NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Premeeting briefing

Pemetrexed for the maintenance treatment of non-small-cell lung cancer

This briefing presents the key 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 this briefing is a summary of the information available and should be read with the full supporting documents.

The manufacturer was asked to provide:

- additional data on overall survival and progression-free survival
- additional data on disease state, response status, first-line treatment, platinum treatment and performance status of patients prior to maintenance therapy
- individual patient data including details of adverse events, dose reductions, hospitalisations, antiemetic therapy, transfusions and scans received
- details on the use of and reasons for initiating second-line therapy
- details of the analysis by geographic region and clarification of the crossover reported in the trial
- further information on patients who had received treatment after progression had occurred, contrary to study protocol

Licensed indication

Pemetrexed is indicated as monotherapy for the maintenance treatment of locally advanced or metastatic non-small cell lung cancer other than predominantly squamous cell histology in patients whose disease has not progressed immediately following platinum-based chemotherapy. First-line treatment should be a platinum doublet with gemcitabine, paclitaxel or docetaxel.

Key issues for consideration

Clinical effectiveness

- Does the Appraisal Committee consider data derived from the JMEN trial to be sufficiently robust to inform the clinical effectiveness of pemetrexed maintenance treatment?
  - The primary outcome was changed from overall survival to progression-free survival in the course of the trial.
  - Histology was not a factor in the randomisation of patients, yet the manufacturer's submission is based on the effectiveness of the non-squamous histology group.

- Does the Committee consider the results of the JMEN trial to be generalisable to patients in the UK?
  - Patients in the JMEN trial were younger and of better performance status (ECOG 0–1) than those expected in UK clinical practice.
  - One-third of the patients were of Asian origin. Evidence suggests that this ethnic group has a more favourable prognosis for non-small-cell lung cancer in general.
  - The trial included second-line treatments which are not used in the UK.
  - The trial allowed unlimited cycles of maintenance therapy.

Cost effectiveness

- Does the Committee consider the capping of pemetrexed treatment costs at 17 cycles without capping the benefits accrued to be appropriate?
- What are the implications of the poor utility data available for this patient population from the JMEN trial?
- What is the Committee's view on the manner in which the utilities are assigned to different trial arms?
  - Patients who enter the model in the same health state are assigned a better utility in the pemetrexed arm than in the placebo arm.

Previous NICE guidance

- Pemetrexed for the first-line treatment of locally advanced or metastatic non-small-cell lung cancer. NICE technology appraisal 181 (2009). Available from www.nice.org.uk/TA181

  - Pemetrexed in combination with cisplatin is recommended as an option for the first-line treatment of patients with locally advanced or metastatic non-small-cell lung cancer only if the histology of the tumour has been confirmed as adenocarcinoma or large-cell carcinoma.

- Pemetrexed for the treatment of non-small-cell lung cancer. NICE technology appraisal 124 (2007). Available from www.nice.org.uk/TA124

  - Pemetrexed is not recommended for the treatment of locally advanced or metastatic non-small-cell lung cancer. (Pemetrexed has now been recommended for the first-line treatment of non-small-cell lung cancer [see above]. TA124 applies to patients who have had prior chemotherapy.)

1 Decision problem

1.1 Decision problem approach in the manufacturer's submission

Population	Patients with locally advanced or metastatic non-small-cell lung cancer of other than predominantly squamous histology (that is, non-squamous, adenocarcinoma, large cell carcinoma or non-small-cell lung cancer 'not otherwise specified') whose disease has not progressed (that is, they have complete response, partial response or stable disease) following four cycles of induction treatment with a platinum doublet (gemcitabine, docetaxel or paclitaxel plus cisplatin or carboplatin).
Intervention	Pemetrexed (500 mg/m^2 iv infusion) on day one of a 21-day cycle, until disease progression.
Comparators	Placebo (watch and wait).
Outcomes	• Health-related quality of life. • Overall survival. • Progression-free survival. • Response rates. • Adverse effects of treatment.
Economic evaluation	Cost-effectiveness analysis results expressed as incremental cost per quality-adjusted life year (QALY) gained. A cost per life year gained analysis is also conducted. The time horizon is 6 years (a lifetime model). Costs are considered from an NHS and personal social services perspective.

1.2 Evidence Review Group comments

1.2.1 Population

The ERG noted that the manufacturer provided evidence for patients who had received a first-line platinum doublet containing gemcitabine, paclitaxel or docetaxel in line with the marketing authorisation.

1.2.2 Intervention

The ERG noted that the JMEN clinical trial placed no limits on the maximum number of chemotherapy cycles administered to patients. The manufacturer considers that maintenance treatment for non-small-cell lung cancer is new to the NHS and although the number of treatment cycles is unknown it is not likely to exceed 20 cycles.

1.2.3 Comparators

The ERG considered the administration of a saline solution in the placebo (watch and wait) plus best supportive care (BSC) arm to be an extra element to the watch and wait policy used in UK clinical practice.

1.2.4 Outcomes

The ERG considered that the manufacturer's key outcomes were consistent with the scope issued by NICE and standard for research in this field

1.2.5 Economic evaluation

The economic model used a 6-year time frame, which is taken to be equivalent to a life-time horizon.

1.2.6 Other issues

Although no specific subgroup analyses were defined in the NICE scope, the manufacturer identified patients with adenocarcinoma histology as an important subgroup of patients from the non-squamous population.

1.3 Statements from professional/patient groups and nominated experts

Professional groups noted that maintenance treatment is a new concept in the management of lung cancer. Although pemetrexed may increase overall survival and progression-free survival, the evidence base is still limited. Because treatment is administered until progression, proactive imaging may have to be performed to determine progression. It was also noted that patients will need injections of vitamin B12 in the course of their treatment. Although no extra staff training would be required, extra capacity might be needed for the increase in patient numbers due to maintenance therapy.

Professional groups suggested that people with adenocarcinoma may benefit more from the technology.

2 Clinical effectiveness evidence

2.1 Clinical effectiveness in the manufacturer's submission

The key clinical evidence comes from one phase III multicentre, double-blind randomised control study (JMEN trial) that reported the efficacy of pemetrexed for the maintenance treatment of people with advanced or metastatic (stage IIIB and IV) non-small-cell lung cancer, other than those with predominantly squamous histology, whose disease had not progressed following treatment with platinum-based, first-line chemotherapy. (A summary of induction therapies is given in table 1 below). All patients had an ECOG performance status of 0 or 1.

Table 1. Summary of induction therapies in the JMEN study (manufacturer's submission page 32)

	Non-squamous population (n=481)		
	Pemetrexed n=325	**Placebo n=156**	**Total N=481**
Specific induction regimen n (%)			
Unknown	1 (0.3)	0 (0.0)	1 (0.2)
Docetaxel + carboplatin	14 (4.3)	6 (3.8)	20 (4.2)
Docetaxel + cisplatin	5 (1.5)	3 (1.9)	8 (1.7)
Gemcitabine + carboplatin	90 (27.7)	37 (23.7)	127 (26.4)
Gemcitabine + cisplatin	107 (32.9)	61 (39.1)	168 (34.9)
Paclitaxel +carboplatin	89 (27.4)	36 (23.1)	125 (26.0)
Paclitaxel +cisplatin	19 (5.8)	13 (8.3)	32 (6.7)

The study was conducted in 83 centres across 20 countries. There were no centres in the UK. A total of 663 patients were randomised 2:1 to either pemetrexed plus BSC (n=441) or placebo plus BSC (n=222). Of these, 481 patients (325 on pemetrexed, 156 on placebo) had non-small-cell lung cancer of non-squamous histology. These patients form the evidence base for this appraisal. Patients in the pemetrexed arm received pemetrexed 500 mg/m^2 on day one of the 21-day cycle, administered as a 10-minute infusion, plus BSC. Patients in the placebo arm received normal saline (0.9% sodium chloride) on day one of the 21-day cycle, administered as a 10-minute infusion, plus BSC. Both arms received prior and concomitant medication with folic acid, vitamin B12, and dexamethasone. Each patient underwent a treatment period and a follow-up period. Patients received study treatment (pemetrexed or placebo) until objective disease progression. Baseline tumour measurements were performed by imaging (predominantly computerised tomography [CT] scan) within 4 weeks of study entry. Tumour response was assessed clinically every 3 weeks and objectively (with radiographic imaging, using the RECIST criteria) every two cycles (6 weeks). The follow-up period began when the patient discontinued study treatment. Investigators followed all patients until

death or study closure (see manufacturer's submission page 35–6, ERG report page 88).

The primary outcome of the study was initially overall survival but was later changed to progression-free survival (see manufacturer's submission page 36). Secondary outcomes were overall survival, objective tumour response rate, disease control rate, adverse events and time to worsening of symptoms. The manufacturer's submission states that an additional prespecified subgroup analysis was planned to evaluate the efficacy of pemetrexed versus placebo in different histological subgroups of non-small-cell lung cancer (see manufacturer's submission page 41).

The manufacturer's submission states that the patent population in the trial is difficult to compare with the patient characteristics from the lung cancer database (LUCADA, 2007), the largest source of information on lung cancer patients in the UK. All of the patients in the JMEN trial had an ECOG performance status of 0-1 compared with 34% of patients in England and Wales who have an ECOG performance status of 0-1. Patients in the JMEN trial were younger (median age of 60 years compared with 71 years in the LUCADA database) and there was a higher proportion of patients with adenocarcinoma (49.5% compared with 25% in the LUCADA database). For further information see page 33 of the manufacturer's submission.

2.1.1 Results

The manufacturer's submission provides data on the efficacy of pemetrexed plus BSC compared with placebo plus BSC for the primary endpoint of progression-free survival, and secondary endpoints of overall survival, tumour response, and disease control. The evidence for health-related quality of life was limited due to a high degree of censoring and missing data.
One-year survival rates were substantially greater in the pemetrexed arm compared with the control arm for both the non-squamous and adenocarcinoma population but were smaller at 2-years. Tables 2 and 3

summarise the effectiveness of pemetrexed plus BSC compared with placebo plus BSC in the treatment of non-squamous and adenocarcinoma groups.

Table 2. Results of the JMEN trial non-squamous population (manufacturer's submission page 47, ERG report page 29)

Endpoint	Pemetrexed (n = 325)	Placebo (n = 56)	HR (95% CI)	p-value
Primary				
PFS median (months)	4.5	2.6	0.44 (0.36–0.55)	< 0.00001
Secondary				
OS median (months)	15.5	10.3	0.70 (0.56–0.88)	0.002
Tumour response (%) (CR + PR)	7.4	1.9		0.018
Disease control rate (%) (CR+PR+SD)	57.7	32.7		< 0.001
Survival rate at 1 year (%)	60	42		
Survival rate at 2 years (%)	28	22		
CI, confidence interval; CR, complete response; OS, overall survival; PR, partial response; PFS, progression-free survival; SD, stable disease.				

Table 3. Results of the JMEN trial adenocarcinoma histology (manufacturer's submission page 47, ERG report page 29)

Endpoint	Pemetrexed (n = 222)	Placebo (n = 106)	HR (95% CI)	p value
Primary				
PFS median (months)	4.7	2.6	0.45 (0.35–0.39)	< 0.00001
Secondary				
OS median (months)	16.8	11.5	0.73 (0.56–0.96)	0.026
Tumour response (%) (CR + PR)	8.1	2.8		0.090
Disease control rate (%) (CR+PR+SD)	61.0	33		< 0.001
Survival rate at 1 year (%)	67	47		
Survival rate at 2 years (%)	29	26		
CI, confidence interval; CR, complete response; OS, overall survival; PR, partial response; PFS, progression-free survival; SD, stable disease.				

Patients in the pemetrexed arm had significantly longer time to worsening for pain compared with patients in the placebo arm (median 8.4 months for pemetrexed versus 4.9 months for placebo). There were no statistically significant differences between treatment groups in terms of time to worsening of any other symptoms including loss of appetite, fatigue, cough, dyspnoea, symptom distress and global quality of life (see manufacturer's submission page 45).

2.1.2 Adverse events

The manufacturer reported that patients in the pemetrexed arm exhibited higher rates of grade 3/4 toxicities (6.3%) compared with patients in the placebo arm (2.3%). Fatigue and neutropenia were the most commonly reported adverse events. Significantly higher percentages of patients in the pemetrexed arm required transfusions (9.5% with pemetrexed versus 5.9% with placebo, p=0.003) and erythropoiesis-stimulating agents (5.9% with pemetrexed versus 1.8% with placebo, p=0.017). There was a statistically significant increase in the incidence of hospitalisations because of drug-related toxicity (5.2% with pemetrexed arm compared versus 0% with placebo, p<0.001) and the proportion of patients discontinuing treatment because of adverse events (4.8% with pemetrexed versus 1.4% with the placebo, p=0.027). For further information see page 51–3 of the manufacturer's submission.

2.1.3 End-of-life criteria

The manufacturer submitted evidence for the consideration of pemetrexed under the end-of-life criteria. The median overall survival of patients with histologically confirmed non-small-cell lung cancer is 232 days (7.6 months) (LUCADA data, 2007). The JMEN trial reports a median survival benefit with pemetrexed of 5.2 months compared with placebo in non-squamous non-small-cell lung cancer and 5.3 months with adenocarcinoma. There is also no other technology licensed for use as maintenance treatment of non-small-cell

lung cancer. The manufacturer's submission estimates that the number of patients eligible to receive pemetrexed for maintenance therapy of non-squamous non-small-cell lung cancer is 949 and the total number of patients eligible to receive pemetrexed for any indication (that is, maintenance treatment of non-small-cell lung cancer, first- and second-line treatment of non-small-cell lung cancer and mesothelioma) is 3,426 (see manufacturer's submission page 48–9).

2.2 Evidence Review Group comments

Overall, the ERG was of the opinion that the assessment carried out by the manufacturer was well designed. However, the ERG had a number of concerns regarding the conduct of the trial and its generalisability to clinical practice in England and Wales.

2.2.1 Generalisability of the results of the trial

None of the trial centres for the JMEN trial were located in the UK. There was a high proportion of Asian patients (35% in the trial population), who have substantially longer absolute overall survival in the trial of18.9 months compared with 13.8 months for the EU population (manufacturer's response to clarification letter page 8). The ERG noted that there is evidence to suggest that this ethnic group has a more favourable prognosis for overall survival in non-small-cell lung cancer in general and thus may be different to most patients treated in England and Wales. However, key effectiveness results depend on relative differences (rather than absolute values), which do not appear to be affected by ethnicity.

The population in the JMEN trial was restricted to patients with an ECOG performance status of 0 or 1 and with few co-morbidities. The ERG's communications with clinical specialists confirmed that patients with ECOG performance status of 0 or 1 and good health status are a relatively small proportion of the total number of non-small-cell lung cancer patients treated in clinical practice in England and Wales.

First-line treatment in the JMEN trial is not comparable with clinical practice in the UK. Thirty two percent of patients in the trial received induction treatment with paclitaxel compared with 1% of patients in the UK.

Second-line treatment in the JMEN trial is also not comparable with clinical practice in the UK. Fifty three percent of patients in the pemetrexed arm and 36% of patients in the placebo arm received second-line treatment not used in the UK. These treatments may have influenced the overall survival estimates observed in the trial and may mean the results do not reflect the survival benefits that might be expected in UK clinical practice.

Patients in the trial received unlimited cycles of pemetrexed, which is unlikely to occur in the UK.

2.2.2 Conduct of the trial

The key clinical evidence is derived from the non-squamous population which was a histological subgroup of the entire trial population. This subgroup was not included in the stratification of the randomisation procedure and the trial was not powered to perform this subgroup analysis.

The ERG did not consider that adequate justification was given for changing the primary endpoint of the JMEN trial from overall survival to progression-free survival. This decision had the effect of truncating the data available for analysis for overall survival, which is of critical importance to the economic evaluation.

The ERG considered the high rate of missing data on health-related quality of life to be a serious limitation.

3 Cost effectiveness

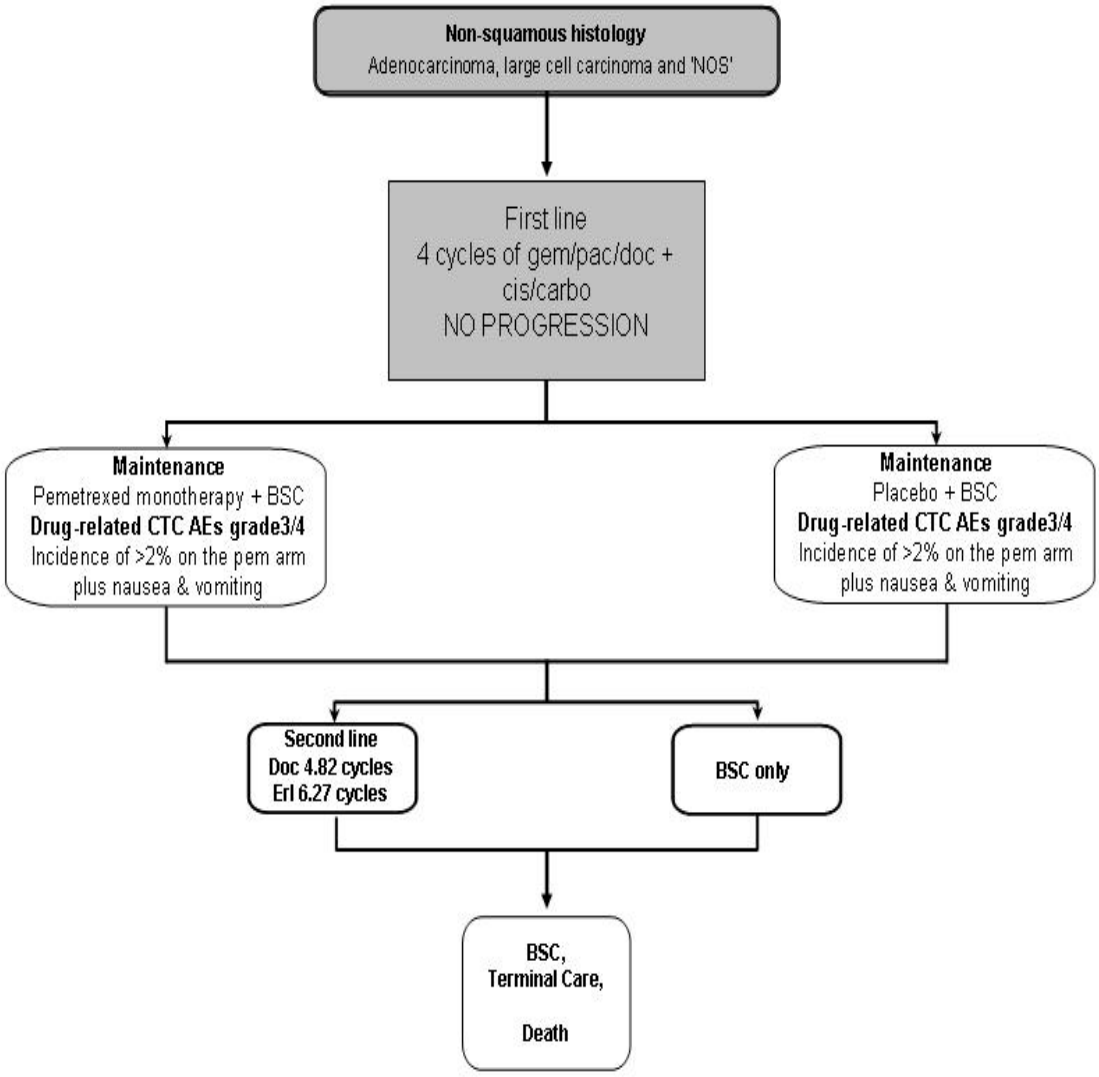
3.1 Cost effectiveness in the manufacturer's submission

The manufacturer stated that the economic evaluation was based on the non-squamous population of the JMEN trial. The adenocarcinoma population was assessed in a subgroup analysis.

3.1.1 Model structure

Patients enter the model at the start of maintenance therapy, which is assumed to begin after four cycles of first-line chemotherapy (consisting of a platinum doublet with gemcitabine, paclitaxel or docetaxel) in patients who have no evidence of disease progression. Patients in the placebo arm receive watch and wait treatment and BSC, and patients in the pemetrexed arm receive treatment in 21-day cycles plus BSC until disease progression, after which they receive second-line therapy. The time horizon of the model is 6 years. The model includes three health states (not progressed, progressed and terminal state). A half-cycle correction is used in the survival outcomes in the model. No half-cycle correction is applied to the costs because most of the costs are incurred at the beginning of the 3-week cycle and it would have minimal effect as cycle duration is short (see manufacturer's submission page 72). Figure 1 shows the structure of the economic model.

Figure 1. Treatment pathway and structure of the economic model (manufacturer's submission page 73)



BSC, best supportive care; CTC AE common terminology criteria for adverse events; NOS, not otherwise specified

3.1.2 Model inputs: effectiveness

The JMEN trial was used to model the effectiveness of pemetrexed plus BSC compared with placebo plus BSC. Overall survival data (29-month) was then

extrapolated beyond the trial period to 72 months. Overall survival was used as the primary outcome in the economic model. The manufacturer did not model progression-free survival but used the number of treatment cycles received as a proxy (see manufacturer's submission page 61–2).

3.1.3 Model inputs: utilities

Data on health related quality of life was not available from the JMEN trial. Utility values were taken from literature estimates. People in the pemetrexed arm were assigned a utility of 0.66 (Nafees et al. 2008), corresponding to stable without progression. People in the placebo arm without progressive disease were assigned a utility of 0.58 (Nafees et al. 2008), corresponding to stable with fatigue. People with progressive disease were assigned a utility of 0.53 (Berthelot et al. 2000). In the base case, disutilities associated with adverse events are not included in the above utility values. However, they were included in a sensitivity analysis. For further information see manufacturer's submission page 88–91 and ERG report page 39.

3.1.4 Treatment capping in the pemetrexed arm

The manufacturer's submission states that in the JMEN trial, patients receiving pemetrexed treatment continued to receive chemotherapy until their disease progressed. This resulted in a mean number of pemetrexed cycles for the non-squamous population of 8.0 (standard deviation [SD] 8.62) and a median of 6.0 cycles (25th–75th percentile 2.5–10.0). For the adenocarcinoma population the mean number of pemetrexed cycles was 8.6 (SD 9.30) and a median of 6.0 cycles (25th–75th percentile 3.0–10.0). There were a small number of extreme outliers receiving up to 55 cycles (7-11% received more than 15-20 cycles). The manufacturer consulted UK clinical specialists who suggested that a maximum number of cycles is likely to be between 8 and 10. The manufacturer therefore incorporates a 'capping rule' in which the maximum number of cycles of pemetrexed is set at 1 SD above the mean. This is equivalent to a maximum of 17 cycles and a mean of 5.84 for

the non-squamous population, and a maximum of 18 cycles and a mean of 6.16 for the adenocarcinoma population. In the economic evaluation, only costs are capped and no adjustment is made to overall survival. No capping or continuation rule is specified in the summary of product characteristics (SPC) (see manufacturer's submission page 60).

3.1.5 Second-line chemotherapy

After disease progression patients were either assigned to second-line chemotherapy or BSC. The manufacturer reported a statistically significant difference in the proportion of patients receiving second-line therapy by arm: 67.3% of patients in the placebo arm and 53.2% of patients in the pemetrexed arm (p=0.004) in the non-squamous population received second-line treatment with docetaxel or erlotinib. Second-line therapies in both arms were assumed to have equivalent efficacy, unit costs and utility. These data were not available for the adenocarcinoma population.

Several second-line treatments were used in the trial, but only docetaxel and erlotinib are included in the model because some of the other therapies are not available or recommended as second-line treatment in the UK. This includes pemetrexed monotherapy, which was received by 18.5% of placebo patients (crossover). The manufacturer assigned a market share of 73% to doxataxel and 23% to erlotinib to reflect their relative proportions as reported in the most recent market share data. It was assumed that docetaxel is provided for 4.8 cycles and erlotinib for 6.3 cycles (see manufacturer's submission page 74).

After second-line chemotherapy, patients enter a terminal phase when they receive BSC only. The final 3-week period of life is designated as 'terminal care' to which a higher cost is assigned. The model continues for a maximum of 6 years, by which time 99% of placebo patients and 96% of pemetrexed patients are expected to have died (see ERG report page 38).

3.1.6 Model inputs: costs

The cost and resource use data were obtained from the JMEN trial, Healthcare Resource Group (HRG) NHS reference costs, MIMS (July 2009) and PSSRU Unit Costs of Health and Social Care 2008. Costs were analysed from the perspective of the NHS in England and Wales. Resource utilisation was based on the patient population specified in the respective SPCs, published literature and clinical specialist opinion. In the model, the cost of pemetrexed was £800 per 500 mg vial and £160 per 100 mg vial. The manufacturer calculated that the cost of treatment per cycle with pemetrexed is £1509.58 excluding administration costs and assuming a body surface area of 1.79 m^2. All unit costs are inflated as necessary to the price year 2008. Costs and outcomes were discounted at the rate of 3.5%. The manufacturer assumed that treatment would be started and monitored in outpatient setting (see manufacturer's submission page 92–4).

Cost-effectiveness results

The incremental cost effectiveness ratios (ICERs) for pemetrexed compared with BSC in the non-squamous population is £33,732 per QALY gained. In the adenocarcinoma subgroup, the ICER is £39,364 per QALY gained. Tables 4 and 5 present a summary of the base-case results. These ICERs have been produced using an exponential survival fitting function.

Table 4. Manufacturer's base case results (manufacturer's submission page 105–6, ERG report page 43,)

	Pemetrexed (pemetrexed / BSC)	Placebo (watch and wait / BSC)	Incremental
Cost results			
Maintenance therapy plus administration	£9903	£299	£9605
Second-line therapy plus administration	£3570	£4516	-£946
AE cost	£34	£5	£29
BSC (with CTX)	£105	£133	-£28
BSC (without CTX)	£1329	£847	£481
Terminal care	£2514	£2518	-£4
Total costs	**£17,455**	**£8318**	**£9137**
Effectiveness results			
Total LYG	1.7	1.26	0.44
Total QALYs	0.97	0.70	**0.27**
ICER			
Cost per LYG			£20,562
Cost per QALY			**£33,732**

AE, adverse event; BSC, best supportive care; CTX, chemotherapy; ICER, incremental cost-effectiveness ratio; LYG, life year gained; QALY, quality-adjusted life year.

NB. When the manufacturer uses the Weibull function the ICER increases to £36,386 per QALY (see manufacturer's submission page 109).

Table 5. Manufacturer's adenocarcinoma subgroup results (manufacturer's submission page 107–8, ERG report page 44)

	Pemetrexed (pemetrexed/ BSC)	Placebo (watch and wait/BSC)	Incremental
Cost results			
Maintenance therapy plus administration	£10,446	£305	£10,141
Second-line therapy plus administration	£3679	£4654	-£975
AE cost	£22	£1	£21
BSC (with CTX)	£71	£109	-£37
BSC (without CTX)	£1481	£1072	£409
Terminal care	£2429	£2432	-£3
TOTAL COSTS	**£18,129**	**£8574**	**£9554**
Effectiveness results			
Total LYG	1.87	1.45	0.42
TOTAL QALYS	1.03	0.79	**0.24**
ICER			
Cost per LYG			£22,788
COST PER QALY			**£39,364**

AE, adverse event; BSC, best supportive care; CTX, chemotherapy; ICER, incremental cost-effectiveness ratio; LYG, life year gained; QALY, quality-adjusted life year.

NB. When the manufacturer uses the Weibull function the ICER increases to £42,922 per QALY (see manufacturer's submission page 109)

Uncertainty was explored in six scenario analyses and 36 one-way sensitivity analyses for both non-squamous and adenocarcinoma populations. Scenario analyses explored the effect of per-vial costing and cycle capping, and included a best case and worse case scenario. The best case scenario produced an ICER of £14,823 per QALY for the non-squamous population. It comprised per-mg costing of pemetrexed, capping treatment at 10 cycles body surface area of 1.8m^2 and no disutility of adverse events, and used the upper 95% confidence interval (CI) for the effectiveness of pemetrexed and the lower 95% CI for BSC. The worst case scenario produced an ICER of £134,666 per QALY for the non-squamous population. It comprised per-vial

costing, mean number of cycles of 8 as per JMEN trial and body surface area of 1.8m^2, and included the disutility of adverse events and conservative efficacy estimates (see manufacturer's submission page 108–16).

Most of the results in the one-way sensitivity analyses had little effect on the base-case ICERs (see manufacturer's submission table 45, page 114-16) The ICERs were sensitive to the incremental survival of pemetrexed treatment. When the incremental survival was reduced from 5.3 months in the base case to 1.15 months, the ICER increased to £105,826 per QALY gained. When the overall survival advantage was reduced by 9.5% to correspond to the 9.5% of patients excluded with the base-case capping rule, the ICER increased to £48,290 per QALY gained.

3.2 Evidence Review Group comments

The ERG focussed on the non-squamous population in accordance with the licensed indication and because the results for the adenocarcinoma population were similar to the non-squamous population. In addition, the ERG preferred the version of the model which used the exponential (rather than Weibull) projection as the basis for comparison, this being the manufacturer's base case. The ERG identified a number of issues relating to the uncertainty around the estimates of cost effectiveness. These are detailed below:

The ERG noted that no direct use was made in the model of the primary trial outcome (progression-free survival), which instead was replaced by the duration of maintenance therapy as a proxy (see ERG report page 50).

The ERG noted that the capping of pemetrexed treatment at 17 cycles was much less than the maximum of 55 cycles in the JMEN trial. The ERG considered that this constrained the costs of maintenance therapy with no corresponding effect on the benefits accrued from use of pemetrexed, which led to bias in favour of pemetrexed. The ERG considered that the most appropriate base case should include the full costs and benefits of

maintenance therapy based on the cycles delivered in the JMEN trial (see ERG report page 55).

The ERG considered that the manner in which the utility values were selected was inappropriate and favoured the pemetrexed arm. Patients entering the model at randomisation were on average in the same clinical state but were assigned different utility values (0.66 for pemetrexed patients and 0.58 for placebo). This is not consistent with data from the JMEN trial in which the rate of grade 3/4 fatigue was noticeably higher in the pemetrexed arm (3.66%) than in the placebo arm (0.64%) (see ERG report page 55–6).

The ERG was concerned about the assumption that overall survival was the same for patients receiving second-line chemotherapy and those who did not. This is because patients not offered further treatment may be deemed of poorer health status and with worse prognosis (see ERG report page 59).

The ERG expressed concern that a probabilistic sensitivity analysis was not undertaken, given the numerous adjustments used in the model. The ERG also considered that the manufacturer did not sufficiently justify the choice of parameters and the parameter values varied in the one-way sensitivity analyses.

The ERG considered that the discounting applied in the model to the four care phases was based on simplistic assumptions. All maintenance chemotherapy cycles were assumed to occur in the first year (consistent with the imposed maximum cycles limit but not with the trial data), all second-line chemotherapy was placed in the first year, all BSC was assumed to occur only in years one or two and all terminal care was assigned to year three (see ERG report page 58).

The ERG did not consider that the additional monitoring of patients on pemetrexed chemotherapy (who were assessed every two cycles) was

consistent with clinical practice in the UK. The manufacturer's submission estimated the cost per additional CT scan to be £112.54 and the cost per additional outpatient follow-up visit to be £124. The ERG considered the appropriate follow up to be at 3, 6 and 12 months and every 6 months thereafter until progression for the BSC arm; and every 4 cycles (12 weeks) until progression in the pemetrexed arm (see ERG report page 58).

The ERG noted that the body surface area distribution used in the model was not representative of the UK population given that 35% of the trial population was of Asian origin. The ERG considers that using a UK source for the distribution of body surface area would lead to a slightly reduced acquisition cost (see ERG report page 56)

The ERG identified a number of errors in the model submitted by the manufacturer including the following:

The half-cycle correction applied to survival estimates appeared to be inappropriate. The ERG considered that the correct approach is to use the area under the curve from the trial analysis unaltered, and then calculate 'mid-cycle' corrected estimates for the remainder of the model duration derived from a parametric model. For further information see ERG report page 57.

The ERG noted that post-progression costs were double discounted in the model. The estimation of QALYs then relies on the double discounted survival values.

The ERG also noted a minor error in the calculation of the proportion of patients assumed to receive docetaxel or erlotinib in second-line therapy. When this is corrected the ICER for the manufacturer's base case ICER rises slightly (see ERG report page 58).

3.2.1 Further ERG analysis

The ERG assessed the impact of the errors on the base case ICER of £33,733 per QALY from the manufacturer's submission (see table 6). The changes that have the most impact on the ICER are the removal of a limit on the number of cycles of treatment and the use of utility values which take into consideration the incidence of adverse events reported in the JMEN trial. The combined effect of these changes is to increase the incremental cost of pemetrexed maintenance treatment by 35% and reduce the incremental QALYs gained by 2%, so that the ICER increases from a base case of £33,732 to £47,239 per QALY gained (see ERG report page 60)

When the ERG combined the effect of all the model corrections the ICER was increased to £51,192 per QALY gained.

The ERG produced an approximate probabilistic analysis around the incremental overall survival gain and the mean cycles per patient. These relationships were then applied to the relevant standard errors of the parameters to yield 1000 randomly generated probabilistic scenarios. The resulting cost-effectiveness acceptability curve shows that there is no measurable probability of pemetrexed being cost effective at a threshold of £30,000 per QALY gained and 50% probability of it being cost effective at thresholds above £51,000 per QALY gained.

Table 6. Effect of corrections and amendments made by ERG to the manufacturer's model for the non-squamous population (ERG report page 66)

	Pemetrexed		**Placebo**		**Incremental**		**ICER**	**Changes**		
Model amendment	Costs	QALYs	Costs	QALYs	Costs	QALYs	(£/QALY)	Costs	QALYs	ICER
Submitted base case	**£17,455**	**0.9697**	**£8318**	**0.6988**	**£9137**	**0.2709**	**£33,732**	**-**	**-**	**-**
All cycles of pemetrexed and revised CTX costs	£20,638	0.9841	£8323	0.6989	£12,315	0.2852	£43,179	+£3,178	+0.0143	+£9447
Revised utility values	£17,455	0.9540	£8318	0.7057	£9137	0.2483	£36,798	-	–0.0226	+£3066
Continuity correction	£17,405	0.9467	£8288	0.6851	£9117	0.2615	£34,860	–£20	–0.0094	+£1128
Correct double discounting	£17,522	1.0006	£8352	0.7149	£9169	0.2857	£32,091	+£32	+0.0148	-£1641
Discounting assumptions	£17,421	0.9617	£8312	0.6909	£9109	0.2708	£33,640	–£60	–0.0001	–£88
Include monitoring costs	£17,838	0.9697	£8452	0.6988	£9386	0.2709	£34,651	+£249	-	+£919
Correct arithmetic	£17,398	0.9658	£8248	0.6953	£9149	0.2706	£33,817	+£12	–0.0003	+£85
Combined effect of above changes	**£20,925**	**0.9539**	**£8370**	**0.6881**	**£12,555**	**0.2658**	**£47,239**	**+£3418**	**–0.0051**	**+£13,507**
Combined effect of all changes including IPD survival analysis (excluding significant protocol violations)	**£20,902**	**0.9851**	**£8382**	**0.7405**	**£12,520**	**0.2446**	**£51,192**	**+£3383**	**–0.0263**	**+£17,460**

CTX, chemotherapy; ICER, incremental cost-effectiveness ratio; IPD, individual patient data; QALY, quality-adjusted life year.

3.2.2 End of life criteria

The ERG analysed the manufacture's case for pemetrexed to be considered under end of life criteria on three key points (see ERG report page 69–71):

Patient life expectancy of less than 24 months:

The manufacturer's submission stated that the overall survival of untreated patients with non-small-cell lung cancer is in the region of 7.9–10.3 months based on LUCADA 2007 and JMEN placebo data. The ERG was in agreement that the mean life expectancy of patients with stage IIIb or IV non-small-cell lung cancer was likely to be less than 24 months.

Life extension of at least 3 months:

The manufacturer presented a mean overall survival benefit of 5.2 months in the pemetrexed arm compared with the placebo arm for the licensed non-squamous population. ERG reanalysis of JMEN trial data, including an alternative method for projecting survival beyond the trial period, gave an estimated mean gain in overall survival of 5.58 months, supporting a life extension of greater than 3 months.

Licensed for a small population

The ERG noted that it is difficult to determine the accuracy of the eligible population. The manufacturer presented two sets of population estimates, one in which the estimated eligible population for maintenance therapy is 949 patients (see manufacturer's submission page 49) and another in which the estimated population ranges between 1121 and 2165 patients (see manufacturer's submission page 125). For the whole of the licensed pemetrexed population (first-line non-small-cell lung cancer, second-line non-small-cell lung cancer, mesothelioma and maintenance therapy) the manufacturer estimates the total licensed population to be 3426 patients, assuming the lower estimate of 949 patients on maintenance therapy. If the

higher estimate of 2165 patients is used then the whole licensed population is 4642 patients.

The ERG considered that the 23% estimate for patients with non-squamous non-small-cell lung cancer who receive first-line chemotherapy is not accurate as this refers to the total proportion of all lung cancer patients (not only non-small-cell lung cancer) who get first-line therapy irrespective of histology or stage of disease. 'Lung cancer' (NICE clinical guideline 24) estimated that approximately 50% of patients with advanced non-small-cell lung cancer were eligible for chemotherapy. If 50% of patients received first-line chemotherapy, then the number of pemetrexed maintenance patients would double to approximately 2000–4000 patients, and the entire population for which pemetrexed is licensed would increase to approximately 6000–9000. The ERG concluded that there is uncertainty as to whether pemetrexed meets the end-of-life criteria for the small patient population. The ERG recommended that more information on the numbers of patients for whom pemetrexed treatment would be appropriate be presented.

4 Authors

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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 Reviews and Implementation Group*:

- Greenhalgh J, McLeod C, Bagust A et al

B Submissions or statements were received from the following organisations:

I Manufacturer/sponsor:

- Eli Lilly and Company

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

- British Thoracic Society Lung Cancer and Mesothelioma Specialist Advisory Group
- Royal college of nurses
- Royal college of pathologists

C Additional references used:

Nafees 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

Berthelot JM, Will BP, Evans WK, Coyle D, Earle CC, Bordeleau L. Decision framework for chemotherapeutic interventions for metastatic non-small-cell lung cancer. Journal of the National Cancer Institute. 2000; 92(16):1321-9