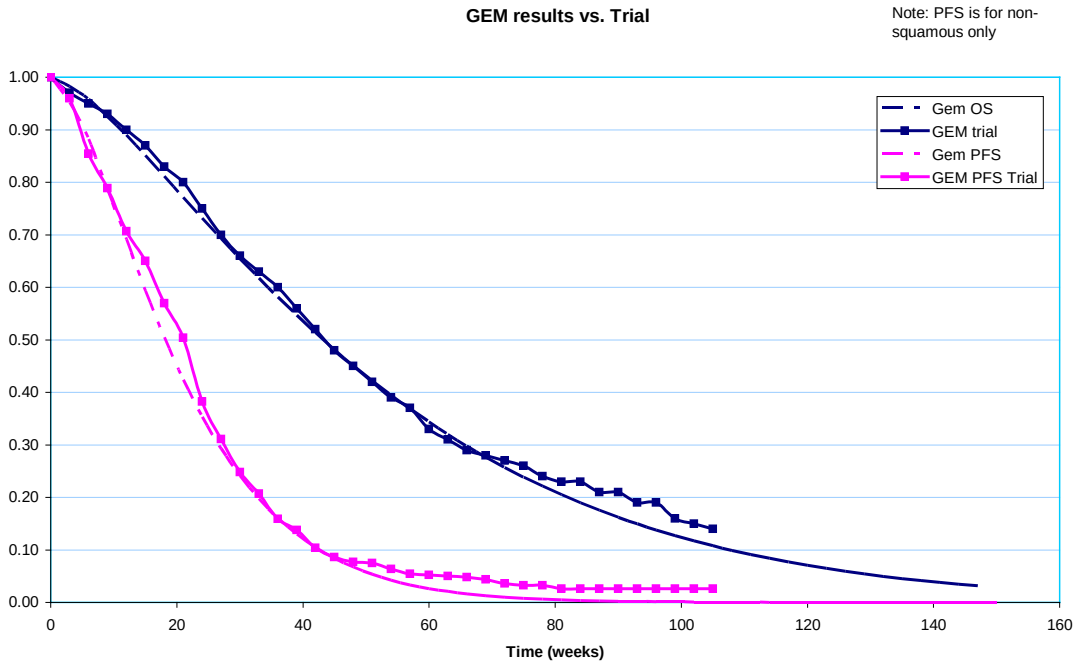
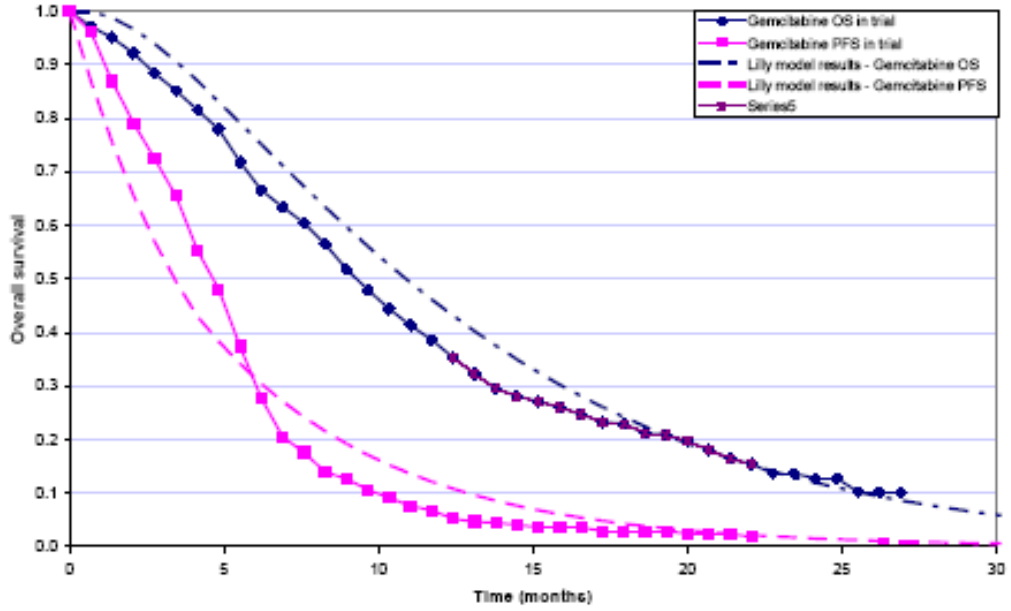


Figure 5. Previous curves by ERG

B Gemcitabine + platinum



Sensitivity Analyses

3.25 A series of one-way sensitivity analyses have been undertaken to test the impact of individual model parameters on the ICER results. The ICER results from the one-way sensitivity analyses are detailed in Table 10.

Table 10. One-way sensitivity analysis

Sensitivity analysis description	Cost per QALY
Base case (adeno and large cell, max 4 cycles)	*£22,202*
Discount rate equal to 0%	£21,467
Discount rate equal to 6%	£22,720
Hospital days for AE varied -50%	£22,355
Hospital days for AE varied +50%	£22,050
Cost of FN set to £1,500	£22,239
Cost of FN set to £3,500	£21,908
Utility estimates set to 2.5th CI	£25,277
Utility estimates set to 97.5th CI	£19,787
OS for PEM set to lower efficacy	£47,776
OS for PEM set to upper efficacy	£14,686
OS for GEM set to lower efficacy	£14,986
OS for GEM set to upper efficacy	£56,632
FN rate to original 3.9%	£22,149
Half-cycle correction turned off	£21,252

PSA – Adeno and large cell carcinoma population

3.26 The results of the probabilistic sensitivity analysis suggest that there is a 43% chance that pemetrexed + cisplatin will be cost-effective at a threshold of £20,000. There is a 58% probability that pemetrexed is cost-effective at a £30,000 threshold.

Figure 6. Cost effectiveness Acceptability curve (adeno + large cell) 4 cycles

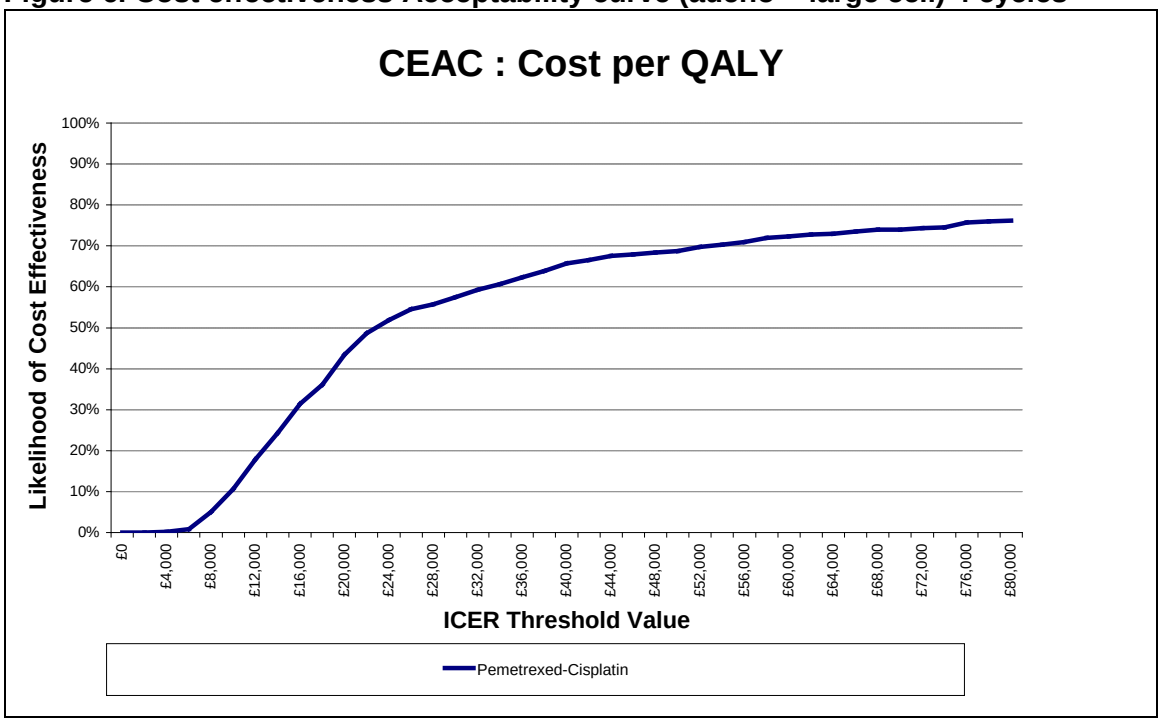
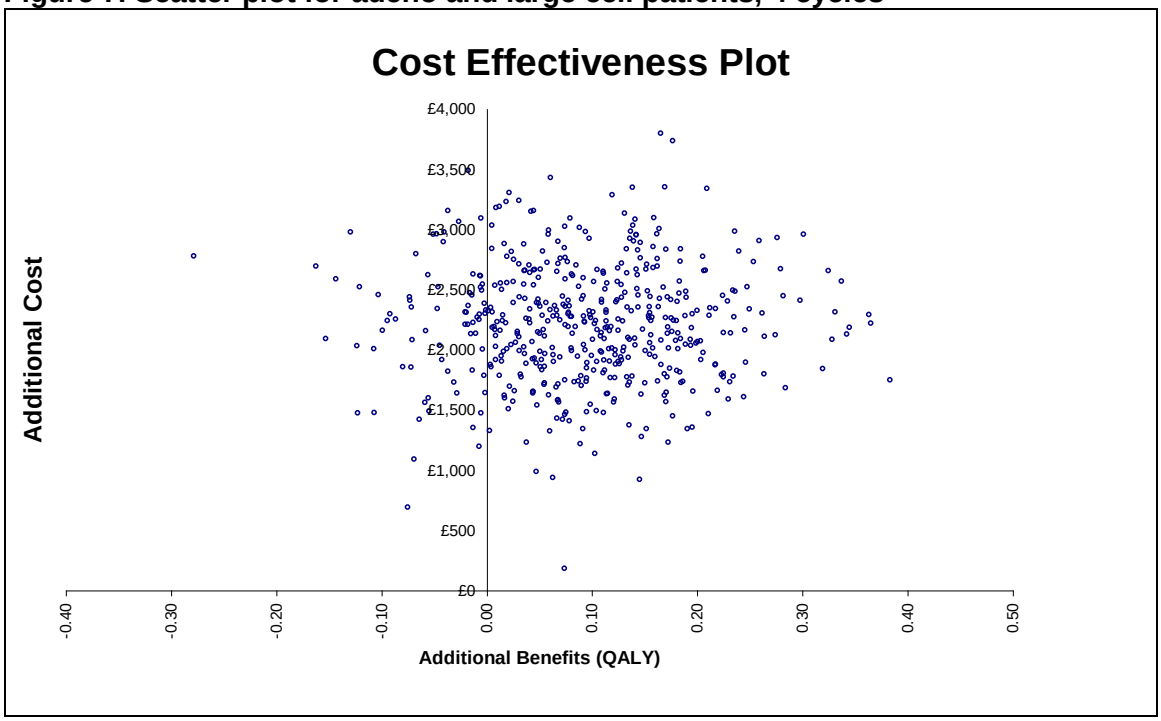


Figure 7. Scatter plot for adeno and large cell patients, 4 cycles



4 Clinical trial-based economic analysis

4.1 The NICE appraisal committee requested that Lilly UK carry out a separate analysis based on the JMDB clinical trial in order to estimate the incremental cost-effectiveness of pemetrexed/cisplatin (pem/cis) compared with gemcitabine/cisplatin (gem/cis).

4.2 The objective of this analysis was to estimate the incremental cost-effectiveness ratio (ICER) for pem/cis versus gem/cis for patients participating in the JMDB study. As a 'within trial' analysis, there was no extrapolation of data after the end of the clinical study with the exception of the application of terminal care and supportive care costs.

4.3 In order to solve the equation:

ICER = ΔCOST (pem/cis-gem/cis)/ΔEFFICACY (pem/cis-gem/cis)

the incremental difference in mean cost for the two arms was divided by the incremental difference in quality adjusted life years (QALYs) for the two arms. Point-estimates were used for overall survival, costs and utility rather than distributions.

Method

4.4 Lilly carried out a 'double-build' process, ie, two researchers independently built and analysed the database to ensure consistency of data outputs. To further validate the quality of this analysis, an external research group was asked to assess the coding and the output of the analysis. The validation process is documented at the end of this report in Appendix 3.

4.5 The analysis was based on individual patient level data. A per-protocol analysis was carried out. As only one person assigned to one arm received the comparator therapy, there was very little difference in the per protocol analysis and the ITT analysis. The two Lilly researchers initially approached this from the two perspectives, but the decision was made to submit on per protocol basis as that had been the approach requested by the ERG at the clarification stage of the process.

4.6 As a within-trial analysis all outcomes were collected during the trial with no extrapolation after the end of the study. For this reason censoring rates for overall survival are relatively high, at 31% for pemetrexed and 24% for gemcitabine, in the licensed patient population. The trial-based analysis has the benefit of reducing uncertainty associated with modelling beyond the end of the trial. However, it is probable that this approach has underestimated the difference between the two arms as the separation of the survival curves occurs towards the end of the trial and continues after the end of the trial.

4.7 The perspective of the analysis was that of an oncology centre: costs collected were chemotherapy acquisition, administration and any treatment for drug-related adverse events. Costs incurred by social care teams, indirect (eg, lost productivity) or intangible costs were not considered with the exception of best supportive care and terminal care costs (that can be multi-agency) which were applied using the mean per patient costs derived from the original submitted model.

Endpoints

4.8 The primary efficacy outcome for this analysis was overall survival. There was no need to consider PFS, which is often used as a proxy endpoint, as there is differentiation between arms in overall survival, the primary endpoint.

4.9 Resource use data included all chemotherapy dose data, adverse event episodes and numbers of hospitalisations. The same unit costs as used in the original submission were applied to these resources in order to calculate mean total costs. These costs were deemed credible by the ERG in their report.

4.10 As with the original economic model, four cycles of treatment were assumed to be the most likely clinical usage in UK practice. Therefore, total costs for each arm include drug acquisition and administration for cycles one to four. Costs associated with adverse events or second-line treatment were not adjusted by cycle. The unit costs applied are given in Tables 11 and 12. In the sensitivity analysis, ICERs are reported based on all cycle costs.

Table 11. Unit costs

Adverse event costs	**Unit cost**	
Neutropenia	£330.93	
Nausea and Vomiting	£700.79	
Fatigue	£38.90	
Diarrhoea	£867.12	
Anaemia	£615.04	
Thrombocytopenia	£341.69	
Cost of FN	£1,720.00	
Chemotherapy costs	**Unit cost**	**cost/mg**
Pemetrexed (100mg vial)	£160.00	£1.60
Pemetrexed (500mg vial)	£800.00	£1.60
Gemcitabine (200mg vial)	£32.55	£0.16
Gemcitabine (1000mg vial)	£162.76	£0.16
Docetaxel (20mg vial)	£162.75	£8.14
Docetaxel (80mg vial)	£534.75	£6.68
Platinums		
Cisplatin (50mg vial)	£25.37	£0.51
Cisplatin (100mg vial)	£50.22	£0.50
Carboplatin (50mg vial)	£22.04	£0.44
Carboplatin (150mg vial)	£56.29	£0.38
Carboplatin (450mg vial)	£168.85	£0.38
Carboplatin (600mg vial)	£260.00	£0.43
Administration		
Outpatient Care	£179.00	
Outpatient Care	£189.00	
Inpatient Care	£430.00	

Table 12. Mean per patient costs for supportive care (from original model)

Supportive care	**Pem/cis**	**Gem/cis**
Best supportive care (mean cost per patient)	£845	£759
Terminal care cost (mean cost per patient)	£2,621	£2,629

4.11 The JMDB trial did not collect quality of life (QoL) data. Based on the utilities reported in the economic model, which were positively reviewed by the ERG, we have maintained the utility advantage associated with pem/cis, applying utility values of 0.65 (pem/cis) and 0.63 (gem/cis) respectively.

Limitations

4.12 This analysis has a number of limitations. These include a non-naturalistic setting (ie, a clinical trial) and a censoring rate of 28% for the licensed population (31% for pem/cis and 24% for gem/cis). This rate of censoring allowed the clinical trial sufficient power for analysis of the primary endpoint, but for an economic analysis it is relatively high in terms of estimating overall survival outcomes. An average UK unit cost has been applied to the number of hospital episodes to account for the geographical variations in length of stay between sites.

Benefits

4.13 The data analysis is timely. A proxy endpoint is not needed as final overall survival data are available. There is little uncertainty regarding the results as there is no extrapolation of data, excepting the concerns with the censored data. The unit costs applied and the utility values used have already been assessed and accepted by an independent review group (Liverpool ERG).

Results

Tables 13 and 14 report a summary of the mean total costs by arm for the adeno and large cell population and the licensed population, based on a maximum of four cycles.

Table 13. Mean summary costs for adeno and large cell population based on four cycles

Mean total cost	Pemetrexed/ cisplatin	Gemcitabine/ cisplatin	Incremental costs
Adverse events	£332.25	£548.17	-£215.91
Chemotherapy	£6,289.77	£4,294.60	£1,995.17
Second-line chemotherapy	£1,846.13	£1,929.18	-£83.06
BSC + Terminal care	£3,466.00	£3,388.00	£78.00
Total	£11,934.15	£10,159.95	£1,774.20

Table 14. Mean summary costs for licensed population based on four cycles

Mean total cost	Pemetrexed/ cisplatin	Gemcitabine/ cisplatin	Incremental costs
Adverse events	£348.50	£551.12	-£202.62
Chemotherapy	£6,253.43	£4,270.50	£1,982.93
Second-line chemotherapy	£1,779.15	£1,885.20	-£106.05
BSC + Terminal care	£3,446.00	£3,388.00	£78.00
Total	£11,847.08	£10,094.82	£1,752.26

4.14 The basecase results are based on costs for four cycles of chemotherapy and adverse event costs associated with episode rates. These factors are varied in the sensitivity analysis. The basecase results are presented in the Table 15 below.

Table 15. Results for base case (maximum four cycles, censored survival data)

Patient group	ICER	Incremental cost	Incremental QALY
Licensed population	£31,157	£1,753	0.056
Adeno + large cell	£24,224	£1,774	0.073

Table 16. Sensitivity analysis

Population	**Licensed**	**Adeno+Large**
Basecase (max four cycles)	*£31,157*	*£24,224*
Including all cycle costs	£42,306	£33,730
Trial hospitalisations at £400 per hospitalisation (rather than episode cost applied to AE rate data)	£34,995	£27,234
Gem constant OS, pem OS decreased by 10%	£177,383	dominated
Gem constant OS pem OS increased by 10%	£15,005	£12,999
No utility benefit for pemetrexed	£45,156	£31,972

Discussion

4.15 The basecase for this trial-based analysis reports an ICER of £24,224 for pem/cis versus gem/cis for the first-line treatment of NSCLC in patients with adeno or large cell carcinoma. This is a based upon a conservative estimate of survival as 31% of pem/cis OS data were censored and 24% of gem/cis OS data were censored, for the licensed population, for the adenocarcinoma plus large cell carcinoma population censoring rates were 32% and 25% respectively. As a greater % of

pem/cis patients were censored than gem/cis patients this more negatively affects pem/cis. However, limiting the duration of cycles to a maximum of four, excludes 23% of all cycles within the trial, therefore the censored survival data is balanced by limiting the duration of therapy to reflect UK practice.

4.16 The one-way sensitivity analysis demonstrates that the model is sensitive to estimates of overall survival. However, in general, the model appears relatively robust with results for the adeno and large cell carcinoma population all falling in the range of ICER £14,000-£36,000.

5 Economic model used for PBAC submission (HTA body, Australia), adapted for the UK.

5.1 The economic model submitted by Lilly Australia to PBAC used Weibull distributions for overall survival. Here we have used the economic model developed in Australia and applied UK unit costs to it, to produce another estimate for the cost-effectiveness of pem/cis compared to gem/cis in the first-line setting.

5.2 The Australian economic model takes the same pragmatic approach as the original NICE submission, focussing on simplifying the model and the number of assumptions required, while capturing the important drivers of cost-effectiveness. There are some conceptual differences between this model and the one submitted to NICE. For example this model includes only second-line treatments that were significantly different between arms, and includes second line therapies not used in England and Wales. Unlike the model submitted to NICE, palliative care and supportive care costs are not included. However, even with these differences, the final ICERs generated are similar suggesting a further degree of confidence in the ICER estimates for pem/cis.

5.3 Appendix 4 presents details of the economic model. To summarise, a deterministic model based on the calculation of overall survival from Weibull distributions was constructed. Resource use was taken from the clinical trial based on chemotherapy doses, administration and adverse events rates. To these, unit costs were applied. Utility values of 0.65 (pem/cis) and 0.63 (gem/cis) were applied respectively. Australian unit costs were replaced with UK unit costs for the purpose of this analysis.

5.4 The basecase for this analysis was the adenocarcinoma plus large cell population. The model duration was 54 months (based on the 30 month trial duration plus two years, at which point the majority of patients had died).

5.5 The model was constructed using a three step process:
Step 1 – (Trial) A preliminary trial-based analysis, ie costs and overall survival data used were taken directly from the trial.
Step 2 - (Calibration) As in step 1 costs were based directly on trial data. However, the life expectancy estimates used in this step of the economic analysis were

generated using the parametric Weibull-based survival analysis, again over the period of the trial.

Step 3 – (Basecase) Extends the duration of the model for overall survival (using Weibull distribution) two years beyond the end of the trial. The effect of these three steps can be seen graphically in figures below.

Figure 8

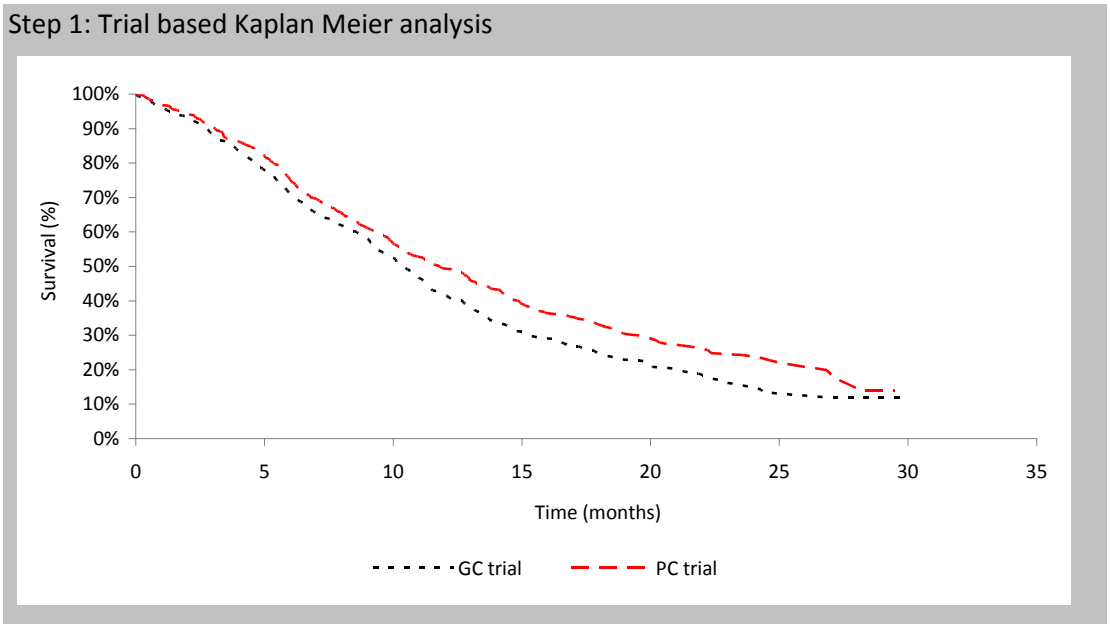


Figure 9

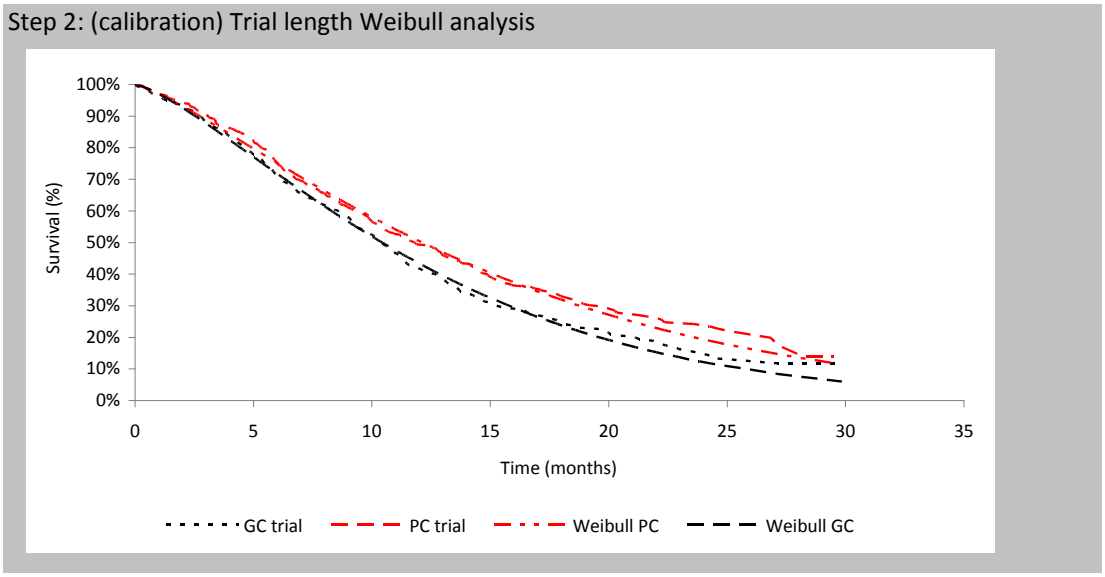


Figure 10

Step 3: (base case) Two year extrapolation Weibull analysis

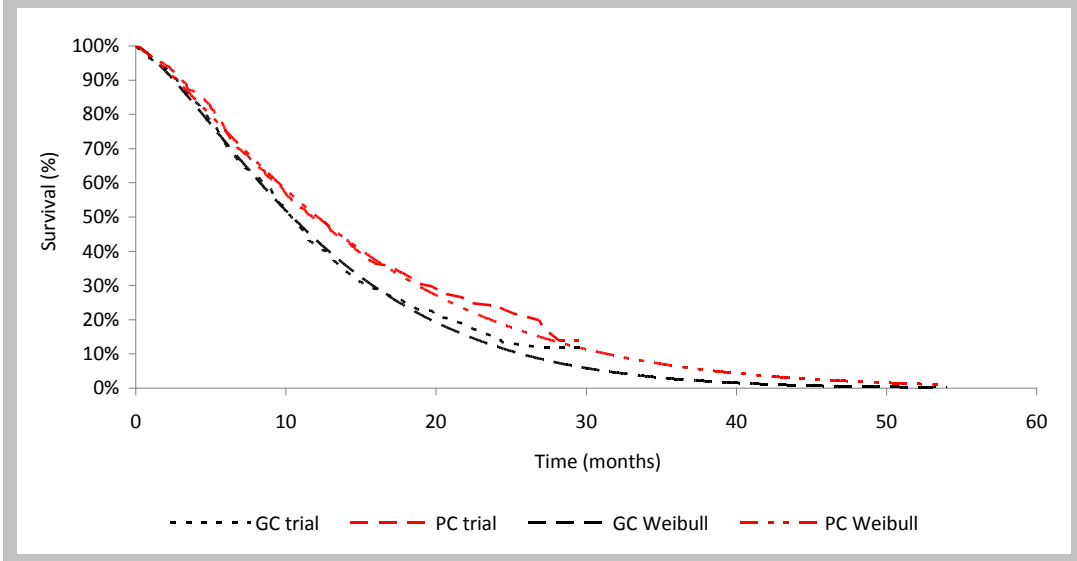
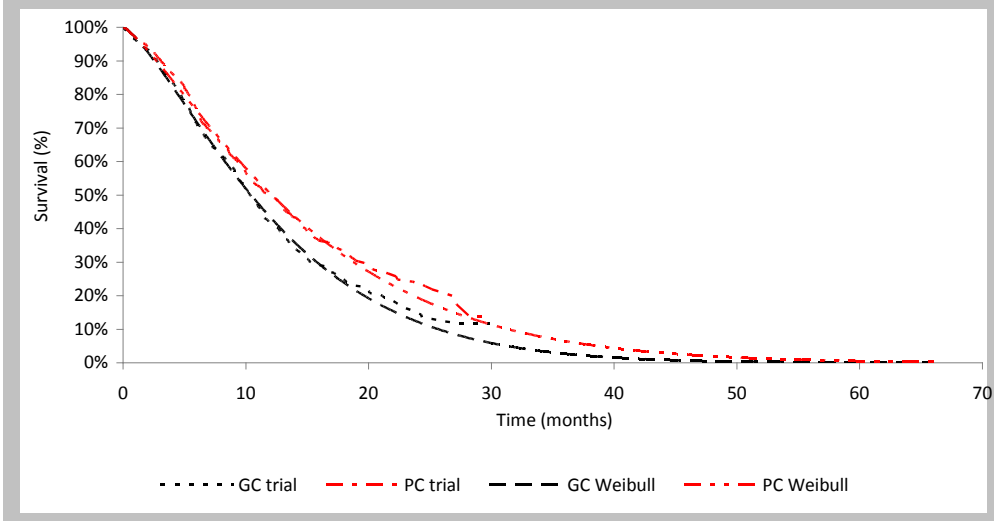


Figure 11

Step 3: (sensitivity) Three year extrapolation Weibull analysis



Results of the Economic Evaluation

5.6 Summary costs are presented in Table 17.

Table 17. Summary of total and incremental treatment costs

Drug	Total cost		
	Pemetrexed + cisplatin arm	**Gemcitabine + cisplatin arm**	**Incremental**
First-line therapy including premedication	£7,385.56	£3,855.86	£3,529.71
Post-discontinuation therapy	£31,497.19	£1,512.74	-£15.55
Transfusion costs	£216.43	£376.15	-£159.72
Cost of treating SAEs & major toxicities	£20.70	£73.28	-£53.57
Total cost	**£9,119.59**	**£5818.03**	**£3,301.56**

5.7 Summary health outcomes are presented in Tables 18 and 19. This model focussed on estimating cost per life year saved as this was considered the most appropriate outcome measure for this disease area. However, a cost per QALY was also calculated. Both results are presented.

Table 18. Mean survival by modeling step and model are for adenocarcinoma and large cell population

	Mean survival (years)		
Step	**PC**	**GC**	**Incremental**
Step 1: (Trial length)	1.17	1.03	0.14
Step 2: (Calibration)	1.15	1.02	0.13
Step 3: Base case (trial length plus two years)	1.23	1.04	0.19
Sensitivity anlaysis (three year extension)	1.24	1.05	0.19

Abbreviations: PC = pemetrexed + cisplatin treatment; GC = gemcitabine + cisplatin treatment
NB. Rounding has been applied

Table 19. QALY outcomes by model arm for adenocarcinoma and large cell population

	Health outcomes (QALYs)		
	PC	**GC**	**Incremental**
Basecase (two year extension)	0.80	0.66	0.14
Sensitivity analysis (three year extension)	0.80	0.66	0.15

5.8 Incremental cost-effectiveness results are presented in Table 20. As shown in Step 2 the Weibull survival function calibrates extremely well to the within trial Kaplan-Meier survival analysis shown in Step 1. It should be noted that both of these survival estimates are truncated and, therefore Step 3 provides the most realistic estimate of patient survival.

Table 20. Incremental cost effectiveness ratios

	Mean survival (years)		
	PC	**GC**	**Incremental**
Step 1: (trial length ~30 months)			
ICER (cost per LYS)			£24,316.60
Step 2: (calibration ~30 months)			
ICER (cost per LYS)			£24,915.33
Step 3: (base case: two year extrapolation – when most patients have died)			
Cost (£)	£9,119.59	£5818.03	£3,301.56
Effect (LY)	0.80	0.66	0.14
ICER (cost per LYS)			£17,635.53
ICER (cost per QALY)			**£23,156.68**
Sensitivity analysis: (three year extrapolation – when all patients have died)			
ICER (cost per LYS)			£17,240.47
ICER (cost per QALY)			**£22,709.96**

5.9 The three year extension tested in the sensitivity analysis is five and a half years in total, which is closest to the six year basecase in the model submitted to NICE. The estimate for the cost-effectiveness of pem/cis compared with gem/cis for the first-line treatment of NSCLC in the adenocarcinoma and large cell carcinoma population based on the submission to PBAC, is consistent with the original model submitted to NICE, the revised model submitted to NICE and the clinical trial data analysis.

6 Pathophysiological basis for differential effect by histology for pemetrexed/cisplatin

6.1 Based on discussions that took place in the public appraisal committee meeting, we thought it would be helpful for the appraisal committee to have further information regarding the differential effect by histology for pemetrexed. Although the pathophysiological basis for this effect has not yet been conclusively established, the consistent predictive effect of histology across pemetrexed studies suggests an underlying molecular basis.

Clinical evidence

6.2 The differential effect of pemetrexed by histology was first observed in a retrospective analysis of data from JMEI, a phase III, randomised trial of pemetrexed/cisplatin in second-line NSCLC (Peterson et al 2007; Hanna et al 2004). A significant treatment-by-histology interaction in this study indicated that patients with non-squamous histology treated with pemetrexed had longer survival compared to all other histological sub-types. Another phase II randomised study (Ohe et al 2008) also demonstrated a significant treatment by histology interaction for pemetrexed in non-squamous NSCLC.

6.3 Based on the results of the above-mentioned studies, a prespecified histology analysis was planned for the study JMDB, prior to database lock and unblinding of the data to the sponsor. The results of this analysis demonstrated a significant treatment by histology interaction for pemetrexed in first-line non-squamous NSCLC. Subsequently, another phase III randomised study of pemetrexed (JMEN, Ciuleanu et al 2008) demonstrated a survival advantage (preliminary overall survival results) for pemetrexed in patients with non-squamous NSCLC in the maintenance setting.

Preclinical data

6.4 Pemetrexed is a multi-targeted antifolate which acts by disrupting crucial folate-dependent metabolic processes essential for cell replication. One of its key target enzymes is thymidylate synthase (TS). Preclinical data suggests that overexpression of TS correlates to reduced sensitivity to pemetrexed in vitro (Sigmund et al 2003; Giovanetti et al 2005) and that expression of TS is lower in adenocarcinoma NSCLC specimens compared to squamous cell carcinoma (Ceppi et al 2006).

6.5 In a companion pharmacogenomic study of the JMDB trial (Scagliotti et al 2007) low TS expression was associated with a longer time to progression (TTP) and time to treatment failure (TTF) for pemetrexed/cisplatin. However, because of a limited number of samples, these findings were not statistically significant and must be considered hypothesis-generating. In a recent study evaluating TS expression, very high TS expression levels were detected in small cell lung cancer (Ceppi et al 2008), a histologic type of lung cancer in which pemetrexed activity is limited.

New clinical trial

6.6 In order to prospectively study the TS hypothesis and to gain a better understanding of which patients would respond best to pemetrexed treatment, Lilly have initiated multicentre, single-arm, phase II study to be conducted in the UK. The primary objective of this study is to determine the correlation between progression free survival (PFS) in these NSCLC patients, and TS expression.

7 References

Briggs A, Sculpher M., Buxton M. (1994). Uncertainty in the economic evaluation of healthcare technologies: the role of sensitivity analysis. Health Economics, 3, 95-104.

Ceppi P, Volante M, Saviozzi S, et al: Squamous cell carcinoma of the lung compared with other histotypes shows higher messenger RNA and protein levels for thymidylate synthase. Cancer 107: 1589-1596, 2006.

Ceppi P, Volante M, Ferrero A et al. Thymidylate synthase expression in gastroenteropancreatic and pulmonary neuroendocrine tumors. Clin Cancer Res 2008;14:1059 –1064.

Ciuleanu TE, Brodowicz T, Belani CP et al. Maintenance pemetrexed plus best supportive care (BSC) versus placebo plus BSC: A phase III study. J Clin Oncol 2008;26(15 suppl):426s. (Study JMEN)

Giovannetti E, Mey V, Nannizzi S, et al: Cellular and pharmacogenetics foundation of synergistic interaction of pemetrexed and gemcitabine in human non-small-cell lung cancer cells. Mol Pharmacol 68:110-118, 2005.

Hanna N, Shepherd FA, Fossella FV, Pereira JR, De Marinis F, von Pawel J et al. Randomised Phase III trial of pemetrexed versus docetaxel in patients with Non-Small-Cell Lung Cancer previously treated with chemotherapy. Journal of Clinical Oncology, 2004, 22 (9): 1589 – 1597.

Ohe Y, Ichinose Y, Nakagawa K et al. Efficacy and safety of two doses of pemetrexed supplemented with folic acid and vitamin B12 in previously treated patients with non-small cell lung cancer. Clin Cancer Res 2008;14: 4206–4212.

Peterson P, Park K, Fossella F et al. Is pemetrexed more effective in adenocarcinoma and large cell lung cancer than in squamous cell carcinoma? A retrospective analysis of a phase III trial of pemetrexed vs docetaxel in previously treated patients with advanced non-small cell lung cancer (NSCLC). J Thorac Oncol 2007;2(suppl 4):316 –317. (Study JMEI)

Scagliotti G, Kaiser C, Biesma B et al. Correlations of biomarker expression and clinical outcome in a large phase III trial of pemetrexed plus cisplatin or gemcitabine plus cisplatin in chemonaive patients with locally advanced or metastatic non-small cell lung cancer (NSCLC). J Thorac Oncol 2007;2(suppl 4):s306.

Sigmond J, Backus HH, Wouters D, et al: Induction of resistance to the multitargeted antifolate pemetrexed (ALIMTA) in WiDr human colon cancer cells is associated with thymidylate synthase overexpression. Biochem Pharmacol 66:431-438, 2003.

Sonnenberg, FA., and Beck JR., (1993). Markov models in medical decision-making: a practical guide. Medical Decision-Making 13,322-38.

Appendix 1

Lambda and gamma estimates used for modified Markov analysis

Time to progression

Pemetrexed + Cisplatin

	All patients	Licensed	Adeno+ large cell	Adeno	Large cell
Lambda	0.017	0.012	0.012	0.012	0.010
Gamma	1.293	1.415	1.392	1.396	1.554

Gemcitabine + Cisplatin

	All patients	Licensed	Adeno+ large cell	Adeno	Large cell
Lambda	0.014	0.010	0.011	0.010	0.005
Gamma	1.307	1.436	1.403	1.430	1.711

Overall survival

Pemetrexed + Cisplatin

	All patients	Licensed	Adeno+ large cell	Adeno	Large cell
Lambda	0.006	0.005	0.004	0.004	0.006
Gamma	1.246	1.255	1.268	1.266	1.240

Gemcitabine + Cisplatin

	All patients	Licensed	Adeno+ large cell	Adeno	Large cell
Lambda	0.005	0.005	0.005	0.005	0.004
Gamma	1.274	1.283	1.270	1.254	1.439

Appendix 2

Quality Assurance Report for Modified model analysis

The quality assurance is limited to the analysis of consistency of calculations in the Excel model workbook within the current structure of Markov states and comparators. Therefore, we did not analyse any structural assumptions in the model. We also did not review the details of sensitivity analysis as we understand that at this stage it is not a high priority.

The analysis included – checking the details of calculation of costs and outcomes in the Markov worksheets, the costs structure in the outputs, the impact of key parameters such as discounting, half-cycle correction, patient's sizes (BSA)

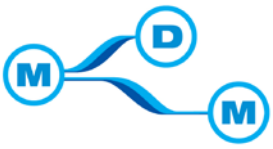
In the table below the error descriptions equally apply to PEM and GEM arms, as the Markov worksheets for these treatments have the same structure.

What was checked	Results	Actions taken
Cost of BSC	Checked if the BSC checkbox (the worksheet Model Set Up) affects the costs. It does affect the cost in both GEM and PEM arms.	None required
Cost BSC and possibly other costs	Unexplained formula for cost calculations.	Unexplained formulas for cost calculations fixed.
Cost by Markov stages	The cost of state "Stable to respond" is omitted in calculations – cells from X297 down are empty and they must be populated	The cost of state "stable to respond" has been included in the analysis.
LY	Errors found. The model's and outcomes calculations start from cycle 0 initially populated in the states *Stable* and *Stable to respond* (row 170). This row was omitted in the calculation of overall survival and quality-adjusted life years	Fixed by developers by making row 171 the initial Markov cycle in the model, both for the calculations of LY and QALY
LY	Error in the calculation of LY in cell PEM PP/ ER169, the arguments in the SUMIF function are not synchronised =SUMIF($F172:$F276,"<="&ncycle,AR171:AR276)*(3/52)	Fixed by developers
QALY	Checked the consistency of QALY weights assigned to the same Markov states in the two treatment arms. Correct in both GEM and PEM arms	
Half-cycle correction - Outcomes	Error in LY. Checked what is affected by the control on the Model Set Up page. Cell B42 on the Data Store page which affects the value of the cell named *uhalfcycle*. The half-cycle correction option only applies to QALYs and not to Life Years.	Half-cycle correction has been applied to the Life Years.
Half-cycle	Half-cycle correction for costs is in the variable *halfcycle*	The controlling half-

What was checked	Results	Actions taken
Correction – Cost	which was set to 1 at the time of the QC. This parameter also applies in the cost formula for drug acquisition and drug admin in the first Markov cycle which is not correct. When *halfcycle* was set to 0.5 it results in a 50% reduction of cost of study drug in cycle 1 which is not correct for the study drug and admin cost as the fist dose is given to all patients. Half-cycle correction must be applied to costs in cycle 1 where the costs are likely to spread within the cycle. Half-cycle correction for costs must be included in the controls in the Mode Set Up worksheet, or *Uhalfcycle used instead of halfcycle* in the formulas, or if you do not intend to use half-cycle correction for costs, remove *halfcycle* from formulas.	cycle correction for costs has been removed from the formulas.
Discounting	Switching off and on the discounting check boxes for costs and outcomes affects both C and E outputs in the model in the "right direction". Discounting not applied to year 1, and is correctly to later Markov cycles.	
Other costs	The checkbox on the page Turn On 2nd Line Treatment on the page Model Set Up affect neither costs nor outcomes. Analysis of the cost breakdown by major cost categories (available in the Markov worksheets for PEM and GEM) cells F:G546 below shows no cost for two categories: 2nd line and "prog cost"	2nd line treatment cost included in the model. The switch on the Model Set Up sheet is working.
Drug wastage	By coincidence, the number of vials per patient matches the n of mg in a vial x BSA so no wastage of the study drug is reflected in the model, and this assumption most likely leads to an underestimation of the cost of study drugs when wastage the cost is based on vials. This can be illustrated by changing the BSA from 1.8 to e.g. 1.7. At BSA = 1.8 the difference between the per cycle cost of PEM for vial based and mg based costing is 0%, however at BSA = 1.7 it is ~6%, at BSA = 1.6 it is 0% again, etc. This may be (partially[1]) captured in the PSA if BSA included there. In order to better estimate the impact of distribution of BSA around the mean on the drug wastage you need to make calculations based on the known or assumed variations of BSA, so that even at the good match between the mean and the required vials there would be wastage.	Treatment cost calculations have changed in the model to reflect the number of vials used in the clinical trial. Therefore, problems with BSA are no longer an issue.

[1] Because the objective of PSA is to explore uncertainty and not variability of patient sizes within the cohort

Appendix 3



MEDICAL DECISION MODELING

Amended Validation of a Cost Effectiveness Analysis of Pemetrexed and Cisplatin vs. Gemcitabine and Cisplatin in the First-Line Treatment of Non-Small Cell Lung Cancer

prepared by:

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Indianapolis, Indiana

prepared for:

Lilly UK

[redacted]

Submitted April 30, 2009
Amended May 5, 2009

1. Introduction

This report is a validation of a cost effectiveness analysis performed by the Health Outcomes group of Lilly UK based on the JMDB trial comparing pemetrexed and cisplatin (Pem/Cis) to gemcitabine and cisplatin (Gem/Cis) in the first-line treatment of non-small cell lung cancer (NSCLC). Medical Decision Modeling (MDM) was asked to evaluate both the technical and philosophical approaches to the model. The principal means of evaluating the analysis has been an examination of the SPSS code through which it was implemented and partial output from that code. A draft of the Lilly analysis document has also been reviewed by MDM.

This is a two-step process where revisions were made following MDM's feedback to Lilly. These can be seen in Sub-section 6 below.

2. Overview of the Model

The model is based on patient-level data gathered in the JMDB trial. (MDM did not have access to the data.) This data included treatment group, histology, the length of overall survival, number of occurrences of grade 3-4 adverse events, actual dosages of cisplatin, gemcitabine, and pemetrexed, the number of hospitalizations, and whether second-line therapy was received. It is important to note that the analysis did not incorporate the actual amount of resources utilized to treat adverse events, nor were quality of life measures available at a patient level. Rather, the analysis turns to sources in the literature for typical costs of hospitalization and treatment of adverse events and also for utilities. The analysis calculates the total cost and number of QALYs per patient. Then the sum and mean of costs and QALYs are calculated, outputted and transferred to Excel for the final ICER calculations.

Only treatment and adverse event-related costs are accounted for in the model. Costs associated with having the disease and indirect costs are not included. Likewise QALYs are accumulated only for the length of the patient's involvement in the trial. No QALYs are accumulated for the period of survival after the end of the trial.

3. In-depth Analysis of SPSS Code

The SPSS code provided to MDM was straightforward and easily readable. Although a number of minor anomalies initially appeared in the code, we believe that all have been rectified. All computations took place on a per patient basis. Only SPSS output presents results accumulated for groups of patients.

The code starts with the computation of the patient's cost of adverse events based on the number of each type of grade 3-4 adverse event times a cost per episode of that adverse event. The source of these event-specific per episode costs was not completely documented in the code, but they are consistent with those used by the Markov model used in the first-line submission to NICE.

First for the pemetrexed treatment arm and then the gemcitabine treatment arm the cost for administration was calculated for both the first four cycles of treatment and for all cycles of treatment. The drug cost was calculated as the product of the actual dosage administered and the per milligram price both for up to first four cycles of treatment and for all cycles of treatment. An AE-related hospitalization cost was calculated as the product of the number of AE-related hospitalizations times a fixed cost. Then total treatment costs were calculated as the sum of administration and drug costs for up to four cycles and for all cycles of treatment. A second-line therapy

cost was applied to patients that had received such therapy. Then two total costs were calculated, both of which included hospitalization costs and second line treatment costs, but one including only treatment costs for the first four cycles of chemotherapy and the other including treatment costs for all cycles received. Finally, QALYs were calculated using a utility of 0.65. For patients in the Gem/Cis arm a second set of QALYs were calculated using a utility of 0.63.

Finally, treatment-specific QALY and total cost statistics were output for all histologies together, only the adenocarcinoma and large cell histologies, adenocarcinoma alone, and large cell alone. Note that in this base case four- cycle and all-cycle total costs included AE-related hospitalization, but not the AE-specific costs initially calculated.

SPSS code was also provided for sensitivity analyses. The first of these changed total costs by substituting the AE-specific costs for AE-related hospitalization costs. Others increased or decreased the number of QALYs for a treatment by 10% while holding the number of QALY's constant for the other treatment; increased and decreased the AE-related hospitalization rate by 10% for the four-cycle costs; and finally set the utility value for both treatment groups to be the same. SPSS output was not provided for these sensitivity analyses.

4 . Comments and Criticisms

Output generated by SPSS allows for the calculation of ICERs using sums of costs and QALYs or means of costs and QALYs. As the numbers of patients in each arm of the trials were different, means should be used. Means have been used in the Lilly written analysis. Apparently, sums were used in the Excel spreadsheet that accompanied it.

In the base case, ICERs have been calculated using the costs of only the initial four cycles but survival reflecting the potential benefit of up to seven Pem/Cis or eight Gem/Cis cycles. The first sensitivity analysis presented is calculated using the costs and QALYs of all cycles. It seems that it should be the base case. Even though UK guidelines may limit first-line use to four cycles, the trial data allowed more and its calculated survival reflects it. An analysis assuming that extra cycles do not increase survival is reasonable.

The base case uses the number of hospitalizations rather than the number of AE episodes to arrive at the cost of adverse events. It appears the use of either would be equally valid. As the ICERs are lower using the AE episode costs, it would be advantageous to use these in the base case rather than using the hospitalization costs.

Drug wastage has not been taken into account in the calculation of drug costs. Ideally, dosage amounts should be rounded up to the nearest increment of vial size.

In the base case a lower utility is used for Gem/Cis than for Pem/Cis. This is defensible for the period of time the patient is receiving Gem/Cis, but for the remainder of the period it is questionable. This reviewer does not know if there is a residual disadvantage to the Gem/Cis patient that persists after treatment with Gem/Cis stops, or if the 0.02 difference is a lifetime average taking into account excess second-line treatment or is only the difference while first-line therapy is occurring.

5. Conclusion

MDM has reviewed the SPSS code, SPSS output, draft analysis, and Excel spreadsheet forwarded to it. The SPSS code appears to be solidly executed. From our perspective, the most defensible model would 1) use means in the calculation of ICERs, 2) use all cycle costs in the base case since this incorporates all treatment costs associated with the survival benefits, 3) incorporate allowance for wastage, 4) use AE episode costs rather than hospitalization costs, and 5) have an adjustment in utilities such that after treatment Gem/Cis patients have the same utility as Pem/Cis patients.

6. Revised Conclusion Based on Lilly Response and Modifications

Most importantly, all ICERs are now calculated based on differences in means. Moreover, the base case now uses AE episode costs as done in the original Markov model, with costs based on hospitalizations now examined in sensitivity analysis. It has been clarified that the 0.02 difference in utility is based upon the average time in each health state within the original model and thus represents the lifetime average of the patient by arm. Therefore, using different utility values as patients proceed from chemotherapy to death is unnecessary.

Two major assumptions remain in this analysis. First, it is assumed that four cycles of platinum-based therapies constitute optimal use and therefore survival is not increased by additional cycles of treatment. The ramifications of this assumption are now completely explored in sensitivity analyses. Second, all chemotherapy costing is based on per milligram usage ignoring wastage. As long as standard dosages approach multiples of vial sizes for all comparators, the overall effect of this on ICERs is probably not large. Moreover, this assumption is applied consistently to all first-line and second-line chemotherapy costs so there is no obvious bias.

Overall, the economic analysis appears to be an accurate and defensible representation of the data obtained from the trial of first-line PEM/CIS vs. GEM/CIS.

Appendix 4

PBAC economic analysis based upon Weibull distributions of clinical trial data

Here we use the economic model developed for PBAC in Australia and applied UK unit costs to it to produce another estimate for the cost-effectiveness of pem/cis compared to gem/cis in the first-line setting.

The Australian economic model takes the same pragmatic approach as the initial NICE submission, focussing on simplifying the model and the number of assumptions required, while capturing the important drivers of cost-effectiveness. There are some conceptual differences between this model and the one submitted to NICE. For example this model includes only second-line treatments that were significantly different between arms, and includes second line therapies not used in England and Wales. Unlike the model submitted to NICE, palliative care and supportive care costs are not included. However, even with these differences, the final ICERs generated are similar suggesting a further degree of confidence in the ICER estimates for pem/cis when compared to gem/cis.

Generation of the base case economic evaluation

The economic analyses are presented in three steps.

Step 1 (trial-based preliminary analysis): presents a preliminary trial-based analysis of the cost-effectiveness of PC versus GC. This trial-based analysis captures:

1) the costs of the primary chemotherapy agents under investigation (ie. PC and GC). This includes pre-medication required for each treatment arm.
2) the costs of post-discontinuation chemotherapy treatment (PDT) where it differed between the trial arms (primarily post discontinuation pemetrexed and gemcitabine exposure).
3) the cost offsets associated with the reduction in the number of transfusions required in patients treated with PC versus GC; and,
4) the costs associated with the treatment of severe adverse events, or major toxicities (grade III or IV) reported in the trial.

It should be noted that the proportion of patients requiring post discontinuation therapy was captured *within* the pivotal trial. The trial-based improvement in life expectancy (over ~ 30 months) from the Kaplan Meier survival analysis is applied in this step. For this step, there is no extrapolation beyond the trial period for costs or outcomes.

Step 2 (calibration): The costs used in this step remain trial-based and are identical to those used in Step 1, above. However, the life expectancy estimates used in this step of the economic analysis are generated using the parametric Weibull-based survival analysis *over the period of the trial*. This step allows the PBAC to compare how well the parametric survival analysis calibrates to the Kaplan-Meier survival analysis over the time-frame of the pivotal RCT.

Step 3 (base case analysis): The costs used in this step are trial-based and are identical to those used in Step 1 and 2, above. However, the life expectancy estimates used in this step of the economic analysis are generated using the

parametric Weibull-based survival analysis extrapolated two years beyond the trial period.

The individual components included in each step of the economic analysis are presented in Table 4.1 below.

Table 4.1 Steps included in the economic evaluation

Step	Costs	Outcomes	Time-frame
Step 1 (Preliminary)	Pre-medication Pemetrexed + cisplatin Gemcitabine + cisplatin Post-discontinuation chemotherapy Transfusion costs SAEs and major toxicities	LYS (based on KM data)	Trial-length (~30 months)
Step 2 (Calibration)	Pre-medication Pemetrexed + cisplatin Gemcitabine + cisplatin Post-discontinuation chemotherapy Transfusion costs SAEs and major toxicities	LYS (based on Weibull survival analysis)	Trial-length (~30 months)
Step 3 (Base case)	Pre-medication Pemetrexed + cisplatin Gemcitabine + cisplatin Post-discontinuation chemotherapy Transfusion costs SAEs and major toxicities	LYS (based on Weibull survival analysis)	Two years beyond the trial (ie ~54-months in total)

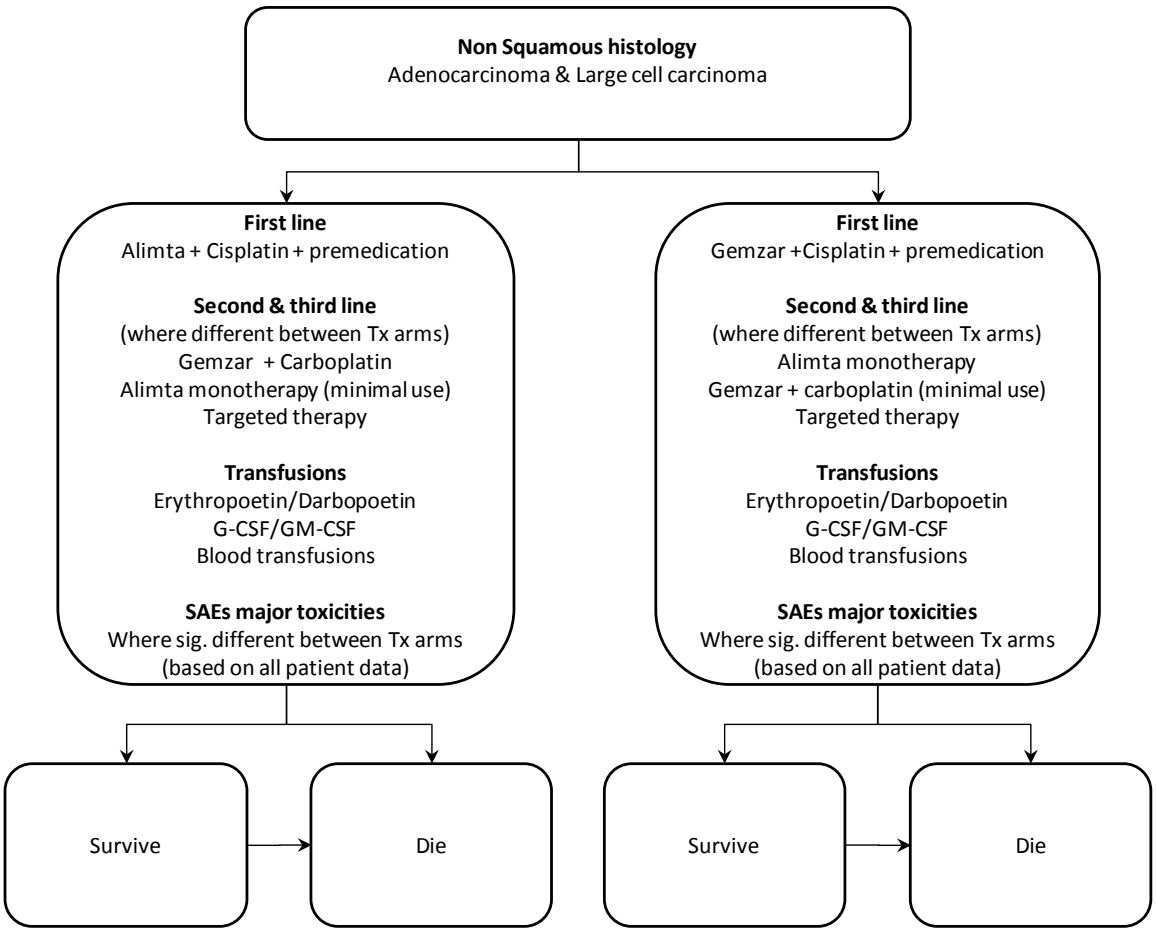
Abbreviations: KM = Kaplan-Meier; LYS = life-years-saved; SAEs = serious adverse events

Structure of the economic evaluation

Figure A 4.1 presents a flow diagram describing the structure of the base-case economic model for patients in the PC and GC arms of the economic model. Though the model is very straightforward, it captures the important characteristics of the treatment pathway; patients incur the mean cost of PC and GC treatment (including the costs of pre-medication) seen in each arm of the trial. The model only captures the costs of post discontinuation chemotherapy treatment (PDT) where the use of this therapy differs significantly between treatment arms (eg. primarily pemetrexed and gemcitabine based chemotherapy). For example, the majority of patients in the pivotal trial received docetaxel as a PDT. However, the proportion of patients that received docetaxel treatment was very similar between treatment arms, and, therefore, capturing the incremental cost of this treatment is of little value in determining the cost-effectiveness of pemetrexed. This approach simplifies the economic model and reduces the number of assumptions that are required, while capturing the important drivers of cost-effectiveness. The model also captures the costs associated with transfusions and products associated with the treatment of neutropenia, anaemia and thrombocytopenia. These costs have little impact on the cost-effectiveness of PC versus GC, but they are clearly different between treatment arms and capturing them improves accuracy of the cost-effectiveness estimate. Finally the model captures the costs associated with SAEs and major toxicities that

were statistically different between arms. Again, the inclusion of these costs makes little difference to the cost-effectiveness of PC versus GC.

Figure A 4.1 Generalised structure of the economic model [note this model refers to adeno+large cell as non-squamous]



Abbreviations: Alimta = pemetrexed; G-CSF = granulocyte colony stimulating factor; Gemzar = gemcitabine; GM-CSF = granulocyte macrophage colony stimulating factor; SAE = serious adverse events; NSCLC = Non-Small Cell Lung Cancer; Tx = treatment

Justification of the structure the economic model

The structure of the economic model is largely informed by the pivotal clinical trial and clinical management algorithms. As described above the model structure is very straightforward.

The costs used in the analysis were derived from the direct health care resource consumption data taken from the pivotal RCT. Each pertinent item of resource use recorded in the trial was identified and specific unit costs were applied. These costs were then summed to determine a mean cost for each arm of the model. The incremental cost was then determined by subtracting the costs in the PC arm from those seen in the GC arm. The costs included in the analyses included the costs of the primary chemotherapy agents under investigation (ie. PC and GC), the costs of pre-medication, the costs of post-discontinuation chemotherapy treatment where it differed between the trial arms (primarily post discontinuation pemetrexed and gemcitabine exposure), cost offsets associated with transfusions, and resource use related to serious adverse events (SAEs) and major toxicities in patients treated with PC versus GC.

The efficacy outcomes in the model (ie. patient survival) were calculated by determining the area under the curve (AUC) of the overall survival function. In Step 1 (preliminary analysis) of the analysis the AUC of the Kaplan-Meier survival function over the trial period was used to determine mean patient survival. Step 2 (calibration) was performed to show that the fitted parametric survival function (Weibull) calibrates appropriately to the trial-based survival estimates presented in Step 1. Only after this calibration was completed was the parametric survival function used to extrapolate beyond the trial period and then only by two years (see Step 3 base case), by which time most of the patients are dead.

Outcomes used in the evaluation

Outcomes

The outcome of interest in this model is life expectancy. The life expectancy estimates used in this economic analysis are generated using the parametric Weibull-based survival analysis extrapolated two years beyond the end of the trial period (ie. 54 months). This extrapolation beyond the trial period was performed to more fully capture the impact of PC and GC on patient survival.

Methods used to generate the results

Modelling methods

Appropriate unit costs were applied to the mean drug use observed in the JMDB trial (ie. premedication, first-line, post-discontinuation treatment and drug costs associated with the transfusions). Similarly, appropriate costs were applied for the administration of these products. The average cost of these interventions was then summed.

The effectiveness (ie. survival) of the treatments was determined, in the base case (Step 3), by calculating the area under the curve (AUC) of the 54 month Weibull-based survival function (ie. two years beyond the trial period).

All costs of treatment occur in the first year of treatment so it was not appropriate to discount costs in the economic model. Patient survival that occurred beyond the first year of the economic model was discounted at 5% per annum. QALYs that occur beyond the first year of the economic model were also discounted at 5% per annum.

Costs were calculated as a single mean figure and applied to the entire cohort in the model. These costs were not apportioned by model cycle and therefore it was not appropriate to apply half-cycle correction to these values. Conversely, the survival outcomes presented in the base-case analysis (ie. Step 3) were accrued over 0.1 month intervals (cycles) for a total of 54 months and, therefore, half-cycle correction was applied to these values. The application of half-cycle correction makes little difference to the results of the base case economic analyses.

Variables in the economic evaluation

Direct health care resources

The following direct health care resources had unit costs applied:

- Unit drug costs
    - Pemetrexed
    - Gemcitabine
    - Cisplatin
- Premedication costs
    - Vitamin B12
    - Folic acid
    - Dexamethasone
- Second line chemotherapy costs were for docetaxel for 3 cycles
- Transfusion products were not included in costs. Transfusions were costed.
- Administration costs
    - Chemotherapy
    - Infusions

Health outcomes

The primary outcome measure for health used in this economic evaluation is overall patient survival, or life-years-saved.

The life expectancy estimates used in this step of the economic analysis are generated using the parametric Weibull-based survival analysis extrapolated two years beyond the trial period (ie. ~54 months). This extrapolation beyond the trial period was performed to more fully capture the impact of PC and GC on patient survival.

Discount rate

All costs of treatment are assumed to occur in the first year of the economic model. Therefore it was not appropriate to discount these costs. Patient survival that occurred beyond the first year of the economic model was discounted at 3.5% per annum. QALYs that occur beyond the first year of the economic model were also discounted at 3.5% per annum.

Results of the economic evaluation

Drug	Total cost		
	Pemetrexed +	Gemcitabine +	Incremental

	cisplatin arm	cisplatin arm	
First-line therapy including premedication	£7,385.56	£3,855.86	£3,529.71
Post-discontinuation therapy	£31,497.19	£1,512.74	-£15.55
Transfusion costs	£216.43	£376.15	-£159.72
Cost of treating SAEs & major toxicities	£20.70	£73.28	-£53.57
Total cost	**£9,119.59**	**£5818.03**	**£3,301.56**

Table A 4.2 Summary mean costs for the non-squamous population

Table A4.2 presents a summary of the trial-based costs generated by each arm of the economic model. The table also presents the incremental costs generated by the model.

Health outcomes

Table A4.3 Mean survival by modeling step and model arm for adenocarcinoma and large cell population

	Mean survival (years)		
Step	**PC**	**GC**	**Incremental**
Step 1: (trial length)	1.17	1.03	0.14
Step 2: (calibration)	1.15	1.02	0.13
Step 3: (base case)	1.23	1.04	0.19
Sensitivity anlaysis (three year extension)	1.24	1.05	0.19

Abbreviations: PC = pemetrexed + cisplatin treatment; GC = gemcitabine + cisplatin treatment
NB. Rounding has been applied

Table A4.4 QALY outcomes by model arm for adenocarcinoma and large cell population

	Health outcomes (QALYs)		
	PC	**GC**	**Incremental**
Basecase (two year extension)	0.80	0.66	0.14
Sensitivity analysis (three year extension)	0.80	0.66	0.15

Incremental costs and effectiveness

Table A4.5 presents the cost-effectiveness results generated by the economic model, by step, for patients with large cell or adenocarcinoma. The table presents the total cost and effect, by treatment arm, as well as the incremental cost-effectiveness ratios (ICERs).

As shown in Step 2 the Weibull survival function calibrates extremely well to the within trial Kaplan-Meier survival analysis shown in Step 1. It should be noted that

both of these survival estimates are truncated and, therefore Step 3 provides the most realistic estimate of patient survival.

Table A4.5 Incremental cost effectiveness ratios

	Mean survival (years)		
	PC	**GC**	**Incremental**
Step 1: (trial length ~30 months)			
ICER (cost per LYS)			£24,316.60
Step 2: (calibration ~30 months)			
ICER (cost per LYS)			£24,915.33
Step 3: (base case: two year extrapolation – when most patients have died)			
Cost (£)	£9,119.59	£5818.03	£3,301.56
Effect (LY)	0.80	0.66	0.14
ICER (cost per LYS)			£17,635.53
ICER (cost per QALY)			**£23,156.68**
Sensitivity analysis: (three year extrapolation – when all patients have died)			
ICER (cost per LYS)			£17,240.47
ICER (cost per QALY)			**£22,709.96**

Abbreviations: PC = pemetrexed and cisplatin treatment; GC = gemcitabine + cisplatin treatment; ICER = incremental cost-effectiveness ratio; LYS = ife-years-saved