NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Pemetrexed for the first line treatment of advanced non-small-cell lung cancer

Premeeting briefing

This briefing presents major issues arising from the manufacturer's submission, Evidence Review Group (ERG) report and statements made by consultees and their nominated clinical specialists and patient experts. Please note that although condensed summary information is included for ease of reference, this briefing should be read in conjunction with the full supporting documents.

The manufacturer was asked to correct errors identified by the ERG in the economic model concerning the survival calculations. The manufacturer was subsequently asked to clarify issues around the clinical trials and cost-effectiveness assumptions. Subsequently the manufacturer was informed of a further error in the model concerning response rates and the model structure. The manufacturer chose to rectify this with further alterations of the model and a validation exercise. In addition, an addendum was provided to update the data from the submission. Evidence reported within this premeeting briefing and in the ERG report is based on the final version of the economic model, the manufacturer's submission and the economic addendum.

Licensed indication

Pemetrexed disodium (Alimta, Eli Lilly) in combination with cisplatin is indicated for the first-line treatment of patients with locally advanced or metastatic non-small-cell lung cancer (NSCLC) other than those with predominantly squamous cell histology.

Key issues for consideration

Clinical effectiveness:

- What is the Appraisal Committee's view of evidence in the manufacturer's submission suggesting that pemetrexed/cisplatin may be superior to

gemcitabine/cisplatin in prolonging overall survival in patients with non-squamous NSCLC, particularly those with adenocarcinoma or large-cell carcinoma?

- What is the Committee's view of the requirement for more specific histological testing than is currently standard across UK centres to identify patients in the manufacturer's target population (patients with non-squamous NSCLC, particularly those with adenocarcinoma or large-cell carcinoma)?
- Based on data presented in the manufacturer's submission, what is the Committee's view on the likely proportion of patients in the UK who would be diagnosed with adenocarcinoma or large-cell carcinoma?
- What is the Committee's view on:
    - the most appropriate comparators to be used in the effectiveness analysis based on current UK clinical practice
    - whether all relevant comparators have been included, taking current practice in the UK into account
    - the indirect comparison analysis undertaken by the manufacturer?

Cost effectiveness:

- What is the Committees view of the ERG conclusions regarding:
    - the errors and inappropriate structural assumptions in the submitted economic model
    - the requirement that the manufacturer's model needs extensive modification, redesign and validation against the clinical trial results, and a full quality audit?

1 Decision problem

1.1 Decision problem approach in the manufacturer's submission

Population	Patients who are chemotherapy-naïve with locally advanced or metastatic NSCLC other than predominantly squamous cell histology, who are unsuitable for surgery. The manufacturer-defined target population is patients with adenocarcinoma or large-cell carcinoma.
Intervention	Pemetrexed (500mg/m^2 iv infusion) in combination with cisplatin (75mg/m^2 iv infusion) on day one of a 21-day cycle, repeated for a maximum of four cycles.
Comparators	Primary comparator: • gemcitabine (1250 mg/ m^2 iv infusion) on day one and day eight in combination with cisplatin (75 mg/m^2 iv infusion) administered after gemcitabine on day one, and then every 21 days. Secondary comparators: • gemcitabine (1250 mg/ m^2 iv infusion) on day one and day eight in combination with carboplatin (AUC of 5) administered after gemcitabine on day one, and then every 21 days • docetaxel (75 mg/m^2 iv infusion) immediately followed by cisplatin (75 mg/m^2 iv infusion) every 21 day
Outcomes	The outcome measures to be considered include: overall survival • progression-free survival • tumour response rate • adverse effects of treatment • health-related quality of life (HRQoL)
Economic evaluation	Cost-effectiveness analysis results expressed as incremental cost per QALY gained. A cost per life year gained analysis was also conducted because this analysis is relevant in disease areas where extended survival is a key outcome of treatment. Time horizon – 6 years (a lifetime model). Costs will be considered from an NHS and personal social services perspective. A continuation rule is modelled to reflect clinical practice of discontinuing treatment in patients who do not respond after three cycles of chemotherapy.

1.2 Evidence Review Group comments

1.2.1 Population

The ERG noted that the manufacturer's statement of the decision problem describes adequately the relevant population, which is patients with locally advanced or metastatic non-squamous NSCLC who are chemotherapy-naïve. However, the ERG noted that the manufacturer's submission also defines a target population of patients with adenocarcinoma or large-cell carcinoma that is narrower than the population of patients described in the summary of product characteristics (that is, patients with locally advanced or metastatic NSCLC other than predominantly squamous cell histology). The ERG commented that patients with NSCLC-not otherwise specified (NSCLC-NOS) histology are excluded from the target population. Therefore, identifying the target population requires a more specific histological diagnosis than is common in UK clinical practice.

1.2.2 Intervention

Pemetrexed is a multi-targeted anticancer antifolate agent, which acts by disrupting folate-dependent metabolic processes that are essential for cell replication. Pemetrexed is administered as a 500mg/m^2 intravenous (iv) infusion in combination with cisplatin (75mg/m^2 iv infusion) on day one of a 21-day cycle.

Pemetrexed in combination with carboplatin is not included in the marketing authorisation and therefore is not considered in the manufacturer's submission.

The manufacturer stated that in England and Wales many cancer centres limit the maximum number of cycles of pemetrexed/cisplatin to four, because treatment guidelines (SIGN and ESMO) show limited or no benefit of extending treatment beyond this point. Therefore, the manufacturer

implemented a continuation rule in the cost-effectiveness analysis where patients who do not respond after three cycles stop treatment, while the remaining patients receive a maximum of four cycles. The manufacturer stated that in clinical practice, response to treatment is measured objectively with Response Evaluation Criteria in Solid Tumors (RECIST) (manufacturer's submission appendix 10.4), which measures tumour shrinkage, or it can be assessed by the clinician subjectively assessing symptom relief, disease stabilisation or improvement in the patient's general wellbeing.

1.2.3 Comparator

The manufacturer's submission stated that the main comparator was gemcitabine in combination with cisplatin. Other comparators included gemcitabine in combination with carboplatin and docetaxel in combination with cisplatin. The manufacturer limited its analyses of other comparators to gemcitabine/carboplatin as it is the most commonly used regimen in the UK (according to its marketing data) and docetaxel/cisplatin as it is one of the remaining platinum combinations used in the UK that is only administered on the first day of each cycle, which is preferred by some patients and centres because it requires fewer visits.

The ERG believed that all comparators should have been considered to be consistent with the original scope and decision problem and to strengthen the evidence base, which suggests little difference in clinical benefit across regimes. Marketing data provided by the manufacturer reported that the UK market share of gemcitabine had increased for the first-line treatment for stage IIIB/IV NSCLC from 53% at the beginning of 2004 to 83% at the beginning of 2008. The ERG stated that vinorelbine's 11% market share is noteworthy, especially when it is considered that the next most common agent, docetaxel, only accounts for 4% of the market.

1.2.4 Outcomes

The ERG considered that the manufacturer adequately described the outcomes of interest in relation to the relevant patient group and/or phase of treatment. However, no trial-derived HRQoL data were presented in the manufacturer's submission because no HRQoL data was collected from the JMDB trial. The ERG stated that this is a key outcome for this group of patients, and exclusion of this from the analysis of any phase III NSCLC trial may be considered a limitation of the evidence.

1.2.5 Economic evaluation

Incremental cost per QALY gained was used as a measure of cost effectiveness, which is in accordance with the NICE reference case.

1.2.6 Time frame

In the JMDB randomised controlled trial (RCT) from which the majority of clinical evidence is derived, patients were appropriately followed up until death or study closure.

1.3 Statements from professional/patient groups and nominated experts

Professional and patient groups commented that first-line treatment of advanced NSCLC is primarily with cisplatin-based chemotherapy. They stated that there was a tendency to replace cisplatin with carboplatin; however the efficacy of carboplatin regimens is currently under investigation. Currently the majority of patients having first-line chemotherapy have gemcitabine as the partner drug in platinum-based therapy.

Professional and patient groups stated that pemetrexed will be administered in an outpatient setting. The professional and patient groups also considered pemetrexed easier to administer than gemcitabine because it has a shorter infusion time (10 minutes) and is not given on day eight of a 21 day cycle. The professional and patient groups considered that pemetrexed's advantage over

alternative chemotherapy include its adverse events profile, which is characterised by a decrease in febrile neutropenia rates, decreased blood transfusions, decreased requirement for platelets and subsequent reduced hospital admissions.

2 Clinical effectiveness evidence

2.1 Clinical effectiveness in the manufacturer's submission

The manufacturer identified and presented data from one RCT which compared pemetrexed/cisplatin to gemcitabine/cisplatin. The study (JMDB) was a large open label phase III, randomised controlled non-inferiority trial. The JMDB trial included 1725 participants with squamous and non-squamous NSCLC. A number of different subgroups were defined by histology type (adenocarcinoma, large-cell carcinoma and NSCLC-not otherwise specified (NOS). Histologic or cytologic diagnosis diagnoses of NSCLC Stage IIIB (not amenable to curative treatment) or IV of the American Joint Committee on Cancer Staging Criteria for NSCLC was were an inclusion criteria to enter the JMDB trial. Diagnosis was based on biopsy and/or cytology samples and immunohisto chemistry in a concordance with the diagnosis protocol procedures in 'Lung cancer' (NICE clinical guideline 24). The manufacturer commented that baseline characteristics were well balanced between treatment arms and histological subgroups.

Outcomes included overall survival, progression-free survival, tumour response and tolerability. The manufacturer did not identify any direct head-to-head trials that compared pemetrexed/cisplatin to gemcitabine/carboplatin or docetaxel/cisplatin and therefore it carried out an indirect comparison.

2.1.1 Pemetrexed/cisplatin compared to gemcitabine/cisplatin

JMDB was a two-arm parallel group, multicentre trial in 26 countries with the majority of patients coming from Western Europe. Patients were over

18 years, chemotherapy-naïve and with a performance status score of 0 or 1. Patients were randomised to pemetrexed/cisplatin (pemetrexed 500 mg/m^2 and cisplatin 75 mg/m^2 every 21 days) or gemcitabine/cisplatin (gemcitabine 1250 mg/m^2 days one and eight of 21 day cycle and cisplatin 75 mg/m^2 every 21 days). Patients received a maximum of six cycles. The median number of cycles was five in both treatment arms. Patients were followed up till death or study closure. The length of the study was 2.5 years.

The main efficacy findings are summarised in table 1 where pemetrexed/cisplatin was found to be non-inferior to gemcitabine/cisplatin for overall survival in the JMDB overall trial population. It was also found that patients with non-squamous NSCLC, adenocarcinoma, large-cell carcinoma and the manufacturer's own defined target population (adenocarcinoma or large-cell carcinoma) had improved overall survival (statistically significant) and progression-free survival (not reported as statistically significant) when given pemetrexed/cisplatin. No significant findings were found for overall survival or progression-free survival in the NSCLC-NOS group, where gemcitabine/cisplatin appeared to lead to improved outcomes. Full results are reported in the addendum of the manufacturer's submission. Response rates were reported to be higher in the overall population and in patients with non-squamous NSCLC and adenocarcinoma, but this was not reported as statistically significant.

Table1 Key efficacy findings in the JMDB trial (intention to treat [ITT] 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]
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
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

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

[a] non-inferiority; [b] superiority

2.1.1.1 Safety

The manufacturer stated that pemetrexed was more tolerable to patients when compared to gemcitabine because of their adverse event profiles. The incidence of grade 3/4 haematological toxicities was significantly lower in the pemetrexed/cisplatin group compared with the gemcitabine/cisplatin group. There were fewer transfusions (all patients) with pemetrexed/cisplatin (16.4%)

compared with gemcitabine/cisplatin (28.9%, $p < 0.001$). Alopecia (hair-loss) was 21% in the pemetrexed/cisplatin group compared with 12% in the gemcitabine/cisplatin group ($p < 0.001$).

2.1.2 Indirect comparison

The manufacturer carried out an indirect comparison of the other comparators (gemcitabine/carboplatin and docetaxel/cisplatin) with pemetrexed/cisplatin. The manufacturer identified studies for inclusion in an indirect comparison by searching MEDLINE. For this search the manufacturer expanded the original search strategy (that was used to identify head-to-head trials with pemetrexed) to include comparative studies of pemetrexed, docetaxel, gemcitabine, paclitaxel, vinorelbine, erlotinib, bevacizumab and gefitinib. From the search results, the manufacturer identified studies that could be mapped to the treatment arms of JMDB. This identified two further phase III, open label RCT trials: gemcitabine/cisplatin compared with gemcitabine/carboplatin (Zatloukal et al. 2003, n = 176) and gemcitabine/cisplatin compared with docetaxel/cisplatin (Schiller et al. 2002, n = 605). All treatments were administered within their licensed indications. The manufacturer considered that the trials were relatively homogenous in terms of patient population and when compared to the JMDB trial. The unadjusted results are presented in tables 2 and 3. The manufacturer noted that the unadjusted comparison suggested that median overall survival and progression-free survival were improved for pemetrexed/cisplatin in patients with squamous and non-squamous NSCLC when compared with the other comparators.

Table 2 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)	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 et al. 2003	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 et al. 2002	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%

OS = overall survival, PFS = progression-free survival

Table 3 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 et al. 2003	51%	30%	7%	13%
Schiller et al. 2002	not reported	not reported	not reported	not reported

The manufacturer stated that in order to compare gemcitabine/carboplatin and docetaxel/cisplatin with pemetrexed/cisplatin, a hazard ratio was calculated for gemcitabine/carboplatin and docetaxel/cisplatin compared with gemcitabine/cisplatin. The hazard ratio was based on median overall survival and was applied to the hazard rate of the gemcitabine/cisplatin arm in the JMDB trial to produce a hazard rate for gemcitabine/carboplatin and docetaxel/cisplatin, adjusted for the JMDB population. This was then used to calculate an adjusted median overall survival estimate for the JMDB population. The manufacturer used this method to adjust the hazard rates for the histology types of interest by using the corresponding hazard rates in JMDB (such as for non-squamous NSCLC). The results are presented in table 4. The manufacturer concluded that these results suggest

pemetrexed/cisplatin has an advantage over gemcitabine/carboplatin and docetaxel/cisplatin in terms of improved overall survival.

Table 4 Summaries of the adjusted results from the indirect comparison

	Pem/cis	Gem/cis	Gem/carbo	Doc/cis
Non-squamous histology	n=618	n=638	n=89	n=289
Median OS (months) (95% CI)	11.0	10.1	9.2	9.5
Median PFS (months)	5.26	4.96	4.01	4.32
Target population adenocarcinoma and large-cell histology	n=512	n=488	n=89	n=289
Median OS (months) (95% CI)	11.8 (10.4-13.2)	10.4 (9.6-11.2)	9.5 (8.10-13.38)	9.8 (8.61--1.48)
Median PFS (months)	5.32	4.67	3.77	4.06

OS = overall survival, PFS = progression-free survival

2.1.2.1 Safety

The manufacturer presented adverse event rates for the four chemotherapy regimens. The manufacturer stated that these results suggest that pemetrexed/cisplatin is associated with lower rates of febrile neutropenia, neutropenia, diarrhoea, anaemia and thrombocytopenia. However, it was also associated with higher rates of fatigue. Further results are reported in the ERG report, page 28.

2.2 Evidence Review Group comments

2.2.1 Direct comparison

The ERG stated that baseline characteristics were well balanced between treatment arms and histological subgroups.

The ERG noted that the findings from the per-protocol analysis presented on request by the manufacturer differed little from the findings from the ITT analysis. The ERG noted that this strengthens considerably the robustness of

the JMDB trial results (per-protocol data presented in clarification letter appendix 1).

The ERG noted that the p-values presented in table 1 are for each separate subgroup, unadjusted for multiple comparisons testing. The ERG noted the p-values were likely not the most appropriate to present because the p-value for the test for interaction would be more appropriate. The test for interaction measures the effect between subgroups. On request, the manufacturer reported the p-values for the test for interaction as p = 0.0024 for squamous NSCLC compared with non-squamous NSCLC and p = 0.0059 across all other subgroups, implying real differences between subgroups.

The ERG stated that the analysis of the JMDB trial also included other pre-stated subgroup analyses, as outlined in the clinical study report. 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 (performance status of 0 versus 1); method of diagnosis (histological versus cytological); and stage of disease (IIIB versus IV). None of these subgroup analyses were reported in the manufacturer's submission but it was reported in the clinical study report that only histology showed significant results in improving overall survival.

2.2.1.1 Quality of life

The ERG considered HRQoL to be an important outcome for this group of patients and its absence from JMDB was a limitation of the trial. It noted that tolerability was assessed in the JMDB trial and therefore HRQoL is addressed indirectly.

2.2.1.2 Safety

The ERG stated that 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 number of reasons (specified in the manufacturer's submission, page 30).

With the exception of nausea, patients receiving pemetrexed reported fewer grade 3/4 toxicities than those receiving gemcitabine. No data on other types of adverse events including serious adverse events were presented in the manufacturer's submission. No safety data were presented by subgroup. The manufacturer stated that no clinically significant safety trends were identified, suggesting that no particular histology type subgroup experienced a different toxicity profile when compared with another subgroup or to the overall treated population.

2.2.2 Indirect comparison

The ERG considered that the search for studies to include in the indirect comparison was incomplete because EMBASE and the Cochrane Library were not searched. The ERG believes that all the comparators specified in the scope (pemetrexed, docetaxel, gemcitabine, paclitaxel and vinorelbine) should also have been included in the indirect comparison analyses. This would have identified five further phase III RCTs for consideration: one comparing gemcitabine/cisplatin with vinorelbine/cisplatin; one comparing paclitaxel/carboplatin with vinorelbine/cisplatin; two comparing docetaxel/carboplatin with vinorelbine/cisplatin; and one comparing vinorelbine/carboplatin with gemcitabine/carboplatin.

The ERG noted that no validity assessment of the included RCTs was undertaken by the manufacturer, although a comparison of baseline characteristics of the included trials was included in the manufacturer's submission. The ERG noted that the trials showed common characteristics, and that baseline characteristics were well balanced between treatment arms within trials. However, important differences were apparent across the three trials in terms of sex, patients with stage IV disease, histology type and

performance status score. The ERG considered that differences in histology type may be of particular relevance.

The ERG had some concerns in relation to the statistical approach that was used. In particular:

- It was shown in the literature that using a ratio of median survival times or rates at a particular point in time may result in serious under- or over-estimation of the treatment effect and major loss of statistical power. The hazard rate incorporates changes over time, whereas the ratio of medians only takes one point on the survival curve into account.

- 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 ERG stated that the manufacturer's submission (page 42) suggests that the treatment arm level hazard rates have been used. Indeed, results in tables 16 and 20 of the manufacturer's submission suggest that arm level response rates and adverse events rate data are compared directly against each other without any recognition of randomisation within trial, with any missing subgroup data assumed to be the same as gemcitabine/cisplatin.

- The ERG stated that the key assumption of an indirect comparison is that the relative effects are exchangeable across the trial settings, that is, 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 used estimates based on each subgroup of the JMDB study to adjust the other trial hazard rates. However, it was not possible to confirm whether the relative effects of gemcitabine/carboplatin versus gemcitabine/cisplatin or

docetaxel/cisplatin versus gemcitabine/cisplatin would be consistent across these subgroups as stated in the manufacturer's submission. The ERG considered that individual patient data would be required to allow a complete and accurate analysis.

The ERG concluded that because key comparators had been excluded from the indirect comparisons analysis and the assumptions underlying the statistical approach employed, the findings from this analysis should be interpreted with caution.

2.3 Statements from professional/patient groups and nominated experts

The professional and patient groups noted that the biological difference between histological subtypes has been identified as a key consideration determining appropriate treatment in cancer care. Professional groups commented that in the JMDB trial, histology was independently assessed in each centre, rather than by a central review of all pathology, improving the external validity of the trial by mirroring clinical practice. Professional groups stated that they considered the trial results to be robust since they were based on pre-specified subgroups based on histology.

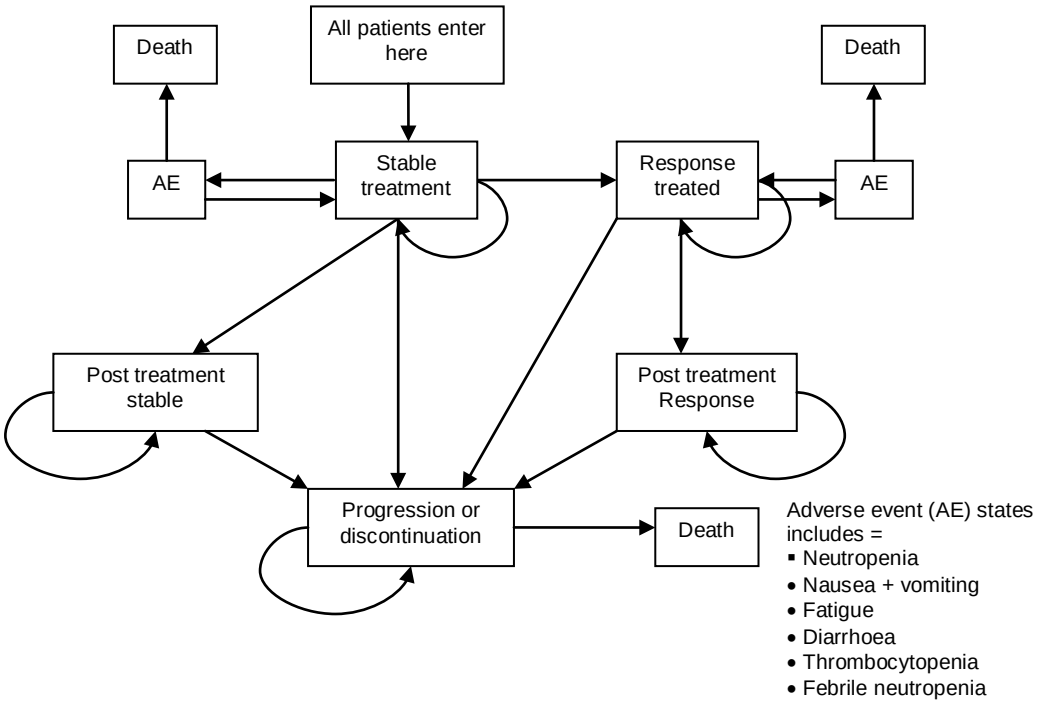
3 Cost effectiveness

3.1 Cost effectiveness in the manufacturer's submission

The manufacturer developed a Markov model which compared pemetrexed/cisplatin, gemcitabine/cisplatin, gemcitabine /carboplatin and docetaxel/cisplatin. All clinical events were modelled via transition probabilities. Treatment effects considered included overall survival, progression-free survival, response rates, adverse events and HRQoL. All effectiveness data used in the model, apart from HRQoL were trial based. The JMDB trial was used for the direct comparison while the results of the indirect comparison were used for the other comparators. The states and structure of

the manufacturers model is summarised in figure 1 (Figure 13 from manufacturer's submission, page 67).

Figure 1 Schematic of manufacturer's model



The model's time horizon of 6 years was considered appropriate. The adverse event states are built into the model as separate mutually exclusive states attached to the stable and treatment response health states, which means that a patient only experiences one adverse event at a time. Each adverse event lasts one cycle apart from febrile neutropenia which is assumed to affect patients over multiple cycles.

Following consultation with clinical experts, the manufacturer incorporated a continuation rule into the model, based on current guidelines that state patients should be given a maximum of four cycles. Therefore patients who do not respond to pemetrexed discontinue treatment after three cycles. This differs from the trial protocol in which patients continue until disease progression. The manufacturer stated that the continuation rule prevents

patients from responding in cycle four onwards, so response rates were under-reported compared with the trial.

The manufacturer stated that to reflect treatment discontinuation after cycle three for non-responders, all chemotherapy costs for the following cycles were removed. Patients continue in the stable state but with a utility decrement attached equivalent to the utility of being in progression. Patients continue in their states as dictated by trial data: the transition rates do not change. However, those in the stable state at this point no longer have the possibility of responding.

The manufacturer undertook a literature review of the utility data related to patients with NSCLC and identified a number of studies, none of which were suitable for inclusion. Instead the manufacturer used the study by Naffes et al. (2008) which was commissioned by the manufacturer for second-line NSCLC, but was assumed by the manufacturer to apply to the first-line setting. The study involved 100 members of the public interviewed with visual analogue scale and standard gamble techniques to elicit societal values. Costs were estimated from the British National Formulary, NHS reference costs, and published literature. The main utilities and costs are presented on page 37 and 39 of the ERG report.

3.1.1 Results

The main results from the manufacturers economic modelling are presented in tables 4, 5 and 6 below.

Table 4 Life year gained, QALYs gained and costs for non-squamous population

	Intervention	LYG	QALYs	Costs (£)
No continuation rule	Pemetrexed +cisplatin	1.13	0.61	11,674
	Gemcitabine + cisplatin	1.05	0.57	10,310
	Gemcitabine + carboplatin	0.97	0.51	9686
	Docetaxel + cisplatin	1.00	0.53	10,294
Continuation rule	Pemetrexed +cisplatin	1.13	0.58	10,857
	Gemcitabine + cisplatin	1.05	0.53	9606
	Gemcitabine + carboplatin	0.97	0.49	9023
	Docetaxel + cisplatin	1.00	0.50	9673

Table 5 Incremental cost-effectiveness results for non-squamous population

	Comparison	Incremental LYG	Incremental QALYs	Incremental costs (£)	ICER (£)
No continuation rule	Pem+cis vs. Gem + cis	0.08	0.041	1364	33,065
	Pem+cis vs. Gem + car	0.15	0.092	1988	21,585
	Pem+cis vs. Doc + cis	0.13	0.075	1380	18,401
Continuation rule	Pem+cis vs. Gem + cis	0.08	0.048	1252	25,967
	Pem+cis vs. Gem + car	0.16	0.094	1834	19,540
	Pem+cis vs. Doc + cis	0.14	0.081	1184	14,675

Table 6: Incremental cost-effectiveness results by histology type

	ICER of pem/cis vs.	Incremental QALYs	Incremental costs (£)	ICER (£)
Adeno-carcinoma	Gem/cis	0.07	1346	18,442
	Gem/carbo	0.13	1927	14,887
	Doc/cis	0.11	1270	11,179
Large-cell carcinoma	Gem/cis	0.18	1466	8056
	Gem/carbo	0.23	2066	9086
	Doc/cis	0.21	1401	6579

The manufacturer conducted both one-way and probabilistic sensitivity analysis. The results of the sensitivity analysis are presented in the ERG report pages 45-47. The scenario analysis demonstrated that the model is most sensitive to changes in chemotherapy costs and survival estimates. Probabilistic sensitivity analysis was not presented in the most up-to-date analyses.

3.2 Evidence Review Group comments

3.2.1 Literature review

The ERG was confident that no published economic evaluations of pemetrexed for the first-line treatment of NSCLC were missed in the review performed by the manufacturer.

3.2.2 Economic Model

3.2.2.1 General points

The ERG considered that the model had an appropriate time horizon for the condition. The ERG noted that the utilities used were not ideal because trial-based utilities would have been preferred. However, the ERG considered that the utilities used were acceptable. The ERG stated that the main costs had been identified.

3.2.2.2 Comparators

The ERG stated that the omission of some standard comparators, and the selection of docetaxel (4% market share) over vinorelbine (11% market share and much less expensive) was problematic, and prevented a full assessment of pemetrexed against NICE-recommended alternatives. The ERG also noted that gemcitabine's patent expires in the UK in March 2009. If the price of gemcitabine falls as a result, this will increase the cost difference between pemetrexed/cisplatin versus gemcitabine/cisplatin and pemetrexed/cisplatin versus gemcitabine/carboplatin and increase the ICERs.

3.2.2.3 Consistency with trial results

The ERG commented that the chosen Markov model structure does not seem to be appropriate because it imposes strong constraints which make it difficult to replicate accurately the trial data used to calibrate the model. The ERG commented that this was particularly noticeable in the calculation of response and survival.

3.2.2.4 Response rates

The ERG stated that to fit the model structure the response rate probabilities were calculated by partitioning the total trial responses between the cycles, using the initial number of patients in the trial as the denominator. These probabilities were then used to estimate the cycle by cycle number of responders. The ERG stated that, since the number remaining on pemetrexed diminishes rapidly each cycle (as patients' disease progresses or they die), the number of responders is underestimated in all cycles but the first. The ERG stated that due to the rigid structure of the model, it was 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 7 shows the discrepancies that the ERG noted for six cycles of treatment between the JMDB trial and the two versions of the model logic. Model estimates were obtained by the ERG by calculating the number of new responses occurring in each of the first six cycles in the model spreadsheets.

Table 7 Response rates for non-squamous patients recorded in the JMDB trial (up to six cycles of chemotherapy) and estimated by original and modified manufacturer's models.

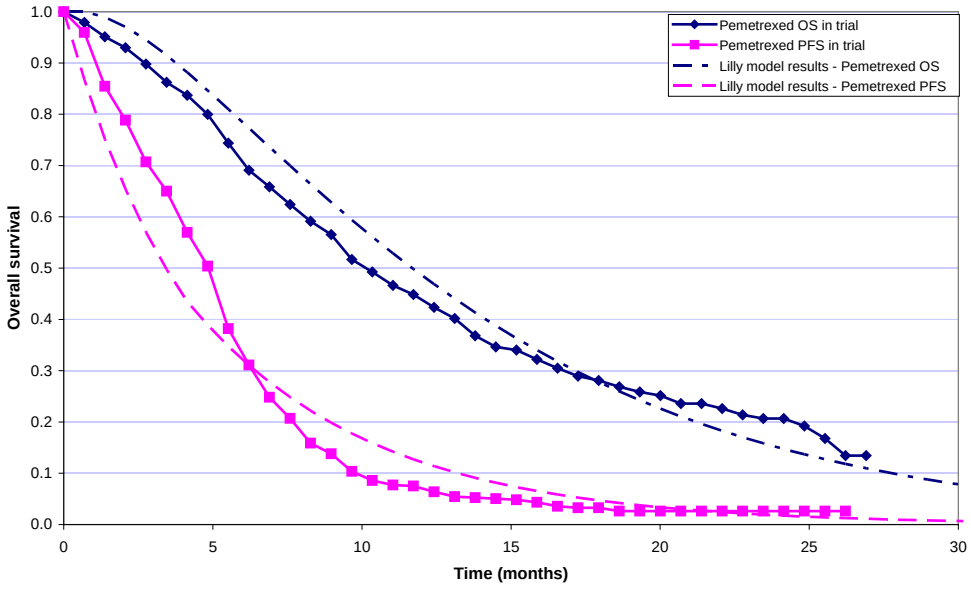
Responses during cycle	Pemetrexed/cisplatin		Gemcitabine/cisplatin	
	JMDB trial	Model	JMDB trial	Model
1	0.00%	0.00%	0.00%	0.00%
2	16.02%	16.02%	14.04%	13.99%
3	1.29%	3.81%	0.32%	2.54%
4	8.58%	3.06%	5.99%	2.11%
5	0.49%	2.46%	0.16%	1.75%
6	2.24%*	1.97%	1.26%#	1.45%
Total	28.64%	27.30%	22.24%	21.84%
Difference Pem vs. Gem	+6.40%	+5.46%		

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

3.2.2.5 Survival

The ERG considered that because overall survival and progression-free survival are the primary outcomes in the JMDB trial, they should be accurately replicated in the economic model for each of the trial subpopulations. The ERG examined Kaplan-Meier curves for the indicated populations and the subpopulations from the model and trial data. The ERG noted that the manufacturer's model appears to overestimate overall survival in both arms and almost all patient groups. For progression-free survival, the ERG commented that the model tends to underestimate in the first 6 months and to overestimate thereafter. Figure 2 is an example for the trial population.

Figure 2: Overall survival and progression-free survival for non-squamous carcinoma patients pem/cis: Kaplan-Meier analyses from JMDB trial data, and estimated by the manufacturer's model. Reproduced from ERG report, page 79 Figure 9.1.



In addition, the ERG noted that lower survival estimates are produced for longer time horizons suggesting an error in the models logic.

The ERG noted that the manufacturer's model assumes that death only occurs from the progressive disease state, and therefore no patients die within the first cycle, and very few in the second cycle (about 1%). The trial data indicate that 4-5% of patients were dead by the end of cycle two.

3.2.2.6 Additional issues

The ERG also identified the following additional issues.

- All transition probabilities during the trial period are assumed to arise from constant risk processes (that is, exponential survival distributions), without any justification.
- The half cycle correction appears to have been disabled for costs and used incorrectly for outcomes.

- The model assumes that adverse events apply only to a single cycle. All adverse events are expected to resolve as soon as chemotherapy is terminated for any reason, therefore no account is taken of cumulative cost or outcome effects of patients suffering multiple concurrent adverse events (for example, within a single hospital admission). This omission can lead to over-estimation of the costs and harms attributable to treatment.

- The manufacturer appropriately highlighted febrile neutropenia as an important adverse event given the associated mortality risk. The estimate used in the model is derived from a meta-analysis. However, the ERG considered that the mortality risk has been implemented incorrectly, effectively multiplying the estimated mortality risk. The value in the meta-analysis was all-cause mortality rather than mortality owing to chemotherapy. The number of events in JMDB was too small to allow effective validation. However, the ERG commented that the model appears to be insensitive to varying the rate of febrile neutropenia.

3.2.2.7 The role of response

The ERG stated that the model structure adopted by the manufacturer is commonly used to represent the action of chemotherapy agents for which patient benefit is primarily driven through objective response (defined as reduction in tumour size by RECIST). It is commonly assumed that such a response is indicative of a benefit in progression-free survival, thereby delaying disease progression and becoming the source of the overall survival gain. Following 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 course of the disease will continue. The JMDB trial is unusual since all the reported gain occurs after disease progression, with progression-free survival effectively identical between the pemetrexed and gemcitabine/cisplatin arms. Following

disease progression there is a modest reduction in mortality hazard, which can be attributed to pemetrexed. This phenomenon is consistent over time.

The ERG stated that it is not clear whether objective response determines the extent of health gain and whether the survival gain is restricted to only those who have responded to treatment, or to all patients exposed to treatment.

The ERG considered that these issues are particularly relevant to the consideration of a 'stopping rule' based on observed response. The ERG stated that if response predicts neither progression-free survival nor post-progression survival, then the use of 'response' as a distinct health state is potentially irrelevant, and could generate misleading results.

3.2.2.8 ERG conclusion

The ERG noted that as a result the submitted model is unable to generate results consistent with the trial evidence, especially with respect to three primary clinical outcomes (overall survival, progression-free survival and response rate). Given that this is the only data inputted into the model, the model should be able to reproduce the results. The ERG cannot conclude whether or not pemetrexed is cost effective compared to currently recommended treatments, but the ERG consider that the evidence submitted by the manufacturer is not sufficiently convincing or robust to support its cost effectiveness.

4 Authors

Dr Andres Roman (Technical Lead) and Prashanth Kandaswamy (Technical Adviser) with input from the Lead Team (John Goulston and Richard Harding)

Appendix A: Sources of evidence considered in the preparation of the premeeting briefing

A The evidence review group (ERG) report for this appraisal was prepared by Liverpool Review and implementation Group, University of Liverpool:

Fleeman N, Bagust A, McLeod C, et al. Pemetrexed for the first line treatment of locally advanced or metastatic non-small cell lung cancer (NSCLC): A Single Technology Appraisal. LRiG, The University of Liverpool, 2009.

B Submissions or statements from the following organisations:

I Manufacturer/sponsor

- Eli Lilly Company Limited

II Professional/specialist, patient/carer and other groups:

- The Roy Castle Lung Cancer Foundation
- British Thoracic Society Lung Cancer and Mesothelioma Specialist Advisory Group
- NCRI/RCP/RCR/ACP/JCCO
- Royal College of Nursing

Additional references used:

Naffes B, Stafford M**,** Gavriel S**,** Bhalla S and Watkins J. Health state utilities for non small cell lung cancer. *Health and Quality of Life Outcomes* 2008, 6:84

Schiller JH, Harrington D, Belani CP et al. Comparison of four chemotherapy regiments for advanced non-small-cell lung cancer. N. Engl. J. Med. 346, 92-98 (2002).

Zatloukal PV, Petruzelka L, Zemanova M, et al: Concurrent versus sequential radiochemo- therapy with vinorelbine plus cisplatin (V-P) in locally advanced non small cell lung cancer. A randomized phase II study. Proc Am Soc Clin Oncol 21:290a, 2003.