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

ERG Report

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Abbreviations:

AE	Adverse events
ASC	Active supportive care
ASCO	American Society of Clinical Oncology
BSA	Body surface area
BSC	Best supportive care
CEAC	Cost-effectiveness acceptability care
CR	Complete response
CRD	Centre for Reviews and Dissemination
ECOG	Eastern Clinical Oncology Group
EMEA	European Medicines Evaluation Agency
ERG	Evidence review group
ICER	Incremental cost-effectiveness ratio
ITT	Intention to treat
NICE	National Institute for Health and Clinical Excellence
NSCLC	Non-small cell lung cancer
OS	Overall survival
PFS	Progression free survival
PPS	Post-progression survival
PR	Partial response
PS	Performance status
PSA	Probabilistic sensitivity analysis
QALY	Quality adjusted life year
QoL	Quality of life
RCT	Randomised controlled trial
RT	Randomised and treated population
SA	Sensitivity analysis
SMC	Scottish Medicines Consortium
STA	Single technology appraisal
TNM	TNM (tumour, nodule, metastasis) classification of malignant tumours
TTTF	Time to treatment failure
TTdP	Time to disease progression
US	United States
WHO	World Health Organisation
WTP	Willingness to pay

Definition of terms:

Complete response	Disappearance of all measurable and evaluable disease
Duration of clinical benefit	The time from the date of randomization to the first date of documented disease progression or death due to any cause for patients who had a best overall tumour response better than progressive disease and was censored at the date of the last follow-up visit for those patients who were still alive and had not progressed
Duration of tumour response	Time from date of first objective status assessment of complete response, or partial response until the first date of documented disease progression or death due to any cause and was censored at the date of last follow up visit for tumour responders who were still alive and had not progressed
Overall survival	Time from randomisation to death (from any cause)
Partial response	More than or equal to 50% decrease in the sum of products of perpendicular diameters of all measurable lesions
Progressive disease	50% increase in the sum of products of all measurable lesions, or worsening of evaluable disease, or appearance of any new lesions
Progression free survival	The time from randomization until documented progression or death from any cause and was censored at the date of the last follow-up visit for patients who were still alive and who had not progressed.
Stable disease	Not qualifying for complete response, partial response or progressive disease.
Time to disease progression	The time from the date of randomization to the first date of documented disease progression and was censored at the date of death for patients who died without documented disease progression or the date of the last follow-up visit for patients who were still alive and who had not progressed
Time to treatment failure	The time from randomization to the date of progression of disease, discontinuation of treatment, or death due to any cause and was censored at the date of the last follow-up visit for patients who did not discontinue, who were still alive, and who did not have disease progression.

NB: definitions are specific to JMEI trial[1]

1 EXECUTIVE SUMMARY

1.1 Scope

This report presents an assessment of the company submission regarding the use of pemetrexed (within the context of the licensed indication) for the treatment of patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) after failure of at least one prior chemotherapy regimen. The report includes an assessment of both the clinical and cost-effectiveness evidence submitted by the company (Eli Lilly).

1.2 Summary of submitted clinical effectiveness evidence

The company submission provided clinical evidence from one head to head randomised controlled clinical trial of pemetrexed versus docetaxel (JMEI). A further eight studies were used to inform an indirect comparison of pemetrexed with docetaxel, erlotinib or best supportive care.

The JMEI trial failed to demonstrate superiority or non-inferiority of pemetrexed over docetaxel. There was no difference in the primary outcome of overall survival or in the secondary efficacy outcomes of progression free survival, time to progressive disease, duration of tumour response, duration of clinical benefit and time to objective tumour response. Time to treatment failure was reported to be statistically significantly improved in the pemetrexed treated patients. This amounted to a difference of six days.

The methods used to perform the indirect comparison were considered by the evidence review group to be inappropriate. The results obtained by the methods employed cannot be considered reliable or meaningful, since they effectively undermine all the benefits of randomization inherent in the source trials and do not adjust for the resulting imbalances between the pooled comparators. The only direct and reliable clinical evidence available, which is relevant to the reference case of this appraisal, is therefore the JMEI trial of pemetrexed versus docetaxel.

Giving the benefit of the doubt to pemetrexed means that at best it could be considered as an equally effective treatment compared to docetaxel.

1.3 Summary of submitted cost-effectiveness evidence

The economic model submitted in support of the company submission is a Markov model comparing pemetrexed with docetaxel. The three main health states are defined in the model as: response, stable and progressive disease. The model is furnished with data from nine randomised controlled trials including JMEI (pemetrexed versus docetaxel). The company reports an incremental cost-effectiveness ratio (ICER) of £18,672 per QALY gained for pemetrexed versus docetaxel with a 67% probability that pemetrexed is cost-effective at a willingness to pay (WTP) of £30,000 per QALY gained.

However, a number of key assumptions and parameters in the model do not seem to be clinically and/or economically justified, particularly in terms of survival rates. For example, the company model assumes a survival benefit for pemetrexed compared to docetaxel. However, the ERG does not believe that this supposition is justified as it is based on flawed pooling methodology. When the more realistic assumption of equivalent survival is incorporated into the model, the ICER rises to £458,333 per QALY gained.

In addition to changes in survival assumptions, when other corrections and adjustments (e.g. drug acquisition costs) relating to the costs of pemetrexed and docetaxel are incorporated into the company model, the ICER increases to £1.2 million per QALY gained with a 5% probability of pemetrexed being cost effective at a WTP of £30,000. Sensitivity analysis undertaken by the ERG yields cost-effectiveness ratios in the range of £391,815 to £1.22million per QALY gained for pemetrexed versus docetaxel.

2 BACKGROUND

2.1 Introduction

The remit of this single technology appraisal is to assess the clinical and cost effectiveness of pemetrexed compared to current standards of care for locally advanced or metastatic non-small cell lung cancer (NSCLC) following failure of previous therapy.

Pemetrexed (*Alimta*®) is a multi-targeted anti-cancer antifolate agent that exerts its action by disrupting crucial folate-dependent metabolic processes essential for cell replication. It inhibits thymidylate synthase, dihydrofolate reductase, and glycinamide ribonucleotide formyltransferase, which are key folate-dependent enzymes for the de novo biosynthesis of thymidine and purine nucleotides.

Three drugs (docetaxel, erlotinib and pemetrexed) are currently licensed for the treatment of advanced NSCLC following the failure of previous chemotherapy treatment. However, at present only docetaxel has been recommended by the National Institute for Health and Clinical Excellence (NICE) for use in the NHS as second-line therapy. Erlotinib is currently being evaluated separately by NICE as a single technology appraisal.

2.2 Epidemiology

Lung cancer is the most common cause of cancer-related death in men, and the second most common cause of cancer-related death after breast cancer in women.[2] In 2002, 37,700 patients were newly diagnosed with lung cancer in the UK accounting for one in seven new cancer cases, with an incidence of about 62-65 per 100,000 population; the incidence of NSCLC is approximately 52 per 100,000 population.[3] Lung cancer is rarely diagnosed in people under 40 years of age, but the incidence rises steeply with age thereafter, peaking in people aged 75 to 84 years.[3]

In the 1950s the male to female ratio for lung cancer cases was 6:1; the ratio is now 3:2 and this is considered to reflect changes in smoking behaviour.[3] There is a strong association between incidence and mortality rates and levels of deprivation.[3]

2.3 Types of lung cancer

There are four main histological classifications of lung cancer; squamous cell carcinoma, adenocarcinoma, large cell carcinoma and small cell carcinoma. Because the behaviour and management of the first three are very similar, they are often grouped together as non-small cell lung cancer. Around 70-80% of lung cancers are NSCLC.[3] Squamous cell carcinomas, adenocarcinomas and large cell carcinomas account for approximately 35%, 15% and 10% respectively of all non-small cell lung cancers.[4] The remainder are small cell lung cancers, which have a distinct natural history and management, and are not addressed in this report.

2.4 Staging of NSCLC

NSCLC is classified according to the TNM classification of malignant tumours staging system. In this system, T refers to the size of the tumour and its spread; N to the number of lymph nodes involved and M to the presence of metastases (see Table 2-1). The TNM system can be categorised further into stages I-IV (see Table 2-2).

Table 2-1 A simplified TNM staging classification system for NSCLC

Primary tumour (T)	
T0	No evidence of primary tumour
T1	Small tumour < 3 cm across
T2	Tumour is > 3 cm or involves main bronchus or invades the visceral pleura.
T3	Tumour of any size that directly invades: chest wall, diaphragm, mediastinal pleura or pericardium
T4	Tumour of any size that invades: mediastinum, heart, great vessels, trachea, oesophagus, or with malignant pleural effusion or pericardial effusion
Regional lymph nodes (N)	
N0	No cancer in any lymph nodes (cancer is localised)
N1	Cancer to lymph nodes nearest affected lung
N2	Cancer in the mediastinal lymph nodes on the same side of affected lung
N3	Cancer in the lymph nodes on the opposite side from the affected lung
Distant metastasis (M)	
M0	No distant metastasis
M1	Cancer spread to another lobe of the lung or another part of the body

Source: Mason (2005)[5]

Table 2-2 Stage grouping by TNM subset

	Tumour				
Nodes		***T1***	***T2***	***T3***	***T4***
	N0	IA	IB	IIB	IIIB
	N1	IIA	IIB	IIIA	IIIB
	N2	IIIA	IIIA	IIIA	IIIB
	N3	IIIB	IIIB	IIIB	IIIB
Metastases	***M1 = Stage IV***				

Source: NICE (2005) 6; Shaded areas indicate diseases states where chemotherapy is recommended

2.5 Aims of treatment

Patients with NSCLC have a number of treatment options depending upon the stage of disease. A proportion of patients in the early stages (I - II, and some stage III) are candidates for surgical resection, provided they have no medical complications and adequate lung function.[6] However, few patients are diagnosed at this early stage.

Approximately 75% of newly diagnosed patients have advanced NSCLC (stage III or IV) of whom two-thirds have advanced metastatic (stage IV) disease. Chemotherapy is recommended for some patients with non-resectable stage III or IV (shaded in Table 2-2) provided they have a good performance status (PS).

Performance status can be measured on a number of scales. Guidance from NICE recommends chemotherapy for patients with stage III or IV NSCLC with a good performance status score of 0 or 1 on the World Health Organisation (WHO) performance status scale, or of 80 to 100 on the Karnofsky Performance Scale.[6] A number of clinical trials use the Eastern Cooperative Oncology Group (ECOG) performance scale. The WHO and ECOG scales are very similar in design and purpose (see Table 2-3).

Stage III and IV NSCLC are generally not considered to be curable, with five-year survival rates of less than 1%.[2] Chemotherapy can be useful in improving patients' quality of life and may offer a modest survival benefit.

Patients with NSCLC should also receive active supportive care (ASC); often referred to as best supportive care (BSC). ASC can be given in conjunction with a chemotherapy regimen, or independently for patients who are intolerant to, or whose performance status contraindicates chemotherapy. The composition of ASC varies

widely but is generally aimed at alleviating the symptoms of cancer and the adverse effects of chemotherapy regimens.

Table 2-3 WHO/ ECOG performance status scale

Score	WHO/ ECOG performance status[6, 7]
0	Asymptomatic
1	Symptomatic, fully ambulatory
2	Symptomatic, in bed < 50% of the day
3	Symptomatic, in bed > 50% of the day but not bedridden
4	Bedridden
5	Dead

2.6 Current treatment options

2.6.1 Clinical guidance in England and Wales

First-line treatment, as recommended by NICE states that chemotherapy should be a combination of a single third-generation drug (docetaxel, gemcitabine, paclitaxel or vinorelbine) plus a platinum drug, either carboplatin or cisplatin.[6] Single agent chemotherapy with a third-generation drug can be offered to patients who cannot tolerate a platinum combination. Evidence suggests that combination therapy increases median survival by approximately nine weeks compared to ASC. The optimal duration of therapy has not been identified; the typical median number of cycles delivered in recent randomised trials is three or four. [6]

For patients who relapse after first-line treatment, NICE recommends consideration of docetaxel monotherapy.[6]

There is currently no defined third-line agent for patients who fail to respond to, or relapse after, first- and second-line treatments. ASC alone will probably be the only option for the majority of patients.

2.6.2 Licensed agents

Three drugs have valid European Union marketing authorisations for use following first-line therapy in the treatment of NSCLC. In 1995, docetaxel (Taxotere®) was licensed for "*the treatment of patients with locally advanced or metastatic non-small cell lung cancer after failure of prior chemotherapy*". The licensing submission for docetaxel was supported by a phase III study comparing docetaxel with BSC.

In 2004, pemetrexed (Alimta®) received its licence "*as monotherapy for the treatment of patients with locally advanced or metastatic non-small cell lung cancer after prior chemotherapy*".[8] The licensing submission for pemetrexed was supported by a phase III study comparing pemetrexed with docetaxel.[1]

In 2005, erlotinib (Tarceva®) was licensed *"for the treatment of patients with locally advanced or metastatic non-small cell lung cancer after failure of at least one prior chemotherapy regimen"*.[9] The licensing submission for erlotinib was supported by a phase III study comparing erlotinib with placebo.[10]

2.6.3 Clinical guidance in other countries

Pemetrexed has not been reviewed by the Scottish Medicines Consortium (SMC), despite the company being asked on several occasions to make a submission. The SMC viewed the company's decision not to submit as a failure to prove their case for pemetrexed and hence the medicine was not recommended for use in Scotland.

Regarding erlotinib, advice from the SMC is that "erlotinib is restricted to use in patients who would otherwise be eligible for treatment with docetaxel. No economic case has been made for those whose performance status would make them ineligible to receive docetaxel".[9]

Pemetrexed is approved for use in the United States for the treatment of locally advanced or metastatic non-small cell lung cancer in adults who have received prior chemotherapy. However, this approval is qualified by the statement "…This indication is based on the surrogate end point of tumour response rate; there are no controlled clinical studies to date demonstrating improvement in disease-related symptoms or increased survival with pemetrexed therapy".[11]

The US National Comprehensive Cancer Network Practice guidelines in NSCLC state that docetaxel, pemetrexed and erlotinib are all established second-line agents.[12]

In 2004 the Pharmaceutical Benefits Advisory Committee, Australia Department of Health, approved pemetrexed for use within its license for patients who failed to respond to previous chemotherapy.[13]

2.6.4 Number of patients treated

Evidence relating to the number of NSCLC patients receiving chemotherapy in England and Wales is scarce and contradictory. In 2001 NICE estimated that, of the 26,400 patients diagnosed with NSCLC, 15% would be potential candidates for chemotherapy; patient numbers receiving chemotherapy were reported to vary from 1,320 to 5,280.[4] When estimating the cost impact of its 2005 guidance on the treatment of lung cancer, NICE used an upper estimate of 30% as the proportion of patients with NSCLC who might potentially receive chemotherapy.[14] It is estimated that a smaller proportion, possibly one third to one half of those receiving first-line therapy, will be suitable for second-line treatment.[8, 15]

In contrast, the Royal College of Physicians estimates that over 16,000 (49%) NSCLC patients a year are eligible for chemotherapy.[2, 14]

One of the reasons for these differences and the increasing use of chemotherapy could be the growing evidence for the benefits of chemotherapy as an adjuvant treatment following surgery and in combination with radical radiotherapy.[2] An assessment of the benefits of adjuvant chemotherapy is not discussed in this appraisal.

2.7 Critique of company background

The company submission provides a generally accurate and thorough discussion of the background to the disease of lung cancer and its treatments. However, the following points are worthy of note.

2.7.1 Comparators

The company present clinical and cost-effectiveness evidence in support of pemetrexed versus docetaxel, erlotinib and active supportive care (ASC). However, erlotinib is not currently approved for second-line use in patients with locally advanced or metastatic NSCLC; nor is it routinely used in clinical practice in England and Wales. For these reasons, the ERG feels that it is inappropriate to consider erlotinib within the scope of this single technology appraisal.

2.7.2 Context and place in therapy

The submission makes several statements concerning the role of pemetrexed, docetaxel and erlotinib in first-, second- and third-line treatment. These comments are critiqued here.

The submission states that taxanes are licensed with cisplatin for use in the first-line treatment of NSCLC and suggests that "in general, if a taxane (docetaxel or paclitaxel) is used first-line, docetaxel is not likely to be used as a second-line option in this patient population." The implication of this is that alternative treatment options to docetaxel are needed in the second-line setting. Clinical opinion (John Green, 14th July 2006) indicates that docetaxel is rarely used in the first-line setting in the UK and is reserved for second-line use. Information in the company submission indicates that "according to IMS market research data in second-line treatment of advanced NSCLC, docetaxel usage was approximately 69%, pemetrexed 10% and erlotinib 6%". Country of origin of the data was not stated.

The submission also suggests "…Erlotinib is licensed for use in second- and third-line settings and that it is currently the only treatment licensed for third-line." The submission argues that if erlotinib is used in second-line setting, patients and physicians will not have a licensed treatment available for use in the third-line setting. However, as noted earlier, the EMEA license statements for each of the three drugs state that they can be used following previous failed therapy. None of the statements explicitly mention second- or third-line settings; this means that any of the agents could potentially be used as a third-line therapy. However, given the adverse event profiles of the chemotherapy regimens there will be a very limited number of patients who would tolerate third-line therapy.

3 CLINICAL EFFECTIVENESS

The company submission includes a systematic review of pemetrexed in second-line treatment of NSCLC, including both direct and indirect comparisons. Firstly we provide a critique of the systematic review methods and then go on to critique the trial evidence and data analysis included in the submission.

3.1 Critique of systematic clinical review

Key aspects of the methodological quality of the company's review of the clinical literature were assessed based on an accepted quality assessment tool [16] and the results are summarised in Table 3-1.

Table 3-1 Quality assessment of the clinical effectiveness review

Quality assessment checklist item	Yes/No
Did the review address a clearly focused research question?	✓
Was the search strategy adequate? (I.e. did the reviewers identify all relevant studies?)	✓
Are the inclusion/exclusion criteria specified?	✓
Did the review include the right type of studies?	✓
Is there a statement of completeness from the company?	✗
Did the reviewers assess the quality of the included studies?	✓/✗
Was the method of data extraction reported?	✓/✗
Were appropriate measures of outcomes used?	✓
If the results of the studies have been combined, was it reasonable to do so?	✗
Are appropriate sub-group analyses presented?	✓
Are the main results of the review reported? (e.g. numerical results included with the CIs)	✓
Are issues of generalisability addressed?	✓

✓=yes, ✓/✗=partially, ✗=no

3.1.1 Search strategy

The literature searches in the submission were clearly reported with details of the search strategies and terms included. Three electronic databases were searched (Medline, Embase and the Cochrane Library) covering the period 1966 to May 2006.

In addition, one set of conference proceedings, American Society of Clinical Oncology (ASCO 2006), and Eli Lilly's unpublished data were searched.

Other relevant databases and conference sites which were not searched include Web of Science, ISI Proceedings and the European Society for Medical Oncology (ESMO) proceedings.

Search terms for electronic databases appropriately included a combination of free-text and index terms (non-small cell lung cancer) combined with drug names (pemetrexed, docetaxel or erlotinib) used as free-text terms.

Although the intervention under appraisal is pemetrexed for relapsed NSCLC, the search strategies used in the submission were appropriately expanded to include comparative studies of docetaxel, erlotinib and BSC for further supporting evidence.

3.1.2 Inclusion and exclusion criteria

Details of inclusion and exclusion criteria are provided in Table 3-2 and are considered appropriate and complete.

3.1.3 Application of inclusion criteria

Information regarding the application of the inclusion criteria (e.g. the number of reviewers involved in the process and whether this was done independently) was not provided in the submission.

A flow diagram and a table of included trials in the submission indicates that, of the 976 (non-duplicated) publications to which the inclusion criteria were applied, a total of nine trials was considered for inclusion in the review. This included one head to head trial that forms the basis of the direct comparison (JMEI[1]), with an additional eight trials to inform indirect comparisons.[17 10, 18-23]

The flow diagram shows the reasons for exclusion at two different stages. A further eight trials were excluded after the articles were retrieved for potential inclusion.

The searching exercise and application of inclusion criteria conducted by the ERG confirms the finding of only one relevant trial used in the direct comparison and an additional eight trials used in the indirect comparison.

Table 3-2 Scope of the literature review

	Clinical effectiveness
Population	Adult patients with locally advanced / metastatic (unresectable) non-small cell lung cancer previously treated with chemotherapy. The number of prior chemotherapy regimens had to be at least one.
Intervention	Pemetrexed
Comparators	Docetaxel
Outcomes	Primary outcome • Overall survival Secondary outcomes • Toxicities (including use of concomitant supportive measures) • Progression-free survival (PFS) • Time to documented progressive disease • Time to treatment failure • Time to objective response • Duration of response • Quality of life measurements
Study design	Phase III randomised controlled trial (RCT)
Inclusion criteria	• Published Phase III Randomised Controlled Trials of single-agent pemetrexed 500mg/m2, single-agent docetaxel 75mg/m2, erlotinib 150mg/day or best supportive care given as second-line treatment in patients with advanced (stage IIIB or IV) NSCLC previously treated with chemotherapy. • At least one treatment arm under consideration and to have reported survival, time to disease progression, toxicity or quality of life data. • Adult patients. • The number of prior chemotherapy regimens had to be at least one.
Exclusion criteria	• Trials with combined modality treatment (chemotherapy plus radiotherapy) were not considered. Trials utilising radiotherapy with curative intent in inoperable patients were not considered. • Studies in which single-agent pemetrexed 500mg/m^2, single-agent docetaxel 75mg/m^2, erlotinib 150mg/day or best supportive care are given as first-line treatment of advanced NSCLC. • Papers published in a language other than English were not considered. • Letters and editorials were not considered. • Chemotherapy naive patients.

3.1.4 Quality assessment

The company included a quality assessment of the nine included trials in the appendices of the submission. These tables include details of randomisation, adequacy of follow up, blinding of outcome assessment, whether the trials were parallel groups or crossover and whether the trial was conducted in the UK. Unfortunately the keys used in these tables are incomplete and it is therefore not possible to interpret the

results. The submission does not report how the data quality assessment was conducted e.g. independently or by more than one reviewer.

3.1.5 Data extraction

The submission reports that data (from all nine trials) were extracted using a structured form. Further details of the data extraction process (e.g. number of reviewers and whether data were extracted independently) were not provided in the submission. Study data tables are extensive but somewhat confusing.

3.1.6 Combination of studies

A meta-analysis was not undertaken by the company as there is only one trial included in the review of direct comparisons. However, the submission pools evidence from a range of studies and carries out indirect comparisons, the results of which are used in the economic analysis. For further detail see section 3.3.

3.2 Direct comparison: pemetrexed versus docetaxel

One international, multi-centre, phase III, randomised, parallel, open label trial (JMEI) involving 571 patients was included in the review (pemetrexed 283: docetaxel 288). Between March 2001 and February 2002, patients were stratified by nine key variables (Table 3-3) to ensure balance across the two treatment arms. A table of comparability is included in the submission and the paper reports that baseline characteristics were comparable across the treatment arms. Randomisation to receive either pemetrexed (500mg/m^2) or docetaxel (75mg/m^2), on the first day of a 21 day cycle, occurred centrally which should ensure allocation concealment. As this was an open label trial, assessors, administrators and patients were not blinded, however, it is stated that personnel from the company (Eli Lilly) were blinded.[24]

Notably, patients received a median of four cycles of treatment with a range of 1 to 20 in the pemetrexed arm and a range of 1 to 14 in the docetaxel arm. In the UK, it is unusual for patients to receive more than four cycles of docetaxel. Also, due to toxicity and non-responders, it is likely that the median number of cycles would be closer to three for UK patients (clinical opinion, Fergus Macbeth, 22nd August 2006).

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Table 3-3 Factors used to balance the treatment arms

Factor	
ECOG Performance Status	Low (2) or High (0 or 1)
Prior platinum-containing chemotherapy	Yes or No
Prior paclitaxel-containing chemotherapy	Yes or No
Baseline homocysteine level	< 12 μM or = 12 μM
No. of prior chemotherapy regimens	1 or 2
Time since last chemotherapy	<3 months or = 3 months
Best response to last prior chemotherapy	complete response/partial response/stable disease or progressive disease or unknown
Disease stage	III(a/b) or IV
Investigation centre	by centre

A total of 541 patients (265 assigned to pemetrexed and 276 to docetaxel) received treatment and were included in the safety analyses.

Results from JMEI were reported in the company submission, one peer-reviewed journal article,[1] one study report, and three published abstracts.[25-27] Data presented in this report have been extracted from both the submission and the peer-reviewed journal article.[1]

3.2.1 Trial characteristics

Study characteristics are summarised in Table 3-4.

There are three issues to note. Firstly the trial was conducted in 23 countries, 11 of which are in the European Union, but there were no study centres in the United Kingdom. As the submission states, there are differences in clinical practice between different countries (e.g. in France 70% of patients will receive active treatment as first-line therapy compared to 30% in the UK). Also, reasons for and rates of hospitalisations differed between countries. Most notably, four of the five patients enrolled in Russia, all to the pemetrexed arm, accounted for 135 hospitalisation days. It is not possible to estimate how these different practices would affect the generalisability of the trial outcomes to UK clinical practice.

In addition, the mean number of patients per site is four (125 centres from 23 countries). Such contextual diversity and small numbers may undermine some of the

benefits of randomization, and also cast doubt on the applicability of results to any one country.

Secondly, the trial excluded patients with significant weight loss (≥ 10%) over the six weeks prior to study entry. This could mean that a proportion of patients otherwise suitable for treatment were excluded from the trial. This could have resulted in a trial population that was healthier and possibly unrepresentative of the general population of patients.

Finally, the mean duration of follow up is stated in the submission (page 41) as 4.6 months (95%CI: 3.90-5.10; range: 0.0 to 18.9 months) for the intention to treat (ITT) population, which seems very short. However, median follow-up for all patients in the trial is reported as 7.5 months (Table 29 of the company submission).

It should also be noted that there are several inconsistencies in the reporting of study results between the company submission and the published paper in relation to the numbers of patients included at various stages of analysis.

Treatment stoppage and cross-over of treatment

Patients were allowed to exit the trial for reasons of treatment failure, toxicity or a decision by the patient or clinician. Following withdrawal from the trial patients could receive additional chemotherapy treatment (the same drug as previously received, the drug from the other arm of the trial or another agent). The published paper reports that 46.6% and 37.2% of patients receiving pemetrexed and docetaxel respectively went on to receive further chemotherapy. No further analysis of the effects of the cross-over treatment is discussed. The US Food and Drug Administration (FDA) reports a sensitivity analysis on the overall survival of patients not receiving further treatment, those receiving docetaxel and those receiving another type of chemotherapy.[28] This analysis does not demonstrate any difference between groups in relation to overall survival. Some aspects of the JMEI trial therefore do not reflect current UK clinical practice as very few patients receive a third regimen of chemotherapy.

Table 3-4 Study characteristics

Study name	Interventions drug & dose, N	Study enrolment	Study design	Outcomes	Location & centres	Inclusion criteria	Exclusion criteria	Follow-up
JMEI	Pemetrexed 500 mg/m^2 iv infusion N=283 Docetaxel 75 mg/m^2 iv infusion N=288 Patients were stratified by: ECOG Performance Status Prior platinum-containing chemotherapy Prior paclitaxel-containing chemotherapy Baseline homocysteine level Number of prior chemotherapy regimens Time since last chemotherapy Best response to last prior chemotherapy Disease stage Investigation centre	March 2001 to February 2002	RCT Phase III	Primary outcome: Overall survival Secondary outcomes: Progression-free survival Time to documented progressive disease Time to treatment failure Time to objective response Duration of response Quality of life measurements (two scales of the LCSS) Toxicities	Multi-centre (135 sites) International (23 countries including Argentina, Austria, Belgium, Brazil, Canada, Czech Rep, France, Germany, Hungary, India, Israel, Italy, Korea, Netherlands, Pakistan, Poland, Portugal, Russia, Singapore, South Africa, Spain, Taiwan, US), The study was not conducted in the UK	Histological or cytological diagnosis of NSCLC with locally advanced or metastatic disease (Stage IIIA, IIIB or IV at entry) that was not amenable to curative therapy. Previous treatment with at least one chemotherapy regimen completed at least two weeks prior to study enrolment. Disease status must have been defined as measurable and/or evaluable disease. Prior radiation therapy was allowed to <25% of the bone marrow. Prior radiotherapy must have been completed at least 2 weeks before study enrolment. Patients must have recovered from the acute toxic effects of the radiotherapy or chemotherapy prior to study enrolment. Performance status of 0 to 2 on the ECOG Scale. Estimated life expectancy of at least 8 weeks. Patient compliance and geographic proximity that allowed adequate follow-up. Adequate organ function Signed informed consent from patient. Male or female patients at least 18 years of age. Male and female patients with reproductive potential must have been using an approved contraceptive method if appropriate	Treatment within the last 30 days with any investigational drug. Prior treatment with either pemetrexed or docetaxel. Active infection that in the opinion of the investigator would have compromised the patient's ability to tolerate therapy. Pregnancy. Breast-feeding. Serious concomitant systemic disorders that would have compromised the safety of the patient or compromise the patient's ability to complete the study, at the discretion of the investigator. Second primary malignancy that is clinically detectable at the time of consideration for study enrolment. Inability to interrupt aspirin or other NSAIDs for a 5-day period (8-day period for long-acting agents such as piroxicam). Presence of clinically detectable (by physical exam) third-space fluid collections, for example, ascites or pleural effusions that could not be controlled by drainage or other procedures prior to study entry. Significant weight loss (that is, ≥10%) over the previous 6 weeks before study entry. History of severe hypersensitivity to polysorbate 80. Inability or unwillingness to take folic acid or vitamin B12 supplementation. CTC Grade 3 or 4 peripheral neuropathy at study entry. Prior radiation to the whole pelvis was not allowed	Median duration follow up 7.5 months

ECOG, Eastern Cooperative Oncology Group, NSAIDs, non steroidal anti inflammatory drugs; CTC, Common Toxicity Criteria; LCSS, Lung Cancer Symptom Scale

3.2.2 Participant characteristics

Information relating to the participant characteristics was reported both in the submission and in the published paper. The participants in the two treatment groups were comparable as would be expected given the stratification within the trial (see Table 12 of company submission for further details).

However, the age of the JMEI trial population (57 to 59 years) merits further discussion. There are no published data on the average age of patients receiving second-line treatment for NSCLC in the UK. Comparisons with other trials included in the company review demonstrate a mean age range of 57 to 63 years. It seems likely that in clinical practice the mean age of the treated population will be younger than the mean age of the diagnosed population although it may not be a low as 57 to 59 years.

3.2.3 Comparator

In the only relevant clinical trial (JMEI) identified by the systematic review of the literature, pemetrexed is compared to docetaxel. Comparison of pemetrexed versus docetaxel is appropriate as in England and Wales docetaxel is the only currently approved agent for second-line therapy for patients with locally advanced or metastatic NSCLC.

3.2.4 Clinical results

The key results of the JMEI trial are presented in Table 3-5. It is worth noting that at one year, 29.7% of the patients in each arm were still alive.

Primary efficacy outcome: overall survival

The median overall survival was reported as 8.3 months in the pemetrexed arm and 7.9 months in the docetaxel arm. The fixed margin method (reported in the submission) demonstrates that the non-inferiority criterion, using a 95% CI of <1.11 for the hazard ratio of pemetrexed over docetaxel, was not met (HR: 0.99, 95% CI: 0.82-1.20, *P*=0.226).

In the original JMEI trial the protocol was designed to test for superiority of pemetrexed over docetaxel; results of this test are not reported in the submission.

Furthermore, the non-inferiority method described above (fixed margin), was only adopted in a subsequent amendment to the trial protocol (dated 03/08/2001).

An additional modification to the trial protocol (which occurred two months after patients completed treatment; a week prior to data locking), included a further statistical test for non-inferiority (percentage of efficacy retention, (Rothmann) method).[29] The Rothmann method was used to test the hypothesis that pemetrexed retains at least 50% of the survival benefit of docetaxel over ASC. As the JMEI trial did not have an ASC arm, survival data from TAX 317[21] (docetaxel versus BSC) were used. Using this method, the company estimates that pemetrexed retains 102% of the survival benefit achieved with docetaxel over ASC (95% CI: 52%-157%, P=0.047).

A statistical review of the JMEI trial was undertaken by the FDA (Wang[28]) which states that "the study [JMEI] failed to demonstrate superior efficacy as per the trial protocol…failed to demonstrate efficacy based on the fixed margin non-inferiority test as defined in the amended protocol…[and] based on the FDA analysis the study failed to demonstrate efficacy based on the percent retention of control effect non-inferiority testing." The ERG agrees with these statements.

Table 3-5 Key results of JMEI trial

Variable	Pemetrexed (n=283)	Docetaxel (n=288)	HR	95% CI	*P value*§
Overall survival Median, months Range, months Patients censored, %	 8.3 0.1-12.9 27.2	 7.9 0-13.4 29.5	0.99*	0.82-1.2*	0.226*
Progression-free survival Median, months† Range, months	 2.9 0-18.2	 2.9 0-19.5	0.97	0.82 -1.16	0.759‡
Time to progressive disease Median, months† Range, months	 3.4 0.5-18.2	 3.5 0.3-19.5	0.97	0.80 - 1.17	0.721‡
Time to treatment failure Median, months† Range, months†	 2.3 0.0-18.2	 2.1 0.0-13.1	0.84	0.71 - 0.997	0.046‡
Duration of tumour response Median, months† Range, months†	 4.6 2.1-15.3	 5.3 1.7-11.7	0.77	0.40 - 1.47	0.427‡
Duration of clinical benefit Median, months† Range, months†	 5.4 1.2-18.2	 5.2 1.5-14.6	0.91	0.71 - 1.16	0.450‡
Time to objective tumour response Median, months Range, months	 1.7 1.2-4.3	 2.9 1.4-7.8	NA	NA	0.105§

HR = hazard ratio; NA = not assessable. * Fixed margin method † Median time-to-event value calculated using Kaplan-Meier method, ‡ Comparison of hazard ratio between treatment arms using the Cox Proportional Hazard model, § Analysis of variance *P* value.

Secondary efficacy outcomes

Of the six secondary efficacy outcomes measured (see Table 3-5) only time to treatment failure (TTTF) was significantly different between the two arms (although this only equates to a difference of six days). The submission suggests that this increase in TTTF "reflects the better safety profile of pemetrexed as fewer patients discontinued because of adverse events or death." However, this reduction in discontinuations in the pemetrexed arm did not lead to a difference in quality of life measures (both observer and patient) between the two treatment arms. The ERG further note that since this was an open label trial, assessors were not blinded and bias in measurement of these subjective outcomes could have been introduced.

The submission concludes that treatment with pemetrexed is as good as docetaxel in the ITT populations with respect to the remaining five secondary endpoints. However, this should not be interpreted as evidence that pemetrexed is 'as good as' docetaxel since the 95% confidence intervals include clinically important differences in both directions.

Quality of life

To assess patients' quality of life the JMEI trial used the Lung Cancer Symptom Scale (LCSS) which comprises a patient scale and an optional observer scale. The average symptom burden index (Table 3-6), which was calculated using the patient scale, demonstrates that there were no statistically significant differences in outcomes between the two treatment arms.

Table 3-6 Summary of average symptom burden index analysis – ITT population

Classification	Pemetrexed (N=227) N (%)	Docetaxel (N=247) N (%)	*P* value*
Improved	48 (21.2)	53 (21.5)	0.1447
Worsened	75 (33.0)	69 (27.9)	
Stable	67 (29.5)	61 (24.7)	
Unknown	37 (16.3)	64 (25.9)	

Abbreviations: ITT, intention to treat; LCSS, Lung Cancer Symptom Scale; N, number of patients in the treatment arm; n, number of patients with classification,. * Mantel-Haenszel chi-square.

The submission reported LCSS observer responses for six individual symptoms (anorexia, fatigue, cough, dyspnoea, haemoptysis, and pain); see Table 20 of the company submission for further details. There were no statistically significant differences between the treatment arms, with the majority of patients remaining stable

or improving. Although baseline rates are not reported, the submission states that the majority of patients had mild or no symptoms at baseline.

Analyses by subgroups

A Cox multiple regression (CMR) model was used to determine the factors that affected overall survival, other than treatment. Poor performance status, three or more months since last chemotherapy and stage IV disease were all associated with significantly shorter overall survival. These variables were included in a Cox proportional hazard model but there was insufficient evidence of a difference in overall survival rates between the two arms after adjusting for these factors (Table 3-7).

Table 3-7 Cox Model subgroup analysis of variables associated with improved survival

Variable	Pemetrexed survival (months)	Docetaxel survival (months)	*P value**
Performance status			
0 or 1	9.4	9.1	0.996
2	3.6	2.2	0.264
Time since last chemotherapy			
≥3 months	9.3	9.2	0.588
<3 months	7.0	6.2	0.670
Stage of disease			
III	9.3	10.3	0.948
IV	7.9	7.2	0.896

*comparison between treatment arms using Cox proportional Hazard model

The submission states that analyses of overall and progression-free survival were performed for subgroups based on gender and age but the results of these analyses are not reported. Furthermore, there is no information or analysis of patients with metastasis, although it is likely that the majority of patients with stage III or IV disease requiring second-line therapy will have metastasis (the submission indicates that 45% of patients present with metastatic disease). Finally, patients with a weight loss >10% in the preceding six weeks were excluded from the study therefore excluding a sub-group of people that would likely have poorer survival after having received chemotherapy.

Adverse events

The rates of haematological and non-haematological toxicities are shown in Table 3-8 and Table 3-9. Of the five grade 3 and grade 4 haematological toxicities reported,

three showed significantly higher rates in the docetaxel arm compared to the pemetrexed arm.

Table 3-8 Grade 3 and grade 4 haematological toxicities[a]

	Pemetrexed N=265 (%)	Docetaxel N=276 (%)	*P* value[b]
Neutropenia	5.3	40.2	< 0.001
Febrile neutropenia	1.9	12.7	< 0.001
Neutropenia with infection	0.0	3.3	0.004
Anaemia	4.2	4.3	0.99
Thrombocytopenia	1.9	0.4	0.116

a Toxicities graded using the National Cancer Institute Common Toxicity Criteria version 2., b Fishers exact test.

Reported non-haematological toxicities primarily included fatigue and nausea in the pemetrexed arm and fatigue and alopecia in the docetaxel arm. Differences in toxicities were shown in all grades of alopecia, (pemetrexed: 6.4%, docetaxel: 37.7%, *P*=<0.001) and in grade 3 or grade 4 ALT (pemetrexed: 1.9%, docetaxel: 0%, *P*=0.028). The submission also reports that there was a trend towards higher rates of grade 3 or grade 4 diarrhoea (pemetrexed: 0.4%, docetaxel: 2.5%, *P*=0.069).

Table 3-9 Non-haematological toxicities (%)

	Pemetrexed N=265		Docetaxel N=276		*P* value[a]
	Any grade	Grade 3 or 4	Any grade	Grade 3 or 4	
Fatigue	34.0	5.3	35.9	5.4	0.99
Nausea	30.9	2.6	16.7	1.8	0.57
Vomiting	16.2	1.5	12.0	1.1	0.72
Pulmonary	0.8	0.0	2.1	1.4	NA[b]
Neurosensory	4.9	0.0	15.9	1.1	NA[b]
Stomatitis	14.7	1.1	17.4	1.1	0.99
Alopecia	6.4	–	37.7	-	< 0.001
Diarrhoea	12.8	0.4	24.3	2.5	0.069
Rash	14.0	0.8	6.2	2.5	1.00
Weight loss	1.1	0.0	1.8	0.7	NA[b]
Oedema	4.5	0.0	8.3	0.0	NA[b]
ALT	7.9	1.9	1.4	0.0	0.028

Abbreviations: ALT, alanine transferase NA, not applicable: a Fishers exact test was used; comparison is between grade 3 and 4 toxicities except for alopecia:
b *P* value not calculated due to small numbers of patients (< 4 when arms combined) experiencing grade 3 or 4 toxicity.

Using the randomised and treated (RT) population the company submission reports detailed information on hospitalisations. A statistically significant difference between

pemetrexed and docetaxel was observed for the rate of hospital admissions due to neutropenic fever (pemetrexed=1.5%, docetaxel=3.4%, *P*=0.001), and in the proportions of patients receiving G-CSF/GM-CSF (pemetrexed=2.6%, docetaxel=19.2%, *P*=0.001), see Table 44 in company submission for further details. However, it is worth noting that differences in the treatment of febrile neutropenia between countries may inflate the use of G-CSF/GM-CS in the trial.

The company also include results of two safety analyses [25, 27] conducted using JMEI trial data. These analyses demonstrate the trend for a reduced "toxicity burden" and an increased "toxicity-survival time", particularly in terms of haematological toxicities, for patients receiving pemetrexed compared to docetaxel (see company submission for further detail). However, it is worth noting that this did not translate into a quality of life advantage for patients.

3.3 Indirect comparisons: pemetrexed versus docetaxel, erlotinib or BSC

The searches conducted by the company and critiqued in section 3.1 identified nine trials that included at least two of the four comparators of interest. Comprehensive details of these nine trials are provided both in the main part of the submission and in the appendices. Unfortunately there are several errors in these tables both in values reported and in definitions of time to treatment progression.

Indirect comparisons can be useful where randomised head to head comparison data are not available. For this purpose the methods outlined by Bucher,[30] and described in the company submission, are most appropriate since they compare hazard ratios and thus maintain the strength of randomisation within each study.

In order to indirectly compare pemetrexed with BSC, data from JMEI and TAX317 could be used to estimate hazard ratios and the corresponding 95% confidence intervals (Table 3-10). The remaining studies identified by the company's search do not provide any useful data for evaluating the relative effects of these treatment options. The company submission does refer to the Bucher indirect method but the method has not been applied correctly since treatment arm level data have been used instead of (log) hazard ratio estimates.

Table 3-10 Direct and indirect comparisons for overall survival endpoint

Pair-wise comparison	Trial(s) used	HR[1]	95% Lower Limit	95% Upper Limit
Direct evidence				
Pemetrexed versus docetaxel	JMEI	**0.99**	**0.82**	**1.20**
Docetaxel versus BSC	TAX317	0.56	0.35	0.88
Indirect evidence				
Pemetrexed versus BSC	JMEI / TAX317	**0.55**	**0.34**	**0.91**

1 HR<1 indicates survival benefit to the first drug in each comparison

The company submission also refers to the paper by Griffin.[31] The methodology presented in this paper applies a Bayesian mixed treatment comparison model to assess cost-effectiveness. The method entails estimating (log) hazard ratios and standard errors for each pair-wise comparison using all available evidence. Hazard rates and mean survival times are then estimated from these hazard ratios rather than from median survival times. The company submission does not use this approach but rather utilises the absolute median survival time for each treatment group in all nine identified studies and pools the median values across trials to enable estimation of hazard rates for each treatment group and hence estimate the mean survival time for the economic analysis. As this approach uses treatment arm level data from each trial, any benefit from randomisation is lost and the data become purely observational. This approach is therefore not the most appropriate. Furthermore, the median survival time is only relevant to one time point and does not incorporate information over the whole time scale as does a hazard ratio.

The best level of evidence available to assess the clinical effectiveness of pemetrexed compared with docetaxel is from the randomised head to head comparison (JMEI). Therefore the pooling of docetaxel arms of other trials is not appropriate.

From the ERG perspective, erlotinib is considered to be beyond the scope of this single technology appraisal, as it is not currently approved for treatment in England and Wales nor is it routinely used in clinical practice. Therefore the indirect comparison of pemetrexed versus erlotinib will not be considered in this report.

In summary, the methods described in section 2.7 of the company submission are not considered appropriate for estimating the relative clinical effects of pemetrexed, docetaxel, erlotinib or best supportive care.

3.4 Summary of clinical evidence

3.4.1 Clinical results

Direct comparison: pemetrexed versus docetaxel

- The JMEI trial failed to show superiority or non-inferiority of pemetrexed over docetaxel for overall survival
- The secondary efficacy outcomes of progression free survival, time to progressive disease, duration of tumour response, duration of clinical benefit and time to objective tumour response showed no statistical differences between the two arms.
- Time to treatment failure was significantly longer (six days longer for patients receiving pemetrexed)
- Significantly fewer patients receiving pemetrexed experienced grade 3 or grade 4 neutropenia, febrile neutropenia or neutropenia with infection.
- Fewer patients receiving pemetrexed experienced any grade of alopecia but more experienced grades 3 or 4 ALT than those receiving docetaxel
- Despite the apparent differences in the number, severity and duration of adverse events there is no difference in quality of life between the treatment arms.

Indirect comparison: pemetrexed versus docetaxel, erlotinib or best supportive care

- The company submission identifies nine trials to inform the indirect comparison of pemetrexed with other treatments
- The ERG believes that the indirect comparison conducted is inappropriate
- For this appraisal, the only valid indirect comparison is pemetrexed versus BSC.

3.4.2 Clinical issues

Direct comparison: pemetrexed versus docetaxel

- Patients with significant weight loss six weeks prior to the trial were excluded which may decrease generalisability of findings
- There were no study sites in the UK
- Median age of patients in JMEI is young compared to other identified trials
- The submission mentions that patients were eligible for further chemotherapy after they had discontinued in JMEI but the percentages are only reported in the paper. The higher % of patients receiving additional chemotherapy on pemetrexed (46.6% versus 37.2% taken from Hanna 2004) could exaggerate the effectiveness of pemetrexed.

Indirect comparison: pemetrexed versus docetaxel, erlotinib or best supportive care

- The pooling of absolute median survival data from other studies is not considered the most appropriate approach because the median value does not take into account data from the whole timescale
- Indirect comparisons provided in the submission were not considered to be appropriate since absolute values are pooled which is equivalent to observational data. More appropriate methods are available that maintain the benefits of randomisation within each component trial
- The most appropriate data to be used are from the single head to head comparison (JMEI).

4 COST EFFECTIVENESS

4.1 Summary of published cost-effectiveness studies identified in the submission

4.1.1 Identification and description of studies

The submission provided details of the electronic search strategy, including the search strings used for each database utilised. However, they did not include a record of the number of hits achieved by each search, nor the number of studies included and excluded at each stage, making replication of the search strategy impossible.

Studies were included in the economic review if they:

- Included a full or partial economic analysis
- Included patients with NSCLC receiving second-line treatment
- Were original and had not been reported elsewhere.

Studies were excluded from the economic review if they:

- Were population based economic models
- Included NSCLC patients receiving first-line treatment
- Included small cell lung cancer patients
- Were editorials, letters or review articles describing data that had been reported elsewhere
- Were not English language papers.

Using these inclusion and exclusion criteria, the company identified three full economic evaluations (none of which included pemetrexed as a comparator), eight studies evaluating costs and resources (two of which included pemetrexed), and 12 studies focussing on patient quality of life.

Studies identified under the heading 'resource use and cost' and 'quality of life' include papers on first-line therapies; whether this is a violation of the inclusion criteria is unclear. If it is not, other relevant studies could have been listed in the search results. Also, the company submission acknowledges that their review of quality of life studies needs to be updated.

4.1.2 Data extraction

The company extracted data from the 23 papers included in the review. The three full economic evaluations, together with the two relevant costing studies were extracted into structured tables collecting data on title, aims, methods, results, and relevance to decision-making in England and Wales. Data were extracted on title, aims and methods from the remaining 18 papers. Both forms of data extraction are simplistic and do not provide sufficient detail for a comprehensive comparison of studies. The limited commentary accompanying the data extraction tables makes it difficult to interpret the overall results of the studies.

The 23 studies from which data have been extracted are heterogeneous in terms of type of evaluation (full economic evaluations and partial economic evaluations) and type of study (empirical cost-effectiveness study, review of cost-effectiveness studies). Only two[32,33] of the included papers appear to be full economic evaluations which are relevant to the UK National Health Service (NHS). Both of these studies assess the cost-effectiveness of docetaxel versus best supportive care.

As none of the papers compared pemetrexed with docetaxel, BSC, or erlotinib, these studies are not directly comparable with the economic evaluation presented in the company submission.

4.1.3 Quality assessment

No formal quality assessment of the included papers is reported.

4.1.4 Summary and conclusions

The economic literature review did not identify any full economic evaluations which compared the use of pemetrexed with docetaxel, erlotinib or BSC for the second-line treatment of NSCLC. A total of three full economic evaluations and 20 partial analyses were identified; however, as discussed above, several resource and costs studies may have been missed. The data extraction of the economic literature undertaken by the company is lacking in depth, and no quality assessment of the included studies is provided. However, given the fact that these studies do not compare the same healthcare technologies as the company's own economic evaluation, this is disappointing but of limited importance.

4.2 Overview of company economic evaluation

4.2.1 Description and critique of company model

The company submitted a Markov model, with the three main health states being defined as: response, stable, and progressive disease (Figure 4-1). A Markov cycle length of 21 days was applied in accordance with the length of treatment with pemetrexed. The model limits the number of cycles in both treatment arms to six. The exit of all patients in the model occurs at death or at three years (which reflects the maximum life expectancy of the population).

Patients are in one of three health states: response, stable, or progressive disease. Each model cycle (21 days), patients can move between health states and experience side-effects, but only in the stable and responding health states.

Stable patients have four main options: respond, continue stable, progress or discontinue (discontinue is a transitory state in which patients move straight to the progressed health state).

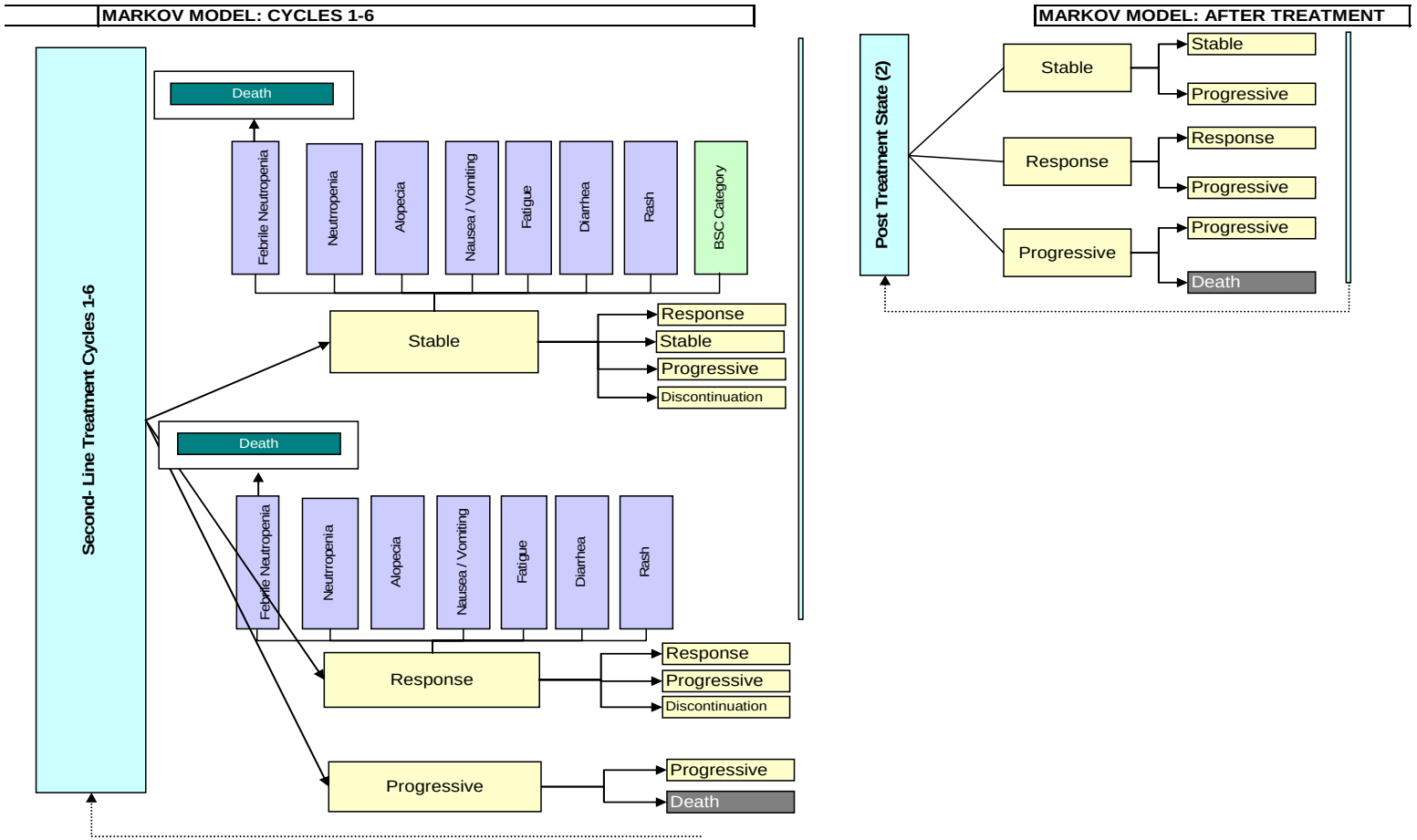
Responding patients have three main options: continue responding, progress or discontinue. However, responding patients cannot move to a stable health state.

Patients in the progressive health state only have two options: continue in the progressive health state or die. Patients in this state no longer receive chemotherapy and therefore do not experience side-effects. Side-effects in the company model appear to be restricted to treatment related events only.

In the model, death only occurs in the progressive health state or for patients experiencing febrile neutropenia. This may not reflect real world events, as patients may die before progressing and / or without experiencing febrile neutropenia.

Furthermore, the model does not allow for patients to die of anything other than cancer, or treatment related causes, which is an unrealistic assumption. In addition, patients cannot die in the first cycle of treatment which artificially inflates the survival benefit in both arms.

Figure 4-1 Schema of Eli Lilly model



4.2.2 Population

The patient population in the company model is second-line NSCLC patients eligible for treatment (according to the licensed indication for the product and comparators).

Subgroups

A subgroup analysis was undertaken on the basis of performance status (ECOG PS0/1 versus PS≥2). The rationale behind this is that patients with an ECOG PS0/1 will typically receive chemotherapy in clinical practice in England and Wales.

4.2.3 Perspective and time horizon

An NHS and Personal Social Service (PSS) perspective is adopted, in accordance with NICE guidelines.[34] The time horizon employed within the company model is three years. Three year survival for patients with III/IV NSCLC seems somewhat optimistic however there is a function which allows the timeframe in the model to be shortened.

4.2.4 Comparator

In the company submission docetaxel is chosen as the main comparator to pemetrexed; this is appropriate as docetaxel is the current standard of care in second-line advanced NSCLC. The model limits the number of cycles in both treatment arms to six, without assuming any loss of efficacy by this truncation. This assumption does not seem justified as analysis of further information supplied by the company indicates that in the pemetrexed arm curtailment to six cycles will lead to a loss of benefit (see section 4.3.5 for more details).

BSC and erlotinib are also selected as comparators. BSC seems an appropriate comparator to pemetrexed. However, as there is no direct comparison of BSC versus pemetrexed, interpretation of clinical trial evidence is limited. From the ERG perspective, erlotinib is considered to be beyond the scope of this single technology appraisal, as it is not currently approved for treatment in England and Wales nor is it routinely used in clinical practice. Therefore the comparison of pemetrexed versus erlotinib will not be considered in this report.

4.2.5 Clinical inputs

Efficacy

The company attempted to estimate several efficacy inputs (overall survival (OS), time to disease progression (TTdP), and response rates) using clinical trial data. The company carried out both direct and indirect comparisons of clinical trial data (see Table 4-1). However, the only direct and reliable clinical evidence available, which is relevant to the reference case of this appraisal, is the JMEI trial of pemetrexed versus docetaxel.[1] For more information see section 4.3.1 of this report.

A number of patients in the pemetrexed arm received docetaxel following disease progression, whereas pemetrexed was not offered to patients progressing in the docetaxel arm. This could lead to bias in results for overall survival, however careful examination of additional details on patient disposition provided by the company have satisfied the ERG that no significant bias is detectable in the submitted trial findings for overall survival.

Health benefits and utilities

Health benefits within the model were assessed using the quality adjusted life year (QALY). Utility values for health states and adverse events were based on multivariate analysis of standard gamble estimates from interviews conducted with 100 members of the general public. The mean utility values used in the model are shown in Table 4-1.

Table 4-1 Clinical inputs utilised in the company model

Model Variable	Value	Source
Efficacy inputs		
Pemetrexed median overall survival (OS)	35.96	Hanna et al., 2004[1] (JMEI trial)
Docetaxel median OS	30.34	Schuette 2005,[22] Fossella 2000,[18] Camps 2005,[17] Hanna 2004,[1] Gridelli 2004,[19] Ramlau 2006,[20] Shepherd 2000[21]
BSC median OS	21.40	Shepherd 2000, Shepherd 2005, Thatcher 2005.
Pemetrexed time to disease progression (TTP)	14.73	JMEI trial[1]
Docetaxel TTP	12.99	Schuette 2005,[22] Fossella 2000,[18] Camps 2005,[17] Hanna 2004,[1] Gridelli 2004,[19] Ramlau 2006,[20] Shepherd 2000[21]
BSC TTP	9.83	Shepherd 2000,[21] Shepherd 2005,[10] Thatcher 2005.[23]
Pemetrexed overall response (OR)	9.19	JMEI trial[1]
Docetaxel OR	6.80	Schuette 2005,[22] Fossella 2000,[18] Camps 2005,[17] Hanna 2004,[1] Gridelli 2004,[19] Ramlau 2006,[20] Shepherd 2000[21]
Utilities (mean)		
Stable disease no AE	0.65	One hundred members of the general public
Stable disease and rash	0.62	One hundred members of the general public
Stable disease and alopecia	0.61	One hundred members of the general public
Stable disease and fatigue	0.58	One hundred members of the general public
Stable disease and nausea & vomiting	0.61	One hundred members of the general public
Stable disease and diarrhoea	0.61	One hundred members of the general public
Stable disease and neutropenia	0.56	One hundred members of the general public
Stable disease and febrile neutropenia	0.56	One hundred members of the general public
Responding disease no AE	0.67	One hundred members of the general public
Responding disease and rash	0.64	One hundred members of the general public
Responding disease and alopecia	0.63	One hundred members of the general public
Responding disease and fatigue	0.6	One hundred members of the general public
Responding disease and nausea and vomiting	0.62	One hundred members of the general public
Responding disease and diarrhoea	0.63	One hundred members of the general public
Responding disease and neutropenia	0.58	One hundred members of the general public
Responding disease and febrile neutropenia	0.58	One hundred members of the general public
Progressive disease	0.47	One hundred members of the general public

Adverse events

Only grade 3 or grade 4 adverse events with an incidence of more than 5% in the clinical trial population are included in the model, with the exception of alopecia. This results in only febrile neutropenia, neutropenia, nausea and vomiting, fatigue, diarrhoea, rash and alopecia being included in the analysis of adverse events. The AE risk rates for pemetrexed were taken directly from the JMEI trial. A pooled analysis of seven trials was undertaken to estimate the AE risk rates for docetaxel. AE discontinuation rates were also estimated in a similar fashion (Table 4-2).

The inclusion of only grade 3 or grade 4 adverse events means that all other adverse events are perceived as being irrelevant or equally balanced between the two treatment arms of the model. In addition, as patients can only experience adverse events whilst on active treatment, logic follows that all AEs must be treatment related. However, in the submission, pain and pulmonary toxicity are highlighted as being symptoms of the disease which are not chemotherapy related; these symptoms and possibly others are not costed in the model.

Table 4-2 Adverse event data utilised in the company model

Adverse events (AE) grade 3/4	Pemetrexed		Docetaxel	
	Value	Source	Value	Source
Rash	0.75	Hanna, 2004 [1]	0.72	Schuette 2005,[22] Fossella 2000,[18] Camps 2005,[17] Hanna 2004,[1] Gridelli 2004,[19] Ramlau 2006,[20] Shepherd 2000[21]
Alopecia (all grades)	6.42	Hanna, 2004 [1]	39.87	Schuette 2005,[22] Fossella 2000,[18] Camps 2005,[17] Hanna 2004,[1] Gridelli 2004,[19] Ramlau 2006,[20] Shepherd 2000[21]
Fatigue	5.28	Hanna, 2004 [1]	4.97	Schuette 2005,[22] Fossella 2000,[18] Camps 2005,[17] Hanna 2004,[1] Gridelli 2004,[19] Ramlau 2006,[20] Shepherd 2000[21]
Nausea and vomiting	4.15	Hanna, 2004 [1]	2.85	Schuette 2005,[22] Fossella 2000,[18] Camps 2005,[17] Hanna 2004,[1] Gridelli 2004,[19] Ramlau 2006,[20] Shepherd 2000[21]
Diarrhoea	0.38	Hanna, 2004 [1]	2.30	Schuette 2005,[22] Fossella 2000,[18] Camps 2005,[17] Hanna 2004,[1] Gridelli 2004,[19] Ramlau 2006,[20] Shepherd 2000[21]
Neutropenia	5.28	Hanna, 2004 [1]	42.91	Schuette 2005,[22] Fossella 2000,[18] Camps 2005,[17] Hanna 2004,[1] Gridelli 2004,[19] Ramlau 2006,[20] Shepherd 2000[21]
Febrile neutropenia	1.89	Hanna, 2004 [1]	12.68	Hanna 2004[1]
AE discontinuation rate	0.07	Hanna, 2004 [1]	0.096	Schuette 2005,[22] Fossella 2000,[18] Camps 2005,[17] Hanna 2004,[1] Gridelli 2004,[19] Ramlau 2006,[20] Shepherd 2000[21]

4.2.6 Resources and costs

A number of resources and costs were included in the model, see Table 4-3.

Table 4-3 Resource use and costs utilised in the company model

Resource use item	Unit cost*	Source
Chemotherapy agents		
Pemetrexed	£800 per 500mg vial	BNF 2006[35]
Docetaxel 0.5ml – 20mg	£162.75	BNF 2006[35]
Docetaxel 2ml – 80mg	£534.75	BNF 2006[35]
Best supportive care	£2,158	Lees 2002[36]
Pre-medications		
Dexamethasone	£42.30	BNF 2006[35]
Folic acid	£2.24	BNF 2006[35]
Vitamin B12	£2.46	BNF 2006[35]
Piriton	£0.19	BNF 2006[35]
Paracetamol	£0.31	BNF 2006[35]
AE-related treatments		
Blood transfusion – whole	£125.07	National Blood Bank
Blood transfusion – platelets	£206.34	National Blood Bank
Blood transfusion – standard red cells	£124.80	National Blood Bank
Steroid cream (Betnovate)	£3.34	BNF 2006[35]
Lomotil	£1.63	BNF 2006[35]
Domperidone	£2.47	BNF 2006[35]
Haemoglobin levels	£3.04	NHS Reference Costs
Electrolytes	£1.65	NHS Reference Costs
Blood cultures	£3.04	NHS Reference Costs
Stool cultures	£6.59	NHS Reference Costs
Complete blood cell count	£3.04	NHS Reference Costs
Differential white blood cell count	£3.04	NHS Reference Costs
Platelet count	£3.04	NHS Reference Costs
Liver function tests	£1.65	NHS Reference Costs
Treatment for febrile neutropenia	£3,860.30	Holmes et al., (2004) [32]
1 day in hospital: chemotherapy with a respiratory system primary diagnosis – non-elective admission	£250.19	NHS Reference costs
Administration time		
Clinic time (1 hour) D98: Chemotherapy with a respiratory system primary diagnosis	£62.91	NHS Reference costs
Palliative care costs	£3,236	NICE (2004)

*pack cost in the case of chemotherapy agents and pre-medications. Inflated to present values

4.2.7 Discounting

Health benefits and costs were discounted at 3.5% in line with current NICE guidance.[34]

4.2.8 Results

Base-case

The base-case results of the company's economic analysis are shown in Table 4-4. In terms of cost per QALY, pemetrexed appears to be cost effective at a willingness to pay (WTP) of £30,000, compared to both docetaxel (ICER £18,672), and BSC (ICER £16,458).

Table 4-4 Base-case results of company submission

	Pemetrexed (Pem)	Docetaxel (Doc)	Best supportive care (BSC)	Incremental	
				Pem v Doc	Pem v BSC
Cost results					
Active treatment cost	£4,591	£2,737	£0	£1,854	£4,591
Non-chemotherapy cost	£671	£772	£0	-£101	£671
AE cost	£89	£424	£0	-£334	£89
BSC costs			£1,871		-£1,871
Palliative care costs	£3,556	£3,599	£3,655	-£43	-£100
Total direct costs	£8,906	£7,532	£5,527	£1,375	£3,379
Effectiveness results					
Total LYG	0.92	0.73	0.60	0.19	0.32
Total QALYs	0.49	0.42	0.29	0.07	0.21
ICER					
Cost per LYG				£7,097	£10, 418
Cost per QALY				£18,672	£16,458

Subgroup analysis

A subgroup analysis on the basis of ECOG PS0/1 was undertaken for pemetrexed versus BSC. The results did not differ significantly from the base-case results of pemetrexed compared to BSC (ICER £12,045 cost per QALY for PS0/1, versus £16,458 for all patients versus BSC).

4.2.9 Sensitivity analysis

Univariate sensitivity analysis (SA) and probabilistic sensitivity analysis (PSA) were conducted and presented within the company submission (for full details please see company submission pp135- pp142).

In terms of univariate SA, the model is most sensitive to survival for both pemetrexed and docetaxel. At the lower end of the pemetrexed 95% CI for survival (29.92 weeks), docetaxel dominates pemetrexed. At the upper end of the pemetrexed 95% CI for survival (42.01 weeks), pemetrexed dominates docetaxel.

The company PSA demonstrates that compared to docetaxel, pemetrexed has a 67% chance of being cost-effective (in terms of cost per QALY) at a WTP of £30,000. When pemetrexed is compared with BSC, there is a greater than 90% chance that it is cost-effective (cost per QALY) at a WTP of £30,000.

4.3 Corrections and adjustments to company model

In this section we consider several aspects of the submitted economic evidence where other assumptions and/or parameters values appear to be justified. In each case the source of our proposed alternative is described, and the magnitude of difference estimated. We then recalculate the cost-utility ratios taking account of all of the quantifiable changes, and present the revised results in tabular and graphical form. Clearly, our critique of the company submission is not exhaustive and we have chosen to focus on the most important issues.

4.3.1 Comparators and evidence for comparison

The company submission presents model results for comparisons of pemetrexed with docetaxel (the current standard therapy), best supportive care and erlotinib (another potential alternative to docetaxel). Central to these economic assessments is an approach to evidence synthesis which relies on pooling survival data (including overall survival and time to disease progression) from multiple studies in respect of docetaxel and BSC arms. The legitimacy of this approach has been discussed in section 3.3 above, where it is concluded that results obtained by these methods cannot be considered reliable or meaningful, since they effectively undermine all the benefits of randomization inherent in the source trials and do not adjust for the resulting imbalances between the pooled comparators.

This has a profound impact on the case put forward by Eli Lilly: pooled comparison with either docetaxel or BSC is excluded as inherently and irredeemably biased, and equally the comparison with erlotinib which also depends on pooling but additionally requires an indirect comparison cannot be considered credible. The only direct and reliable evidence available which is relevant to the reference case of this appraisal is the JMEI trial of pemetrexed verses docetaxel. However, the discussion in section 3.2.4 highlights that the JMEI trial investigators failed to establish equivalence of effect or even non-inferiority with regard to overall survival of pemetrexed compared to docetaxel. Thus there could be grounds on which to dismiss all the submitted economic results as unreliable.

However, we may instead choose to adopt a more pragmatic position: on the basis of the Kaplan-Meier analysis of overall survival for the JMEI trial we may accept that there is no realistic difference between the trial arms, and therefore base an analysis of costs and outcomes on the assumption of outcome equivalence. This then reduces the analysis to one which depends on a single trial, adjusted as appropriate to UK clinical practice and costs.

Although this is an appealing option, it causes serious problems for the relevance and reliability of the submitted Markov model, which uses a series of intermediate states and differential transition rates to generate important gains in survival for pemetrexed relative to all alternative treatments. Clearly, if we accept that survival equivalence is itself a generous assumption, then the submitted model appears to have failed the primary validation test - to reproduce the single most important clinical outcome. The ERG have therefore concluded that it is unlikely that the submitted model, even with minor modifications and parameter changes, could be used as the basis for generating useable cost-effectiveness evidence. Indeed, a quite different model structure would be required to constrain survival to true equivalence between treatments, and this is beyond the scope of the ERG in preparing this assessment report.

4.3.2 Outcomes

In the company submission results were presented from an updated analysis of the one primary and six secondary outcomes from the JMEI trial. These confirm that there is no significant difference in the primary outcome (overall survival) between

pemetrexed and docetaxel. A similar finding was also noted for five of the secondary outcomes:

- Progression-free survival

- Time to progressive disease

- Duration of tumour response

- Duration of clinical benefit

- Time to objective tumour response

Only one secondary measure (time to treatment failure) appears to show a small advantage for pemetrexed in median TTTF (2.3 vs. 2.1 months, p = 0.046). In terms of model states and events, this implies that there should be no differences in patient time spent in the three states (stable, response, progression) which govern the calculation of survival and state specific quality of life. The only possible difference implied by these results is that some docetaxel patients will discontinue active therapy earlier than those on pemetrexed, but with no impact on response, or the timing of progression or death. Thus if the small apparent difference in TTTF were to be allowed, its effect on the cost-effectiveness analysis would be solely that of reducing the mean number of treatment cycles (and therefore the cost) for docetaxel patients. However, by costing treatment in terms of the actual treatments given in the trial this effect is already accounted for.

In the absence of differences in overall survival or time spent in health states, the only valid outcome differences are the utility effects of treatment-related adverse events. The overall utility gain claimed for pemetrexed over docetaxel has been re-estimated after applying a half-cycle correction (not used in the company model), and then disaggregated into components attributable to modelled survival gain, and treatment-related adverse events (Table 4-5).

Table 4-5 Modelling QALY gain and its components

	QALYs gained
Modelled gain in QALYs (pemetrexed - docetaxel)	**+ 0.07361 per patient**
Modelled gain in QALYs with ½ cycle correction	+ 0.07346 per patient
QALYs gained from survival differences	+ 0.07043 per patient
QALYs gained from treatment-related AEs	+ 0.00304 per patient

Thus, when survival equivalence is assumed, the utility benefits which can be attributed to pemetrexed in place of docetaxel are drastically reduced (from 0.07361 to 0.00304).

Substituting 0.003 QALYs (ERG revised QALY gain) in place of 0.07 (company estimate), yields an ICER of £458,333 per QALY gained. This ICER far exceeds normally accepted values.

4.3.3 Resources and costs

Drug acquisition: pemetrexed

For both pemetrexed and docetaxel, the authors of the company model employ a misleading simplification when estimating the amount of chemotherapy agent required. They have assumed the same average usage of the drug for every patient, irrespective of physical characteristics. In fact, dosing is calculated individually according to a patient's body surface area (BSA), at 500 mg/m^2 for pemetrexed and 75mg/m^2 for docetaxel. To exemplify the impact of realistic dose calculations we have assumed a normal distribution of BSA among patients with a mean of 1.83m^2 and standard deviation of 0.21. This is consistent with results of a large Australian survey of chemotherapy patients reported in 2004.[32]

Taking account of the distribution of BSA, we estimate that a mean of 2.21 vials of pemetrexed are needed per cycle of treatment, costing £1768.55 per cycle. To this must be added the cost of medication with dexamethasone (tablets rather than the more costly liquid form), vitamin supplementation and liver and blood tests, giving a total cost of pemetrexed chemotherapy of £1790.94. Using the mean number of cycles given in the JMEI trial (4.39), we estimate the mean cost per patient as £7,862. Note that there is no assumption here of any vial sharing between patients treated at the same time.

Drug acquisition: docetaxel

Using the same method to calculate docetaxel dosing, we estimate that on average patients will use 1.44 large vials (80mg) and 1.63 small vials (20mg) per cycle of treatment; this contrasts with the Eli Lilly assumption of one large and three small vials per cycle. This approach results in a mean docetaxel acquisition cost (including

the cost of dexamethasone medication, piriton, paracetamol and blood test) increasing slightly from £1,043.19 per cycle used in the company model to £1,045.08 per cycle, a difference of £1.89 per cycle. Using the mean number of cycles given in the JMEI trial (3.93), we estimate the mean cost per patient as £4,108.

Drug administration costs

The submitted model uses micro-costing to estimate the cost of drug administration, based on an expected difference in infusion time between the two agents. However, in practice, patient treatments are coded and costed in the NHS on the basis of the setting of administration, as either in-patient or day case/regular attender events, and costed using the appropriate NHS reference/tariff cost. To re-estimate administration costs we have used the proportions of patients requiring in-patient admission in the JMEI trial (10.6% of pemetrexed cycles and 13.9% of docetaxel cycles) applied to the NHS 2005/6 tariff costs for D98 (chemotherapy with primary respiratory diagnosis) for admitted patient care (£373) and regular attender (£151). In addition we have made an assumption that admitted patients require transportation to and from the chemotherapy centre, and have included costs of two NHS patient transport services per cycle (£49 per journey - PSSRU 2005).

Overall the estimated cost of administration during treatment is then estimated to be £812 per patient receiving pemetrexed and £769 per patient on docetaxel.

Summary of chemotherapy costs

Taking acquisition and administration costs together, we arrive at estimates for the total cost of chemotherapy per patient of £8,678 for pemetrexed and £4,877 for docetaxel, a difference of £4,613 per patient. This contrasts with the estimates presented in the company submission; £5,262 for pemetrexed and £3,509 for docetaxel. The dominant factor leading to these differences is the number of cycles of treatment given to patients. The ERG estimates have adopted the JMEI trial drug usage patterns which are compatible with the assumption of equivalence of overall survival which was discussed in section 4.3.1 above. By contrast, the Eli Lilly model generates different numbers of cycles based on assumptions about progression and discontinuation rates, as well as limiting the maximum permitted cycles to 6 per patient. Thus the base-case submitted results use 3.38 cycles of pemetrexed and 3.21 cycles of docetaxel, compared to 4.39 and 3.93 respectively in the JMEI trial. It is

admitted in the submission that it is difficult to estimate the likely loss of efficacy that would result from truncating treatment at 6 cycles. By reducing therapy costs without any corresponding reduction in benefits, the submitted model risks biasing the results in favour of pemetrexed.

Adverse event costs

The company submission estimates that drug-related adverse events incur a mean cost per patient of £89 when pemetrexed is given, and £424 when docetaxel is used, i.e. a cost saving of £334 per patient from pemetrexed. In is instructive to analyse these figures by the seven adverse events featured in the model (Table 4-6)

Table 4-6 Adverse events in the company model

Adverse event	Cost per episode	Cost per patient			Proportion of difference
		Pemetrexed	Docetaxel	Difference	
Febrile neutropenia	£3860.30	£43.96	£359.72	-£315.76	94.4%
Neutropenia	£72.05	£2.20	£20.74	-£18.54	5.5%
Nausea / vomiting	£974.03	£23.24	£15.14	+£8.10	-2.4%
Fatigue	£586.06	£17.88	£16.02	+£1.86	-0.6%
Diarrhoea	£982.94	£2.10	£12.26	-£10.16	3.0%
Rash	£3.34	£0.01	£0.01	£0.00	0.0%
Alopecia	£0.00	£0.00	£0.00	£0.00	0.0%
All types		£89.38	£423.88	-£334.49	100.0%

Clearly the most important type of adverse event considered by the model is febrile neutropenia, where the higher incidence among docetaxel patients combined with the very large cost per episode yields a substantial mean cost saving in the pemetrexed arm. Advice from clinical advisors indicated that all such patients would be admitted to hospital for a 5-7 day period (50% admitted via the Accident and Emergency department), followed by an additional out-patient consultation and an additional general practitioner (GP) visit. Costing the hospital resources using NHS Reference Costs 2004 and the GP visit at PSSRU costs, suggests an expected cost for an episode of febrile neutropenia of £2257.50. As a result the modelled cost saving in the treatment of adverse events due to use of pemetrexed falls to £203.39 per patient.

Non treatment-related costs

The model does not account for costs of care which do not arise directly from an active treatment, any treatment-related adverse events or palliative care at the end of life. The exception is the cost of BSC when comparing active agents to BSC. However, the various care components which arise independently of an active treatment can occur at any time. By ignoring these costs in the active arms of comparisons, the modellers are systematically biasing results against BSC. The model includes an option to add in BSC costs after disease progression, but this only partly answers the problem. Since no evidence is offered to suggest that such costs differ between active therapies, we should presume that they apply equally throughout patients' remaining lifetime, so that they make no net contribution to incremental costs on the basis of survival equivalence.

Palliative care costs

The model assumes a standard cost applies to every patient for palliative (or terminal) care, and this is introduced at the time of death. The only difference between the agents in this cost component therefore arises from differential discounting on the assumption that pemetrexed patients die later than docetaxel patients (overall survival gain). If survival equivalence is assumed the incremental cost difference of £43 per patient disappears.

4.3.4 Cost-utility results

Applying all the alterations and adjustments described above to the company model produces the results shown in Table 4-7. The substitution of docetaxel by pemetrexed leads to higher incremental costs per patient and almost no increase in incremental benefits for the patient. As a consequence the previously advantageous cost-effectiveness ratio has been dramatically changed to one which far exceeds normally acceptable values. This extreme sensitivity is due to the very small value of incremental benefit, which renders the ICER highly unstable to small changes. What is clear from this analysis is that there are significant additional costs associated with substitution of docetaxel by pemetrexed, but the net benefits measured in terms of conventional utility values are extremely small. Thus adoption of pemetrexed could not be justified if the assumption of survival equivalence is accepted.

Table 4-7 Cost-effectiveness summary table updated for identified corrections and amendments to the company model

	Pemetrexed	Docetaxel	Incremental
Costs results			
Drug acquisition and administration	£8,678	£4,877	£3,801
Non-treatment related	£1,871	£1,871	£0
Adverse event treatment	£71	£275	-£203
Palliative care	£3,599	£3,599	£0
Total cost	**£14,220**	**£10,622**	**£3,598**
Effectiveness results			
Overall mean survival (months)	8.76	8.76	0.00
Total QALYs	**0.4396**	**0.4366**	**0.0030**
ICER			
Cost per QALY			**£1,185,164**

It is not possible to carry out a fully revised probabilistic sensitivity analysis as it would be necessary to carry out extensive redesign of the submitted model. In particular, the Markov model structure cannot accommodate the imposition of a binding constraint on overall survival and time to progression, without definition of all transition probabilities. Instead by way of illustration we have made very simple average adjustments to both the net incremental cost per patient and the net incremental QALY gain in the original PSA replications to reassess the impact of likely changes to the cost-acceptability curve (Figure 4-2) and the distribution of uncertainty on the cost-effectiveness plane (Figure 4-3).

Figure 4-2 Modified cost-acceptability curve using company PSA results adjusted for average incremental cost and outcome alterations

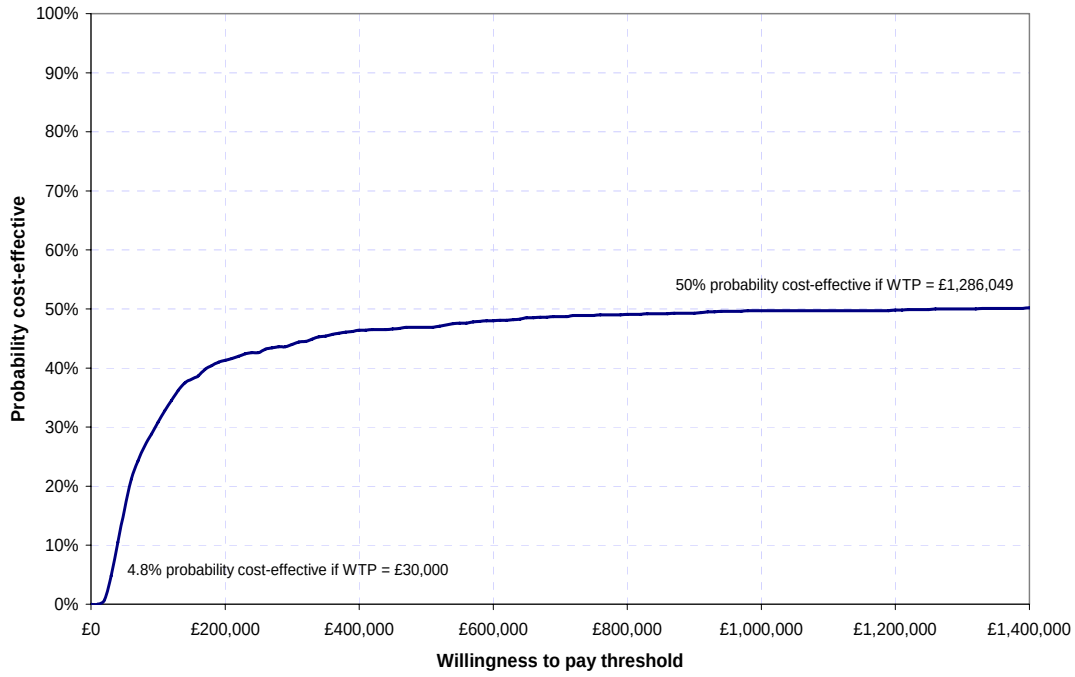
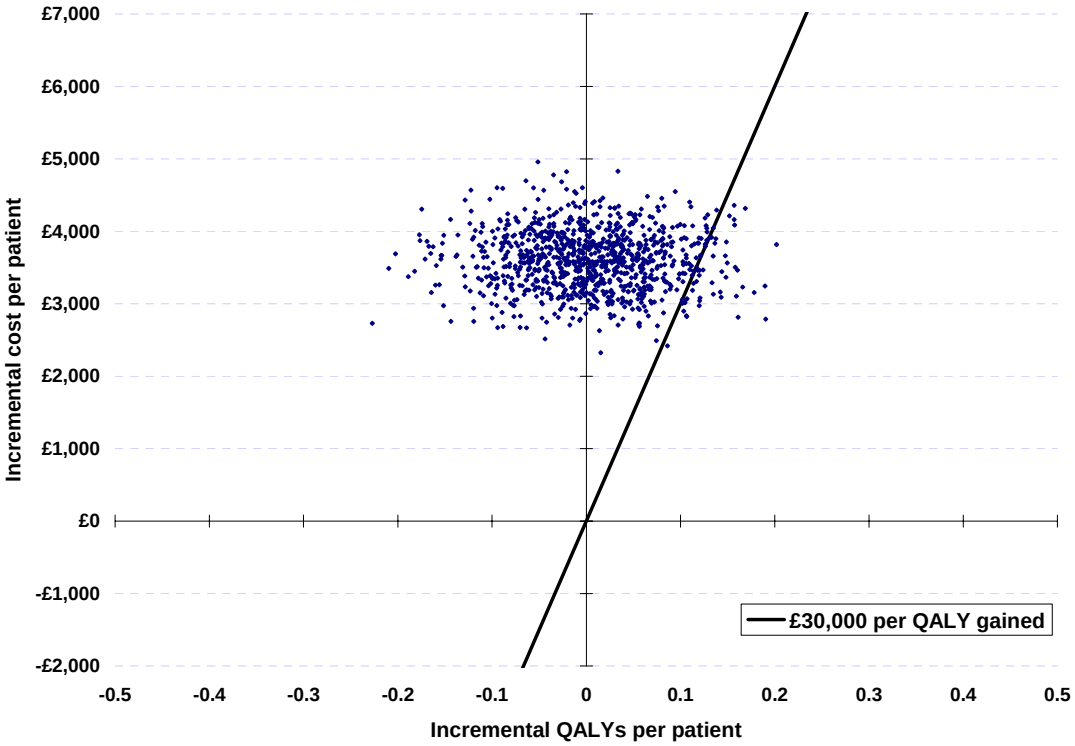


Figure 4-3 Modified cost-effectiveness uncertainty scatter plot using company PSA results adjusted for average incremental cost and outcome alterations



4.3.5 ERG sensitivity analysis

Dosing assumptions

The estimation of pemetrexed and docetaxel dosing costs described in section 4.3.2 may be questioned on two grounds:

(1) that the assumed mean body surface area (BSA) is too high, and that patients may have suffered significant weight loss since their first course of chemotherapy;

(2) that our calculations imply an overly precise application of the standard formula, which may not be necessary in clinical practice.

Unfortunately, it is not normal practice in published trials to report BSA (or patient height and weight from which BSA may be estimated) so it is difficult to find additional sources to validate the Australian survey findings we have used (mean BSA = 1.833). One additional study has been identified which reported details of 283 patients undergoing chemotherapy for solid tumours in the Netherlands[37] (61% male, 30% NSCLC), and recorded a mean BSA of 1.86 (SD 0.19) thus providing some confirmation of the basis for our calculations.

Dooley et al[38]discusses the clinical impact of dose rounding and concludes "that dose rounding to within 5% of calculated dose would not have any significant clinical effect on either response or toxicity. This, of course, is a practical judgement and has not been tested in a controlled manner."

We consider the joint effect of these two factors on the cost of docetaxel, and on the cost-effectiveness of pemetrexed in Table 4-8. It is apparent that these uncertainties in the calculation of drug costs are not sufficient to lead to acceptable cost-effectiveness ratios.

Treatment cycle assumptions

It is reported by clinical experts that in UK practice, chemotherapy is frequently limited to a maximum of 4 cycles per patient, and suggested that the economic evaluation should be based on this pragmatic rule. The submitted model results are based on the assumption that treatment for both pemetrexed and docetaxel is limited to a maximum of six cycles per patient. It is further assumed that such truncation of the trial dosing has no detrimental effect on the outcomes of the trial. Review of additional information provided by the company in response to a question from the

ERG reveals that although all docetaxel responders were identified within six cycles, the last pemetrexed responder was not recorded until cycle ten. The median number of cycles given was similar for pemetrexed (3.10) and docetaxel (3.03), and is unaffected by limiting the maximum number of cycles to four or more. A sensitivity analysis has been carried out to compare four truncation options with the base case scenario (based on full trial dosing) and the results are shown in Table 4-9. In all cases it is assumed that response rates are not affected by imposing a cycle limit - a conservative position. The costs of chemotherapy reduce in proportion to the mean number of cycles per patient - for pemetrexed from 4.39 in the trial to 2.99, 3.71 and 4.17 for 4, 6 and 10 cycles respectively, and for docetaxel from 3.93 in the trial to 2.95, 3.63 and 3.64 respectively. It is clear that although limiting the number of cycles does reduce the incremental costs in all cases, this effect is not sufficient to lead to cost effectiveness for pemetrexed compared to docetaxel.

Table 4-8 Sensitivity analyses - costing pemetrexed and docetaxel for lower mean BSA and dose rounding

	Pemetrexed (cost per patient)	Docetaxel (cost per patient)	ICER (cost per QALY)
The ERG Base Case (BSA = 1.833, no rounding)	**£8,678**	**£4,877**	**£1,185,164**
BSA = 1.75, no rounding	£8,340	£4,767	£1,116,777
BSA = 1.75, dose rounding = -5%	£8,458	£4,606	£1,201,862
BSA = 1.75, dose rounding = +5%	£8,341	£4,890	£1,079,785
BSA = 1.833, dose rounding = -5%	£8,656	£4,743	£1,221,799
BSA = 1.833, dose rounding = +5%	£8,834	£5,027	£1,186,729

Table 4-9 Sensitivity analyses - costing pemetrexed and docetaxel for limited cycles of treatment, assuming full trial efficacy

	Pemetrexed (cost per patient)	Docetaxel (cost per patient)	ICER (cost per QALY)
The ERG Base Case (no limitation)	**£8,678**	**£4,877**	**£1,185,164**
4 cycles docetaxel, 4 cycles pemetrexed	£5,912	£3,654	£676,766
6 cycles docetaxel, 6 cycles pemetrexed	£7,329	£4,508	£862,063
6 cycles docetaxel, 10 cycles pemetrexed	£8,246	£4,508	£1,164,135
10 cycles docetaxel, 10 cycles pemetrexed	£8,246	£4,513	£1,162,654

4.4 Summary of cost-effectiveness evidence

4.4.1 Economic evaluation results

Base case: company

- The company report an ICER of £18,672 for pemetrexed versus docetaxel with a 67% probability that pemetrexed is cost effective at a WTP of £30,000 per QALY gained. In the model this ICER is achieved by assuming a survival benefit for pemetrexed compared to docetaxel.

Base case: ERG

- Using the more realistic assumption of equivalent survival for pemetrexed compared to docetaxel, the company ICER increases from £18,672 to £458,333 per QALY.

- Survival was not the only unjustified assumption within the model.

- A number of key assumptions and parameters in the model do not seem to be clinically and / or economically justified. Once these assumptions are adjusted to more realistic estimates, the ICER increases to £1.2 million per QALY, with a 5% probability that pemetrexed is cost-effective at a WTP threshold of £30,000 per QALY gained.

4.4.2 Economic issues

- The ERG believes that the approach to evidence synthesis (pooling) adopted by the company is not meaningful.

- The only direct and reliable evidence available is the JMEI trial of pemetrexed versus docetaxel, which could not prove non inferiority of pemetrexed compared to docetaxel.

- Adjustments and corrections to the company model yield an ICER which far exceeds accepted values.

- Given the relatively high cost of pemetrexed and the marginal health benefits gained in comparison to docetaxel, discussion of further economic issues seems unnecessary.

5 DISCUSSION

The company presents a case for the replacement of docetaxel by pemetrexed as second-line therapy for NSCLC patients with locally advanced or metastatic disease. A phase III head to head randomised controlled trial compared pemetrexed with docetaxel (JMEI). This trial failed to demonstrate superiority or non-inferiority of pemetrexed over docetaxel for overall survival. However, the company claim that there is a survival advantage for pemetrexed compared to docetaxel, yielding an ICER of £18,672 per QALY gained. This supposition is based on the results of modelling using clinical efficacy evidence obtained by pooling docetaxel arms from seven clinical trials and subsequent indirect analysis rather than utilising the head to head trial of pemetrexed versus docetaxel. The ERG believes that the efficacy results obtained by these methods cannot be considered reliable or meaningful, since they effectively undermine all the benefits of randomisation inherent in the source trials and do not adjust for the resulting imbalances between the pooled comparators.

In order to compare docetaxel with pemetrexed, only the JMEI head to head trial results should have been employed. However, even this trial may be subject to questions about its reliability; in particular, the ERG observes that patients were recruited from a large number of centres (125) and countries (23), with a mean number per site of only four. Such contextual diversity and small numbers may undermine some of the benefits of randomization, and also cast doubt on the applicability of results to any one country.

The company submitted an economic model based on a Markov architecture with three main health states (defined as response, stable disease, and progressive disease), and a cycle length of 21 days projected to a maximum survival of 36 months. The model results were generated assuming that treatments are limited to a maximum of six cycles per patient. Death only occurs when patients are in the progressive disease state or for patients experiencing febrile neutropenia. This may not reflect real world events, as patients may die before progression is confirmed and/or without experiencing febrile neutropenia. Furthermore, the model does not allow for patients to die of any non-cancer causes or other treatment related causes. In addition, patients cannot die in the first cycle of treatment, which serves to inflate the survival benefit in both arms artificially.

Adverse events in the company model are restricted to treatment related events only, thus for patients whose disease has progressed there is no further explicit reckoning of either the costs or effects of adverse events.

Despite the real problems associated with the JMEI trial, it may be employed in an economic evaluation if we make the generous assumption that pemetrexed can be considered as an equally effective treatment compared to docetaxel. Incorporating this assumption into the submitted model, the ICER rises to £458,333 per QALY gained. This extreme sensitivity is due to the very small value of justifiable incremental benefit in the absence of survival gain, which renders the ICER highly unstable to small changes in costs and benefits.

When other corrections and adjustments (e.g. drug acquisition costs) relating to the costs of pemetrexed and docetaxel are incorporated into the company model, the ICER increases to over £1 million per QALY gained. Thus, adoption of pemetrexed cannot be justified if the assumption of survival equivalence is accepted. Furthermore, as the JMEI trial could not prove non-inferiority of pemetrexed compared to docetaxel there remains the possibility that docetaxel may in fact dominate pemetrexed (i.e. be more costly and also less clinically effective).

5.1 Implications for future research

Future work is necessary in order to undertake a comprehensive comparison between all relevant treatment strategies for the second-line treatment of stage IIIb/IV NSCLC patients. A full systematic review and meta-analysis of trials assessing all relevant chemotherapy options and best supportive care could inform such a comparison.

Finally, there is a paucity of data describing chemotherapy up-take in England and Wales. Coordinated data collection of current chemotherapy statistics, including the number of patients eligible for treatment, the number of patients receiving first-line and second-line chemotherapy and the types of chemotherapy delivered, is essential if the true budget impact of new treatments is to be estimated.

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