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

ERG Report

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Abbreviations:

AE(s)	Adverse event(s)
ASCO	American Society of Clinical Oncology
BNF	British National Formulary
BSA	Body surface area
BSC	Best supportive care
CEAC	Cost-effectiveness acceptability curve
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
CSR	Clinical study report
Docetaxel/cisplatin	Docetaxel plus cisplatin
ECOG	Eastern Cooperative Oncology Group
EMEA	European Medicines Agency
EQ-5D	EuroQol 5D (a standardised instrument used as a measure of health outcome)
ERG	Evidence Review Group
Gemcitabine/carboplatin	Gemcitabine plus carboplatin
Gemcitabine/cisplatin	Gemcitabine plus cisplatin
HEED	Health Economic Evaluation Database
HR	Hazard ratio
HRQoL	Health related quality of life
ICD 10	International Classification of Diagnosis
ICER	Incremental cost-effectiveness ratio
IPD	Individual patient data
ITT	Intention to treat
iv	Intravenous
JMDB	Name of trial comparing pemetrexed/cisplatin with gemcitabine/cisplatin
KPS	Karnofsky performance status
LYG	Life year gained
LUCADA	Lung Cancer Data
MS	Manufacturer's submission
NHS EED	NHS Economic Evaluation Database
NICE	National Institute for Health and Clinical Excellence
NSCLC	Non-small cell lung cancer
NSCLC-NOS	Non-small cell lung cancer not otherwise specified
OS	Overall survival
Pemetrexed/cisplatin	Pemetrexed plus cisplatin
PFS	Progression free survival
PP	Per protocol
PS	Performance status
PSA	Probabilistic sensitivity analysis
PSS	Personal Social Services
PSSRU	Personal Social Services Resource Unit
QALY	Quality adjusted life year
QoL	Quality of life
RCT	Randomised controlled trial
SA	Sensitivity analysis
SPC	Summary of Product Characteristics
STA	Single Technology Appraisal
TTF	Time to treatment failure
WTP	Willingness to pay

1 SUMMARY

The remit of the Evidence Review Group (ERG) is to comment on the clinical and cost-effectiveness evidence submitted to the National Institute for Health and Clinical Excellence (NICE) as part of the single technology appraisal (STA) process. Clinical and economic evidence has been submitted to NICE from Eli Lilly in support of the use of pemetrexed (Alimta®) for the first-line treatment of non-small cell lung cancer (NSCLC) within its current license. The manufacturer submission (MS) describes the use of pemetrexed in combination with cisplatin (pemetrexed/cisplatin) compared with: gemcitabine/cisplatin (primary comparison), gemcitabine/carboplatin and docetaxel/cisplatin.

In April 2008, the Committee for Medicinal Products for Human Use (CHMP), European Medicines Agency (EMEA), adopted a positive opinion to extend the use of pemetrexed (Alimta®) to include the first-line treatment of patients with NSCLC, other than predominantly squamous cell histology.

1.1 Summary of submitted clinical-effectiveness evidence

The majority of the evidence described in the MS is derived from a phase III open label randomised controlled trial (RCT) known as the JMDB trial.[1] This RCT compared the use of pemetrexed/cisplatin with gemcitabine/cisplatin in 1725 patients with NSCLC.

The trial achieved its primary objective to demonstrate noninferiority of pemetrexed/cisplatin to gemcitabine/cisplatin for overall survival. As pemetrexed is only indicated for the first-line treatment of patients with non-squamous NSCLC, a subgroup analysis of 1252 first-line patients with non-squamous NSCLC was presented which reported superiority of pemetrexed/cisplatin on the primary outcome of overall survival (OS) compared to gemcitabine/cisplatin: median overall survival of 11.0 months compared to 10.1 months, adjusted hazard ratio (HR) = 0.84 (95% Confidence Interval [CI]: 0.74-0.96). In the manufacturer's target population (n=1000), median overall survival was 11.8 months compared to 10.4 months, adjusted HR=0.81 (95% CI: 0.70-0.94).

In the population of patients with non-squamous NSCLC, median progression free survival (PFS) was 5.3 months for pemetrexed/cisplatin compared to 5.0 months for gemcitabine/cisplatin, adjusted HR=0.90 (95% CI: 0.79-1.02) but this was not reported to be superior. Tumour response rates were reported to be higher for pemetrexed/cisplatin (29% compared to 22%) but significance tests were not reported.

With the exception of nausea, pemetrexed/cisplatin appeared to be more tolerable than gemcitabine/cisplatin in terms of grade 3/4 toxicities. No safety issues related to pemetrexed/cisplatin arose beyond those already previously documented.

Because no other studies were found comparing pemetrexed/cisplatin with any other relevant comparator, additional evidence was presented from two phase III RCTs comparing gemcitabine/cisplatin with gemcitabine/carboplatin and docetaxel/cisplatin. The MS reported both comparators to fare less well with regard to OS, PFS and tumour response compared with gemcitabine/cisplatin and therefore pemetrexed/cisplatin. No significant differences were reported for tolerability regarding cisplatin regimens. However gemcitabine/carboplatin reported less non-haematologic toxicity in terms of nausea and vomiting and more haematoxicity in terms of an increased incidence of thrombocytopenia than gemcitabine/cisplatin.

1.2 Summary of submitted cost-effectiveness evidence

The manufacturer did not identify any published cost-effectiveness analyses of pemetrexed for the first-line treatment of patients with NSCLC, and therefore developed a *de novo* economic model to present their economic case. However, due to a series of problems identified by the ERG with the manufacturer's economic model, three different versions of the model were submitted to NICE and considered by the ERG. In addition, the MS was resubmitted and an economic addendum was also provided. Evidence reported within this ERG report is based on the final version of the model, the final version of the MS and the economic addendum.

The manufacturer developed a Markov model to evaluate the cost effectiveness of pemetrexed/cisplatin compared to gemcitabine/cisplatin, docetaxel/cisplatin and gemcitabine/carboplatin. The clinical data used in the economic evaluation are primarily generated from the JMDB trial, with two further trials used to conduct indirect analyses. Although the economic evaluation is trial-based, there is also a modelling component to allow the extrapolation of health effects beyond the 30 month trial period up to 6 years. The manufacturer's economic evaluation adopts a lifetime horizon (taken as 6 years) for the consideration of costs and benefits and the perspective is that of the UK NHS and Personal Social Services (PSS).

The ICERs estimated by the manufacturer's model (third version) range from £8,056 to £33,065, depending on the comparator, the population and the application of a continuation rule.

1.3 Commentary on the robustness of submitted evidence

1.3.1 Strengths

The JMDB trial was a randomised controlled head to head clinical trial. It was of good quality, well-designed, used robust randomisation techniques and was suitably powered to demonstrate the primary noninferiority objective of the trial.

1.3.2 Weaknesses

Only one relevant trial (JMDB) was identified which directly compared pemetrexed/cisplatin with any comparator of interest (gemcitabine/cisplatin). Indirect comparisons analysis was therefore undertaken by the manufacturer to attempt to compare the effects of pemetrexed/cisplatin with other comparators.

Evidence from the indirect comparisons should be treated with caution as key comparators were excluded from the indirect comparisons analysis. In addition, the statistical approach employed to generate the findings is not considered to be the most optimal as calculations were based on median survival times and individual trial arm level data from within trials were compared, thus ignoring the benefits of randomisation.

Examination of the third version of the economic model submitted to NICE and considered by the ERG showed that, although minor modifications had been made to correct some of the problems identified by the ERG with earlier versions, the underlying structural problem and logic errors had not been addressed and the model was still unable to replicate the response rates arising in the clinical trial. These serious flaws rendered it impossible for the ERG to provide reliable ICERs.

1.3.3 Areas of uncertainty

While the non-squamous and target population subgroups in the JMDB trial were pre-defined and contained a large number of patients, the trial was designed to test for noninferiority in patients with squamous and non-squamous NSCLC. This may question the validity of generalising findings from subgroups. On the other hand, it should be noted that the subgroup analysis was pre-defined based on emerging trends from a previous study[2] and a large number of patients were included in these subgroups in the JMDB trial. Thus the confidence in the robustness of the subgroup analyses is increased.

Because only 2.5% of patients were recruited from the UK and because patients in the trial population appear to be younger and fitter than all patients with NSCLC, there is some uncertainty as the extent to which the JMDB efficacy results could be replicated in clinical practice.

Due to the limited number of comparators considered and the statistical method employed for the indirect comparisons analysis, the ERG believes that the findings from this analysis should be treated with caution.

There are a number of features of the manufacturer's economic model (including the two previous versions) which give cause for concern:

- the chosen model design is not obviously suitable for modelling the disease and treatments described in the published clinical trial, imposing as it does serious constraints on the possibility of representing the observed patterns of response to treatment and progression of disease

- the implementation of the model is marked by examples of basic errors with marked consequences

- there is little evidence of a systematic approach by the manufacturer to identifying and eliminating errors in the development of the model, or of attempting to replicate the prime source of information for the model, i.e., the JMDB trial itself

- the restriction of comparators to those which are relatively high cost is likely to give a misleading impression of the true cost-effectiveness of pemetrexed regimen. Furthermore, gemcitabine will be off patent in the UK from March 2009 and may soon become available in generic form at a lower price. This was not considered in the manufacturer's model

- the methods used for adjusting treatment effects (positive and negative) when a scenario is used with fewer treatment cycles than in the trial evidence, are not obviously robust and defensible and may tend to over-estimate the outcome benefits to be expected from use of pemetrexed/cisplatin, while under-estimating the additional cost

Taken together, all of these issues and uncertainties lead the ERG to conclude that the model is not sufficiently robust to provide a suitable cost-effectiveness estimate upon which the appraisal committee can base a decision.

1.4 Key issues

Clinical:

The findings provide important evidence warranting further exploration that pemetrexed/cisplatin may be superior to gemcitabine/cisplatin in terms of prolonging OS in patients with non-squamous NSCLC, particularly those with adenocarcinoma or large cell

carcinoma. Identifying patients in the manufacturer's target population requires more specific histological testing than is standard across all UK centres at present. Based on data presented in the MS, the proportion of patients in the UK who would be diagnosed with adenocarcinoma or large cell carcinoma is currently unknown.

As no other regimens recommended by NICE were compared in head-to-head clinical trials with pemetrexed/cisplatin the manufacturer undertook an indirect comparisons analysis. This suggested pemetrexed/cisplatin to be the most efficacious regimen when also compared with gemcitabine/carboplatin, the most common regimen in the UK, or docetaxel/cisplatin. However the ERG is of the opinion that not all relevant comparators were included and because of the statistical method employed to undertake the analysis, these findings must be treated with caution.

Economics:

The identification of serious errors and inappropriate structural assumptions in the submitted economic model means that, even in its modified form, it is not able to provide robust cost-effectiveness estimates upon which to base a decision. The model requires extensive modification and redesign, which is beyond the remit of the ERG. It is also the opinion of the ERG that, following such alterations, the model will need to be subjected to thorough validation against the clinical trial results, and a full quality audit since it is likely that further model inconsistencies may be present which have not yet been identified.

2 BACKGROUND

2.1 Critique of the manufacturer's description of the underlying health problem

In the context section of the MS (section 4), the manufacturer describes the key issues relating to the underlying health problem and associated risk factors as presented in Box 2-1 and Table 2.1.

Box 2-1 Summary of the manufacturer's description of the underlying health problem

Lung cancer is the leading cause of death worldwide (Rosell et al 2004).[3] Non-small cell lung cancer (NSCLC) accounts for approximately 80% of all lung cancers diagnosed. The main sub-types of NSCLC are squamous cell carcinoma (33%), adenocarcinoma (25%) and large cell carcinoma (4%), with the remaining 36% being NSCLC 'not-otherwise specified' (NSCLC-NOS) (LUCADA[Lung Cancer Data], 2007).[4]

Over 38,000 people in the England and Wales were diagnosed with lung cancer in 2005 [Table 2.1] making it the second most commonly diagnosed cancer, after breast cancer, equivalent to more than 100 people per day being diagnosed with lung cancer. The link between smoking and lung cancer is well established: approximately 90% of lung cancer is the result of tobacco smoke. The link between smoking and poverty has also been proven; making lung cancer a disease that disproportionately affects people in the lowest socio-economic groups (Cancer Research UK, 2008,[5] LUCADA ,2007).[4] Survival from lung cancer is poor. It was responsible for approximately 34,000 deaths in 2006 and is the most common cause of cancer death in the UK, accounting for more than one-in-five. Only 7% of lung cancer patients survive over five years after diagnosis.

One reason for this poor prognosis is the late identification of the disease. Lung cancer is asymptomatic in the early stages - about two-thirds of patients are not diagnosed until it has reached advanced stages of the disease and is not amenable to curative treatment. Another reason, which explains the UK's relatively poor performance in comparison with other developed countries, is low active anti-cancer treatment rates.

Table 2.1 Lung cancer statistics in the UK (Cancer Research UK, 2008)[5]

Lung cancer - UK	Males	Females	Persons
Number of new cases (UK 2005)	22,259	16,339	38,598
Rate per 100,000 population[a]	61.3	36.8	47.4
Number of deaths (UK 2006)	19,600	14,550	34,150
Rate per 100,000 population[a]	52.3	31.3	40.4
One-year survival rate (for patients diagnosed 2000-2001[b], England & Wales)	25%	26%	-
Five-year survival rate (for patients diagnosed 2000-2001[b], England & Wales)	7%	7%	-

[a]age-standardised to the European population [b] period estimates

The ERG believes that the MS provides an accurate description of the underlying health problem including details of incidence, prevalence and aetiology.

2.2 Critique of the manufacturer's overview of current service provision

The MS refers extensively to Lung Cancer Data (LUCADA) from the National Lung Cancer Audit.[4] This reports 25% of first-line NSCLC patients in England and Wales received chemotherapy in 2006, although rates do vary by treatment centre. It is noted in the MS that this is low by international standards. However, it is not explicitly stated in the LUCADA report that this is the case for first-line chemotherapy in patients with NSCLC. Furthermore, data completeness for treatment in LUCADA is around 75% (varying by treatment centre) and therefore the actual numbers of patients treated are likely to be underestimated in the data presented. This means comparisons with international figures must be treated with a degree of caution. As cancer registration is conducted regionally throughout the UK and supplied to the Office for National Statistics for the provision of national cancer statistics, the ERG suggests that the manufacturer may have wished to utilise this data for making comparisons with both individual trial and international data.

Guideline recommendations for the use of agents in relation to platinum chemotherapy are accurately summarised in the MS (Box 2-2).

Box 2-2 Platinum doublet chemotherapy combinations: Guidelines

The current NICE guideline[6] recommends that chemotherapy should be offered to patients with stage III or IV NSCLC and good performance status to improve survival, disease control and quality of life. This should consist of a combination of a single third-generation drug (docetaxel, gemcitabine, paclitaxel or vinorelbine) plus a platinum drug. Either carboplatin or cisplatin may be administered, taking into account their toxicities, efficacy and convenience. Patients who are unable to tolerate a platinum combination may be offered single-agent chemotherapy with a third-generation agent.

The current SIGN [Scottish Intercollegiate Guidelines Network] guideline[7] states that chemotherapy with a platinum-based combination doublet regimen should be considered in all stage IIIB and IV NSCLC patients who are not suitable for curative resection or radical radiotherapy and are fit enough to receive chemotherapy. It further states that in these patients, the number of chemotherapy cycles given should not exceed four. No particular chemotherapy doublet or platinum agent is recommended in the guideline.

The European Society for Medical Oncology (ESMO)[8] has published clinical recommendations for diagnosis, treatment and follow-up of NSCLC. The recommendation for the treatment of stage IV disease states that "*Platinum-based combination chemotherapy prolongs survival, improves quality of life, and controls symptoms*"

The MS describes current UK practice with regard to chemotherapy combinations (Box 2-3). Accurately describing clinical practice is problematic because of variability in practice across the UK.

The MS also states that every advance in chemotherapy has incrementally increased quantity and quality of life for patients, with pemetrexed having the most favourable survival rates of all drugs, when administered with cisplatin. The survival rates reproduced by the

manufacturer (MS, Figure 1, pg15) appear to support the statement regarding quantity of life. However, evidence for an improvement in health related quality of life (HRQoL) is scant in the MS although input from our clinical advisors indicated that gemcitabine is a relatively low toxicity regimen.

Box 2-3 Platinum doublet chemotherapy combinations: current UK practice

Gemcitabine with a platinum accounts for over 80% market share in this patient group (UK Market Research Data, 2008).[9]

There is variation between oncologists as to which platinum is preferred. The hydration needed for cisplatin, which requires more hospital time than carboplatin, deters some clinicians from using it. The licensed indication for gemcitabine is in combination with cisplatin. Although in previous years, the majority of use was in combination with carboplatin, the platinum combination agents are now used more equally since publication of a meta-analysis suggesting superior efficacy associated with cisplatin.[10, 11]

According to clinical experts, four cycles of platinum chemotherapy is standard practice in England and Wales. Data from a large observational pan-European trial in NSCLC demonstrated that the median duration of first-line therapy for gemcitabine plus platinum combination was 12.3 weeks which, based on a 3 week cycle, would equate to 4.1 cycles.

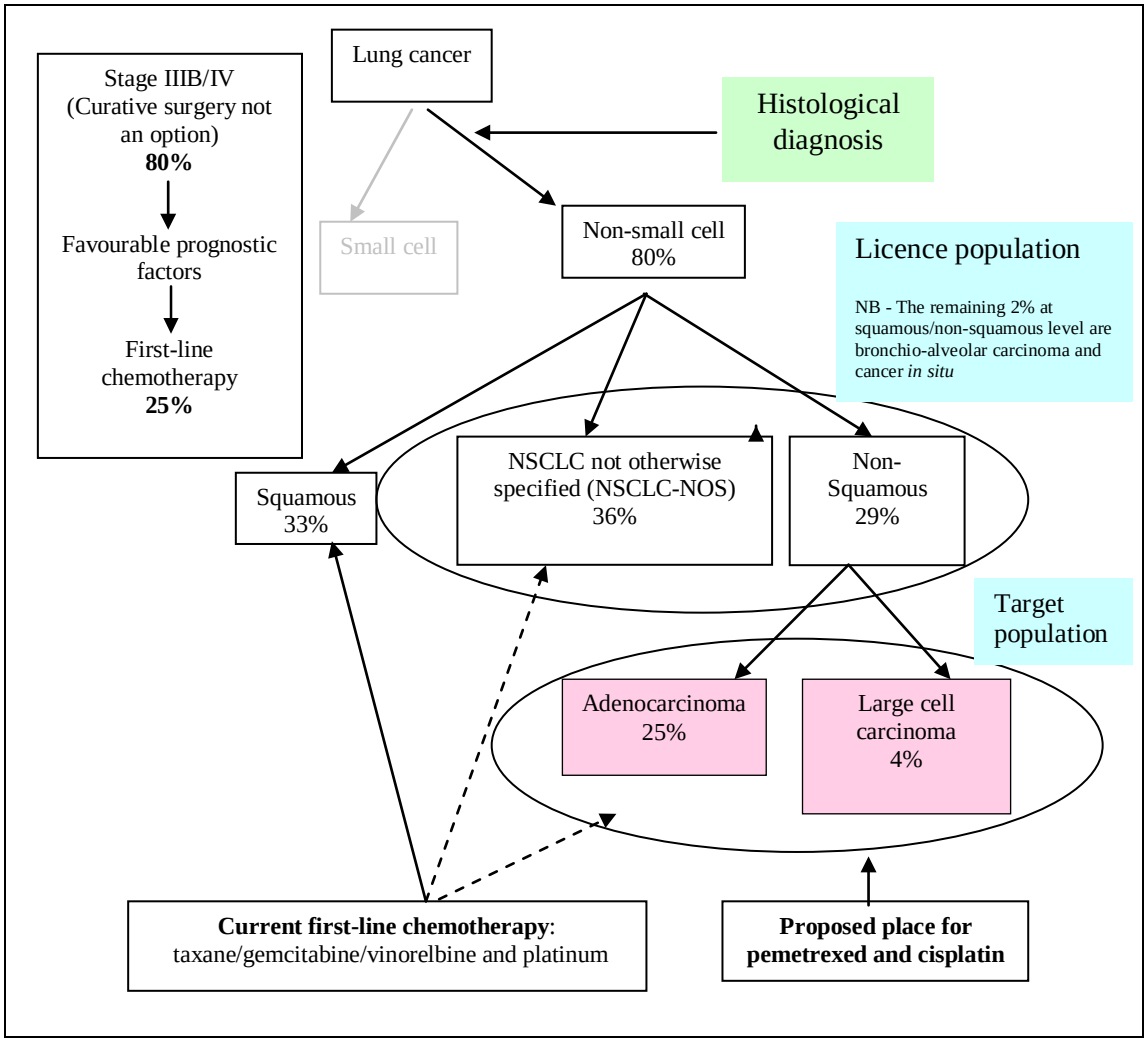

Figure 2.1 Treatment pathway for NSCLC patients in England and Wales

The MS provides a diagram outlining the current treatment pathways and the proposed place for pemetrexed within this (Figure 2.1). It is noted in the MS that currently, lung cancer diagnosis distinguishes only between small cell and non-small cell cancers, as treatment differs depending on this although it proposes that a more specific target population of patients with adenocarcinoma or large cell carcinoma is given pemetrexed/cisplatin than the population stipulated in the licensed population.

LUCADA[4] reports two-thirds (67%) of patients had a histological diagnosis in 2006 (with variations by treatment centre) whereas an optimum rate of 80–85% is recommended. According to this audit, around a third of patients are classified as having squamous NSCLC, around a third adenocarcinoma or large cell carcinoma and around a third NSCLC-NOS. The ERG argues that if available, national cancer statistics from cancer registry data would have been more accurate for estimating proportions by histological classification.

The MS notes uncertainty regarding the accuracy of histological classification. The study cited[12] reports 87% accuracy in diagnosing squamous cell carcinoma, 80% for adenocarcinoma and 50% for large cell carcinoma. The MS argues that as more therapies require this level of specificity and analysis becomes more common, the level of accuracy will improve and the proportion of tumours classified as NSCLC-NOS will decrease. The ERG notes that not all treatment centres may possess the resources to undertake such tests. Arguably of greater importance, such specificity is currently deemed unnecessary, e.g. where an individual is too frail to undergo chemotherapy (input from our clinical advisors suggests that around three quarters of patients who present are not suitable for radical therapy). However, where therapy is a real choice for a patient and where this has proven clinical benefit, this degree of analysis is likely to be welcomed by clinicians.

3 CRITIQUE OF THE MANUFACTURER'S DEFINITION OF THE DECISION PROBLEM

The final scope issued by NICE and the manufacturer's definition of the decision problem is described in the MS (pg9-10) and the summary table is reproduced here (Table 3.1).

Table 3.1 Final scope issued by NICE and the manufacturer's definition of the decision problem as taken from the manufacturer's submission

	Final scope issued by NICE	**Decision problem addressed in the MS**
Population	Patients with chemotherapy-naïve locally advanced or metastatic NSCLC other than predominantly squamous cell histology who are unsuitable for surgery.	Patients who are chemotherapy naïve with locally advanced or metastatic NSCLC other than predominately squamous cell histology, who are unsuitable for surgery. The target population in this submission is patients with adenocarcinoma or large cell carcinoma.
Intervention	Pemetrexed in combination with cisplatin	Pemetrexed (500mg/m^2 iv infusion) in combination with cisplatin (75mg/m^2 iv infusion) on Day 1 of a 21-day cycle, repeated for a maximum of four cycles.
Comparator(s)	Platinum-based chemotherapy (carboplatin or cisplatin) in combination with gemcitabine, docetaxel, paclitaxel or vinorelbine	Primary comparator: gemcitabine/cisplatin Secondary comparators: gemcitabine/carboplatin and docetaxel/cisplatin
Outcomes	The outcome measures to be considered include: • Overall survival • Progression free survival • Response rates • Adverse effects of treatment • Health-related quality of life	The outcome measures to be considered include: • Overall survival • Progression free survival • Tumour response rate • Adverse effects of treatment • Health-related quality of life
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective.	Cost-effectiveness analysis results expressed as incremental cost per QALY gained. A cost per Life Year (cost per LY) gained analysis was also conducted as this type of analysis is relevant in disease areas where extended survival is a key outcome of treatment. Time horizon will be 6 years (a lifetime model). Costs will be considered from an NHS and Personal Social Services perspective. A continuation rule is also modelled to reflect clinical practice of discontinuing treatment in patients who do not respond after three cycles of chemotherapy.
Special considerations and other issues	If evidence allows subgroups of patient populations in whom the technology is clinically effective and cost effective should be considered. These may be related to histology	This submission will be based on the licensed population: patients with NSCLC other than predominantly squamous cell histology. The evidence in the submission also supports the use of pemetrexed/cisplatin in the target population – patients with adenocarcinoma or large cell carcinoma.

iv=intravenous; LY=life year; NSCLC=non-small cell lung cancer; QALY=quality adjusted life year

3.1 Population

The manufacturer's statement of the decision problem describes the relevant population, i.e. patients with locally advanced or metastatic non-squamous NSCLC who are chemotherapy-naïve. However it should be noted that the MS also defines a target population of patients with adenocarcinoma or large cell carcinoma which is narrower than the population of patients with non-squamous NSCLC described in the final scope for whom the drug is licensed. Thus patients with NSCLC-NOS are excluded from the target population. As noted above in section 2.2, identifying the target population requires a more specific histological diagnosis than is currently the norm across all UK treatment centres.

3.2 Intervention

The technology of interest in the MS is pemetrexed (Alimta®), a multi-targeted anti-cancer antifolate agent that exerts its action by disrupting crucial folate-dependent metabolic processes essential for cell replication. It was approved by the European Commission for the first-line treatment of NSCLC (other than predominantly squamous cell histology) in combination with cisplatin on 8th April 2008. In this group of patients, it is indicated for patients with locally advanced or metastatic NSCLC. As carboplatin is not in the licence for pemetrexed, excluding the use of pemetrexed/carboplatin in the MS is appropriate.

Pemetrexed is administered as a 500mg/m^2 intravenous (iv) infusion in combination with cisplatin (75mg/m^2 iv infusion) on day 1 of a 21-day cycle, repeated for a maximum of four cycles. However, while four cycles is the maximum number recommended by the SIGN guidelines[7] and is generally the maximum according standard practice in the UK, the trial used to provide the majority of the clinical evidence within this MS permitted six cycles.

3.3 Comparators

The stated comparators in the final scope are platinum-based chemotherapy (cisplatin or carboplatin) in combination with gemcitabine, docetaxel, paclitaxel or vinorelbine as recommended by NICE.[6] In the definition of the decision problem, the manufacturer has limited its consideration to gemcitabine/carboplatin as it is the most commonly used regimen in the UK and docetaxel/cisplatin as it is one of the remaining platinum combinations used in the UK which is only administered on the first day of each cycle. Market data provided by the manufacturer as a PowerPoint slide shows gemcitabine to be the most commonly used agent in the UK, particularly in combination with carboplatin (gemcitabine/carboplatin was 4.5 times more common than gemcitabine/cisplatin at the end of the first quarter in 2008). Additional marketing data provided on request reported that the use of gemcitabine (with any

other agent) had increased markedly as a proportion of the UK market share for first line stage IIIB/IV NSCLC from 53% at the beginning of 2004 to 83% at the beginning of 2008.[9] Over the same period, the use of the next most common agent, vinorelbine, which is the most commonly administered with cisplatin, had fallen from 20% to 11% (peaking at 24% in 2005). Nevertheless, 11% is still a significant share of the market, especially when it is considered that docetaxel (the next most common agent) only accounts for 4% of the market.

Meta-analyses referenced in the MS[10, 11, 13] support the manufacturer's assertion that there is little to choose between the different agents in terms of efficacy. However, a meta-analysis using individual patient data (IPD)[10] indicated that in first-line treatment of patients with non-squamous NSCLC, carboplatin-based chemotherapy was associated with a statistically significant increase in mortality (HR=1.11; 95% CI: 1.01-1.21). Another meta-analysis of patients with squamous and non-squamous NSCLC reported that compared with other cisplatin-only based treatment arms, there was a marginal improvement for gemcitabine/cisplatin for both OS (HR=0.87; 95% CI: 0.81—0.94) and PFS (HR=0.84; 95% CI: 0.78—0.90) although this was not limited to platinum doublet therapy.[13] Meta-analyses of adverse events (AE)[10, 11] in patients with NSCLC suggest that cisplatin-based chemotherapy is associated with severe nausea and vomiting and nephrotoxicity while carboplatin is associated with severe thrombocytopenia.

To be consistent with the original scope and decision problem and to strengthen the evidence base suggesting there is little difference across regimes, the ERG believes that all comparators should have been considered for the indirect comparisons analysis.

3.4 Outcomes

The relevant outcomes used to measure clinical effectiveness cited in the scope and decision problem include efficacy outcomes (OS, PFS, response rates), tolerability of treatment and HRQoL. The manufacturer adequately describes the outcomes of interest in relation to the relevant patient group and/or phase of treatment reflecting the single list of clinical outcomes identified in the final scope issued by NICE. However, no HRQoL data were presented in the MS. This is arguably a key outcome for this group of patients, and exclusion of this from the analysis of any phase III NSCLC trial may be considered to be a limitation.

3.5 Time frame

In the RCT from which the majority of clinical evidence is derived, patients were appropriately followed up until death or study closure. Overall survival and PFS are censored and do not provide information on the course of disease beyond 24 months.

3.6 Other relevant factors

No relevant subgroup analyses are explicitly stated in the final scope issued by NICE although it was stated these should be considered where evidence allows and suggests these may be related to histology. As noted above (section 3.1), the MS also includes a target population of adenocarcinoma or large cell carcinoma patients. The ERG is confident that the subgroup analyses are appropriate.

4 CLINICAL EFFECTIVENESS

Table 4.1 provides an outline of the key background/clinical information and its location within the MS. Its purpose is to signpost the reader to the main areas of background/clinical information within the MS.

Table 4.1 Key non-economic information in the MS

Key information	Pages in the MS	Key tables/figures in the MS
Description of technology	pg5-8	
Statement of decision problem	pg9-10	
Context/background	pg14-20	Table 1 Figure 1 Figure 2 Figure 3 Figure 4
Equity and equality	pg21	
Literature search:		
Search strategies	Appendix 2	
Study selection	pg22-23	Flow diagram showing study selection, pg22
Clinical effectiveness evidence:		
Trial information: methods, participants, outcomes and statistical analysis	pg23-33 Appendix 8	Figure 5 Table 2 Table 3 Table 4 Table 5 Table 6 Consort diagram, pg30
Trial quality assessment	pg34-35	
Outcomes	pg36	Table 7
Trial results: efficacy	pg36-40	Table 8 Table 9 Table 10
Trial results: safety	pg48-49	Table 17 Table 18,
Indirect comparisons information: comparators, methods, eligibility criteria and participants	pg41-45 Appendix 6 Appendix 7	Figure 11 Table 11 Table 12 Table 13
Indirect comparisons: efficacy	pg46-47	Table 14 Table 15 Table 16
Indirect comparisons results: safety	pg49-50	Table 19 Table 20
Interpretation of clinical evidence	pg51-53	

4.1 Critique of manufacturer's approach

4.1.1 Description of manufacturer's search strategy and comment on the appropriateness of the chosen search strategy.

The scope of the literature search was to identify studies which compared the intervention (pemetrexed/cisplatin) with another comparator in the first-line NSCLC setting. This search was then refined to consider only therapies identified in the decision problem.

Search terms for electronic databases (MEDLINE, EMBASE and the Cochrane Library) appropriately included a combination of free-text and index terms combined with drug names used as free-text terms. In addition to electronic searches, phase III RCTs were sought from the published literature and unpublished data held by the manufacturer, and full references were also checked for any additional studies that may have provided useful and relevant clinical data.

Using this search strategy, the manufacturer initially found 42 trials from EMBASE and MEDLINE and one unpublished trial from its internal database. Of these, two references (one published and one unpublished) relating to the JMDB trial by Scagliotti 2008[1] were included in the review. The search strategy conducted by the ERG confirms the finding of only one relevant direct comparison trial.

4.1.2 Statement of the inclusion/exclusion criteria used in the study selection and comment on whether they were appropriate.

Table 4.2 shows the inclusion and exclusion criteria presented in the MS.

Table 4.2 Inclusion and exclusion criteria

Inclusion	Exclusion
• Phase III randomised trial • Reports data for gemcitabine/cisplatin or pemetrexed/cisplatin plus other comparator (docetaxel/cisplatin, gemcitabine/carboplatin) • Patients in first-line treatment of NSCLC • Patients have to be categorised as stage IIIB or IV • Patients have a performance status ≤ 2 (or > 70 if Karnofsky scale)	• Dose finding trial • Phase II randomised controlled trial • Trial using radiotherapy as a comparator • Trial focussing on patients with a performance score=2 only • Foreign language not understood • Published before 2000 • Incomplete data on: o Demographic data (age, gender) o Baseline data (performance status at start of trial, histological diagnosis not clearly reported)

The inclusion and exclusion criteria appear, on the whole, to be appropriate. However the exclusion of both paclitaxel and vinorelbine doublets may be regarded as a limitation to the

manufacturer's stated objectives, particularly given their inclusion in the original scope and decision problem.

4.1.3 Relevant studies that were not included in the submission

A further pemetrexed study conducted by the Norwegian Lung Cancer Group was identified by the ERG. Details of this study were presented at the 12th World Conference on Lung Cancer in 2007.[14] As with the JMDB trial, in this study patients received either pemetrexed or gemcitabine although in combination with carboplatin. As carboplatin is used outside the indicated licence of both drugs and more specifically because the scope is explicit in stating that only patients taking pemetrexed/cisplatin should be included, the ERG is of the opinion that the exclusion of this study is justified. However, because the primary outcome in the Norwegian trial was HRQoL, it could arguably provide evidence for this outcome.

4.1.4 Description and critique of manufacturer's approach to validity assessment

The validity assessment carried out by the manufacturer (and reviewed by the ERG in Appendix 1) demonstrated that the JMDB trial was methodologically of good quality. However, the ERG notes that only a small proportion (2.5%) of patients were enrolled from the UK and the trial population was generally healthier and younger when compared to the patients described in LUCADA[4] although the representativeness of LUCADA to the UK picture was discussed earlier. The MS justifiably argues that healthier and younger patients participate in clinical trials; inclusion criteria are designed to restrict patient entry in order to limit confounding factors. Patients with ECOG PS=2 are also unlikely to be treated with cisplatin-based treatment in the UK as it is deemed to be too toxic for them by physicians.

4.1.5 Description and critique of manufacturers outcome selection

The outcome measures reported in the decision problem in the MS are standard outcomes for cancer trials and match those specified in the scope and are therefore appropriate.

4.1.6 Description and critique of the statistical approach used

As the systematic review only found one pemetrexed/cisplatin trial, no meta-analysis was undertaken. Generally the statistical approach employed in the trial appeared appropriate. In particular, the subgroup analysis was pre-stated in the manufacturer's statistical analysis plan,[15] based on findings emerging from a retrospective analysis of a trial of second-line pemetrexed.[2] While efficacy results were only presented for an ITT population and not the per-protocol (PP) population as would be expected for a noninferiority trial, given the vast majority of patients received the treatment to which they were randomised, differences between the two analyses would be expected to be small. This was confirmed by the

manufacturer who provided PP efficacy data on request. Arguably the most problematic statistical limitation was the lack of any correction for multiple testing thus increasing the likelihood of significant results emerging by chance.

4.1.7 Summary statement

The systematic review in the MS, which identified only one trial comparing pemetrexed/cisplatin to another relevant comparator, was complete and reasonable. The search strategy was adequately reported. All relevant clinical trials were identified and validity of the one included trial was discussed by the manufacturer. The clinical outcomes reported in the single relevant RCT identified cover relevant outcomes outlined in the final scope issued by NICE (OS, PFS, tumour response and tolerability). However no HRQoL data were collected. Statistical methods were described in full and appropriately applied.

4.2 Summary of submitted evidence

4.2.1 Summary of JMDB trial results

The majority of the clinical effectiveness evidence described in the MS is derived from a phase III, open label RCT which compared pemetrexed/cisplatin with gemcitabine/cisplatin. The JMDB trial included 1725 patients with either squamous or non-squamous NSCLC and a number of different subgroups were defined by histology type (Table 4.3). Baseline characteristics were well balanced between treatment arms and histological subgroups.

Table 4.3 Number of patients in the JMDB trial by treatment arm and histology subgroup

	Numbers analysed		
Population	**All patients**	**pemetrexed/ cisplatin**	**gemcitabine/ cisplatin**
All randomised patients (intent-to-treat)	1725	862	863
Patients with non-squamous histology	1252	618	634
Target population (adenocarcinoma or large cell carcinoma)	1000	512	488
Patients with adenocarcinoma	847	436	411
Patients with large cell carcinoma	153	76	77
Patients with NSCLC-NOS	252	106	146

NSCLC-NOS= non-small cell lung cancer not otherwise specified

JMDB trial data presented in this report were extracted from the MS with additional information being provided by the manufacturer in clarification of questions raised by the ERG.

Table 4.4 Dose adjustments, reductions, omissions and delays in the JMDB trial (intention to treat population)

Cycle and dose adjustment	Pemetrexed/cisplatin (n=839)	Gemcitabine/cisplatin (n=830)
No of cycles per patient		
Median (range)	5.0 (1-7[a])	5.0 (1-8[b])
Total number of cycles administered (mean)	3,648 (4.4)	3,626 (4.4)
Dose adjustment on Day 1		
Pemetrexed (Number [%])	54 [1.5%]	-
Gemcitabine (Number [%])	-	362 [10%]
Cisplatin (Number [%])	64 [1.8%]	154 [4.2%]
Doses omitted on Day 8		
Gemcitabine (Number [%])	Not applicable	339 [9.3%]

[a]One patient on the cisplatin/pemetrexed arm received more than six cycles; [b]four patients on the cisplatin/gemcitabine arm received more than six cycles.

In both treatment arms in the JMDB trial, patients received on average just over four treatment cycles (Table 4.4). As noted in section 2.2 above, four cycles of platinum chemotherapy is standard practice in England and Wales. Thus the efficacy results in the JMDB trial may differ slightly to those that could be expected from four cycles in practice.

Trial dose adjustments (delays, reductions and omissions) were less frequent in patients treated with pemetrexed/cisplatin compared with those treated with gemcitabine/cisplatin.

Efficacy

Findings from the PP analysis presented to the ERG on request by the manufacturer differed little from the findings from the ITT analysis which strengthens the robustness of the JMDB trial results (PP data are not presented in this report).

The main efficacy findings are summarised in Table 4.5 where pemetrexed/cisplatin was found to be noninferior to gemcitabine/cisplatin for OS in the JMDB overall trial population. It was also found that patients with (i) non-squamous NSCLC (ii) adenocarcinoma, (iii) large cell carcinoma and (iv) the manufacturer's own defined target population (adenocarcinoma or large cell carcinoma) also had improved OS (statistically significant) and PFS (not reported as statistically significant) when given pemetrexed/cisplatin. No significant findings were found for OS or PFS in the NSCLC-NOS group, where gemcitabine/cisplatin appeared to lead to improved outcomes. Response rates were reported to be higher in (i) the overall population, (ii) patients with non-squamous NSCLC and (iii) adenocarcinoma but were not reported as being statistically significant.

Table 4.5 Key efficacy findings in the JMDB trial (intention to treat analysis)

Patient Group	Median (months) (95% CI) or response rate (%)		Adjusted HR (95% CI)	p-value (superiority)
	pemetrexed/ cisplatin	gemcitabine/ cisplatin		
Overall survival				
All randomised patients including squamous NSCLC (N=1725)	10.3 (9.8-11.2)	10.3 (9.6-10.9)	0.94 (0.84-1.05)	p<0.001[a] p=0.259[b]
Patients with non-squamous histology (N=1252)	11.0 (10.1-12.5)	10.1 (9.3-10.9)	0.84 (0.74-0.96)	P=0.011[b]
Target patients: adenocarcinoma or large cell carcinoma(N=1000)	11.8 (10.4-13.2)	10.4 (9.6-11.2)	0.81 (0.70-0.94)	p=0.005[b]
Patients with adenocarcinoma (N=847)	12.6 (10.7-13.4)	10.9 (10.1-11.9)	0.84 (0.71-0.99)	p=0.033[b]
Patients with large cell carcinoma (N=153)	10.4 (8.6–14.1)	6.7 (5.5-9.0)	0.67 (0.48-0.96)	p=0.027[b]
Patients with NSCLC-NOS (N=252)	8.6 (6.8-10.2)	9.2 (8.1-10.6)	1.08 (0.81-1.45)	p=0.586[b]
Progression free survival				
All randomised patients including squamous NSCLC (N=1725)	4.8 (4.6 - 5.3)	5.1 (4.6 - 5.5)	1.04 (0.94 - 1.15)	Not reported
Patients with non-squamous histology (N=1252)	5.3 (4.7-5.5)	5.0 (4.6-5.4)	0.95 (0.84 – 1.06)	Not reported
Target patients: adenocarcinoma or large cell carcinoma(N=1000)	5.3 (4.8-5.7)	4.7 (4.4-5.4)	0.90 (0.79-1.02)	Not reported
Patients with adenocarcinoma (N=847)	5.5 (4.9-5.7)	5.0 (4.5-5.5)	0.90 (0.78-1.03)	Not reported
Patients with large cell carcinoma (N=153)	4.4 (3.0-5.8)	4.2 (3.5-4.7)	0.89 (0.65-1.24)	Not reported
Patients with NSCLC-NOS (N=252)	4.5 (4.0-5.5)	5.6 (4.7-5.9)	1.28 (0.99-1.67)	Not reported
Tumor response rate				
All randomised patients including squamous NSCLC (N=1725)	27.15%	24.68%	Not applicable	Not reported
Patients with non-squamous histology (N=1252)	28.64%	22.24%	Not applicable	Not reported
Target patients: adenocarcinoma or large cell carcinoma(N=1000)	Not reported	Not reported	Not applicable	Not reported
Patients with adenocarcinoma (N=847)	28.90%	21.65%	Not applicable	Not reported
Patients with large cell carcinoma (N=153)	27.63%	27.27%	Not applicable	Not reported
Patients with NSCLC-NOS (N=252)	Not reported	Not reported	Not applicable	Not reported

NSCLC-NOS= non-small cell lung cancer not otherwise specified
[a] noninferiority; [b] superiority

The ERG suggests caution in interpreting the p-values in Table 4.5 as they are p-values for each separate subgroup, unadjusted for testing for multiple comparisons. In the absence of corrections for multiple testing, p-values that are preferred are the p-values for the test for interaction. For the histology subgroup analysis, these were requested from the manufacturer and were reported to be p=0.0024 for squamous versus non-squamous and p=0.0059 across all subgroups. Taken alongside the findings emerging from an earlier trial of second-line

therapy,[2] this does add weight to the likelihood of there being real differences across subgroups, as opposed to the findings occurring by chance.

Analysis of the JMDB trial also included other pre-stated subgroup analyses, as outlined in the clinical study report (CSR).[15] These were by: age (<65 versus ≥65), sex (male versus female); ethnic origin (Caucasian versus East/Southeast Asian versus Other), smoking status (ever-smoker versus never-smoker), ECOG performance (PS=0 versus PS=1), method of diagnosis (histological versus cytological) and stage of disease (IIIB versus IV). None of these subgroup analyses were reported in the MS but it was reported in the CSR that only histology produced significant results.

Quality of life

No HRQoL results were presented in the MS; HRQoL is considered by the ERG to be another important outcome for this group of patients although it may be countered that as tolerability was assessed in the JMDB trial, HRQoL is addressed, albeit indirectly.

Tolerability

In the JMDB trial, all patients who received at least one dose of pemetrexed, gemcitabine, or cisplatin were evaluated for tolerability. This was a smaller patient population (n=1669) than that included in the efficacy analysis (n=1725) because 56 patients did not receive the allocated treatment (for a variety of reasons which were all specified in the MS).

With the exception of nausea, patients receiving pemetrexed reported fewer grade 3/4 toxicities than those receiving gemcitabine (Table 4.6). No data on other types of AEs such as all AEs or serious AEs were presented in the MS. Nor was any safety data presented by subgroup; the MS states that no clinically significant safety trends were identified suggesting that no one histology type subgroup experienced a different toxicity profile when compared to another subgroup or to the overall treated population. However, additional safety analysis was presented to the EMEA[16] which reported pemetrexed/cisplatin to compare favourably to gemcitabine/cisplatin (Table 4.7).

Patients receiving pemetrexed/cisplatin required significantly fewer transfusions compared with those on gemcitabine/carboplatin (

Table **4.8**). In addition, the administration of erythropoietic and granulocyte colony-stimulating factors was significantly lower in favour of pemetrexed/cisplatin. The lower use of haematopoietic-stimulating agents and transfusions for patients receiving

pemetrexed/cisplatin is consistent with the lower incidence of haematologic toxicities observed in the patients.

Table 4.6 Percentage of patients with CTC grade 3/4 drug related adverse events in the JMDB trial

Toxicity	pemetrexed/cisplatin (n=839)	gemcitabine/cisplatin (n=830)	p-value
Any CTC laboratory toxicity*	22.6%	39.9%	<0.001
Neutropenia	15.1%	26.7%	<0.001
Anaemia, haemoglobin	5.6%	9.9%	0.001
Thrombocytopenia, platelets	4.1%	12.7%	<0.001
Febrile neutropenia	1.3%	3.7%	0.002
Alopecia, any grade	11.9%	21.4%	<0.001
Nausea	7.2%	3.9%	0.004
Vomiting	6.1%	6.1%	1.000

CTC= common toxicity criteria

Table 4.7 All adverse events in the JMDB trial as reported to the EMEA[16]

	Number of patients with an event			
	Regardless of drug causality		Possibly drug related	
	pemetrexed/ cisplatin (n=839)	gemcitabine /cisplatin (n=830)	pemetrexed/ cisplatin (n=839)	gemcitabine /cisplatin (n=830)
Patients with ≥ 1 SAE	294 (35.0%)	315 (38.0%)	139 (16.6%)	136 (16.4%)
Serious, unexpected, reportable event	NA	NA	11 (1.3%)	4 (0.5%)
Discontinuation due to SAE	30 (3.6%)	46 (5.5%)	15 (1.8%)	23 (2.8%)
Deaths (on study)	63 (7.5%)	53 (6.4%)	9 (1.1%)	6 (0.7%)
Deaths (within 30 days of last dose)	13 (1.5%)	14 (1.7%)	0	0
Patients with ≥ 1 TEAE	812 (96.8%)	807 (97.2%)	751 (89.5%)	755 (91.0%)

AE=adverse event; NA=not applicable; SAE=serious adverse event; TEAE=treatment-emergent adverse event

Table 4.8 Concomitant medications and transfusions for all randomised patients in the JMDB trial

Concomitant medications/transfusions	pemetrexed/cisplatin	gemcitabine/cisplatin	p-value
Erythropoietin or darbepoetin	10.4%	18.1%	<0.001
Granulocyte colony-stimulating factors	3.1%	6.1%	0.004
Any transfusion	16.4%	28.9%	<0.001
Red blood cells	16.1%	27.3%	<0.001
Platelets	1.8%	4.5%	0.002

The EMEA[16] concluded that overall, the safety profile of pemetrexed/cisplatin in patients with NSCLC was consistent with the known safety profile in patients with mesothelioma. Taking into account the better haematotoxicity and the slightly worse nephrotoxicity profiles in

pemetrexed/cisplatin patients, this regimen was regarded as being safer than gemcitabine/cisplatin.

4.2.2 Indirect comparisons analysis

As only one head to head trial was identified comparing pemetrexed/cisplatin to another comparator (gemcitabine/cisplatin), an indirect comparisons analysis was also carried out by the manufacturer.

To identify studies for inclusion in the indirect comparisons analysis, a search of MEDLINE was conducted by the manufacturer. This is considered to be an incomplete search because at the very least EMBASE and the Cochrane Library should also have been searched. For this search, the strategies described in the MS were expanded to include other comparative studies of pemetrexed, docetaxel, gemcitabine, paclitaxel, vinorelbine, erlotinib, bevacizumab, and gefitinib. The manufacturer then applied criteria in order to ensure that only studies that could be mapped back to one of the two arms in the JMDB clinical trial would be included, effectively limiting inclusion to studies of gemcitabine/cisplatin. This identified two further phase III, open label RCT trials which compared gemcitabine/cisplatin with gemcitabibe/carboplatin[17] and docetaxel/cisplatin.[18] The ERG questions the reasoning for limiting studies to comparisons with gemcitabine/cisplatin, particularly when such a broad search strategy was employed.

Considering that the ERG believes trials examining all comparators specified in the scope should have been included in the indirect comparisons analysis, five further phase III RCTs would have been appropriate for consideration: one comparing gemcitabine/cisplatin to vinorelbine/cisplatin,[19] one comparing paclitaxel/carboplatin[20] to vinorelbine/cisplatin, two comparing docetaxel/carboplatin to vinorelbine/cisplatin[21, 22] and one comparing vinorelbine/carboplatin to gemcitabine/carboplatin.[23]

No validity assessment of the trials included in the indirect comparisons analysis was undertaken by the manufacturer although it was reassuring that the trials showed common characteristics (Appendix 2). A comparison of the baseline characteristics across all three of the trials in the indirect comparisons analysis was performed, the manufacturer stating that: "the patient characteristics were well balanced between the treatment groups and comparable to those of the JMDB trial." (MS, pg46) On examination of Table 13 in the MS (pg45), this is clearly not the case. While baseline characteristics were well balanced between treatment arms within trials, important differences were apparent across the three trials in terms of varying proportions of males, of patients with stage IV disease, histology type and

performance status. In particular, the differences in histology type (as summarised in Table 4.9) may be of particular relevance.

Table 4.9 Proportion of patients with specific NSCLC diagnoses in the trials included in the manufacturer's submission

Source	Squamous cell carcinoma	Adenocarcinoma	Large cell carcinoma	NSCLC–NOS
JMDB trial	27%	49%	9%	15%
Zatloukal 2003[17a]	51%	30%	7%	13%
Schiller 2002[18]	not reported	not reported	not reported	not reported

[a] Proportions of patients in this trial were only reported by treatment arm thus proportions for the whole population have been calculated by the ERG from data reported in the published paper

The unadjusted findings, as reported in the published papers of the individual studies are presented in Table 4.10, suggesting that the median OS and PFS was improved for pemetrexed/cisplatin in patients with squamous and non-squamous NSCLC when compared to the other comparators. In addition, despite subgroup analysis not being reported in any trial other than the JMDB trial, the manufacture presents findings by subgroup (Appendix 3) suggesting efficacy to be also improved in patients with non-squamous NSCLC and the manufacturer's defined target population. However, because of the statistical approach employed to generate these findings (highlighted below), the ERG believes the findings should be treated with caution

Table 4.10 Summary of the unadjusted trial results for all patients including squamous NSCLC taken from the individual trial reports

Study	Treatment arm	Median (range) OS (months)	Median (range) PFS (months)	Median response rate
JMDB trial (ITT population)[1]	pemetrexed/cisplatin (n=862) gemcitabine/cisplatin (n=863)	10.3 (9.8-11.2) 10.3 (9.6-10.9)	4.8 (4.6-5.3) 5.1 (4.6-5.5)	27% 25%
Zatloukal 2003[17]	gemcitabine/cisplatin (n=87) gemcitabine/carboplatin (n=89)	8.8 (6.7-10.5) 8.0 (6.9-11.4)	5.9 (4.3-6.7) 4.8 (4.0-5.6)	41% 29%
Schiller 2002[18]	gemcitabine/cisplatin (n=301) docetaxel/cisplatin (n=304)	8.1 (7.2-9.4) 7.4 (6.6-8.8)	4.2 (3.7-4.8) 3.7 (2.9-4.2)	22% 17%

The MS reports some differences in terms of tolerability between pemetrexed/cisplatin, gemcitabine/cisplatin and docetaxel/cisplatin with pemetrexed faring relatively well for febrile neutropenia (1.17% compared to 3.28% gemcitabine/cisplatin and 9.02% docetaxel/cisplatin), neutropenia (15.04% compared to 23.77% gemcitabine/cisplatin and 26.03% docetaxel/cisplatin) diarrhoea (0.98% compared to 1.84% gemcitabine/cisplatin and 6.15% docetaxel/cisplatin), anaemia (3.91% compared to 9.63% gemcitabine/cisplatin) and thrombocytopenia (2.93% compared to 10.45% gemcitabine/cisplatin). Pemetrexed/cisplatin

fared less well for fatigue (6.45% compared to 3.89% gemcitabine/cisplatin and 3.60% docetaxel/cisplatin). It is not reported if any of these differences are statistically significant.

While having less non-haematologic toxicity in terms of nausea and vomiting (statistically significant, p=0.013), gemcitabine/carboplatin was reported to be more haematoxic in terms of an increased incidence of thrombocytopenia than gemcitabine/carboplatin. These findings appear to be consistent with the meta-analyses which have examined differences in tolerability between cisplatin and carboplatin regimens.[10, 11] Indirect analysis comparisons reported gemcitabine/carboplatin patients to have the lowest rates of nausea/vomiting (2.92% compared to 13.28% pemetrexed/cisplatin, 9.22% gemcitabine/cisplatin and 5.53% docetaxel/cisplatin). However, in addition to issues with the statistical approach highlighted below, the findings should be treated with caution as they are based on observational data across trials in which the results by gemcitabine/cisplatin are not presented. Thus there may be differences in toxicity profiles for gemcitabine/cisplatin across the three trials.

The ERG has a number of concerns in relation to the statistical approach utilised to make indirect comparisons for a number of reasons. (i) It has been shown in the literature[24] that using a ratio of median survival times or survival rates at a particular point in time (as the manufacturer did) may result in serious under- or over-estimation of the treatment effect and major loss of statistical power. The HR incorporates changes over time, whereas the ratio of medians only takes one point on the survival curve into account. Other methods such as those proposed by Parmar[25] should be used to approximate the HR within a trial instead. (ii) It is widely recognised that indirect comparisons should be based on a comparison of relative effects rather than arm level estimates as the former maintains randomisation within a trial. The description in step 1, 2 and step 3 in the MS (pg42) suggests that the treatment arm level hazard rates have been used. Indeed results in table 16 and 20 of the MS suggest that arm level response rates and adverse events rate data are compared directly against each other without any recognition for randomisation within trial with any missing subgroup data assumed to be the same as gemcitabine/cisplatin. (iii) The key assumption of an indirect comparison is that the relative effects are exchangeable across the trial settings i.e. there are no treatment effect modifiers; within the JMDB trial there is clearly an effect modifier in the form of histology which should be accounted for in the indirect comparison. This would require HR estimates for the histology subgroups from all trials to be used in the calculations. The manufacturer uses estimates based on each subgroup of the JMDB study to adjust the other trial hazard ratios. However, it is not possible to confirm whether the relative effects of gemcitabine/carboplatin versus gemcitabine/cisplatin[17] or docetaxel/cisplatin versus gemcitabine/cisplatin[18] would be consistent across these subgroups as stated by the MS.

Individual patient data would be required to allow a complete and accurate analysis. As a further point to note, the JMDB trial HRs are from models adjusted for stratification factors which are not adjusted for across the other trials included in the indirect comparison.

4.3 Critique of submitted evidence synthesis

There is convincing evidence presented by the manufacturer from the good quality JMDB trial that pemetrexed/cisplatin is noninferior to and safer than, gemcitabine/cisplatin for the overall NSCLC population. For patients with non-squamous NSCLC and the manufacturer's defined target group of adenocarcinoma or large cell carcinoma, there is evidence that pemetrexed/cisplatin may be superior to gemcitabine/cisplatin. However, in UK practice gemcitabine/cisplatin is not used as often as gemcitabine/carboplatin. Gemcitabine/carboplatin was included in the indirect comparisons analysis; the results suggest that pemetrexed/cisplatin is also superior to gemcitabine/carboplatin. No significant differences were reported for tolerability regarding cisplatin regimens but gemcitabine/carboplatin reported less non-haematologic toxicity in terms of nausea and vomiting and more haematoxicity in terms of an increased incidence of thrombocytopenia than gemcitabine/cisplatin. However the ERG believes the efficacy and tolerability evidence cited in support of pemetrexed/cisplatin in relation to other comparators is less convincing because not all NICE recommended comparators were considered and the statistical analysis employed for the indirect comparisons presented in the MS had limitations. Thus the findings from the indirect comparisons analysis should be treated with caution.

4.4 Summary of clinical evidence

4.4.1 Clinical results

- The results of the JMDB trial showed that the median OS was noninferior in all NSCLC patients receiving pemetrexed/cisplatin compared with those receiving gemcitabine/cisplatin (10.3 months [95% CI: 9.8-11.2] versus 10.3 months [95% CI: 9.6-10.9]; p<0.001).
- The JMDB trial also reported patients with non-squamous NSCLC had significantly greater OS with pemetrexed/cisplatin (median 11.0 months [95% CI: 10.1-12.5]) than those receiving gemcitabine/cisplatin (median 10.1 months [95% CI: 9.3-10.9], adjusted HR=0.84 [95% CI: 0.74-0.96]; p=0.011); Pemetrexed/cisplatin was not reported to be superior to gemcitabine/cisplatin for the secondary endpoint of PFS: median 5.3 months (95% CI: 4.7-5.5) versus 5.0 months (95% CI: 4.6-5.4), adjusted HR=0.95 (95% CI: 0.84-1.06); Tumour response rates were higher for pemetrexed/cisplatin (28.64% versus 22.24%) but significance tests were not reported.
- More favourable findings are suggested for the manufacturer's defined target population of patients with adenocarcinoma or large cell carcinoma.
- Pemetrexed/cisplatin appears to have a more favourable safety profile than gemcitabine/cisplatin.
- The manufacturer also presents evidence from an indirect comparison analysis to support the argument that pemetrexed/cisplatin compares favourably with gemcitabine/carboplatin and docetaxel/cisplatin in terms of efficacy and tolerability.

4.4.2 Clinical issues and uncertainties

- While the presented subgroup analysis of patients with non-squamous NSCLC and patients in the manufacturer's defined target population were a secondary (pre-defined) objective of the JMDB trial, the findings warrant further exploration.
- Identifying patients in the manufacturer's defined target population requires more specific histological testing than is standard across all UK centres at present.
- The proportion of patients with non-squamous NSCLC who would be diagnosed with adenocarcinoma or large-cell carcinoma is currently unknown.
- Because of the exclusion of key comparators from the indirect comparisons analysis and the assumptions underlining the statistical approach employed, the findings from this analysis should be treated with caution.

5 ECONOMIC EVALUATION

5.1 Introduction

This section provides a structured critique of the economic evidence submitted by the manufacturer. The two key components of the economic evidence presented in the MS are (i) a systematic review of the relevant literature, and (ii) a report of the manufacturer's *de novo* economic evaluation. Due to problems with the manufacturer's model, however, a total of three submissions and one addendum were provided (see section 5.5.1 for a detailed history of model versions). Our critique of the manufacturer's economic evaluation is based on the third and final version of the MS (dated 21st January 2009) and the addendum (dated 23rd January 2009). See Table 5-1 for a summary of key information points in the MS and addendum.

Table 5-1 Key information in the MS

Key information	**Pages in the MS (Addendum – no page numbers)**	**Key tables/figures in the MS (Addendum)**
Details of the systematic review of the literature	MS pg54-60	MS Tables 21-22
Technology, patients, comparator, perspective and time horizon	MS pg61-65	
Framework for model-based evaluation	**(Addendum – no page numbers)** MS pg65-74	**(Addendum Table 23a)** MS Tables 24-30; Figure 13
Assumptions incorporated in model	MS pg74-79	MS Table 31
Clinical evidence used in economic evaluation	MS pg80-81	
Measurement and valuation of health effects	MS pg81-84	MS Table 32-33
Resource identification, measurement and valuation	MS pg84-91	MS Tables 34-42
Methods of sensitivity analysis and statistical analysis	MS pg91-95	
Model validity	MS pg95	MS Table 43
Results – base case analysis	**(Addendum – no page numbers)**	**(Addendum Tables 44-51)**
Results – subgroup analysis	**(Addendum – no page numbers)**	**(Addendum Tables 52-59)**
Results – sensitivity analysis	**(Addendum – no page numbers)**	**(Addendum Tables 60-61 and unnumbered table)**
Model validity – modelled life years gained versus mean survival	MS pg116	MS Table 62
Drivers of economic results	MS pg116-117	
Interpretation of economic evidence	MS pg117-118	
Assessment of factors relevant to the NHS and other parties	MS pg119-124	MS Tables 63-69

5.2 Overview of manufacturer's cost-effectiveness review

The manufacturer undertook a systematic review of the economic literature, interpreting the aim of this exercise to include all studies relevant to the development of an economic model. They state: "The literature review to support the economic evaluation has a number of

requirements: to identify efficacy, cost and utility data and also to identify cost-effectiveness models to inform the structure and development of the model and cost-effectiveness studies including the comparators being evaluated" (MS, pg54).

The manufacturer identified the clinical efficacy literature using the search strategy and methods outlined in the clinical section of the MS. This has already been discussed (see section 4 above), and is not considered further here.

With regard to the cost and utility data and the cost-effectiveness literature, the manufacturer states: "Having recently carried out an extensive literature review for the submission of pemetrexed in the second-line setting for NSCLC, we address the remaining points by updating that search" (MS, pg54). Details of this updated search are described below.

5.2.1 Identification and description of studies

The manufacturer updated a previous search strategy (from pemetrexed for the second-line treatment of NSCLC); brief details of the initial search and the update are provided in Appendix 10.3 of the MS. Key databases such as Ovid Medline (R), EMBASE and CRD NHS Economic Evaluation Database were searched. The updated search covered the period from 2006-2008.

The pre-specified inclusion/exclusion criteria were described as:

1) Inclusion criteria:
    a. Non-small cell lung cancer
    b. Advanced
    c. First-line setting
    d. An economic model
    e. The intervention under consideration had to be a chemotherapy
    f. Full journal article
    g. Original articles
2) Exclusion criteria
    a. Abstracts only
    b. Critiques/structured abstracts
3) Limits
    a. English language
    b. Last 10 years
    c. Duplicates removed

Using these criteria the manufacturer identified a total of 208 studies, of which 203 were excluded (no further details provided in the MS). The five remaining studies were retrieved in full and after reading only one was subsequently included (the manufacturer does not state which study this is, but presumably it is Maniadakis[26]).

In terms of economic evaluations, a table of included studies is presented in Appendix 10.3 of the MS which includes three economic evaluations; however, in the main body of the report (MS pg55-57), four economic studies are presented (Maniadakis being the addition[26]). The reason for this discrepancy is unclear but it is probably due to a simple formatting error. No quality assessment of included economic evaluations was presented in the MS. The ERG notes that none of the identified studies included pemetrexed as a comparator, and so the studies are not directly related to the decision problem described in the final scope.

Using this search the manufacturer also identified two cost analyses and ten utility studies, though it is unclear what inclusion criteria were utilised. Quality assessment of these studies was not presented.

5.2.2 Summary and conclusions

The manufacturer's review of the published cost-effectiveness evidence was confusing and poorly described. Nevertheless, the ERG is reasonably confident that no published economic evaluations of pemetrexed for the first-line treatment of NSCLC were missed.

5.3 Overview of manufacturer's economic evaluation

The manufacturer undertook a *de novo* economic evaluation of pemetrexed in combination with cisplatin for the first-line treatment of patients with locally advanced or metastatic NSCLC, other than predominantly squamous cell histology.

5.3.1 Description of manufacturer's economic model

The manufacturer used a Markov structure to model the costs and outcomes associated with pemetrexed/cisplatin versus gemcitabine/cisplatin (with gemcitabine/carboplatin and docetaxel/cisplatin as secondary comparators). A schema of the manufacturer's model is presented in Figure 5.1.

All clinically important events were modelled via transition probabilities. The passage of time was divided into three-weekly cycles, which corresponds with the length of a chemotherapy treatment cycle. The model has three main health states, which replicate those in the JMDB study:[1] response, stable disease and progression. There is also a death state, which is all absorbing. Each health state has a utility attached to it per cycle. States during the treatment phase also have treatment costs attached per cycle. In the post-treatment phase, progression has a best supportive care (BSC) cost attached to it per cycle. Stable disease or responding in the post-treatment phase have utility values attached per cycle but no costs, as it is assumed the extra costs associated with BSC are only required once the disease has progressed.

Seven AE states (neutropenia, nausea and vomiting, fatigue, diarrhoea, anaemia, thrombocytopenia, febrile neutropenia) are built into the model as separate states that can be added to the stable disease or treatment response health states. Each AE is mutually exclusive, which means that patients can experience only one AE at a time but as they move through the model they may experience more AEs. Each AE is also bounded within a cycle (i.e. starts and finishes within the same cycle); the exception is neutropenia which is assumed to last for the duration of treatment. Adverse events have associated disutilities, costs and for febrile neutropenia, risk of death (3.9%, taken from a published study).

All patients enter the model in a baseline stable state and from here patients can stay in the stable state or move to response or progression. It is assumed that patients who move into response remain in that state until they enter progression. Patients in progression, entering from either stable or response, move either into second-line treatment or death. During each cycle, each member of the cohort may remain in the same health state or move to another state; the exception is death. Patients can be stable or responding while on active treatment or after treatment has ended. The model captures this latter option, after treatment has ended, in the two health states post-treatment stable and post-treatment response. Patients can also discontinue treatment, through their choice, physician choice or following an AE. These patients are included in the progression state as it is assumed that treatment discontinuation leads directly to disease progression.

Second-line therapy is received by approximately 53% (pemetrexed/cisplatin) and 56% (gemcitabine/cisplatin) patients based on JMDB trial[1] data. In the model, second-line treatment is a single state in which costs are incurred as a lump sum as the patients enter the state; no additional benefit is accrued and no utility value is attached.

In relation to the issue of first-line and second-line chemotherapy the manufacturer states that:

"It is not possible to disaggregate the effect of first-line therapy from second-line therapy in the overall efficacy results. Therefore, the simplifying assumption was made, that all second-line therapies have equivalent efficacy, safety and duration. Costs associated with docetaxel and erlotinib are assumed to be equal in the light of the FAD [final appraisal determination] for erlotinib which recommends erlotinib based on the premise that it has equivalent efficacy, and should therefore have equivalent cost, to docetaxel" (MS, pg67).

The model was extrapolated beyond the 30 month JMDB trial[1] up to six years. To achieve this, the median values for OS observed in the JMDB trial[1] were converted into a per cycle

risk of death (transition probability). This per cycle risk of death was then used to extrapolate the data to six years.

A continuation rule was also incorporated into the manufacturer's model. The manufacturer states:

"The continuation rule is based on the separation of patients into those who respond and those who do not respond to chemotherapy. Essentially, those who respond to chemotherapy receive the maximum of four cycles of treatment; those who do not respond receive only three cycles of therapy" (MS, pg62).

The manufacturer concedes that, "The continuation rule implemented in the model prevents patients from responding in cycles 4 onwards, so under-reporting response rates compared with the trial", but does not appear to consider this an issue (MS, pg62). The ERG, however, believes that the ability of the model to replicate the trial results upon which it is based (i.e. JMDB[1]) is a fundamental requirement. Ignoring this fact raises serious questions about model validity. This is discussed in greater detail in section 5.5 below.

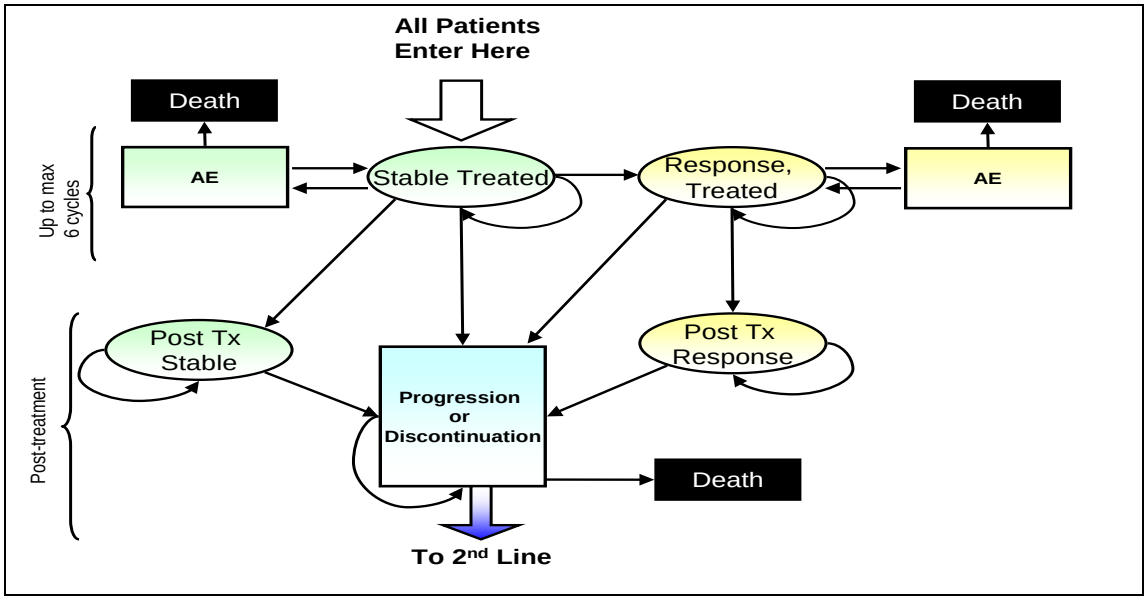

Figure 5.1 Schema of manufacturer's model

5.3.2 Parameters and values

Key parameters and values used in the manufacturer's model are presented below in Table 5-2 to Table 5-8.

Table 5-2 Utility values for health states and adverse events in the MS

Health State	Assigned Utility Value/Disutility
Stable	0.65
Response	0.67
Progression	0.47
Febrile Neutropenia	-0.090
Neutropenia	-0.089
Fatigue	-0.073
Diarrhoea	-0.047
Nausea/Vomiting	-0.048
Anaemia	-0.073 (Considered same disutility as fatigue)
Thrombocytopenia	-0.089 (Considered same disutility as neutropenia)

Table 5-3 Overall survival model inputs

	Pemetrexed/ cisplatin	Gemcitabine /cisplatin	Gemcitabine /carboplatin	Docetaxel/ cisplatin
Non-squamous	**n=618**	**n=634**	**n=89**	**n=289**
Median overall survival (months) (95% CI)	11.0 (10.1-12.5)	10.1 (9.3-10.9)	9.2 (6.7-17.2)	9.5 (8.0-11.5)
Overall survival hazard ratio (95% CI) relative to gemcitabine/cisplatin	0.84 (0.74-0.96)		1.1 (1.52-0.59)	1.06 (0.88-1.27)
Adenocarcinoma	**n=436**	**n=411**	**n=89**	**n=289**
Median overall survival (months) (95% CI)	12.6 (10.7-13.4)	10.9 (10.1-11.9)	10.0 (7.2-18.6)	10.3 (8.7-12.5)
Overall survival hazard ratio (95% CI) relative to gemcitabine/cisplatin	0.84 (0.71-0.99)		1.1 (1.52-0.59)	1.06 (0.88-1.27)
Large cell carcinoma	**n=76**	**n=77**	**n=89**	**n=289**
Median overall survival (months) (95% CI)	10.4 (8.6–14.1)	6.7 (5.5-9.0)	6.1 (4.4-11.4)	6.3 (5.3-7.6)
Overall survival hazard ratio (95% CI) relative to gemcitabine/cisplatin	0.67 (0.48-0.96)		1.1 (1.52-0.59)	1.06 (0.88-1.27)

CI=confidence interval

Table 5-4 Response rates – ITT population for all histology groups following the response rate amendment.

	Pemetrexed/ cisplatin	Gemcitabine/ cisplatin	Gemcitabine/ carboplatin	Docetaxel/ cisplatin
Non-squamous histology (without continuation rule)	**n=618**	**n=634**	**n=89**	**n=289**
Response rate	25.89%	20.35%	14.36%	16.09%
% of responding patients who respond during the first three cycles of treatment	61.88%	68.99%	68.99%	68.99%
Non-squamous histology (with continuation rule)	**n=618**	**n=634**	**n=89**	**n=289**
Response rate	25.89%	20.35%	14.36%	16.09%
% of responding patients who respond during the first three cycles of treatment	66.88%	70.54%	70.54%	70.54%
Adenocarcinoma	**n=436**	**n=411**	**n=89**	**n=289**
Response rate	25.23%	18.98%	13.40%	15.01%
% of responding patients who respond during the first three cycles of treatment	65.45%	70.51%	70.51%	70.51%
Large cell carcinoma	**n=76**	**n=77**	**n=89**	**n=289**
Response rate	27.63%	25.97%	18.34%	20.54%
% of responding patients who respond during the first three cycles of treatment	85.71%	80.00%	80.00%	80.00%

Table 5-5 Proportion of patients who experience a grade 3/4 adverse event in any cycle of the model

	Pemetrexed/ cisplatin (n=618)	Gemcitabine/ cisplatin (n=634)	Gemcitabine/ carboplatin (n=89)	Docetaxel/ cisplatin (n=289)
Neutropenia	14.90%	25.62%	25.62%	28.06%
Nausea/ Vomiting	14.24%	10.34%	3.27%	6.21%
Fatigue	6.62%	4.43%	4.43%	4.17%
Diarrhoea	1.16%	1.48%	1.48%	4.93%
Anaemia	4.97%	10.18%	10.18%	5.45%
Thrombocytopenia	3.64%	10.84%	10.84%	10.84%
FN – Cycle 1	0.12%	1.80%	1.80%	4.95%
FN – Cycle 2	0.24%	0.42%	0.42%	1.17%
FN – Cycle 3+	0.96%	1.06%	1.06%	2.91%

FN=Febrile neutropenia

Table 5-6 Chemotherapy costs used in the model

	Mean cost per patient per cycle	Mean number of cycles per patient**	Mean total cost per patient
Pemetrexed/cisplatin	£1440 + £75.59	3.80	£5,759.24
Gemcitabine/cisplatin	(£390.62 x 2*) + £75.59	3.81	£3,264.52
Gemcitabine/carboplatin	(£390.62 x 2*) + £190.89	3.75	£3,645.49
Docetaxel/cisplatin	£1023 + £75.59	3.79	£4,163.66

*Day 1 and Day 8 gemcitabine administration. ** mean number of cycles for non-squamous population without the continuation rule applied.

Table 5-7 Chemotherapy administration costs used in the model

	Resource utilisation	Unit cost	Total per cycle
Pemetrexed/cisplatin	1 x HRG SB14Z (inpatient)	£430	£430
Gemcitabine/cisplatin	1 x HRG SB14Z (inpatient) 1 x HRG SB15Z (outpatient)	£430 £189	£619
Gemcitabine/carboplatin	1 x HRG SB14Z (outpatient) 1 x HRG SB15Z (outpatient)	£179 £189	£368
Docetaxel/cisplatin	1 x HRG SB14Z (inpatient)	£430	£430

SB12Z = deliver simple parental chemotherapy at 1st attendance; SB13Z = Deliver more complex chemotherapy at 1st attendance; SB14Z = deliver complex chemotherapy including prolonged infusional treatment at 1st attendance; SB15Z = deliver subsequent elements of a chemotherapy cycle

Table 5-8 Adverse events costs used in the model

Adverse event	Unit cost
Neutropenia	£330.93
Nausea and vomiting	£700.79
Fatigue	£38.90
Diarrhoea	£867.12
Anaemia	£615.04
Thrombocytopenia	£314.69
Febrile neutropenia	£1720.00

5.3.3 Treatment effectiveness within the MS

In the MS the following treatment effects are considered: OS, PFS, response rates, AEs and QoL (utility). All effectiveness data used in the model, apart from QoL (which is discussed separately below in section 5.3.6), are trial based. The efficacy data for the primary comparison of pemetrexed/cisplatin and gemcitabine/cisplatin are based on the JMDB trial,[1] and are as described in section four of the ERG report and shown in Table 5-3 above. For the secondary comparisons (gemcitabine/carboplatin and docetaxel/cisplatin) two RCTs were used and indirect analysis methodology was utilised, which is also described in section four of the ERG report.

As the model had a time horizon of up to six years - well beyond any of the trials - it was necessary to extrapolate the clinical results. The manufacturer did this by using median OS figures and converting them into transition probabilities (per cycle risk of death), assuming an exponential survival model. The ERG notes that the published survival curves do not appear to follow exponential trajectories. Furthermore, the fit of the modelled survival to the published curves is poor, leading to underestimation of survival in the model.

5.3.4 Population

The population in the economic evaluation is limited to patients with non-squamous NSCLC who are not amenable to surgery. The manufacturer further limits this to patients with adenocarcinoma and large cell carcinoma, excluding NSCLC-NOS patients due "their poor survival". As the model is based on trial data, "there is an assumption of good performance status, an ECOG PS of 0 or 1". Furthermore, as this is a first-line therapy, patients are considered to be chemotherapy naïve.

5.3.5 Comparator technology

In the economic evaluation, pemetrexed/cisplatin is primarily compared with gemcitabine/cisplatin, which was the comparison used in the head-to-head RCT, JMDB.[1] Two secondary comparators were also considered: gemcitabine/carboplatin and docetaxel/cisplatin using indirect comparison methodology.

The ERG notes that neither vinorelbine nor paclitaxel were considered as relevant comparators in the MS, both of which were specified in the final scope issued by NICE. The manufacturer does not justify this exclusion but simply states that, "The total market share of these combinations is only approximately 15% of the first-line NSCLC market" (MS, pg41). The ERG further notes that the market share of vinorelbine (11%) as presented in supplementary material provided by the manufacturer,[9] is greater than that of docetaxel (4%). Therefore, the manufacturer's inclusion of docetaxel but exclusion of vinorelbine based on market share data appears incongruous.

5.3.6 Health related quality of life

The manufacturer states that: "Quality of life data were not collected as part of the JMDB study, or reported by Schiller et al. (2002) or Zatloukal et al. (2003)" (MS, pg82). The manufacturer therefore undertook a literature review of the utility data related to patients with NSCLC and identified a number of studies; none of which were deemed suitable for inclusion. Instead, a manufacturer sponsored study, Naffes et al., (2008),[27] was utilised, which was commissioned for second-line NSCLC but considered applicable to a first-line

setting. This study involved 100 members of the general public, who were recruited through a local London newspaper and each paid £25 for their time. The health states described in this process were progressive disease, stable disease and responding disease, together with several toxicities: neutropenia, febrile neutropenia, nausea/vomiting, diarrhoea, rash and fatigue. The visual analogue scale (VAS) and standard gamble (SG) interview technique were used to elicit societal valuations from members of the general public. The health state valuations from the SG interview technique were analysed using a mixed model analysis with random effects on the participant level to determine the change in utility score associated with moving between stages of disease and from no toxicity to one of the toxicities specified. The raw data were transformed using a logistic transformation (transformed utility= log ((1-utility)/utility)). See Table 5-2 above (section 5.3.2) for a list of the utility values for all disease states and toxicities presented in the MS.

The manufacturer states that, "The values obtained in this study were consistent with other published utility estimates in this disease area but add further detail on the impact of toxicity on NSCLC patients' lives" (MS, pg83). They present a table of published utility studies (MS, pg83) which shows utilities ranging from 0.33 for end of life to 0.71 for responding disease. This is in line with those used in the MS, however the ERG notes that end of life is not explicitly considered in the model, only progression. Hence, the utility associated with the last few weeks of a modelled patient's life may be optimistic compared to values observed in real world patients.

5.3.7 Resources and costs

The following resource use and unit costs were identified by the manufacturer (MS, pg84), as follows:

Medication
- Chemotherapy and platinum acquisition
- Concomitant medication (assumed to be incorporated into the NHS HRGs used, however we report the values to show they are relatively inexpensive)

Administration
- Chemotherapy administration (NHS HRGs were used which include concomitant medications)

Adverse events
- Febrile neutropenia
- Neutropenia
- Nausea and Vomiting
- Fatigue
- Diarrhoea
- Anaemia
- Thrombocytopenia

Best supportive care

Palliative care

The manufacturer states: "Only minimal resource utilisation rate data were collected as part of the JMDB trial" (MS, pg85). This included data on rates of transfusions and rates of AEs. Due to this data deficit, several non-trial sources of resource data were utilised by the manufacturer, including published literature and expert opinion.

Costs data were based on British National Formulary (BNF) prices for drugs, UK NHS reference costs for services and published literature (inflated as required, to a base year of 2008). See Table 5-6 to Table 5-8 above (section 5.3.2 of ERG report) for a list of some of the key costs included in the manufacturer's model.

5.3.8 Perspective, time horizon and discounting

Costs are estimated from the perspective of the NHS (in line with NICE guidance) and outcomes are equally in line with NICE guidance being expressed as quality adjusted life years (QALYs); both of which are captured over a six year time horizon. The manufacturer interprets six years as a lifetime model as most patients do not live beyond this period. Both costs and benefits are discounted at a rate of 3.5%, which is also in line with current NICE guidance.

5.3.9 Model validation

To validate the modelled data against the clinical trial, the manufacturer compared trial medians and means with the means produced in the model (see MS, pg117: Table 62). No other model validation is reported in the MS.

5.3.10 Results included in the MS

Base case results

The base case results (non-squamous population) of the manufacturer's model are presented below in Table 5-9, with and without the continuation rule applied. The incremental cost-effectiveness ratio (ICER) for pemetrexed/cisplatin versus gemcitabine/cisplatin in the non-squamous population is £33,065 without the continuation rule, and £25,967 with the continuation rule applied.

Table 5-9 Costs per additional LYG and QALY gained for non-squamous population.

	Comparison with pemetrexed/cisplatin	Incremental QALY	Incremental Cost	ICER (Incremental cost per QALY)
Without continuation rule	versus gemcitabine/cisplatin	0.041	£1,364	£33,065
	versus gemcitabine/carboplatin	0.092	£1,988	£21,585
	versus docetaxel/cisplatin	0.075	£1,380	£18,401
With continuation rule	versus gemcitabine/cisplatin	0.048	£1,252	£25,967
	versus gemcitabine/carboplatin	0.094	£1,834	£19,540
	versus docetaxel/cisplatin	0.081	£1,184	£14,675

Subgroup results

The results for the subgroups are presented below in Table 5-10, split into adenocarcinoma and large cell carcinoma. All results are with the continuation rule applied. The ICER for pemetrexed/cisplatin versus gemcitabine/cisplatin is £18,442 in the adenocarcinoma subgroup, and £8,056 in the large cell subgroup.

Table 5-10 Costs per additional LYG and QALY gained for patients with adenocarcinoma and large cell carcinoma.

	ICER of pemetrexed/cisplatin	Incremental QALY	Incremental Cost	ICER (Incremental cost per QALY)
Adeno-carcinoma	versus gemcitabine/cisplatin	0.07	£1,346	£18,442
	versus gemcitabine/carboplatin	0.13	£1,927	£14,887
	versus docetaxel/cisplatin	0.11	£1,270	£11,179
Large cell carcinoma	versus gemcitabine/cisplatin	0.18	£1,466	£8,056
	versus gemcitabine/carboplatin	0.23	£2,066	£9,086
	versus docetaxel/cisplatin	0.21	£1,401	£6,579

5.3.11 Sensitivity analyses

The manufacturer conducted both scenario analysis (one-way) and probabilistic sensitivity analysis (PSA). The manufacturer's scenario analysis (taken from the Addendum dated 23 January 2009) is shown in Table 5-11 below, for both the base case population and the subgroup populations. The scenario analysis demonstrates that the model is most sensitive to changes in chemotherapy costs and survival estimates. In conclusion, the manufacturer states that: "The scenario analysis demonstrates that pemetrexed/cisplatin is a cost-effective therapy

compared to gemcitabine/cisplatin if a continuation rule is applied or used within the target population [of patients with adenocarcinoma or large cell carcinoma]."(Manufacturer's Addendum, 23 January 2009)

Details of the updated PSAs (cost-effectiveness and CEAC plots) were not included in this addendum and therefore have not been included here.

Table 5-11 Manufacturer's scenario analysis results

	No continuation rule	Continuation rule	Continuation rule	Continuation rule
Base case	**Non-squamous ICER=£33,065**	**Non-squamous ICER=£25,967**	**Adenocarcinoma ICER =£18,442**	**Large cell carcinoma ICER=£8,056**
Costs				
All costs decreased by 25%	£25,416	£20,009	£14,441	£6,731
Chemotherapy costs decreased by 25%	£20,867	£16,721	£12,265	£5,726
Chemotherapy costs increased by 25%	£45,263	£35,213	£24,620	£10,386
All costs (excluding chemotherapy drugs) decreased by 25%	£37,614	£29,255	£20,618	£9,061
All costs (excluding chemotherapy drugs) increased by 25%	£28,284	£22,504	£16,155	£6,993
Per mg costing	£36,880	£28,779	£20,302	£8,815
HRG procurement and delivery costs applied	-£60,401	-£43,625	-£27,716	-£10,384
	PEMETREXED DOMINATES	PEMETREXED DOMINATES	PEMETREXED DOMINATES	PEMETREXED DOMINATES
Chemotherapy administration costs - Lower quartile from HRG (£210)	£33,056	£25,777	£18,285	£8,097
Chemotherapy administration costs - upper quartile from HRG (£795)	£33,080	£26,282	£18,704	£7,987
BSC/palliative care decreased by 25%	£33,113	£26,010	£18,498	£8,103
BSC/palliative care increased by 25%	£33,017	£25,924	£18,387	£8,009
Cost of FN increased to £3884 (from £1720)	£32,282	£25,276	£17,921	£7,959
Gemcitabine drug acquisition cost discount of 20%	£45,275	£34,987	£24,413	£10,482
Pemetrexed drug acquisition cost discount of 20%	£8,865	£9,092	£7,231	£3,639
Second-line costs excluded	£35,813	£28,322	£19,992	£8,678
Half cycle correction included	£32,212	£26,066	£18,490	£8,060

ICER, FN, BSC

	No continuation rule	Continuation rule	Continuation rule	Continuation rule
Base case	**Non-squamous ICER=£33,065**	**Non-squamous ICER=£25,967**	**Adenocarcinoma ICER =£18,442**	**Large cell carcinoma ICER=£8,056**
Resource use				
Hospital days for AEs decreased by 50%	£33,616	£26,330	£18,638	£8,242
Hospital days for AEs increased by 50%	£32,514	£25,604	£18,246	£7,870
Utility				
Disutility assigned to AEs decreased by 50%	£33,656	£26,283	£18,565	£8,089
Disutility assigned to AEs increased by 50%	£32,495	£25,658	£18,322	£8,023
Assume no disutility assigned to AEs (so only have a cost impact in model)	£34,268	£26,607	£18,688	£8,122
Utility weights assigned to health states all lower of 95% confidence interval	£37,375	£28,591	£20,793	£9,230
Utility weights assigned to health states all upper of 95% confidence interval	£29,648	£23,807	£16,569	£7,142
Efficacy				
Lower 95% limit for pemetrexed survival	GEMCITABINE DOMINATES	GEMCITABINE DOMINATES	GEMCITABINE DOMINATES	GEMCITABINE DOMINATES
Upper 95% limit for pemetrexed survival	£13,210	£11,543	£11,503	£5,058
Lower 95% limit for gemcitabine survival	£17,414	£14,852	£12,757	£6,569
Upper 95% limit for gemcitabine survival	GEMCITABINE DOMINATES	£205,992	£56,097	£21,502
Patient population				
Mean body surface area (BSA) 1.6m^2	£30,730	£24,108	£17,189	£7,624
Mean body surface area 2.0m^2	£40,487	£31,584	£22,183	£9,499

Base case	No continuation rule Non-Squamous ICER=£33,065	Continuation rule Non-squamous ICER=£25,967	Continuation rule Adenocarcinoma ICER=£18,442	Continuation rule Large cell carcinoma ICER=£8,056
Model parameters				
Time horizon 2 years	£44,664	£33,428	£25,704	£7,754
Time horizon 4 years	£33,799	£26,428	£19,022	£8,021
Discounting rates				
Discounting rates 0% for costs and benefits	£32,011	£25,235	£17,865	£8,048
Discounting rates 6% for costs and benefits	£33,803	£26,478	£18,849	£8,063

*The cost per QALY for the non-squamous population reflects pemetrexed's licensed population: adenocarcinoma, large cell carcinoma and the non-small cell lung cancer not otherwise specified (NSCLC-NOS) patients. The statistically significant survival advantage of pemetrexed/cisplatin compared with gemcitabine/cisplatin observed in the adenocarcinoma and large cell group is not seen in the NSCLC-NOS group, which is why the cost per QALY increases. The HRG costs for procurement and delivery are as follows
Pemetrexed/cisplatin £1294; gemcitabine/cisplatin £2020; gemcitabine/carboplatin £1523; docetaxel/cisplatin £181

5.4 Assessment of the manufacturer's economic model

Table 5-12 tests how closely the manufacturer's submitted economic evaluation accords with the requirements for a base case analysis as set out in the NICE reference case checklist,[28] and Table 5-13 summarises the ERG's appraisal of the economic evaluation conducted by the manufacturer using the Drummond 10-point checklist.[29]

In general, it can be seen that the manufacturer's economic evaluation does not fully adhere to the NICE reference case, in particular with regards to the inclusion of all relevant comparators. Similarly, the manufacturer's economic evaluation does not satisfy the Drummond checklist,[29] again due to the omission of key comparators, but also due to problems with valuing outcomes and use of indirect methodology. See section 5.5 for a detailed critique of the manufacturer's economic model.

Table 5-12 NICE reference case checklist[28]

Attribute	Reference case	Does the *de novo* economic evaluation match the reference case?
Comparator(s)	Therapies routinely used in the NHS, including technologies regarded as current best practice	Therapies routinely used in the NHS include, gemcitabine, vinorelbine, docetaxel and paclitaxel in combination with a platinum. The manufacturer **did not** include vinorelbine or paclitaxel
Perspective costs	NHS and Personal Social Services (PSS)	The economic evaluation is carried out from the perspective of the NHS. No PSS costs are described in the MS
Perspective benefits	All health effects on individuals	Health effects to the individual are captured via QALYs
Form of economic evaluation	Cost-effectiveness analysis	Cost-effectiveness analysis
Time horizon	Sufficient to capture differences in costs and outcomes	The time horizon chosen was a lifetime horizon, which for this patient group was believed to be within six years. This appears appropriate
Synthesis of evidence on outcomes	Systematic review	All outcome data are derived from RCTs. Indirect methodology was utilised, although this was **not** applied correctly
Outcome measure	Quality adjusted life years (QALYs)	QALYs were used, which is appropriate
Health states for QALY	Described using a standardised and validated instrument	Quality of life data were not available from any of the trials, therefore a published QoL study was utilised. This is **not** ideal but the utility values appear to be reasonable
Benefit valuation	Time-trade off or standard gamble	The QoL study utilised SG interview techniques, which is acceptable
Source of preference data for valuation of changes in HRQL	Representative sample of the public	The QoL study was based on responses from 100 members of the general public. It is not clear how representative this sample is
Discount rate	An annual rate of 3.5% on both costs and health effects	Benefits and costs, where appropriate, have been discounted using the 3.5% rate
Equity	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	All QALYs estimated by the economic model have the same weight
Sensitivity analysis	Probabilistic sensitivity analysis (PSA)	PSA was undertaken by the manufacturer.

MS=manufacturer submission; RCT=randomised controlled trial; QoL=quality of life; QoL=quality of life questionnaire; ERG=Evidence Review Group; SG=standard gamble

Table 5-13 Critical appraisal checklist[29]

Item	Critical appraisal	ERG comment
Was a well-defined question posed in answerable form?	No	The manufacturer did not fully address answer the decision problem as not all comparators were included in the analysis, namely vinorelbine and paclitaxel
Was a comprehensive description of the competing alternatives given?	Yes	The manufacturer described the chosen comparators adequately
Was the effectiveness of the programme or services established?	No	Evidence from the JMDB trial demonstrated the clinical noninferiority of pemetrexed/cisplatin compared to gemcitabine/cisplatin. The trial was not powered to detect subgroup analyses, which the manufacturer relies on heavily in the model. Also, for the comparisons with docetaxel/cisplatin and gemcitabine/carboplatin, the manufacturer conducted indirect analysis, however, the methodology employed to achieve this was flawed
Were all the important and relevant costs and consequences for each alternative identified?	Yes	Key costs and consequences were identified
Were costs and consequences measured accurately in appropriate physical units?	Not consistently	For example, the BSA value used to calculate chemotherapy costs does not represent NSCLC patients in the UK
Were the cost and consequences valued credibly?	No	For example, modelled OS and PFS were inaccurate and overestimated some trial values
Were costs and consequences adjusted for differential timing?	Yes	The method of discounting was appropriate
Was an incremental analysis of costs and consequences of alternatives performed?	Yes	ICERs (cost per QALY gained and cost per LYG) were presented for the base case population and subgroups
Was allowance made for uncertainty in the estimates of costs and consequences?	Yes	Univariate SA and PSA were undertaken by the manufacturer
Did the presentation and discussion of study results include all issues of concern to users?	No	Not all comparators have been included

ERG= Evidence Review Group; BSA=body surface area; MS=manufacturer submission; QALY=quality adjusted life year; LYG=life year gained; SA=sensitivity analysis; PSA=probabilistic sensitivity analysis; ICER=incremental cost-effectiveness ratio

5.5 Detailed critique of manufacturer's economic model

5.5.1 History of model versions

As part of the MS an economic model was made available to the ERG on 5th December 2008. After a day spent analysing the model, the ERG identified a serious problem concerning model predictions of OS, such that a proportion of patients could never die (14% of pemetrexed patients). The errors had a strong influence on the cost-effectiveness results. This was traced to two straightforward coding spreadsheet errors, and in accordance with previous discussions with NICE and representatives of pharmaceutical manufacturers, the ERG immediately notified the manufacturer via NICE of the problem and invited them to amend the economic results in their submission document. The communication from the ERG stated that:

"This information is drawn to your attention immediately, since you may wish to consider a thorough quality review of the submitted model, and possible amendments to the results in the submitted evidence before the ERG continue their consideration of that evidence. It must be emphasised that this is only the first substantive problem identified after 1 day spent exploring the model, and other problems may be found."

On December 15th 2008 a modified submission including a revised version of the model was received from the manufacturer. Following detailed examination of the revised model by the ERG another serious discrepancy was identified; it proved impossible to replicate the JMDB chemotherapy response rates within the revised model, which are primary model drivers of outcomes and costs. The cause of this new problem appeared to relate to a combination of the model structure and a misunderstanding of the processes required to populate a Markov model with appropriate transition probabilities. The ERG determined that this problem could not be resolved easily, and would require a redesign of the core worksheets of the spreadsheet model. Since this is beyond the remit of the ERG, and would probably take more time to carry out reliably than remained within the STA timetable, the ERG communicated to NICE on January 9th 2009 their recommendation (quoted below) that the manufacturer should consider withdrawing their submission and model to allow a full reworking and validation of the model.

"Both the original survival error and this new problem could have been detected through validation of the model. The ERG has therefore reluctantly concluded that it is difficult to have any confidence in the submitted model and its results, and cannot be sure that further serious errors do not still remain to be uncovered. We believe that the manufacturer may

wish to withdraw the model at this stage in order to undertake a thorough comprehensive review and validation of all aspects of their model, prior to resubmission."

During a teleconference (January 13th 2009) between representatives of NICE, the manufacturer and the ERG, the nature of the identified error was clarified and the ERG's concerns about the credibility of the model and its results were communicated to the manufacturer, who agreed to consider the options of withdrawing the model, or submitting another revised version. On January 21st 2009, the manufacturer submitted a third version of the model together with additional evidence previously requested by NICE and the ERG in line with the standard STA process. Examination of the third model revealed that, although some minor modifications had been made to some formulae and a parameter value, the underlying structural problem and logic errors had not been addressed, and the model was still unable to replicate the response rates arising in the clinical trial. **As a consequence, the ERG is unable to express any confidence in any of the submitted models or the cost-effectiveness results obtained from their use.**

5.5.2 Structure and assumptions

The economic model submitted by the manufacturer is based on a classic Markov architecture, representing changes in patients' condition through four transition probability matrices (relating to treatment cycles 1 and 2, subsequent treatment cycles (up to 6), and any cycles following discontinuation of treatment). The implementation of this design is quite elaborate and at times difficult to follow due to limited explanatory annotation in the main calculation worksheets. Sometimes quite straightforward features appear to rely on elaborate logic chains, and this can allow coding logic errors to go undetected.

In evaluations which are reliant on a single clinical trial as the source of efficacy data, it is important that a model should be able to reproduce closely the findings of the trial. However, in this case, the chosen Markov model structure does not appear to be appropriate in this respect, since it imposes some strong constraints which make it impossible to replicate the data used to calibrate the model to an acceptable level of accuracy. In particular, 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. Furthermore 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, PFS and response rate which are discussed in detail below).

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.

The model allows patients to move between four health states ('stable disease', 'response to treatment', 'progressive disease' and death). However this structure is elaborated by a further 20 sub-states, representing patients in 'stable disease' or 'response to treatment' states suffering from ten specified AEs. A further three states are available in the model to represent the number of patients considered stable, responsive and progressed after receiving a second-line chemotherapy regimen. However, this feature is **not** activated in the submitted version of the model.

The AEs in the model are assumed to apply only to a single cycle, with the exception of non-febrile neutropenia where a majority of patients are assumed to experience the problem over multiple cycles. All AEs are expected to resolve as soon as chemotherapy is terminated for any reason. 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.

The 'base case' analysis submitted by the manufacturer assumes a maximum of four treatment cycles are administered per patient, in line with UK clinical practice. However, since the evidence of effectiveness is derived from the JMDB trial[1] which specified up to six cycles be given, great care must be taken in adjusting these data to an alternative protocol. In particular, it is essential that the model logic is able to replicate the clinical effects seen in the trial (confirmed response and survival) seen in the trial with six cycles of treatment. Only after this validation is demonstrated can assumptions be considered concerning loss of effect when treatment is truncated.

5.5.3 Major errors and omissions identified

Chemotherapy response rates

As described above a serious error was detected by the ERG in the method by which transition probabilities are generated for chemotherapy responses, and their use to estimate the proportion of patients responding in each arm of the economic evaluation. The method used involves partitioning the total trial responses between cycle 2 and subsequent cycles, and calculating two response rate probabilities using the initial number of patients in the trial population as the denominator. These probabilities were then used to estimate the cycle by cycle number of responders, multiplying the number of 'at risk' patients at the start of each cycle by the relevant probability. However, the latter are only valid for use with the whole population: since the number at risk diminishes rapidly each cycle (as patients suffer disease progression or death), the number of responders is seriously underestimated in all cycles but the first. Due to the inflexible structure of the model, it is not possible to replicate the trial results accurately by simply modifying parameter values, and a substantial model redesign would be necessary to achieve acceptable results.

Table 5-14 demonstrates the discrepancies between the JMDB response data with 6 cycles of treatment and the two versions of the model logic dealing with this problem. Model estimates were obtained by calculating the number of new responses occurring in each of the first six cycles in the model spreadsheets (these figures are not produced automatically by the model). Despite the modellers' attempts to remedy the problem by adjusting parameter values and amending some model logic, the underestimation remains systematic in both the intervention and comparator arms. The phenomenon is evident for all patient populations. It should be noted that a validation spreadsheet submitted by the manufacturer in support of their third model version contained several formula errors leading to misleading results.

Table 5-14 Response rates for non-squamous patients: recorded in JMDB trial (up to 6 cycles of chemotherapy), and estimated by original and modified manufacturer's models.

Responses during cycle	Pemetrexed/cisplatin			Gemcitabine/cisplatin		
	JMDB trial	1st model	3rd model	JMDB trial	1st model	3rd model
1	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%
2	16.02%	13.86%	16.02%	14.04%	12.16%	13.99%
3	1.29%	2.04%	3.81%	0.32%	1.34%	2.54%
4	8.58%	1.70%	3.06%	5.99%	1.14%	2.11%
5	0.49%	1.42%	2.46%	0.16%	0.96%	1.75%
6	2.24% *	1.18%	1.97%	1.26% #	0.82%	1.45%
Total	28.64%	20.21%	27.30%	22.24%	16.42%	21.84%
Difference Pem vs. Gem	+6.40%	+3.79%	+5.46%			

* includes 6 patients recorded as responding off trial at unknown time. # includes 3 patients recorded as responding off trial at unknown time

Overall survival and progression free survival

Overall survival and PFS are primary outcomes from the JDMB clinical trial,[1] and therefore should be accurately replicated in the economic model for each of the trial sub-populations. However, the model allows direct comparison of model estimated OS with only trial OS data for a single (unspecified) sub-population and shows a poor fit to all sub-populations. No PFS trial data are provided for comparison. Moreover, Kaplan-Meier survival charts were not provided for all sub-populations in the MS.

To rectify this omission, the ERG requested the relevant patient events and censored patients for each sub-population in the NICE clarification letter, to allow survival curves to be derived and compared to model estimates.

The requested trial data were provided by the manufacturer in their response to the NICE letter of clarification. The ERG has generated Kaplan-Meier survival plots for both OS and PFS, and these are shown in Appendix 4 of the ERG report, together with the latest model estimates for comparison. The manufacturer's model appears to overestimate OS in both arms and almost all patient subgroups. For PFS, the model tends to produce under-estimates in the first six months and to over-estimate thereafter. In no instance can the fit of the model be considered a good fit to the JMDB[1] data.

Another source of anxiety concerning the model arises from a comparison of Figures 15 & 16 in the manufacturer's submission which show modelled OS for the non-squamous population based on 3-year and 6-year time horizons. The only difference between these displays should be that the 3-year horizon is truncated at the midpoint of the 6-year chart, all estimated OS values remaining the same at all time points. This is clearly not true, with survival estimates noticeably lower in the 6-year horizon chart, indicating that a serious problem may remain in the model logic.

Comparators

The final scope for this appraisal identifies the standard comparators as: "Platinum-based chemotherapy (carboplatin or cisplatin) in combination with gemcitabine, docetaxel, paclitaxel or vinorelbine." This follows the conclusions of the NICE clinical guideline on the diagnosis and treatment of lung cancer (CG24), [6] and the Clegg review[30] which found no evidence to support differential benefits between the four third-generation agents in combination with platinum-based chemotherapy.

Unfortunately, the manufacturers of pemetrexed have chosen not to implement comparison with all four specified comparators. The submitted model contains four chemotherapy options: pemetrexed/cisplatin, gemcitabine/cisplatin, gemcitabine/carboplatin and docetaxel/cisplatin.

Evidence on market share was presented which indicated that gemcitabine currently has a dominate position in the UK with 83%. However, the other three products remain in use, the most common being vinorelbine. The omission of some standard comparators, and the selection of docetaxel (4% market share) over vinorelbine (11% market share and much less expensive with IV administration) is problematic, and prevents a full assessment of pemetrexed against currently recommended and used alternatives.

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.

5.5.4 Other model errors and issues identified

Mid-cycle correction

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.

Careful examination of the model logic indicates that most costs do not appear to need correction due to a complicated 'adding back' procedure for costs incurred by people progressing during the cycle, and other short-term/one-off costs being confined to one cycle. Only outcomes and BSC costs need a mid-cycle correction adding to provide consistency with the inbuilt correction for other costs.

Response rates and number of cycles

The submitted model includes a facility for reducing the maximum number of chemotherapy treatment cycles offered to patients. This has the effect of reducing the cost of treatment and thus reducing the incremental cost of pemetrexed. In addition, reducing the number of cycles of chemotherapy alters the incidence rate in each cycle for response to treatment, AE discontinuation rates, and febrile neutropenia but in such a way that the total incidence experienced by patients does not change when the maximum allowed treatment is reduced

from six to four cycles. This reduces the costs for pemetrexed but with no corresponding loss of benefits.

Response rates in cycle 3 - logic error

A minor error has been detected in formulae referring to estimating the response rate occurring during cycle 3, which leads to the model using intermediate calculations as parameter values, rather than the correct final calculated rates. This has the effect of slightly overstating the additional benefits attributable to pemetrexed compared to other chemotherapy agents.

Adverse events: frequency and related mortality

Febrile neutropenia is appropriately singled out for particular attention in the submitted model in relation to associated mortality. Based on a published meta-analysis of clinical trials,[31] a mortality risk of 3.9% is introduced for patients suffering febrile neutropenia at the start of each treatment cycle. This serves to yield a small advantage to pemetrexed in any comparison, but is questionable on several grounds:

- Paul's meta-analysis[31] uses results for mortality risk per patient for up to 30 days post-discharge. By contrast, the model applies the mortality risk each cycle effectively multiplying the estimated mortality for patients suffering multiple episodes (it appears that about 1.4 episodes per patient is typical).

- Paul's primary outcome measure is all-causes mortality,[31] which is likely to be considerably higher than mortality specifically related to chemotherapy, when mortality due to NSCLC itself is excluded.

- the numbers of relevant mortality events reported in the JMDB trial[1] are too small (two cases in 1639 patients) to allow any meaningful validation of the adopted parameter value.

Notwithstanding these issues, the model results are effectively insensitive to substituting a parameter value of 0% in place of 3.9%.

Chemotherapy costs

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. In addition, the fixed average value used for all patients ($1.80m^2$) may

misrepresent the values found in UK NSCLC patients (males: 1.89 m^2; females: 1.65m^2) which were identified from a recent survey[32] of three UK cancer centres. These figures, weighted for gender balance in NSCLC patients, yield a mean BSA of 1.82m^2. The costs of chemotherapy drugs per cycle in 12 regimens were re-estimated using this BSA value and are shown in Table 5-15. It is noteworthy that the MS presented cost-effectiveness results for the most expensive comparator (docetaxel) but not for the least expensive (vinorelbine IV).

Table 5-15 Chemotherapy costs per cycle (excluding administration costs)

Treatment	Submitted cost per cycle	Re-estimated cost per cycle	Change in cost per cycle
Pemetrexed + Cisplatin	£1,515,59	£1,597.22	+ £81.63
Pemetrexed + Carboplatin	£1,630.89	£1,707.51	+ £76.62
Gemcitabine + Cisplatin	£856.83	£853.03	- £ 3.80
Gemcitabine + Carboplatin	£972.13	£963.32	- £ 8.81
Docetaxel + Cisplatin	£1,098.59	£1,108.94	+ £10.35
Docetaxel + Carboplatin	£1,213.89	£1,219.23	+ £ 5.34
Paclitaxel + Cisplatin	Not used	£939.47	N/A
Paclitaxel + Carboplatin	Not used	£1,049.76	N/A
iv Vinorelbine + Cisplatin	Not used	£260.45#	N/A
iv Vinorelbine + Carboplatin	Not used	£370.74#	N/A
Oral Vinorelbine + Cisplatin	Not used	£980.47#	N/A
Oral Vinorelbine + Carboplatin	Not used	£1,090.76#	N/A

mean cost per cycle assuming five cycles of treatment; iv=intravenous

Model validation

The MS reports that validity of the model structure and assumptions was endorsed by the Advisory Board of consultant oncologists and manufacturer representatives. No information was provided to describe what steps were taken to ensure internal validity of the model with respect to the realisation of the design and assumptions in the Excel workbook, or the verification of specific model outputs against published trial results. The model itself does not show evidence of built-in validation features.

Role of treatment response

The model structure adopted by the manufacturer is commonly used to represent the action of chemotherapy agents for which patient benefit is primarily mediated through objective response (defined as reduction is tumour size). A common assumption is that such a response leads directly to a delay in the onset of progressive disease, and that this additional PFS is the primary source of survival gain. Following the confirmation of disease progression it is usually assumed that the choice of chemotherapy will have little or no effect on the subsequent course of the disease, and that once active treatment is discontinued the natural

history of the disease resumes as before. This trial is unusual in that almost all the reported health gain occurs *after* disease progression, with PFS effectively identical between pemetrexed and gemcitabine trial arms (see Figure 5.2). Following disease progression there is a modest reduction in mortality hazard, which can be attributed to pemetrexed. This advantage persists indefinitely throughout the trial period indicating that it does not attenuate over time.

This observation raises two questions relevant to the design of the economic model:

- what (if any) is the role of an objective response in determining the nature and extent of health gain in this trial?

- is the reduction of mortality risk demonstrated following disease progression confined to patients exhibiting an objective response to chemotherapy, or is it enjoyed by all patients exposed to treatment?

These questions are important since they have implications for the design of the model, and are particularly pertinent to any attempt to adjust outcome gains for altered dosing regimens (either through reducing the maximum of treatment cycles, or through imposing a 'stopping rule' based on observed response). If response predicts neither PFS nor post-progression survival, then the use of 'response' as a distinct health state is at best irrelevant, and at worst liable to generate misleading results. In principle it may be necessary to restructure the model either to remove 'response' altogether as a category, or to extend the role of categories of response to accommodate more careful analysis of the trial data.

Unfortunately, response was not a variable included in any of the reported Cox regressions of efficacy outcomes reported in the clinical trial report, and it is not possible to draw any conclusions without access to the IPD from the JMDB trial.[1] In particular, the mechanisms employed in the submitted models to adjust outcomes for reduced drug exposure cannot be considered reliable until these questions are resolved, since they are predicated on assumptions about the timing of treatment response before and after the point at which treatment is deemed to be terminated.

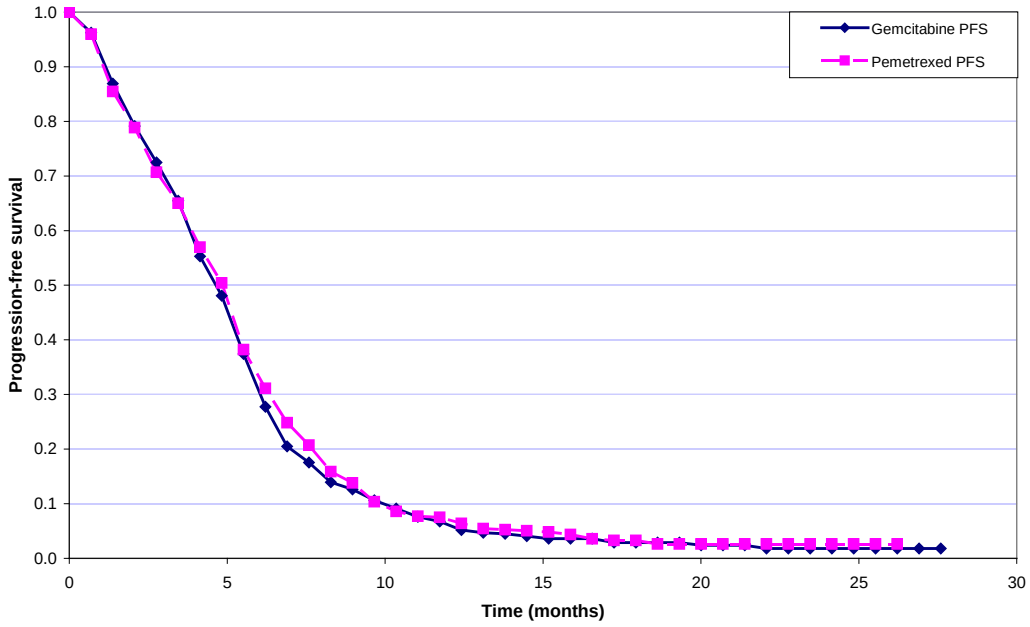

Figure 5.2 Progression free survival for patients with for non-squamous NSCLC: Kaplan-Meier analyses from JMDB trial data.

5.5.5 Summary of modelling critique

There are a number of features of the submitted model (all three versions) which give cause for caution and concern:

- the chosen model design is not obviously suitable for modelling the disease and treatments described in the published clinical trial, imposing as it does serious constraints on the possibility of representing the observed patterns of response to treatment and progression of disease with anything approaching realism;

- the implementation of the model is marked by examples of basic errors with far-reaching consequences;

- there is little evidence of a systematic approach to identifying and eliminating errors in the development of the model, or of attempting to replicate the prime source of information for the model - the trial itself;

- the restriction of comparators to those which are relatively high cost is likely to give a misleading impression of the true cost effectiveness of pemetrexed regimen. Furthermore, gemcitabine's patent in the UK expires in March 2009, which is likely to lead to a reduction in the price of gemcitabine when generic versions become available. This has not been considered in the manufacturer's model;

- the methods used for adjusting treatment effects (positive and negative) when a scenario is used with fewer treatment cycles than in the trial evidence, are not obviously robust and defensible and may tend to over-estimate the outcome benefits to be expected from use of pemetrexed, while under-estimating the additional cost.

- the role of response to treatment in determining the observed survival advantage for pemetrexed in patients with non-squamous NSCLC is not clear, and without further detailed analysis of JMDB[1] IPD there are serious questions unanswered concerning the suitability of the structure and assumptions underlying the submitted model.

The fact that three versions of the model have been reviewed, and still important problems remain unresolved, explains why the ERG is not able to express any confidence in the submitted models, and cannot support the cost-effectiveness results presented. The difficulties encountered have made it impossible for the ERG to carry out a comprehensive in depth analysis and review of all aspects of the model, as would normally be undertaken, and therefore it is quite likely that additional significant problems may be identified on further investigation. The proposed treatment regimen may or may not be cost effective compared to currently recommended treatments, but the evidence submitted by the manufacturer is not sufficiently convincing or robust to support a decision on the matter. The ERG is of the opinion that the structure of the submitted models is flawed and does not reflect a believable case with regards to the cost effectiveness of this intervention. For a credible case to be made by the manufacturer, the ERG considers that the latest version of the economic model would have to be restructured and further validated. The ERG is concerned that the necessary modifications/corrections/amendments to the model might take longer than is considered appropriate under the current STA timelines.

5.6 Summary of economic evidence

5.6.1 Economic evaluation results

Base-case: Manufacturer

- The manufacturer reports an ICER of £33,065 per QALY gained for the comparison of pemetrexed/cisplatin versus gemcitabine/cisplatin in the non-squamous population without the continuation rule applied, and £25,967 with the continuation rule applied. Comparing pemetrexed/cisplatin with gemcitabine/carboplatin and docetaxel/cisplatin gives ICERs in the range of £14,675-£21,585.

- The ICER for pemetrexed/cisplatin versus gemcitabine/cisplatin is £18,442 in the adenocarcinoma subgroup and £8,056 in the large cell subgroup (with the continuation rule applied). Comparing pemetrexed/cisplatin with gemcitabine/carboplatin and docetaxel/cisplatin gives even lower ICERs (not exceeding £14,887).

- Results of the PSA conducted by the manufacturer suggest that, based on current assumptions and evidence available, pemetrexed/cisplatin is likely to be cost effective at a WTP of £30,000 per QALY gained.

Base-case: ERG

- The ERG identified a series of flaws in the submitted model(s). Some of these flaws are so substantial and inherent to the model structure that it is not possible to remedy them and provide revised ICERs.

5.6.2 Economic issues and uncertainties

- The chosen model design is not obviously suitable for modelling the disease and treatments described in the published clinical trial, imposing as it does serious constraints on the possibility of representing the observed patterns of response to treatment, progression of disease and overall survival.

- The implementation of the model is marked by examples of basic errors with far-reaching consequences.

- There is little evidence of a systematic approach to identifying and eliminating errors in the development of the model, or of attempting to replicate the prime source of information for the model - the trial itself.

- The restriction of comparators to those which are relatively high cost is likely to give a misleading impression of the true cost effectiveness of pemetrexed regimen. In addition, the forthcoming end of patent protection for gemcitabine may significantly reduce its cost, which is not considered in the manufacturer's economic model.

- The methods used for adjusting treatment effects (positive and negative) when a scenario is used with fewer treatment cycles than in the trial evidence, are not obviously robust and defensible and may tend to over-estimate the outcome benefits to be expected from use of pemetrexed, while under-estimating the additional cost.

- **Taken together, all of these issues and uncertainties lead the ERG to conclude that the model is not able to provide robust cost-effectiveness estimates upon which to base a decision.**

6 SUMMARY OF ADDITIONAL WORK BY ERG

Due to the serious flaws identified by the ERG in relation to the manufacturer's economic model, the ERG was unable to do more than critique the manufacturer's economic model, which is presented in Section 5 of the ERG report. No reliable cost-effectiveness results can be generated from the manufacturer's model as it stands. A substantial rebuilding of the model would need to be undertaken before this could be remedied, which is beyond the remit of the ERG.

7 DISCUSSION

The systematic literature review conducted by the manufacturer was designed to identify the clinical evidence available for the assessment of efficacy for the first-line use of pemetrexed/cisplatin in patients with non-squamous NSCLC. This yielded only one trial, a well-conducted phase III randomised open label trial known as the JMDB trial.[1] The ERG is confident that all published trial reports of pemetrexed/cisplatin were identified by the manufacturer.

The JMDB trial is being hailed in many quarters as a landmark trial not only because it reports that pemetrexed/cisplatin is clinically noninferior to gemcitabine/cisplatin in all patients with NSCLC but more specifically, because it reports pemetrexed/cisplatin to be superior for patients with non-squamous NSCLC in terms of OS. Based on these findings, the manufacturer presents a case for the first-line use of pemetrexed/cisplatin instead of gemcitabine/cisplatin in patients with non-squamous NSCLC, particularly in the manufacturer's own defined target population of patients with adenocarcinoma or large cell carcinoma. As the JMDB trial was designed primarily to test for noninferiority in all patients with NSCLC (squamous and non-squamous), the validity of generalising findings from subgroups may be questioned. However, as it is one of the largest ever studies in NSCLC to date, the subgroup differences are encouraging and warrant further exploration.

Identifying patients in the manufacturer's target population requires more specific histological testing than is standard across all UK centres at present. A study of preoperative histological classification of lung cancer[12] suggests that diagnosing adenocarcinoma may be a particular challenge. In the JMDB trial, this group represented half of all patients. The known proportion of patients with adenocarcinoma in the UK is not presented in the MS which reports only LUCADA.[4] This audit data suggests the proportion of patients with NSCLC may be around a quarter. Thus the accurate diagnosis for this significant group of patients may be a particular challenge.

Very few patients in the JMDB trial were recruited in the UK, just 2.5%. Furthermore, the patients in this trial appear to be generally younger and fitter than all patients in England and Wales with NSCLC. Thus there is a degree of uncertainty as to whether similar results could be replicated for all patients with NSCLC in England and Wales although it could be argued that this is the case when considering any trial results for any disease for any population.

In the absence of any other head-to-head clinical trials of pemetrexed/cisplatin with other platinum doublets other than gemcitabine/cisplatin, the manufacturer undertook an indirect

comparison analysis. While the scope listed a range of appropriate comparators (docetaxel, gemcitabine, paclitaxel or vinorelbine in combination with cisplatin or carboplatin) which were based on NICE clinical guidelines,[6] the manufacturer limited its additional indirect comparisons to gemcitabine/carboplatin, the most commonly used regimen in the UK, and docetaxel/cisplatin. As neither comparator was found to fare as well as gemcitabine/cisplatin, it was suggested that pemetrexed/cisplatin was the most efficacious regimen. Aside from the fact that confidence in these results would have been increased had the full range of appropriate regimens been considered, the ERG believes the method employed to undertake this analysis contained methodological limitations; calculations were based on median survival times and individual trial arm level data from within trials were compared. Thus comparisons of pemetrexed/cisplatin with any other regimen other than gemcitabine/cisplatin should be treated with caution.

The cost-effectiveness section of the MS considers the comparisons of pemetrexed/cisplatin versus gemcitabine/cisplatin, docetaxel/cisplatin and gemcitabine/carboplatin. The ICERs estimated by the manufacturer range from £8,056 to £33,065 depending on the comparator, the population and the application of a continuation rule. The manufacturer believes this to be a good indication of the cost-effectiveness of pemetrexed/cisplatin.

The ERG, however, found a number of substantial problems with the model and the approach to the economic evaluation, which present serious challenges to the credibility of the model and the reliability of its results as an aid to decision making. A total of three versions of the model were submitted to the ERG following the identification by the ERG of mistakes in the model and the manufacturer's attempts to rectify them. Unfortunately, each resubmission failed to adequately address the crucial problems at the heart of the model.

Firstly, the chosen model design is not obviously suitable for modelling the disease and treatments described in the published clinical trial, imposing as it does serious constraints on the possibility of representing the observed patterns of response to treatment and progression of disease with anything approaching realism.

Secondly, the implementation of the model is marked by examples of basic errors with far-reaching consequences. There is little evidence of a systematic approach to identifying and eliminating errors in the development of the model, or of attempting to replicate the prime source of clinical information used in the model - the JMDB trial itself.

Thirdly, the final scope for this appraisal identifies the standard comparators as: "Platinum-based chemotherapy (carboplatin or cisplatin) in combination with gemcitabine, docetaxel,

paclitaxel or vinorelbine." Unfortunately, the manufacturer has chosen not to undertake a comparison with all four specified comparators. The submitted model does not consider paclitaxel or vinorelbine; the latter drug is especially problematic as it is substantially cheaper (when administered intravenously) than pemetrexed, gemcitabine or docetaxel. This omission means that even if the model were robust, important comparators would have been ignored by the manufacturer. In addition, the forthcoming end of patent protection for gemcitabine may significantly reduce its cost, which is also not considered in the manufacturer's economic model.

Fourthly, the methods used for adjusting treatment effects (positive and negative) when a scenario is used with fewer treatment cycles than in the trial evidence, are not obviously robust and defensible and may tend to over-estimate the outcome benefits to be expected from use of pemetrexed, while under-estimating the additional cost.

Finally, the role of response to treatment in determining the observed survival advantage for pemetrexed in patients with non-squamous NSCLC is not clear, and without further detailed analysis of IPD from JMDB, serious questions remain unanswered concerning the suitability of the structure and the assumptions underlying the submitted model.

The identification of serious errors and inappropriate structural assumptions in the submitted model means that, even in its modified form, it is not able to provide robust cost-effectiveness estimates upon which to base a decision. The model requires extensive modification and redesign, which is beyond the remit of the ERG. It is also the opinion of the ERG that, following such alterations, the model will need to be subjected to thorough validation against the clinical trial results, and a full quality audit since it is likely that further model inconsistencies may be present which have not yet been identified.

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9 APPENDICES

Appendix 1: Validity assessment of the JMDB trial

Table 9-1 The manufacturer's approach to validity assessment and ERG comment

Evaluative criteria	Response in MS (verbatim)	ERG comment
How was allocation concealed?	Allocation was not concealed as this was an open-label trial due to differing administration schedules for each arm.	Even in open-label trials it is possible to blind the allocation of treatment. Elsewhere in the MS it is also noted that: "The patient and the physician did not know the patient's treatment until the patient was randomly assigned to a treatment arm." It is stated in response to the next question that a computerised, interactive, voice-activated response system at a central location controlled random assignment. Thus the treatment allocation was in fact concealed.
What randomisation technique was used?	A computerised, interactive, voice-activated response system (IVRS) at a central location controlled random assignment.	The manufacturer's response here should be part of the response to the previous question. The MS states a central randomisation system assigned patients to treatment arms according to a two-step process. First, there was an overall stratification based on whether the investigative centre was participating in the companion biomarker study. Second, within each of the two overall strata, randomisation occurred independently, according to the method of Pocock and Simon.[33] In each stratum, a given patient was assigned with probability 0.75 to the treatment arm that minimized imbalances among six equally weighted prognostic factors: disease stage (IIIB versus IV); ECOG PS (0 versus 1); history of brain metastases (yes versus no); sex (male versus female); basis for initial pathological diagnosis (histopathological versus cytological); investigative centre. These stratification factors were independent of the pre-specified histology analyses.
Was a justification of the sample size provided?	Sample size justification is provided in section 6.4.5 of the MS. Of note, this is the largest study in this patient population to date.	The sample size method is actually provided in section 6.3.5 of the MS. Based on this, the JMDB trial would be adequately powered for testing for differences between the two arms of the trial in all patients, although it would not be adequately powered for the subgroups. Furthermore, randomisation was not stratified by these subgroups and so the chances of there being confounding factors is increased.

Evaluative criteria	Response in MS (verbatim)	ERG comment
Was follow-up adequate?	Yes. Each patient underwent a treatment period and a follow-up period. The treatment period consisted of 21-day treatment cycles. Patients received up to 6 cycles of assigned treatment. The follow-up period began when the treatment period was completed. Patients were to be followed up with periodic tumour response evaluation until disease progression. All patients were followed until death or study closure (length of the study 30 months). Of the 1725 (ITT) patients that entered the trial, 1270 deaths had occurred at the time the database was locked.	This is an adequate procedure and notes that only one patient was lost to follow-up which is an excellent follow-up rate.
Were the individuals undertaking the outcomes assessment aware of allocation?	Yes, this was an open-label trial	Common to all intravenous cytotoxic trials, in open-label trials such as this where administration schedules are quite different, the blinding of treatment is impossible. Nevertheless, it would be possible to take steps to blinding outcome assessment and analysis. Some partial blinding was undertaken as elsewhere in the MS it is noted that both the manufacturer and all investigative sites "remained blinded to treatment group assignments for the aggregate database until the final analysis."
Was the design parallel-group or crossover? Indicate for each crossover trial whether a carry-over effect is likely.	The trial design was parallel-group. Subsequent therapy was at investigator discretion, so some crossover did occur. The rate of crossover was low and unlikely to affect the comparison of survival between treatment arms. Overall, fewer patients on the pemetrexed/cisplatin arm received post study systemic anticancer treatment (chemotherapy, targeted therapy, or immunotherapy) than patients on the gemcitabine/cisplatin arm (52.6% versus 56.1%), and significantly fewer patients on the pemetrexed/cisplatin arm received chemotherapy agents post study (41.5% versus 47.3%, p=0.018). Details of post study chemotherapy are provided in appendix 10.8.	There is a high level of post-treatment which may impact on the results, particularly in a noninferiority trial. However, as the proportion of patients is relatively similar by treatment arm, the risk of bias is minimised. It is noted that it is patients in the gemcitabine arm who received significantly more therapy. This may suggest that this group of patients were fitter and so lived longer but the ERG does not believe this would significantly impact on the findings. Additional analysis undertaken for the EMEA which excluded patients who switched treatment indicate findings consistent with those when such patients were not excluded.

Evaluative criteria	Response in MS (verbatim)	ERG comment
How do the included in the RCT participants compare with patients who are likely to receive the intervention in the UK? Consider factors known to affect outcomes in the main indication, such as demographics, epidemiology, disease severity, setting.	The baseline patient, disease characteristics, and prognostic factors were well balanced between treatment arms. Patients in JMDB were generally fitter (PS0-1), younger compared to average lung cancer patients in the UK (LUCADA, 2007). This can be expected for a clinical trial in which the inclusion criteria restrict patients entered in order to limit confounding factors. More patients have adenocarcinoma and fewer have NSCLC-NOS than seen in LUCADA. This is likely to be a result of changing histology distributions that show adenocarcinoma increasing as the proportion of men to women with lung cancer decreases as the effect of more women smoking and static male smoking rates present themselves in the lung cancer incidence statistics.	The baseline patient, disease characteristics, and prognostic factors were well balanced between treatment arms in the JMDB trial. Patients in the JMDB trial differed to average lung cancer patients in the UK. This would be expected from clinical trials. Furthermore, while it is noted that patients with ECOG PS=2 are included in other trials of this patient group, most UK physicians would not consider these patients for cisplatin based therapy as it is often too toxic for them. The JMDB trial required more specific testing than may be routine common practice where it is not deemed necessary to classify non-squamous patient. This could also explain some of the differences in the data between the trial and the data from the National Lung Cancer Audit.
Were the study groups comparable?	Yes, the treatment arms were well balanced with respect to demographic characteristics.	The treatment arms were well balanced in the JMDB trial.
Were the statistical analyses used appropriate?	See section 6.4.5 above for statistical analyses	In addition to ITT analysis, PP analysis should have been presented. PP analysis was presented on request. p-values may have been adjusted for multiple comparisons although these p-values in themselves were probably not the most appropriate to present. Rather the p-value for the test for interaction across the four subgroups (patients with squamous histology, patients with adenocarcinoma, patients with large cell carcinoma and patients with NSCLC-NOS) by trial arm (pemetrexed/cisplatin and gemcitabine/cisplatin) would have been more appropriate. PP analysis was presented on request.
Was an intention-to-treat analysis undertaken?	Yes. ITT was undertaken for efficacy evaluations, but randomised and treated (patients who received at least one dose of pemetrexed/cisplatin or gemcitabine/cisplatin) were analysed for safety.	The PP analysis should also have been presented for efficacy evaluation in the JMDB trial. PP analysis was presented on request.
Were there any confounding factors that may attenuate the interpretation of the results of the RCT(s)?	There are no confounding factors.	The high level of post-treatment may be argued to be considered a confounding factor.

Evaluative criteria	Response in MS (verbatim)	ERG comment
Was the RCT conducted in the UK (or were one or more centres of the multinational RCT located in the UK)? If not, where was the RCT conducted, and is clinical practice likely to differ from UK practice?	This was a multi-centre trial in 26 countries with majority of the patients coming from Western Europe. Approximately 3% of patients were from the UK. Germany recorded the highest number of patients enrolled in the trial (11%). The study was closely monitored to identify and evaluate any violations of good clinical practice (GCP) and clinically important protocol violations (defined as those deviations from the protocol that could have potentially affected patient safety, data integrity, or the conclusions drawn from the study). Overall, the number of protocol violations in this study was balanced between treatment arms and low in incidence, such that they were not likely to have affected the analyses or conclusions of this trial.	Very few patients were from the UK. The specificity required for diagnosing histology types in the JMDB trial may be not be adhered to in all treatment centres in clinical practice in the UK.
For pharmaceuticals, what dosage regimens were used in the RCT? Are they within those detailed in the Summary of Product Characteristics?	See section 6.4.1 for dosage regimens. These are in line with the SPC.	The dosing regimens are appropriate in the JMDB trial.

ECOG=Eastern Cooperative Oncology Group; EMEA=European Medicines Agency; ITT=Intention to treat; LUCADA=Lung Cancer Audit Data; MS=manufacturer's submission; NSCLC=non-small cell lung cancer; NSCLC-NOS= non-small cell lung cancer not otherwise specified; PP=per protocol; PS=performance status; SPC=Summary of Product Characteristics

Appendix 2: Trial and baseline characteristics of the JMDB trial and the two trials included in the indirect comparisons analysis

Table 9.2 Summary of the characteristics of the trials included in the manufacturer's submission

Study, trial design and number of participants	Intervention/ comparator	Inclusion criteria	Exclusion criteria	Outcomes
JMDB trial (Scagliotti 2008):[1] Randomised, multi-centre open-label phase III noninferiority trial conducted between July 2004 and December 2005. 177 centres participated (n=1725)	pemetrexed 500 mg/m^2 iv infusion over 10 minutes on day 1 plus cisplatin 75 mg/ m^2 iv infusion administered as per local practice 30 minutes after pemetrexed on day 1, every 21 days gemcitabine 1250 mg/ m^2 iv infusion over 30-60 minutes on day 1 and day 8 plus cisplatin 75 mg/m^2 iv infusion administered as per local practice 30 minutes after gemcitabine on day 1, every 21 days both treatment arms received prior and concomitant medication with folic acid, vitamin B_{12}, and dexamethasone as recommended in the pemetrexed SPC and concomitant supportive therapies (e.g. erythropoietic agents or granulocyte colony-stimulating factors) were also allowed maximum 6 cycles allowed in both arms	• histologic or cytologic diagnosis of NSCLC Stage IIIB or IV American Joint Committee on Cancer Staging Criteria for NSCLC • no prior systemic chemotherapy for lung cancer • at least 1 uni dimensionally measurable lesion meeting RECIST criteria • performance status of 0 or 1 on the ECOG Scale • at least 18 years of age • adequate organ function • prior radiation therapy completed at least 4 weeks before study enrolment was allowed to <25% of the bone marrow. Prior radiation to the whole pelvis was not allowed • signed informed consent on file • male and female patients with reproductive potential must have been using an approved contraceptive method, if appropriate • Female patients with childbearing potential must have had a negative serum pregnancy test within 7 days prior to study enrolment • estimated life expectancy of ≥12 weeks • patient compliance and geographic proximity that allowed for adequate follow-up	• received treatment within the last 30 days with a drug that had not received regulatory approval • peripheral neuropathy of ≥CTC Grade 1 • inability to comply with protocol or study procedures • a serious concomitant systemic disorder that would have compromised the patient's ability to complete the study • a serious cardiac condition within 6 months • second primary malignancy that was clinically detectable at the time of consideration for study enrolment • documented brain metastases • presence of clinically detectable (by physical exam) third-space fluid collections • significant weight loss (≥10%) over the previous 6 weeks • concurrent administration of any other antitumor therapy • inability to interrupt aspirin or other nonsteroidal anti-inflammatory agents for a 5-day period (8-day period for long-acting agents, such as piroxicam) • inability or unwillingness to take folic acid or vitamin B_{12} supplementation • inability to take corticosteroids • pregnant or breast-feeding	Primary: • overall survival Secondary: • time to progression of disease • overall response • tolerability

Study, trial design and number of participants	Intervention/ comparator	Inclusion criteria	Exclusion criteria	Outcomes
Zatloukal 2003: [17] Randomised, multicentre open-label phase III trial conducted between December 1999 and December 2001. Nine centres participated (n=176)	gemcitabine 1200mg/m^2 iv over 30 minutes on day 1 and day 8 plus cisplatin 80mg/m^2 iv administered at least 4 hours after gemcitabine on day 1, every 21 days gemcitabine 1200mg/m^2 + carboplatin AUC 5.0 mg/ml/min iv administered at least 4 hours after gemcitabine on day 1, every 21 days maximum 6 cycles allowed in both arms	• chemo naive patients with histologic or cytologic diagnosis of Stage IIIb or IV NSCLC not eligible for curative surgery or radiotherapy • patients between ages of 18 and 75 years, with bi-dimensionally measurable lesions at least 1 cm by 1 cm (or 2 cm by 2 cm by physical examination) • prior radiation therapy was permitted as long as the irradiated area was not the only source of measurable disease • no other form of therapy was allowed for at least 3 weeks before entering the study • patients with an estimated life expectancy of at least 12 weeks and adequate bone marrow reserve • KPS ≥70	• patients with active infection, symptomatic central nervous system metastases, pregnancy, second primary malignancy, or serious concomitant systemic disorders incompatible with the study • patients with inadequate liver function or inadequate renal function	Primary: • tolerability Secondary: • overall response • time to progression of disease • overall survival
Schiller 2002:[18] Randomised, multicentre open-label phase III trial conducted between October 1996 and May 1999 (n=1207)	paclitaxel 135mg/m^{2}over 24-hour period on day 1 plus cisplatin 75mg/m^2 on day 2, every 21 days gemcitabine 1000mg/m^2 on days 1, 8 and 15 plus cisplatin 100mg/m^2 on day 1 every 28 days docetaxel 75mg/m^2 on day 1 plus cisplatin 75mg/m^2 on day 1, 21 days paclitaxel 225mg/m^2 over 3-hour period on day 1 plus carboplatin AUC 6.0 mg/ml/min on day 1, 21 days no maximum number of cycles specified for any treatment arm	• confirmed disease, measurable or not measurable; an age of at least 18 years • adequate haematological, hepatic and renal function • prior radiation therapy at symptomatic sites was permitted provided that the indicator had not been irradiated and that the radiation therapy had been completed before chemotherapy was initiated • patients with stable brain metastases	• patients who had received prior chemotherapy	Primary: • overall survival Secondary: • time to progression of disease • overall response • tolerability

AUC=area under the curve; CTC= Common Toxicity Criteria; ECOG=Eastern Cooperative Oncology Group; iv =intravenous; KPS=Karnofsky performance status; NSCLC= Non-small cell lung cancer; SPC=Summary of Product Characteristics

Table 9.3 Summary of the baseline and disease characteristics of the trials included in the manufacturer's submission

Study	Treatment arm	Demographics	Performance Status	Stage of disease	Histological type	Number of cycles
JMDB trial[1]	pemetrexed/cisplatin (n=862)	Male: 70.2% Female: 29.8% Median age: 61.1years (Range: 29-83 years)	ECOG 0: 35.4% ECOG 1: 64.5%	IIIB, dry: 16% IIIB, wet: 7.8% IV: 76.2%	Squamous: 28.3% Adenocarcinoma: 50.6% Large cell: 8.8% Others: 12.3%	Patients received a median number of 5 cycles (range 1-8)
	gemcitabine/cisplatin (n=863)	Male: 70.1% Female: 29.9% Median age: 61 years (Range:26-79 years)	ECOG 0: 35.6% ECOG 1: 64.2%	IIIB, dry: 18.4% IIIB, wet: 5.9% IV: 75.7%	Squamous: 26.5% Adenocarcinoma:47.6% Large cell: 8.9% Others: 16.9%	
Zatloukal 2003[17]	gemcitabine/cisplatin (n=87)	Male: 77% Female: 23% Median age: 63 years (Range: 39-75 years)	Karnofsky[a] >80: 69% >70 <80: 31%	IIIB: 41% IV: 59%	Squamous: 56% Adenocarcinoma: 26% Large cell: 7% Others: 10%	Patients received a median number of 4 cycles (range 0-6).
	gemcitabine/carboplatin (n=89)	Male: 76% Female: 24% Median age: 62 years (Range: 46-76 years)	Karnofsky[a] >80: 67%[a] >70 <80: 33%[a]	IIIB: 38% IV: 62%	Squamous: 46% Adenocarcinoma: 33% Large cell: 7% Others: 15%	
Schiller 2002[18]	gemcitabine/cisplatin (n=301)	Male: 62% Female: 38% Median age: 64 years (Range: 32-87 years)	ECOG 0: 33% ECOG 1: 62% ECOG 2: 5%	IIIB: 14% IV or recurrent disease: 86%	Not reported	Not reported
	docetaxel/cisplatin (n=304)	Male: 63% Female: 37% Median age: 63 years (Range: 34-84 years)	ECOG 0: 32% ECOG 1: 62% ECOG 2: 6%	IIIB: 14% IV or recurrent disease: 86%	Not reported	

[a]It is assumed in the MS that a Karnofsky score > 70 is equivalent to a PS ≤ 2

Appendix 3: Findings from the indirect comparisons analysis presented in the MS

Table 9.4 Summary of the indirect comparisons results for patients with non-squamous NSCLC by subgroup

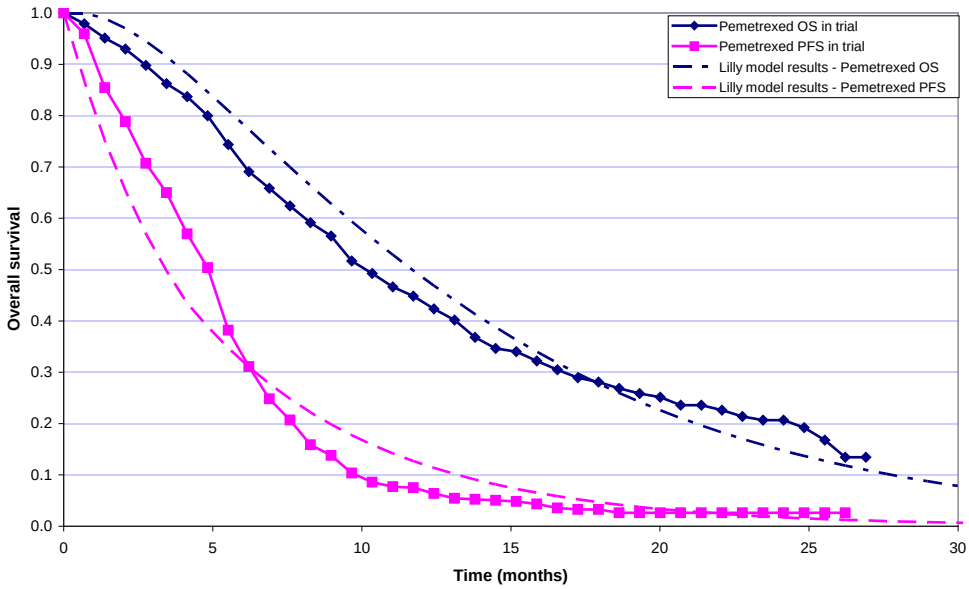
	Subgroup	Treatment arm	Median (range) OS (months)	OS adjusted hazard ratio	Median (range) PFS (months)	PFS adjusted hazard ratio	Median response rate *[%first 3 cycles]*
JMDB trial[1]	non-squamous (n=1252)	pemetrexed/cisplatin (n=618)	11.0 (10.1-12.5)	0.84 (0.74-0.96)	5.3 (4.7-5.5)	0.95 (0.84 – 1.06)	28.64% *[60.45%]*
		gemcitabine/cisplatin (n=634)[b]	10.1 (9.3-10.9)	p=0.011[d]	5.0 (4.6-5.4)	p values not reported	22.24% *[64.54%]*
	target[a] (n=1000)	pemetrexed/cisplatin (n=244)	11.8 (10.4-13.2)	0.81 (0.70-0.94)	5.3 (4.8-5.7)	0.90 (0.79-1.02)	not reported
		gemcitabine/cisplatin (n=229)	10.4 (9.6-11.2)	p=0.005[d]	4.7 (4.4-5.4)	p values not reported	not reported
	adenocarcinoma (n=847)	pemetrexed/cisplatin (n=436)	12.6 (10.7-13.4)	0.84(0.71-0.99)	5.5 (4.9-5.7)	0.90 (0.78-1.03)	28.90% *[57.14%]*
		gemcitabine/cisplatin (n=411)	10.9 (10.1-11.9)	p=0.033[d]	5.0 (4.5-5.5)	p values not reported	21.65% *[61.80%]*
	large cell (n=153)	pemetrexed/cisplatin (n=76)	10.4(8.6–14.1)	0.67 (0.48-0.96)	4.4 (3.0-5.8)	0.89 (0.65-1.24)	27.63% *[85.71%]*
		gemcitabine/cisplatin (n=77)	6.7 (5.5-9.0)	p=0.027[d]	4.2 (3.5-4.7)	p values not reported	27.27% *[76.19%]*
Zatloukal 2003[17]	non-squamous	gemcitabine/cisplatin	not calculated	not reported	not calculated	not reported	not reported
		gemcitabine/carboplatin (n=89)[c]	9.2		4.01		15.70% *[64.54%]*
	target[a]	gemcitabine/cisplatin	not calculated	not reported	not calculated	not reported	not reported
		gemcitabine/carboplatin (n=89)[c]	9.5 (8.10-13.38)		3.77		not reported
	adenocarcinoma	gemcitabine/cisplatin	not reported	not reported	not reported	not reported	not reported
		gemcitabine/carboplatin (n=89)[c]	not reported		not reported		15.29% *[61.80%]*
	large cell	gemcitabine/cisplatin	not reported	not reported	not reported	not reported	not reported
		gemcitabine/carboplatin (n=89)[c]	not reported		not reported		19.25% *[76.19%]*
Schiller 2002[18]	non-squamous	gemcitabine/cisplatin	not calculated	not reported	not calculated	not reported	not reported
		docetaxel/cisplatin (n=289)[c]	9.5		4.32		17.59% *[64.54%]*
	target[a]	gemcitabine/cisplatin	not calculated	not reported	not calculated	not reported	not reported
		gemcitabine/carboplatin (n=289)[c]	9.8 (8.61-11.48)		4.06		not reported
	adenocarcinoma	gemcitabine/cisplatin	not reported	not reported	not reported	not reported	not reported
		docetaxel/cisplatin (n=289)[c]	not reported		not reported		17.13% *[61.80%]*
	large cell	gemcitabine/cisplatin	not reported	not reported	not reported	not reported	not reported
		docetaxel/cisplatin (n=289)[c]	not reported		not reported		21.57% *[76.19%]*

OS= overall survival; PFS=progression free survival

[a] target population=adenocarcinoma + large cell carcinoma; [b] n=638 according to Table 15 of MS but in all other Tables in MS; [c] number as stated in MS but these are the number of all patients in the trial as these are not presented by subgroup in the source paper - all subsequent values for OS, PFS and response rate are calculated by manufacturer; [d] superiority

Appendix 4: Kaplan-Meier survival charts for JMDB clinical trial data, compared to manufacturers model estimates

A Pemetrexed + platinum



B Gemcitabine + platinum

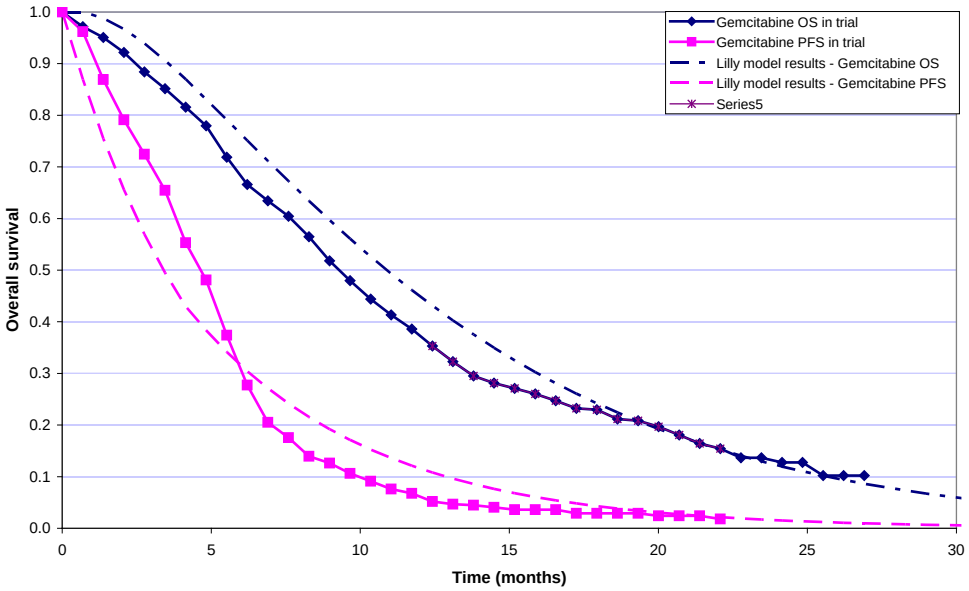
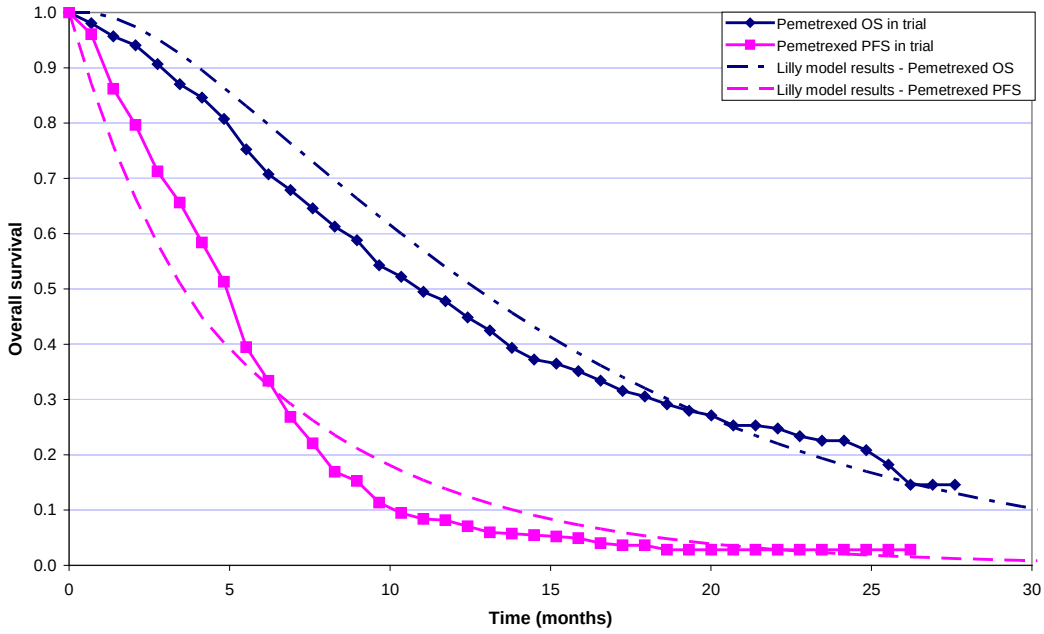


Figure 9.1 Overall survival and progression free survival for non-squamous carcinoma patients: Kaplan-Meier analyses from JMDB trial data, and estimated by the modified (3rd) manufacturer's model.

A Pemetrexed + platinum



B Gemcitabine + platinum

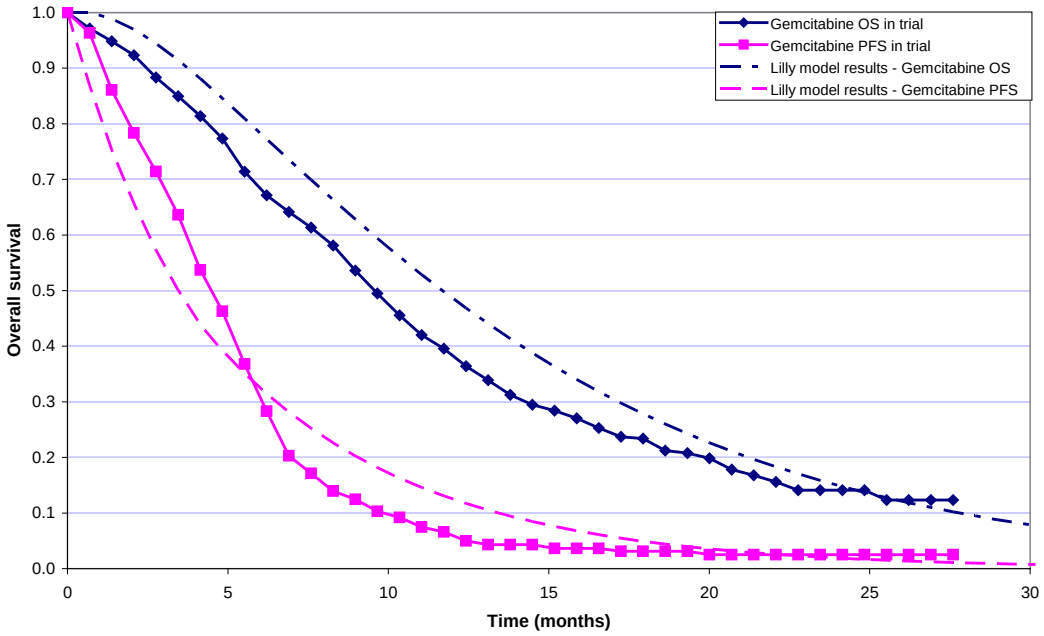
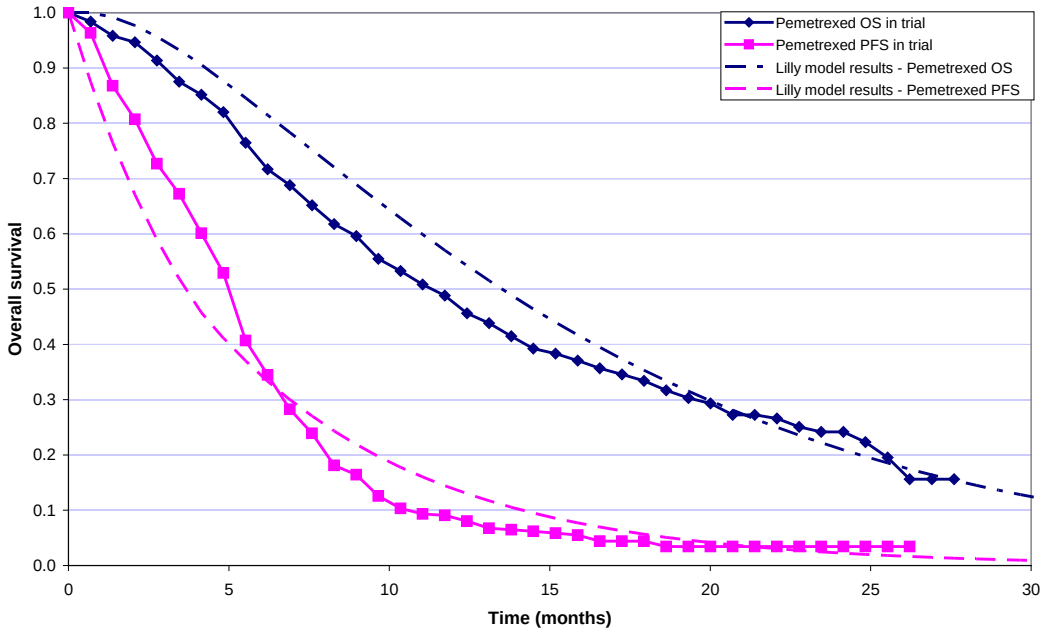


Figure 9.2 Overall survival and progression free survival for patients with adenocarcinoma and large cell carcinoma: Kaplan-Meier analyses from JMDB trial data, and estimated by the modified (3rd) manufacturer's model.

A Pemetrexed + platinum



B Gemcitabine + platinum

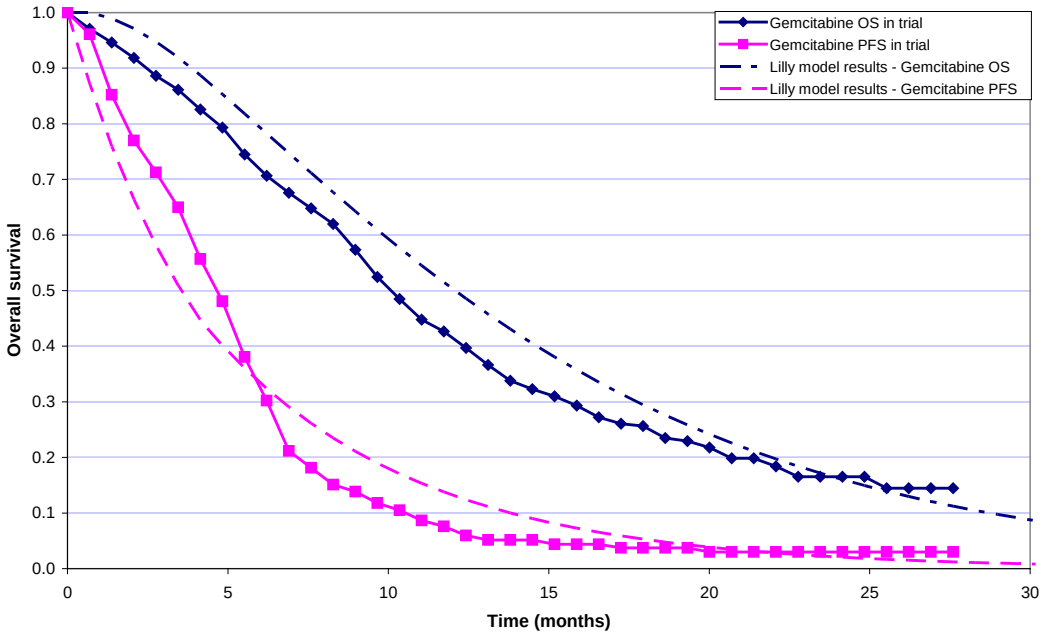
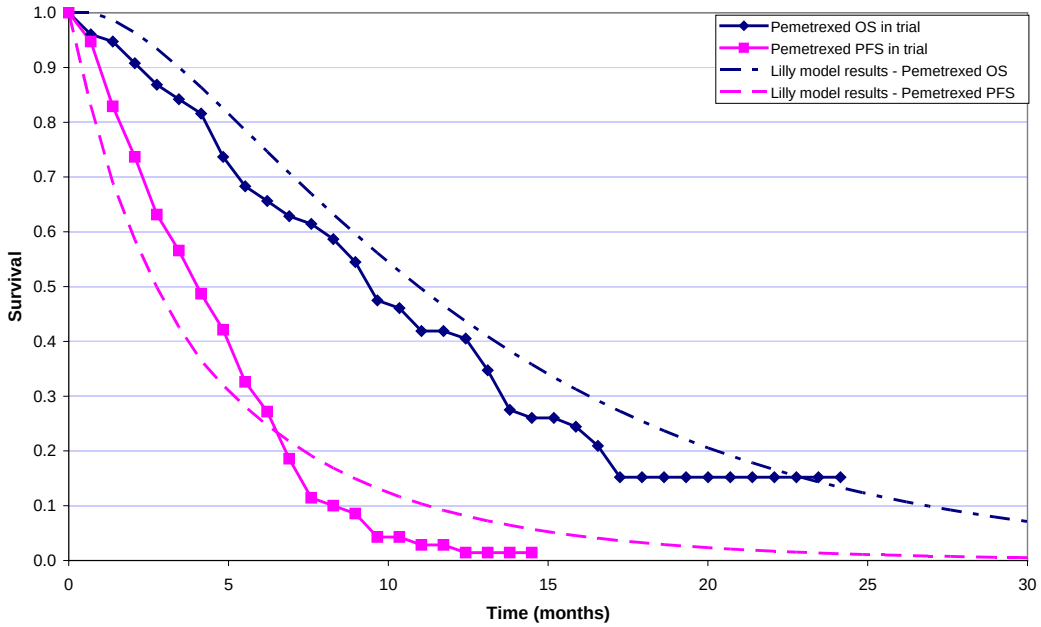


Figure 9.3 Overall survival and progression free survival for patients with adenocarcinoma: Kaplan-Meier analyses from JMDB trial data, and estimated by the modified (3rd) manufacturer's model.

A Pemetrexed + platinum



B Gemcitabine + platinum

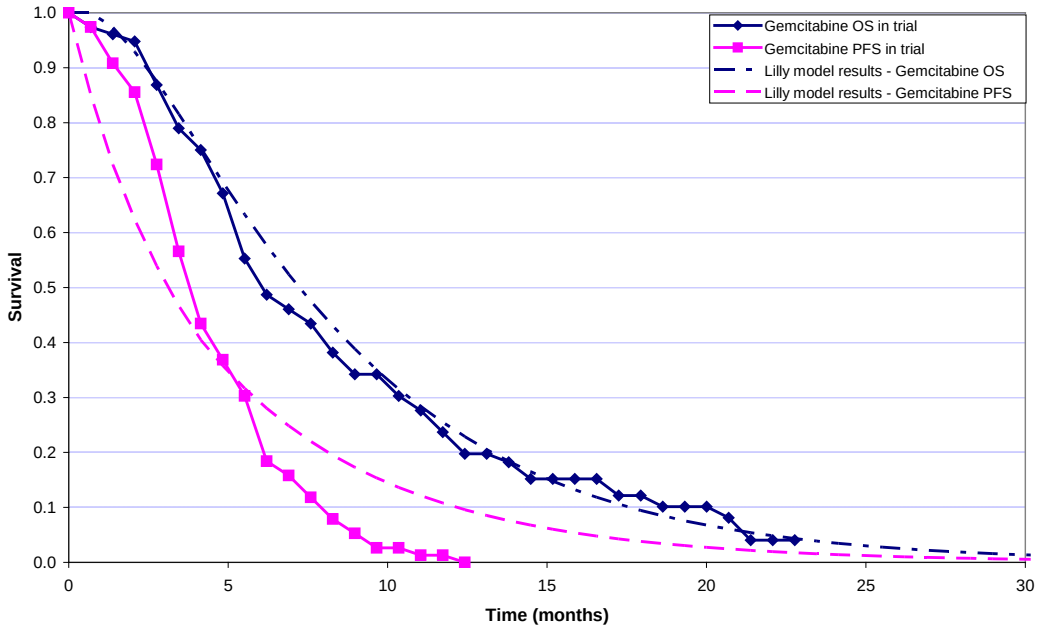


Figure 9.4 Overall survival and progression free survival for large cell carcinoma patients: Kaplan-Meier analyses from JMDB trial data, and estimated by the modified (3rd) manufacturer's model.