PEMETREXED IN THE TREATMENT OF NON-SMALL-CELL LUNG CANCER

SINGLE TECHNOLOGY APPRAISAL (STA) SUBMISSION TO THE NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

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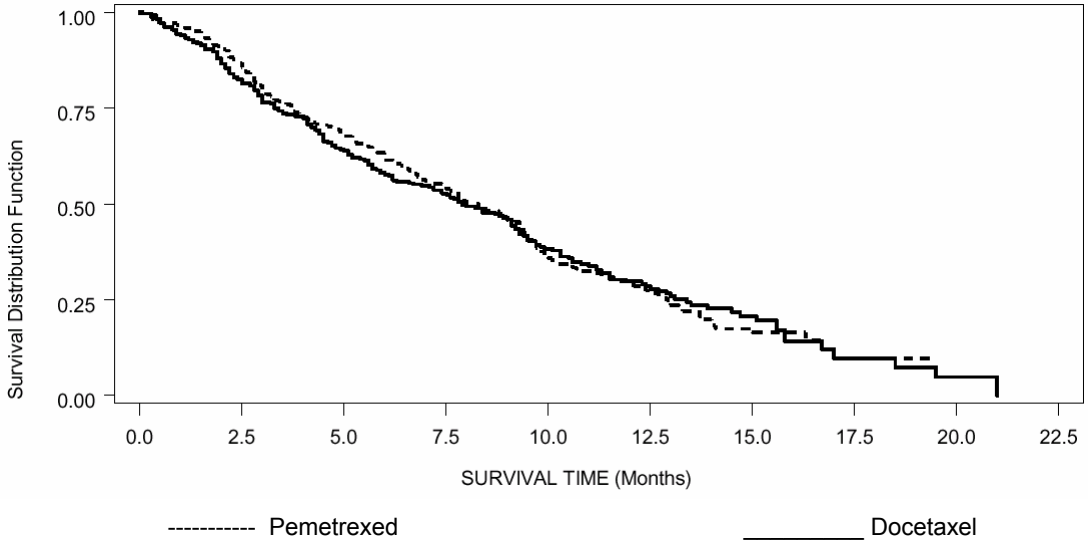
Executive Summary for NICE: Pemetrexed in Non-Small Cell Lung Cancer (NSCLC)	
Remit	The remit of this appraisal is to assess the clinical and cost effectiveness of pemetrexed compared to current standards of care in second-line advanced non-small cell lung cancer (NSCLC).
Intervention(s):	Pemetrexed is indicated as monotherapy for the treatment of patients with locally advanced or metastatic NSCLC who have relapsed after prior chemotherapy. In patients treated for second-line NSCLC, the recommended dose of pemetrexed is 500mg/m^2 body surface area administered as an intravenous infusion over 10 minutes on the first day of each 21-day cycle. The basis of the licence is a phase III registration trial in which 571 patients were randomly assigned to receive either pemetrexed 500mg/m^2 (n=283) or docetaxel 75mg/m^2 (n=288); every 21 days. Eligible patients had a performance status 0 to 2, previous treatment with one prior chemotherapy regimen for advanced NSCLC and adequate organ function. The primary end point was overall survival. Secondary endpoints included time-to-disease progression (TTPD), progression-free survival (PFS), tumour response, Health-related quality of life (HRQoL) and adverse effects of treatment.
Clinical Results of Pemetrexed phase III registration trial	***Primary Efficacy Outcomes*** The primary outcome of this study was the overall survival of the ITT patients. Median survival time was 8.3 versus 7.9 months (p =0.226) for pemetrexed and docetaxel, respectively. **Summary of Survival Time (months), ITT population**  ---------- Pemetrexed _____ Docetaxel Using Rothmannn methodology, analysis showed that treatment with pemetrexed was as good as treatment with docetaxel in the ITT population with respect to overall survival. In the best case, pemetrexed retained greater than 100% of the survival benefit of docetaxel, and in the worst case at least 52% of the benefit over BSC. ***Secondary Efficacy Outcomes*** The results presented in table below illustrated there were no significant differences in progression-free survival (PFS), time to progressive disease (TTPD), median time to tumour response, median duration of tumour response and median duration of clinical benefit. For time-to-treatment failure (TTTF), there was a statistically significant difference between treatment arms, favouring pemetrexed where TTTF took statistically significantly longer in pemetrexed-treated compared to docetaxel-treated patients (p = 0.046).

Variable Median (range), months[†]	Pemetrexed (n=283)	Docetaxel (n=288)	HR	95% CI	*p*-value[§]
PFS	2.9 (0-18.2)	2.9 (0-19.5)	0.97	0.82 to 1.16	0.759[‡]
TTPD[†]	3.4 (0.5-18.2)	3.5 (0.3-19.5)	0.97	0.80 to 1.17	0.721[‡]
TTTF	2.3 (0.0-18.2)	2.1 (0.0-13.1)	0.84	0.71 to 0.997	0.046[‡]
Duration of tumour response	4.6 (2.1-15.3)	5.3 (1.7-11.7)	0.77	0.40 to 1.47	0.427[‡]
Duration of clinical benefit	5.4 (1.2-18.2)	5.2 (1.5-14.6)	0.91	0.71 to 1.16	0.450[‡]
Time to objective tumour response	1.7 (1.2-4.3)	2.9 (1.4-7.8)	NA	NA	0.105[§]

Abbreviations: ITT, intent-to-treat; HR, hazard ratio; NA, not assessable.

[*] pemetrexed (n=282) in time-to-treatment failure analysis.

[†] 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.

Subgroup analysis

Cox multiple regression analysis was used to identify factors other than treatment intervention that affected the overall survival and to estimate the treatment effect adjusting for these factors in the ITT population. The table below shows the comparison between treatment arms using Cox proportional hazard model (Hanna et al, 2004).

Cox model subgroup analysis of variables associated with improved survival

Variable	Pemetrexed Survival (months)	Docetaxel Survival(months)	*p*-value for within group difference
Performance Status			
0/1 vs. 2	9.4 vs. 3.6	9.1 vs. 2.2	<0.001
Time since last chemotherapy			
≥3 months vs. <3 months	9.3 vs. 7.0	9.2 vs. 6.2	0.004
Stage of disease			
III vs. IV	9.3 vs. 7.9	10.3 vs. 7.2	0.026

Patients of good performance status, greater time since previous chemotherapy and those with stage III locally advanced disease lived significantly longer than patients of poor performance status, less than 3 months since prior chemotherapy or those with stage IV metastatic disease. There was no significant difference when comparing survival values gained within sub-groups by treatment arm i.e. both arms benefited similarly with these prognostic factors.

Quality-of-Life Analysis

The LCSS patient scale consists of nine 100-mm visual analogue scales (VAS) and scores are reported from 0 to 100, with zero representing the best score. The average symptom burden index was calculated from the average of the six symptom items (anorexia, fatigue, cough, dyspnea, haemoptysis, and pain). A total score was calculated from the average of the nine LCSS values.

Summary of Average Symptom Burden Index (ASBI) Analysis – ITT Population

Classification	Pemetrexed (n=227) (%)	Docetaxel (n=247)(%)	*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.

Safety results

All treated patients (RT, N=541) were assessed for toxicity. Haematological toxicity is summarised in the table below. Patients receiving docetaxel experienced significantly higher rates of neutropenia, neutropenic fever, infections and hospitalisations due to neutropenic events compared to patients receiving pemetrexed. Furthermore a greater proportion of patients on the docetaxel arm required hospitalisation as a result of other drug- related adverse events (excluding neutropenic complications), compared to those on the pemetrexed arm (10.5% versus 6.4%, p = 0.092).

Grade 3 and Grade 4 haematological toxicities [a]

Toxicity (%)	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.

Non-haemotological toxicities are summarised in the table below. There was a significantly higher rate of alopecia (p < 0.001) and a trend toward higher rates of grade 3 and grade 4 diarrhoea (p = 0.069) for patients receiving docetaxel. An increase in ALT was the only toxicity that was higher in the pemetrexed arm (p = 0.028).

Non-haematological toxicities

Toxicity (%)	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.

Hospitalisations and supportive care data from JMEI are shown in the table below. The use of granulocyte-colony stimulating factors (G-CSFs) was substantially increased for patients receiving docetaxel when compared to pemetrexed. Only four patients in the docetaxel arm and one patient in the pemetrexed arm received G-CSFs as prophylaxis without a prior event of neutropenia. The remaining patients used G-CSF during treatment of neutropenia (n = 49) in the docetaxel arm; (n = 5) on the pemetrexed arm or as prophylaxis for subsequent cycles following an episode of neutropenia.

Hospitalisations and supportive care

	Pemetrexed n=265 %	**Docetaxel n=276 %**	***p* value[a]**
≥ 1 hospitalisation for neutropenic fever	1.5	13.4	**< 0.001**
≥ 1 hospitalisation for any other drug-related AE	6.4	10.5	0.092
G-CSF/GM-CSF	2.6	19.2	**< 0.001**
Erythropoietin	6.8	10.1	0.169
RBC transfusions	16.6	11.6	0.1078

Abbreviations: G-CSF, granulocyte colony-stimulating factor; GM-CSF, granulocyte-macrophage colony-stimulating factor; AE, adverse event.
[a] Fishers exact test.

Summary of clinical benefits of pemetrexed

- In JMEI, there was clinically equivalent efficacy demonstrated between the two agents but there were clinically and statistically significant differences in the toxicity profiles of the two chemotherapy treatments.
- There were higher rates of neutropenia (with and without complications) and significantly more frequent use of G-CSF for the treatment of neutropenia in patients on docetaxel-treated, compared to pemetrexed-treated patients (p<0.001).
- Importantly pemetrexed-treated patients were hospitalised for neutropenic fever a total of 29 days compared to docetaxel-treated patients who were hospitalised for neutropenic fever a total of 195 days. Significantly more patients on the docetaxel arm (13.4%) were hospitalised at least once during the course of the study than on the pemetrexed arm (1.5%) for neutropenic fever ($p < 0.001$).
- There was a significantly higher rate of alopecia ($p < 0.001$) and a trend toward higher rates of grade 3 and grade 4 diarrhoea ($p = 0.069$) for patients receiving docetaxel.
- Patients treated with pemetrexed derived similar symptom benefits compared to docetaxel patients but also spent significantly more survival time ($p<0.05$) without experiencing adverse events.

Relevant Comparators to pemetrexed in the UK

The comparators for pemetrexed (500mg/m^2) in second-line NSCLC are:

- Docetaxel (75mg/m^2 every 21 days)
- Erlotinib (150mg/daily)
- Best supportive care

In the second-line setting, pemetrexed, docetaxel and erlotinib are the only licensed treatments for advanced NSCLC. On a national level, it has been estimated that 10% of UK patients who have received first-line treatment will go on to receive active treatment second- line outside of clinical trials. There is wide variation in the proportion of NSCLC patients receiving active

	treatment second-line but this is unlikely to exceed 50% at any one cancer centre. As patients who do not receive chemotherapy are given BSC, and these represent the majority of second-line NSCLC patients, it is important to include BSC as a comparator.
Economic analysis	The aim of the economic evaluation was to determine which therapy options in second-line NSCLC provide the greatest benefit and cost-effectiveness for the NHS. A Markov model was constructed to perform the economic evaluation. The analytic technique used was a cost-utility analysis (CUA). A utility study was conducted with 100 members of the general public, in accordance with the NICE reference case, to derive values for QALY calculations. A cost per Life Year (cost per LY) analysis was also conducted as this type of analysis is relevant in disease areas where extended survival is a key outcome of treatment. Docetaxel was considered the reference case for the analysis because (1) it is the standard of active therapy in the UK and (2) it is recommended by NICE. Best supportive care was the reference case, as the standard of care, for reasons explained above. Therefore comparisons to both reference cases have been reported in order to reflect the real decision problem facing NHS decision makers. Costs and outcomes for the model were based upon a systematic review and pooled analysis of all phase III randomised clinical trials in relevant comparators; pemetrexed, docetaxel, erlotinib and BSC. The incremental cost per QALY for pemetrexed compared to docetaxel was £18,672, and compared to BSC was £16,458, demonstrating that pemetrexed is a cost-effective treatment option for patients in this setting within the NHS. **Pemetrexed compared to standard active therapy: docetaxel** **Pemetrexed** / **Docetaxel** / **Incremental** COSTS Active Treatment Cost: £4,591 / £2,737 / £1854 Non Chemo Cost: £671 / £772 / -£101 AE Cost: £89 / £424 / -£334 Palliative care costs: £3,556 / £3,599 / -£43 **Total Direct Cost**: **£8,906** / **£7,532** / **£1375*** BENEFITS Quality-adjusted Life Years (QALYs): 0.49 / 0.42 / 0.07 Life Years (LY): 0.92 / 0.73 / 0.19 **ICER** **Cost per additional LYG**: **£7,097** / Reference case / N/A **Cost per additional QALY**: **£18,672** / Reference case / N/A *Numbers do not compute due to rounding; non chemo costs = cost of premedication+administration costs The higher acquisition costs of pemetrexed compared to docetaxel are partially offset by the lower pre-medication and administration costs in combination with lower adverse event and palliative care costs. Patients receiving pemetrexed experience greater benefits compared to docetaxel in terms of life years gained and quality-adjusted life years. When the costs and benefits are combined the resulting ICERs demonstrate that pemetrexed is a cost-effective option.

Pemetrexed compared to standard of care: BSC

	Pemetrexed	Best supportive care	Incremental
COSTS			
Active Treatment Cost	£4,591	£0	£4,591
Non Chemo Cost	£671	£0	£671
AE Cost	£89	£0	£89
BSC costs	£0	£1,871	-£1,871
Palliative care costs	£3,556	£3,655	-£100*
Total Direct Cost	**£8,906**	**£5,527**	**£3,379**
BENEFITS			
Quality-adjusted Life Years (QALYs)			
Life Years (LY)	0.49	0.29	0.21*
ICER	0.92	0.60	0.32
Cost per additional LYG	**£10,418**	Reference case	N/A
Cost per additional QALY	**£16,458**	Reference case	N/A

*Numbers do not compute due to rounding; non chemo costs = cost of premedication+administration costs

When pemetrexed is compared to best supportive care the improved life years and quality adjusted life years offset additional costs of therapy and result in ICERs that demonstrate pemetrexed to be a cost effective option to BSC.

Key considerations

In routine clinical practice, patients have differing clinical needs and preferences for treatment. Physicians need to be able to select the most suitable therapy for each individual patient, taking into account patient preferences and clinical characteristics.

Below the key considerations are presented together with additional points of relevance.

For some physicians and some patients, the toxicity burden of docetaxel outweighs the potential survival benefit and another chemotherapy option with similar survival outcomes, but less toxicity, would be preferred.

- In JMEI, clinically equivalent efficacy was demonstrated between the two agents but there were clinically and statistically significant differences in the toxicity profiles of the two chemotherapy treatments, particularly in terms of febrile neutropenia, diarrhoea and alopecia.

Patients of good performance status (PS 0/1) are expected to benefit more from active chemotherapy than patients of poorer performance status (PS 2/3). Sub-group analysis has been used to reflect this.

- Patients of good performance derived significantly greater survival benefit than patients of poorer performance status, 9.4 months/9.1 months for pemetrexed/docetaxel patients of PS 0/1 compared to 3.6/2.2 months survival respectively in PS 2 patients. These are the patients who tend to receive chemotherapy in the UK as they obtain greater survival benefit and also are better able to tolerate chemotherapy. Pemetrexed has demonstrated the same survival benefit in these patients but does not cause the same level of toxicity as docetaxel.

In general, if a taxane (docetaxel or paclitaxel) was used first-line, docetaxel is not likely to be used as a second-line option in this patient population.

- Docetaxel is also licensed in the first-line treatment of advanced NSCLC and is being increasingly used in this setting. In general, if a taxane (eg docetaxel) is used in the first-

	line setting, it 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 required in the second-line setting. ***Erlotinib is licensed for use in second- and third-line settings. Currently it is the only treatment licensed for third-line. If erlotinib is used in second-line setting, patients and physicians do not have a licensed treatment available for use in the third-line setting.*** ▪ The opportunity for second and third line therapy options in NSCLC is an important advance in treatment of NSCLC patients, who historically have not received as much active treatment as patients with other tumours (e.g. breast) due to lack of available options. Erlotinib increases third line options for advanced NSCLC and therefore the benefits of active treatments for patients who are not eligible for further chemotherapy.
Conclusions	In JMEI, clinically equivalent efficacy was demonstrated between the two agents but there were clinically and statistically significant differences in the toxicity profiles of the two chemotherapy treatments, particularly in terms of febrile neutropenia, diarrhoea and alopecia. Docetaxel is an effective current standard of active therapy for patients in second-line setting and pemetrexed offers a valuable addition to the clinical treatment options available to patients and physicians. The incremental cost per LY and cost per QALY for pemetrexed in second line NSCLC are below £20,000, both when compared to docetaxel and BSC. Pemetrexed is a cost-effective option for patients being treated in second line NSCLC within the NHS.

Contents

Abbreviations

ASCO	American Society of Clinical Oncology
BID	Twice daily
BNF	British National Formulary
BSC	Best supportive care
CEA	Cost Effectiveness Analyses
CI	Confidence interval
CIC	Commercial in Confidence
DOC	Docetaxel
ERL	Erlotinib
G-CSF	Granylocyte colony stimulating factor
HR	Hazard Ratio
HRQoL	Health-related quality of life
IC	Incremental cost
ICE	Incremental cost-effectiveness
ICER	Incremental cost-effectiveness ratio
ITT	Intention-to-treat
K-M	Kaplan-Meier
LCSS	Lung cancer symptom scale
LY	Life Year
LYS	Life-year saved
MR	Market research
NICE	National Institute for Health and Clinical Excellence
NSCLC	Non-Small Cell Lung Cancer
NR	Not reported
OS	Overall survival
PEM	Pemetrexed
PFS	Progression Free Survival
PFY	Progression Free Life Year
PS 0/1	WHO Performance Status 0 or 1
QALY	Quality Adjusted Life Year
QoL	Quality of life
QPFY	Quality Adjusted Progression Free Life Year
RCT	Randomised controlled trial
SIGN	Scottish Intercollegiate Guidelines Network
SMC	Scottish Medicines Consortium
SPC	Summary of Product Characteristics
TTPD	Time to progressive disease
TTTF	Time to treatment failure
UK	United Kingdom
VAS	Visual analogue scale

1. Background

1.1 Summary of decision problem

The remit of this appraisal is to assess the clinical and cost effectiveness of pemetrexed compared to current standards of care in second-line advanced non-small cell lung cancer (NSCLC). Various treatment scenarios including other licensed therapies in second-line NSCLC (docetaxel and erlotinib) will be explored as will Best Supportive Care (BSC). The aim of the economic evaluation is to determine which therapy options provide the greatest benefit and cost-effectiveness.

1. Intervention

Pemetrexed is indicated as monotherapy for the treatment of patients with locally advanced or metastatic NSCLC after prior chemotherapy. In patients treated for NSCLC, the recommended dose of pemetrexed is 500mg/m^2 body surface area administered as an intravenous infusion over 10 minutes on the first day of each 21-day cycle.

2. Population, including subgroups

The registration phase III clinical trial, JMEI, included patients with advanced NSCLC who had relapsed following prior chemotherapy. The trial population reflects patients who currently receive second-line chemotherapy in UK clinical practice.

The sub-group analysis in this appraisal will focus upon good performance status patients (PS 0/1). The reasons for selecting good performance status are:

- these patients have been shown to experience better survival outcomes
- data are available for this analysis across most of the relevant comparator treatment options (except best supportive care)
- patients of good performance status are easily identifiable in the UK clinical setting.
- currently in the UK it is patients with good performance status who are likely to receive 2^{nd} line chemotherapy for their advanced disease.

3. Relevant comparator(s)

The comparators for pemetrexed in second-line NSCLC are:

- Docetaxel
- Erlotinib
- Best supportive care

In the second-line setting, pemetrexed, docetaxel and erlotinib are the only licensed treatments for advanced NSCLC. On a national level, it has been estimated that 10% of UK patients who have received first-line treatment will go on to receive active treatment second-line outside of clinical trials. There is wide variation in the proportion of NSCLC patients receiving active treatment second-line but this is unlikely to exceed 50% at any one cancer centre. As patients who do not receive chemotherapy are given BSC, and these represent the majority of second-line NSCLC patients, it is important to include BSC as a comparator.

4. Outcomes

Clinical outcome measures include:

- Overall survival
- Time-to-disease progression
- Progression-free survival
- Tumour response
- Health-related quality of life
- Adverse effects of treatment.

Economic outcomes include:

- Incremental cost per quality-adjusted life year
- Incremental cost per life year gained
- Resource utilisation
- Chemotherapy costs
- Administration costs
- Concomitant medications/pre-medication
- Costs of treating adverse events

The time horizon (3 years) for the economic evaluation reflects the life expectancy of patients with locally advanced or metastatic NSCLC after having received prior chemotherapy. The costs were considered from a NHS and Personal Social Services perspective. A utility study conducted in line with the NICE reference case was undertaken to support the economic evaluation.

5. Key issues

1) For some physicians and some patients, the toxicity burden of docetaxel outweighs any potential survival benefit and another chemotherapy option with similar survival outcomes, but less toxicity would be preferred.

2) Patients of good performance status (PS 0/1) are expected to benefit more from active chemotherapy than patients of poorer performance status (PS 2/3). Sub-group analysis has been used to reflect this.

3) 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.

4) In the JMEI trial, pemetrexed was compared to an active licensed and NICE recommended comparator, docetaxel.

5) Erlotinib is licensed for use in second- and third-line settings. Currently it is the only treatment licensed for third-line. If erlotinib is used in second-line setting, patients and physicians do not have a licensed treatment available for use in the third-line setting.

1.2 Description of technology under assessment

6. Give the brand name, approved name and where appropriate, therapeutic class.

Brand Name	Alimta®
Approved name	Pemetrexed Disodium
Therapeutic Class	Anti-neoplastic, Anti-folate

7. Does the technology have a UK marketing authorisation/CE marking for the indications detailed in this submission? If yes, please give the date it received it. If no, please state current UK regulatory status, with relevant dates (for example, date of application and/or expected approval dates).

Alimta® (pemetrexed) was approved by European Agency for the Evaluation of Medicinal Products in September 2004.

8. Does the technology have regulatory approval outside of the UK?

Pemetrexed has been approved for treatment of NSCLC in the European Union, and in 73 countries including Australia and United States. A full list of approved countries is available on request.

9. If the technology has not been launched, please supply the anticipated launch date for the UK.

This is not applicable as pemetrexed has been commercially available in the UK since November 2004.

10. Is the technology subject to any other form of Health Technology Assessment either in the UK or elsewhere? If so, what is the timescale for completion?

Pemetrexed has been reviewed by Pharmaceutical Benefits Advisory Committee (PBAC) in Australia.

Lilly did not submit to the Scottish Medicines Consortium (SMC) and therefore received the recommendation below automatically. Pemetrexed has been approved for use by the SMC in Malignant Pleural Mesothelioma.

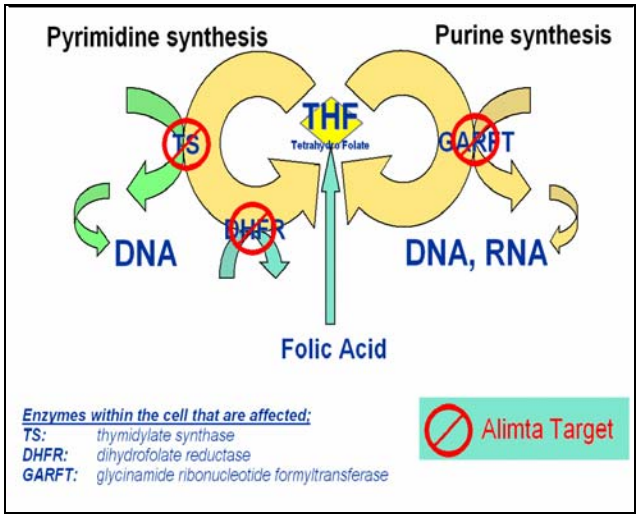
PBAC	PBAC approved Pemetrexed for NSCLC in November 2004.
SMC	Pemetrexed is not recommended for use within NHS Scotland as monotherapy for the treatment of patients with locally advanced or metastatic non-small cell lung cancer after prior chemotherapy.

11. What is the principal mechanism of action of the technology?

Pemetrexed is a multi-targeted anti-cancer antifolate agent that exerts its action by disrupting crucial folate-dependent metabolic processes essential for cell replication.

Pemetrexed is the first cancer medicine to be available that acts on at least 3 distinct enzyme target sites.

Pemetrexed Key Enzyme target sites



12. For pharmaceuticals, what formulation(s) (for example, ampoule, vial, sustained release tablet), strength(s) and pack size(s) will be available?

Formulation	Powder in Type I glass vial with rubber stopper
Strength	Each vial contain 500mg of pemetrexed
Pack Size	Single vial per pack

13. What is the acquisition cost of the technology (minus VAT)? If the unit cost of the technology is not yet known, please provide details of the anticipated unit cost, including the range of possible unit costs. For devices, provide the list price and average selling price.

The acquisition cost for a 500mg single vial of pemetrexed is £800.

14. What are the (proposed) main indication(s)?

Indication under consideration in this STA:

Pemetrexed is indicated as monotherapy for the treatment of patients with locally advanced or metastatic NSCLC after prior chemotherapy

Other Indications

Pemetrexed in combination with cisplatin is indicated for the treatment of chemotherapy-naive patients with unresectable malignant pleural mesothelioma.

15. What is the proposed course of treatment? For pharmaceuticals, list the dose, dosing frequency, length of course and anticipated frequency of repeat courses of treatment.

Dose	500mg/m^2, 10-minute infusion
Dosing Frequency	Every 21 days
Length of course	Median/mean of 4 cycles (based on pemetrexed registration trial, however clinical practice may vary)
Frequency of Repeat Courses	None

16. What other therapies, if any, are likely to be prescribed as part of a course of treatment?

Pre-Medication Regimen (please refer to SPC for further information)

- Corticosteroid
- A corticosteroid should be given the day prior to, on the day of, and the day after pemetrexed administration.
- Vitamin Supplementation
  Patients must take oral folic acid or a multivitamin containing folic acid (350 to 1,000 micrograms) on a daily basis. At least five doses of folic acid must be taken during the seven days preceding the first dose of pemetrexed, and dosing must continue during the full course of therapy and for 21 days after the last dose of pemetrexed. Patients must also receive an intramuscular injection of vitamin B12 (1000 micrograms) in the week preceding the first dose of pemetrexed and once every three cycles thereafter. Subsequent vitamin B12 injections may be given on the same day as pemetrexed.
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17. For patients being treated with this technology, are there any other aspects that need to be taken into account? For example, are there additional tests or investigations needed for selection, or particular administration requirements, or is there a need for monitoring of patients over and above usual clinical practice for this condition? If yes, provide details.

The level of monitoring for pemetrexed is in similar to that expected with most other chemotherapies – please see appendix 1, which contains the pemetrexed SPC, for further information.

18. For pharmaceuticals, please provide a Summary of Product Characteristics (SPC) or draft SPC as an appendix to the submission.

SPC provided in Appendix 1.

19. For devices, please provide the (anticipated) CE marking, including the indication for use, (draft) technical manual and details of any different versions of the same device, as an appendix to the submission.

Not applicable. Pemetrexed is not a device.

20. What is the current usage of the technology in the NHS? Include details of use in ongoing clinical trials.

- According to IMS market research data (Quarter 4, 2005) in second-line treatment of advanced NSCLC, docetaxel's usage was approximately 69%, pemetrexed 10% and erlotinib 6%.
- There are no Lilly-sponsored clinical trials in second-line NSCLC that are actively recruiting. The summaries below are ongoing Lilly-sponsored Clinical trials with pemetrexed in 1st line NSCLC.

Study: A Randomized Phase III Trial of pemetrexed and cisplatin Versus gemcitabine and cisplatin in Patients with Locally Advanced or Metastatic Chemotherapy-Naive Non-Small Cell Lung Cancer

Major Inclusion criteria: Patients at least 18 years old, with NSCLC Stage IIIB (not amenable to curative treatment) or IV, with no prior systemic chemotherapy for lung cancer, ECOG performance status of 0 or 1 and adequate organ function

Design: This is a multicentre, randomized, open-label study. Approximately 1700 patients will be enrolled in this study. Eligible patients will be randomly assigned to receive either pemetrexed and cisplatin (experimental arm, Arm A) or gemcitabine and cisplatin (control arm, Arm B). Patients in both treatment arms will receive folic acid and vitamin B_{12} supplementation.

Patients will receive up to six cycles of assigned treatment (control or experimental). The follow-up period begins when the treatment period is completed. Patients are to be followed up with periodic tumour response evaluation until disease progression. All patients will be followed up until death or study closure.

No of patient planned accrued: Planned = 40, Accrued = 46

Status: Closed to enrolment - all patients in follow-up

Study: A Phase I Study of Sequential Doublet Therapy: Gemcitabine in Combination with Carboplatin Followed by pemetrexed in Combination with gemcitabine in Chemonaive Patients with Inoperable Locally Advanced or Metastatic Non-Small Cell Lung Cancer

Major Inclusion Criteria

Inoperable locally advanced or metastatic non-small cell lung cancer (NSCLC), stages IIIB & IV, good performance status, no previous chemotherapeutic regimens.

Design:

This is an open-label, dose-finding non-randomised study of gemcitabine/carboplatin and pemetrexed /gemcitabine, when administered sequentially every 14 days, in chemo-naive patients with inoperable and locally advanced or metastatic non-small cell lung cancer (NSCLC).

This study involves intravenous administration of a combination of gemcitabine and carboplatin on day 1 followed by pemetrexed and gemcitabine on day 15. A cycle will be 28 days. One dose of pemetrexed, two doses of gemcitabine, and one dose of carboplatin administered every 28 days define one cycle of therapy.

No. of patients planned/accrual: Approximately 25 pts planned, currently 12 pts on trial

Status: Recruiting

1.3 Context

21. Please provide a brief overview of the disease and current treatment options.

Epidemiology

Lung cancer, and in particular, non-small cell lung cancer (NSCLC), remains the leading cause of cancer death throughout the world (Rosell et al., 2004). NSCLC accounts for

approximately 80% of lung cancers diagnosed. In most people it is related to cigarette smoking - approximately 9 out of 10 lung cancers are caused by smoking. In the UK tobacco consumption is recognised single greatest cause of preventable illness and early death, with more than 120,000 people dying each year from smoking-related diseases (Cancer Research UK).

In 2002, there were 37,700 new cases of lung cancer diagnosed in England and Wales according to Cancer Research UK. In 2003, there were 28,733 deaths from lung cancer with more lung cancer deaths in females than from breast cancer. The incidence and mortality trends for lung cancer are very similar because most people diagnosed with lung cancer have very poor prognosis (<12 months).

Prognosis

The majority of patients with lung cancer present with advanced disease: approximately 30% with locally advanced disease and 45% with metastatic disease. The prognosis for these patients is poor, with 5-year survival rates ranging from 5% to 15% for stage IIIB disease and <5% for stage IV disease (Bonomi, 2004).

Treatment Goals

The search for new chemotherapeutic regimens for the treatment of NSCLC is motivated not only by the desire to increase the objective tumour response and survival rates, but also by the desire to reduce toxicity, decrease symptoms, and improve the psychological wellbeing of treated patients (Ettinger, 2000). In inoperable advanced NSCLC, palliative chemotherapy is established and aims at palliation of symptoms, improvement of quality of life and prolongation of survival (Malayeri et al., 2001).

Treatment Options

For patients confronting advanced disease, chemotherapy is an essential option for disease control and palliation. Although a number of effective first-line regimens exist, virtually all patients with advanced NSCLC will have disease relapse. For these patients, identifying the optimal treatment course remains a challenge (Bonomi, 2004). The first-line treatment of advanced NSCLC is based on the combination of platinum and one of the following agents: taxanes, gemcitabine, vinorelbine. There are no significant differences in efficacy among these combinations suggesting that the maximum efficacy has been reached (Seve & Dumontet, 2005).

In the second-line setting pemetrexed, docetaxel and erlotinib are the licensed options available for treatment of advanced NSCLC.

For those patients who may be eligible to receive third-line treatment of their advanced cancer, erlotinib is the only licensed therapeutic option in the UK.

22. What was the rationale for the development of the new technology?

Pemetrexed showed clinical activity in the second-line treatment of advanced NSCLC in a phase II study (Smit, 2003). There were 9 responses, 1 complete and 8 partial, in 80 evaluable patients in the second-line study, including responses in patients who had prior platinum-containing regimens. The median survival time for patients on pemetrexed (5.8 months, with 21.3% of patients censored) is within the range seen in docetaxel studies.

Docetaxel has been approved as second-line therapy for NSCLC as a single agent with studies showing response rates ranging from 6% to 21% and survival times of 6 to 11 months in patients with advanced disease. Since docetaxel was the first drug to be approved for second-line NSCLC, it served as the comparator to pemetrexed.

Based on the similar efficacy seen with pemetrexed and docetaxel in separate trials and the need for more options of chemotherapy with lower toxicity rates than docetaxel (especially with respect to incidence of Grade 3 or 4 febrile neutropenia) a multinational phase III clinical trial comparing these two chemotherapy agents in the second-line treatment of NSCLC was undertaken.

23. What is the suggested place in therapy for this technology with respect to treatments currently available?

Three products are currently licensed for second-line treatment of advanced NSCLC: pemetrexed 500mg/m^2 every 21 days, docetaxel 75mg/m^2 every 21 days and erlotinib 150mg/day every 28 days. Best Supportive Care (BSC) is not a treatment that requires a formal licence.

Docetaxel is currently the most widely used regimen for the treatment of second-line NSCLC. However, alternatives to docetaxel are required for the following reasons:

- Docetaxel is generally restricted to those patients have a very good performance status. This is due to the toxicity profile of docetaxel. Patients may not be able to tolerate the toxicities and therefore may not receive the recommended 4 cycles of therapeutic dose of chemotherapy without the addition of G-CSF's.
- The incidence of alopecia with docetaxel is 38%. Many patients do not want to lose their hair (body and head hair) and would prefer a regimen which offers a lower probability of hair loss, particularly if their 1st line treatment has not resulted in significant alopecia.
- Taxanes (docetaxel or paclitaxel) are licensed with cisplatin for use in the first- line treatment of NSCLC. In instances where a taxane has been used as first-line treatment, docetaxel is not likely to be used as a second-line option in this patient population.

The licensed alternatives to docetaxel are pemetrexed and erlotinib.

Pemetrexed is considered an alternative for patients also suitable for treatment with docetaxel because pemetrexed offers similar survival benefit but with reduced toxicity (Hanna et al, 2004).

In addition, pemetrexed should be considered for the following:

1) Patients not able/willing to tolerate the toxicity profile of docetaxel.

2) Patients wishing to avoid alopecia, a side effect associated with docetaxel treatment. This may be a consideration in patients who have not lost their hair with first-line chemotherapy.

3) Patients who have received a taxane for first-line treatment of NSCLC.

Analyses from the phase III registration trial (JMEI) of pemetrexed vs. docetaxel show that patients with a good performance status (PS 0-1) are most suitable for treatment with pemetrexed as they have a greater survival gain and are better able to tolerate therapy than patients with PS 2.

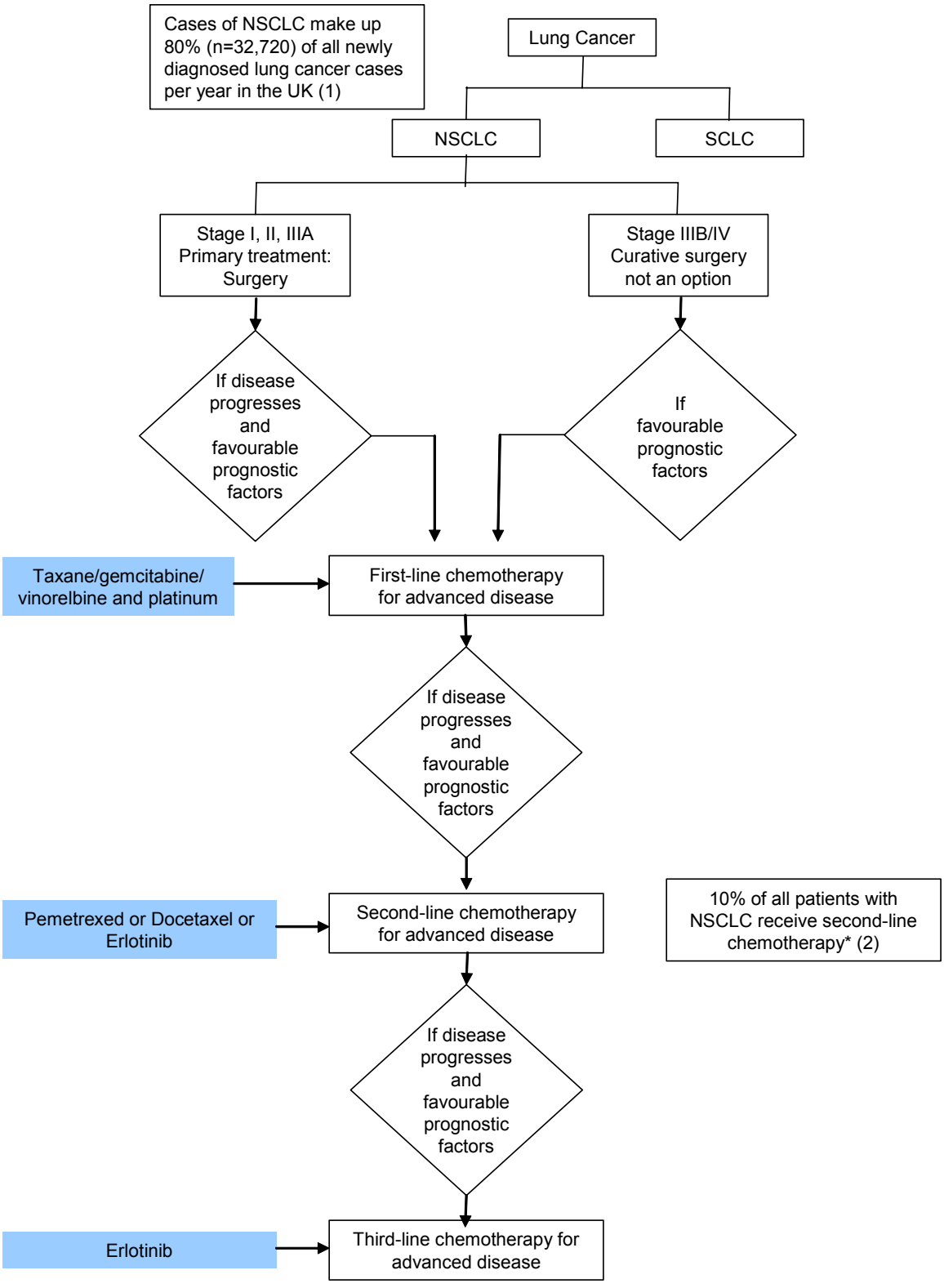
Erlotinib is licensed for NSCLC after failure of at least one prior chemotherapy regimen. The registration trial of erlotinib (BR21) recruited 3rd line patients (49%) and/or those not eligible for further chemotherapy. On the basis of this study, the erlotinib Summary of Product

Characteristics (SPC) states that when prescribing erlotinib, factors associated with prolonged survival (eg smoking status) should be taken into account. It also states that no survival benefit or other clinically relevant effects of the treatment have been demonstrated in patients with EGFR-negative tumours. The BR21 study and the SPC therefore suggest that erlotinib could be considered for patients not eligible for chemotherapy and who fall within these sub-groups.

As the only licensed treatment for third-line NSCLC, physicians may also want to reserve erlotinib for third line treatment in order to provide patients with a suitable licensed alternative to best supportive care.

The figure below illustrates the treatment of patients with lung cancer and shows the licensed and/or NICE recommended treatments at each point of disease progression.

Place of Pemetrexed in the treatment of Non-small Cell Lung Cancer



1. Clegg et al (2001). Health Technology Assessment 2001; 5(32).
2. Data on file, Estimate from ACTION study (observational study in 967 patients, 197 from UK.)

24. Describe any current variation in services and/or uncertainty about best practice, including cost effectiveness.

On a national level, it has been estimated that 10% of UK patients who have received 1st line chemotherapy will go on to receive active treatment in the 2nd line setting outside of clinical trials.

There is wide variation in the proportion of NSCLC patients receiving active treatment in the 2nd line setting but this is unlikely to exceed 50% at any one cancer centre.

25. Provide details of any relevant guidelines or protocols.

- Guidelines on the non-surgical management of lung cancer have also been produced by COIN (1999), however these have not been updated to reflect the more recent treatment modalities and as such are not discussed further.
- The guidelines produced by NICE on diagnosis and treatment of NSCLC state that chemotherapy should be offered to patients with stage III or IV NSCLC and good performance status (WHO 0, 1 or a Karnofsky score of 80-100) to improve survival, disease control and quality of life. Chemotherapy for first-line treatment of advanced NSCLC should be a combination of a single third-generation drug (docetaxel, gemcitabine, paclitaxel or vinorelbine) plus a platinum drug. Either carboplatin or cisplatin may be administered. Patients who are unable to tolerate a platinum combination may be offered single-agent chemotherapy with a third-generation drug. Docetaxel monotherapy should be considered if second-line treatment is appropriate for patients with locally advanced or metastatic NSCLC in whom relapse has occurred after previous chemotherapy (NICE, 2005).
- According to the updated 2003 guidelines of the American Society of Clinical Oncology (ASCO) on the treatment of advanced NSCLC, docetaxel can be considered the standard second-line chemotherapy in patients relapsing after frontline therapy (Pfister, 2003). This was based on 2 phase III trials (TAX 317 and TAX 320) that demonstrated the superiority of docetaxel at 75mg/m^2 in the parameters of survival, quality of life, and disease/symptom control when compared to best supportive care or alternative single-agent chemotherapy (Shepard 2000, Fossella 2000). ASCO guidelines did not endorse use of other agents in second-line because of lack of evidence (pemetrexed and erlotinib were not yet approved at time of guidelines).
- The Scottish Intercollegiate Guidelines Network (SIGN) advise chemotherapy with a platinum-based doublet regimen for all patients who are not suitable for curative resection or radical radiotherapy (first-line) and second line chemotherapy with docetaxel 75mg/m^2 for stage IIIB/IV NSCLC patients with good performance status (SIGN, 2005).
- The Ontario Practice Guidelines advise that if survival is the main outcome of interest for a patient who is a candidate for second-line therapy, it is reasonable to offer docetaxel 75mg/m^2 every three weeks to medically suitable patients, with a full discussion of the benefits, limitations, and toxicities. However, if quality of life is the outcome of interest for a patient who is a candidate for second-line therapy, single-agent docetaxel is an option that may result in improved quality of life and reduced disease-related symptoms when compared to best supportive care (Ontario Practice Guideline Report, 2004). As far as erlotinib monotherapy is concerned, this is recommended as third-line treatment for NSCLC patients who have failed previous chemotherapy and who maintain a good performance status. Erlotinib is also an option for second-line therapy for patients who are not candidates for second-line chemotherapy (Feld et al., 2006).
- In March 2006, the Cancer Care Ontario published its evidence based review of second-line systemic treatment for recurrent or progressive non-small cell lung cancer. The guideline assessed the benefits (in terms of survival and/or quality of life) of

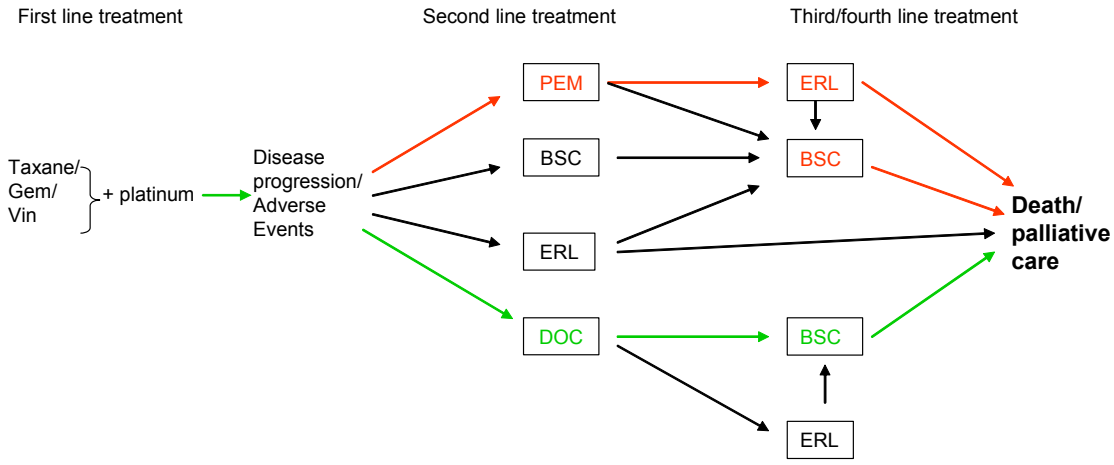
systemic therapy compared to BSC, which systemic treatment offered the greatest improvement in benefits and the doses and schedules of the different systemic agents for 2nd line NSCLC. Docetaxel, at the UK licensed dose of 75mg/m^2, is recommended as 2nd line therapy, with erlotinib recommended as 3rd line therapy. Options for 2nd line therapy are pemetrexed and erlotinib. (Noble, 2006)

1.4 Comparator(s)

26. Describe the relevant comparator(s) and provide a justification for your selection. In some cases, comparisons with more than one comparator or combination-therapy comparators will be necessary. The Institute considers the most relevant comparators to be those that the new technology is attempting to displace from UK practice.

In the second-line setting, pemetrexed, docetaxel and erlotinib are the only licensed treatments for advanced NSCLC. As patients who do not receive chemotherapy are given BSC, and these represent the majority of second line NSCLC patients, it is important to include BSC as a comparator

Relevant Comparators for the Evaluation of Pemetrexed



Taxane = Docetaxel or Paclitaxel, Gem – Gemcitabine, Vin – Vinorelbine,
PEM – Pemetrexed, BSC – Best Supportive Care, ELR – Erlotinib, DOC – Docetaxel

Docetaxel

Docetaxel (Taxotere ®) is a semisynthetic taxane, a class of anticancer agents that bind to beta tubulin, thereby stabilising microtubules and inducing cell-cycle arrest and apoptosis. Docetaxel was first approved for the treatment of anthracycline-refractory metastatic breast cancer in the mid-1990s (Montero et al., 2005).

Docetaxel dose of 75mg/m^2 is the licensed dose in 2nd-line treatment of NSCLC.

Erlotinib

Erlotinib (Tarceva®) is a human epidermal growth factor receptor type 1 / epidermal growth factor receptor (HER1/ EGFR) tyrosine kinase inhibitor (Herbst & Bunn, 2003). Erlotinib

selectively inhibits the intracellular tyrosine kinase activity of the epidermal growth factor receptor (EGFR) (Silvestri & Rivera, 2005).

Best Supportive Care/Active Symptom Control

Common symptoms of lung cancer include fatigue, loss of appetite, weight loss, breathlessness, cough, chest pain, haemoptysis. Many of these symptoms can be very debilitating and considerably reduce quality of life (NICE lung cancer guidelines, 2005).

Best supportive care (BSC) is defined as treatment given with the intent to maximise quality of life without a specific antineoplastic regimen. Best supportive care excludes surgery, immunotherapy, radiotherapy (with the exception of palliative radiotherapy), anticancer hormonal therapy, and systemic chemotherapy in which the goal is to either eradicate or slow the progression of the disease. Patients will receive BSC as judged by their treating physician.

Those therapies considered acceptable include, but are not limited to, treatment with antibiotics, analgesics, antiemetics, thoracentesis, pleurodesis, supplemental oxygen, blood transfusions, nutritional support (enteral or parenteral), and/or focal external beam radiation given for symptom control for pain, cough, dyspnea, or hemoptysis. Palliative treatment is defined as treatments given primarily to relieve pain or other disease symptoms. (NICE Lung cancer guidelines, 2005).

27. What are the main differences in the indications, contraindications, cautions, warnings and adverse effects between the proposed technology and the main comparator(s)?

Docetaxel and pemetrexed are both standard cytoxic agents indicated for 2nd line chemotherapy. As cytotoxics, both are associated with similar adverse event profiles in terms of haematological toxicity, e.g. neutropenia, leucopenia, febrile neutropenia, and also non-haematological effects such as diarrhoea and vomiting. However, pemetrexed is associated with a significantly lower incidence of these toxicities. Also, docetaxel is associated with hair loss in many patients and this is not a toxicity associated with pemetrexed.

Erlotinib is not a typical chemotherapy agent, but is a molecular-targeted agent; the mode of action for erlotinib is related to the EGFR expression of the tumour. As such, the adverse event profile/warnings for erlotinib are different to docetaxel and pemetrexed. In both the FDA and EMEA (and the SPC) documents a caution was added that there is no pharmacological reason for using erlotinib in EGFR negative patients, there was no data or rationale to support the existence of a clinically meaningful effect in EGFR negative patients and that EGFR status should be known and taken into account together with all factors associated with response to treatment in order to allow for a rational choice of treatment. Therefore, patients would need to be identified in terms of their EGFR status prior to initiation of therapy.

Appendix 2 tabulates the indications, contraindications, cautions, warnings and adverse effects between pemetrexed, docetaxel and erlotinib using information from the relevant SPCs.

2 Clinical evidence

2.1 Identification of studies

A review of the published literature aimed to:

- Identify a rigorous and relevant evidence base for second-line treatments of NSCLC;
- Identify the key clinical parameters to inform the design of the economic model;
- Identify the necessary efficacy data from studies for extraction in order to populate the economic model; and
- Determine appropriate ranges for point estimates for use in the sensitivity analyses.

A wide range of sources was consulted to identify the pivotal published Phase III randomised controlled trials for each of the main treatment comparators. Phase III randomised controlled trials were sought from the published literature and unpublished data held by Eli Lilly & Co. Abstracts for all identified trials were reviewed and full text articles obtained. Full references were also checked for any additional studies that may have provided useful and relevant clinical data.

28. Describe the strategies used to retrieve relevant clinical data both from the published literature and from unpublished data held by the company. The methods used should be justified with reference to the decision problem. Sufficient detail should be provided to enable the methods to be reproduced, and the rationale for any inclusion and exclusion criteria used should be provided.

Specify:

29. the specific databases searched and service provider used (for example, Dialog, DataStar, OVID, Silver Platter), including at least:

- Medline
- Embase
- Medline (R) In-Process
- The Cochrane Library

30. the date the search was conducted and

31. the date span of the search

A protocol was prepared for the literature search, detailing inclusion and exclusion criteria and search terms, search dates and data span searched. Articles were identified in electronic database searches of OVID Medline® (1966 to January Week 4, 2006) (Table 1), the Cochrane Library (2006, Issue 1) - Cochrane Database of Systematic Reviews (Table 2), the American Society of Clinical Oncology (ASCO) Abstracts Database (www.lungca.asco.org) (Table 3) and EMBASE (Table 4).

Databases Searched	Dates when the searches were conducted	Date span of the search
OVID MEDLINE (R) in-Progress, Other Non-Indexed Citations, OVID MEDLINE (R)	14th February 2006	1966 to January Week 4, 2006
The Cochrane Library	9th February 2006	
American Society of Clinical Oncology (ASCO) Abstracts Database (lungca.asco.org).	13th February 2006	
EMBASE	11th May 2006	1980 to 2006 week 18

32. the complete search strategies used, including all the search terms: Textwords (free text), Subject Index Headings (e.g. MeSH) and the relationship between the search terms (e.g. Boolean)

The complete search strategies are presented in Tables 1 – 4.

Table 1: OVID Medline ® Search Strategies

Search String	Description # 1
1	Search (non-small-cell lung carcinoma/drug therapy[majr] AND human[mh] AND english[la])
2	((NSCLC[ti] OR ((lung[ti] OR lungs[ti] OR pulmonary[ti] OR bronchus[ti] OR brochogenic[ti] OR bronchial[ti] OR bronchoalveolar[ti] OR alveolar[ti]) AND (non-small-cell[ti] OR nonsmall-cell[ti] OR non-oat-cell[ti] OR squamous[ti] OR adenosquamous[ti] OR large-cell[ti])
3	(non-small-cell[ti] OR nonsmall-cell[ti] OR non-oat-cell[ti] OR squamous[ti] OR adenosquamous[ti] OR large-cell[ti])
4	(cancer*[ti] OR carcinoma*[ti] OR adenocarcinoma*[ti] OR malignan*[ti] OR tumor*[ti] OR tumour*[ti] OR neoplasm*[ti])))
5	(chemotherapy[ti] OR drug therapy[ti] OR chemoimmunotherapy[ti] OR biochemotherapy[ti]))
6	Phase III [ti]
7	#1 OR #2 AND #3 AND #4 AND #5 AND #6
Search String	**Description # 2**
1	Pemetrexed.mp. [mp=title, original title, abstract, name of substance word, subject heading word]
2	Lung cancer.mp. [mp=title, original title, abstract, name of substance word, subject heading word]
3	Limit to (humans and English language)
4	#1 AND #2 AND #3
Search String	**Description # 3**
1	Docetaxel.mp. [mp=title, original title, abstract, name of substance word, subject heading word]
2	Lung cancer.mp. [mp=title, original title, abstract, name of substance word, subject heading word]
3	Limit to (humans and English language)
4	#1 AND #2 AND #3
Search String	**Description # 4**
1	Erlotinib.mp [mp=title, original title, abstract, name of substance word, subject heading word]
2	Lung cancer.mp. [mp=title, original title, abstract, name of substance word, subject heading word]
3	Limit to (humans and English language)
4	#1 AND #2 AND #3

Search String	Description # 5
1	Best supportive care [mp=title, original title, abstract, name of substance word, subject heading word]
2	Lung cancer.mp. [mp=title, original title, abstract, name of substance word, subject heading word]
3	Limit to (humans and English language)
4	#1 AND #2 AND #3

Table 2: Cochrane Library Search Strategy

Search String	Description
1	Lung cancer in Record Title

Table 3: ASCO Search Strategy

Search String	Description
1	Lung Cancer AND second line (find in clusters) Clusters were: non-small cell lung cancer; small cell lung cancer; malignant, mesotheslioma, tumor biology, research health services research, solid tumors, breast cancer

Table 4: Embase Search Strategy

Search String	Description
1	Lung Tumor/ OR (((lung$ or pulmon$) adj15 – neoplasm$) or cancer or adenocarcinom$ or carcinoma$ or tumor$ or tumors$).mp OR lung non small cell cancer/ OR non small cell.ti,ab OR NSCLC.ti,ab
2	Phase 3 clinical trial/ AND Second line.ti,ab
3	#1 AND #2

33. Details of any additional searches, for example searches of company databases (include a description of each database)

The electronic literature searches were supplemented with information from internal company sources, to try to identify any unpublished studies.

34. The inclusion and exclusion criteria

Inclusion Criteria

- Published Phase III Randomised Controlled Trials of single-agent pemetrexed 500mg/m^2, single-agent docetaxel 75mg/m^2, 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.
- In addition, the trials were required to have at least one treatment arm under consideration and to have reported survival, time to disease progression, toxicity or quality of life data. Trials including patients who had received prior chemotherapy were eligible.

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.

Types of Participants

- Inclusion Criteria.

- Adult patients with advanced / metastatic (unresectable) non-small cell lung cancer previously treated with chemotherapy. The number of prior chemotherapy regimens had to be at least one.

Exclusion Criteria

- Chemotherapy naive patients.

35. The data abstraction strategy.

After the selection of relevant trials, data were extracted using a structured form. The form was designed to capture information on:

- Details of the trial (authors, year of publication, journals, period and country of study, number of centres, study design, sample size)
- Patient characteristics (age, gender, stage of disease, performance status, weight loss, tumour histology and prior treatment status) and
- Details of the intervention and outcomes (dosage, frequency of administration, toxicity, response rate, survival rate and quality of life)

2.2 Study selection

2.2.1 Complete RCT list

36. Provide a list of all RCTs that compare the intervention with other therapies, including placebo. The list must be complete and will be validated by searches conducted by the assessors.

Where data from a single study have been drawn from more than one source (e.g. a poster and a published report) and/or where trials are linked (e.g. an open-label extension to an RCT), this should be made clear.

A list of all RCTs is presented in table 5

Table 5: Randomised phase III clinical trials In Second-Line NSCLC

Author	Major Inclusion Criteria	Schema	No. pts / planned accrual	Status
Gridelli et al., (2004). The DISTAL 01 study	Advanced NSCLC	Docetaxel 75mg/m^2 every 3 weeks vs. docetaxel 33.3mg/m^2 every week.	220	Published
Georgoulias et al., (2003)	Advanced NSCLC	Docetaxel vs. docetaxel-cisplatin	Preliminary analysis	Published
Hanna et al., (2004) (JMEI Trial)	Advanced NSCLC	Pemetexed 500mg/m^2 IV day 1 (21 day cycle) Docetaxel 75mg/m^2 day 1 (21 day cycle)	571	Published
Hanna et al., (2004) (JMEI Trial)	Advanced NSCLC	Pemetexed 500mg/m^2 IV day 1 (21 day cycle) Docetaxel 75mg/m^2 day 1 (21 day cycle)	571	Published
Shepherd et al., (2005)	Stage IIIB or IV NSCLC	Oral erlotinib 150mg/m^2 Placebo	731	Published
Cohen et al., (2005) (same trial as Shepherd et al., (2005)	Stage IIIB or IV NSCLC	Oral erlotinib 150mg/m^2 Placebo	731	Published
Tsao et al., (2005) (same trial as Shepherd et al., (2005)	Stage IIIB or IV NSCLC	Oral erlotinib 150mg/m^2 Placebo	731	Published
Shepherd et al., (2000) TAX 317 Study	Histologic or cytologic proof of unresectable locally advanced or metastatic NSCLC	Docetaxel 75mg/m^2 day 1 (21 day cycle) BSC	203	Published
Fossella et al., (2000) TAX 320 Study	Locally advanced or metastatic NSCLC	Docetaxel 100mg/m^2 (day 1, 21 day cycle) Docetaxel 75mg/m^2 (day 1, 21 day cycle) Vinorelbine 30mg/m^2 (days 1, 8 and 5 of each 21 day cycle) or ifosfamide 2mg/m^2/d day1 through 3 of each 21 day cycle	373	Published
Schuette et al., (2005)	Stage IIIB or IV NSCLC	Docetaxel 75mg/m^2 day 1 (21 day cycle) Docetaxel 35mg/m^2 day 1, 7, 14 (21 day cycle)	208	Published
Camps et al., (2006)	Pre-treated advanced NSCLC	Docetaxel 75mg/m^2 day 1 (21 day cycle) Docetaxel 36mg/m^2 day 1, 7, 14 (21 day cycle)	259	Published
Thatcher et al., (2005)	Locally advanced or metastatic NSCLC	Gefitinib 250mg/day or placebo tablets	1,692	Published
Ramlau et al., (2006)	Stage III or IV NSCLC	Oral topotecan 2.3mg/m^2 on days 1 to 5 IV docetaxel 75mg/m^2 day 1 (21 day cycle)	829	Published
Roszkowski et al., (2000)	Unresectable or metastatic NSCLC	Docetaxel 100mg/m^2 day 1 (21 day cycle) BSC	207	Published

2.2.2 Relevant RCT list

37. List all randomised trials that compare the technology directly with the main comparator(s). If there are none, state this.

Where data from a single study have been drawn from more than one source (e.g. a poster and a published report) and/or where trials are linked (e.g. an open-label extension to an RCT), this should be made clear.

In second line NSCLC, pemetrexed has been studied in a head-to-head comparison with docetaxel in the following Phase III trial:

- JMEI trial (Hanna et al., 2005)

Similarly, a head-to-head comparison of docetaxel has been compared to best supportive care in the following Phase III trial:

- Shepherd et al., (2000)

Furthermore, erlotinib has been directly compared to placebo in the following phase III trial:

- Shepherd et al., (2005)

Fossella et al., (2000), Gridelli et al., (2004), Camps et al., (2006), Ramlau et al., (2006), Thatcher et al., (2005) and Schuette et al., (2005) provided additional data on docetaxel 75mg/m^2 and best supportive care (where relevant) for use in an indirect comparison with pemetrexed.

Table 6: Types of Comparison with pemetrexed 500mg/m^2

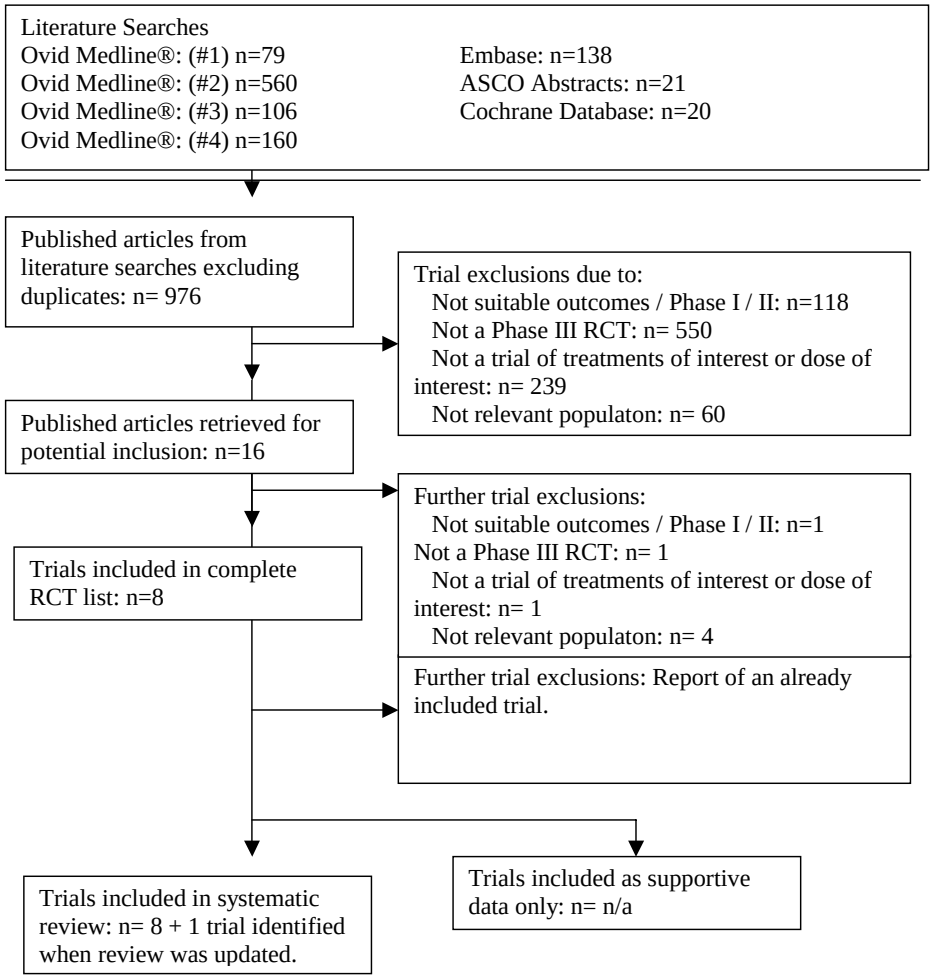
Alternative treatments	Type of Comparison with pemetrexed 500mg/m^2	Source
Docetaxel monotherapy 75mg/m^2	Direct comparison	Hanna et al., (2004)
	Indirect comparison	Shepherd et al., (2000) Fossella et al., (2000) Schuette et al., (2005) Gridelli et al., (2004) Camps et al., (2006) Ramlau et al., (2006)
Best Supportive Care	Indirect comparison	Shepherd et al., (2000) Thatcher et al., (2005)
Erlotinib 150-mg/day	Indirect comparison	Shepherd et al., (2005)

38. Please provide details of relevant ongoing studies from which additional evidence is likely to be available in the next 6–12 months.

The Assessment of Cost and outcomes of chemotherapy In an Observational setting in patients with advanced NSCLC (ACTION) study was a pan-European study which started in 2003 and closed in April 2006. The study recruited 967 patients across Europe, of which 193

were from the UK. Baseline data from the study has been presented (Pimental, 2005). The final results from this study may be ready for publication within a year but will not include pemetrexed data as the medicine was not licensed at the time of recruitment. However, they will provide data on the QOL and resource use in patients receiving second-line treatment in the UK

39. A flow diagram of numbers of number of studies included and excluded at each stage should be provided as per the QUORUM statement.



2.3 Summary details of RCTs

40. As a minimum, the summary should include information on the following aspects of the study but the list is not exhaustive. Where there is more than one RCT please tabulate the information.

This section summarises the key results of the one head-to-head phase III registration trial of pemetrexed, study JMEI. Summaries of the remaining clinical trials identified in the table 6 above, will be detailed in the section 2.7.

JMEI is randomised clinical trial comparing pemetrexed to the current UK standard of active chemotherapy, docetaxel. Study JMEI is the registration trial for pemetrexed in NSCLC and has been reported by Hanna et al, 2004.

Table 7: Citations of the comparative randomised trial of pemetrexed versus docetaxel included in this submission

Trial	Trial Report/Publication
JMEI (Pemetrexed registration trial)	Clinical study report: a phase III trial of pemetrexed versus docetaxel in patients with locally advanced or metastatic Non-small Cell Lung Cancer (NSCLC) who were previously treated with chemotherapy, April 2003
	Hanna N, Shephard FA, Fossella V, Pereira JR, De Marinis F, von Pawel J et al. Randomised phase III trial of pemetrexed versus docetaxel in patients with Non-small Cell lung cancer previously treated with chemotherapy. J Clin Oncol 2004; 22 (9): 1589-1597

2.3.1 Methods

41. Describe the trial design (e.g. degree and method of blinding and randomisation) and interventions.

Trial Design

The JMEI study was a randomised, controlled, open-label, multicenter trial that entered 698 patients at 135 investigational sites in 23 countries from March 2001 to February 2002. Of these, 571 (81.8%) patients were randomly assigned (enrolled) to either the pemetrexed or the docetaxel arm.

Table 8: Characteristics of the JMEI trial

Design	Location[1]	Follow-up	Patient population
Open-label, parallel group, randomised study	International Multicentre	Until death or study closure.	Patients with locally advanced (stage IIIa or IIIb) or metastatic NSCLC (stage IV) who had been previously treated with chemotherapy

[1]A total of 135 study centers were located in 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.

Patients were randomly assigned to receive either pemetrexed or docetaxel in this parallel, open-label trial. The algorithm of Pocock and Simon, using a probability factor of 0.75, was applied to balance the treatment arms for the following factors (Pocock and Simon 1975).

- 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)
- number 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 (CR/PR/SD or PD) or unknown]
- disease stage (III[A/B] or IV)
- investigation center (by center).

The primary objective of this study was the comparison of overall survival between the two study arms, which was performed on an intention-to-treat (ITT) basis. The ITT population

incorporated all patients randomly assigned to a treatment arm, regardless of whether they received the study drug.

Docetaxel was chosen as the active control in this study because it was (at the time) the only approved therapy for second-line NSCLC (Food and Drug Administration [FDA], 1999; Committee for Proprietary Medicinal Products [CPMP], 2000).

Secondary objectives were to compare:

- 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

Dose Regimen

The treatment regimen for each of the arms in trial JMEI is presented in the table below. Study therapy was allowed to continue until there was evidence of progressive disease, the patient experienced unacceptable toxicity, the investigator decided to discontinue the patient, or the patient requested discontinuation. The dose of pemetrexed and docetaxel are in accordance with that recommended in the SPCs for each therapy.

Table 9: Treatment regimen in the JMEI trial

Drug	Dose	Time
Patients randomly assigned to the pemetrexed arm:		
Pemetrexed	500 mg/m^2 iv infusion	Approximately 10 minutes (8 – 15 minutes) on Day 1 of a 21-day cycle
Folic acid	350 – 1000μg	Oral dose daily beginning approximately 1-2 weeks prior to the first dose of pemetrexed and continuing daily until 3 weeks after the last dose of
Vitamin B_{12}	1000μg IM	Approximately 1–2 weeks prior to the first dose of pemetrexed and approximately every 9 weeks until 3 weeks after the last dose of pemetrexed.
Dexamethasone	4 mg, orally BID (or equivalent regimen)	Taken on the day before, the day of, and the day after each dose of pemetrexed, unless clinically contraindicated. Higher or additional doses were permitted for reasons other than routine rash prophylaxis (eg, antiemetic prophylaxis).

Drug	Dose	Time
Patients randomly assigned to the docetaxel arm		
Docetaxel	75 mg/m^2 iv infusion	Approximately 1 hour on Day 1 of a 21-day cycle
Dexamethasone	16 mg orally, daily (eg, 8 mg BID) or equivalent regimen	For 3 days starting 1 day prior to each dose of docetaxel (or equivalent regimen), unless clinically contraindicated, to reduce the severity of fluid retention and hypersensitivity reactions.

Abbreviations; IV, intravenous; IM, intramuscular; BID, twice daily

2.3.2 Population

42. Provide details of the inclusion and exclusion criteria and describe the patient characteristics at baseline. Highlight any differences between study groups.

Patient Population

The inclusion criteria for the JMEI study are presented in table 10. Patients were included in this study only if all criteria were met. Briefly, patients were male or females at least 18 years of age, with histologic or cytologic diagnosis of NSCLC with locally advanced or metastatic disease (Stage IIIA, IIIB or IV at entry) that was not amenable to curative therapy, who had previously received chemotherapy, with an estimated life expectancy of at least 8 weeks, and adequate organ functioning.

Table 10: Inclusion Criteria for JMEI

	Inclusion criteria
1	Histologic or cytologic diagnosis of NSCLC with locally advanced or metastatic disease (Stage IIIA, IIIB or IV at entry) that was not amenable to curative therapy.
2	Previous treatment with at least one chemotherapy regimen as outlined below: neoadjuvant chemotherapy or neoadjuvant followed by adjuvant chemotherapy (only a single regimen was allowed) or adjuvant chemotherapy or chemotherapy for advanced disease. Patients were also eligible if they had received one chemotherapy regimen as neoadjuvant, neoadjuvant followed by adjuvant, or adjuvant chemotherapy and a different chemotherapy regimen for advanced disease. Only a single regimen was allowed for prior therapy of advanced disease.
3	Disease status must have been defined as measurable and/or evaluable disease.
4	Prior chemotherapy must have been completed at least 2 weeks prior to study enrolment, and the patient must have recovered from the acute toxic effects of the regimen.
5	Prior radiation therapy was allowed to <25% of the bone marrow. Prior radiation to the whole pelvis was not allowed. Prior radiotherapy must have been completed at least 2 weeks before study enrolment. Patients must have recovered from the acute toxic effects of the treatment prior to study enrolment.
6	Performance status of 0 to 2 on the ECOG Scale.
7	Estimated life expectancy of at least 8 weeks.
8	Patient compliance and geographic proximity that allowed adequate follow-up.
9	Adequate organ function including the following: Adequate bone marrow reserve: ANC (segmented and bands) ≥1.5 x 10 9 /L, platelets ≥100 x 10 9 /L, and haemoglobin ≥9 g/dL. Hepatic: bilirubin less than or equal to the ULN, AST and ALT <=1.5 x ULN, alkaline phosphatase <=5 x ULN. Renal: CrCl ≥45 mL/min using the lean body mass formula only

	Inclusion criteria
10	Signed informed consent from patient.
11	Male or female patients at least 18 years of age.
12	Male and female patients with reproductive potential must have been using an approved contraceptive method if appropriate (for example, [IUD], birth control pills, or barrier device) during and for 3 months after the study. Females with childbearing potential must have had a negative serum pregnancy test within 7 days prior to study enrolment.

Abbreviations: ALT, alanine transaminase; AST, aspartate transaminase; ULN, upper limit of normal; ANC, absolute neutrophil count; CrCl, calculated creatinine clearance; IUD, intrauterine device; ECOG, Eastern Cooperative Oncology Group.

Patients were excluded from the study for any of the reasons presented in table 11. The criteria for enrolment were to be followed explicitly. If a patient who did not meet enrolment criteria was inadvertently enrolled, that patient was to be discontinued from the study.

Table 11: Exclusion criteria in JMEI

	Exclusion criteria
1	Treatment within the last 30 days with any investigational drug.
2	Active infection that in the opinion of the investigator would have compromised the patient's ability to tolerate therapy.
3	Pregnancy.
4	Breast-feeding.
5	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.
6	Second primary malignancy that is clinically detectable at the time of consideration for study enrolment.
7	Inability to interrupt aspirin or other NSAIDs for a 5-day period (8-day period for long-acting agents such as piroxicam).
8	Brain metastasis. Patients who were symptomatic for brain metastasis must have had a pre-treatment CT or MRI of the brain. A patient with documented brain metastasis at the time of study entry was to be excluded from entering in the study. Patients with prior brain metastasis could be considered if they had completed their treatment for brain metastasis, no longer required corticosteroids, and were asymptomatic.
9	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.
10	Significant weight loss (that is, $\geq$10%) over the previous 6 weeks before study entry.
11	Prior treatment with either pemetrexed or docetaxel.
12	History of severe hypersensitivity to polysorbate 80.
13	Inability or unwillingness to take folic acid or vitamin B_{12} supplementation.
14	CTC Grade 3 or 4 peripheral neuropathy at study entry.

Abbreviations: NSAIDs, non steroidal anti inflammatory drugs; CTC, Common Toxicity Criteria; CT, computed tomography; MRI, magnetic resonance imaging; NSAIDs, nonsteroidal anti-inflammatory drugs

Table 12: Baseline Patient and Disease Characteristics (ITT population)

Characteristic	% of Patients Pemetrexed Group (n=283)	Docetaxel Group (n=288)
Sex		
Male	68.6	75.3
Female	31.4	24.7
Age, years		
Median	59	57
Range	22-81	28-87
Performance status		
0 or 1	88.6	87.6
2	11.4	12.4
Stage IV	74.9	74.7
Prior Platinum	92.6	89.9
CR/PR to prior platinum	34.7	37.5
Prior paclitaxel	25.8	27.8
CR/PR to prior paclitaxel	39.7	35.0
Best response, any prior chemotherapy		
CR/PR	35.7	36.5
SD	37.5	32.3
PD/unknown or not evaluable	26.9	31.3
Time since last chemotherapy		
< 3 months	50.4	48.1
Histology		
Adenocarcinoma	54.4	49.3
Squamous cell carcinoma	27.6	32.3
Homocysteine level		
< 12 μ mol/L	71.4	68.9
Prior Radiation	44.2	45.5

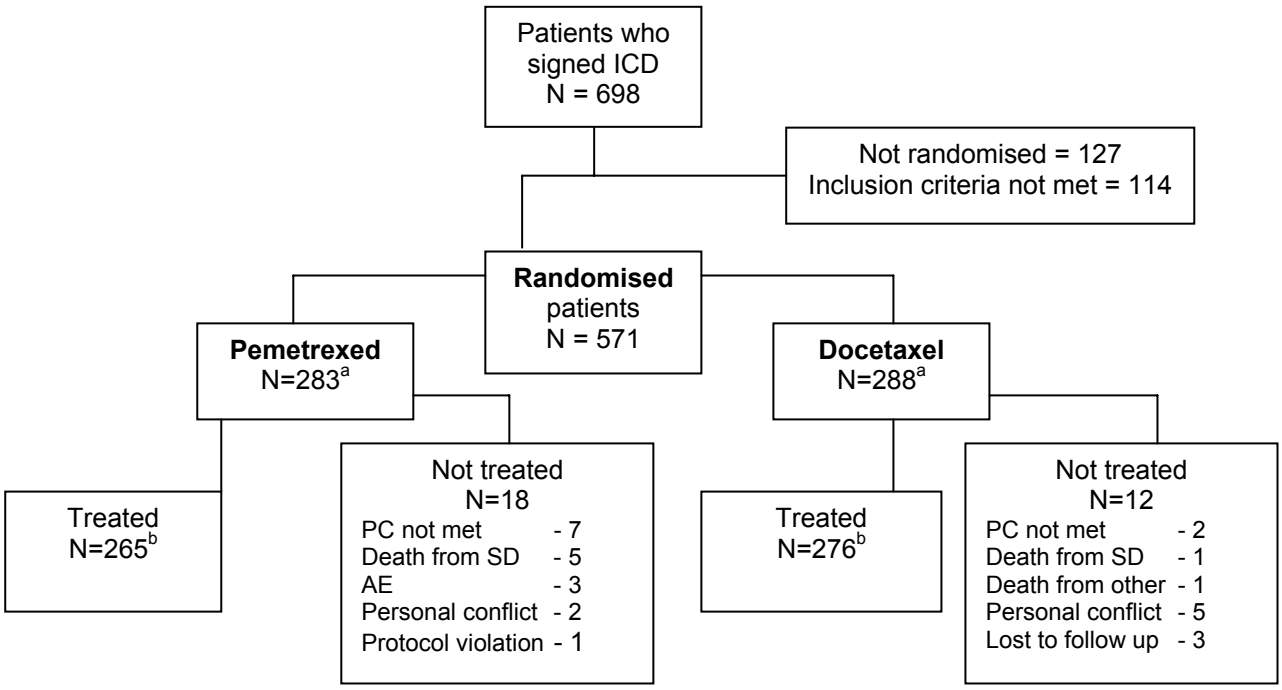
Abbreviations: CR, complete response; PR, partial response, SD, stable disease; PD, progressive disease

2.3.3 Patient numbers

43. Provide details of the numbers of patients eligible to enter the trial, randomised, and allocated to each treatment. Provide details of patients who crossed over treatment groups and dropped out from the trial. This information should be presented as a CONSORT flow chart.

The figure below displays the flow of the patients who entered Study JMEI. Of the 698 entered patients, 283 patients were randomly assigned to the pemetrexed arm, and 288 patients were randomly assigned to the docetaxel arm. A total of 114 patients did not meet the protocol inclusion criteria, and 13 patients could not be randomised because of unspecified reasons.

JMEI study design and disposition of patients in JMEI



Abbreviations: AE, adverse event; PC, protocol criteria; SD, study disease; ICD, informed consent document.
[a] Intention to treat (ITT) population
[b] Randomised and treated (RT) population

2.3.4 Outcomes

44. Provide details of the outcomes investigated and the measures used to investigate those outcomes. This may include therapeutic outcomes and patient-related outcomes such as assessment of quality of life, social outcomes etc. and any arrangements to measure concordance. Where appropriate, also provide details of the principal outcome measure(s) including details of length of follow-up, timing of assessments, scoring methods, evidence of validity and current status of the measure (e.g. approval by professional bodies, licensing authority, etc.).

Table 13: Definitions of efficacy outcome measures

Endpoint	Definition
Overall Survival	Survival was defined as the time from the date of randomisation to date of death due to any cause. Overall survival time was to be censored at the date of the last follow-up visit for patients who were still alive when the database was locked.
Progression-free survival (PFS)	Defined as the time from the date of randomisation to the first date of documented disease progression or death due to any cause.
Time to treatment failure	Defined as the time from the date of randomisation to the date of the first of the following events: discontinuation of study therapy, progression of disease, or death due to any cause.
Time to progressive disease	Defined as the time from the date of randomisation to the first date of documented disease progression.
Time to response	Defined as any patient exhibiting a best study response of CR or PR (based on CT, MRI, or plain x-ray, and/or palpation) or partial response in nonmeasurable disease (PRNM) from time of randomisation to the first declaration of response.

Endpoint	Definition
Duration of tumour response	Defined as time from first objective status of a CR or PR or PRNM to first observation of progressive disease or death due to any cause.
Duration of clinical benefit	Time from the date of randomisation to the first observation of progressive disease or death due to any cause for patients with CR, PR, PRNM, or SD.
Toxicity	Safety measures that were used in the study included physical examinations, and clinical laboratory tests (haematology, blood chemistries, and creatinine clearance). Patients were rated for toxicity prior to each cycle by using the NCI CTC scale, Version 2.
LCSS	A validated, lung cancer-specific QoL instrument, the Lung Cancer Symptom Scale (LCSS) has been included in this study (Hollen *et al*., 1994). The LCSS is comprised of a patient scale and an optional observer scale. The patient scale includes six symptom questions and three summation questions, while the observer scale includes the same six symptom questions. Only patients for whom there is a validated translation in a language in which they were fluent were required to complete the LCSS.

Abbreviations; CR, complete response; PR, partial response; PRNM, partial response in non-measurable disease; SD, stable disease.

Table 14: Assessments and procedures performed during JMEI

Baseline Assessment	
No more than 4 weeks before study enrolment	Radiologic imaging studies (CT or MRI scan [where available], and plain x-ray) for baseline tumour assessments. Response to prior chemotherapy
No more than 2 weeks before study enrolment:	Medical history and physical examination, including measurements of height, weight, blood pressure, and pulse rate. Evaluation of performance status. Concomitant medication notation Tumour measurement of palpable lesions.
Approximately 1 to 2 weeks prior to study enrolment	Vitamin metabolite panel: homocysteine, cystathionine, methylmalonic acid, methylcitrate (total, I and II).
Within 7 days of study enrolment	Haematology: haemoglobin, leukocytes (WBC), platelets, neutrophils (sum of segmented and bands), lymphocytes, and monocytes. Blood chemistries: bilirubin, AP, ALT, AST, blood urea nitrogen (BUN), creatinine, calcium, and electrolytes (sodium, potassium). Calculated creatinine clearance. A serum pregnancy test for females with childbearing potential. LCSS patient scale baseline evaluation. LCSS observer scale baseline evaluation.

During the study	
Weekly	The LCSS patient scale was to be administered on Day 8, Day 15, and one day prior to, or the day of, the next cycle of either docetaxel or pemetrexed treatment, before the infusion began. In case of cycle delays lasting more than 5 days, additional LCSS patient scale assessments were performed weekly
Prior to each cycle of treatment:	▪ weight measurements, and body surface area calculation ▪ performance status evaluation ▪ limited medical history and physical examination ▪ the LCSS observer scale was to be completed before the next cycle of chemotherapy was administered.
Prior to every other cycle of treatment:	▪ CT or MRI scan for patients whose disease was being monitored by CT or MRI scan ▪ plain x-ray for patients whose disease was being monitored by plain x-ray ▪ Tumor measurement of palpable lesions (done prior to drug administration).
Post study follow up	
Efficacy Outcomes	Assessments continued to be performed approximately every 6 weeks until the patient had documented progression of disease OR received post-study chemotherapy, surgery, or other treatment, OR for 6 months from the last dose of study therapy, whichever occurred first. Each patient's assessments continued until death or until study closure
LCSS	The LCSS patient and observer scales were completed at the time the patient discontinued from study therapy. If the patient did not receive any post-study chemotherapy, surgery, or other treatments for the patient's cancer, the LCSS patient and observer scales were to be completed at approximately 30 days, and again at approximately 3 months after the last dose of study drug. If the patient discontinued from study therapy more than 30 days after the last dose of study drug, the 30-day post-dose LCSS observer scale was not completed; however, the observer scale was to be still completed approximately 3 months after the last dose of study drug.
Toxicity	After each patient discontinued study therapy, the investigator made every effort to continue to evaluate the patient for delayed toxicity by clinical and laboratory evaluations as clinically indicated. Every attempt was to be made to obtain haematology and chemistry approximately 30 days after the last dose of pemetrexed or docetaxel. The patient was to be followed approximately every 30 days until toxicity resolved

2.3.5 Statistical analysis and definition of study groups

45. State the primary hypothesis or hypotheses under consideration and statistical analysis used in testing hypotheses. Also provide details of the power of the study and a description of sample size calculation including assumptions. Provide details of how the analysis took account of patients who withdrew (e.g. a description of the intention-to treat analysis including censoring methods; whether a per-protocol analysis was undertaken). Provide details of any subgroup analyses that were undertaken.

The study was designed to enroll at least 520 patients, randomly and evenly assigned to pemetrexed or docetaxel. The study protocol design was based on the assumption that in overall survival, the hazard ratio (HR) of pemetrexed to docetaxel is approximately constant over the period of observation. Superiority of pemetrexed in overall survival was defined by HR <1.00. Non-inferiority of pemetrexed in overall survival was defined by HR<1.11.

Hazard ratio was estimated from the study data by using the Cox proportional hazards model with therapy arm as the only cofactor (Cox 1972). From the Cox model, a two-tailed 95% confidence interval for HR was used to simultaneously evaluate the null hypotheses of

HR $\geq$1.00 (pemetrexed not superior) and HR $\geq$1.11 (pemetrexed inferior).

Assuming no more than 26% censoring, the sample size of 520 patients allows for the observance of 385 deaths. The sample size was chosen based on the following operating characteristics of an analysis based on 385 deaths:

- For a true value of HR of 0.75, there was an 80% chance of demonstrating statistically significant superiority of pemetrexed;
- For a true value of HR of 0.83, there was an 81% chance of demonstrating statistically significant noninferiority of pemetrexed.

Statistical power was calculated using the formula

• Prob{Z < [(385)1/2 (x - y) – 1.96 x1/2 (y + 1)] / x1/2 (y + 1)},

where Z is the standard normal variate, x is the null hazard ratio, and y is the alternative hazard ratio.

In addition, the hypothesis that pemetrexed retained ≥ 50% of the survival benefit of docetaxel over best supportive care (BSC) using historical data (Shepherd et al, 2000) was prospectively planned in the statistical analysis plan approved before data lock. Percent of efficacy of docetaxel over BSC, which is retained by pemetrexed, was calculated based on the following method:

% efficacy retained = 1˜ [log hazard ratio (HR) (pemetrexed over docetaxel)/ log HR (BSC over docetaxel)]

The 95% confidence interval (CI) of this percentage of benefit was calculated using Rothmann's Z* statistic (Rothmann et al. 2003).

All patients randomly assigned to a treatment arm in this study, excluding the 4 patients entered by Investigator Number 137, were evaluated for overall survival; this population was defined as the intent to treat (ITT) population. The 4 patients from Site 137 were excluded from all analyses because the investigator at this site did not meet regulatory requirements.

Subgroups analyses

Analyses of overall and progression-free survival were performed for subgroups based on gender, age, and other important factors deemed as appropriate. First, the treatment-by-subgroup interaction was tested at the 0.10 level of significance to determine whether treatment differences were consistent for each subgroup category. Then a subsequent model for each subgroup was fitted with only therapy as fixed effect to determine the treatment differences in each subgroup category. The Cox proportional hazard model was used to test equality of survival distribution between treatments across the subgroup categories.

2.4 Critical appraisal

For each of the following methodological topics, choose the description that best fits each trial. If there is more than one trial, tabulate the responses, highlighting any 'commercial in confidence' data. Your results will be validated by the assessor.

2.4.1 Randomisation

46. Which of the following best describes the randomisation?

A) No details of randomisation are available, or the method used was inadequate (e.g. randomisation according to the day of the week, even/odd medical record numbers).

B) An insecure randomisation method was used, where clinical staff could possibly learn of the treatment assignment (e.g. randomisation sequence kept in the clinical area and open/unblinded trial; treatment assignment kept in consecutive 'sealed' envelopes and open/unblinded trial).

C) A secure randomisation method was used, where the randomisation sequence was kept away from the clinical area and administered by staff not directly involved in patient care.

Patients were randomly assigned to receive either pemetrexed or docetaxel in this parallel, open-label trial. Randomisation was controlled by computerised codes generated via an interactive voice response system (IVRS) controlled from a central location. Each patient's treatment was not assigned until time of randomisation.

Therefore this study is categorised as

C) A secure randomisation method was used, where the randomisation sequence was kept away from the clinical area and administered by staff not directly involved in patient care

2.4.2 Adequacy of follow-up

47. Which of the following best describes the adequacy of follow-up?

A) There were significant numbers of drop-outs with no assessment of trial outcome(s) in the subjects who dropped out, and drop-out rates differed between treated and control groups.

B) There were some drop-outs with no assessment of trial outcome(s) in the subjects who dropped out, and drop-out rates were (approximately) equivalent in treated and control groups.

C) Trial outcome(s) were assessed in all treated and control subjects.

Based on the primary endpoint of the trial (ie, survival time), this study was categorised as:

C) Trial outcome(s) were assessed in all treated and control subjects

2.4.3 Blinding of outcomes assessment

48. Which of the following best describes the blinding of the outcomes assessment?

A) There was an inadequate attempt (or no attempt) to blind observer(s), and the measurement technique was subject to observer bias (e.g. blood pressure measurement with standard sphygmomanometer; measurement of vertebral height on an X-ray).

B) The observer(s) were kept fully blinded to treatment assignment, or the measurement technique was not subject to observer bias (e.g. measurement of bone mineral density or survival).

This was a randomised, open-label study with the identity of the treatment known to the investigators and patients. However Lilly personnel were blinded to the patient treatment assignment to minimise bias and prevent the sponsor from observing results until the analysis plan was finalised and the database officially locked.

Therefore the blinding in trial JMEI cannot be categorised according the descriptions presented above but instead is categorised as:

There was an inadequate attempt (or no attempt) to blind observer(s), however the measurement technique was not subject to observer bias (for example survival, the primary outcome of trial JMEI).

Importantly the primary endpoint of this study was survival, which is an objective measure, not subjective to observer bias.

2.4.4 Other

49. Was the design parallel-group or cross-over? Indicate for each cross-over trial whether a carry-over effect is likely.

Patients were randomly assigned to receive either pemetrexed or docetaxel in this parallel, open-label trial. However, patients may have crossed-over, at the investigator's discretion, if further treatment was warranted, following the primary treatment phase.

50. Was the trial conducted in the UK (or were one or more centres of the multinational trial located in the UK)? If not, where was the trial conducted and is clinical practice likely to differ from UK practice?

JMEI was conducted at 135 investigational study sites in 23 countries, including Germany, France, Spain, Portugal, Canada and the United States. The study was not conducted in the UK. UK clinical practice is unlikely to differ from that studied. G-CSFs are frequently used in clinical trials involving docetaxel but are not frequently used prophylactically in the UK to prevent febrile neutropenia. However, in JMEI G-CSFs were not routinely used prophylactically so use is likely to reflect UK practice.

51. How do the subjects included in the trial compare with patients who are likely to receive the drug in the UK? Consider factors known to affect outcomes in the main indication such as demographics, epidemiology, disease severity, setting.

The patient population in JMEI is similar to those likely to be treated with an active agent in the second-line setting in the UK (generally good performance status). The incidence and prevalence of NSCLC are similar in UK as other geographies but the use of active treatment is lower in the UK than in other European countries (e.g. 70% of patients in France receive 1st line chemotherapy compared to approximately 30% in the UK). This influences the number of patients likely to go on to receive second-line treatment. Most patients in the UK are diagnosed with advanced disease and are therefore not eligible for surgery. For these patients, active treatments represent the best option to increase survival.

52. For pharmaceuticals, what dosage regimens were used in the trial? Are they within those detailed in the Summary of Product Characteristics?

The dosage regimens used in JMEI are in line with the pemetrexed and docetaxel SPCs.

53. What was the median (and range) duration of follow-up in the trial?

The median duration of follow-up in the ITT population was 4.6 months (3.90, 5.10 95%CI); with the range of 0.00 months to 18.90 months.

2.5 Results of the comparative randomised trials

54. Provide the results for all relevant outcome measure(s). If there is more than one trial, tabulate the responses, highlighting any 'commercial in confidence' data. The information may be presented graphically to supplement text and tabulated data. Data from intention-to-treat analyses should be presented wherever possible.

For each outcome:

- describe the unit of measurement
- report the size of the effect; for dichotomous outcomes, the results ideally should be expressed as both relative risks (or odds ratios) and risk (or rate) differences. For time-to-event analysis, the hazard ratio is an equivalent statistic
- provide a 95% confidence interval
- provide the number of patients included in the analysis
- state whether 'intention-to-treat' was used for the analysis
- discuss and justify definitions of any clinically important differences.

Primary Efficacy Outcome

The primary analysis for this trial was the comparison of survival between the two treatment arms in the intention-to-treat (ITT) population.

Survival in the ITT population, JMEI

A total of 283 patients on the pemetrexed arm and 288 patients on the docetaxel arm were included in the survival analysis of the ITT population. The overall survival in the pemetrexed arm was compared with that in the docetaxel arm for testing non-inferiority using the following methods:

- fixed margin method; and
- percentage of efficacy retention (Rothmannn) method (Rothmannn *et.al*., 2003)

Fixed-Margin Non-inferiority Method

It was established that if the overall survival in the pemetrexed arm is 10% worse than that observed in the docetaxel arm, the non-inferiority of pemetrexed to docetaxel would be achieved. This would translate to an upper bound of the 95% CI <1.11 for the hazard ratio (HR) of pemetrexed over docetaxel.

The results of the overall survival from the trial (as shown in table 15 below) show that the median overall survival time for patients treated with pemetrexed was 8.3 months compared with 7.9 months for those treated with docetaxel. The hazard ratio (HR) was 0.99, (95% CI of 0.82 to 1.20) with a non-inferiority *p*-value of 0.226 for testing HR of 1.11. The non-inferiority criterion was not met using this method. It follows from the observed CI that the overall survival in the pemetrexed arm was 22% better than that in the docetaxel arm in the best-case scenario and 16.7% worse in the worst-case scenario.

Percentage of Efficacy Retention (Rothmannn) Method

Fixed margin method does not consider the variability from the historical trial of control treatment compared with the historical control. Percentage of efficacy retention method (Rothmannn *et.al.,* 2003), makes it less complicated to evaluate the experimental treatment's efficacy by estimating the percentage of the control treatment's benefit over a historical control retained by the experimental treatment.

A prospectively planned analysis based on Rothmannn method was included in the Statistical Analysis Plan (SAP) of the study before the data were unblinded. This was to test the hypothesis that pemetrexed retains at least 50% of the survival benefit of docetaxel over best supportive care (BSC). Because the current trial could not have a BSC arm, historical data were used to infer about the HR of docetaxel over BSC. This method assumes that the HR of docetaxel over BSC is constant across both trials. The Rothmannn method takes into account the variability within each trial in estimating the 95% CI for the percentage of benefit retained by the experimental drug.

The non-inferiority margin to test the above hypothesis was determined using data from a randomised comparative trial of patients with advanced NSCLC who had received prior chemotherapy randomised to docetaxel or BSC (Shepherd *et al.,* 2000). In this trial, where 104 patients were randomly assigned to receive either 75 mg/m 2 docetaxel or corresponding BSC, the HR of docetaxel over BSC was estimated to be 0.56 (95% CI: 0.35 to 0.88). Setting the percentage of historical benefit at 50% and maintaining an approximate one-sided 2.5% type I error, an upper 95% CI bound of <1.21 for the HR of pemetrexed over docetaxel is required to establish the non-inferiority of pemetrexed. The HR in the ITT population was 0.99 (95% CI: 0.82 to 1.20) with a non-inferiority *p*-value of 0.047 for testing whether pemetrexed retained 50% of docetaxel's survival benefit. This means that the non-inferiority criteria were met using the Rothmannn method.

The estimate of the percentage of survival benefit (docetaxel over BSC) retained by pemetrexed was 102% with the lower 95% CI bound of 52% (p = 0.047). Thus, pemetrexed statistically significantly retained at least 50% of docetaxel's survival benefit over BSC. This means that the upper limit of the 95% CI for log HR of pemetrexed over docetaxel was entirely below 50% of the lower limit of 63.8% CI for log HR of docetaxel over BSC, thus preserving a one-sided type I error of 0.025.

Table 15 below presents the summary of survival time (months) for the ITT population using both the methods described above.

Table 15: Summary of Survival (Months) - ITT

	ITT Patients (N=571)	
	Pemetrexed (n=283)	**Docetaxel (n=288)**
Minimum	0.1	0
25th Percentile	3.7	3.4
Median	8.3	7.9
95% CI for median	(7.0-9.4)	(6.3-9.2)
75th Percentile	12.9	13.4
Maximum	19.5	21.0
Percent of patients surviving at least:		
3 months	79.6	76.4
6 months	61.5	57.6
9 months	45.8	46.0
12 months	29.7	29.7
Percent censored	27.2	29.5

	ITT Patients (N=571)	
	Pemetrexed (n=283)	Docetaxel (n=288)
Fixed Margin Method		
Hazard Ratio	0.99	
95% CI for hazard ratio	(0.82 – 1.20)	
NI *p*-value for testing HR of 1.11	0.226	
Rothmannn Method		
% efficacy retained by pemetrexed	102%	
95% CI for % benefit retained	(52% - 157%)	
NI *p*-value for testing 50% retention	0.047	

Abbreviations: CI, confidence interval; HR, hazard ratio; ITT, intention to treat; N or n, number of patients in the treatment arm; NI, non-inferiority.

On an intent-to-treat basis, the median survival time for pemetrexed was 8.3 months versus 7.9 months for docetaxel (HR, 0.99; 95% CI, 0.82 to 1.2; non-inferiority $p = 0.226$). Using the Rothmannn method, the estimate of the percentage survival benefit (of docetaxel over Best Supportive Care) retained by pemetrexed was 102% with the lower 95% CI bound of 52% and was statistically significant ($p = 0.047$).

K-M curve showing survival in pemetrexed vs docetaxel (p=0.226)

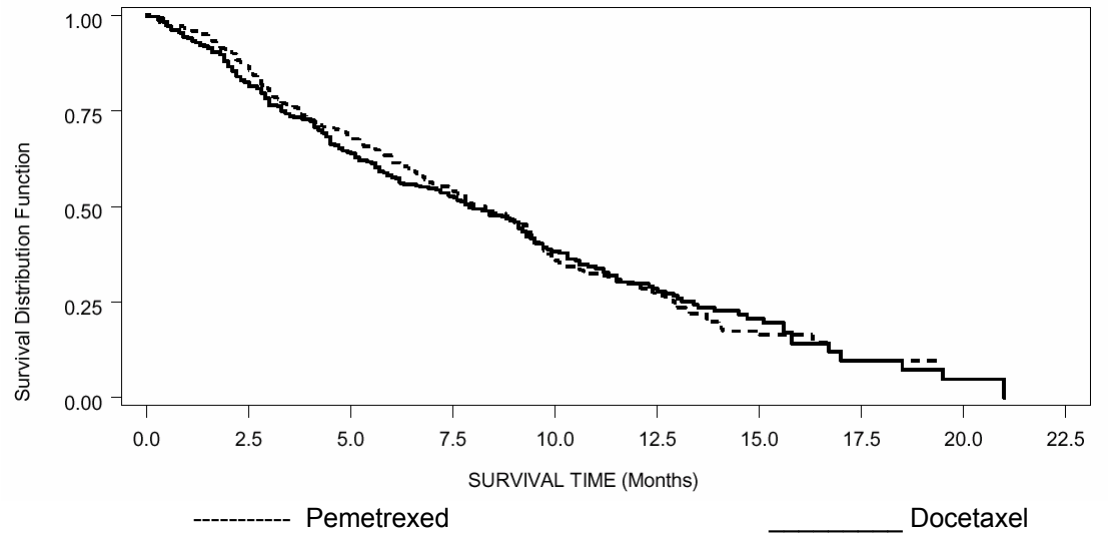


Table 16: Mean survival data using Kaplan-meier and Weibull method

Population	Method	All	Pemetrexed	Docetaxel
ITT	KM	8.8106	8.5561	8.7444
ITT	Weibull	9.3112	9.2790	9.3459

As can be seen from table 16 the mean survival data is similar to the median survival data presented in table 15 above.

Multiple regression analysis for prognostic factors

Cox multiple regression (CMR) analysis was used to identify factors other than treatment intervention that affected the overall survival and to estimate the treatment effect adjusting for

these factors in the ITT population. Table 17 presents a summary of model selection on overall survival in the ITT population.

Table 17: Summary of Model Selection on Overall Survival – ITT Population

Variable	*p*-value	HR	95% Lower Limit	95% Upper Limit
Treatment (pemetrexed versus docetaxel)	0.051*	0.93	0.76	1.13
Performance Status (0/1 versus 2)	<0.001	0.25	0.19	0.34
Time since last chemotherapy (≥3 months versus <3 months)	0.004	0.74	0.60	0.90
Stage (III versus IV)	0.026	0.77	0.60	0.97

Abbreviations: HR, hazard ratio (adjusted); ITT, intention to treat. * Testing noninferiority for HR of 1.11.

This analysis showed a borderline statistical significance for the noninferiority test against HR of 1.11 (p=.051). Because the adjusted Cox model eliminated the variability due to the factors predictive of survival, the survival differences in this model reflect the true treatment effect more closely (in contrast to the unadjusted p-value of 0.226). This means that the noninferiority criteria were closely met using the fixed margin method in the adjusted model.

The table 18 shows the comparison between treatment arms using Cox Proportional hazard model (Hanna et al, 2004).

Table 18: Cox Model subgroup analysis of variables associated with improved survival

Variable	Pemetrexed Survival (months)	Docetaxel Survival (months)	P*
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*

Performance status was explored in the economic analysis to assess the impact upon the cost-effectiveness of pemetrexed as data was available across all active comparators for the analysis and this sub-group reflects patients treated second-line in the UK. Stage of disease is a good prognostic indicator of survival but insufficient data was available to investigate the cost-effectiveness across active treatments; however the clinical benefits are clear across all three active agents (see section 2.7 for data on erlotinib).

Updated Analysis on JMEI

Demarinis et al (2006) presented an updated analysis of JMEI using data available 23 months after the original analysis. The updated survival analysis (performed after 519 deaths) indicated similar median survival times for pemetrexed (8.3 months; 95% CI: 7.0-9.4) and docetaxel (8.0 months; 95% CI: 6.6-9.3), and comparable hazard ratios (HR) (original 0.99 [95% CI: .82-1.20] vs updated 0.97 [95% CI: .81-1.15]). Percent of docetaxel benefit over best supportive care retained by pemetrexed was similar in both analyses: original 102% (95% CI: 52%-157%) vs updated 106% (95% CI: 68%-163%). Cox multiple regression analysis again

showed that the two drugs were similar in survival after adjusting for factors significantly associated with increased survival.

Secondary Efficacy Outcomes

The results presented in table below illustrated there are no significant differences in progression-free survival, median time to response, median duration of response and median duration of clinical benefit. For time-to-treatment failure (TTTF), there was a statistically significant difference between treatment arms, favouring pemetrexed where TTTF took statistically significantly longer in pemetrexed-treated compared to docetaxel-treated patients (p = 0.046). These results, in favor of pemetrexed reflect the better safety profile of pemetrexed as fewer patients discontinued because of adverse events or death on study.

Variable	Pemetrexed (n=283)	Docetaxel (n=288)	HR	95% CI	*P*[§]
Progression-free survival					
Median, months[†]	2.9	2.9			
Range, months	0-18.2	0-19.5	0.97	0.82 to 1.16	0.759[‡]
Patients censored, %	6.4	10.4			
Time to progressive disease					
Median, months[†]	3.4	3.5	0.97	0.80 to 1.17	0.721[‡]
Range, months	0.5-18.2	0.3-19.5			
Patients censored, %	24.7	27.8			
Time to treatment failure			0.84	0.71 to 0.997	0.046[‡]
Median, months[†]	2.3	2.1			
Range, months[†]	0.0-18.2	0.0-13.1			
Patients censored, %	1.4	1.7			
Duration of tumour response					
Median, months[†]	4.6	5.3	0.77	0.40 to 1.47	0.427[‡]
Range, months[†]	2.1-15.3	1.7-11.7			
Patients censored, %	25.0	16.7			
Duration of clinical benefit					
Median, months[†]	5.4	5.2			
Range, months[†]	1.2-18.2	1.5-14.6	0.91	0.71 to 1.16	0.450[‡]
Patients censored, %	10.3	13.9			
Time to objective tumour response					
Median, months	1.7	2.9	NA	NA	0.105[§]
Range, months	1.2-4.3	1.4-7.8			

Abbreviations: ITT, intent-to-treat; HR, hazard ratio; NA, not assessable.

[*] pemetrexed (n=282) in time-to-treatment failure analysis.

[†] 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.

Quality-of-Life Analysis

LCSS – Patient scale

The patient scale consists of nine 100-mm visual analogue scales (VASs) and scores are reported from 0 to 100, with zero representing the best score. The average symptom burden index was calculated from the average of the six symptom items (anorexia, fatigue, cough, dyspnea, haemoptysis, and pain). A total score was calculated from the average of the nine LCSS values.

A total of 474 patients (pemetrexed, n=227; docetaxel, n=247) were assessable for the average symptom burden index, (ASBI), analysis of the patient LCSS. Table 19 presents a summary of the ASBI for the ITT population by treatment arm:

Table 19: Summary of Average Symptom Burden Index (ASBI) 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.

There was no significant difference in the distribution of numbers of patients reporting changes in the ASBI between the two arms of the study, as shown in the table above.

LCSS – Observer scale

The LCSS observer scale (a 5-point categorical scale) was completed by study site personnel. Scores are reported on a scale from 0 to 100, with 100 representing the best possible score. The observer rated six individual symptoms: anorexia, fatigue, cough, dyspnea, hemoptysis, and pain. A total score was calculated from the average of the six LCSS values.

A total of 472 patients (pemetrexed, n=239; docetaxel, n=233) were evaluable for observer LCSS analysis. Table 20 below summarises sustained changes in observer LCSS scores for anorexia, fatigue, cough, dyspnea, hemoptysis, pain, and total (average) for the ITT population by treatment arm. Patients were classified with “insufficient data” if there were too few post-baseline assessments to confirm changes.

Table 20: LCSS Observer Scale Response – ITT Population

LCSS Observer Scores		Pemetrexed (N=239) n (%)	Docetaxel (N=233)[1] n (%)	*p-value*[2]
Anorexia	Improved	35 (14.6)	38 (16.3)	0.337
	Stable	98 (41.0)	104 (44.6)	
	Failure	46 (19.2)	37 (15.9)	
	Insufficient Data	60 (25.1)	54 (23.2)	
Fatigue	Improved	34 (14.2)	40 (17.2)	0.589
	Stable	97 (40.6)	92 (39.5)	
	Failure	48 (20.1)	47 (20.2)	
	Insufficient Data	60 (25.1)	54 (23.2)	
Cough	Improved	42 (17.6)	37 (15.9)	0.545
	Stable	110 (46.0)	113 (48.5)	
	Failure	27 (11.3)	29 (12.4)	
	Insufficient Data	60 (25.1)	54 (23.2)	
Dyspneoa	Improved	27 (11.3)	30 (12.9)	0.416
	Stable	125 (52.3)	109 (47.0)	
	Failure	27 (11.3)	39 (16.8)	
	Insufficient Data	60 (25.1)	54 (23.3)	
Haemoptysis	Improved	11 (4.6)	8 (3.4)	1.000
	Stable	157 (65.7)	162 (69.8)	
	Failure	11 (4.6)	8 (3.4)	
	Insufficient Data	60 (25.1)	54 (23.3)	
Pain	Improved	38 (15.9)	44 (19.0)	0.800
	Stable	115 (48.1)	100 (43.1)	
	Failure	25 (10.5)	34 (14.7)	
	Insufficient Data	61 (25.5)	54 (23.3)	
Total (average)	Improved	64 (26.8)	65 (28.0)	0.712
	Stable	44 (18.4)	48 (20.7)	
	Failure	70 (29.3)	65 (28.0)	
	Insufficient Data	61 (25.5)	54 (23.3)	

Abbreviations: ITT = intention to treat; LCSS = Lung Cancer Symptom Scale; N = number of patients in the treatment arm; n = number of patients with observer scores.
[1] N = 232 for dyspneoa, haemoptysis, pain, total. [2] Mantel-Haenszel chi-square.

There were no differences in distributions of changes in observer scale scores between the treatment arms. Scores for the majority of patients remained stable or improved for individual symptoms, the majority of patients had mild or no symptoms at baseline. This is a positive result as, in theory, progression of disease that occurred without treatment or with BSC would have resulted in the worsening of lung cancer symptoms.

The LCSS is a symptom scale rather than a scale measuring quality of life. Therefore, it is difficult to assess the impact of differential toxicity of the QoL of patients who received docetaxel or pemetrexed. However, data shown below in section 2.8 demonstrates that patients receiving pemetrexed spend less survival time with toxicities and also experience less severe toxicities, so it is reasonable to assume they derive a Qol benefit from this.

De Marinis et al (2006) evaluated the benefit of second-line treatment of NSCLC in terms of symptom palliation and whether it occurred with less than a major response. Using data from JMEI, analysis was performed on patients who had baseline data with the LCSS and who had received >1 cycle of treatment. Pateints were grouped by best overall response: complete/partial, or stable disease versus progressive disease. The results of the analysis demonstrated that patients achieving tumour response or stable disease have a greater likelihood of patient-reported benefit than patients with progressive disease.

Efficacy conclusions

- Treatment with pemetrexed was as good as docetaxel in the ITT populations with respect to the following endpoints:
- progression-free survival
- time to progressive disease
- response rate
- time to response
- duration of response
- duration of clinical benefit.
- Treatment with pemetrexed was associated with statistically significantly longer time to treatment failure compared with docetaxel.
- No differences in survival were observed between the treatment arms after adjusting for independent prognostic factors. The Cox regression analyses showed a borderline statistical significance for the noninferiority test between treatment groups for HR of 1.11
- The primary outcome of this study was the overall survival of the ITT patients. The non-inferiority criteria were not met using the fixed margin method for testing HR of 1.11. However, the original analysis specified in the study protocol, using Rothmannn methodology, showed that treatment with pemetrexed was as good as treatment with docetaxel in the ITT population with respect to overall survival. Pemetrexed retained greater than 100% of the survival benefit of docetaxel, and in the worst case at least 52% of the benefit over BSC. The non-inferiority criteria using the Rothmannn method was met for testing whether pemetrexed retained 50% of docetaxel's survival benefit.
- No differences in the patient or observer LCSS scores were observed between the treatment arms; both arms showed benefits in terms of stable and improved symptoms for patients.

55. Where interim trial data are quoted this should be clearly stated along with the point at which data were taken and the time remaining until completion of that trial. Analytical adjustments should be described to cater for the interim nature of the data.

The final survival data is presented in this submission. This analysis met the criteria in the statistical analysis plan.

56. If the trial measures a number of outcomes, discuss whether and how an adjustment was made for multiple comparisons in the analysis.

No planned multiplicity adjustments were made to any of the analyses. One primary analysis was completed, and all other analyses were considered secondary. All confidence intervals for all analyses were constructed using 95% levels (that is, all statistical tests were performed using 5% significance levels. General tendencies in *p*-values less than or equal to 0.05 were noted and discussed.

57. Other relevant data that may assist in interpretation of the results may be included, such as adherence to medication and/or study protocol.

Pemetrexed or docetaxel was intravenously administered only at the investigational sites. Vitamin B_{12} supplementation for patients receiving pemetrexed was to be administered as an intramuscular injection at the investigational sites. As a result, patient compliance monitoring was ensured. Patients who returned for subsequent on-drug study visits received study drug unless they encountered toxicity problems or their disease had progressed. In the period before the first dose of pemetrexed, compliance with folic acid supplementation requirements was to be monitored through the use of a medical interview documented in the patient chart. While on study therapy, patient compliance with folic acid supplementation requirements was to be monitored through medical interviews.

2.6 Meta-analysis

58. Where more than one study is available consideration should be given to undertaking a meta-analysis. The following steps should be used as a minimum.

- Perform a statistical assessment of heterogeneity. If the visual presentation and/or the statistical test indicate the trial results are heterogeneous, try to provide an explanation for the heterogeneity.
- Statistically combine (pool) the results for both relative risk reduction and absolute risk reduction using both the fixed effects and random effects models (giving four combinations in all).
- Provide an adequate description of the methods of statistical combination and justify their choice.
- Undertake sensitivity analysis where appropriate
- Tabulate and/or graphically display the individual and combined results.

No attempt was made to meta analyse the results from the clinical trial, since there was only one phase III trial where pemetrexed had been given in second-line NSCLC patients, which was compared to docetaxel. A pooled analysis comparing treatments was performed, details are provided below.

2.7 Indirect/mixed treatment comparisons

59. In circumstances where there are no RCTs that directly compare the technology with the comparator(s) of interest consideration should be given to using indirect/mixed treatment comparisons. Give a full description of the methodology used and provide a justification for the approach.

Randomised controlled trials [generally] provide the most reliable evidence of treatment effectiveness as observed differences between the treatment arms can be confidently

attributed to differences in the treatment(s) being evaluated. However, as explained in Section 2.6, most of the identified phase III trials of NSCLC that met the inclusion criteria for the appraisal did not directly compare all of the specific treatments of interests. There have been many examples where this situation has occurred in previous health technology assessments. For this reason data was compared across phase III clinical trials using two methodologies: pooled estimates and indirect comparison. Pooled estimates include a larger number of trials and therefore more patients. Indirect comparison uses a single comparator to anchor the analysis, in this case BSC.

Pooling Methodology

Data were available for pemetrexed and erlotinib from the JMEI trial and Shepherd et al., (2005) study respectively. In the case of docetaxel and best supportive care, data presented from more than one study and these data were pooled together to reflect this. Weighted values were produced from the absolute values reported in each study that took into account the number of patients in each trial (with the more populated trials achieving greater weight). Confidence intervals were estimated for each of these weighted values.

Pooled Mean: Suppose we have m number of estimates x(i), of sample size n(i), for the population expected value m, the pooled estimate is:

$\sum n(i)x(i) / \sum n(i)$, both sums are over all values of i = 1, 2,. . ., m.

Pooled Variance: Since the sample variance is also an unbiased estimate of population variance s2, therefore, it is a good idea to pool the estimates to get a single estimate from m number of estimates S(i)2, of sample size n(i), the pooled estimate is:

$\sum(n(i) - 1)*S(i)2 / (\sum n(i) - m)$, both sums are over all values of i = 1, 2,…, m

Indirect comparison methodology

The difficulty with indirect comparisons is that they are subject to greater bias (especially selection bias) compared to head-to-head randomized comparisons, as the benefit of randomization does not hold across the trials.

The indirect comparisons performed were based on the hazard ratios for median survival and applied to a common comparator, which in this evaluation was best supportive care. Hazard ratios represent the most accurate of these measures for comparing survival across treatment, because they are specifically designed to allow for censoring and time to an event. The method applied in this study was based on that proposed by Bucher et al., (1997).

Suppose T_{BA} is the result of a direct comparison of intervention B versus A and T_{CA} is the direct comparison of intervention C versus A. Then, the estimate of the adjusted indirect comparison of intervention B versus C (T'_{BC}) is calculated by:

$$T'_{BC} = T_{BA} - T_{CA}$$

And its standard error is:

$$SE\ (T'_{BC}) = \sqrt{(SE\ (T_{BA})^2 + SE\ (T_{CA})^2)}$$

Where SE (T_{BA}) and SE (T_{CA}) are the standard errors of T_{BA} and T_{CA} respectively (Song et al., 2003).

The baseline absolute hazard (h) and its variance was calculated according to the following formulae:

$$h = -LN(0.5) / t$$

$$Var(h) = h2/r$$

Where t = median weeks survival; r = number of events.

Using this approach, the baseline absolute hazard (h) can then be converted into a mean survival time for time to disease progression and overall survival, by simply taking the inverse of the hazard (1/h) (Griffin et al., 2006).

An exponential approximation of these data was assumed. Survival estimates were then linked to the time to disease progression. The relative risk of response was used. In the case of the adverse event (AE) data, these data were pooled for each treatment.

Detailed scrutiny of the identified phase III trials was performed to ensure that the patients included in each trial were respectively comparable. All of the trials included patients receiving second-line treatment received in the same doses of the comparator drugs in question. All patients had received at least one chemotherapy drug previously.

The tables below summarise the key evidence from the studies identified in the systematic review of the clinical evidence, both pooled absolute values and indirect comparison of trial data. In the interest of brevity of the main submission, additional comparative information on primary hypotheses, randomisation, adequacy of follow-up, blinding of outcomes, parallel-group or cross-over and details of where trials were conducted can be found in Appendix 3.

Table 21: Trial Design

Study	Role in Economic Analysis	Trial design
Hanna et al., (2004)	Base Case	Multinational, randomised, phase III study conducted between March 2001 and February 2002.
Shepherd et al., (2000)	Base Case	Multinational, randomised, phase III study conducted between November 1994 and December 1998. 36 centres participated in the trial: 16 from the United States, 10 from Canada, 3 from Finland, 2 each from the United Kingdom and Poland, and one each from Hungary and Puerto Rico.
Shepherd et al., (2005)	Base Case	International, randomised placebo-controlled, double-blind Phase III trial conducted between August 2001 and January 2003.
Schuette et al., (2005)	Sensitivity Analysis	Multicenter, randomised, Phase III trial involving 19 centers in Germany between April 2000 and September 2003.
Fossella et al., (2000)	Sensitivity Analysis	Multicenter, open-label, randomised Phase III trial involving 23 centers in the United States between June 1995 and January 1998.
Gridelli et al., (2004)	Sensitivity Analysis	Multicenter, randomized controlled clinical trial in Italy between December 2000 and August 2002
Camps et al., (2006)	Sensitivity Analysis	Randomised controlled Phase III trial involving 33 Spanish centres between July 2000 and February 2003.
Thatcher et al., (2005)	Sensitivity Analysis	Double-blind, placebo-controlled, multicentre, randomised controlled Phase III trial involving 210 centres in 28 countries across Europe, Asia, Central and South America, Australia and Canada
Ramlau et al., (2006)	Sensitivity Analysis	Multicentre, randomised Phase III study involving 30 countries outside of the United States between October 31, 2001 and April 30, 2003.

Table 22: Inclusion Criteria

Study	Role in Economic Analysis	Inclusion Criteria
Hanna et al., (2004)	Base Case	Patients with histologic or cytologic confirmation of NSCLC with stage III or IV disease not amenable to curative therapy were assessed for eligibility. Eligible patients met the following criteria: treatment with only one prior chemotherapy regimen for advanced disease (one additional prior regimen was allowed for neoadjuvant, adjuvant or neoadjuvant plus adjuvant therapy); measurable or evaluable disease; an Eastern Cooperative Oncology Group (ECOG) PS of 0 to 2; and adequate bone marrow, renal, and hepatic function.
Shepherd et al., (2000)	Base Case	To be eligible for study, all patients must have received prior treatment with a platinum-containing (cisplatin or carboplatin) chemotherapy regimen. They may have received more than one chemotherapy regiment but could not have been treated previously with taxanes, including paclitaxel. All patients were required to have histologic or cytologic proof of unresectable locally advanced or metastatic NSCLC. Because response was only a secondary end point of this study, patients with both measurable and evaluable indicator lesions were eligible. Each patient was required to have a performance status of 2 or lower on the Eastern Cooperation Oncology Group (ECOG) scale, adequate hematologic parameters (WBC count $\geq 3.5 \times 10^9$/ L, absolute neutrophil count $\geq 2.0 \times 10^9$/L, platelet count $\geq 100{,}000 \times 10^9$/L, serum creatinine level of 2.0 mg/dL or lower, total bilirubin level less than or equal to the institutional upper limit of normal (ULN), and hepatic enayme levels of 1.5 times the ULN or lower (with the exception of alkaline phosphatase, which could be up to five times the ULN). Patients were still considered eligible if they had received prior radiation therapy, provided that 25% or less of their total bone marrow had been irradiated, but had to wait 30 days before entry onto the study. They were also required to wait 21 days before entry onto the study after being treated with any chemotherapy, immunotherapy, or biologic systemic anticancer therapy (42 days for mitmycin and nitrosoureas).
Shepherd et al., (2005)	Base Case	Patients 18 years of age or older with an Eastern Cooperative Oncology Group (ECOG) performance status of 0 and 3 were eligible in the presence of documented pathological evidence of non-small cell lung cancer. The patients had to have received one or two regimens of combination chemotherapy and not be eligible for further chemotherapy. Patients 70 years of age or older may have received therapy with one or two single agents. Patients had to have recovered from any toxic effects of therapy and were randomly assigned to the study treatment at least 21 days after chemotherapy (14 days after treatment with vinca alkaloids or gemcitabine) and 7 days after radiation. Adequate hematologic and biochemical values were required.
Schuette et al., (2005)	Sensitivity Analysis	Patients enrolled had advanced or metastatic NSCLC (confirmed histologically, with a tumor that was measurable by clinical and/or radiologic examination), were aged 18 to 75 years, and had received more than one previous chemotherapy regimen for their disease. Patients who had received prior paclitaxel chemotherapy were permitted providing their disease had not progressed within 3 months of completely paclitaxel treatment. Patients were also required to have an Eastern Cooperative Oncology Group performance status of 0 to 2, and adequate renal, cardiac, hepatic, and hematologic function as indicated by the following parameters: absolute neutrophil count ≥ 2 x 109/L, thrombocytes ≥ 100 x 109/L, hemoglobin $\geq$ 10g/dL, total bilirubin ≤ 1.25 x the upper limit of normal range (ULN), ALT and AST ≤ 1.5 x ULN, alkaline phosphatase ≤ 5 x ULN, creatinine ≤ 1.15 x ULN.

Study	Role in Economic Analysis	Inclusion Criteria
Fossella et al., (2000)	Sensitivity Analysis	Eligible patients had locally advanced or metastatic NSCLC that had progressed during or after one or more platinum-based regimens. Before study entry, a minimum of 21 days must have elapsed since any prior chemotherapy. Patients may have had either measurable or assessable lesions. Eastern Cooperative Oncology Group performance status of 0 to 2 was required, as was adequate bone marrow (absolute granulocyte count of ≥2.0 x 10^9 cells/L and platelet count of ≥100 x 10^9 cells / L), hepatic (total bilirubin level within normal limits, alkaline phosphatase level ≤ five times the upper limit of normal, and serum transaminase ≤ 1.5 times the upper limit of normal), and renal (serum creatinine level ≤ 2.0 mg/dL or creatinine clearance ≥ 60 mL/min) function. No restriction was based on the number of prior chemotherapy regimens, the amount of prior chemotherapy, or the agents used (which may have included paclitaxel). Patients who had received prior radiation therapy were eligible provided that at least 30 days had elapsed from completion of radiation to study entry. Patients with treated brain metastases were eligible provided that they were neurologically stable.
Gridelli et al., (2004)	Sensitivity Analysis	Patients younger than 75 years were required histological or cytological proof of NSCLC, stage IV or IIIB with malignant pleural effusion and/or metastatic supraclavicular lymphnodes, evidence of progressive disease durin or after first-line chemotherapy, ECOG performance status 0-2, adequate haematology (absolute neutrophil count ≥ 2000mm^{-3}, platelets ≥ 100 000mm^{-3} and haemoglobin ≥10gdl^{-1}) and bichemistry (serum creatinine ≤1.25 x upper normal limt, SGOT and SGPT and bilirubin ≤1.25 x upper normal limt, unless due to liver metastases), availability to complete QoL questionnaires, written informed consent. Complete history and physical examination, routine haematology and biochemistry, staging with chest radiographs, chest, brain and abdominal computed tomography (CT), and QoL assessment were required before randomisation.
Camps et al., (2006)	Sensitivity Analysis	All patients had histologically or cytologically confirmed recurrent advanced NSCLC previously treated with at least one platinum-based chemotherapy regimen that did not include docetaxe. Before study entry, a minimum of 28 days had to have elapsed since previous chemotherapy. In addition, patients had to have measurable or evaluable disease, an Eastern Cooperative Oncology Group (ECOG) PS ≤2, be older than 18 years, and have a life expectancy of at least 12 weeks. Adequate hematologic (absolute neutrophil count ≥1500/ml, platelet count > 100 000/ml), hepatic (total bilirubin level ≤1.5 x the upper limit of normal), and renal (creatinine concentration ≤2 x the upper limit of normal) parameters were required.
Thatcher et al., (2005)	Sensitivity Analysis	The study included patients aged 18 years or older with histologically or cytologically proven, locally advanced or metastatic NSCLC that was not curable with surgery or radiotherapy, who had receied one or two previous chemotherapy regimens and who were refractory to (defined as recurrent or progressive disease within 90 days of the last chemotherapy dose) or intolerant of their latest chemotherapy regimen. The patients had WHO performance status of 0-2 (those were performance status 3 were also eligible if the investigator believed that poor performance status was not predominantly due to comorbidity(and a life expectancy of at least 8 weeks.

Study	Role in Economic Analysis	Inclusion Criteria
Ramlau et al., (2006)	Sensitivity Analysis	Eligible patients had histologically or cytologically confirmed stage III or IV NSCLC with measurable or nonmeasurable disease, were not candidates for curative surgery or radiotherapy, and met the following inclusion crtieria: ≥ 18 years old, disease progression after one line of standard chemotherapy (cisplatin not mandatory), Eastern Cooperative Oncology Group PS ≤2, hemoglobin ≥ 9.0 g/dL, WBC count ≥ 3,500/µL, platelets ≥ 100,000/µL, neutrophils ≥1500/µL, serum creatinine ≤ 1.5mg/dL, and creatinine clearance (CrCl) ≥ 60mL/min, serum bilirubin within normal limits, AST and ALT ≤ 1.5 x upper limit of normal (ULN), alkaline phosphatase ≤2.5 x ULN, and life expectancy of ≥ 3 months. Prior radiotherapy was allowed if ≥ 24 hours had passed, marked bone marrow suppression was not expected, and the patient had recovered from reversible toxic effects. Measurable or nonmeasurable disease could be in the field of radiation if ≥6 weeks had elapsed and disease progression was confirmed radiologically.

Table 23: Exclusion Criteria

Study	Role in Economic Analysis	Exclusion Criteria
Hanna et al., (2004)	Base Case	Patients with prior docetaxel or pemetrexed treatment, Common Toxicity Criteria (CTC) ≥ grade 3 peripheral neuropathy, an inability to interrupt nonsteroidal anti-inflammatory drugs, uncontrolled pleural effusions, symptomatic or uncontrolled brain metastases, or significant weight loss (≥10% body weight in the preceding 6 weeks) were ineligible.
Shepherd et al., (2000)	Base Case	Patients were excluded if they had symptomatic or uncontrolled brain metastases or peripheral neuropathy greater than National Cancer Institute grade 2.
Shepherd et al., (2005)	Base Case	Patients with prior breast cancer, melanoma, or hypernephroma were ineligible, as were those with other malignant diseases (except basal-cell skin cancer) within the preceding five years. Other exclusion criteria were symptomatic brain metastases, clinically significant cardiac disease within one year, ventricular arrhythmias requiring medication, and clinically significant ophthalmologic or gastrointestinal abnormalities.
Schuette et al., (2005)	Sensitivity Analysis	Exclusion criteria were: disease progression while undergoing prior paclitaxel chemotherapy, known brain metastases or secondary neoplasia, myocardial insufficiency or myocardial infarction within the preceding 6 months, severe renal or hepatic insufficiency, pre-existing motor or sensor neurotoxicity ≥ WHO grade 2, severe psychologic disease, active infection, or other condution that could compromise protocol compliance, simultaneous administration of other antineoplastic medications, and pregnancy and/or lactation.
Fossella et al., (2000)	Sensitivity Analysis	NR
Gridelli et al., (2004)	Sensitivity Analysis	Patients with symptomatic brain metastases or prior invasive malignancies were excluded.

Study	Role in Economic Analysis	Exclusion Criteria
Camps et al., (2006)	Sensitivity Analysis	Patients were excluded if they had symptomatic or uncontrolled brain metastases or peripheral neuropathy equal to or greater than the National Cancer Institute grade 2. Patients who had received prior radiation therapy were considered eligible provided 30% or less of their total bone marrow had been irradiated, but 28 days had to have elapsed after radiation therapy before entering the study.
Thatcher et al., (2005)	Sensitivity Analysis	Exclusion criteria were: presence of small-cel lung cancer alone or with NSCLC; administration of the last dose of single-agent chemotherapy within the previous 14 days or combination chemotherapy within the previous 21 days; untreated or clinically unstable newly diagnosed metastases in the central nervous system; less than 1 week since completion of previous radiotherapy or persistence of any radiotherapy-related toxic effects; unresolved chronic toxic effects from previous anticancer therapy; known serious hypersensitivity to gefitinib or any of the table excipients; inability to swallow tablets; other coexisting malignant disease (apart from basal-cell carcinoma); absolute neutrophil count less than 1.0 x 109/L or platelet count less than 100 x 109/ L, serum bilirubin concentration more than 3 times the upper limit of the reference range(at the local laboratory for the study centre); and alanine or aspirate aminotransferase concentration more than 5 times the upper limit of the reference range; more than 2 previous chemotherapy regimens for NSCLC, previous treatment with an experimental agent of which the main mechanism of action is inhibition of epidermal growth factor receptor or its associated tyrosine kinase; concomitant use of phenytoin, carbamazepine, rifampicin, barbiturates, or St John's wort; sever or uncontrolled systemic disease; clinically active interstitial lung disease (except uncomplicated lymphangitic carcinomatosis)pregnancy; and breast feeding.
Ramlau et al., (2006)	Sensitivity Analysis	Patients were excluded for symptomatic CNS metastases, concomitant or previous malignancies other than NSCLC within the last 5 years (except for adequately treated basal or squamous cell carcinoma of the skin, carcinoma-in-situ of the cervix, or localized low-grade prostate cancer), prior taxane treatment, pre-existing grade ≥ 2 neuropathy (National Cancer Institute Common Toxicity Criteria), infection, severe comorbidities, GI conditions affecting absorption, hypersensitivity, or other contraindication to study. Concomitant chemotherapy, radiotherapy, or immunotherapy was not allowed.

Table 24: Patient Characteristics

Study	Role in Economic Analysis	Number of treatment cycles	Demographics	Disease Severity etc.	Histologic type
Hanna et al., (2004) (Pemetrexed) (n=283)	Base Case	The median number of cycles of chemotherapy was 4 in each group with a range of 1 to 20 Patients received 96.6% of the planned dose-intensity of pemetrexed.	Male = 68.6% Female = 31.4% Median age = 59 Range= 22-81	Performance status 0 or 1 = 88.6% 2 = 11.4% Stage IV = 74.9%	Time since last chemotherapy < 3 months = 50.4% Histology Adenocarcinoma = 54.4% Squamous cell carcinoma = 27.6% Homocysteine levels < 12 µmol/L = 68.9% Prior radiation = 45.5%
Hanna et al., (2004) (Docetaxel) (n=288)	Base Case	The median number of cycles of chemotherapy was 4 in each group with a range of 1 to 14 Patients received 94.4% of the planned dose-intensity of docetaxel	Male = 75.3% Female = 24.7% Median age = 57 Range= 28-87	Performance status 0 or 1 = 87.6% 2 = 12.4% Stage IV = 74.7%	Time since last chemotherapy < 3 months = 48.1% Histology Adenocarcinoma = 49.3% Squamous cell carcinoma = 32.3% Homcysteine levels < 12 µmol/L = 68.9% Prior radiation = 45.5%.
Shepherd et al., (2000) (n=55) Docetaxel 75mg/m^2 arm	Base Case	A total of 451 treatment cycles was administered. The 55 patients treated with docetaxel 75mg/m^2 received a median of four treatment cycles. At both doses (75mg/m^2 and 100mg/m^2) treatment could be delivered every 3 weeks in approximately 90% of cycles	Sex Male (n=35, 63.6%) Female (n=20, 36.4%) Median age = 61 Range=37-73	Stage IIIA / B = 15 (27.3%) IV = 40 (72.7%) Performance status 0 = 13 (23.6%) 1 = 28 (50.9%) 2 = 14 (25.5%)	No. of prior regimens 1 = 44 (80.0%) 2 = 7 (12.7%) ≥ 3 = 4 (7.3%) Best response to cisplatin PR/CR = 14 (25.5%) NC = 31 (56.4%) PD = 10 (18.2%)

Study	Role in Economic Analysis	Number of treatment cycles	Demographics	Disease Severity etc.	Histologic type
Shepherd et al., (2000) (n=100) BSC Arm	Base Case	N/A	Sex Male (n=65, 65.0%) Female (n=35, 35%) Median age = 61 Range=28-77	Stage IIIA / B = 19 (19.0%) IV = 81 (81.0%) Performance status 0 = 22 (22.0%) 1 = 53 (53.0%) 2 = 25 (25.0%	No. of prior regimens 1 = 76 (76.0%) 2 = 15 (15.0%) ≥ 3 = 9 (9.0%) Best response to cisplatin PR/CR = 37 (37.0%) NC = 43 (43.0%) PD = 20 (20.0%)
Shepherd et al., (2005) (n=488)	Base Case	Erlotinib	Age (yr) Median = 62 Range = 34-87 < 60 (% of patients) = 42.6 ≥ 60 (% of patients) = 57.4 Sex (% of patients) Male = 64.5 Female = 35.5 Race or ethnic group (% of patients) Asian = 12.9 Other = 87.1	Performance status (% of patients) 0 = 13.1 1= 52.5 2= 25.8 3= 8.6 Weight loss >10% of patients = 11% EGFR protein expression (% of patients) Positive = 24% Negative = 19.1% Unknown = 56.9%	Pathological subtype (% of patients) Adenocarcinoma = 50.4% Squamous-cell carcinoma = 29.5% Other = 20.1% Prior chemotherapy (% of patients) 1 regimen = 50.6% 2 or more regimens = 49.4% Platinum-based therapy = 92.0% Response to prior chemotherapy (% of patients) Complete or partial response = 38.1% Stable disease = 34.0% Progressive disease = 27.9% Smoking status (% of patients) Current smoker or ever smoked = 73.4% Never smoked = 21.3% Unknown = 5.3%

Study	Role in Economic Analysis	Number of treatment cycles	Demographics	Disease Severity etc.	Histologic type
Shepherd et al., (2005) (n=243)	Base Case	Placebo	Age (yr) Median = 59 Range = 32-89 < 60 (% of patients) = 51.0 ≥ 60 (% of patients) = 49.0 Sex (% of patients) Male = 65.8 Female = 34.2 Race or ethnic group (% of patients) Asian = 12.2 Other = 87.8	Performance status (% of patients) 0 = 14.0 1= 54.3 2= 23.0 3= 8.6 Weight loss >10% of patients = 12% EGFR protein expression (% of patients) Positive = 27.6% Negative = 19.8% Unknown = 52.6%	Pathological subtype (% of patients) Adenocarcinoma = 49.0% Squamous-cell carcinoma = 32.1% Other = 18.9% Prior chemotherapy (% of patients) 1 regimen = 50.2% 2 or more regimens = 49.8% Platinum-based therapy = 91.8% Response to prior chemotherapy (% of patients) Complete or partial response = 37.9% Stable disease = 34.2% Progressive disease = 28.0% Smoking status (% of patients) Current smoker or ever smoked = 77.0% Never smoked = 17.3% Unknown = 5.8%
Schuette et al., (2005) (n=103). Docetaxel 75mg/m^2	Sensitivity Analysis	4 (1-8) 32.0% of patients received ≥ 6 treatment cycles	Age, years Median = 63 Range = 42-80 Sex Male = 73.8% Female = 26.2%	ECOG PS 0 = 34 (33.0%) 1 = 55 (53.4%) 2 = 12 (11.7%) Nonassessable = 2 (1.9%)	Squamous cell carcimona = 42 (40.8%) Adenocarcinoma = 31 (30.1%) Large cell = 9 (8.7%) Other = 21 (20.4%)

Study	Role in Economic Analysis	Number of treatment cycles	Demographics	Disease Severity etc.	Histologic type
Fossella et al., (2000) (n=125)	Sensitivity Analysis	The median number of cycles was 3 in each docetaxel group (range 1-28). Responding patients received a median of 10 cycles of chemotherapy. Patients with stable disease received a median of 6 cycles of chemotherapy.	Age, years Median = 59 Sex Male = 65.6% Female = 34.4%	Performance status 2 = 18% Stage IV = 90%	Histology Adenocarcinoma = 56% Squamous = 18% Other = 26% ≥ 3 organs involved = 33% Prior chemotherapy ≥ 2 prior chemotherapy regimens = 26%
Gridelli et al., (2004)	Sensitivity Analysis	69% of patients received at least half of the planned therapy (3 cycles)	Age, years Median = 62 Range = 26-74 Sex Male = 88 (80%) Female = 22 (20%)	PS 0 = 35 (32%) 1 = 58 (53%) 2 = 17 (15%)	Stage IIIB = 21 (19%) IV = 89 (81%) Histotype Squamous / epidermoid = 31 (28%) Adenocarcinoma = 58 (53%) Large cells = 3 (3%) Mixed = 3 (3%) Undefined = 15 (14%) Previous treatment with platinum No = 16 (15%) Yes = 94 (85%)

Study	Role in Economic Analysis	Number of treatment cycles	Demographics	Disease Severity etc.	Histologic type
Camps et al., (2006) (n=129)	Sensitivity Analysis	A total of 577 cycles were administered in the docetaxel 75mg/m^2 with a median number of 3 cycles.	Age, years Median = 61 Sex Male = 93% Female = 7%	ECOG performance status 0 = 31 (24%) 1 = 77 (59.7%) 2 = 21 (16.3%)	Number of prior lines (n, %) 1 = 113 (87.6%) 2 = 16 (12.4%) 3 – Platinum-based CT = 122 (94.6%) Paclitaxel-based CT = 19 (15%) Time from PD to CT = 2.9 Range = 0-88.7) Metastatic sites Lymph nodesLiver Adrenal Brain 1 metastatic site = 27 (20.9%) 2 metastatic sites = 34 (26.4%) >2 metastatic sites = 68 (52.7%)
Thatcher et al., (2005) (n=563)	Sensitivity Analysis	N/A	Age, years Median = 61 Sex Male = 67% Female = 33%	WHO performance status 0 = 70 (12%) 1 = 318 (56%) 2 = 145 (26%) ≥3 = 29 (5%)	Histology Adenocarcinoma = 255 (45%) Bronchioalveloar = 16 (3%) Squamous cell = 187 (33%) Large cell = 33 (6%) Mixed = 13 (2%) Undifferentiated = 58 (10%) Current disease status Locally advanced = 113 (20%) Metastatic = 450 (80%) Number of previous chemotherapy regimens 0 = 1 1 = 274 (49%) 2 = 281 (50%) ≥3 = 7 (1%)

Study	Role in Economic Analysis	Number of treatment cycles	Demographics	Disease Severity etc.	Histologic type
Ramlau et al., (2006)	Sensitivity Analysis	The median number of cycles received was 4 (range 1-19).	Age, years Mean = 58.7 SD = 9.5 Range = 24-82 Sex Male = 310 (75%) Female = 105 (25%)	Performance status 0 = 76 (18%) 1 = 273 (66%) 2 = 65 (16%) 4 = 1 (<1%)	Stage Locally advanced unresectable = 117 (28%) Metastatic = 298 (72%) Histology Adenocarcinoma = 159 (38%) Squamous cell carcinoma = 181 (44%) Large cell carcinoma = 37 (9%) Other = 37 (9%) Missing = 1 (<1%) Prior cancer therapy 1 prior chemotherapy regimen = 414 (99%) > 1 prior chemotherapy = 1 (<1%) Surgery = 165 (40%) Radiotherapy = 147 (35%)

Table 25: Patient Numbers

Study	Role in Economic Analysis	Numbers of patients eligible to enter the trial	Numbers of patients randomised	Number of patients allocated to each treatment
Hanna et al., (2004)	Base Case	571	571	265 of 283 patients randomly assigned to pemetrexed received at least one cycle of therapy (18 patients received no treatment due to: failure to meet inclusion criteria [n=7], death from disease [n=5], other adverse events [n=3], personal conflict [n=2], or protocol violation [n=1]. 276 of 288 patients randomly assigned to docetaxel received at least one cycle of therapy (12 patients received no treatment due to failure to meet inclusion criteria [n=2], death from disease or any cause [n=2], personal conflict [n=5], loss to follow-up [n=3]. At the time of analysis, 409 (71.6%) of 571 patients had died. All 571 patients were assessable for survival, and 538 of 541 patients (n=265 for pemetrexed, 276 for docetaxel) who received therapy were assessable for response.
Shepherd et al., (2000)	Base Case	NR	204	100 randomised to the BSC arm and 104 to the docetaxel arm (49 at 100mg/m^2 and 55 at 75mg/m^2).
Shepherd et al., (2005)	Base Case	NR	731	731 patients were randomly assigned to erlotinib (488) or placebo (243). 22 patients (12 assigned to erlotinib and 10 assigned to placebo) were ineligible for the following reasons; 3 prior chemotherapy regimens (9); single-agent chemotherapy for patients less than 70 years of age (2); inadequate time since the last treatment (5); abnormal biochemistry results (4); and symptomatic brain metastases (2). All 731 patients were included in the efficacy analyses, and 727 treated patients (485 assigned to erlotinib and 242 assigned to placebo) were included in the safety analyses. 8 patients assigned to erlotinib (1.6%) and 18 assigned to placebo (7.4%) received other EGFR inhibitors after study medication was discontinued. 4 patients who underwent randomization did not receive treatment.
Schuette et al., (2005)	Sensitivity Analysis	215	215	107 patients were allocated to the docetaxel 3-weekly schedule. Of these 1 was ineligible, 1 died before treatment started and 2 withdrew their consent. 103 patients were analysed for efficacy and 102 analysed for toxicity. 108 patients were allocated to the docetaxel weekly schedule. Of these 1 was ineligible, 1 died before treatment started and 1 withdrew his/her consent. 105 patients were analysed for efficacy and 105 analysed for toxicity.

Study	Role in Economic Analysis	Numbers of patients eligible to enter the trial	Numbers of patients randomised	Number of patients allocated to each treatment
Fossella et al., (2000)	Sensitivity Analysis	373	373	125 patients were allocated to docetaxel 100mg/m^2, 125 were allocated to docetaxel 75mg/m^2 and 123 patients were allocated to V/I. All patients were included in the survival analysis. Three randomised patients (one in each arm) did not have NSCLC and so, were excluded from the time to disease progression analysis (n=370). Twelve patients never received treatment after randomization (4 patients per arm), and they have been excluded from the safety analysis (n=361). The 12 nontreated patients and the 3 treated patients without a diagnosis of NSCLC were excluded from the response assessment analysis (n=358).
Gridelli et al., (2004)	Sensitivity Analysis	NR	220	220 patients were randomized; 21 were found ineligible after randomization because they had not filled in baseline QoL (16 cases), progressed during adjuvant chemotherapy (two cases) or during second-line chemotherapy (two cases) and one case because of a previous neoplasm. After randomization, 3 patients did not receive the assigned treatment. In the 3-week arm, two refused treatment, one suffered progression of brain metastases and one had acute clinical deterioration, before starting chemotherapy.
Camps et al., (2006)	Sensitivity Analysis	NR	131	131 patients were randomized of which 129 received the treatment as allocated.
Thatcher et al., (2005)	Sensitivity Analysis	1,836	563	1 patient did not start treatment.
Ramlau et al., (2006)	Sensitivity Analysis	NR	829	829 patients were randomly assigned; 414 to topotecan and 415 to docetaxel. Of the 415 patients allocated to the docetaxel treatment, 14 received no treatment and 23 had protocol violation. 415 patients were assessed for efficacy (ITT), 401 assessed for dose exposure, safety (modified ITT) and 376 assessed for QoL (modified ITT excluding single centre).

Table 26: Study Endpoints: Primary

Study	Role In Economic Analysis	Study Endpoints: Primary	Methods Used
Hanna et al., (2004)	Base Case	Overall survival	Unless otherwise noted, all tests of hypotheses were conducted at the alpha level = 0.05, with a 95% CI. Cox proportional models were used to compare the overall survival time and other time-to-event end points between the treatment arms. Kaplan-Meier estimates were used to assess the median time to event parameters, except for time to response using analysis of variance. The overall survival time was defined as the time from the date of randomisation to date of death due to any cause. Patients who were alive on the date of last follow-up were censored on that date.
Shepherd et al., (2000)	Base Case	Survival	Survival was calculated from the date of randomisation until the date of death. Survival time was censored for loss of contact or initiation of antitumor therapy, including subsequent chemotherapy, immunotherapy, or surgery.
Shepherd et al., (2005)	Base Case	Overall Survival	NR
Schuette et al., (2005)	Sensitivity Analysis	1-year survival and median survival.	Overall survival was assessed using the Kaplan-Meier method.
Fossella et al., (2000)	Sensitivity Analysis	Survival.	Survival was calculated from the date of randomisation until death. The survival time was estimated for each treatment using the Kaplain-Meier method. The overall survival curves estimated by this method were compared between treatment groups by a log-rank test. A descriptive point of the K-M curve, such as median survival (50^{th} percentile in each distribution) is shown with 95% confidence intervals. Other descriptive points such as differences in progression-free survival at 26 weeks and the 1-year survival rates were compared between treatments by a X^2 test in a post-hoc analysis.
Gridelli et al., (2004)	Sensitivity Analysis	Quality of life	The primary endpoint of the study was quality of life. Three instruments were applied. The EORTC QLQ-C30, the EORTC QLQ-LC13 and the daily diary card (DDC). The EORTC QLQ-C30 explores functional scales (physical, role, emotional, social, and cognitive functioning) symptoms (fatigue, pain, emesis, dyspnea, insomnia, appetite, diarrhea, constipation), financial impact, and global health status. The EORTC QLQ-LC13 assesses lung cancer symptoms. Scores were computed according to EORTC rules. Questionnaires were administered before randomization and 3 weeks after beginning of therapy in both arms; a third questionnaire was administered before the third cycle in the 3-week arm and before the second cycle in the weekly arm. The Daily diary card was designed by the Medical Research Council Lung Cancer Working Party to capture rapid and transient changes of sleeping, mood, well-being, level of activity, nausea, vomiting, appetite loss and pain. DDC was collected after 3 and 6 weeks.
Camps et al., (2006)	Sensitivity Analysis	1 year survival	1-year survival was calculated using the Kaplan-Meier method. One year survival rates and 95% CI were compared between groups for the difference between proportions.
Thatcher et al., (2005)	Sensitivity Analysis	Overall survival	Assessed from the date of randomization to the date of a patient's death; participants alive at data cut-off were censored in the analysis at the last time they were known to be alive.
Ramlau et al., (2006)	Sensitivity Analysis	1 year survival	

Table 27: Study Endpoints: Secondary

Study	Role In Economic Analysis	Study Endpoints: Secondary	Methods Used
Hanna et al., (2004)	Base Case	Toxicities (including use of concomitant supportive measures), objective response rates, progression-free survival, time to progressive disease, time to treatment failure, time to response, duration of response, and quality of life measurements.	PFS was the time from randomisation until documented progression or death from any cause and was censored at the date of the last followup visit for patients who were still alive and who had not progressed. TPD was defined as the time from the date of randomisation to the first 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. TTF was defined as the time from randomisation 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. Tumor response was assessed using the Southwest Oncology Group criteria and required confirmation at least 4 weeks after initial response (Complete response defined as complete disappearance of all measurable and evaluable disease; partial response defined as ≥50% decrease in the sum of products of perpendicular diameters of all measurable lesions; progressive disease defined as 50% increase in the sum of products of all measurable lesions, or worsening of evaluable disease, or appearance of nay new lesions; and stable disease defined as not qualifying for CR, PR, or PD. Duration of tumor response was defined as the time from the date of the first objective status assessment of CR or PR until the first date of documented disease progression or death due to any cause and was censored at the date of the last follow-up visit for tumor responders who were still alive and had not progressed. As far as quality of life was concerned, for each patients, LCSS scores were rated as improved, stable or worsened based on comparison with baseline. The average symptom burden index (ASBI) was the average of the six symptom-specific questions regarding anorexia, fatigue, cough, dyspnea, hemoptysis, and pain. Meaningful change for the ASBI was defined as at least half of the SD of the baseline. ASBI for all patients that was maintained for at least 4 consecutive weeks. Meaningful change for observer LCSS scales was defined as at least a one-point change on the five-point scale that was maintained for at least two cycles. Changes in LCSS scores that could not be confirmed were classified as unknown.
Shepherd et al., (2000)	Base Case	Objective tumor response and duration of response, as well as changes in QOL determined on the basis of the QOL instruments, changes in performance status and weight, and changes in analgesic use.	Objective tumor response and duration of response were assessed only in the docetaxel arm. Standard World Health Organization response criteria were applied, and all responses had to be confirmed in 28 days or more after the initial documentation of response. Response duration was calculated from the date of randomisation until the date of documentation of disease progression.

Study	Role In Economic Analysis	Study Endpoints: Secondary	Methods Used
Shepherd et al., (2005)	Base Case	Secondary end points included progression-free survival, overall response rate (complete and partial), duration of response, toxic effects, and quality of life.	Responses were assessed with the use of the Response Evaluation Criteria in solid tumors (RECIST), and toxic effects were assessed according to the Common Toxicity Criteria of the National Cancer Institute (Version 2.0). The European Organization for Research and Treatment of Cancer (EORTC) quality-of-life questionnaire (QLQ-C30) and the quality-of-life questionnaire for patients with lung cancer (QLQ-LC13) were used to evaluate patients' quality of life.
Schuette et al., (2005)	Sensitivity Analysis	Tumor response, time to progression, toxicity, and quality of life.	Tumor response was assessed after every second cycle using International Union Against Cancer standard criteria. Complete response (CR) was defined as the disappearance of all tumor indications, confirmed by two examinations ≥ 4 weeks apart. Partial response (PR) was defined as an estimated ≥ 50% decrease in tumor size, confirmed by two examinations ≥ 4 weeks apart with no new lesions detected. Progressive disease was defined as the appearance of any new tumor lesions or a ≥ 25% increase in the size of existing tumor lesions. Where responses did not quality as CR, PR, or progressive disease (i.e., no significant changes over ≥ 4 weeks), they were reported as stable disease. Toxicity was assessed after every cycle and graded using WHO criteria. Quality of life was self-assessed using the European Organisation for Research and Treatment of Cancer (EORTC) QLQ C-30 questionnaire at baseline, after every second cycle and at the end of treatment in both treatment arms. After completion of therapy, patients were monitored at 12-weekly intervals until disease progression or death.
Fossella et al., (2000)	Sensitivity Analysis	Response rate, response duration, time to progression, and toxicity.	Tumor responses were assessed radiographically every 2 cycles. Designations of complete response, partial response, no change, and progressive disease were based on the standardized response definitions established by the World Health Organization. Duration of response and time to progression were calculated as time from randomization to the first objective evidence of tumor progression. Toxicity evaluations were based on the National Cancer Institute's common toxicity criteria. Adverse events not included in that toxicity scale (e.g. fluid retention, hypersensitivity reaction, onychodystophy, and asthenia) were graded as mild (grade 1), moderate (grade 2), severe (grade 3), or life-threatening (grade 4).
Gridelli et al., (2004)	Sensitivity Analysis	Overall survival, response rates, toxicity.	Overall survival was defined as the interval from date of randomization and death of death or date of last follow-up information for living patients. Objective response, categorized according to RECIST was evaluated at the end of the third and sixth cycles of treatment (approximately 9 and 18 weeks) in the standard arm and after six and 12 administrations (approximately 8 and 16 weeks) in the experimental arm. The best response was recorded for each patient and confirmation was not performed. Patients who stopped treatment because of toxicity or refusal or death before restaging were defined as nonresponders in the calculation of response rate. Time to disease progression was not described or analysed because of the bias determined by the unequal cycle duration in the two treatment arms. For toxicity assessment, haematology was repeated weekly and biochemistry at 3 and 6 weeks in both arms. Toxicity was coded according to NCI-CTC. The worst degree of toxicity experienced during the treatment was computed for each patient.

Study	Role In Economic Analysis	Study Endpoints: Secondary	Methods Used
Camps et al., (2006)	Sensitivity Analysis	Time to progression, median survival and duration of response	Time to progression was calculated from the date of randomization until progression or death due to malignant disease; patients who received follow-up therapy prior to documented disease progression were censored at the time of the secondary therapy. Median survival was calculated from the date of randomization until progression or death due to malignant disease; patients who received follow-up therapy prior to documented disease progression were censored at the time of randomization to the date of death or date of last contact. Duration of response was calculated from the date of the first response until progression or death due to malignant disease. All secondary end point calculations were performed using the Kaplan-Meier method. All randomly assigned patients who received at least one dose of docetaxel were included in the intention-to-treat survival and efficacy analysis. Patients who received one dose of docetasxel were also analysed for safety. Adverse events between treatment arms were compared using Fisher's exact test for 2 x 2 tables.
Thatcher et al., (2005)	Sensitivity Analysis	Time to treatment failure, objective response rate, quality of life and tolerability	Time to treatment failure was calculated as the time from the date of randomization to the date at which the patient discontinued therapy owing to unacceptable toxic effects, no further clinical benefit (assessed by an investigator), the patient's choice, or death from any cause. Tumor progression (as defined by RECIST criteria) was not necessarily classed as treatment failure; patients could continue to receive treatment as long as they continued to derive clinical benefit. Patients in whom treatment had not failed at data cut-off were censored for time to treatment failure at the time of their last on-study visit. Tumours were assessed at baseline; the specific imaging modality was at the discretion of the investigator. The protocol recommended that subsequent imaging was undertaken at least every 8 weeks. The rate of objective responses (defined as all patients with complete responses plus those with partial responses) was calculated according to standard criteria. Changes in quality of life (assessed with the functional assessment of cancer therapy, lung questionnaire) and disease-related symptoms (assessed with the seven-item lung-cancer subscale of the questionnaire) were assessed every 4 weeks. For changes in disease-related symptoms to be classed as clinically relevant, the score on the lung-cancer subscale had to increase by at least 2 points. Adverse events were monitored and graded by the National Cancer Institute common toxicity criteria version 2.0 and coded according to the Medical Dictionary for Regulatory Activities terminiology. Routine laboratory monitoring (including biochemistry, haematology, and urine analysis) was done.
Ramlau et al., (2006)	Sensitivity Analysis	Overall survival (all-cause mortality), time to disease progression, response rate, response duration, time to response, quality of life, and toxicities.	Randomly assigned patients were observed until at least 1 year after randomization, and then until death. Patients were observed every 3 months after completing treatment.

Table 28: Drug Regimens Used In The Trials

Study	Role In Economic Analysis	Drug	Dosage Regimen	Are they within those detailed in the Summary of Product Characteristics?
Hanna et al., (2004)	Base Case	Pemetrexed 500mg/m^2	Pemetrexed 500mg/m^2 as a 10-minute intravenous infusion	Yes
Hanna et al., (2004)	Base Case	Docetaxel 75mg/m^2	Docetaxel 75mg/m^2 given as a 1-hour infusion on day 1 every 3 weeks (3-weekly).	Yes
Shepherd et al., (2000)	Base Case	Docetaxel 75mg/m^2	Docetaxel 75mg/m^2 given intravenously over 1 hour every 3 weeks.	Yes
Shepherd et al., (2000)	Base Case	BSC	Patients randomized to the BSC arm were treated with whichever therapy was judged to be appropriate by the treating physician. This treatment could have included treatment with antibiotics, analgesic drugs, transfusions and palliative radiotherapy.	N/A
Shepherd et al., (2005)	Base Case	Erlotinib 150mg	Oral erlotinib, at a dose of 150mg daily.	Yes
Shepherd et al., (2005)	Base Case	BSC	NR	N/A
Schuette et al., (2005)	Sensitivity Analysis	Docetaxel 75mg/m^2	Docetaxel 75mg/m^2 given intravenously on day 1 every 3 weeks (3-weekly).	Yes
Fossella et al., (2000)	Sensitivity Analysis	Docetaxel 75mg/m^2	Docetaxel 75mg/m^2 given as a 1-hour infusion on day 1 every 3 weeks (3-weekly).	Yes
Gridelli et al., (2004)	Sensitivity Analysis	Docetaxel 75mg/m^2	Docetaxel 75mg/m^2 given as a 1-hour infusion on day 1 every 3 weeks (3-weekly).	Yes
Camps et al., (2006)	Sensitivity Analysis	Docetaxel 75mg/m^2	Docetaxel 75mg/m^2 given as a 1-hour infusion on day 1 every 3 weeks (3-weekly).	Yes
Thatcher et al., (2005)	Sensitivity Analysis	BSC	NR	N/A
Ramlau et al., (2006)	Sensitivity Analysis	Docetaxel 75mg/m^2	Docetaxel 75mg/m^2 given as a 1-hour infusion on day 1 every 3 weeks (3-weekly).	Yes

Table 29: Median Duration of Follow-Up

Study	Role in Economic Analysis	Treatment	Median follow-up (Range)
Hanna et al., (2004)	Base Case	Pemetrexed 500mg/m^2 vs. Docetaxel 75mg/m^2	7.5 months.
Shepherd et al., (2000)	Base Case	Docetaxel 75mg/m^2 vs. BSC	NR
Shepherd et al., (2005)	Base Case	Erlotinib vs. BSC	NR
Schuette et al., (2005)	Sensitivity Analysis	Docetaxel 75mg/m^2	8 months. All surviving patients had a minimum follow-up time of 12 months.
Fossella et al., (2000)	Sensitivity Analysis	Docetaxel 75mg/m^2	On removal from the study, patients were to be observed every 2 months until death to assess adverse events, quality of life, disease status, and survival.
Gridelli et al., (2004)	Sensitivity Analysis	Docetaxel 75mg/m^2	NR
Camps et al., (2006)	Sensitivity Analysis	Docetaxel 75mg/m^2	NR
Thatcher et al., (2005)	Sensitivity Analysis	BSC	7.2 months
Ramlau et al., (2006)	Sensitivity Analysis	Docetaxel 75mg/m^2	NR

Table 30: Median Overall Survival: Indirect comparison of Absolute Values Extracted From the Phase III Studies

Trial	Product	N	Survival (Months)	Lower Range (Months)	Upper Range (Months)	Survival (Weeks)	Lower Range (Weeks)	Upper Range (Weeks)
Hanna et al., (2004)	Pemetrexed 500mg/m^2	283	8.3	NR	NR	35.97	NR	NR
Hanna et al., (2004)	Docetaxel 75mg/m^2	288	7.9	NR	NR	34.23	NR	NR
Shepherd et al., (2000)	Docetaxel 75mg/m^2	55	7.5	NR	NR	32.50	NR	NR
Shepherd et al., (2005)	Erlotinib	488	6.7	NR	NR	29.03	NR	NR
Shepherd et al., (2000)	BSC	100	4.6	NR	NR	19.93	NR	NR
Shepherd et al., (2005)	BSC	243	4.7	NR	NR	20.37	NR	NR

Table 31: Median Overall Survival: Pooled Analyses: Absolute Values Extracted From the Phase III Studies

Trial	Product	N	Survival (Months)	Lower Range (Months)	Upper Range (Months)	Survival (Weeks)	Lower Range (Weeks)	Upper Range (Weeks)
Schuette et al., (2005)	Docetaxel 75mg/m^2	103	6.3	4.68	7.84	27.30	20.28	33.97
Fossella et al., (2000)	Docetaxel 75mg/m^2	125	5.7	NR	NR	24.70	NR	NR
Camps et al., (2005)	Docetaxel 75mg/m^2	129	6.6	5.5	7.7	28.6	23.83	33.37
Ramlau et al., (2006)	Docetaxel 75mg/m^2	415	NR	NR	NR	30.7	NR	NR
Gridelli et al., (2004)	Docetaxel 75mg/m^2	110	NR	NR	NR	29.0	21.00	36.00
Thatcher et al., (2005)	BSC	563	5.1	NR	NR	22.1	NR	NR

Table 32: Time to Disease Progression: Indirect Comparison of Absolute Values Extracted From the Phase III Studies

Trial	Product	N	TtDP (Months)	Lower Range (Months)	Upper Range (Months)	TtDP (Weeks)	Lower Range (Weeks)	Upper Range (Weeks)
Hanna et al., (2004)	Pemetrexed 500mg/m^2	283	3.4	0.5	18.2	14.73	2.17	78.87
Hanna et al., (2004)	Docetaxel 75mg/m^2	288	3.5	0.3	19.5	15.17	1.30	84.50
Shepherd et al., (2000)	Docetaxel 75mg/m^2	55	NR	NR	NR	10.60	NR	NR
Shepherd et al., (2005)	Erlotinib	488	2.2	NR	NR	9.53	NR	NR
Shepherd et al., (2000)	BSC	100	NR	NR	NR	6.70	NR	NR
Shepherd et al., (2005)	BSC	243	1.8	NR	NR	7.80	NR	NR

Table 33: Time to Disease Progression: Pooled Analyses: Absolute Values Extracted From the Phase III Studies

Trial	Product	N	TtDP (Months)	Lower Range (Months)	Upper Range (Months)	TtDP (Weeks)	Lower Range (Weeks)	Upper Range (Weeks)
Schuette et al., (2005)	Docetaxel 75mg/m^2	103	3.4	2.1	4.8	14.73	9.10	20.80
Fossella et al., (2000)	Docetaxel 75mg/m^2	124	NR	NR	NR	8.50	6.70	11.00
Camps et al., (2005)	Docetaxel 75mg/m^2	129	2.7	1.6	3.8	11.70	6.93	16.47
Ramlau et al., (2006)	Docetaxel 75mg/m^2	415	NR	NR	NR	13.1	NR	NR
Gridelli et al., (2004)	Docetaxel 75mg/m^2	110	NR	NR	NR	NR	NR	NR
Thatcher et al., (2005)	BSC	563	2.6	NR	NR	11.27	NR	NR

Table 34: Response Rates: Indirect Comparison of Absolute Values Extracted From the Phase III Studies

Trial	Product	N	Overall Response Rates (%)
Hanna et al., (2004)	Pemetrexed 500mg/m^2	283	9.1
Hanna et al., (2004)	Docetaxel 75mg/m^2	288	8.8
Shepherd et al., (2000)	Docetaxel 75mg/m^2	55	5.5
Shepherd et al., (2005)	Erlotinib	427	8.9
Shepherd et al., (2000)	BSC	100	NR
Shepherd et al., (2005)	BSC	211	<1

Table 35: Response Rates: Pooled Analyses: Absolute Values Extracted From the Phase III Studies

Trial	Product	N	Overall Response Rates (%)
Schuette et al., (2005)	Docetaxel 75mg/m^2	103	12.6
Fossella et al., (2000)	Docetaxel 75mg/m^2	120	6.7
Camps et al., (2005)	Docetaxel 75mg/m^2	129	9.3
Ramlau et al., (2006)	Docetaxel 75mg/m^2	415	5
Gridelli et al., (2004)	Docetaxel 75mg/m^2	110	2.7
Thatcher et al., (2005)	BSC	563	1.3

Toxicity

The tables below summarise the key adverse events from the clinical trials identified for the clinical and economic evaluation. More detailed information on the safety results from the pemetrexed registration trial are provided in section 2.8

Table 36: Incidence of Grade 3 / 4 Adverse Events: Indirect comparison of Absolute Values Extracted From the Phase III Studies

			GRADE 3-4 ADVERSE EVENTS (n)								
Trial	Product	N	Anemia	Neutropenia	Febrile Neutropenia	Nausea / vomiting	Diarrhoea	Asthenia	Fatigue	Alopecia (any grade)	Rash
Hanna et al., (2004)	Pemetrexed 500mg/m^2	265	11	14	5	11	1	NR	14	17	2
Hanna et al., (2004)	Docetaxel 75mg/m^2	276	12	111	35	8	7	NR	15	104	2
Shepherd et al., (2000)	Docetaxel 75mg/m^2	55	3	37	1	4	1	10	NR	NR	NR
Shepherd et al., (2005)	Erlotinib	485	NR	NR	NR	29	29	NR	92	NR	44
Shepherd et al., (2000)	BSC	100	NR	NR	NR	6	0	28	NR	NR	NR
Shepherd et al., (2005)	BSC	242	NR	NR	NR	6	1	NR	56	NR	0

Table 37: Incidence of Grade 3 / 4 Adverse Events: Pooled Analyses: Absolute Values Extracted From the Phase III Studies

			GRADE 3-4 ADVERSE EVENTS (n)								
Trial	Product	N	Anemia	Neutropenia	Febrile Neutropenia	Nausea / vomiting	Diarrhoea	Asthenia	Fatigue	Alopecia (any grade)	Rash
Schuette et al., (2005)	Docetaxel 75mg/m^2	102	6	21	2	5	NR	NR	NR	NR	NR
Fossella et al., (2000)	Docetaxel 75mg/m^2	121	0	65	10	5	2	15	NR	NR	NR
Camps et al., (2005)	Docetaxel 75mg/m^2	129	3	19	10	1	1	18		80	
Ramlau et al., (2006)	Docetaxel 75mg/m^2	401	NR	NR	11	11	11	6	17	140	NR
Gridelli et al., (2004)	Docetaxel 75mg/m^2	107	3	20	5	0	3	NR	7	40	NR
Thatcher et al., (2005)	BSC	562	NR	NR	NR	4	5	15	NR	NR	1

Table 38: Treatment Discontinuation Rates: Indirect Comparison of Absolute Values Extracted From the Phase III Studies

Trial	Product	N	Toxicity	Consent Withdrawal
JMEI Study Report (PBAC Submission)	Pemetrexed 500mg/m^2	283	21	12
JMEI Study Report (PBAC Submission)	Docetaxel 75mg/m^2	288	25	18
Shepherd et al., (2000)	Docetaxel 75mg/m^2	55	NR	NR
Shepherd et al., (2005)	Erlotinib	485	26	NR
Shepherd et al., (2000)	BSC	100	NR	NR
Shepherd et al., (2005)	BSC	242	4	NR

Table 39: Treatment Discontinuation Rates: Pooled Analysis of Absolute Values Extracted From the Phase III Studies

Trial	Product	N	Toxicity	Consent Withdrawal
Schuette et al., (2005)	Docetaxel 75mg/m^2	103	10	4
Fossella et al., 2000	Docetaxel 75mg/m^2	121	7	NR
Camps et al., 2005	Docetaxel 75mg/m^2	129	9	7
Ramlau et al., 2006	Docetaxel 75mg/m^2	415	49	NR
Gridelli et al., 2004	Docetaxel 75mg/m^2	106	12	NR
Thatcher et al., 2005	BSC	563	13	NR

Table 40: Summary of key Quality of Life results from key studies

Author	Treatment Assessed	QoI Measurement used	Results
Hanna et al (2004)	Pemetrexed vs Docetaxel (Active treatment vs Active treatment)	Lung Cancer Symptom Scale (LCSS)[a] & Average Symptom Burden Index (ASBI)[b]	There was no difference in the LCSS scores between the study arms. Patients on both arms rated with similar rates of improvement or stabilisation of anorexia, fatigue, cough, dyspnoea, haemoptysis and pain.
Dancey et al (2004)	Docetaxel vs BSC (TAX317 study, efficacy results reported by Shepherd 2000) (Active treatment vs BSC)	Lung Cancer Symptom Scale (LCSS) & EORTC QLQ-C30[c]	Statistically significant difference in patient-rated pain scores in favour of docetaxel overall, trends in favour of docetaxel were noted in observer-rated scale for pain and fatigue for all docetaxel patients. The authors concluded that second-line docetaxel treatment improved survival with a trend toward less deterioration in QoL versus BSC.
Shepherd et al 2005	Erlotinib vs BSC/placebo (Active treatment vs BSC/placebo)	EORTC QLQ-C30 & Quality of life questionnaire for patients with lung cancer (QLQ-LC13)	Statistically significant median time to deterioration in favour of erlotinib with respect to: Cough (4.9mo vs3.7 mo) Dyspnoea (4.7 mo vs 2.9mo) Pain (2.8mo vs 1.9mo)

a – LCSS is designed to capture impact of disease symptoms likely to be affected by treatment and focuses on physical, functional and global domains
b - ASBI – average of the six symptom-specific questions regarding anorexia, fatigue, cough, dyspnoea, haemoptysis and pain.
c – consists of 30-item questionnaire incorporating a global health/QoL scale , function scale, symptom scales.

2.8 Comparative safety

60. Give a brief overview of the safety of the technology compared to the comparator(s). Give incidence rates if appropriate.

Evidence from comparative trials and regulatory summaries is preferred; however, findings from non-comparative trials may sometimes be relevant. For example, they may demonstrate a relative lack of adverse effects commonly associated with the comparator or the occurrence of adverse effects not significantly associated with other treatments. If any of the main trials are primarily designed to assess a safety outcome (for example, they are powered to detect significant differences between treatments with respect to incidence of an adverse effect) these should be reported here in the same detail as described previously (section 3) for efficacy trials.

Patient Exposure in JMEI

A total of 571 patients (ITT) were randomly assigned to either the pemetrexed or the docetaxel-treated arm. Of the 283 patients randomly assigned to the pemetrexed arm, 265 (93.6%) received at least one dose of pemetrexed, and of the 288 patients randomly assigned to the docetaxel arm, 276 (95.8%) received at least one dose of docetaxel. This makes up the randomised and treated (RT) patient population in this submission. 18 (6.4%) patients in the pemetrexed arm and 12 (4.2%) patients in the docetaxel arm did not receive study therapy.

The table below displays a summary of the number of completed treatment cycles for the RT patients. Patients on both treatment arms completed a median of 4 cycles of therapy. A total of 90 (34.0%) patients on the pemetrexed arm and 88 (31.9%) patients on the docetaxel arm completed at least six cycles of therapy. One patient on the pemetrexed arm completed 20 cycles of treatment and 1 patient on the docetaxel arm completed 14 cycles of treatment.

Furthermore, the distribution of the weekly mean dose of pemetrexed administered per patient during the study compared with docetaxel patients is summarised. Patients on both treatment arms received >94% of the planned dose. A total of 1164 doses (cycles) of pemetrexed were administered to 265 patients on the pemetrexed arm and 1085 doses (cycles) of docetaxel were administered to 276 patients on the docetaxel arm.

Table 41: Summary of cycles given – RT population

	Pemetrexed N = 265	Docetaxel N = 276
Mean	4.4	3.9
Median	4.0	4.0
Standard deviation	3.3	2.5
Minimum	1.0	1.0
Maximum	20.0	14.0
Dose delivered:		
Planned mean/ patient (mg/m^2/wk)	166.7	25
Delivered weekly mean/patient	161.0	23.6
% planned DI (delivered/planned)	96.6%	94.4%

Abbreviations: DI, dose intensity

Toxicity

All treated patients (RT, N=541) were assessed for toxicity. Haematological toxicity is summarised in table 42. Patients receiving docetaxel experienced significantly higher rates of neutropenia, neutropenic fever, infections and hospitalisations (see resource utilisation) due to neutropenic events compared to patients receiving pemetrexed. Furthermore a greater proportion of patients on the docetaxel arm required hospitalisation as a result of other drug-related adverse events (excluding neutropenic complications), compared to those on the pemetrexed arm (10.5% versus 6.4%, p = 0.092).

Table 42: 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.

Table 43: 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.

Non-haematalogical toxicities are summarised in the table above. The use of granulocyte colony- stimulating factors (G-CSFs) was substantially increased for patients receiving docetaxel when compared to pemetrexed. Only four patients in the docetaxel arm and one patient in the pemetrexed arm received G-CSFs as prophylaxis without a prior event of neutropenia. The remaining patients used G-CSF during treatment of neutropenia (n = 49) in the docetaxel arm; (n = 5) on the pemetrexed arm or as prophylaxis for subsequent cycles following an episode of neutropenia. There were no statistically significant differences in the incidences of thrombocytopenia, anaemia, RBC transfusions, or use of erythropoietin between treatment groups.

There was a significantly higher rate of alopecia ($p < 0.001$) and a trend toward higher rates of grade 3 and grade 4 diarrhoea ($p = 0.069$) for patients receiving docetaxel. An increase in ALT was the only toxicity that was higher in the pemetrexed arm ($p = 0.028$).

Resource utilisation

Medical resource utilisation data were collected prospectively to help define the quantity of supportive care used by this study population. The data presented include hospitalisations, transfusions, non-diagnostic medical procedures, and relevant concomitant medications. Protocol-required interventions, however, are not discussed.

Blood Transfusions, Hospitalisations and Growth Factors

Hospitalisations, growth factor and transfusion needs are summarised in **table below.**

Table 44: Hospitalisations and supportive care

	Pemetrexed N=265 (%)	Docetaxel N=276 (%)	*p* value[a]
≥ 1 hospitalisation for neutropenic fever	1.5	13.4	**< 0.001**
≥ 1 hospitalisation for any other drug-related AE	6.4	10.5	0.092
G-CSF/GM-CSF	2.6	19.2	**< 0.001**
Erythropoietin	6.8	10.1	0.169
RBC transfusions	16.6	11.6	0.1078

Abbreviations: G-CSF, granulocyte colony-stimulating factor; GM-CSF, granulocyte-macrophage colony-stimulating factor; AE, adverse event.

[a] Fishers exact test.

Transfusions

The number of transfusions in the study was small; 45 (17%) patients on the pemetrexed arm and 32 (11.6%) patients on the docetaxel arm received ≥1 transfusion. On both treatment arms, the most common transfusion was red blood cells (RBC). Although the incidence of CTC Grade 2, 3, or 4 anaemia was similar between the arms more patients on the pemetrexed arm received transfusions of RBC, while more patients on the docetaxel arm received erythropoietin. The number of patients receiving platelet transfusions in this study was small, this may reflect the low incidence of CTC Grade 3 or 4 thrombocytopenia observed in this study

Hospitalisations

For the purposes of this submission hospitalisation data were analysed in the RT population:

A summary of hospitalisations for the RT population is presented in table below. If multiple reasons for a hospitalisation were listed, the hospitalisation was only counted once, the reason was assigned in the following order: febrile neutropenia, drug-related adverse event, non drug-related adverse event, study drug administration, protocol tests, and social reasons.

Significantly more patients on the docetaxel arm (13.4%) were hospitalised at least once during the course of the study than on the pemetrexed arm (1.5%) for neutropenic fever ($p < 0.001$). Other drug-related adverse events demonstrated a similar numerical trend in favour of pemetrexed (pemetrexed 6.4% vs docetaxel 10.5%, $p < 0.092$).

Although more admissions and days of hospitalisation were attributed to febrile neutropenia and other drug-related adverse events in the docetaxel arm than in pemetrexed-treated patients, more admissions and days of hospitalisations were attributed to adverse events not related to study drug therapy in the pemetrexed than in the docetaxel arm. The median number of days of hospitalisation due to non-drug-related adverse events was 5 in both arms, although more pemetrexed-treated patients had hospitalisations which lasted at least 15 days. In most cases, the patient was discharged after discontinuation from the study.

Importantly pemetrexed-treated patients were hospitalised for neutropenic fever a total of 29 days compared to docetaxel-treated patients who were hospitalised for neutropenic fever a total of 195 days (see table below)

Table 45: Summary of hospitalisations – RT population

	Pemetrexed (N=265)	Docetaxel (N=276)
Number of cycles of therapy	1164	1085
Hospitalisations, n (%)[a]	129 (48.7)	146 (52.9)
▪ Study drug administration	53 (20.0)	57 (20.7)
▪ Adverse events (all)	84 (31.7)	112 (40.6)
▪ Febrile neutropenia [c]	4 (1.5)	37 (13.4)
▪ Other drug-related	17 (6.4)	29 (10.5)
▪ Non drug-related	69 (26.0)	66 (23.9)
▪ Protocol tests	43 (16.2)	31 (11.2)
▪ Social reasons	17 (6.4)	16 (5.8)
Hospitalisations (admissions)	337	364
▪ Study drug administration	123	151
▪ Adverse events (all)	113	147
▪ Febrile neutropenia [c]	4	43
▪ Other drug-related	17	29
▪ Non drug-related	92	75
▪ Protocol tests	72	49
▪ Social reasons	29	17
Hospitalisations (days)	1722	1410
▪ Study drug administration	314	314
▪ Adverse events (all)	885	833
▪ Febrile neutropenia [c]	29	195
▪ Other drug-related	131	151
▪ Non drug-related	725	487
▪ Protocol tests	143	100
▪ Social reasons	380	163

Abbreviations: n = number of patients hospitalised.
[a] Patients may have been admitted for multiple reasons
[b] As determined by investigator
[c] Only investigator collected data

A greater proportion of hospitalisations in the pemetrexed arm were attributed to protocol tests than in the docetaxel arm. However, a greater proportion of hospitalisations in the docetaxel arm

were attributed to drug administration than for pemetrexed. When these reasons are considered together, the total numbers are similar between the treatment arms.

More admissions and days of hospitalisation for social reasons were reported in the pemetrexed arm. This type of hospitalisation accounts for the days that a patient remains in the hospital between protocol events for convenience and not for adverse events.

Hospitalisation for social reasons is more likely to be related to a specific local health care system or to individual patient needs (for example, distance from patient's home to investigative site or availability of caregiver). Social reasons were reported most commonly at sites in Germany, Pakistan, and Russia. Four of the 5 patients enrolled in Russia, all to the pemetrexed arm, accounted for 135 days.

Summary of concomitant medications

The concomitant medications considered in this summary were 5-HT_3 antagonists, G-CSFs, erythropoietin, and parenteral antibiotics. The number of patients receiving 5-HT_3 antagonists was similar between arms and the incidence of nausea and vomiting were not different between arms based on Grade 3 or 4 CTC toxicities, therefore, these data were not further explored. (table 46 below) summarises the total number of courses of therapy for the other concomitant medications of interest. Courses of therapy completed prior to randomisation, begun after discontinuation from therapy, or with missing start date were not considered in the calculations. Patients on the docetaxel arm received more courses of G-CSF and parenteral antibiotics than patients on the pemetrexed arm.

Table 46: Summary of use of select concomitant medications – RT population

Medication	Pemetrexed (N=265)		Docetaxel (N=276)	
	Number of patients n(%)	Courses of therapy	Number of patients n(%)	Courses of therapy
G-CSF	7 (2.6)	10	53 (19.2)	100
Erythropoietin	18 (6.8)	48[a]	28 (10.1)	58[b]
Antibiotics (iv or im)	52 (19.6)	106	70 (25.4)	151
Febrile neutropenia	3 (1.1)	6	19 (6.9)	38
Neutropenia/leukopenia	0	0	5 (1.8)	16
Pneumonia	12 (4.5)	21	12 (4.3)	28
Pyrexia	9 (3.4)	23	10 (3.6)	24
Sepsis	0	0	2 (0.7)	6

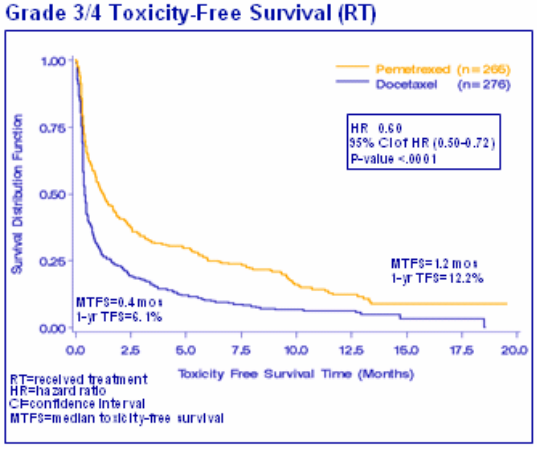
Abbreviations: G-CSF, granulocyte colony-stimulating factor; iv, intravenous; im, intramuscular.
[a]one patient received erythropoietin intermittently and had 25 courses.
[b]one patient received erythropoietin intermittently and had 22 courses.

Exploratory analyses on toxicity based on JMEI

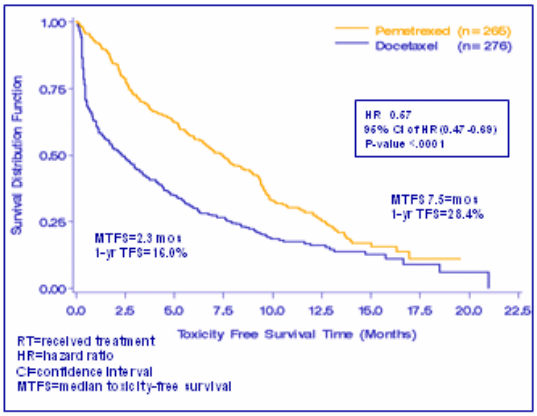
An exploratory risk-benefit analysis was undertaken by Pujol et al (2004) using toxicity-free survival as a measure to compare survival distribution of pemetrexed and docetaxel for patients without occurrence of grade 3/4 toxicity and in patients without occurrence of only grade 4 toxicity. Toxicity-free survival was defined as the time from randomisation to the first date of any grade 3/4 toxicity or death from any cause. The result of this unique analysis are shown below:

	Mean time (days)		
	Docetaxel 238 patients	Pemetrexed 212 patients	P-value
Haematological toxicity grade			
Time spent receiving chemotherapy	77.9	88.8	0.278
Time with no drug-related toxicity	42.3	69.7	<0.001
Time with toxicity Grade 1	5.2	7.6	0.688
Time with toxicity Grade 2	5.5	8.5	0.587
Time with toxicity Grade 3	10	2.1	<0.001
Time with toxicity Grade 4	14.9	0.9	<0.001
Non-Haematological toxicity grade			
Time with no drug-related toxicity	16.4	22.8	0.04
Time with toxicity Grade 1	21.6	32.9	0.027
Time with toxicity Grade 2	28.3	28.3	0.39
Time with toxicity Grade 3	10.3	4.6	0.001
Time with toxicity Grade 4	1.2	0.3	0.02

Grade 3/4 Toxicity-Free Survival (RT)



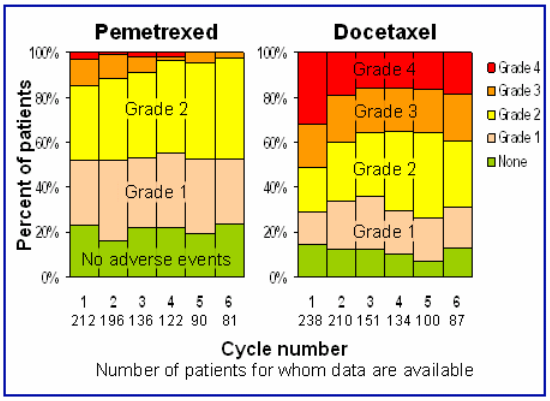
Grade 4 Toxicity-Free Survival (RT)



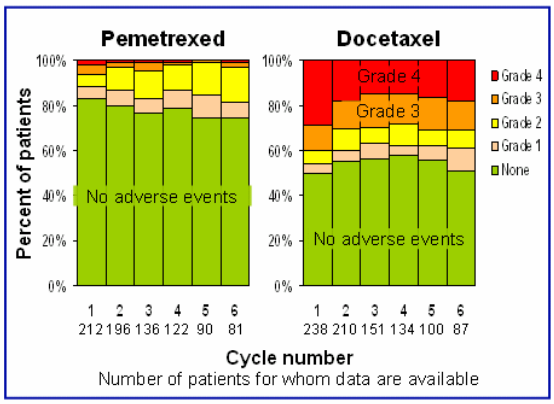
Although the results of JMEI demonstrate the favourable toxicity profile of pemetrexed over docetaxel, this analysis confirms the superior risk-benefit profile of pemetrexed over docetaxel in second-line treatment of advanced NSCLC.

In 2005, Bhalla et al performed an analysis to assess toxicity burden of patient receiving pemetrexed compared to docetaxel. Time spent receiving chemotherapy and the adverse events (AE) experienced were derived using the JMEI database and a summary was generated for each patient showing the number of cycles in which a patient was suffering from ≥1 AE. The toxicity burden of the 'average' patient the analysis produced estimates of the mean time a patient could spend with no AEs and mean time with CTC grade 1-4 AEs while receiving chemotherapy. The assessments are presented for haematological and non-haemotological AEs:

Pemetrexed vs Docetaxel JMEI patients
Non-haematological Adverse Events



Pemetrexed vs Docetaxel JMEI patients
Haematological Adverse Events



In general AEs (haematological and non-haemotological) experienced by patients on pemetrexed were of lower severity compared to patients treated with docetaxel, and patients on pemetrexed spent a lower proportion of time on chemotherapy experiencing grade 3/4 toxicities.

This type of analysis is useful in illustrating the heterogenous nature of AE's because traditional reporting of incidence of AEs do not quantify the impact of AEs on patients in terms of severity and duration of time spent experiencing AEs.

This analysis concluded that patients who received pemetrexed spent a statistically significant longer time without haematological or non-haemotological AEs and statistically significant shorter time experiencing grade 3/4 AEs, compared to docetaxel treated patients.

Safety conclusions

- Incidence of any Grade 3 or 4 laboratory toxicity was very low in the pemetrexed arm (5.3% versus 40.2%). There were statistically significantly fewer Grade 3 and 4 toxicities of neutropenia and leukopenia on the pemetrexed arm compared with docetaxel arm. Grade 3 or 4 increased alanine aminotransferase was statistically significantly less frequent in the docetaxel arm. The incidence of Grade 3 or 4 thrombocytopenia was low, and the incidence of Grade 3 or 4 anaemia was similar on both treatment arms.
- Statistically significantly more dose reductions occurred in the docetaxel arm compared with the pemetrexed arm. Most of the reductions were associated with neutropenia and febrile neutropenia.
- Incidence of any Grade 3 or 4 nonlaboratory toxicity was very low in the pemetrexed arm (<6%). Infection with Grade 3 or 4 neutropenia, febrile neutropenia, and alopecia (all grades) were statistically significantly less frequent in the pemetrexed arm. CTC Grade 2 to 4 myalgia, arthralgia, and neuropathy (sensory) were significantly lower in the pemetrexed arm. Incidence of other clinically important events such as diarrhoea, vomiting, nausea, stomatitis, and fatigue were similar between the two treatment arms.
- The use of G-CSF and antibiotics was significantly less in the pemetrexed arm compared with the docetaxel arm. More patients on the docetaxel arm received erythropoietin, while more patients on the pemetrexed arm received RBC transfusions.

2.9 Interpretation of clinical evidence (400 word maximum)

61. Provide a brief statement of the relevance of the evidence base to the decision problem. Include a discussion of the relevance of the outcomes assessed in clinical trials to the clinical benefits experienced by patients in practice.

All phase III clinical trials presented as part of the evidence base involved patients receiving 2nd line NSCLC therapy at licensed doses used in the UK. Therefore, overall the evidence base is relevant to the decision problem. Key decision areas from the decision problem are discussed below:

For some physicians and some patients, the toxicity burden of docetaxel outweighs the potential survival benefit and another chemotherapy option with similar survival outcomes, but less toxicity, would be preferred.

- In JMEI, there was clinically equivalent efficacy demonstrated between the two agents but there were clinically and statistically significant differences in the toxicity profiles of the two chemotherapy treatments.
- There were higher rates of neutropenia (with and without complications) and significantly more frequent use of G-CSF for the treatment of neutropenia in patients on docetaxel-treated, compared to pemetrexed-treated patients (p<0.001).
- Importantly pemetrexed-treated patients were hospitalised for neutropenic fever a total of 29 days compared to docetaxel-treated patients who were hospitalised for neutropenic fever a total of 195 days.
- Significantly more patients on the docetaxel arm (13.4%) were hospitalised at least once during the course of the study than on the pemetrexed arm (1.5%) for neutropenic fever (p < 0.001). More admissions and days of hospitalisation were attributed to febrile neutropenia and other drug-related adverse events in the docetaxel arm than in pemetrexed-treated patients.
- There was a significantly higher rate of alopecia (p < 0.001) and a trend toward higher rates of grade 3 and grade 4 diarrhoea (p = 0.069) for patients receiving docetaxel.
- In exploratory analyses, patients on pemetrexed experienced significantly longer toxicity-free survival compared to docetaxel (Grade 3/4–free survival: 1.2 months/pem vs 0.4 months/docetaxel, p<0.001 & Grade 4-free survival only: 7.5 month/pem vs 2.3 months/docetaxel, p<0.001). In another exploratory analysis, it was found that patients treated with pemetrexed statistically spent significantly longer time without haematological or non-haematological adverse events.

Patients of good performance status (PS 0/1) are expected to benefit more from active chemotherapy than patients of poorer performance status (PS 2/3). Sub-group analysis has been used to reflect this.

- Patients of good performance derived significantly greater survival benefit than patients of poorer performance status, 9.4 months/9.1 months for pemetrexed/docetaxel patients of PS 0/1 compared to 3.6/2.2 months survival respectively in PS 2 patients. These are the patients who tend to receive chemotherapy in the UK as they obtain greater survival and also are better able to tolerate chemotherapy. Pemetrexed has demonstrated the same survival benefit in these patients but does not cause the same level of toxicity as docetaxel.

In general, if a taxane (docetaxel or paclitaxel) was used first-line, docetaxel is not likely to be used as a second-line option in this patient population.

- Docetaxel is also licensed in the first-line treatment of advanced NSCLC and is being increasingly used in this setting. According to expert clinical opinion sought by Lilly, in

general, if a taxane (eg docetaxel) is used in the first-line setting, it 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.

Erlotinib is licensed for use in second- and third-line settings. Currently it is the only treatment licensed for third-line. If erlotinib is used in second-line setting, patients and physicians do not have a licensed treatment available for use in the third-line setting.

- The opportunity for 2nd and 3rd line therapy options in NSCLC is an important advance in treatment of NSCLC patients, who historically have not received as much active treatment as patients with other tumours (e.g. breast) due to lack of available options. Erlotinib increases 3rd line options for advanced NSCLC and therefore the benefits of active treatments for patients who are not eligible for further chemotherapy.

Physician/patient choice in essential in NSCLC

Choice of chemotherapy for the patient should focus on providing the most suitable treatment for the patient type. For example,

- If a patient has received a taxane (paclitaxel or docetaxel) in the first line setting the only active treatment options for this patient would then be either erlotinib or pemetrexed.
- Patients not able/willing to tolerate the toxicity profile of docetaxel, pemetrexed can be considered as it provides similar efficacy but with reduced toxicity.
- If a physician wished to treat a patient with active treatment but had concerns regarding diarrhoea, vomiting, rash, alopecia or febrile neutropenia; then pemetrexed can be considered since these adverse events are more likely to be associated with other approved treatment options in 2nd line advanced NSCLC.

62. Identify any factors that may influence the applicability of study results to patients in routine clinical practice; for example, issues relating to conduct of the trial versus clinical practice or the choice of eligible patients. State any criteria that would be used in clinical practice to select suitable patients based on the evidence submitted. What proportion of the evidence base is for the dose(s) given in the SPC?

- Doses of chemotherapy in the relevant key trials are in-line with SPC for all relevant comparators considered in the evidence base for this appraisal.
- G-CSFs are not used routine in the UK, particularly prophylactically. However, they are used in many phase III clinical trials involving docetaxel. The prophylactic use in trials reduces the risk of febrile neutropenia in docetaxel patients so this needs to be considered when appraising the evidence base for docetaxel. In JMEI, the trial involving pemetrexed and docetaxel, prophylactic use of G-CSFs was not routine and in fact was extremely low (4 docetaxel patients, 1 pemetrexed patient).
- In general, patients receive a greater number of cycles of therapy in clinical trials than in a routine clinical setting. Therefore lower use of therapy and lower efficacy results would be expected in routine practice compared to clinical trials; this is not likely to differentiate between active treatments, although those with higher toxicity (e.g. docetaxel) are more likely to have reduced dose and duration of therapy.

3 Cost effectiveness

3.1 Published cost-effectiveness estimates

3.1.1 Identification and description of studies

63. Describe the strategies used to retrieve relevant cost-effectiveness studies from the published literature and from unpublished data held by the company. The methods used should be justified with reference to the decision problem. Sufficient detail should be provided to enable the methods to be reproduced and the rationale for any inclusion and exclusion criteria used should be provided.

Specify:

A review of the published literature aimed to both identify all relevant published economic evaluations of second-line NSCLC and to identify the important parameters needed to inform the design of the economic model.

64. the specific databases searched and service provider used (for example, Dialog, DataStar, OVID, Silver Platter), including at least:

- Medline
- Embase
- Medline (R) In-Process
- Health Economic Evaluation Database
- NHS Economic Evaluation Database (NHS EED)

A protocol was prepared for the literature searches, detailing inclusion and exclusion criteria and search terms, search dates, and data span searched. Articles were identified in electronic database searches of

- OHE NEED,
- CRD NHS Economic Evaluation Database (NHS EED) –
- DARE,
- NHS EED, HTA
- EMBASE
- OVID MEDLINE (R) in-Progress,
- Other Non-Indexed Citations,
- OVID MEDLINE (R)
- the American Society of Clinical Oncology (ASCO) Abstracts Database (www.lungca.asco.org)
- National Coordinating Centre for Health Technology Assessment (www.ncchta.org)
- Broad search terms ensured that no studies were inadvertently excluded.

65. the date the search was conducted

Databases Searched	Dates when the searches were conducted	Date span of the search
OHE NEED	09/02/2006	Last updated 30th January 2006
CRD NHS Economic Evaluation Database (NHS EED). All databases searched: DARE, NHS EED, HTA	09/02/2006	
EMBASE	13/02/2006	1980 to 2006 week 06
OVID MEDLINE (R) in-Progress, Other Non-Indexed Citations, OVID MEDLINE (R)	13/02/2006	1966 to present
American Society of Clinical Oncology (ASCO) Abstracts Database (lungca.asco.org).	13/02/2006	
National Coordinating Centre for Health Technology Assessment	13/02/2006	

66. the date span of the search

See table in previous question.

67. the complete search strategies used, including all the search terms: Textwords (free text), Subject Index Headings (e.g. MeSH) and the relationship between the search terms (e.g. Boolean)

The complete search strategies are presented in the table below.

Database	Search String	Description
OHE NEED	1	Compound search: Keyword: Lung
CRD NHS Economic Evaluation Database	1	Lung cancer (all fields) All records
EMBASE	1	Lung Tumor/ OR (lung$ or pulmon$ adj15 - neoplas$ or cancer or adenocarcinom$ or carcinom$ or tumor$ or tumors$).mp [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] OR Lung non small cell cancer/ OR Non small cell. ti,ab OR NSCLC.ti,ab
	2	Phase 3 clinical trial/
	3	Economic$. mp.
	4	#1 AND #2 AND #3
OVID MEDLINE (R) In progress	1	exp lung neoplasms/ OR (((lung$ or pulon$) adj15 neoplas$) or cancer or adenocarcinom$ or carcinom$ or tumor$).mp. or tumour$.ti,ab. [mp=ti, ot, ab,nm,hw] OR exp Carcinoma, non-small cell lung/ OR non small cell.ti,ab. OR NSCLC.ti,ab
	2	Economic$.mp.
	3	Phase 3 clinical trial/
	4	# 1 AND #2 AND #3
ASCO	1	Lung Cancer AND Economic (find in clusters) Clusters were: non-small cell lung cancer; small cell lung cancer; malignant, mesotheslioma, tumor biology, research health services research, solid tumors, breast cancer
National Coordinating Centre for Health Technology Assessment	1	Searched on lung cancer

68. details of any additional searches, for example searches of company databases. Include a description of each database

The internal company publication approval database was searched for economic publications including Pemetrexed. Prior to Lilly submitting a publication, approval is required. The internal database which publication approvals are routed was searched.

69. the inclusion and exclusion criteria

Inclusion Criteria

Studies were included in the economic review if they included a full or partial economic evaluation of patients with NSCLC receiving second-line treatment AND were original studies describing data that had not been reported elsewhere.

Exclusion Criteria

Studies were excluded from the review if they were population-based economic models, studies of first-line treatments, studies looking at patients with small cell lung cancer, letters to editors and review articles describing data that had been reported elsewhere and editorials. Non-English language papers were excluded.

70. the data abstraction strategy.

Descriptive summary information relating to each study was extracted that included the aims [of the study], methods employed, choice of analytic technique and key results. No formal synthesis of the reported outcomes was performed because of methodological differences between the respective studies.

3.1.2 Description of identified studies

71. Please provide a brief overview of each study, stating the aims, methods, results and relevance to decision-making in England and Wales.

Economic evaluations

Study	**Holmes et al., (2004). A cost-effectiveness analysis of docetaxel in the second-line treatment of non-small cell lung cancer.**
Aims	To develop a model to assess the economics of second-line treatment of non-small cell lung cancer (NSCLC) from the perspective of the UK NHS, based on the resources and outcomes from a clinical trial comparing docetaxel 75mg/m^2 with best supportive care (BSC).
Methods	The area under the survival curve for each treatment was analysed and the difference in mean survival between the docetaxel group and the BSC group was calculated as 3.82 months. Measurable incremental costs for the docetaxel group were largely driven by drug acquisition and administration. These cost drivers, as well as toxicity treatment costs and cost offsets, were varied in the sensitivity analysis.
Results	The base case cost-effectiveness analysis (mean values) reported a cost per life-year gained of £13, 863 for docetaxel 75mg/m^2 (year 2000/2001 values). Sensitivity analysis showed that the number of treatment cycles per patient, which affected total treatment cost, had most influence on the cost per life-year gained in the base case scenario. Using the 95% confidence intervals around the mean number of treatment cycles, the base case cost per life-gained varied from £10,985 to £16,738. Using the 95% confidence intervals around the mean difference in survival, to represent the best and worst case scenarios, the cost per life year saved ranged from £10,020 to £32,781. The study concluded that docetaxel 75mg/m^2 in 3-weekly cycles is a cost-effective second-line treatment for pre-treated NSCLC in terms of survival gains made for a reasonable increase in costs.
Relevance to decision-making in England and Wales	Docetaxel 75mg/m^2 is a relevant comparator arm for the UK. The cost perspective was that of the NHS as this was the economic evaluation on which the NICE decision regarding docetaxel for 2nd line NSCLC treatment was based.

Study	**Leighl et al., (2002). Economic analysis of the TAX 317 Trial: Docetaxel versus best supportive care as second-line therapy of advanced non-small-cell lung cancer.**
Aims	To determine the cost-effectiveness (CE) of second-line docetaxel compared with best supportive care (BSC) in the TAX 317 trial, a randomised clinical trial of second-line chemotherapy in non-small-cell lung cancer.
Methods	A retrospective cost-effectiveness analysis of the TAX 317 trial was undertaken, evaluating direct medical costs of therapy from the viewpoint of Canada's public health care system. Costs were derived in 1999 Canadian dollars, and resource use was determined through prospective trial data.
Results	The incremental survival benefit in the docetaxel arm over BSC was 2 months (p=0.047). The cost-effectiveness of docetaxel was $53,749 per year of life gained. For patients treated with docetaxel 75mg/m^2, the cost-effectiveness was $31,776 per year of life gained. In unvariate analysis, cost-effectiveness estimates were most sensitive to changes in survival, ranging from $18,374 to $117,434 with 20% variation in survival at the recommended dose. The largest cost center in both arms was hospitalization, followed by the cost of drugs, investigations, radiotherapy, and community care. BSC patients had fewer hospitalizations than patients in the chemotherapy arm and were more often palliated at home. The cost-effectiveness estimate of $31,776 per year of life gained is within an acceptable range of health care expenditures, and the total costs of therapy are similar to those of second-line palliative chemotherapy for other solid tumors.
Relevance to decision-making in England and Wales	This economic evaluation was based upon the same clinical trial as Holmes 2004 (above) but the perspective was that of the Canadian health care system. The results were consistent with the UK model.

Study	**Clegg et al., (2002). Clinical and cost-effectiveness of paclitaxel, docetaxel, gemcitabine, and vinorelbine in non-small cell lung cancer: a systematic review.**
Aims	To review the evidence on the clinical and cost-effectiveness of four of the new generation drugs for patients with lung cancer.
Methods	A systematic review of RCTs identified from 11 electronic databases (including Medline, Cochrane Library and Embase), referene lists and contact with experts and industry was performed to assess clinical effectiveness of paclitaxel, docetaxel, gemcitabine and vinorelbine. Clinical effectiveness was assessed using the outcomes of patient survival, quality of life, and adverse effects. Cost-effectiveness was assessed by development of a costing model and presented as incremental cost per life year saved (LYS) compared with best supportive care (BSC).
Results	Of the 33 RCTs included, 5 were judged to be of good quality, 10 of adequate quality, and 18 of poor quality. Gemcitabine, paclitaxel, and vinorelbine as first-line treatment and docetaxel as second line treatment appear to be more beneficial for non-small cell lung cancer than BSC and older chemotherapy agents, increasing patient survival by 2-4 months against BSC and some comparator regimens. These gains in survival do not appear to be at the expense of quality of life. Survival gains were delivered at reasonable levels of incremental cost-effectiveness for vinorelbine, vinorelbine plus cisplatin, gemcitabine, gemcitabine with cisplatin, and paclitaxel with cisplatin regimens compared with BSC. The review concluded with the statement that 'although the clinical benefits of the new drugs appear relatively small, their benefit to patients with lung cancer appears to be worthwhile and cost-effective'.
Relevance to decision-making in England and Wales	The economic evaluation was primarily concerning first-line therapies but did also include docetaxel as a second-line therapy. The study is also relevant to UK decision making as it provides cost data regarding BSC.

Studies of Resource Use and Cost

The published health economic literature on lung cancer focuses primarily on first-line treatment. A dearth of studies exist that adequately and comprehensively describe the costs of patient care from a UK perspective. Of the cost studies available, the perspective of the evaluation is narrow i.e. coverage of hospital treatment costs alone – from the point of diagnosis to death as in the case of Wolstenholme & Whynes (1999). The table below summarises the studies identified from the review looking specifically at resource use and costs. Two cost analyses involving pemetrexed are reported first and then the remaining results of the literature search.

Pemetrexed cost studies

Study	**Bushill-Mathews et al 2003., Reducing health care burden for treatment of toxicity associated with pemetrexed or docetaxel in patients with advanced non-small cell lung cancer who previously received chemotherapy: Application to the UK setting**
Aims	To summarise the incidence and costs for the most costly toxicity related supportive care for pemetrexed and docetaxel.
Methods	Based on phase III clinical trial data, evaluating direct medical costs of key investigator-determined drug related adverse events. Includes hospitalisations, transfusions, erythropoietin, granulocyte colony-stimulating factors (GCSF) and parenteral antibiotics. Unit costs were sourced from UK NHS casemix data(published in 2002) and UK national drug prices.
Results	The most common reason for drug-related hospitalisation for both arms was febrile neutropenia (4 admissions in the pemetrexed arm vs 43 in the docetaxel arm).

	Pemetrexed (N=265)	**Docetaxel (N=276)**
Total hospitalisations	£75	£274
Outpatient transfusions	£2	£0
Erythropoietin	£61	£70
granulocyte colony-stimulating factors (GCSF)	£13	£128
parenteral antibiotics	£85	£116
Total	£235	£588

Relevance to decision-making in England and Wales	The costs are from an NHS perspective and for the relevant treatments under consideration for this analysis.

Study	**T. Dilla et al 2006., Budget impact of pemetrexed (Pemetrexed®) in the treatment of non-small cell lung cancer (NSCLC) in Spain**
Aims	To compare the budget impact of pemetrexed to docetaxel, from the perspective of the Spanish healthcare system.
Methods	The costs included in the analysis were: drug acquisition costs (considering a median of 4 cycles per treatment), pre-medications costs (according to the summary of product characteristics), cost of colony stimulating growth factors (CSF, data from clinical trial), and cost of the management of adverse reactions (neutropenia and febrile neutropenia; data from clinical trial).
Results	The economic impact of pemetrexed for the Spanish healthcare system is low and it can be considered reasonable compared to docetaxel. Treatment with pemetrexed leads to substantial cost savings in the management of adverse events due to the favourable adverse-effect profile compared to docetaxel.
Relevance to decision-making in England and Wales	The treatment arms are relevant to the UK. Due to the toxicity profiles less is spent on treating adverse events for patients receiving Pemetrexed.

All other search results

Reference	Title	Aim	Methods
Sagmeister et al., (1991)	Assessment of the costs of a febrile neutropenic event in chemotherapy as a basis for socio-economic evaluations of new cancer treatments.	To assess all costs of a febrile neutropenic event in cancer patients undergoing chemotherapy.	Collection of cost data from hospitals in Germany and Switzerland
Maslove et al., (2004)	Estimation of the additional costs of chemotherapy for patients with advanced non-small cell lung cancer	To measure the costs of treating advanced NSCLC. 1st line therapy.	Retrospective collection of resource use data from hospital records. Case notes from 194 patients were inspected in 8 centres.
Vergnenègre et al., (1996)	Cost analysis of hospital treatment – two chemotherapic regimens for non-surgical non-small cell lung cancer.	To compare the costs of two regimens of chemotherapy (mitomycin+navelbine+ cisplatin vs. mitomycin+vindesine+ cisplatin. 1st line therapy	Clinical evaluation during chemotherapy incorporated events enabling construction of an event tree.
Wolstenholme & Whynes (1999)	The hospital costs of treating lung cancer in the United Kingdom	To estimate the direct economic costs of the hospital treatment of lung cancer	The records of a sample of patients drawn from the Trent Region were used. A full audit of resource-using hospital events was compiled for 253 patients, for 4 years, following initial diagnosis or until death, if occurring earlier.
Godfrey (2001)	The economic and social costs of lung cancer and the economics of smoking prevention.	A short review article focused on the economic costs and implications of smoking	Very little discussion of lung cancer
Braud et al., (2003)	Direct treatment costs for patients with lung cancer from first recurrence to death in France	To determine the direct treatment cost of lung cancer management from progression to death from the viewpoint of the hospital.	A retrospective, descriptive study was performed using data from 100 patients who died from lung cancer and who had received treatment from 4 different types of hospitals.

Studies of Quality of Life

A larger body of literature exists on patients' quality of life and utility with non-small cell lung cancer. The study by Earle et al., (2000) acted as a useful source that synthesised all of the available utility estimates, however the systematic review performed needs to be updated. The study by Dancey et al., (2004) was probably the most applicable study to the economic model – being based on the Phase III trial of docetaxel vs. best supportive care.

Reference	Title	Aim	Methods
Earle et al., (2000) (inc review of Berthelot et al, Gould et al, Smith et al, reported in section 3.2.6.2)	Systematic overview of cost-utility assessment in oncology	To critically review the CUA literature and its role in informing clinical oncology practice, research priorities, and policy.	The English-language literature was searched between 1975 and 1997 for CUAs. Two readers abstracted from each article descriptions of the clinical situation and patients, the methods used, study perspective, the measures of effectiveness, costs included, discounting, and whether sensitivity analyses were performed. The readers then made subjective quality assessments. Utility values from the reviewed papers, along with information on how and from whom utilities were measured were also extracted.
Trippoli et al., (2001)	Quality of life and utility in patients with non-small cell lung cancer	To measure quality of life and utility in patients with non-small cell lung cancer using the SF-36 and the EuroQOL questionnaires; to evaluate the impact of some clinical variables on quality of life and utility; and to assess the correlation between the measurements produced by the 2 questionnaires	A cross-sectional study involving 95 patients from 15 Italian hospitals with NSCLC who completed both questionnaires was performed.
Hesling et al., (1998)	Quality of life and survival in patients with advanced non-small cell lung cancer receiving supportive care plus chemotherapy with carboplatin and etoposide or supportive care only. A Multicentre Randomised Phase III trial. 1st line	To evaluate the effects of chemotherapy on the quality of life and survival of patients with advanced non-small cell lung cancer (stage IIIB or IV).	In a controlled multicentre trial, patients were rnadomised to received supportive are only or supportive care plus chemotherapy. Quality of life was measured at randomisation and prior to each treatment course and at corresponding 4-week intervals in the control arm, using the EORTC QLQ-C30 +LC13 questionnaire. 48 patients were randomised (supportive care 26, chemotherapy 22), being eligible for comparative analyses. Another 102 patients, 97 of which received chemotherapy, were subsequently included in the study on an individual treatment preference basis. Data from these patients were used for confirmative purposes.

Reference	Title	Aim	Methods
Dancey et al., (2004)	Quality of life assessment of second-line docetaxel versus best supportive care in patients with non-small cell lung cancer previously treated with platinum-based chemotherapy: results of a prospective, randomized phase III trial.	To investigate quality of life in NSCLC patients treated with either second-line docetaxel or best supportive care.	Patients were assessed with the Lung Cancer Symptom Scale (LCSS) and/or QLQ-C30 (with LC13 module) every 3 weeks.
Fallowfield & Harper (2005)	Health-related quality of life in patients undergoing drug therapy for advanced non-small cell lung cancer	A review article describing the validated tools for assessing lung-cancer-specific symptoms and HRQoL, and RCTs with HRQoL evaluations in patients with advanced NSCLC.	1st and 2nd line treatment. A literature search of PubMed was used.
Thatcher et al., (1997)	Improving quality of life in patients with non-small cell lung cancer: Research experience with Gemcitabine	A review article describing key studies of 1st line treatment of chemotherapy vs. best supportive care (older and more recent trials).	1st line treatment.
Brown et al., (2005)	Assessment of quality of life in the supportive lung setting of the Big Lung Trial in non-small cell lung cancer.	To evaluate the quality of life implications of primary treatment (i.e. surgery, radical radiotherapy) or supportive care in non-small cell lung cancer patients.	1st line treatment.
Paesmans (2002)	Benefits of chemotherapy for quality of life in patients with advanced non small cell lung cancer.	To analyse the quality of life results reported in the published randomized clinical trials that compare chemotherapy with best supportive care and integrate quality of life as a trial's endpoint.	1st and 2nd line treatment
Feld (1987)	Quality of life in patients with non-small cell lung cancer treated with chemotherapy	Short review article discussing the difficulties of defining quality of life in lung cancer and methodological aspects such as the timing of questionnaires when attempting to measure quality of life	1st line.

Reference	Title	Aim	Methods
Fernandez et al., (1989)	Quality of life during chemotherapy in non-small cell lung cancer patients.	To establish the correlation between the Karnofsky performance status (KPS) and objective response (OR) and to examine the relationship between the level of physical activity as measured by visual analogue scales (VAS) and OR.	With the VAS, they tested changes in symptoms, weight loss, anorexia and quality of life. The scores obtained on categorical scales with those on VAS in measuring the side effects of chemotherapy, such as nausea and vomiting. Finally, they studied the correlations between the Karnofsky performance status and quality of life as well as between activity level and quality of life.
A. Brown., et al (2004)	Pemetrexed versus docetaxel in second-line treatment of advanced non-small cell lung caner: Evaluating patient preference	Evaluating patient preference in second-line treatment of advanced non-small cell lung cancer.	Discrete choice conjoint analysis methodology was used to quantify patient treatment preference and willingness to pay. Review of data, along with expert opinion, identified clinically meaningful toxicities that were statistically significantly different between treatment arms. Logistic regression analysis was applied to the stated scenario preferences against the individual attribute levels.
Lloyd et al., (2005) (see also section 3.2.6.2)	Health state utility scores in Lung Cancer: a community survey	The study was designed to elicit UK based societal utility scores for non-treatment specific health states in NSCLC.	Health states were developed using an iterative process of interviews and focus groups. Preferences were elicited using Standard Gamble with 78 members of the general public.

3.2 De novo economic evaluation(s)

72. In the absence of a relevant published economic evaluation, manufacturers should submit their own economic evaluation.

3.2.1 A note on the Reference Case

73. When estimating cost effectiveness, particular emphasis should be given to adhering to the 'Reference Case' (see NICE 'Guide to the Methods of Technology Appraisal'). Reasons for deviating from it should be clearly explained. Particularly important features of the reference case include:

3.2.2 Technology (300 word maximum)

74. How is the technology (assumed to be) used within the economic evaluation? For example, give indications, and list concomitant treatments, doses, frequency and duration of use. The description should also include assumptions about continuation and cessation of the technology.

Indication for use	Pemetrexed is indicated as monotherapy for the treatment of patients with locally advanced or metastatic non-small cell lung cancer, after prior chemotherapy.
Administration	The drug is to be administered intravenously, under the supervision of a physician qualified in the use of cytotoxic anti-cancer therapy.
Dose and frequency	The recommended dose of pemetrexed for *Non-small cell lung cancer:* is 500mg/m² BSA, given by ten-minute infusion, on day 1 of each 21-day cycle.
Pre-medication	Supplement with 1000 micrograms intramuscular vitamin B_{12} and oral folic acid (350 to 1000 micrograms) to reduce toxicity (for full details see Summary of Product Characteristics [SPC]). To reduce the incidence and severity of skin reactions, a corticosteroid should be given the day prior to, on the day of, and the day after pemetrexed administration - this should be equivalent to 4mg of dexamethasone administered orally twice a day.
Duration of use	In the clinical trial the median and mean length of treatment was four 21 day cycles.
Cessation	Within the clinical trial cessation took place on disease progression. However, in second-line treatment of NSCLC, response rates are relatively low and the priority for treatment is to achieve stable disease, as this is considered a positive clinical outcome due to the relief and control of disease symptoms (dyspnea, pain). Cessation in clinical practice is likely to take place on disease progression or as a result of patient choice.

3.2.3 Evaluation design and structure

3.2.3.1 Patients

75. What group(s) of patients is /are included in the economic evaluation? Do they reflect the licensed indication? If not, how and why are there differences? What are the implications of this for the relevance of the evidence base to the decision problem; in other words, specify the data-gap.

Patients included in the economic evaluation are those eligible for second-line treatment and reflect the licensed indication for the products/comparators under consideration.

76. Was the analysis carried out for any subgroups of patients? If so, how was this subgroup identified, what clinical information is there to support the biological plausibility and how was the statistical analysis undertaken?

A sub-group analysis was performed on three treatments (docetaxel, pemetrexed and erlotinib) using patients' performance status (PS 0/1 vs PS $\geq$2). Patients of good performance status are easily identified in routine clinical practice and also tend to reflect the type of patients who currently receive active treatment in a second-line setting.

In order to identify this sub-group, a descriptive synthesis identifying the different types of sub-group analysis reported in the phase III clinical studies was undertaken. Good performance status was identified as a common defining prognostic factor for all three active regimens i.e. patients of good performance status gained improved survival with active treatment (docetaxel,

pemetrexed, erlotinib) compared to patients who were of poorer performance status (≥ PS 2). Performance status was the only variable where a sub-group analysis of this and patients receiving pemetrexed, docetaxel and erlotinib was possible. The analysis was undertaken by adjusting overall survival as this data was available for all three regimens. Assumptions had to be made regarding the time to disease progression as this data was not available for all three regimens.

The published paper of the erlotinib trial (Shepherd et al., 2005) did not provide absolute values of median survival or time to disease progression by performance status, but instead reported hazard ratios (95% CI) for median survival by performance status. It was possible to extract the absolute median survival by performance status from an earlier slide set presented at ASCO (Shepherd et al. 2004).

77. Were any obvious subgroups not considered? If so, which ones, and why were they not considered?

There are prognostic factors for docetaxel and pemetrexed such as stage of disease and time since previous exposure to therapy which improve survival outcomes. However, data on these factors was not available for erlotinib or BSC so a comparison was not possible. Similarly, some prognostic factors improve outcomes for erlotinib patients e.g. non smoker but are not applicable to docetaxel or pemetrexed as they are related to the distinct EGFR related mode of action specific to erlotinib (see clinical section 1.3 and Appendix 2).

78. At what points do patients 'enter' and 'exit' the evaluation? Do these points differ between treatment regimens? If so, how and why?

All patients enter and exit the evaluation at the same points. Patients enter at the point where 2nd line treatment is initiated for NSCLC. The exit of all patients from the model is at death or 3 years, depending on which occurs first. The span of 3 years reflects the maximum life expectancy of the patient population. The time horizon can be adjusted in the electronic version of the economic model.

3.2.4 Comparator technology

79. What comparator(s) was/were used and why was it/were they chosen? The choice of comparator should be consistent with the information provided in Section X of your submission.

The NSCLC model evaluates the cost-utility of pemetrexed 500mg/m^2 compared to docetaxel which is the standard active therapy in the UK. It also compares pemetrexed and docetaxel as active comparators to Best Supportive Care (BSC), as this is considered standard of care, representing the clinical management of at least 50% of NSCLC patients in the UK. In addition, erlotinib, which is licensed for 2nd line/3rd line NSCLC patients who, based on the registration trial, are not eligible for further chemotherapy, and is therefore compared to BSC.

See section 1.4 in clinical section on the choice of comparators.

3.2.5 Study perspective

80. Did the perspective reflect NICE's Reference Case? If not, how and why did it differ?

The perspective adopted followed the NICE reference case. The economic evaluation was considered from the National Health Service (NHS) and Personal Social Services (PSS) perspective. Costs incurred by patients and their relatives, such as direct or indirect productivity losses or out-of-pocket expenses incurred by attending hospital appointments were not estimated. The reason for exclusion was that the guide to the methods of technology appraisals

5.3.3.1 states that they should not be included if the inclusion of a wider set of costs was not expected to influence the results significantly. It was considered important to include costs and outcomes of subsequent/palliative care beyond the treatment under appraisal. The utility study was conducted in line with reference case methodology.

81. What time horizon was used in the analysis and what was the justification for this choice?

The time horizon used was three years. Three years reflects the maximum life expectancy of the patient population within the clinical trials and was validated by expert clinical opinion.

This time horizon can be adjusted in the electronic version of the model to represent one and two years.

3.2.6 Framework

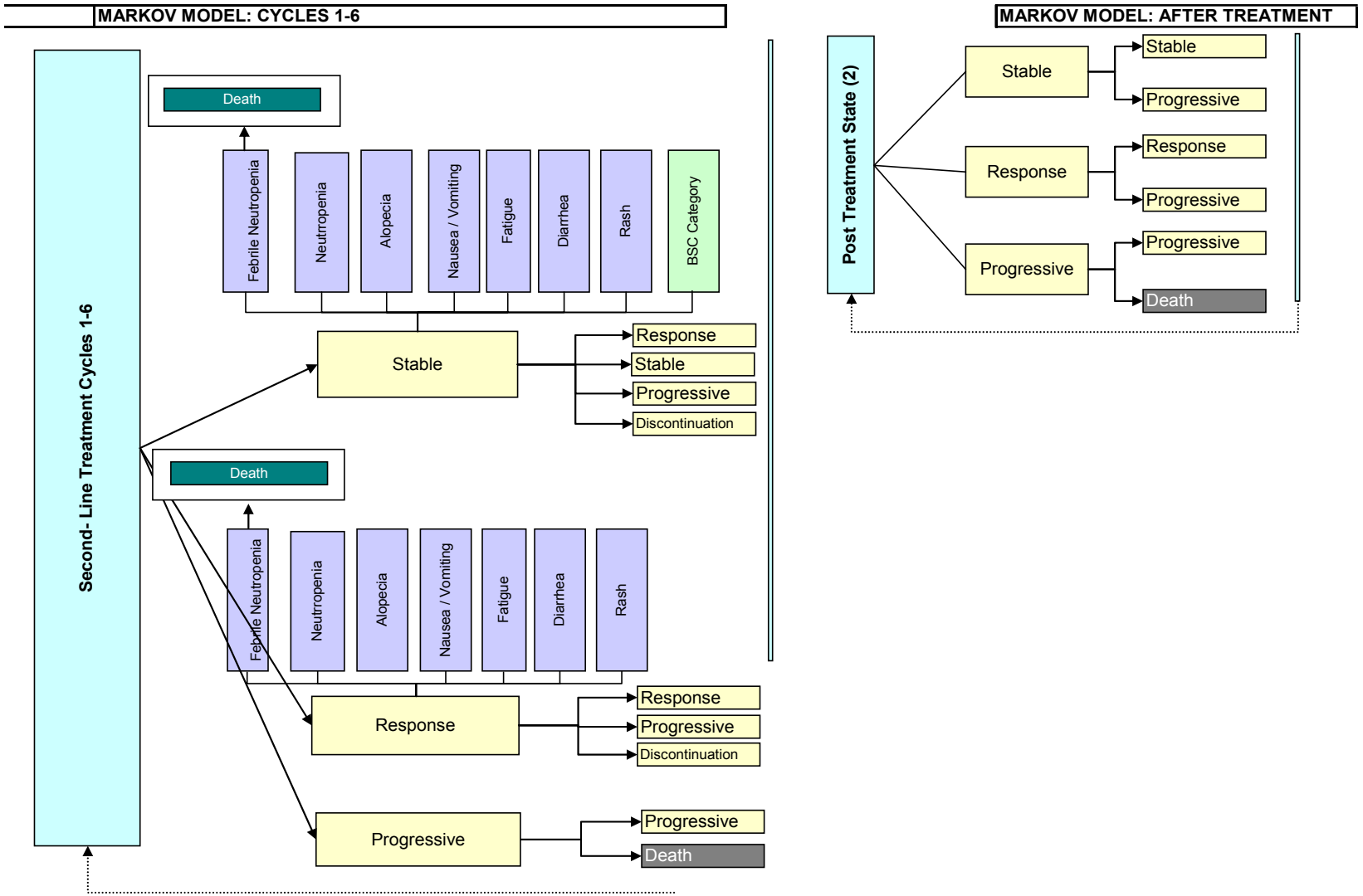
3.2.6.1 Model-based evaluations

82. Please provide the following.

Description of the model type.

A Markov model was used to model the costs and consequences of the different treatment options. A Markov model is a multi-state transitory model that allows patients to make transitions among various health states, at different rates, over extended periods. All clinically important events are modelled as transitions from one state to another. The passage of time is divided into intervals called cycles, chosen to represent a clinically meaningful time interval. During each cycle, each member of the cohort may remain in the same state of health or move to another state, except when the state is absorbing. The utility associated with spending one cycle in a particular state is referred to as the incremental utility. The net probability of making a transition from one state to another during a given cycle is called a transition probability. The simulation considers a hypothetical cohort of patients beginning the process.

A schematic of the model. For models based on health states, direction(s) of travel should be indicated on the schematic on all transition pathways.


MARKOV MODEL: CYCLES 1-6
Second- Line Treatment Cycles 1-6
Death
Febrile Neutropenia
Neutropenia
Alopecia
Nausea / Vomiting
Fatigue
Diarrhea
Rash
BSC Category
Stable
Response
Stable
Progressive
Discontinuation
Death
Febrile Neutropenia
Neutropenia
Alopecia
Nausea / Vomiting
Fatigue
Diarrhea
Rash
Response
Response
Progressive
Discontinuation
Progressive
Progressive
Death
MARKOV MODEL: AFTER TREATMENT
Post Treatment State (2)
Stable
Stable
Progressive
Response
Response
Progressive
Progressive
Progressive
Death

Summary description

Patients are in one of three main heath states, response, stable and progressive disease. The markov cycle duration is 21 days, and for each model cycle patients face a risk of moving health state and also of experiencing a treatment- related AE. For AEs there is a utility and cost implication. Stable and responding patients can either move to Progressive Disease or remain in current state. Stable patients may also achieve a delayed response and move to the response state. The model assumes death follows Progressive Disease. Patients who have responded and then progress move directly to the progressive state. Discontinuation is a transition state from which patients leave the active treatment stage of the model and move straight to progression i.e. post-treatment phase. Patients on treatment (i.e. stable or response states) have a risk of experiencing a life threatening AE (e.g. Febrile Neutropenia) which can involve hospitalised care. Febrile Neutropenia (FN) also carries a risk of death. Surviving patients are placed into one of 3 health states at this stage, and are then challenged with further treatment and risks of further AEs.

A list of all variables that includes their value, range (distribution) and source.

The absolute values are included in the clinical section 2.7. The following pooled values for input variables (95% CI) use in the economic model are given below:

- Efficacy – survival, time to disease progression, response
- AE risk
- AE discontinuations

Values for good performance status sub-group are also given below. For further details of calculations and inputs please see Appendix 4. For utility values for each health state see section 3.2.6.2, for resource use/unit costs see section 3.2.7.

Pooling Methodology

Data were available for pemetrexed and erlotinib from the JMEI trial and Shepherd et al., (2005) study respectively. In the case of docetaxel and best supportive care, data presented from more than one study and these data were pooled together to reflect this. Weighted values were produced from the absolute values reported in each study that took into account the number of patients in each trial (with the more populated trials achieving greater weight). Confidence intervals were estimated for each of these weighted values.

Pooled Mean: Suppose we have m number of estimates x(i), of sample size n(i), for the population expected value m, the pooled estimate is:

$\sum n(i)x(i) / \sum n(i)$, both sums are over all values of i = 1, 2,. . ., m.

Pooled Variance: Since the sample variance is also an unbiased estimate of population variance s2, therefore, it is a good idea to pool the estimates to get a single estimate from m number of estimates S(i)2, of sample size n(i), the pooled estimate is:

$\sum(n(i) – 1)*S(i)2 / (\sum n(i) – m)$, both sums are over all values of i = 1, 2,…, m

Efficacy inputs

Note: months have been converted to weeks using 4.3 recurring

Table 47: Pooled Median Survival

Treatment	Total pooled sample N	Source	Survival (weeks)	Lower CI (Weeks)	Upper CI (weeks)	Pooled variance
Pemetrexed	283	Hanna et al., 2004	35.96	29.92	42.01	9.51
Docetaxel	1225	Schuette 2005, Fosella 2000, Camps 2005, Hanna 2004, Gridelli 2004, Ramlau 2006, Shepherd 2000 (TAX317b only).	30.34	24.35	42.73	9.35
Erlotinib	488	Shepherd 2005	29.03	25.32	32.75	3.6
BSC	906	Shepherd 2000, Shepherd 2005, Thatcher 2005.	21.40	18.01	24.03	2.98

Table 48: Pooled Time to disease progression

Treatment	Total pooled sample N	Source	TTDP (weeks)	Lower CI (Weeks)	Upper CI (weeks)	Pooled variance
Pemetrexed	283	Hanna et al., 2004	14.73	12.26	17.21	1.60
Docetaxel	1225	Schuette 2005, Fosella 2000, Camps 2005, Hanna 2004, Gridelli 2004, Ramlau 2006, Shepherd 2000 (TAX317b only).	12.99	10.05	15.93	2.25
Erlotinib	488	Shepherd 2005	9.53	8.31	10.75	0.39
BSC	906	Shepherd 2000, Shepherd 2005, Thatcher 2005.	9.83	8.40	11.27	0.53

Table 49: Pooled Response rates

Treatment	Total pooled sample N	Source	Response (%)	Lower CI (%)	Upper CI (%)	SE (%)
Pemetrexed	283	Hanna et al., 2004	9.19	5.82	12.55	1.72
Docetaxel	1225	Schuette 2005, Fosella 2000, Camps 2005, Hanna 2004, Gridelli 2004, Ramlau 2006, Shepherd 2000 (TAX317b only).	6.80	3.01	10.60	1.93
Erlotinib	488	Shepherd 2005	8.90	6.20	11.60	1.38

Note: not applicable for BSC as response is not possible if active treatment not given.

AE inputs

AE risk rates (%) for grade 3 or 4 adverse events

Treatment	Source	N	Febrile Neutro-penia	Neutro-penia	Nausea / vomiting	Fatigue	Diarrhoea	Rash	Alopecia all grades
Pemetrexed	Hanna et al., 2004	265	1.89	5.28	4.15	5.28	0.38	0.75	6.42
Docetaxel	Schuette 2005, Fosella 2000, Camps 2005, Hanna 2004, Gridelli 2004, Ramlau 2006, Shepherd 2000 (TAX317b only).	1191	12.68*	42.91	2.85	4.97	2.30	0.72	39.87
Erlotinib	Shepherd 2005		0	0	5.98	18.97	5.98	9.07	0

Note: not applicable for BSC as no adverse event risk if active treatment not given. *From Hanna 2004 only. See assumptions table.

AE Discontinuation rates

Treatment	Total pooled sample N	Source	Rate (%)	SE (%)
Pemetrexed	283	Hanna et al., 2004	0.07	0.0156
Docetaxel	1162	Schuette 2005, Fosella 2000, Camps 2005, Hanna 2004, Gridelli 2004, Ramlau 2006, Shepherd 2000 (TAX317b only).	0.096	0.021
Erlotinib	485	Shepherd 2005	0.05	0.0102

Note: not applicable for BSC as response is not possible if active treatment not given.

Good performance status inputs

Table 50: Pooled Median Survival, time to disease progression and response rates.

Treatment	Total pooled sample N	Source	Survival (weeks)	TTDP (weeks)	Response rates
Pemetrexed	283	Hanna et al., 2004	40.73	14.73	9.60%
Docetaxel	1225	Schuette 2005, Fosella 2000, Camps 2005, Hanna 2004, Gridelli 2004, Ramlau 2006, Shepherd 2000 (TAX317b only).	39.43	15.17	8.30%
Erlotinib	488	Shepherd 2005	35.97	13.00	7.70%
BSC	906	Shepherd 2000, Shepherd 2005, Thatcher 2005.	29.47	11.27	

AE risk and discontinuation rates for good performance status are as for pooled analysis on entire sample.

A separate list of all assumptions and a justification for each assumption.

Table 51: Methodological Assumptions

Assumptions	Assumption Description	Justification
Time Horizon	Three years in base case. Varied within sensitivity analysis.	Clinical experts endorsed that this time horizon was a suitable length for 2nd line NSCLC patients in the UK.
Pooling of best supportive care and docetaxel data in the base case	A pooled comparison was used for the base case to incorporate all phase III clinical trial data on BSC and docetaxel. The other treatment arms only had one phase III clinical trial each. In the sensitivity analysis the different treatments were also compared using an indirect comparison to best supportive care. Data from the two Shepherd et al., studies (2000, 2005) were pooled for the BSC arm in this analysis as BSC was the common comparator.	Pooling of the best supportive care and docetaxel phase III clinical trial data was considered appropriate in order to reflect results from a larger population of patients. Clinical experts agreed that all relevant phase III clinical trials had been included.
Conversion of monthly clinical trial estimates to weekly estimates	In order to make meaningful comparisons between the different treatments, data reported in months was converted into weeks using the formula (months * 4.3333). This applied to the overall survival data, time to disease progression and the duration of response data.	This conversion was performed in order to standardize the data between the different trials to avoid any methodological bias.
Choice of inflation indices	The unit costs for all resource items, other than drugs, were inflated to present values (2005-2006). An inflation index for 2005-2006 was estimated based on the same rate of increase between 2003/04 and 2004/05.	Inflation indices were taken from the Unit Costs of Health and Social Care Publication (2005), University of Kent. This increases the validity of the model to reflect the current economic case.
Sources of unit cost data	The BNF prices 51 (2006) for each of the chemotherapy products and associated medications are used in the model. The hospitalization costs were based on the most up-to-date NHS Reference Costs and inflated to present values. Cost data supplied by the National Blood Bank was used for the blood and blood product unit costs. The most up-to-date NHS Reference Costs were used for the laboratory and radiology tests. The costs for best supportive care were sourced from the published literature and inflated to present values.	This is standard practice in economic evaluation and reflects the NICE reference case.

Assumptions	Assumption Description	Justification
Sources of BSC costs/resource use	BSC costs were sourced from Lees et al, a study in NSCLC. The cost of hospice and hospitalizations were removed from the overall BSC cost as it was felt that this care was included within palliative care costs.	This was considered best available source of BSC costs as these are poorly defined and variable in the literature and were used in previous NICE submission.
Sources of palliative care costs	It is assumed that all patients are assigned a standard cost for palliative care before death. This cost is based on an economic review by the University of Sheffield, NICE (2004).	This was considered the best available source of palliative care costs relating to cancer and was further based on previous interaction with NICE.
Scheduling of response rates	It was assumed in the base case that all responding patients would begin to receive a response at cycle 2.	This assumption was based on analyses of the JMEI trial that found patients to respond to their treatment at cycle 2. The same assumption was applied to erlotinib, where these detailed data were absent.
Time to disease progression	It was assumed that the time to disease progression would be different for responding patients vs. those who did not achieve a response.	This was based on analysis of the JMEI trial data.
Time from response to disease progression	The time from response to disease progression was also determined for responding patients. This was achieved using the data from the JMEI trial on: a. Overall time to disease progression for each treatment b. Time to disease progression for responding patients c. Response rates for each treatment a) and b) were used to determine the time to disease progression for non-responders using a weighted combination of mean times from assumed exponential time to disease progression curves. The same assumption was applied to the erlotinib trial, where these detailed data were absent.	This was based on analysis of the JMEI trial data
Sequencing of health states	It was assumed that patients who move into the 'response' health state remain there until they progress or discontinue, at which point they move to the 'progressive' health state.	This assumption was endorsed by expert clinical opinion.
	It was assumed that once the progressive health state has been entered, patients either remain in this state or move to the death state.	This assumption is based on previous models developed for metastatic breast cancer (Cooper et al., 2003) that assumes that patients in the progressive state will not achieve a response from their existing chemotherapy treatments. This assumption was endorsed by expert clinical opinion.

Assumptions	Assumption Description	Justification
	It was assumed that patients could only enter the death state from the progressive health state (except in the case of febrile neutropenia (FN). It was thus implicit in this assumption that other than FN, patients would not die from any other cause other than progression.	The model applies the logic that a patient with die from non-small cell lung cancer after their disease has progressed (and not before), except if they experience febrile neutropenia. A risk of death following this adverse event was determined. This assumption was endorsed by the clinical advisory panel.

Table 52: Dose Reductions and Treatment Discontinuations

Assumptions	Assumption Description	Justification
Dose reductions. Dose delays	The model does not take into account the effect of dose reductions/dose delays.	The impact of dose reductions/delays is already included in the phase III clinical trial survival estimates. It is difficult to assess the impact of dose reduction on efficacy outside of these clinical trials as evidence on this is limited.
Discontinuation rates	Discontinuation of treatment was incorporated into the model and included discontinuations due to serious adverse events and discontinuations due to patients' wishes.	Discontinuations due to adverse events and patients' wishes represented the two main reasons for discontinuation of treatment.

Table 53: Assumptions Relating to Treatment-Related Adverse Events (AEs)

Assumptions	Assumption Description	Justification
Study of adverse events	It was decided to include only grade 3 / 4 toxicities with the exception of alopecia (where all grades were studied).	This assumption was made on the basis that AE grades 1/ 2 , apart from alopecia, have minimal impact on patients' quality of life and costs of treatment. The exclusion of grade 1/ 2 adverse events was endorsed by expert clinical opinion.
Coverage of adverse events (AEs)	The following adverse events were reflected in the model; Grade 3 / 4 Febrile Neutropenia; alopecia (including all grades); fatigue; diarrhoea, nausea / vomiting; neutropenia and rash. The following adverse events were excluded from the model: Weight loss, pulmonary, leukopenia, pain, nail changes, thrombocytopenia, neurosensory, stomatitis and fluid retention / oedema.	This assumption was based on the incidence of adverse events (>5% in all of the identified clinical trials). Pain can be considered symptoms of disease rather than treatment-induced toxicities. Leukopenia is a laboratory toxicity. The exclusion of pulmonary was based on advice from clinical experts on the basis that pulmonary toxicity is actually generally driven by symptoms not toxicity and is poorly defined. Evidence for this is in Shepherd 2000 where nearly a third of BSC patients have grade 3 or 4 'pulmonary toxicity' when they are not on active treatment when only 20% of docetaxel patients had this toxicity.

Assumptions	Assumption Description	Justification
Incidence of adverse events	It is assumed in the model that adverse events are mutually exclusive of one another.	Extraction of JMEI trial data by adverse events showed that there were very few patients where more than one grade 3 / 4 adverse event occurred concurrently in the selected toxicities. The implication of this assumption is that it may overestimate treatment costs of AEs for patients whom experienced multiple AEs simultaneously. This assumption was endorsed by expert clinical opinion.
Utility decrement associated with the occurrence of serious adverse events	In the base case, utility values associated with experiencing a serious adverse event were taken from a large utility study of 100 members of the general public. The sensitivity analysis varied utility values used to investigate impact on findings.	Based on the NICE reference case.
Frequency of adverse events by health state	The model makes no distinction between the frequency of adverse events by health state. Therefore AE rates were applied equally for stable and responding patients. It was assumed that patients will not experience any adverse events once they progress.	There is no evidence to suggest that patients experience differential rates of adverse events depending on the health state to which they are assigned (e.g. response or stable).
Differences in clinical outcome based on the incidence of adverse events	No attempt was made to model any potential differences in clinical outcome (i.e. survival, response, progression) based on the incidence of adverse events, with the exception of febrile neutropenia where a probability of death is determined (see below).	The effect of adverse events on outcome is incorporated by introducing discontinuation rates into the model based on adverse events.
The study by Shepherd et al., (2005) reports grades 3-5 AEs.	The adverse event data reported in this study (Shepherd et al., 2005) covered grades 3-5. Grade 5 means death. In order to ensure comparable data, 1 death from each group, was excluded (i.e. the grade 5 data).	This was further endorsed by expert clinical opinion.
Duration of adverse events	It is assumed in the model that if patients experience severe or total alopecia that their utility decrement will continue until they enter the progressive state or stop treatment.	This assumption is based on studies that have shown that patients' quality of life continues to be affected by hair loss.
	It is assumed that for all other AEs that they are resolved (treated) in the same cycle within which they occurred and the utility decrement is linked to a single cycle duration, excluding rash.	This was based on feedback from the clinical advisory board.

Assumptions	Assumption Description	Justification
Scheduling of Adverse Events: Rash	In the base case, a constant risk of rash (grade 3 / 4) per cycle was assumed for docetaxel and pemetrexed. For the erlotinib rash, it was assumed based on Cohen et al., (2005) that all patients likely to experience rash would do so in the first cycle. As the duration of erlotinib rash lasts 2 cycles, the incidence rate of erlotinib was doubled to account for this as in a Markov model it is not possible to tag patients who receive rash across more than 1 cycle. This was varied in the sensitivity analysis (i.e. the incidence rate was not doubled here).	Based on detailed data from the JMEI trial and the FDA report on erlotinib (Cohen et al., 2005).
Scheduling of Adverse Events: Alopecia	A constant risk of alopecia (all grades) per cycle was assumed.	The risk of the AE is based on the relevant clinical trial data for the appropriate arm. However the assumption of the risk being constant is based on detailed data from the JMEI trial.
Scheduling of Adverse Events: Diarrhoea	A constant risk of diarrhoea (grade 3 /4) per cycle was assumed.	The risk of the AE is based on the relevant clinical trial data for the appropriate arm. However the assumption of the risk being constant is based on detailed data from the JMEI trial.
Scheduling of Adverse Events: Fatigue	A constant risk of fatigue (grade 3 / 4) per cycle was assumed.	The risk of the AE is based on the relevant clinical trial data for the appropriate arm. However the assumption of the risk being constant is based on detailed data from the JMEI trial.
Scheduling of Adverse Events: Febrile Neutropenia	It was assumed that most cases of febrile neutropenia would occur after the first cycle and after that, a constant risk (per cycle) was assumed.	The risk of the AE is based on the relevant clinical trial data for the appropriate arm. However the assumption of the risk being constant is based on detailed data from the JMEI trial.
Scheduling of Adverse Events: Neutropenia	A constant risk of neutropenia (grade 3 / 4) per cycle was assumed.	The risk of the AE is based on the relevant clinical trial data for the appropriate arm. However the assumption of the risk being constant is based on detailed data from the JMEI trial.
Scheduling of Adverse Events: Nausea / vomiting	A constant risk of nausea / vomiting (grade 3 / 4) per cycle was assumed.	The risk of the AE is based on the relevant clinical trial data for the appropriate arm. However the assumption of the risk being constant is based on detailed data from the JMEI trial.
Risk of death following febrile neutropenia	It was assumed that the risk of death following febrile neutropenia would be the same across the different treatment arms. No changes to this are proposed in the sensitivity analysis due to the paucity of data reported in the trials.	The death risk was taken from a meta analysis of 23 studies involving 4,938 patients by Paul et al., (2005) which reflected a general cohort [of patients] making no distinction between those that had been hospitalised and those that had not.
Hospitalisation rates for AEs	It was assumed that data on hospital duration and rates would be taken from the expert opinion with JMEI trial data to adapt trial data to UK practice where appropriate.	Clinical advisory panel and hospitalization data from the JMEI trial.

Table 54: Assumptions Relating to the Sub-Group Analysis

Assumptions	Assumption Description	Justification
Sub-Group Analysis By Performance Status	Given the absence of data on time to disease progression for erlotinib vs. placebo by performance status, the same ratio between this (performance status) and overall time to disease progression found in the JMEI trial was applied to the erlotinib trial data in order to estimate this.	This assumption was made in the absence of any supporting data.

Table 55: Treatment-Related Assumptions

Assumptions	Assumption Description	Justification
Number of treatment cycles in the model	The model assumes the duration of therapy is linked to time to disease progression and discontinuation for which this data is drawn from the phase III RCTs. The maximum number of treatment cycles in the base case was set to 6. The median number of treatment cycles was 4 for both arms in the JMEI trial. The erlotinib registration trial had a mean treatment duration of 125 days, the median treatment duration of erlotinib was assumed to be 84 days/four 21 day cycles (see SMC link in reference list). Therefore the average number of cycles for all treatments in the model was 4. In the sensitivity analysis the days to disease progression range between 69 and 112 days depending upon whether erlotinib is used until progression (i.e. beyond the maximum number of cycles). The number of treatment cycles was varied in the sensitivity analysis by reducing the number of maximum cycles but this will only impact costs not outcomes.	It is difficult to estimate the impact on efficacy of reduced duration of therapy. The clinical panel endorsed that it was unlikely that treatment duration in the UK would exceed 6 cycles.
Costs of radiotherapy	Patients tend to receive radiotherapy after completion of the first line of treatment but prior to the second line of treatment. For this reason, the economic model excludes the costs of radiotherapy.	This decision was further endorsed by the clinical advisory panel.
Best supportive care vs. placebo	It was assumed that patients randomized to the placebo arm of the Shepherd et al., (2005) trial received the same care as those receiving best supportive care in the Shepherd et al. (2000) trial.	Based on expert clinical opinion.

Assumptions	Assumption Description	Justification
Costs of best supportive care	In the base case BSC costs are set to zero for the active therapies as it was assumed that active treatment delays the need for BSC and that these patients would progress to palliative care treatment following relapse before death i.e. active treatment reduces the need for terminal care. This assumption was tested in the sensitivity analysis in two ways: 1) at the point at which patients reach the progressive health state following their second-line therapy, the model assumes that they receive best supportive care (i.e. immediately after their second-line treatment stops) at an estimated cost. The same assumption applies to patients who are stable / responsive after successful completion of their second-line therapy. 2) There is also a function within the model that allows users to restrict the costs of best supportive care to those patients who progress. This implies that patients who are stable / responsive after 2nd line treatment only receive best supportive care when they progress (and not before).	The base case assumption was made to reflect experience of UK patients treated with active agents and endorsed by clinical experts. As there is uncertainty around the definition and costs of BSC, the sensitivity analysis was used to test this assumption.
Treatment doses	It was assumed in the base case that the identified treatments would be administered in the doses listed below: ▪ Docetaxel 75mg/m^2 ▪ Pemetrexed 500mg/m^2 ▪ Erlotinib 150mg daily ▪ Best supportive care (BSC)	Agreed / licensed doses within the appraisal scope
Body Surface Area (BSA)	In order to estimate the treatment costs, it is assumed in the model that patients will have a body surface area of 1.7m^2 ACTION pan European observational study of 196 NSCLC patients from the UK showed that the average BSA was 1.8 (at diagnosis) but in the model this was reduced to 1.7 to reflect the likelihood that patients with 2nd line NSCLC have lost weight since initial diagnosis prior to 1st line treatment.	This was considered a fair assumption and was endorsed by clinical experts.

Assumptions	Assumption Description	Justification
Utility estimates for best supportive care	The utility decrement associated with patients receiving best supportive care is typically worse than those in a stable health state receiving active treatment. For the model to reflect this, it was decided in the base case to assign the utility decrement associated with a performance status of 2 (which was 0.50) determined from a study of 967 patients with advanced NSCLC involved in an ongoing observational study (ACTION) who are being treated in normal clinical practice (i.e. outside of a trial). 193 of the 967 patients are from the UK.	ACTION pan European observational study of which 196 patients are from the UK
Use of Granulocyte-colony factors (GCS-F)	The costs of the use of GCS-F have not been included in the economic model as the routine use of these products within the UK has not as yet been established. For this reason the pooled analysis of the rate of febrile neutropenia was based on Hanna 2004 rather than pooled estimates as the Hanna trial did not require the use of routine GCS-Fs and therefore most closely reflects UK clinical practice.	Endorsed by clinical experts

83. Why was this particular type of model used?

Given the complex and long lasting therapeutic and pathologic follow-up of patients, Markov models are particularly suited to evaluating treatments for NSCLC. This is because Markov models take into account continuous risks over time, specific timing and recurrence of events - all three determining factors to simulate the course of the patient in this pathology. Using this model, as opposed to a conventional decision tree, will then give a more accurate and realistic evaluation of medical care.

84. What was the justification for the chosen structure/how was disease progression represented?

The structure reflected the natural course of disease and treatment outcomes, namely tumour response, disease progression and survival. The structure was endorsed by clinical opinion.

85. Is this consistent with a coherent and currently accepted theory of disease progression?

The definition presented for disease progression is consistent with that used globally within various clinical trials for oncolytics. The theory was endorsed by clinical opinion.

86. What were the sources of information used to develop and inform the structure of the model?

- clinical studies, phase III clinical trials
- economic studies –based on phase III clinical trials
- practising oncologists
- oncology pharmacists

Please see review of literature used for economic evaluation in 3.1.2.

87. What other structures/measures of disease progression could have been used to inform the structure of the model? Why were they rejected?

None

88. Does the model structure reflect all essential features of the condition that are relevant to the decision problem? If not, why not?

Within the model more features are included than within any previous model published within this setting. This model incorporates survival, time to disease progression, response and toxicity. Previous models have not included toxicity in terms of (dis)utility, only in terms of cost. In addition to this the utilities used are derived from a utility study which uses the NICE reference case recommendation of standard gamble with the general public. The utility study uses general public preferences rather than proxy respondents.

Not all toxicities that a patient may experience were included. This was due to the low incidence rate. The exclusion of low incidence toxicities (less than 6%) was validated by expert clinical opinion. Pulmonary toxicity was excluded on the basis of expert clinical opinion as they considered this description was primarily related to a mixture of symptoms and is poorly defined. This is corroborated by the high incidence of pulmonary 'toxicity' in the BSC arm of Shepherd et al 2000 when these patients were not receiving an active treatment. The inclusion of all toxicities would have caused increased complexity to the model and was unlikely to significantly change the model results.

89. For discrete time models, what was the model's cycle length, and why was this length chosen? Does this length reflect a minimum time over which the pathology or symptoms of a disease could differ? If not, why not?

The cycle length for the model is 3 weeks. The markov cycle length represents one cycle of chemotherapy as specified within the summary of product characteristics. The cycle length was deemed appropriate based on clinical opinion.

90. If appropriate, was a half-cycle correction used in the model? If not, why not?

A half cycle correction is not used within the model. The reason for not utilising a half cycle correction is that as the cycle length is very short at 21 days, therefore the half cycle correction would be 10.5 days. Including a half cycle correction would make very little difference to the end result.

91. Are costs and clinical outcomes extrapolated beyond the trial follow-up period(s)? If so, what are the assumptions that underpin this extrapolation and why are they justified? In particular what assumption was used about the longer-term difference in effectiveness between the technology and its comparator?

Costs are extrapolated beyond the trial follow up period.

It was assumed in the base case that no patients receive erlotinib as a third line therapy as this is not currently common practice in the UK.

It is assumed that all patients will receive a standard cost for palliative care prior to death. The average cost of specialist palliative care per cancer death per year of £3,236 (NICE 2004) is applied across all treatment arms. It was assumed that patients who receive active treatment do not receive BSC whilst being treated but on progression incur palliative care costs following therapy.

3.2.6.2 Non-model-based economic evaluations

Was the evaluation based on patient-level data from a clinical trial or trials?

Not applicable.

Provide details of the clinical trial, including the rationale for its selection.

Not applicable.

Were data complete for all patients included in the trial? If not, what were the methods employed for dealing with missing data for costs and health outcomes?

Not applicable.

Were relevant data collected for all patients in the trial? If data were collected for a subgroup of patients in the trial, how were the data extrapolated to a full trial sample?

Not applicable.

3.2.7 Evidence

3.2.7.1 Clinical evidence

Where relevant, answers to the following questions should be derived from and consistent with, the clinical evidence section of the submission. Cross references should be provided. If alternative sources of evidence have been used, the method of identification, selection and synthesis should be provided and a justification for the approach provided.

92. How was the baseline risk of disease progression estimated (also state which treatment strategy represents the baseline)?

The baseline risks for disease progression were taken from the published clinical trials and additional analyses were conducted using the Hanna et al 2004 clinical trial data for which patient level data was accessible.

93. How were the relative risks of disease progression estimated?

The relative risks were taken from the published clinical trials and additional analyses were conducted using the Lilly sponsored clinical trials for which patient level data was accessible.

94. Were intermediate outcome measures linked to final outcomes (such as patient survival and quality-adjusted life years [QALYs])? If so, how was this relationship estimated, what sources of evidence were used and what other evidence is there to support it?

Intermediate economic outcome measures linked to final outcomes are included. The linked clinical/health outcome measures are listed below:

- quality-adjusted life year
- life year gained

95. Were the health effects of adverse events associated with the technology included in the economic evaluation? If not, would their inclusion increase or decrease the estimated cost effectiveness of this technology?

The costs and consequences of CTC grade 3 and 4 adverse events were included in the economic evaluation. CTC grade 1 and 2 adverse events were excluded apart from alopecia as this represents a key concern for patients/physicians. It is likely that inclusion of the adverse events in the model would increase the estimated cost-effectiveness of pemetrexed due to the generally higher incidence of patient-felt grade 1 and 2 adverse events (e.g. diarrhoea, alopecia, neurosensory) for patients receiving docetaxel 75mg/m^2.

96. Was expert opinion used to estimate any clinical parameters? If so, how were the experts identified, to which variables did this apply, and what was the method of elicitation used?

Phase III clinical trial data was predominantly the source used to provide values for clinical parameters.

Expert opinion was used to

- validate the overall structure of the model ensuring that it reflected the natural course of the disease in the UK
- identify the algorithms associated with the treatment of adverse events,
- the pre-medications used prior to the administration of the chemotherapy treatments
- the most likely outcomes and costs (for patients surviving beyond their 2nd-line therapy) according to current UK clinical practice.

The method of elicitation was to use a round table discussion with practising oncologists and oncology pharmacists. In instances where alignment was not immediate, discussion followed to obtain consensus.

The clinical experts were identified if they met (one or more/ all of the) following criteria:

- Oncologists currently treating NSCLC patients
- Oncology pharmacist

97. What remaining assumptions regarding clinical evidence were made? Why are they considered to be reasonable?

See previous question, and section 3.2.5.1 regarding assumptions and justification.

3.2.7.2 Measurement and valuation of health

98. Which health benefits were measured and how was this undertaken?

Health states were developed for NSCLC patients to describe the burden of progressive disease, stable disease and responding disease in NSCLC patients and the impact of toxicities (Nafees et al 2006, submitted). These health states included symptom burden and the impact of six grade III-IV toxicities and hair loss associated with active treatment of patients with advanced lung cancer. The six grade III-IV toxicities included neutropenia, febrile neutropenia, nausea / vomiting, diarrhoea, rash and fatigue. These were chosen to mirror the health states and toxicities in the economic model, where serious toxicities with $\geq$6% incidence in key phase III trials were included. A review of the literature was performed to identify symptoms and HRQoL related to chemotherapy treatment for stable, responding and progressive disease. The review findings were used to develop an interview discussion guide and to guide the draft health state descriptions in terms of symptom-burden and impact

on areas of functioning. The interview discussion guide was then used in interviews with 5 oncology physicians and 5 oncology specialist nurses. Experts were asked to draw on their clinical experience to identify how functioning and HRQoL are affected in progressive disease, stable disease and responding disease in NSCLC, and to comment on the accuracy of the draft health states. Discussion focused on patients' symptom burden and HRQoL. Draft health states were then revised based upon the interviews and literature review. The visual analogue scale (VAS) and standard gamble interview were used to elicit societal evaluations in a representative group of members of the general public. One hundred members of the general public were recruited.

Analysis of standard gamble data produced the utility values associated with the health states of stable, response and progression and any adverse event resulting from treatment. A series of intra-patient multivariate analyses was undertaken to ascertain the most appropriate model to estimate mean utilities. Initial models estimated the mean utility adjusted for age, gender and own health as measured by EQ-5D total score. At baseline, the model gives the utility for a patient with worst health. Several models were generated, including those excluding within-patients correlations such as GLM and Genmod. Repeated measurement models were also carried out. A likelihood ratio test was performed to test different covariance matrices (unstructured, compound symmetry and toeplitz) against each other. Secondly, the need for a random-effects model was compared against that of fixed effects. All models were that of repeated measured which were clustered at the patient level. The final model specification was a fixed effect repeated measurement model with an unstructured covariance matrix. All covariates were excluded in the final model.

Table 56: Utility Values for the Health States with / without Adverse Events

Adverse Events within each category	Mean utility values
STABLE DISEASE	
No AE	0.65
Grade 3 / 4 Rash	0.62
Grade 3 /4 Alopecia	0.61
Grade 3 /4 Fatigue	0.58
Grade 3 / 4 Nausea / Vomiting	0.61
Grade 3 / 4 Diarrhoea	0.61
Grade 3 / 4 Febrile Neutropenia	0.56
Grade 3 / 4 Neutropenia	0.56
RESPONDING DISEASE	
No AE	0.67
Grade 3 / 4 Rash	0.64
Grade 3 /4 Alopecia	0.63
Grade 3 /4 Fatigue	0.6
Grade 3 / 4 Nausea / Vomiting	0.62
Grade 3 / 4 Diarrhoea	0.63
Grade 3 / 4 Febrile Neutropenia	0.58
Grade 3 / 4 Neutropenia	0.58
PROGRESSIVE DISEASE	0.47

The values obtained in this study are consistent in terms of the key health states (stable, responding disease) with other published utility estimates but add further detail in terms of the impact of toxicity on NSCLC patients' lives (see below). For example

Alternative published utility values in NSCLC

Table 57: Utility values for advanced NSCLC based on reported literature

Health state	Utility estimate	Utility values range	Authors	Year	Rated by
Metastatic NSCLC with chemotherapy	0.6	0.55-0.65	Berthelot et al	2000	Physicians
Local/regional/metastatic NSCLC	0.69	0.69-0.88	Earle et al	2000	Investigators
Regional/distant/recurrent NSCLC	0.7	0.5-0.9	Gould et al	2003	Physicians and nurses
Metastatic NSCLC on chemotherapy	0.7	0.6-1.00	Smith et al	1995	Physicians and nurses
Responding disease lung cancer	0.71	0.664-0.756	Lloyd et al	2005	General public
Stable lung cancer with oral treatment	0.63	0.58-0.68	Lloyd et al	2005	General public
Stable lung cancer with IV treatment	0.583	0.528-0.638	Lloyd et al	2005	General public
Progressive lung cancer with no treatment	0.415	0.357-0.473	Lloyd et al	2005	General public
End of life	0.332	0.276-0.388	Lloyd et al	2005	General public

ACTION was a pan European observational study in patients with advanced NSCLC who were being treated in normal clinical practice (i.e. outside of a trial). The table above shows the utilities for patients whom completed the EQ-5D and EQ-VAS just prior to treatment with chemotherapy. The utility values gained have been grouped by performance status in the table below. These values demonstrate how important it is to treat patients with NSCLC and therefore delay progression which results in poorer performance status.

Table 58: Utility values for advanced NSCLC patients by WHO performance status (Pimental, 2005)

WHO PS	0	1	2	3	4
n=967					
EQ-5D mean (SD)	0.8 (0.2)	0.7 (0.3)	0.5 (0.3)	0.2 (0.3)	-0.3 (0.2)
EQ-VAS mean (SD)	75 (16)	63 (19)	51 (19)	44 (20)	16 (12)

EQ-5D = EuroQol-5D; EQVAS = EuroQol-5D visual analogue scale Source: Pimental et al 2005.

99. Which health benefits were valued? How and why were these values selected? What other values could have been used instead?

See previous question

100. Were health benefits measured and valued in a manner that was consistent with NICE's Reference Case? If not, which approach was used?

All health benefits were measured and valued in accordance with the NICE reference case.

101. Which possible (dis)health benefits were excluded from the evaluation (for example, adverse events of treatment)?

The (dis)benefits excluded from the model were those of adverse events grades 1 and 2.

102. If health benefits were not expressed using QALYs, what health outcome measure was used and what was the justification for this approach?

Health benefits are expressed in terms of QALYs and also in terms of LYG as survival is the most important outcome in the treatment of advanced NSCLC.

3.2.8 Resource identification, measurement and valuation

103. What resources were included in the evaluation (the list should be comprehensive and as disaggregated as possible)?

The following resources were included in the evaluation:

- Pre-medications
- Treatments/ Best supportive care
- Administration time
- Laboratory tests
- Radiology tests
- Provision of blood and blood products
- Provision of topical products
- Hospitalisations for adverse events
- Post-study clinical management
- Palliative care

The source of best supportive care costs was identified through a systematic search of the published literature via CancerLIT, EMBASE and Ovid Medline®. The following search terms were used to identify 31 studies, however none of which contained costs relating to UK patients that could be used in the health economic model. For this reason, the study by Lees et al., (2002) was used as this was used in a previous NICE appraisal for NSCLC and referenced by Clegg et al (2002).

Search String	Description # 1
1	Best supportive care.mp
2	Active sumptom control.mp
3	Lung cancer.mp
4	Mesothelioma.mp
5	1 and 3 (695)
6	Remove duplicates from 5 (409)
7	Best supportive care.ti (117)
8	7 and 1 (117)
9	8 and 3 (72)
10	Remove duplicates from 9 (31)
11	From 9 keep 1-3 (3)
12	From 10 keep 1-31 (31)

104. How were the resources measured?

Resources use within the model was measured based on a number of measures:

- Clinical trial data
- Expert clinical opinion

- Treatment protocols
- Published literature
-

105. Were the resources measured using the same source(s) of evidence as the baseline and relative risks of disease progression?

Yes

106. What source(s) of information were used to value the resources?

Drug acquisition costs

- Doses were calculated according to an assumed BSA of 1.7m^2. Two methods were used to calculate the unit costs. The first method assumes that if any part of the vial / tablet was not used it was thrown away (i.e. per vial costing). The second method assumes that it is not thrown away (per mg costing).
- The acquisition costs were obtained from the BNF (51, 2006).

Administration costs

- The unit costs for inpatient administration were sourced from the UK Department of Health's National Reference Costs.

Pre-medication costs

- The BNF (51) 2006 was used.

Post-chemotherapy costs

- The BNF (51) 2006 was used.

Palliative care costs

- These were based on an economic review by the University of Sheffield, NICE (2004).

107. What is the (anticipated) acquisition cost excluding VAT of the intervention(s)?

£800 per pack of 1 vial, 500mgs.

108. Were the resources measured and valued in a manner consistent with the Reference Case? If not, how and why do the approaches differ?

Yes

109. Were resource values indexed to the current price year?

All drug prices were obtained using the most recent BNF (51, 2006).

The year 1999-2000 was the earliest year for which resource values were available i.e. for the costs of best supportive care, followed by costs for palliative care which was 2003. Where the resource values were not available for 2006, they were inflated to the current price year of 2006. The methodology applied to inflate the costs was based on an estimated value using data for 2004/2005 (E) from the University of Kent's reported inflation indices (HP&P Index).

Resource use category	Resource use item	Unit cost (pack cost in the case of chemotherapy agents and pre-medications) Inflated to present values	Source
Chemotherapy agents	Pemetrexed	£800 per 500mg vial	BNF 51, 2006
	Docetaxel 0.5ml – 20mg	£162.75	BNF 51, 2006
	Docetaxel 2ml – 80mg	£534.75	BNF 51, 2006
	Erlotinib 100mg tablet	£1,324.14	BNF 51, 2006
	Erlotinib 150mg tablet	£1,631.53	BNF 51, 2006
	Best supportive care	£2,158	Lees et al., 2002
Pre-medications	Dexamethasone	£42.30	BNF 51, 2006
	Folic acid	£2.24	BNF 51, 2006
	Vitamin B12	£2.46	BNF 51, 2006
	Piriton	£0.19	BNF 51, 2006
	Paracetamol	£0.31	BNF 51, 2006
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 51, 2006
	Lomotil	£1.63	BNF 51, 2006
	Domperidone	£2.47	BNF 51, 2006
	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)
	1 day of a stay 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	Palliative care costs	£3,236	NICE (2004)

110. Provide details and a justification for any assumptions that were made in the estimation of resource measurement and valuation.

The table below describes how the resources associated with the administration of the treatments were determined.

Product	Clinic Administration Times	Justification	Source
Erlotinib 150mg	None	Tablet form therefore infusion times are not applicable. However monitoring of the patient is included every 4 weeks.	Expert clinical opinion
BSC	N/A	Some monitoring and management of patients would be expected to have an impact upon outpatients – however it is difficult to quantify this and was therefore not included in the costs, potentially underestimating the true level of resource use related to BSC.	Expert clinical opinion
Docetaxel 75mg/m^2	3 hours and 30 minutes	2.5 hours are spent prior to treatment during which time blood tests are performed, the doctor is seen, the pharmacist will prepare the drugs and the pre-medications given. 1 hour is spent receiving the docetaxel chemotherapy treatment.	Expert clinical opinion
Pemetrexed 500mg/m^2	2 hours and 40 minutes	2. 5 hours are spent prior to treatment during which time blood tests are performed, the doctor is seen, the pharmacist will prepare the drugs and the pre-medications given. 10 minutes is spent receiving the pemetrexed treatment.	Expert clinical opinion

The table below describes how the resources associated with the pre-medications used prior to administration of the treatments were determined.

Product	Pre-Medications Used (Product, dose and frequency)	Justification
Erlotinib 150mg	None	SPC
BSC	N/A	N/A
Docetaxel 75mg/m^2	Dexamethasone 8mg, 24 hours ; 12 and 6 hours before treatment 3 day supply of dexamethasone Piriton: dose not known. Expected 4mg by mouth Paracetamol 500mgx2	Based on clinical opinion
Pemetrexed 500mg/m^2	To reduce the incidence and severity of skin reactions, a corticosteroid should be given the day prior to, on the day of, and the day after pemetrexed administration. The corticosteroid should be equivalent to 4mg of dexamethasone administered orally twice a day. To reduce toxicity, patients treated with pemetrexed must also receive vitamin supplementation. Patients must take oral folic acid or a multivitamin containing folic acid (350 to 1,000 micrograms) on a daily basis. At least 5 doses of folic acid must be taken during the 7 days preceding the first dose of pemetrexed, and dosing must continue during the full course of therapy and for 21 days after the last dose of pemetrexed. Patients must also receive an intramuscular infection of vitamin B_{12} (1000 micrograms) in the week preceding the first dose of pemetrexed and once every 3 weeks thereafter. Subsequent vitamin B_{12} injections may be given on the same day as pemetrexed.	SPC

The table below describes how the resources and unit costs associated with the treatment of adverse events were determined.

Adverse Events And Best Supportive Care	Treatment Algorithms	Justification	Original Unit Costs (£)	Inflated Unit Costs (£)
Best Supportive Care	The costs of BSC were taken from Lees et al., (2002) and inflated to 2005/06 prices.	This source was deemed the most detailed estimate of the costs for BSC.	£2,158	£2,158 (in total). A cost per 3-weekly cycle was estimated. Hospice/hospitalisation costs were excluded as these overlapped with palliative care costs.
Grade 3 / 4 Rash (erlotinib rash)	There is no standard treatment for rash other than a topical steroid cream. Betnovate was assumed as the treatment of choice.	Agreed by the clinical advisory panel	£3.34	£3.34. These were not inflated.

Adverse Events And Best Supportive Care	Treatment Algorithms	Justification	Original Unit Costs (£)	Inflated Unit Costs (£)
Grade 3 / 4 Rash (pemetrexed rash)	There is no standard treatment for rash other than a topical steroid cream. Betnovate was assumed as the treatment of choice.	Agreed by the clinical advisory panel	£3.34	£3.34. These were not inflated.
Alopecia (all grades)	Use of the Cold cap system was not costed. The costs of wigs were excluded.	Agreed by the clinical advisory panel despite wide use in UK on the basis this was a capital cost.	N / A	N / A
Grade 3 /4 Fatigue	Blood transfusion (2 units given) Tests: Haemoglobin levels 8 days spent in hospital based on JMEI trial data (6.9% of patients). Non-hospitalised costs (100%-6.9% of patients) include the costs of the bloods and the test and a day spent in hospital (to receive the bloods etc).	Duration of hospitalisation was taken from the JMEI trial for grade 3 / 4 fatigue. The clinical advisory panel advised on the other treatments performed.	An average of the unit costs of whole blood, platelets and standard red cells was used: Whole blood: £120.48 Baseline National Price (2004/2005) National Blood Bank Platelets: £198.76 Baseline National Price (2004/2005) National Blood Bank Standard Red Cells: £120.22 Baseline National Price (2004/2005) National Blood Bank Haemoglobin levels: £2.93	Whole Blood: £125.07

Adverse Events And Best Supportive Care	Treatment Algorithms	Justification	Original Unit Costs (£)	Inflated Unit Costs (£)
				Platelets: £206.34
			Cost of a day in hospital (non-elective admission for chemotherapy with a respiratory system diagnosis): £241	
			D98: Chemotherapy with a Respiratory System Primary Diagnosis: £303	
				Standard Red Cells: £124.80
				Haemoglobin levels: £3.04
				Cost per day in hospital: £250.19 (x 8 days) in 6.9% of patients
				£314.55 (93.1% of patients)

Adverse Events And Best Supportive Care	Treatment Algorithms	Justification	Original Unit Costs (£)	Inflated Unit Costs (£)
Grade 3 /4 Diarrhoea	Laboratory Tests: Electrolytes, blood cultures, stool cultures 4 tabs as a starting dose + 2 tabs every 6 hrs (i.e. a 2 day course) 10.5 days spent in hospital based on JMEI trial data (25% of patients in trial) but adjusted to 5 days for 70% of patients as advised by the clinical advisory panel. Assume that for the 30% of patients who don't stay in hospital, a day of hospitalisation is included (to reflect the tests etc).	Duration of hospitalisation was advised by the clinical advisory panel who also advised on the other treatments performed.	Lomotil (diphenoxylate hydrochloride 2.5 mg, atropine sulphate 25 micrograms) net price 20 = £1.63 Electrolytes: £1.59 Blood cultures: £2.93 Stool cultures: £6.35 Cost of a day in hospital (non-elective admission for chemotherapy with a respiratory system diagnosis): £241. D98: Chemotherapy with a Respiratory System Primary Diagnosis: £303	£1.63 for 20 tablets. Costs not inflated. Electrolytes = £1.65 Blood cultures: £3.04 Stool cultures: £6.59 Cost per day in hospital: £250.19 (x 5 days) in 60% of patients £314.55 (40%) of patients)

Adverse Events And Best Supportive Care	Treatment Algorithms	Justification	Original Unit Costs (£)	Inflated Unit Costs (£)
Grade 3 / 4 nausea and vomiting	Laboratory Tests: Electrolytes Intravenous fluids (sodium chloride infusion) – not costed. Domperidone 20mg x 3 per day Although the JMEI trial did not have any patients with grade 3 / 4 nausea and vomiting requiring treatment in hospital, it was assumed in the model that patients would require 5 days of hospitalised care in 70% of patients. Assume that for the 30% of patients who don't stay in hospital, a day of hospitalization is included.	The clinical advisory panel advised on the other treatments performed.	Electrolytes: £1.59 Domperidone 10mg 30 tab pack - 5 day treatment at 60mg per day: £2.35 for the course. Cost of a day in hospital (non-elective admission for chemotherapy with a respiratory system diagnosis): £241 D98: Chemotherapy with a Respiratory System Primary Diagnosis: £303	Electrolytes = £1.65 Domperidone (not inflated) Cost per day in hospital: £250.19 (x 5 days) (60% of patients) £314.55 (40% of patients)
Grade 3 / 4 neutropenia	There is no standard treatment for grade 3 / 4 neutropenia although a 4.5 day stay in hospital was observed in the JMEI trial data in 6.4% of patients.	The absence of standard treatment was noted by the clinical advisory panel.	Cost of a day in hospital (non-elective admission for chemotherapy with a respiratory system diagnosis): £241	Cost per day in hospital: £250.19 (x 4.5 days) in 6.4% of patients.

Adverse Events And Best Supportive Care	Treatment Algorithms	Justification	Original Unit Costs (£)	Inflated Unit Costs (£)
Grade 3 / 4 febrile neutropenia (hospitalised)	Due to the variability in clinical practice, the treatment and costs of febrile neutropenia was taken from the study by Holmes et al., (2004). It was assumed all patients were hospitalised for febrile neutropenia.	This was advised by the clinical advisory panel.	£3,582	£3,860.30

3.3 Analysis of data

3.3.1 Time preferences

111. Were costs and health benefits discounted at the rates specified in NICE's Reference Case?

An annual discount rate of 3.5 % is applied for both costs and benefits, which is based on the rates specified within the NICE reference case. For results potentially sensitive to the discount rate used, sensitivity analysis is varied between the rates of 0% and 6%. It is worth noting that the discount rates have minimal impact on the results due to the short survival of this patient population.

3.3.2 Non-linearity

112. Was probabilistic sensitivity analysis (PSA) undertaken? If not, why not? If it was, the distributions and their sources should be clearly stated; including the derivation and value of 'priors'.

A probabilistic sensitivity analysis was conducted in the model to take account of the simultaneous effect of uncertainty relating to model parameter values. The variables included were:

- Overall survival
- Time to disease progression
- Time to disease progression for responders
- Response rates
- Utility values
- Treatment discontinuation rates

Confidence intervals on the median statistics used to summarise these parameters were determined based on an assumption of exponential curve forms for time to disease progression and overall survival. This allowed a standard error for the median to be estimated from the overall standard deviation of the patient sample for each treatment. These were used to draw repeated samples for the median overall survival, time to disease progression, time to disease progression for responders, utility values and treatment discontinuation rates.

In the PSA the uncertainties in the parameter values for the key clinical variables in the model were considered simultaneously by repeatedly sampling mean/median parameter values from a series of assigned distribution types, based on the point estimates and the standard error statistics for each average parameter values.

The analyses were run over 5,000 iterations.

Standard Errors (SE) for the median and mean parameter estimates were generated assuming that time to event data followed a constant risk over time (and exponential distribution) and rate data followed a standard binomial distribution. The SE of the mean value was then calculated based on standard equations for these distribution forms.

- SE of the binomial mean = SQRT [(P * Q) / N]
- where; p is the number experiencing the event of interest,
- N is the total number of patients
- Q is defined as (N – P)
- SE of the exponential median = SD / SQRT (N)
- where; SD = SQRT (Variance)
- Variance = 1 / (Lambda)^2
- Lambda = ln(2) / median OR 1 / mean

The standard errors for the utility weights have been calculated differently, using the underlying regression model fitted to the health states and adverse event explanatory variables. The published SE on the coefficients for each explanatory variable were used to simulated 1000 iterations for each utility values. The resulting data was then used to define the SE to the mean utility weights used in the model.

The SE values and point estimates of the parameter values were used to define assumed normal or beta distributions to each of the average parameter values. A random number was then used to independently resample from each distribution.

3.3.3 Statistical analysis

113. How were rates or probabilities based on intervals transformed into (transition) probabilities?

A cohort analysis was undertaken in the Markov model to simulate the prognosis of a hypothetical cohort of 1,000 individuals on each treatment. For each cycle in the model, individuals are moved between health states according to the associated transition probabilities. This results in a new allocation of the cohort between the various health states for the subsequent cycle. The model assumes that all individuals initially enter the model at the initiation of treatment (initially placed in a stable disease state). For each iteration or cycle of the model, the cost and utility accrued for each cycle, referred to as the cycle sums, is calculated for each treatment regime separately by the following formulae (Sonnenberg and Beck, 1993).

Cycle sum (utility) = $\sum_{1}^{N} n_s U_{sk},$

Cycle sum (cost) = $\sum_{s=1}^{N} n_s C_{sk},$

Where N is the number of health states, n_s is the number of individual in state s where k represents the treatment groups.

U_s is the cycle utility of health state s (i.e. the utility that is associated with spending one cycle in a particular health state) and C_s is the cycle cost of health state s (i.e. the costs that is associated with spending one cycle in a particular health state).

At the end of each iteration the cumulative utility and cumulative cost are obtained by adding the cycle sums together. The mean costs and utilities are then calculated by dividing the cumulative utility and cumulative cost by 1,000 individuals.

Transition probabilities are required to allow patients to move between the defined health states and were obtained from the clinical trial data and the published phase III trials. Note that in some cases, some of the probabilities are derived from other probabilities.

When the outcome of interest is based on binary data the log-odds scale will be used. When outcomes are measured on a continuous scale (e.g. times to events), the weighted (by the inverse of the variance) mean of the medians outcome will be used for the analysis. Normal distributions will be assumed throughout.

Where the data is expressed in terms of a median time to an event, transition probabilities will be estimated via rates (Miller and Homan, 1994) as follows:

$$R = \frac{-\ln\{1 - P(t_0, t_j)\}}{j}$$

Here $P(t_0, t_j)$ is the cumulative probability between times t_0 and t_j which is estimated with uncertainty via $P(t_0, t_j) = -\ln(\text{time to an event}) / \mu$ where μ will be estimated from any meta analysis of trial data performed (note that this is most likely to occur with the two trials described for docetaxel monotherapy). R is the rate per cycle and j represents the relevant number of equal time intervals required by the model (for example if $P(t_0, t_j)$ represent the 12-month cumulative probability then to obtain the rate per month j would equal 12). Then the transition probability per cycle, P, is given by:

$$P = 1 - \exp(-R)$$

This assumes that the instantaneous transition probability remains constant during the entire period (i.e. exponential reduction in the eligible population).

Where the information is expressed as a proportion (e.g. the proportion of patients responding or the proportion of patients progressive), transition probabilities will be estimated by (Miller and Homan, 1994):

$$P = 1-\{1-P(t_0, t_j)\}^{1/j}$$

Where $P(t_0, t_j)$ and j are defined as above. Again, it is assumed that the true transition probability remains constant over the time period.

For binary data, that is the probability than an individual will transit from one state to another within a specified time period, the transition probability will be calculated as follows:

$$P = 1\text{-}[1 - \text{pooled response rate}]^{1/\text{no. of treatment cycles}}$$

114. Is there evidence that (transition) probabilities should vary over time for the condition at hand? If so, has this been included in the evaluation? If there is evidence that this is the case, but it has not been included, provide an explanation of why it has been excluded.

Probability	Definition [6]	Values			
		PEM	ERL	DOC	BSC
Pstable [3]	Probability of being in a stable state at each cycle	1 – probability of being in response or progression or death			
Presp [2]	Probability of response in the first cycle of response (cycle 2)	4.2%	4.1%	3.1%	-
	Probability of response per subsequent cycles up until cycle 6	1.3%	1.2%	0.9%	-
	First Response Cycle	2	2	2	-
Pprog	Probability of progression per cycle up until cycle 6: for responders	7.1%	12.2%	9.6%	19.1%
	Probability of progression per cycle up until cycle 6: for non-responders	15.2%	22.3%	16.0%	19.1%
Pdeath [1]	Probability of death per cycle for patients after progression (based on Overall Survival – Time to Progression)	9.3%	10.1%	11.3%	16.5%
PdeathFN	Probability of death from febrile neutropenia (for each FN infection)	3.9%			
Pfebrile	Probability of febrile neutropenia per cycle (cycles 1)	0.00%	0.00%	8.33%	-
	Probability of febrile neutropenia per cycle (cycles 2)	1.13%	0.00%	1.81%	-
	Proportion of febrile neutropenia risk in cycle 3-6 [4]	0.75%	0.00%	2.54%	-
PAE [5]	Probability of nausea/vomiting per cycle	0.70%	1.02%	0.48%	-
	Probability of diarrhea per cycle	0.06%	1.02%	0.39%	-
	Probability of fatigue per cycle	0.90%	3.44%	0.85%	-
	Probability of rash per cycle	0.13%	1.57%	0.12%	-
	Probability of neutropenia per cycle	0.90%	0.00%	8.92%	-
	Probability of alopecia per cycle	1.10%	0.00%	8.13%	-
PdropoutAE[7]	Probability of treatment discontinuation due to AEs	1.28%	0.91%	1.68%	-

[1] Based on the difference between Overall Survival and Time to Progression
[2] Assumes that the majority of the treatment response is achieved early in the treatment and the remaining response is achieved at a constant rate per cycle over the remaining treatment cycles
[3] Calculated in the model as the patients who remain in the stable state after applying per cycle probabilities of progression, response or death
4. Based on FN per cycle data from; Hanna et al., (2004) trial for Pemetrexed® and Docetaxel.
[5] Based on AE rates taken from the pooled trial data for each treatment option
[6] Transition rates for response, probability and death have been derived by assuming an exponential curve form for the time to event – i.e. an assumed constant risk per cycle for treatment response, progression and death (for response an initial higher response rate was included for the first cycle of response)
[7] Based on the pooled discontinuation rates resulting from AEs or patient request from the identified trial

3.3.4 Validity

115. Describe the measures that have been taken to validate and check the model.

A variety of steps were undertaken to validate and check the model:

- Expert clinical opinion was sought to comment on the
- decision problem
- validate the model structure
- agree upon sensitivity analysis and ranges
- Two researchers independently conducted a technical review of the working model
- A consistency check with the published literature was employed as a means of external validation
- The national thoracic oncology advisor and thoracic brand manager were involved in validating
- the model structure,
- decision problem
- agreeing upon sensitivity analysis.

3.4 Results

3.4.1 Base-case result and PSA

116. What was the base-case result (e.g. costs, QALYs and incremental cost per QALY) and was it based on PSA?

The findings of the cost-effectiveness model demonstrate that pemetrexed is a cost-effective option of care in second-line NSCLC when compared both to docetaxel, the standard therapy in terms of active treatment options, and also when compared to BSC, which is currently the standard of care, as it represents the clinical management of around 50% of patients in the UK.

Pemetrexed compared to standard active therapy: docetaxel

The higher acquisition costs of pemetrexed compared to docetaxel are partially offset by the lower pre-medication and administration costs in combination with lower adverse event and palliative care costs. Patients receiving pemetrexed experience greater benefits compared to docetaxel in terms of life years gained and quality-adjusted life years. When the costs and benefits are combined, the resulting ICERs demonstrate that pemetrexed is a cost-effective option.

Costs, benefits and ICERs of pemetrexed compared to docetaxel

	PEM	DOC	Incremental
COSTS			
Active Treatment Cost	£4,591	£2,737	£1,854
Non Chemo Cost†	£671	£772	-£101
AE Cost	£89	£424	-£334
Palliative care costs	£3,556	£3,599	-£43
Total Direct Cost	**£8,906**	**£7,532**	**£1,375***
BENEFITS			
Quality-adjusted Life Years (QALYs)	0.49	0.42	0.07
Life Years (LY)	0.92	0.73	0.19

*Numbers do not compute due to rounding; † non chemo cost = cost of pre-medications + cost of administration

ICER	Pemetrexed compared to docetaxel
Incremental costs	£1,375
Incremental LY	0.19
Incremental QALY	0.07
Cost per additional LYG	**£7,097**
Cost per additional QALY	**£18,672**

Pemetrexed compared to standard of care: BSC

When pemetrexed is compared to best supportive care the improved life years and quality adjusted life years offset additional costs of therapy and result in ICERs that demonstrate that pemetrexed is a cost effective option of care compared to BSC.

Costs, benefits and ICERs of pemetrexed compared to BSC

	PEM	BSC	Incremental
COSTS			
Active Treatment Cost	£4,591	£0	£4,591
Non Chemo Cost	£671	£0	£671
AE Cost	£89	£0	£89
BSC costs	£0	£1,871	-£1,871
Palliative care costs	£3,556	£3,655	-£100*
Total Direct Cost	**£8,906**	**£5,527**	**£3,379**
BENEFITS			
Quality-adjusted Life Years (QALYs)	0.49	0.29	0.21*
Life Years (LY)	0.92	0.60	0.32

*Numbers do not compute due to rounding

ICERS	Pemetrexed compared to BSC
Incremental costs	£3,379
Incremental LY	0.32
Incremental QALY	0.21
Cost per additional LYG	**£10, 418**
Cost per additional QALY	**£16,458**

The incremental cost per LY and cost per QALY for pemetrexed are well below £20,000, both when compared to standard active therapy and standard of care. This demonstrates that pemetrexed is a cost-effective option for patients in this setting within the NHS.

Comparison to BSC with other active comparators

Choice of active therapy needs to be based upon clinical properties that influence the appropriateness of each therapy for individual patients. Therefore, we have also compared

the other active comparators, docetaxel and erlotinib, to BSC to reflect the decision problem facing physicians in the UK and the results are shown below. The results show that active therapy is cost-effective compared to BSC.

Note: The erlotinib results are based upon 4 cycles of therapy (84 days.) The actual duration of therapy in the UK was not known so the results are also shown on the basis of treatment until progression (112 days to progression), following the advice from clinical experts upon their use of erlotinib in the UK. The Detailed Advice Document issued by the Scottish Medicines Consortium on erlotinib (No. 220/05, December 2005) stated the mean duration of treatment with erlotinib to be 125 days.

Costs, benefits and ICERs of docetaxel and erlotinib compared to BSC

Base case costs and benefits.				
	DOC	**ERL (84)**	**ERL (prog)**	**BSC**
COSTS				
Active Treatment Cost	£2,737	£3,025	£4,388	£0
Non Chemo Cost	£772	£317	£416	£0
AE Cost	£424	£107	£107	£0
BSC / 3rd Line Costs	£0	£0	£1,046	£ 1,871
Palliative Care Costs	£3,599	£3,612	£3,612	£ 3,655
Total Direct Cost	**£7,532**	**£7,061**	**£8,107**	**£ 5,527**
BENEFITS				
Quality-adjusted Life Years (QALYs)	0.40	0.39	0.39	0.29
Life Years (LY)	0.73	0.77	0.77	0.60
Reference case: Active comparators compared to BSC				
	DOC	**ERL (84)**	**ERL (prog)**	**BSC**
Incremental costs	£2,005	£1,534	£2,580	Ref
Incremental LYG	0.13	0.17	0.17	Ref
Incremental QALY	0.13	0.11	0.11	Ref
Cost per additional LYG	£15,339	£8,946	£15,049	Ref
Cost per additional QALY	£15,220	£14,279	£24,020	Ref

Palliative care is the main element of treatment costs for all therapies but the cost of chemotherapy is the cost that drives differentiation between the active therapies. The administration and pre-medication costs vary for the therapies; docetaxel has the higher administration costs, but lower pre-medication costs than pemetrexed . BSC has the lowest total treatment costs but the survival gain is the smallest as is the quantity of QALYs gained by patients. Looking at the QALYs/LYGs, survival gained is consistently greater in active therapies vs BSC and the additional utility of survival offsets any decrement due to AEs.

Docetaxel, as the current standard of active therapy, provides survival gains at the lowest incremental cost when compared to BSC but is associated with greater toxicity, whilst BSC is the lowest cost option of care for patients. However, as discussed in the clinical section 1.3, new regimens for the treatment of NSCLC aim to increase the objective tumour response and survival rates as well as to reduce toxicity, decrease symptoms and improve psychological well being for patients. In inoperable advanced NSCLC, active treatment is well established in the UK and achieves both palliation of symptoms and improvement of QoL in addition to the prolongation of survival.

Validity/robustness of results: It is of note that the results for docetaxel compared to BSC found in this economic evaluation were very similar to previous ICERs published and considered within a NICE appraisal that recommended docetaxel for use in the UK (£13,863 [95% CI £10,985 to £16,738 for 2000/2001 values], Holmes 2004)) even though this analysis did not incorporate the cost of managing adverse events.

Factors influencing cost-effectiveness of pemetrexed.

Various key scenarios have been explored in terms of the impact upon the cost-effectiveness estimates for pemetrexed.

Administration

The administration costs and time for the patient vary between the different treatment regimens. For all three therapies, patients will need an initial visit to outpatients for laboratory tests and consultant advice about treatment. Docetaxel requires approximately 3.5 hours in the clinic, which includes laboratory tests, nurse time, consultant time and chair time for the infusion. The patient may also receive cold cap treatment whilst being infused as this can help reduce alopecia. Pemetrexed patients need some pre-medication, usually received in their GP practice, and a similar outpatient visit to docetaxel but with 50 minutes less time being infused and no need for cold cap. Erlotinib will require laboratory testing and consultant appointments in outpatients approximately once every 4 weeks to monitor treatment/assess tumour response as, at this time, the pharmacy tend to release only one months prescription until the next visit.

[redacted]

[redacted]

Duration of therapy

In clinical practice duration of therapy can differ from clinical trials. However, it is very difficult to establish the impact on efficacy of duration of therapy, as in clinical trials patients tend to be treated until progression/discontinuation due to adverse events. In JMEI, both

pemetrexed and docetaxel were used for a mean and median of 4 cycles. The Detailed Advice Document issued by the Scottish Medicines Consortium on erlotinib (No. 220/05, December 2005) stated the mean duration of treatment with erlotinib to be 125 days but the costs have been shown for 84 days. It is difficult to establish exact figures but duration of therapy has a distinct impact upon the acquisition costs and subsequent cost-effectiveness so this would be important to clarify for UK clinical practice.

In the economic model, duration of therapy was driven by the time to disease progression and discontinuation rates and equated to an average of four 21-day cycles for all three active regimens. As can be seen from the sensitivity analysis, when the maximum number of cycles possible in the model was reduced to 4 for all active treatments, the average cost of therapy was reduced from £7,532 to £6,725 for docetaxel and £8,906 to £7,655 for pemetrexed, as the mean number of cycles was reduced as a consequence of limiting the maximum number of cycles. No influence on efficacy is incorporated in the model. It could be expected that as you reduce the number of cycles you also reduce the efficacy so this must be taken into consideration. Findings in terms of the incremental cost per QALY vary from £16,458 base case to £10,412 when compared to BSC for pemetrexed, and £15,220 base case to £9,234 for docetaxel.

Costs, benefits and ICERs of pemetrexed, docetaxel and erlotinib compared to BSC with a maximum duration of therapy of 4 cycles

Base case costs and benefits.				
	PEM	**DOC**	**ERL**	**BSC**
COSTS				
Chemotherapy Cost	£3,492	£2,097	£3,953	£0
Non Chemo Cost	£510	£591	-£197	£0
AE Cost	£97	£438	£129	
BSC / 3rd Line Costs	£0	£0	£611	£1,871
Terminal Costs	£3,555	£3,599	£3,612	£3,655
Total Direct Cost	**£7,655**	**£6,725**	**£8,108**	**£5,527**
BENEFITS				
Quality-adjusted Life Years (QALYs)	0.49	0.42	0.39	0.29
Life Years (LY)	0.92	0.73	0.77	0.60

Reference case: BSC – base case				
	PEM	**DOC**	**ERL**	**BSC**
Incremental costs	£2,128	£1,198	£2,581	£0
Incremental QALY	0.20	0.13	0.11	reference
Cost per additional LYG	£6,559	£8,769	£15,141	reference
Cost per additional QALY	£10,412	£9,234	£24,191	reference

Patient/physician choice of therapy

In a real life clinical setting, patients are not homogeneous and physicians need to be able to choose the best therapy for each individual patient, taking into account patient preferences for

treatment choice. All three active licensed treatment options for 2nd line NSCLC (pemetrexed, docetaxel and erlotinib) are cost effective against the standard of care, best supportive care, and should therefore be made available to patients and treating physicians. As all three options are cost effective, treatment choice should focus on providing the most suitable treatment for the individual patient. For example,

- If a patient has received a taxane (paclitaxel or docetaxel) in the first line setting the only active treatment options for this patient would then be either erlotinib or pemetrexed.
- The FDA and EMEA do not deem erlotinib suitable for an EGFR negative patient. Therefore either docetaxel or pemetrexed would be suitable for this patient.
- If a patient or physician wished to treat a patient with active treatment but had concerns regarding severe diarrhoea & vomiting and febrile neutropenia, it would be preferable to use pemetrexed.

The table below shows which treatments may be suitable for different scenarios.

Possible reasons for active treatment selection for pemetrexed, docetaxel and erlotinib

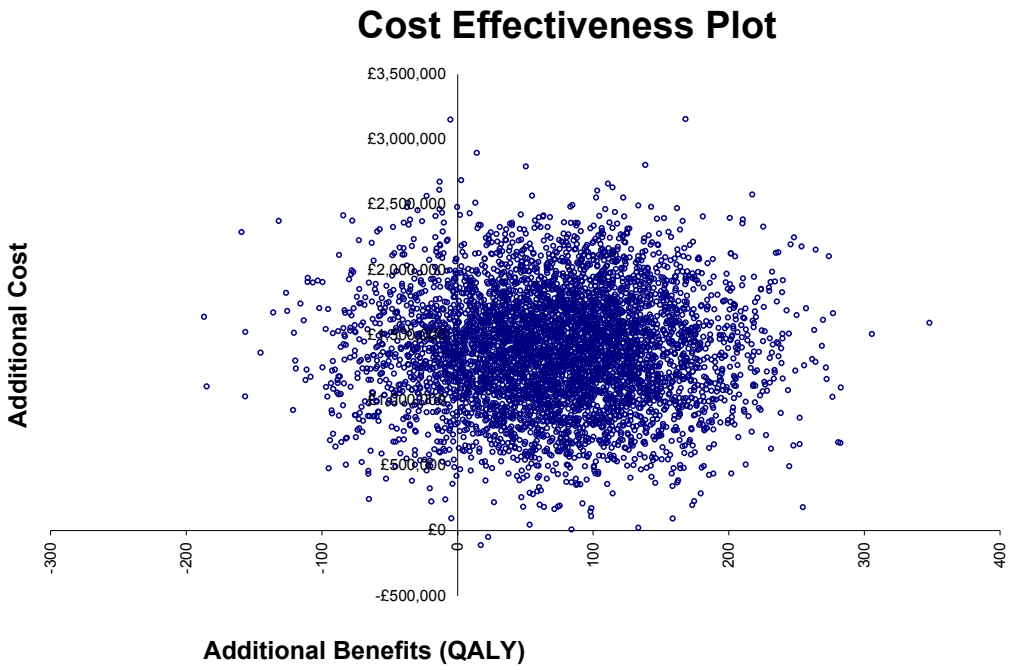
Reasons for treatment choices	Pemetrexed	docetaxel	erlotinib
Increased survival, reduction in symptoms	✓	✓	✓
patient or physician concerns of febrile neutropenia	✓	×	✓
patient or physician concerns of diarrhoea & vomiting	✓	×	×
patient or physician concerns of alopecia	✓	×	✓
patient received taxane first-line	✓	×	✓
oral therapy	×	×	✓
IV therapy	✓	✓	×
EGFR negative patient	✓	✓	×

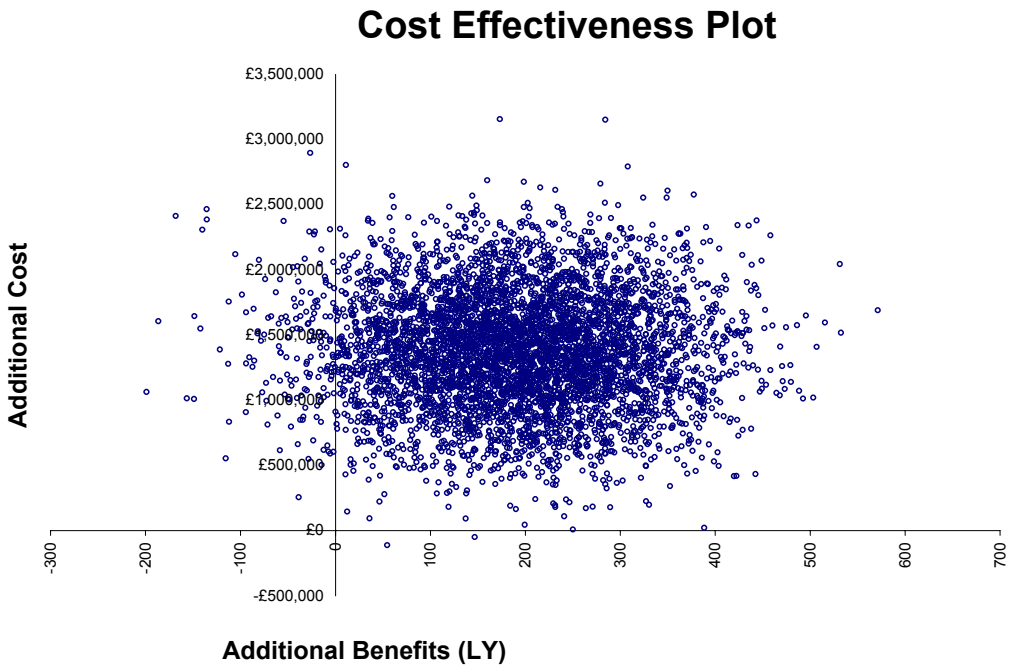
117. Please provide cost-effectiveness acceptability curves and scatterplots on cost-effectiveness quadrants.

PSA analysis was conducted using 5000 iterations, the results of which can be seen below, first for pemetrexed compared to the standard active comparator docetaxel and then to the standard of care BSC.

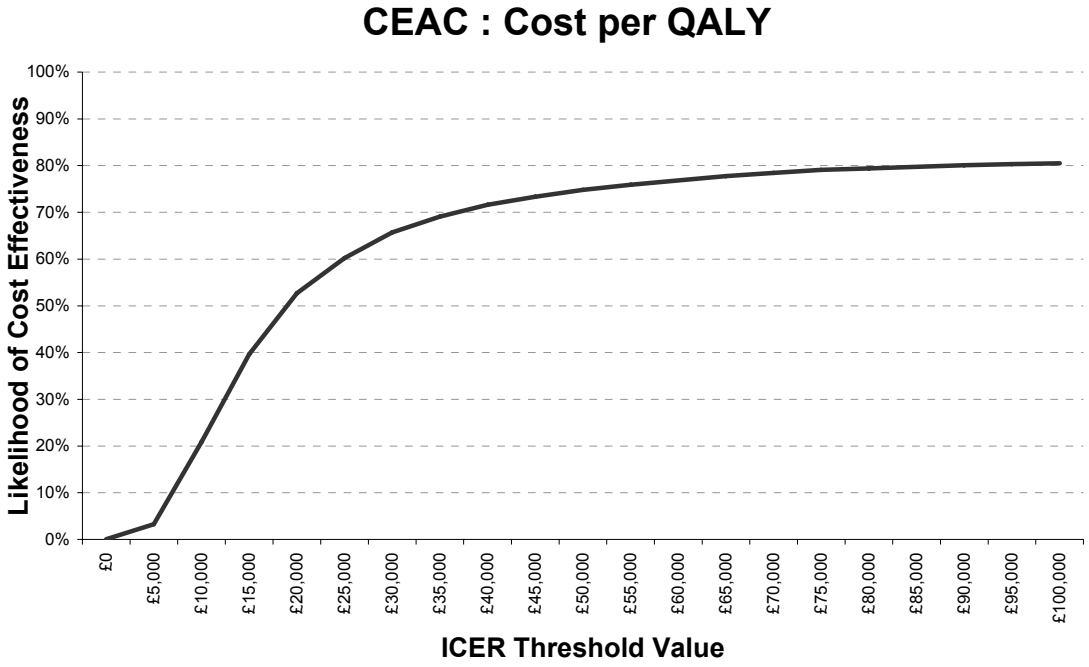
Comparison: Pemetrexed vs Docetaxel

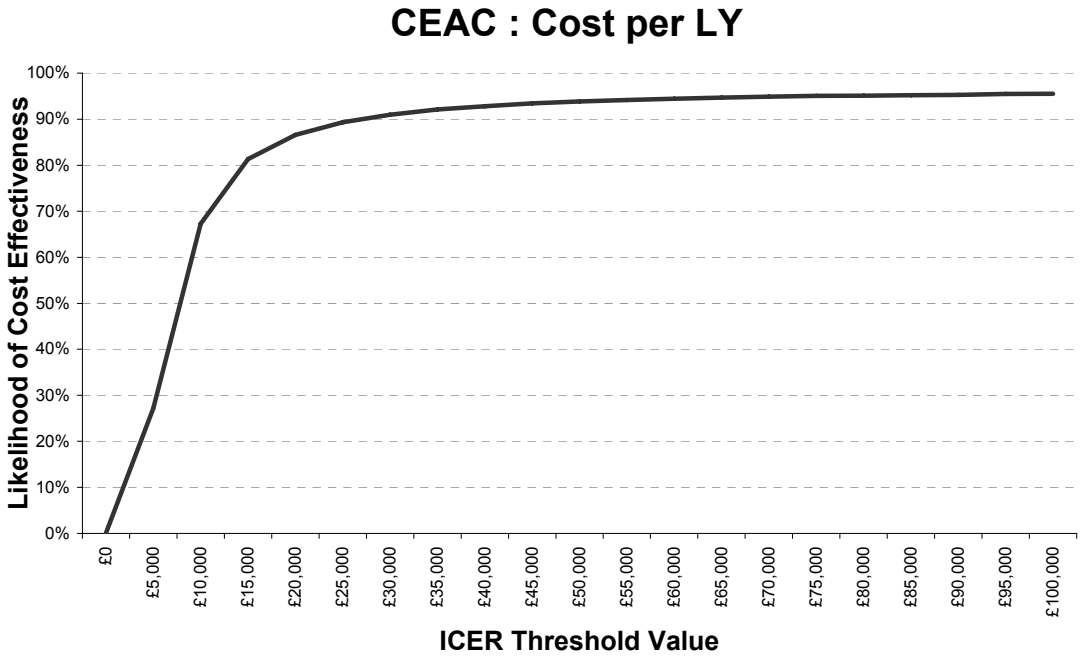
The plot data demonstrates that the majority of simulations resulted in additional costs and benefits for pemetrexed over docetaxel (the top right quadrant). This suggests that there is only a small probability of pemetrexed having a worse outcome than docetaxel (top and bottom left hand quadrants of the CE plane). Also there is only a negligible likelihood that the benefits of pemetrexed would be achieved by being cost saving (i.e. that pemetrexed would dominate docetaxel).





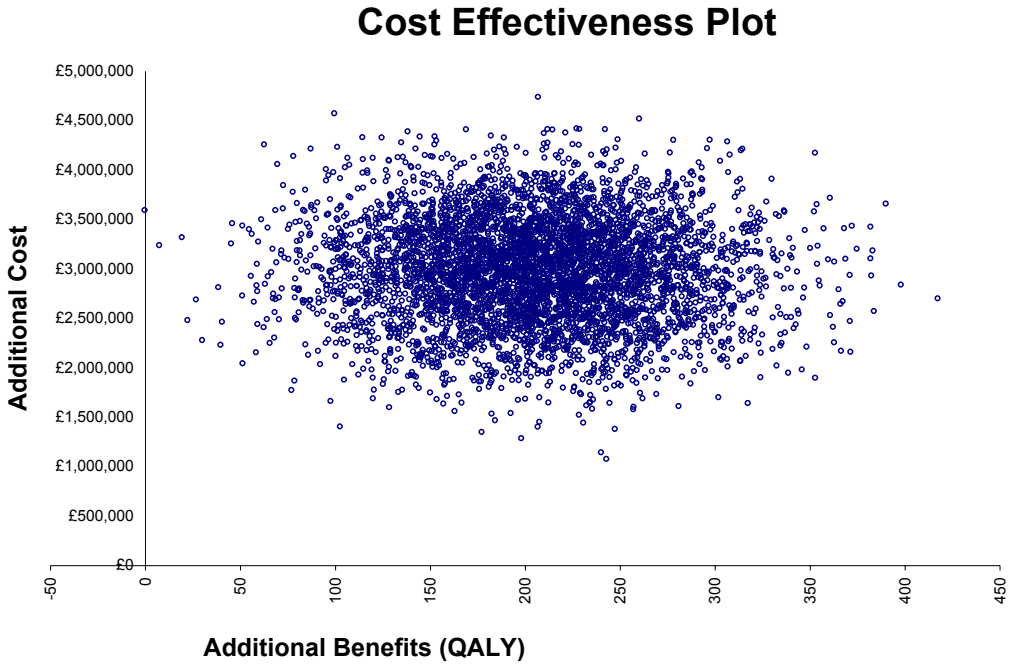
The cost effectiveness acceptability curves (CEAC) show the likelihood of pemetrexed being cost effective compared to docetaxel when considered across a range of thresholds for the cost per QALY and LY. Below is the CEAC for the incremental cost per QALY for pemetrexed compared to docetaxel. The CEAC plot shows that pemetrexed has a >90% likelihood of having a cost per LY value below £30,000 and a 67% likelihood of having a cost per QALY below £30,000.

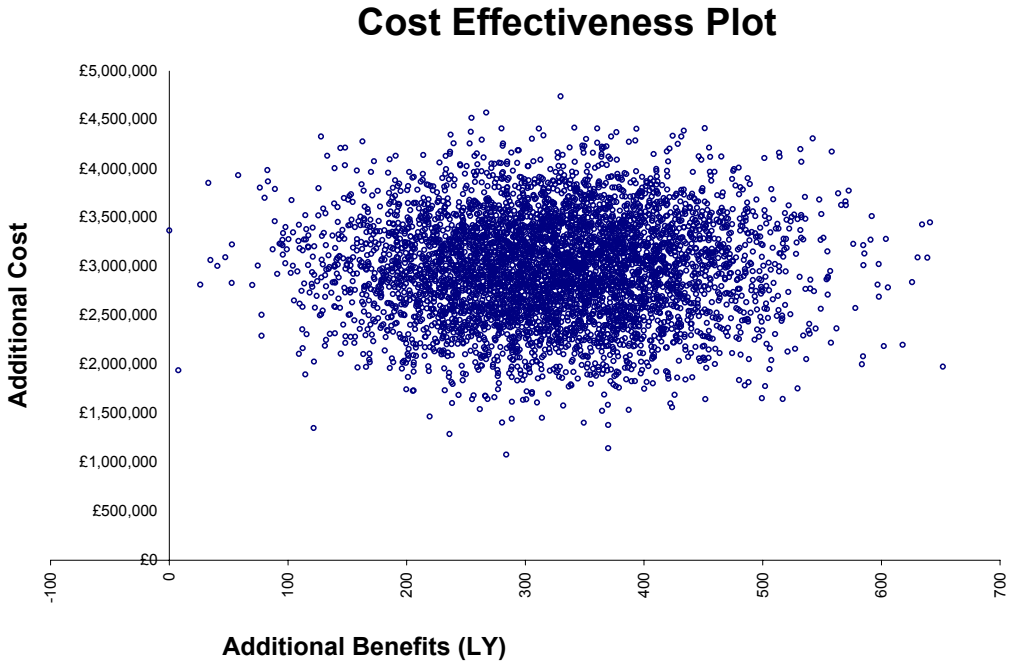




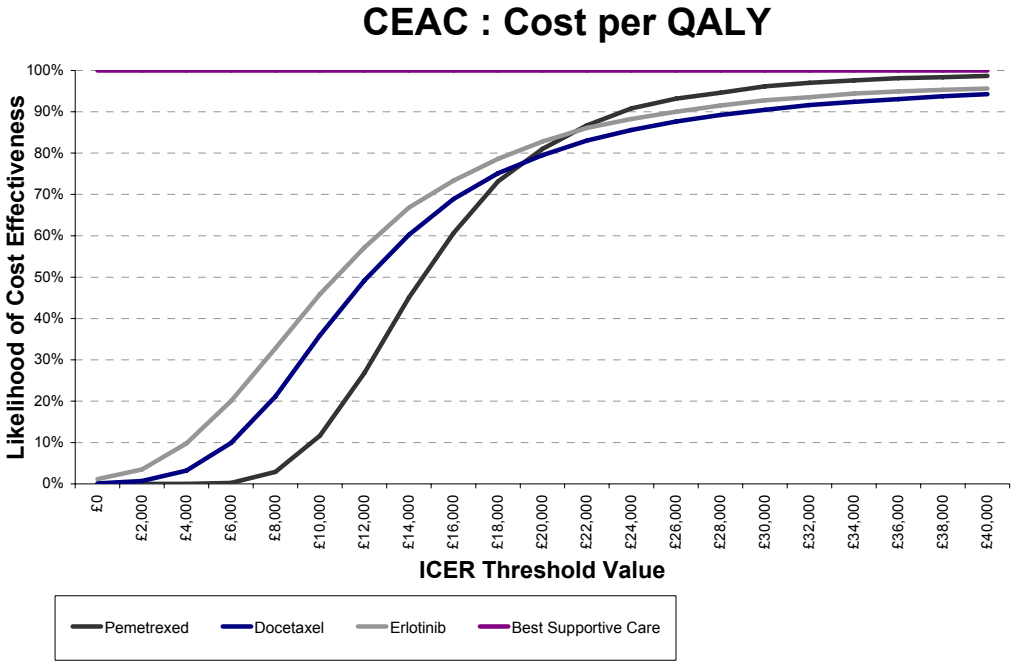
Comparison: Pemetrexed vs BSC

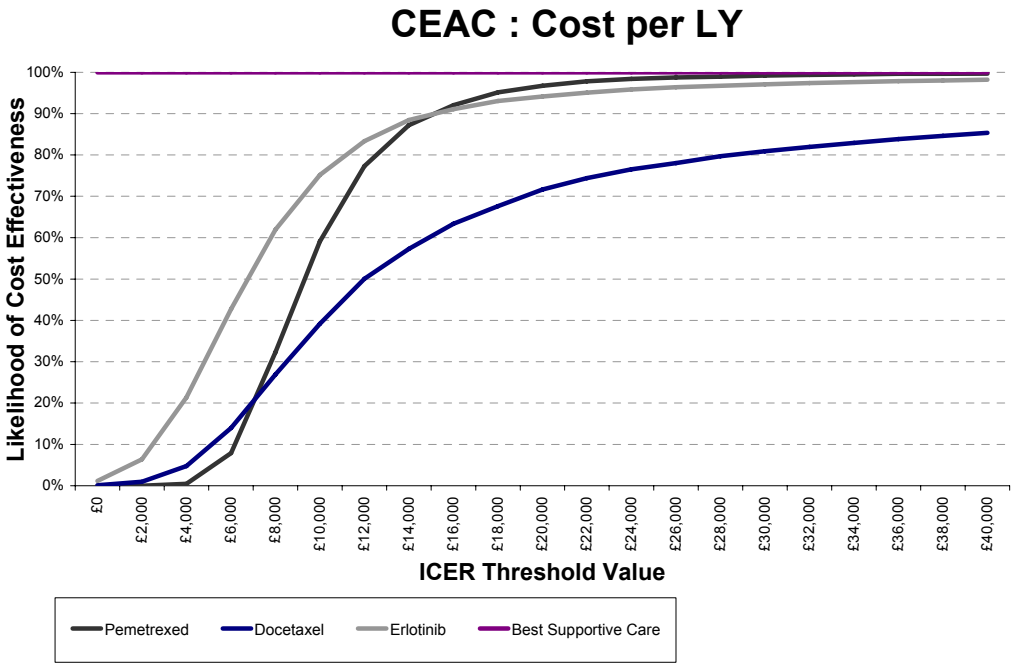
The plot data demonstrates that all the simulations resulted in additional costs and benefits for pemetrexed over the standard of care BSC (the top right quadrant of the CE plane). This suggests that there is no probability of pemetrexed having a poorer outcome than BSC. The cost effectiveness acceptability curves (CEAC) show the likelihood of pemetrexed being cost effective compared to BSC when considered across a range of thresholds for the cost per QALY and LY.





The cost effectiveness acceptability curves (CEAC) show the likelihood of pemetrexed being seen as cost effective compared to BSC when considered across a range of thresholds for the cost per QALY and LY. Below are the CEACs for the incremental cost per QALY for pemetrexed compared to BSC. The CEAC plot shows that pemetrexed has a 90% likelihood of having a cost per QALY value below £30,000 and a >90% likelihood of having a cost per LY below £30,000 compared to BSC.





118. Were results reported for different subgroups of patients? If so, what were the results for them?

Performance status sub-group analysis

The comparison of relevance for PS 0/1 is to a reference case of BSC as it is to reinforce the base that PS 0/1 patients are more appropriate for active treatment in NSCLC. In addition, the performance status prognostic factor did not increase differentiation between active products but showed similar increases in incremental benefit versus BSC.

The results for performance status PS 0/1 patients compared to all patients (i.e. PS 0,1 and ≥2) were investigated using the model. As can be seen, the results do not differ significantly from the base case for £12,045 per QALY for PS/01 patients vs BSC compared to £16,458 per QALY for all patients vs BSC. This is partly due to the fact that most patients in the trial are PS 0/1 and also due to the fact that time to disease progression had to be based upon the overall sample as data was only available for overall survival for all three active treatments. In routine clinical practice, it is likely that active regimens, particularly docetaxel which, is associated with a higher risk of serious adverse events, would not be given to patients of ≥PS 2 as they would have difficulty tolerating treatment. However, all three regimens do deliver greater survival gains in patients of good performance status (9.4 vs 8.3 months for pemetrexed, 9.1 vs 7.9 for docetaxel months, 8.3 vs 6.7 months for erlotinib).

Pemetrexed compared to standard of care: BSC

	PEM	BSC	Incremental
COSTS			
Active Treatment Cost	£4,591	£0	£4,591
Non Chemo Cost	£671	£0	£671
AE Cost	£89	£0	£89
BSC costs	£0	£1,871	-£1871
Palliative care costs	£3,467	£3,655	-£188
Total Direct Cost	**£8,818**	**£5,527**	**£3,291**
BENEFITS			
Quality-adjusted Life Years (QALYs)	0.56	0.29	0.27
Life Years (LY)	1.07	0.60	0.47

*Numbers do not compute due to rounding

ICER	**Pemetrexed compared to BSC**
Incremental costs	£3,291
Incremental LY	0.47
Incremental QALY	0.27
Cost per additional LYG	£6,992
Cost per additional QALY	£12,045

3.4.2 One-way/multiway sensitivity analysis

Sensitivity analysis should be conducted over a plausible range of prices for technologies whose final price/acquisition cost has not been confirmed.

119. Which variables were subject to sensitivity analysis?

One-Way Sensitivity Analysis

A range of one-way sensitivity analyses were run using the economic model to consider the variation in the incremental cost, incremental benefit and ICER outcomes when viable ranges of parameter values were independently considered.

The list of sensitivity scenarios are summarised below.

Time horizon
This was reduced from 3 years to 1 year to investigate the impact on results.

Costs

- **Discount rates** were varied from the baseline to between 0% and 6%.
- **All unit costs**, apart from chemotherapy drug acquisition costs, were varied by +/- 25%.
- **Drug acquisition costs**: were varied for docetaxel by -25% from list price to show the impact of potential procurement discounts. To be conservative we have assumed no discount for pemetrexed. The impact of per vial pricing compared to per mg pricing was also investigated. The body surface area was varied between 1.6 and 1.8 m^2 to reflect potential variation in average body size of patients with NSCLC.
- **Drug treatment variation:** Erlotinib use was continued to progression to reflect the uncertainty around duration of treatment and in response to advice from clinical experts in the UK that they treat to progression with erlotinib.
- **Duration of treatment:** The model assumes the duration of therapy is linked to time to disease progression and discontinuation from the phase III clinical trials. It is difficult to estimate the impact on efficacy of reduced duration of therapy. Therefore, the duration of therapy was varied by reducing the number of maximum cycles possible - however this will only impact on the costs in the model and not clinical outcomes. For all active treatments the maximum number of cycles was reduced to 4 cycles in the sensitivity.
- **Administration Time and Setting:** This was varied for chemotherapy treatment from 50% to 200% of baseline values i.e. from half to double. This was to represent potential variation in local clinical practice. Administration costs for pemetrexed were set to the assumption that the patient could receive the infusion at home to investigate impact of hospital versus home based administration.
- **Hospitalisations:** The number of hospitalisation days for AEs from 50% to 200% of baseline in order to reflect variation in local practice. The range of variation was broader than the values seen in the JMEI trial and is anticipated to capture the maximum probable variation in clinical practice. Hospitalisation rates for adverse events (FN, diarrhoea and nausea/vomiting) were varied +/- 25% from the baseline values.

Outcomes

- **Survival** was varied between the upper and lower 95% confidence intervals each survival estimate was varied individually
- **Time to progression** was varied between the minimum and maximum hazard rate for time to progression (based on CI) – each estimate was varied individually
- **Survival** was varied between the upper and lower 95% confidence interval for survival – each survival estimate was varied individually
- **Time to progression** was varied between the upper and lower 95% confidence interval for time to progression – each estimate was varied individually
- **Indirect efficacy comparison** was investigated based upon an anchored value for BSC
- Discount rates were varied between 0-6%.

Utilities

- **Stable/Response** on treatment utilities were varied by setting both to 0.6 and 0.7
- **Adverse event disutility** (representing an AE cost impact only) was varied from 0 to 150% of baseline disutility

120. What were the main findings of the sensitivity analysis?

Altering part of the model structure (Time horizon) while impacting the results still yielded ICERs that remained within an acceptable range.
The one way sensitivity analysis found that when altering the costs within the model the resulting ICERs remained within standard threshold levels. Reducing the drug acquisition costs of docetaxel to incorporate potential procurement discounts of up to 25% increases the ICER for pemetrexed from £18,672 to £27,968 compared to docetaxel. These estimates are still within acceptable thresholds. When switching from a per mg to vial based costing, the ICER for pemetrexed compared to docetaxel goes up to £22,228: the base is set to a per mg costing to reflect the availability of a 100 mg vial for pemetrexed in 2007 which will reduce wastage.

The model is sensitive to survival, both for docetaxel and pemetrexed. As the survival gains obtained are very similar, this produces cost per QALYs with wide variation. At the lower end of the 95% CI pemetrexed is dominated by docetaxel as it offers a tiny QALY gain of 0.0004 per patient at additional cost. Using the same lower 95% CI scenario for docetaxel results in an ICER of £9,010 for pemetrexed compared to docetaxel. However, when the indirect efficacy comparison method is used over that of the pooled analysis, based upon hazard ratios for the same pemetrexed survival data, the cost per QALY for pemetrexed compared to docetaxel is £31,612. In the PSA it can be seen that pemetrexed has a 60-80% likelihood of being cost effective within the standard thresholds of acceptability, and only a very small number of estimates lie within the higher cost / lower benefit quadrant (the North/West quadrant).

Table 59: One way sensitivity analysis for pemetrexed vs. docetaxel

	Incremental cost		Incremental benefit		Incremental ICER	
Variable	**min**	**max**	**min**	**max**	**Min**	**max**
Base case	**£1375**		**0.074**		**£18,672**	
Time dependent variables						
Time horizon	£1,375	£ 1,128	0.074	0.036	£18,672	£31,625
Costs						
All unit costs (exc. 2nd line drug)	£1,415	£ 1,334	0.074	0.074	£19,227	£18,118
Drug acquisition costs (DOC -25%)	£ 2,059	£ 1,339	0.074	0.074	£27,968	£18,672
Per vial drug costing	£1,375	£ 1,636	0.074	0.074	£18,672	£22,228
Duration of treatment (max 4 cycles)	£1,375	£ 930	0.074	0.075	£18,672	£12,459
Administration	£1,375	£ 921	0.074	0.074	£18,672	£12,505
Hospitalisations	£1,384	£ 1,355	0.074	0.074	£18,807	£18,402
Outcomes						
Survival 95% CI – DOC	£1,339	£ 1,540	0.149	-0.067	£9,010	-£22,831
TTDP 95% CI – DOC	£1,403	£ 1,354	0.038	0.110	£36,823	£12,301
Survival 95% CI – PEM	£1,433	£ 1,286	0.000	0.142	dominated	£9,089
TTDP 95% CI – PEM	£1,342	£ 1,402	0.102	0.044	£13,134	£31,741
Indirect efficacy comparison	£1,375	£ 1,339	0.074	0.042	£18,672	£31,612
Utilities						
Stable/Response	£1,375	£1,375	0.069	0.078	£19,977	£17,705
Adverse event disutility	£1,375	£1,375	0.071	0.075	£19,476	£18,265

Table 60: One way sensitivity analysis for pemetrexed vs. BSC

	Incremental cost		Incremental benefit		Incremental ICER	
Variable	**min**	**max**	**min**	**max**	**min**	**max**
Time dependent variables						
Time horizon	£3,379	£2,843	0.205	0.124	£16,458	£22,939
Costs						
All unit costs (exc. 2nd line drug)	£3,693	£3,066	0.205	0.205	£17,986	£14,929
Per vial drug costing	£3,379	£4,190	0.205	0.205	£16,458	£20,403
Duration of treatment	£3,379	£2,128	0.205	0.204	£16,458	£10,412
Administration	£ 2	£3,946	0.205	0.205	£15,077	£19,219
Hospitalisations	£3,365	£3,409	0.205	0.205	£16,387	£16,600
Outcomes						
Survival 95% CI – DOC	£3,379	£3,379	0.205	0.205	£16,458	£16,458
TTDP 95% CI – DOC	£3,379	£3,379	0.205	0.205	£16,458	£16,458
Survival 95% CI – PEM	£3,438	£3,291	0.132	0.273	£26,008	£12,045
TTDP 95% CI – PEM	£3,347	£3,407	0.234	0.176	£14,309	£19,369
Indirect efficacy comparison	£3,379	£3,510	0.205	0.341	£16,458	£10,298
Utilities						
Stable/Response	£3,379	£3,379	0.189	0.220	£17,878	£15,354
Adverse event disutility	£3,379	£3,379	0.206	0.205	£16,406	£16,486

121. Has the uncertainty associated with structural uncertainty been investigated? To what extent could/does this type of uncertainty change the results?

The structural assumptions which contain uncertainty within this model are as follows:

- Number of cycles within the model

For pemetrexed and docetaxel the median and mean number of cycles was 4. Clinical opinion supported the maximum use of 6 cycles in UK clinical practice. Therefore the impact of extending the cycle numbers would be expected to have limited impact on cost.

- Constant risk of AEs (other than a few specified toxicities which are loaded in first cycles of treatment)

The clinical trial data showed no evidence of time variable risks other than FN and initial response levels, so a constant risk and exponential assumption were applied for all other risks and probabilities. If evidence supported the inclusion of variation in the distribution of response rates and AE's over time the effect would be unlikely to make any significant difference to over treatment costs and benefits (events would simply happen a cycle earlier or a cycle later).

- Mutually exclusive AE events

The impact surrounding the structural uncertainty is that it may overestimate the costs of AEs if a patient had more than one adverse hospitalised event at the same time. However, extraction of the JMEI clinical trial data by adverse events showed that there were very few patients where more than one adverse event occurred at the same time.

3.4.3 Interpretation of economic evidence (300 word maximum)

122. Are the results from this economic evaluation consistent with the published economic literature? If not, why do the results from this evaluation differ and why should the results in the submission be given more credence than those in the published literature?

There are very few publications investigating the cost of 2nd line chemotherapy in NSCLC, not just those reflecting UK practice but reflecting any health care system across the globe. However, there is a published economic model which is highly relevant, the analysis of docetaxel vs. BSC from an NHS perspective. The estimate for the cost-effectiveness of docetaxel compared to BSC (as reference case) reported in the NICE appraisal of docetaxel also showed that docetaxel was cost-effective compared to BSC and at a similar ratio to that derived from this model, £13,863 (95% CI £10,985 to £16,738 for 2000/2001 values), for which NICE gave a positive recommendation on the basis of cost per life year. The inclusion of utility estimates that encompass efficacy and toxicity increases the credibility of this evaluation compared to the prior model.

The SMC resubmission of erlotinib shows the cost per QALY of erlotinib to be £22,500 when the number of cycles of docetaxel is 4. The results of this model are in line with these results.

123. Is the economic evaluation relevant to all groups of patients who could potentially use the technology?

The target population for patients treated with pemetrexed is indicated as monotherapy for the treatment of patients with locally advanced or metastatic non-small cell lung cancer, after prior chemotherapy. The economic evaluation is relevant to all groups of patients who may potentially utilise the chemotherapy combination under investigation.

124. What are the main strengths and weaknesses of the evaluation? How should these affect the interpretation of the results?

Strength	Impact on interpretation of results
An extremely large public preference utility study with 100 participants conducted to date has been incorporated into the study	Reduced assumptions Reduced uncertainty Allows the impact of AEs to be considered in the utility calculations
The utility study has been conducted according to the NICE reference case	Improved societal perspective
The model has been validated and scrutinised by a variety of people with differing areas of expertise	Robust model structure
Comprehensive model based on systematic review and synthesis of all data available	Robust model structure
First model to incorporate AE data	Robust model structure/ completeness of model

Weakness	Impact on interpretation of results
No patient level data available on erlotinib	Could have proved useful in supporting time dependency assumptions and limiting the need to form conclusion on docetaxel based average median values only.
Potential difference between trial and clinical practice dosages	If docetaxel, pemetrexed or erlotinib dose reduction is more prevalent in clinical practice than in clinical trials then the achievable survival outcomes at the licensed dose could be lower than those supported in trial protocol context.
Lack of any single head-to-head comparison in a phase III trial of all the considered treatments.	A head-to-head trial of all treatment options would obviously have been the best type of evidence base upon which to derive parameter values. An alternative would have been to use indirect relative risk effects through a common comparator (to link the outcome data to a common baseline). This was not available. Therefore the model is based on pooled weighted absolute outcomes. This therefore places a high weight on larger studies and also has implications in terms of ensuring patient cohorts are as comparable as possible.
Utility and cost applied to AEs experienced by greater than 6% of patients in the trials, and included the high cost large impact AEs (limited number of AEs excluded: ALT/AST, thrombocytopenia, leukopenia, abdominal pain, myalgia, alkaline phosphatase)	Expanding to all AEs would have minimal impact on results. This would only add to the completeness of the model.

125. What further analyses could be undertaken to enhance the robustness/completeness of the results?

If grade 1 and 2 adverse events were reported for all clinical trials the costs and associated utilities could have been built into the model which would have added to the completeness of the model.

If analysis in terms of clinical outcomes and adverse effects by the lines of therapy for erlotinib was available, this would have added to the robustness and completeness of the results.

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5 Appendices

Appendix 1 –ALIMTA▼SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Alimta* 500mg powder for concentrate for solution for infusion.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains 500mg of pemetrexed (as pemetrexed disodium).

Each vial must be reconstituted with 20ml of sodium chloride 9mg/ml (0.9%) solution for injection resulting in 25mg/ml of solution. The appropriate volume of required dose is removed from the vial and further diluted to 100ml with sodium chloride 9mg/ml (0.9%) solution for injection (see section 6.6).

For excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder for concentrate for solution for infusion.

A white to either light yellow or green-yellow lyophilised powder.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Alimta in combination with cisplatin is indicated for the treatment of chemotherapy naive patients with unresectable malignant pleural mesothelioma.

Alimta is indicated as monotherapy for the treatment of patients with locally advanced or metastatic non-small cell lung cancer after prior chemotherapy.

4.2 Posology and method of administration

Alimta must only be administered under the supervision of a physician qualified in the use of anti-cancer chemotherapy.

The Alimta solution must be prepared according to the instructions provided in section 6.6.

Malignant Pleural Mesothelioma

In patients treated for malignant pleural mesothelioma, the recommended dose of Alimta is 500mg/m^2 of body surface area (BSA) administered as an intravenous infusion over 10 minutes on the first day of each 21-day cycle.

The recommended dose of cisplatin is 75mg/m^2 BSA infused over two hours approximately 30 minutes after completion of the pemetrexed infusion on the first day of each 21-day cycle. Patients must receive adequate anti-emetic treatment and appropriate hydration prior to and/or after receiving cisplatin (see also cisplatin Summary of Product Characteristics for specific dosing advice).

Non-Small Cell Lung Cancer

In patients treated for non-small cell lung cancer, the recommended dose of Alimta is 500mg/m^2 BSA administered as an intravenous infusion over 10 minutes on the first day of each 21-day cycle.

Pre-Medication Regimen

To reduce the incidence and severity of skin reactions, a corticosteroid should be given the day prior to, on the day of, and the day after pemetrexed administration. The corticosteroid should be equivalent to 4mg of dexamethasone administered orally twice a day (see section 4.4).

To reduce toxicity, patients treated with pemetrexed must also receive vitamin supplementation (see section 4.4). Patients must take oral folic acid or a multivitamin containing folic acid (350 to 1,000 micrograms) on a daily basis. At least five doses of folic acid must be taken during the seven days preceding the first dose of pemetrexed, and dosing must continue during the full course of therapy and for 21 days after the last dose of pemetrexed. Patients must also receive an intramuscular injection of vitamin B_{12} (1000 micrograms) in the week preceding the first dose of pemetrexed and once every three cycles thereafter. Subsequent vitamin B_{12} injections may be given on the same day as pemetrexed.

Monitoring

Patients receiving pemetrexed should be monitored before each dose with a complete blood count, including a differential white cell count (WCC) and platelet count. Prior to each chemotherapy administration, blood chemistry tests should be collected to evaluate renal and hepatic function. Before the start of any cycle of chemotherapy, patients are required to have the following: absolute neutrophil count (ANC) should be $\geq$1,500 cells/mm^3 and platelets should be $\geq$100,000 cells/mm^3.

Creatinine clearance should be $\geq$45ml/min.

The total bilirubin should be $\leq$1.5-times upper limit of normal. Alkaline phosphatase (AP), aspartate transaminase (AST or SGOT), and alanine transaminase (ALT or SGPT) should be $\leq$3-times upper limit of normal. Alkaline phosphatase, AST, and ALT $\leq$5-times upper limit of normal is acceptable if liver has tumour involvement.

Dose Adjustments

Dose adjustments at the start of a subsequent cycle should be based on nadir haematologic counts or maximum non-haematologic toxicity from the preceding cycle of therapy. Treatment may be delayed to allow sufficient time for recovery. Upon recovery, patients should be retreated using the guidelines in *Tables 1, 2, and 3*, which are applicable for Alimta used as a single-agent or in combination with cisplatin.

Table 1. **Dose Modification Table for Alimta (as Single-Agent or in Combination) and Cisplatin - Haematologic Toxicities**

Nadir ANC <500/mm^3 and nadir platelets ≥50,000/mm^3	75% of previous dose (both Alimta and cisplatin)
Nadir platelets ≤50,000/mm^3 regardless of nadir ANC	50% of previous dose (both Alimta and cisplatin)

If patients develop non-haematologic toxicities ≥ Grade 3 (excluding neurotoxicity), Alimta should be withheld until resolution to less than or equal to the patient's pre-therapy value. Treatment should be resumed according to the guidelines in *Table 2*.

Table 2. **Dose Modification Table for Alimta (as Single-Agent or in Combination) and Cisplatin - Non-Haematologic Toxicities**[a, b]

	Dose of Alimta (mg/m^2)	**Dose for Cisplatin (mg/m^2)**
Any Grade 3 or 4 toxicities except mucositis	75% of previous dose	75% of previous dose
Any diarrhoea requiring hospitalisation (irrespective of grade) or Grade 3 or 4 diarrhoea	75% of previous dose	75% of previous dose
Grade 3 or 4 mucositis	50% of previous dose	100% of previous dose

[a]National Cancer Institute Common Toxicity Criteria (CTC).
[b]Excluding neurotoxicity.

In the event of neurotoxicity, the recommended dose adjustment for Alimta and cisplatin is documented in *Table 3*. Patients should discontinue therapy if Grade 3 or 4 neurotoxicity is observed.

Table 3. **Dose Modification Table for Alimta (as Single-Agent or in Combination) and Cisplatin - Neurotoxicity**

CTC* Grade	**Dose of Alimta (mg/m^2)**	**Dose for Cisplatin (mg/m^2)**
0-1	100% of previous dose	100% of previous dose
2	100% of previous dose	50% of previous dose

*National Cancer Institute Common Toxicity Criteria (CTC).

Treatment with Alimta should be discontinued if a patient experiences any haematologic or non-haematologic Grade 3 or 4 toxicity after 2 dose reductions or immediately if Grade 3 or 4 neurotoxicity is observed.

Elderly: In clinical studies, there has been no indication that patients 65 years of age or older are at increased risk of adverse events compared to patients younger than 65 years old. No dose reductions other than those recommended for all patients are necessary.

Children and adolescents: Alimta is not recommended for use in patients under 18 years of age, as safety and efficacy have not been established in this group of patients.

Patients with renal impairment (s*tandard Cockcroft and Gault formula or glomerular filtration rate measured Tc99m-DPTA serum clearance method):* Pemetrexed is primarily eliminated unchanged by renal excretion. In clinical studies, patients with creatinine clearance of ≥45ml/min required no dose adjustments other than those recommended for all patients. There are insufficient data on the use of pemetrexed in patients with creatinine clearance below 45ml/min; therefore, the use of pemetrexed is not recommended (see section 4.4).

Patients with hepatic impairment: No relationships between AST (SGOT), ALT (SGPT), or total bilirubin and pemetrexed pharmacokinetics were identified. However, patients with hepatic impairment, such as bilirubin >1.5-times the upper limit of normal and/or transaminase >3.0-times the upper limit of normal (hepatic metastases absent) or >5.0-times the upper limit of normal (hepatic metastases present), have not been specifically studied.

4.3 Contra-indications

Hypersensitivity to pemetrexed or to any of the excipients.

Breast-feeding must be discontinued during pemetrexed therapy (see section 4.6).

Concomitant yellow fever vaccine (see section 4.5).

4.4 Special warnings and precautions for use

Pemetrexed can suppress bone marrow function as manifested by neutropenia, thrombocytopenia, and anaemia (or pancytopenia) (see section 4.8). Myelosuppression is usually the dose-limiting toxicity. Patients should be monitored for myelosuppression during therapy and pemetrexed should not be given to patients until absolute neutrophil count (ANC) returns to ≥1500 cells/mm^3 and platelet count returns to ≥100,000 cells/mm^3. Dose reductions for subsequent cycles are based on nadir ANC, platelet count, and maximum non-haematologic toxicity seen from the previous cycle (see section 4.2).

In the Phase 3 mesothelioma trial, overall less toxicity and reduction in Grade 3/4 haematologic and non-haematologic toxicities, such as neutropenia, febrile neutropenia, and infection with Grade 3/4 neutropenia, were reported when pre-treatment with folic acid and vitamin B_{12} was administered. Therefore, patients treated with pemetrexed must be instructed to take folic acid and vitamin B_{12} as a prophylactic measure to reduce treatment-related toxicity (see section 4.2).

Skin reactions have been reported in patients not pre-treated with a corticosteroid. Pre-treatment with dexamethasone (or equivalent) can reduce the incidence and severity of skin reactions (see section 4.2).

An insufficient number of patients has been studied with creatinine clearance of below 45ml/min. Therefore, the use of pemetrexed in patients with creatinine clearance of <45ml/min is not recommended (see section 4.2).

Patients with mild to moderate renal insufficiency (creatinine clearance from 45 to 79ml/min) should avoid taking non-steroidal anti-inflammatory drugs (NSAIDs), such as ibuprofen, and aspirin (>1.3g daily) for 2 days before, on the day of, and 2 days following pemetrexed administration (see section 4.5).

All patients eligible for pemetrexed therapy should avoid taking NSAIDs with long elimination half-lives for at least 5 days prior to, on the day, and at least 2 days following pemetrexed administration (see section 4.5).

The effect of third space fluid, such as pleural effusion or ascites, on pemetrexed is unknown. In patients with clinically significant third space fluid, consideration should be given to draining the effusion prior to pemetrexed administration.

Due to the gastro-intestinal toxicity of pemetrexed given in combination with cisplatin, severe dehydration has been observed. Therefore, patients should receive adequate anti-emetic treatment and appropriate hydration prior to and/or after receiving treatment.

Serious cardiovascular events, including myocardial infarction and cerebrovascular events, have been uncommonly reported during clinical studies with pemetrexed, usually when given in combination with another cytotoxic agent. Most of the patients in whom these events have been observed had pre-existing cardiovascular risk factors (see section 4.8).

Immunodepressed status is common in cancer patients. As a result, concomitant use of live attenuated vaccines (except yellow fever) is not recommended (see section 4.5).

Pemetrexed can have genetically damaging effects. Sexually mature males are advised not to father a child during the treatment and up to 6 months thereafter. Contraceptive measures or abstinence are recommended. Owing to the possibility of pemetrexed treatment causing irreversible infertility, men are advised to seek counselling on sperm storage before starting treatment.

Women of childbearing potential must use effective contraception during treatment with pemetrexed (see section 4.6).

4.5 Interaction with other medicinal products and other forms of interaction

Pemetrexed is mainly eliminated unchanged renally by tubular secretion and to a lesser extent by glomerular filtration. Concomitant administration of nephrotoxic drugs (eg, aminoglycoside, loop diuretics, platinum compounds, cyclosporin) could potentially result in delayed clearance of pemetrexed. This combination should be used with caution. If necessary, creatinine clearance should be closely monitored.

Concomitant administration of substances that are also tubularly secreted (eg, probenecid, penicillin) could potentially result in delayed clearance of pemetrexed. Caution should be made when these drugs are combined with pemetrexed. If necessary, creatinine clearance should be closely monitored.

In patients with normal renal function (creatinine clearance $\geq$80ml/min), high doses of non-steroidal anti-inflammatory drugs (NSAIDs, such as ibuprofen >1600mg/day) and aspirin at higher dosage ($\geq$1.3g daily) may decrease pemetrexed elimination and, consequently, increase the occurrence of pemetrexed adverse events. Therefore, caution should be made when administering higher doses of NSAIDs or aspirin at higher dosage concurrently with pemetrexed to patients with normal function (creatinine clearance $\geq$80ml/min).

In patients with mild to moderate renal insufficiency (creatinine clearance from 45 to 79ml/min), the concomitant administration of pemetrexed with

NSAIDs (eg, ibuprofen) or aspirin at higher dosage should be avoided for 2 days before, on the day of, and 2 days following pemetrexed administration (see section 4.4).

In the absence of data regarding potential interaction with NSAIDs having longer half-lives, such as piroxicam or rofecoxib, the concomitant administration with pemetrexed should be avoided for at least 5 days prior to, on the day, and at least 2 days following pemetrexed administration (see section 4.4).

Pemetrexed undergoes limited hepatic metabolism. Results from *in vitro* studies with human liver microsomes indicated that pemetrexed would not be predicted to cause clinically significant inhibition of the metabolic clearance of drugs metabolised by CYP3A, CYP2D6, CYP2C9, and CYP1A2.

Interactions Common to all Cytotoxics

Due to the increased thrombotic risk in patients with cancer, the use of anticoagulation treatment is frequent. The high intra-individual variability of the coagulation status during diseases and the possibility of interaction between oral anticoagulants and anti-cancer chemotherapy require increased frequency of INR (International Normalised Ratio) monitoring, if it is decided to treat the patient with oral anticoagulants.

Concomitant Use Contra-Indicated

Yellow fever vaccine: Risk of fatal generalised vaccinale disease (see section 4.3).

Concomitant Use Not Recommended

Live attenuated vaccines (except yellow fever): Risk of systemic, possibly fatal, disease. The risk is increased in subjects who are already immunosuppressed by their underlying disease. Use an inactivated vaccine where it exists (poliomyelitis) (see section 4.4).

4.6 Pregnancy and lactation

There are no data from the use of pemetrexed in pregnant women but pemetrexed, like other anti-metabolites, is suspected to cause serious birth defects when administered during pregnancy. Animal studies have shown reproductive toxicity (see section 5.3). Pemetrexed should not be used during pregnancy unless clearly necessary, after a careful consideration of the needs of the mother and the risk for the foetus (see section 4.4).

Women of childbearing potential must use effective contraception during treatment with pemetrexed.

Pemetrexed can have genetically damaging effects. Sexually mature males are advised not to father a child during the treatment and up to 6 months thereafter. Contraceptive measures or abstinence are recommended. Owing to the possibility of pemetrexed treatment causing irreversible infertility, men are advised to seek counselling on sperm storage before starting treatment.

It is not known whether pemetrexed is excreted in human milk and adverse effects on the suckling child cannot be excluded. Breast-feeding must be discontinued during pemetrexed therapy (see section 4.3).

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. However, it has been reported that pemetrexed may cause fatigue. Therefore, patients should be cautioned against driving or operating machines if this event occurs.

4.8 Undesirable effects

The table below provides the frequency and severity of undesirable effects that have been reported in >5% of 168 patients with mesothelioma who were randomised to receive cisplatin and pemetrexed and 163 patients with mesothelioma randomised to receive single-agent cisplatin. In both treatment arms, these chemonaive patients were fully supplemented with folic acid and vitamin B_{12}.

System Organ Class	Frequency	Event*	Pemetrexed/Cisplatin (n = 168)		*Cisplatin* (n = 163)	
			All Grades Toxicity (%)	Grade 3-4 Toxicity (%)	All Grades Toxicity (%)	Grade 3-4 Toxicity (%)
Blood and lymphatic system disorders	Very common	Neutrophils/ granulocytes decreased	56.0	23.2	13.5	3.1
		Leucocytes decreased	53.0	14.9	16.6	0.6
		Haemoglobin decreased	26.2	4.2	10.4	0.0
		Platelets decreased	23.2	5.4	8.6	0.0
Eye disorders	Common	Conjunctivitis	5.4	0.0	0.6	0.0
Gastro-intestinal disorders	Very common	Nausea	82.1	11.9	76.7	5.5
		Vomiting	56.5	10.7	49.7	4.3
		Stomatitis/ pharyngitis	23.2	3.0	6.1	0.0
		Anorexia	20.2	1.2	14.1	0.6
		Diarrhoea	16.7	3.6	8.0	0.0
		Constipation	11.9	0.6	7.4	0.6
	Common	Dyspepsia	5.4	0.6	0.6	0.0
General disorders	Very common	Fatigue	47.6	10.1	42.3	9.2
Metabolism and nutrition disorders	Common	Dehydration	6.5	4.2	0.6	0.6
Nervous system	Very common	Neuropathy - sensory	10.1	0.0	9.8	0.6

disorders	Common	Dysgeusia	7.7	0.0	6.1	0.0
Renal and urinary disorders	Very common	Creatinine elevation	10.7	0.6	9.8	1.2
		Creatinine clearance decreased **	16.1	0.6	17.8	1.8
Skin and subcutaneous tissue disorders	Very common	Rash	16.1	0.6	4.9	0.0
		Alopecia	11.3	0.0	5.5	0.0

*Refer to National Cancer Institute CTC version 2 for each grade of toxicity, except the term “creatinine clearance decreased”** which is derived from the term “renal/genitourinary other”.

Very common - ≥10%; Common is normally defined as >1% and <10%. For the purpose of this table, a cut-off of 5% was used for inclusion of all events where the reporter considered a possible relationship to pemetrexed and cisplatin.

Clinically relevant CTC toxicities that were reported in >1% and ≤5% (common) of the patients that were randomly assigned to receive cisplatin and pemetrexed include: increased AST, ALT, and GGT, infection, pyrexia, febrile neutropenia, renal failure, chest pain, and urticaria.

Clinically relevant CTC toxicities that were reported in ≤1% of the patients that were randomly assigned to receive cisplatin and pemetrexed include arrhythmia and motor neuropathy.

The table below provides the frequency and severity of undesirable effects that have been reported in >5% of 265 patients randomly assigned to receive single-agent pemetrexed with folic acid and vitamin B_{12} supplementation and 276 patients randomly assigned to receive single-agent docetaxel. All patients were diagnosed with locally advanced or metastatic non-small cell lung cancer and received prior chemotherapy.

System Organ Class	Frequency	Event*	Pemetrexed n = 265		Docetaxel n = 276	
			All Grades Toxicity (%)	Grade 3-4 Toxicity (%)	All Grades Toxicity (%)	Grade 3-4 Toxicity (%)
Blood and lymphatic system disorders	Very common	Haemoglobin decreased	19.2	4.2	22.1	4.3
		Leucocytes decreased	12.1	4.2	34.1	27.2
		Neutrophils/ granulocytes decreased	10.9	5.3	45.3	40.2
	Common	Platelets decreased	8.3	1.9	1.1	0.4
Gastro-intestinal disorders	Very common	Nausea	30.9	2.6	16.7	1.8
		Anorexia	21.9	1.9	23.9	2.5
		Vomiting	16.2	1.5	12.0	1.1
		Stomatitis/ pharyngitis	14.7	1.1	17.4	1.1
		Diarrhoea	12.8	0.4	24.3	2.5
	Common	Constipation	5.7	0.0	4.0	0.0
General disorders	Very common	Fatigue	34.0	5.3	35.9	5.4
	Common	Fever	8.3	0.0	7.6	0.0
Hepatobiliary disorders	Common	SGPT (ALT) elevation	7.9	1.9	1.4	0.0
		SGOT (AST) elevation	6.8	1.1	0.7	0.0
Skin and subcutaneous tissue disorders	Very common	Rash/ desquamation	14.0	0.0	6.2	0.0
	Common	Pruritus	6.8	0.4	1.8	0.0
		Alopecia	6.4	0.4	37.7	2.2

*Refer to National Cancer Institute CTC version 2 for each grade of toxicity.

Very common - ≥10%; Common is normally defined as >1% and <10%. For the purpose of this table, a cut-off of 5% was used for inclusion of all events where the reporter considered a possible relationship to pemetrexed.

Clinically relevant CTC toxicities that were reported in >1% and ≤5% (common) of the patients that were randomly assigned to pemetrexed include: sensory neuropathy, motor neuropathy, abdominal pain, increased creatinine, febrile neutropenia, infection without neutropenia, allergic reaction/ hypersensitivity, and erythema multiforme.

Clinically relevant CTC toxicities that were reported in ≤1% of the patients that were randomly assigned to pemetrexed include supraventricular arrhythmias.

Clinically relevant Grade 3 and Grade 4 laboratory toxicities were similar between integrated Phase 2 results from three single-agent pemetrexed studies (n = 164) and the Phase 3 single-agent pemetrexed study described above, with the exception of neutropenia (12.8% versus 5.3%, respectively) and alanine transaminase elevation (15.2% versus 1.9%, respectively). These differences were likely due to differences in the patient population, since the Phase 2 studies included both chemonaive and heavily pre-treated

breast cancer patients with pre-existing liver metastases and/or abnormal baseline liver function tests.

Serious cardiovascular and cerebrovascular events, including myocardial infarction, angina pectoris, cerebrovascular accident, and transient ischaemic attack, have been uncommonly reported during clinical studies with pemetrexed, usually when given in combination with another cytotoxic agent. Most of the patients in whom these events have been observed had pre-existing cardiovascular risk factors.

Rare cases of hepatitis, potentially serious, have been reported during clinical studies with pemetrexed.

Pancytopenia has been uncommonly reported during clinical trials with pemetrexed.

During post-marketing surveillance, the following adverse reactions have been reported in patients treated with pemetrexed:

Rare cases of colitis have been reported in patients treated with pemetrexed.

4.9 Overdose

Reported symptoms of overdose include neutropenia, anaemia, thrombocytopenia, mucositis, sensory polyneuropathy, and rash. Anticipated complications of overdose include bone marrow suppression as manifested by neutropenia, thrombocytopenia, and anaemia. In addition, infection with or without fever, diarrhoea, and/or mucositis may be seen. In the event of suspected overdose, patients should be monitored with blood counts and should receive supportive therapy as necessary. The use of calcium folinate/folinic acid in the management of pemetrexed overdose should be considered.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Folic acid analogues. *ATC code:* L01BA04.

Alimta is a multi-targeted anti-cancer antifolate agent that exerts its action by disrupting crucial folate-dependent metabolic processes essential for cell replication.

In vitro studies have shown that pemetrexed behaves as a multi-targeted antifolate by inhibiting thymidylate synthase (TS), dihydrofolate reductase (DHFR), and glycinamide ribonucleotide formyltransferase (GARFT), which are key folate-dependent enzymes for the *de novo* biosynthesis of thymidine and purine nucleotides. Pemetrexed is transported into cells by both the reduced folate carrier and membrane folate binding protein transport systems. Once in the cell, pemetrexed is rapidly and efficiently converted to polyglutamate forms by the enzyme folylpolyglutamate synthetase. The polyglutamate forms are retained in cells and are even more potent inhibitors of TS and GARFT. Polyglutamation is a time- and concentration-dependent process that occurs in tumour cells and, to a lesser extent, in normal tissues. Polyglutamated metabolites have an increased intracellular half-life resulting in prolonged drug action in malignant cells.

Clinical Efficacy

EMPHACIS, a multi-centre, randomised, single-blind Phase 3 study of Alimta plus cisplatin versus cisplatin in chemonaive patients with malignant pleural mesothelioma, has shown that patients treated with Alimta and cisplatin had a clinically meaningful 2.8-month median survival advantage over patients receiving cisplatin alone.

During the study, low-dose folic acid and vitamin B_{12} supplementation was introduced to patients' therapy to reduce toxicity. The primary analysis of this study was performed on the population of all patients randomly assigned to a treatment arm who received study drug (randomised and treated). A subgroup analysis was performed on patients who received folic acid and vitamin B_{12} supplementation during the entire course of study therapy (fully supplemented). The results of these analyses of efficacy are summarised in the table below.

Efficacy of Alimta Plus Cisplatin vs Cisplatin in Malignant Pleural Mesothelioma

	Randomised and Treated Patients		**Fully Supplemented Patients**	
Efficacy Parameter	Alimta/Cisplatin (n = 226)	Cisplatin (n = 222)	Alimta/Cisplatin (n = 168)	Cisplatin (n = 163)
Median overall survival (months) (95% CI)	12.1 (10.0-14.4)	9.3 (7.8-10.7)	13.3 (11.4-14.9)	10.0 (8.4-11.9)
Log rank *P*-value*	0.020		0.051	
Median time to tumour progression (months) (95% CI)	5.7 (4.9-6.5)	3.9 (2.8-4.4)	6.1 (5.3-7.0)	3.9 (2.8-4.5)
Log rank *P*-value*	0.001		0.008	
Time to treatment failure (months) (95% CI)	4.5 (3.9-4.9)	2.7 (2.1-2.9)	4.7 (4.3-5.6)	2.7 (2.2-3.1)
Log rank *P*-value*	0.001		0.001	
Overall response rate** (95% CI)	41.3% (34.8-48.1)	16.7% (12.0-22.2)	45.5% (37.8-53.4)	19.6% (13.8-26.6)
Fisher's exact *P*-value*	<0.001		<0.001	

Abbreviation: CI = confidence interval.
**P*-value refers to comparison between arms.
**In the Alimta/cisplatin arm, randomised and treated (n = 225) and fully supplemented (n = 167).

A statistically significant improvement of the clinically relevant symptoms (pain and dyspnoea) associated with malignant pleural mesothelioma in the Alimta/cisplatin arm (212 patients) versus the cisplatin arm alone (218 patients) was demonstrated using the Lung Cancer Symptom Scale. Statistically significant differences in pulmonary function tests were also observed. The separation between the treatment arms was achieved by improvement in lung function in the Alimta/cisplatin arm and deterioration of lung function over time in the control arm.

There are limited data in patients with malignant pleural mesothelioma treated with Alimta alone. Alimta at a dose of 500mg/m^2 was studied as a

single-agent in 64 chemonaive patients with malignant pleural mesothelioma. The overall response rate was 14.1%.

A multi-centre, randomised, open-label Phase 3 study of Alimta versus docetaxel in patients with locally advanced or metastatic NSCLC after prior chemotherapy has shown median survival times of 8.3 months for patients treated with Alimta (intent to treat population n = 283) and 7.9 months for patients treated with docetaxel (ITT n = 288).

Efficacy of Alimta vs Docetaxel in NSCLC - ITT Population

	Alimta	Docetaxel
Survival time (months) • Median (m) • 95% CI for median • HR • 95% CI for HR • Non-inferiority *P*-value (HR)	(n = 283) 8.3 (7.0-9.4) 0.99 (.82-1.20) .226	(n = 288) 7.9 (6.3-9.2)
Progression free survival (months) • Median • HR (95% CI)	(n = 283) 2.9 0.97 (.82-1.16)	(n = 288) 2.9
Time to treatment failure (TTTF - months) • Median • HR (95% CI)	(n = 283) 2.3 0.84 (.71-.997)	(n = 288) 2.1
Response (n: qualified for response) • Response rate (%) (95% CI) • Stable disease (%)	(n = 264) 9.1 (5.9-13.2) 45.8	(n = 274) 8.8 (5.7-12.8) 46.4

Abbreviations: CI = confidence interval; HR = hazard ratio; ITT = intent to treat; n = total population size.

5.2 Pharmacokinetic properties

The pharmacokinetic properties of pemetrexed following single-agent administration have been evaluated in 426 cancer patients with a variety of solid tumours at doses ranging from 0.2 to 838mg/m^2 infused over a 10-minute period. Pemetrexed has a steady-state volume of distribution of 9 l/m^2. *In vitro* studies indicate that pemetrexed is approximately 81% bound to plasma proteins. Binding was not notably affected by varying degrees of renal impairment. Pemetrexed undergoes limited hepatic metabolism. Pemetrexed is primarily eliminated in the urine, with 70% to 90% of the administered dose being recovered unchanged in urine within the first 24 hours following administration. Pemetrexed total systemic clearance is 91.8ml/min and the elimination half-life from plasma is 3.5 hours in patients with normal renal function (creatinine clearance of 90ml/min). Between patient variability in clearance is moderate at 19.3%. Pemetrexed total systemic exposure (AUC) and maximum plasma concentration increase proportionally with dose. The pharmacokinetics of pemetrexed are consistent over multiple treatment cycles.

The pharmacokinetic properties of pemetrexed are not influenced by concurrently administered cisplatin. Oral folic acid and intramuscular vitamin B_{12} supplementation do not affect the pharmacokinetics of pemetrexed.

5.3 Preclinical safety data

Administration of pemetrexed to pregnant mice resulted in decreased foetal viability, decreased foetal weight, incomplete ossification of some skeletal structures, and cleft palate.

Administration of pemetrexed to male mice resulted in reproductive toxicity characterised by reduced fertility rates and testicular atrophy. This suggests that pemetrexed may impair male fertility. Female fertility was not investigated.

Pemetrexed was not mutagenic in either the *in vitro* chromosome aberration test in Chinese hamster ovary cells, or the Ames test. Pemetrexed has been shown to be clastogenic in the *in vivo* micronucleus test in the mouse.

Studies to assess the carcinogenic potential of pemetrexed have not been conducted.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Mannitol
Hydrochloric acid
Sodium hydroxide

6.2 Incompatibilities

Pemetrexed is physically incompatible with diluents containing calcium, including lactated Ringer's injection and Ringer's injection. In the absence of compatibility studies (with other drugs and diluents), this medicinal product must not be mixed with other medicinal products.

6.3 Shelf-life

Two years.

6.4 Special precautions for storage

Unopened vial: This medicinal product does not require any special storage conditions.

Reconstituted and infusion solutions: When prepared as directed, reconstitution and infusion solutions of Alimta contain no antimicrobial preservatives. Chemical and physical in-use stability of reconstituted and infusion solutions of pemetrexed were demonstrated for 24 hours at refrigerated temperature or 25°C. From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2 to 8°C, unless reconstitution/dilution has taken place in controlled and validated aseptic conditions.

6.5 Nature and contents of container

Powder in Type I glass vial. Rubber stopper.

Pack of 1 vial.

6.6 Instructions for use/handling and disposal

1. Use aseptic technique during the reconstitution and further dilution of pemetrexed for intravenous infusion administration.

2. Calculate the dose and the number of Alimta vials needed. Each vial contains an excess of pemetrexed to facilitate delivery of label amount.

3. Reconstitute 500mg vials with 20ml of sodium chloride 9mg/ml (0.9%) solution for injection, without preservative, resulting in a solution containing 25mg/ml pemetrexed. Gently swirl each vial until the powder is completely dissolved. The resulting solution is clear and ranges in colour from colourless to yellow or green-yellow without adversely affecting product quality. The pH of the reconstituted solution is between 6.6 and 7.8. **Further dilution is required**.

4. The appropriate volume of reconstituted pemetrexed solution should be further diluted to 100ml with sodium chloride 9mg/ml (0.9%) solution for injection, without preservative, and administered as an intravenous infusion over 10 minutes.

5. Pemetrexed infusion solutions prepared as directed above are compatible with polyvinyl chloride and polyolefin lined administration sets and infusion bags.

6. Parenteral medicinal products should be inspected visually for particulate matter and discolouration prior to administration. If particulate matter is observed, do not administer.

7. Pemetrexed solutions are for single use only. Any unused product or waste material should be disposed of in accordance with local requirements.

Preparation and administration precautions: As with other potentially toxic anti-cancer agents, care should be exercised in the handling and preparation of pemetrexed infusion solutions. The use of gloves is recommended. If a pemetrexed solution contacts the skin, wash the skin immediately and thoroughly with soap and water. If pemetrexed solutions contact the mucous membranes, flush thoroughly with water. Pemetrexed is not a vesicant. There is not a specific antidote for extravasation of pemetrexed. There have been few reported cases of pemetrexed extravasation, which were not assessed as serious by the investigator. Extravasation should be managed by local standard practice as with other non-vesicants.

7. MARKETING AUTHORISATION HOLDER

Eli Lilly Nederland BV, Grootslag 1-5, NL-3991 RA Houten, The Netherlands.

8. MARKETING AUTHORISATION NUMBER

EU/1/04/290/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 20 September 2004
Date of renewal of authorisation: -

10. DATE OF REVISION OF THE TEXT

February 2006

LEGAL CATEGORY

POM

*ALIMTA (pemetrexed) is a trademark of Eli Lilly and Company. AT2M

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Appendix 2

Table 61: Differences in the indications, contraindications, cautions, warnings and adverse effects between the proposed technology and the main comparators.

	Pemetrexed	Erlotinib	Docetaxel
Indications	1. Monotherapy for the treatment of patients with locally advanced or metastatic non-small cell lung cancer after prior chemotherapy. 2. In combination with cisplatin is indicated for the treatment of chemotherapy naive patients with unresectable malignant pleural mesothelioma	Erlotinib is indicated for the treatment of patients with locally advanced or metastatic non ‾ small cell lung cancer after failure of at least one prior chemotherapy regimen. No survival benefit or other clinically relevant effects of the treatment have been demonstrated in patients with EGFR- negative tumours	1. For the treatment of patients with locally advanced or metastatic non-small cell lung cancer after failure of prior chemotherapy. 2. In combination with cisplatin for the treatment of patients with unresectable, locally advanced or metastatic non-small cell lung cancer, in patients who have not previously received chemotherapy for this condition.
Mode of Action	Pemetrexed is an multi-targeted anti-cancer antifolate agent that exerts its action by disrupting crucial folate-dependent metabolic processes essential for cell replication. Pemetrexed is unqiue in that it antagonises at least 3 different enzymes	Docetaxel is an antineoplastic agent which acts by promoting the assembly of tubulin into stable microtubules and inhibits their disassembly which leads to a marked decrease of free tubulin. The binding of docetaxel to microtubules does not alter the number of protofilaments. Docetaxel has been shown *in vitro* to disrupt the microtubular network in cells which is essential for vital mitotic and interphase cellular functions	Erlotinib is an epidermal growth factor receptor/ human epidermal growth factor receptor type 1 (EGFR also known as HER1) tyrosine kinase inhibitor. Erlotinib potently inhibits the intracellular phosphorylation of EGFR. EGFR is expressed on the cell surface of normal cells and cancer cells. In non ‾ clinical models, inhibition of EGFR phosphotyrosine results in cell stasis and/or death
Contra-indications	Hypersensitivity to pemetrexed or to any of the excipients. Concomitant yellow fever vaccine.	Severe hypersensitivity to erlotinib or to any of the excipients.	Hypersensitivity to the active substance Docetaxel or to any of the excipients. Contraindicated in; patients with baseline neutrophil count of <1,500 cells/mm^3; in pregnant or breast-feeding women; in patients with severe liver impairment since there is no data available.

	Pemetrexed	Erlotinib	Docetaxel
Cautions	Pre-medication: 1000 micrograms vitamin B_{12} intramuscular and oral folic acid (350 to 1000 micrograms) Corticosteroid to reduce skin reactions. Dose adjustments should be based on nadir haematological counts or maximum non-haematological toxicity. Delay or withhold treatment in the presence of haematological toxicity, neurotoxicity, and/or impaired hepatic/renal function. Not recommended for use in patients under 18 years of age. Renal impairment: Creatinine clearance should be ≥45ml/min Hepatic impairment: Patients with hepatic impairment have not been specifically studied.	Concomitant use of CYP3A4 substrates and modulators may require dose adjustment Hepatic impairment Erlotinib has not been studied in patients with hepatic impairment. Use of Erlotinib in patients with severe hepatic impairment is not recommended Renal impairment: Has not been studied in patients with renal impairment (serum creatinine concentration>1.5 times the upper normal limit). Use of Erlotinib in patients with severe renal impairment is not recommended. The safety and efficacy of erlotinib has not been studied in patients under the age of 18 years. Use of Erlotinib in paediatric patients is not recommended.	Hepatic impairment: For patients who have both elevations of transaminase (ALT and/or AST) greater than 1.5 times the upper limit of the normal range (ULN) and alkaline phosphatase greater than 2.5 times the ULN, the recommended dose of docetaxel is 75 mg/m^2. For patients with serum bilirubin >ULN and/or ALT and AST >3.5 times the ULN associated with alkaline phosphatase >6 times the ULN, docetaxel should not be used unless strictly indicated. No data are available in patients with hepatic impairment treated by docetaxel in combination. The experience in children and adolescents is limited.
Warnings	Myelosuppression is usually the dose-limiting toxicity In patients with clinically significant third space fluid, consideration should be given to draining the effusion prior to administration. Serious cardiovascular events, including myocardial infarction and cerebrovascular events, have been uncommonly reported when pemetrexed is given in combination with other cytotoxic agents; most of these patients had pre-existing cardiovascular risk. Concomitant use of live attenuated vaccines is not recommended.	Concomitant treatment with potent inducers or potent inhibitors of CYP3A4 should be avoided Plasma concentrations could be reduced by smoking. Fatal cases of interstitial lung disease (ILD reported uncommonly in patients treated for of non ¯ small cell lung cancer (NSCLC) or other advanced solid tumours. Reported diagnoses in patients suspected of having ILD included pneumonitis, interstitial pneumonia, interstitial lung disease, obliterative bronchiolitis, pulmonary fibrosis, Acute Respiratory Distress Syndrome (ARDS), and lung infiltration. Confounding or contributing factors such as concomitant or prior chemotherapy, prior radiotherapy, pre ¯ existing parenchymal lung disease, metastatic lung disease, or pulmonary infections were frequent. In patients who develop acute onset of new and/or progressive unexplained pulmonary symptoms such as dyspnoea, cough and fever, Erlotinib therapy should be interrupted pending diagnostic	Premedication consisting of an oral corticosteroid, such as dexamethasone 16 mg per day for 3 days starting 1 day prior to docetaxel administration, unless contraindicated, can reduce the incidence and severity of fluid retention as well as the severity of hypersensitivity reactions. In the case of severe neutropenia (<500 cells/mm^3 for seven days or more) during a course of docetaxel therapy, a reduction in dose for subsequent courses of therapy or the use of appropriate symptomatic measures are recommended Hypersensitivity reactions may occur within a few minutes following the initiation of the infusion of docetaxel, thus facilities for the treatment of hypotension and bronchospasm should be available. If hypersensitivity reactions occur, minor symptoms such as flushing or localised cutaneous reactions do not require interruption of

	evaluation. If ILD is diagnosed, Erlotinib should be discontinued and appropriate treatment initiated as necessary. Diarrhoea in approx 50 % of patients on Erlotinib There have been rare reports of hypokalaemia and renal failure (including fatalities) secondary to severe dehydration, mainly in patients receiving concomitant chemotherapy. The effect of antacids, proton pump inhibitors and H2 antagonists on the absorption of erlotinib have not been investigated but absorption may be impaired, leading to lower plasma levels. Caution should be exercised when these medicinal products are combined with erlotinib.	therapy. However, severe reactions, such as severe hypotension, bronchospasm or generalised rash/erythema require immediate discontinuation of docetaxel and appropriate therapy. Patients who have developed severe hypersensitivity reactions should not be re-challenged with docetaxel. Localised skin erythema of the extremities (palms of the hands and soles of the feet) with oedema followed by desquamation has been observed. Severe symptoms which lead to interruption or discontinuation of docetaxel treatment were reported The development of severe peripheral neurotoxicity requires a reduction of dose Contraceptive measures must be taken during and for at least three months after cessation of therapy.

	Pemetrexed	Erlotinib	Docetaxel
Adverse effects	Haematological: Very common: Anaemia, leucopenia, thrombocytopenia, neutropenia. Common: Febrile neutropenia and infection without neutropenia. Uncommon: Pancytopenia. Gastro-intestinal: Very common: Nausea, vomiting, stomatitis/pharyngitis, anorexia, diarrhoea, constipation. Common: Dyspepsia, abdominal pain. Rare: Colitis. General: Very common: Fatigue. Common: Fever, conjunctivitis. Metabolism and nutrition: Common: Dehydration. Nervous system: Very common: Neuropathy - sensory. Common: Neuropathy - motor, dysgeusia. Renal and urinary: Very common: Creatinine elevation, creatinine clearance decreased. Hepatobiliary: Common: SGPT (ALT) elevation and SGOT (AST) elevation, increased GGT. Rare: Cases of hepatitis, potentially serious, have been reported during trials. Skin and subcutaneous tissue: Very common: Rash/desquamation, alopecia. Common: Urticaria, allergic reaction/hypersensitivity, erythema multiforme, pruritus. Cardiovascular and cerebrovascular: Uncommon: Myocardial infarction, angina pectoris, cerebrovascular accident, arrhythmias, transient ischaemic attack. (Usually when given in combination with other cytotoxic agents and with pre-existing cardiovascular risk.) Common: Chest pain.	Rash (75 %) and diarrhoea (54 %) were the most commonly reported adverse drug reactions (ADRs). Most were Grade ½ in severity and manageable without intervention. Grade ¾ rash and diarrhoea occurred in 9 % and 6 %, respectively in Erlotinib ⁻ treated patients and each resulted in study discontinuation in 1 % of patients. Dose reduction for rash and diarrhoea was needed in 6 % and 1 % of patients, respectively. In study BR.21, the median time to onset of rash was 8 days, and the median time to onset of diarrhoea was 12 days. Gastrointestinal: Common: Gastrointestinal bleeding. In clinical studies, some cases have been associated with concomitant warfarin administration and some with concomitant NSAID administration. Hepatobiliary: Common: Liver function test abnormalities (including increased alanine aminotransferase [ALT], aspartate aminotransferase [AST], bilirubin). These were mainly mild or moderate in severity, transient in nature or associated with liver metastases. Eye: Common: Keratitis. Corneal ulceration was reported in one patient receiving Erlotinib with concurrent chemotherapy, as a complication of mucocutaneous inflammation. Respiratory, thoracic and mediastinal: Uncommon: Serious interstitial lung disease (ILD), including fatalities, in patients receiving Erlotinib for treatment of NSCLC or other advanced solid tumours	The most commonly reported adverse reaction was neutropenia, which was reversible and not cumulative Docetaxel 75mg/m² single agent:Very common: Neutropenia (89.8%; G4: 54.2%); Anemia (93.3%; G3/4: 10.8%); Infections (10.7%; G3/4: 5%); Thrombocytopenia (10%; G4: 1.7%). Common: Febrile neutropenia (8.3%). Immune system disorders: Hypersensitivity reactions have generally occurred within a few minutes following the start of the infusion of docetaxel and were usually mild to moderate. The most frequently reported symptoms were flushing, rash with or without pruritus, chest tightness, back pain, dyspnoea and drug fever or chills. Severe reactions were characterised by hypotension and/or bronchospasm or generalized rash/erythema. Docetaxel 75mg/m² single agent: common (2.5%, no severe) Some cases of anaphylactic shock, sometimes fatal, have been reported. Skin and subcutaneous tissue: Reversible cutaneous reactions have been observed and were generally considered as mild to moderate. Rash including severe hand and foot syndrome, pruritus. Less frequently, severe symptoms such as eruptions followed by desquamation which rarely lead to interruption or discontinuation of docetaxel treatment were reported. Severe nail disorders are characterised by hypo- or hyperpigmentation and sometimes pain and onycholysis. Very rare: cutaneous lupus erythematosus, erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis. Docetaxel 75mg/m² single agent: Very common: Alopecia (38%); Cutaneous reactions (15.7%; G3/4: 0.8%). Common: Nail changes (9.9%; severe 0.8%).

Fluid retention: Peripheral oedema and less frequently pleural effusion, pericardial effusion, ascites and weight gain have been reported. The peripheral oedema usually starts at the lower extremities and may become generalised with a weight gain of 3 kg or more. Fluid retention is cumulative in incidence and severity. Docetaxel 75mg/m² single agent: very common (24.8%; severe 0.8%)
Gastrointestinal: Docetaxel 75mg/m² single agent: Very common: Nausea (28.9%; G3/4: 3.3%); Stomatitis (24.8%; G3/4: 1.7%); Vomiting (16.5%; G3/4: 0.8%); Diarrhoea (11.6%; G3/4: 1.7%). Common: Constipation (6.6%).
Nervous system: The development of severe peripheral neurotoxicity requires a reduction of dose. Mild to moderate neuro-sensory signs are characterised by paresthesia, dysesthesia or pain including burning. Neuro-motor events are mainly characterised by weakness. Docetaxel 75mg/m² single agent:Very common: Neurosensory (24%; G3: 0.8%). Common: Neuromotor (9.9%; G3/4: 2.5%).
Cardiac; Docetaxel 75mg/m² single agent: Common: Cardiac dysrhythmia (2.5%, no severe); Hypotension (1.7%).
Hepato-biliary: Docetaxel 75mg/m² single agent:Common: G3/4 bilirubin increase (<2%).
Metabolism and nutrition: Docetaxel 75mg/m² single agent: Very common: Anorexia (19%).
Ear and labyrinth: Rare cases of ototoxicity, hearing disorders and/or hearing loss have been reported.
Musculoskeletal, connective tissue and bone: Docetaxel 75mg/m² single agent: Common: Myalgia (5.8%). Docetaxel 75mg/m² single agent: Very common: Asthenia (48.8%; severe 12.4%); Pain (10.7%).

Appendix 3

Primary Hypotheses

Study	Role In Economic Analysis	Primary Hypotheses	Sample Size Calculations
Hanna et al., (2004)	Base Case	The study was designed to have an 81% chance of demonstrating noninferiority for survival time (defined as pemetrexed arm ≤ 10% worse than docetaxel arm) for pemetrexed when compared to docetaxel using the true hazard ratio (HR) to be 0.83.	This translated to an upper bound of the 95% CI less than 1.11 for the HRG of pemetrexed over docetaxel. In addition, the hypothesis that pemetrexed retained ≥ 50% of the survival benefit of docetaxel over BSC using data from the randomized comparative trial of docetaxel versus BSC by Shepherd et al was prospective planned (percent retention method). In the trial reported by Shepherd et al, the HR of docetaxel over BSC was estimated to be 0.56 (95% CI, 0.35 to 0.88). Setting the percentage of historical benefit at 50% and maintaining an approximate one-sided 2.5% type I error, an upper 95% CI bound of less than 1.21 for the HR of pemetrexed over docetaxel was required to establish the noninferiority of pemetrexed.
Shepherd et al., (2000)	Base Case	The sample size was chosen as the basis of a log-rank test used to compare the survival of the two randomised groups. Comparisons of survival for the two halves of the study were made between the patients treated at docetaxel doses of either 100mg/m2 or 75mg/m^2 and the corresponding ?BSC patients in that part of the trial.	A sample size of 100 patients per group was estimated on the basis of a projected median survival of 7 months in the docetaxel group and 4 months in the BSC group and on the basis of the log-rank test with an alpha level of 5% (two-sided) and a power of 90% to compare the groups. The sample size was not estimated for an analysis intended to compare results within the four strata, as defined by performance status and response to prior therapy.
Shepherd et al., (2005)	Base Case	The trial was designed to detect, with 90 percent power and a two-sided type I error if 5 percent, a 33 percent improvement in median survival from four month as estimated in the placebo group.	For the final analysis, 582 deaths were required and were projected to occur with a sample size of 700 patients enrolled over a period of 14 months 6 months of follow-up. The required number of deaths had occurred by January 2004, and the database was locked as of April 23, 2004. There was no interim analysis. Tumor responses were validated centrally for the first 333 patients in the trial.
Schuette et al., (2005)	Sensitivity Analysis	The study was designed to detect whether or not there was a significant difference in the 1-year survival rates between the 3-weekly and weekly treatment arms, using an equivalence tolerance of 2%.	On the basis of a minimum expected 1-year survival rate of 15% and maximum expected 1-year survival rate of 30%, 102 patients per group were required to test the equivalence of the two regimens with a certainty of 80%. The test significance level was α = .05.

Study	Role In Economic Analysis	Primary Hypotheses	Sample Size Calculations
Fossella et al., (2000)	Sensitivity Analysis	The sample size of this study was based on the assumption that median survival in the group treated with either docetaxel dose would be approximately 7.5 months, compared with 5 months in the group with the V/I control treatment.	Given this assumption, a sample size of 360 patients (120 per treatment arm) would allow for the detection of the overall survival advantage in either docetaxel arm at an alpha level of 5% (one-sided) and 80% power. Although, a one-sided test error was the basis for determination of the sample size, all statistical tests were performed based on a two-sided error of 5%.
Gridelli et al., (2004)	Sensitivity Analysis	Global health status scale (items 29 and 30) of EORTC QLQ-C30 after 3 weeks from the start of chemotherapy was used to plan sample size.	A 90% power to detect an effect size of 50% (i.e. a difference between mean scores of global health status equal to 50% of the standard deviation) after 3 weeks of chemotherapy was palnned. Such an effect size has been correlated with conditions of 'moderate' or 'very much' positive changes in a subjective satisfaction questionnaire. With a two-sided significance level of 0.05, a total of 172 patients were needed. Assuming a 25% drop-out rate, 215 patients were required.
Camps et al., (2006)	Sensitivity Analysis	Calculation of sample size of the study was based on the assumption of an equal expected 1 year survival for both arms i.e. 20% and the maximum allowed difference was 15%	A total of 123 patients per group was estimated on the basis of an alpha level of 5% (two-sided) and a power of 80% to compare the groups, assuming a 10% drop-off of patients.
Thatcher et al., (2005)	Sensitivity Analysis	The sample size required a total of 696 adenocarcinoma deaths for a 33% improvement in survival to be detected with 90% power, with allowance for up to 15% crossover to gefitinib in the placebo group.	The postulated 33% improvement in survival for gefitinib-treated patients was relative and assumed a median survival was best supportive care of 5.2 months (directly equivalent to 1-year survival of 20%). To provide 90% for a survival advantage to be detected in the overall population similar to that seen for erlotinib, at least 900 deaths would be needed.
Ramlau et al., (2006)	Sensitivity Analysis	380 patients per group were required.	The sample size was based on an assumed 1-year survival rate of 37% in both groups and a two-group large-sample normal approximation test of proportions with a one-sided 0.025 significance level, 81% power and a protocol-specified absolute margin of noninferiority for 1-year survival of 10%.

Critical Appraisal

Randomisation

Study	Role In Economic Analysis	A	B	C
Hanna et al., (2004)	Base Case	X		
Shepherd et al., (2000)	Base Case	X		
Shepherd et al., (2005)	Base Case			X
Schuette et al., (2005)	Sensitivity Analysis	X		
Fossella et al., (2000)	Sensitivity Analysis	X		
Gridelli et al., (2004)	Sensitivity Analysis			X
Camps et al., (2006)	Sensitivity Analysis			X
Thatcher et al., (2005)	Sensitivity Analysis			X
Ramlau et al., (2006)	Sensitivity Analysis	X		

Key

A) No details of randomisation are available, or the method used was inadequate (e.g. randomisation according to the day of the week, even / odd medical record numbers). An insecure randomisation method was used, where clinical staff could possibly learn of the treatment assignment (e.g. randomisation sequence kept in the clinical area and open / unblended trial; treatment assignment kept in consecutive 'sealed' envelopes and open / unblended trial).

B) A secure randomisation method was used, where the randomisation sequence was kept away from the clinical area and administered by staff not directly involved in patient care.

Adequacy of Follow-Up

Study	Role In Economic Analysis	A	B	C
Hanna et al., (2004)	Base Case			X
Shepherd et al., (2000)	Base Case			X
Shepherd et al., (2005)	Base Case			X
Schuette et al., (2005)	Sensitivity Analysis		X	
Fossella et al., (2000)	Sensitivity Analysis			X
Gridelli et al., (2004)	Sensitivity Analysis			X
Camps et al., (2006)	Sensitivity Analysis		X	
Thatcher et al., (2005)	Sensitivity Analysis		X	
Ramlau et al., (2006)	Sensitivity Analysis			X

Key

A. There were significant numbers of drop-outs with no assessment of trial outcome(s) in the subjects who dropped out, and drop-out rates differed between treated and control groups.
1 There were some drop-outs with no assessment of trial outcomes(s) in the subjects who dropped out, and drop-out rates were (approximately) equivalent in treated and control groups.
B. Trial outcome(s) were assessed in all treated and control subjects.

Blinding of Outcomes Assessment.

Study	Role In Economic Analysis	A	B
Hanna et al., (2004)	Base Case		See section 2.4.3
Shepherd et al., (2000)	Base Case	NR	NR
Shepherd et al., (2005)	Base Case	NR	NR
Schuette et al., (2005)	Sensitivity Analysis	NR	NR
Fossella et al., (2000)	Sensitivity Analysis	NR	NR
Gridelli et al., (2004)	Sensitivity Analysis	X	
Camps et al., (2006)	Sensitivity Analysis	NR	NR
Thatcher et al., (2005)	Sensitivity Analysis		X
Ramlau et al., (2006)	Sensitivity Analysis	X	

Key

A) There was an inadequate attempt (or no attempt) to blind observer(s), and the measurement technique was subject to observer bias (e.g. blood pressure measurement with standard sphygmomanometer; measurement of vertebral height on an x-ray.
B) The observer(s) were kept fully blinded to treatment assignment, or the measurement technique was not subject to observer bias (e.g. measurement of bone mineral density or survival).

Parallel-Group or Cross-Over

Study	Role In Economic Analysis	Design (parallel-group or cross-over)	Likely existence of a cross-over effect
Hanna et al., (2004)	Base Case	Parallel-group	Patients were randomly assigned to receive either pemetrexed or docetaxel in this parallel, open-label trial. However, patients may have crossed-over, at the investigator's discretion, if further treatment was warranted, following the primary treatment phase.
Shepherd et al., (2000)	Base Case	Parallel-group	N/A
Shepherd et al., (2005)	Base Case	Parallel-group	N/A
Schuette et al., (2005)	Sensitivity Analysis	Parallel-group	N/A
Fossella et al., (2000)	Sensitivity Analysis	Cross-over	Because more than one third of patients continued to receive additional chemotherapy on removal from study and more than 50% of patients in the V/I control group received a taxane (cross-over), another intent-to-treat survival analysis was carried out that censored survival at the time when patients received subsequent chemotherapy on removal from study. In this analysis, the confounding effects of the post study chemotherapy on survival were expected to be minimized so that comparisons of docetaxel doses to the control would be robust.
Gridelli et al., (2004)	Sensitivity Analysis	Parallel-group	N/A
Camps et al., (2006)	Sensitivity Analysis	Parallel-group	N/A
Thatcher et al., (2005)	Sensitivity Analysis	Parallel-group	N/A
Ramlau et al., (2006)	Sensitivity Analysis	Cross-over	In the docetaxel arm, 3 patients (1%) received topotecan post study.

Trial Conducted in UK

Study	Role In Economic Analysis	Trial conducted in the UK (Y/N)	Were one or more centres of the multinational trial located in the UK?
Hanna et al., (2004)	Base Case	NR	NR
Shepherd et al., (2000)	Base Case	Yes	Yes (n = 2 / 36)
Shepherd et al., (2005)	Base Case	No	No
Schuette et al., (2005)	Sensitivity Analysis	No	No
Fossella et al., (2000)	Sensitivity Analysis	No	No
Gridelli et al., (2004)	Sensitivity Analysis	No	No
Camps et al., (2006)	Sensitivity Analysis	No	No
Thatcher et al., (2005)	Sensitivity Analysis	Yes	Yes
Ramlau et al., (2006)	Sensitivity Analysis	NR	NR

Appendix 4

Median Overall Survival: Absolute Values

Trial	Product	N	Survival (Months)	Lower Range (Months)	Upper Range (Months)	Survival (Weeks)	Lower Range (Weeks)	Upper Range (Weeks)
Hanna et al., (2004)	Pemetrexed 500mg/m^2	283	8.3	NR	NR	35.97	NR	NR
Shepherd et al., (2005)	Erlotinib	488	6.7	NR	NR	29.03	NR	NR
Hanna et al., (2004)	Docetaxel 75mg/m^2	288	7.9	NR	NR	34.23	NR	NR
Shepherd et al., (2000)	Docetaxel 75mg/m^2	55	7.5	NR	NR	32.50	NR	NR
Schuette et al., (2005)	Docetaxel 75mg/m^2	103	6.3	4.68	7.84	27.30	20.28	33.97
Fossella et al., (2000)	Docetaxel 75mg/m^2	125	5.7	NR	NR	24.70	NR	NR
Camps et al., (2005)	Docetaxel 75mg/m^2	129	6.6	5.5	7.7	28.6	23.83	33.37
Ramlau et al., (2006)	Docetaxel 75mg/m^2	415	NR	NR	NR	30.7	NR	NR
Gridelli et al., (2004)	Docetaxel 75mg/m^2	110	NR	NR	NR	29.0	21.00	36.00
Shepherd et al., (2000)	BSC	100	4.6	NR	NR	19.93	NR	NR
Shepherd et al., (2005)	BSC	243	4.7	NR	NR	20.37	NR	NR
Thatcher et al., (2005)	BSC	563	5.1	NR	NR	22.1	NR	NR

Median Overall Survival: Calculations Performed to Determine Pooled Data By Treatment

POOLED WEIGHTED BY PATIENT NUMBERS

Pemetrexed	N	Survival (weeks)	95% L (weeks)	95% U (weeks)	Variance		Assumed Exponential Survival lamda	sd	se
Hanna et al., 2004	283	35.96			9.51253363	←	0.019273415	51.88494	3.0842396
Pooled Median	35.96		upper	42.01					
Pooled Variance	9.51		lower	29.92					
PSA	37.63								

Docetaxel 75mg/m2	N	Survival (weeks)	95% L (weeks)	95% U (weeks)	Variance	Var2		Assumed Exponential Survival lamda	sd	se
Schuette et al., 2005	103	27.30	20.28	33.97	12.2022395	1244.6284				
Fossella et al., 2000	125	24.70			10.1584229	1259.6444	←	0.028062855	35.634293	3.1872281
Camps et al., 2005	129	28.60	23.83	33.37	5.91440066	757.04328				
Hanna et al., 2004	288	34.23			8.46931501	2430.6934	←	0.020247883	49.38788	2.9102088
Gridelli et al., 2004	110	29.00	21.00	36.00	14.6423365	1596.0147				
Ramlau., 2006	415	30.70			4.72691434	1956.9425	←	0.022578084	44.290738	2.1741468
Shepherd et al., 2000	55	32.50			39.9711303	2158.441	←	0.02132777	46.887228	6.3222726
Pooled Median	30.34		upper	42.73						
Pooled Variance	9.35		lower	24.35						
PSA	29.90									

Erlotinib	N	Survival (weeks)	95% L (weeks)	95% U (weeks)	Variance		Assumed Exponential Survival lamda	sd	se
Shepherd et al., 2005	488	29.03			3.5951447	←	0.023874369	41.885924	1.8960867
Pooled Median	29.03		upper	32.75					
Pooled Variance	3.60		lower	25.32					
PSA	28.99								

BSC	N	Survival (weeks)	95% L (weeks)	95% U (weeks)	Variance	Var2		Assumed Exponential Survival lamda	sd	se
Shepherd et al., 2000	100	19.93			8.26993803	818.72386	←	0.034773537	28.7575	2.87575
Shepherd et al., 2005	243	20.37			3.55284314	859.78804	←	0.034033675	29.382663	1.8848987
Thatcher et al., 2005	563	22.10			1.80558754	1014.7402	←	0.031364367	31.883315	1.3437215
Pooled Median	21.40		upper	24.03						
Pooled Variance	2.98		lower	18.01						
PSA	19.79									

Time to Disease Progression: Absolute Values

Trial	Product	N	TtDP (Months)	Lower Range (Months)	Upper Range (Months)	TtDP (Weeks)	Lower Range (Weeks)	Upper Range (Weeks)
Hanna et al., (2004)	Pemetrexed 500mg/m^2	283	3.4	0.5	18.2	14.73	2.17	78.87
Shepherd et al., (2005)	Erlotinib	488	2.2	NR	NR	9.53	NR	NR
Hanna et al., (2004)	Docetaxel 75mg/m^2	288	3.5	0.3	19.5	15.17	1.30	84.50
Shepherd et al., (2000)	Docetaxel 75mg/m^2	55	NR	NR	NR	10.60	NR	NR
Schuette et al., (2005)	Docetaxel 75mg/m^2	103	3.4	2.1	4.8	14.73	9.10	20.80
Fossella et al., (2000)	Docetaxel 75mg/m^2	124	NR	NR	NR	8.50	6.70	11.00
Camps et al., (2005)	Docetaxel 75mg/m^2	129	2.7	1.6	3.8	11.70	6.93	16.47
Ramlau et al., (2006)	Docetaxel 75mg/m^2	415	NR	NR	NR	13.1	NR	NR
Gridelli et al., (2004)	Docetaxel 75mg/m^2	110	NR	NR	NR	NR	NR	NR
Shepherd et al., (2000)	BSC	100	NR	NR	NR	6.70	NR	NR
Shepherd et al., (2005)	BSC	243	1.8	NR	NR	7.80	NR	NR
Thatcher et al., (2005)	BSC	563	2.6	NR	NR	11.27	NR	NR

Time to Disease Progression: Calculations Performed to Determine Pooled Data By Treatment

POOLED WEIGHTED BY PATIENT NUMBERS

Pemetrexed	N	TTP (weeks)	95% L (weeks)	95% U (weeks)	Variance	Assumed Exponential Survival lamda	sd	se
Hanna et al., 2004	283	14.73			1.59645981	0.047046551	21.255543	1.2635109
Pooled Median	14.73		upper	17.21				
Pooled Variance	1.60		lower	12.26				
PSA	13.72							

Docetaxel	N	TTP (weeks)	95% L (weeks)	95% U (weeks)	Variance	Var2	Assumed Exponential Survival lamda	sd	se
Schuette et al., 2005	103	14.73			4.38638958	447.41174	0.047046551	21.255543	2.0943709
Fossella et al., 2000	124	8.50	6.70	11.00	1.20327468	148.00279			
Hanna et al., 2004	288	15.17			1.66237957	477.10294	0.045702363	21.880706	1.289333
Shepherd et al., 2000	55	10.60			4.25204761	229.61057	0.065391243	15.292567	2.0620494
Camps et al., 2005	129	11.70	6.93	16.47	5.92276656	758.11412			
Ramlau., 2006	415	13.10	12.00	16.00	1.04123282	431.07039			
Pooled Median	12.99		upper	15.93					
Pooled Variance	2.25		lower	10.05					
PSA	12.46								

Erlotinib	N	TTP (weeks)	95% L (weeks)	95% U (weeks)	Variance	Assumed Exponential Survival lamda	sd	se
Shepherd et al., 2005	488	9.53			0.38762531	0.072708306	13.753587	0.6225956
Pooled Median	9.53		upper	10.75				
Pooled Variance	0.39		lower	8.31				
PSA	8.93							

BSC	N	TTP (weeks)	95% L (weeks)	95% U (weeks)	Variance	Var2	Assumed Exponential Survival lamda	sd	se
Shepherd et al., 2000	100	6.70			0.93432654	92.498327	0.103454803	9.6660568	0.9666057
Shepherd et al., 2005	243	7.80			0.52110511	126.10744	0.088865707	11.252935	0.7218761
Thatcher et al., 2005	563	11.27			0.46927227	263.73102	0.061522412	16.254239	0.6850345
Pooled Median	9.83		upper	11.27					
Pooled Variance	0.53		lower	8.40					
PSA	9.32								

Time to Disease Progression: Detailed Calculations Performed For Pemetrexed to Determine Time to Disease Progression For Responders and Non-Responders

Pemetrexed

Hanna et al., Randomized phase III trial of pemetrexed versus docetaxel in patients with non-small-cell lung cancer previously treated with chemotherapy
J Clin Oncol. 2004 May 1;22(9):1589-97.

	N	TTP (weeks)	95% L (weeks)	95% U (weeks)	Variance
Hanna et al., 2004	24	35.32			108.16595
POOLED					

Assumed Exponential Survival

lamda	sd	se
0.019626782	50.950788	10.400286

Median TTP (responders)	35.32
Median TTP (all patients)	14.73
Ratio	2.40

Point Est

Median TTP - all patients	14.73	TTP(all)	from the point estimate value for all treated patients
Median TTP - responders	35.32		from Hanna et al
Median TTP - non responders	12.65	TTP(nresp)	calculated using response rate, TTP and TTP(resp)
Median TTP - responders	28.41	from response to progression	

Response rate	0.09	converts TTP to mean and
Mean TTP - all patients	21.26	weighted averages the TTP for non responders
Mean TTP - responders	50.95	assumes exponential TTP
Mean TTP - non responders	18.25	
Median TTP - non responders	12.65	

PSA

Median TTP - all patients	11.46	TTP(all)	from the PSA value for all treated patients
Median TTP - responders	24.32	TTP(resp)	from Hanna et al
Median TTP - non responders	10.11	TTP(nresp)	calculated using response rate, TTP and TTP(resp)
Median TTP - responders	17.41	from response to progression	

Response rate	0.09	converts TTP to mean and
Mean TTP - all patients	16.53	weighted averages the TTP for non responders
Mean TTP - responders	35.08	
Mean TTP - non responders	14.59	
Median TTP - non responders	10.11	

Time to Disease Progression: Detailed Calculations Performed For Docetaxel to Determine Time to Disease Progression For Responders and Non-Responders

Docetaxel

Uses a TTP ratio derived from the Hanna et al Study
Docetaxel arm

Median TTP (responders)	32.07
Median TTP (all patients)	15.17
Ratio	2.11

provides a ratio of TTP based on TTP(responders) / TTP(all treated)

POOLED

Point Est

Median TTP - all patients	12.99	TTP(all)	from the point estimate value for all treated patients
Median TTP - responders	27.4596681	TTP(resp)	calculated using ratio
Median TTP - non responders	11.93	TTP(nresp)	calculated using response rate, TTP and TTP(resp)
Median TTP - responders	20.55		from response to progression

0.00	32.0642

Response rate	0.07
Mean TTP - all patients	18.74
Mean TTP - responders	39.62
Mean TTP - non responders	17.21
Median TTP - non responders	11.93

converts TTP to mean and weighted averages the TTP for non responders

PSA

Median TTP - all patients	14.37	TTP(all)	from the PSA value for all treated patients
Median TTP - responders	30.38	TTP(resp)	calculated using ratio
Median TTP - non responders	13.66	TTP(nresp)	calculated using response rate, TTP and TTP(resp)
Median TTP - responders	23.47		from response to progression

Response rate	0.04
Mean TTP - all patients	20.73
Mean TTP - responders	43.83
Mean TTP - non responders	19.71
Median TTP - non responders	13.66

converts TTP to mean and weighted averages the TTP for non responders

Time to Disease Progression: Detailed Calculations Performed For Erlotinib to Determine Time to Disease Progression For Responders and Non-Responders

Erlotinib

Uses a TTP ratio derived from the Hanna et al Study
Pemetrexed arm

Median TTP (responders)	35.32
Median TTP (all patients)	14.73
Ratio	2.40

provides a ratio of TTP based on TTP(responders) / TTP(all treated)

POOLED

Point Est

Median TTP - all patients	9.53	TTP(all)	from the point estimate value for all treated patients
Median TTP - responders	22.85	TTP(resp)	calculated using ratio
Median TTP - non responders	8.23	TTP(nresp)	calculated using response rate, TTP and TTP(resp)
Median TTP - responders	15.94		from response to progression

0.00	31.20

Response rate	0.09
Mean TTP - all patients	13.75
Mean TTP - responders	32.97
Mean TTP - non responders	11.88
Median TTP - non responders	8.23

converts TTP to mean and weighted averages the TTP for non responders

PSA

Median TTP - all patients	9.70	TTP(all)	from the PSA value for all treated patients
Median TTP - responders	23.25	TTP(resp)	calculated using ratio
Median TTP - non responders	8.10	TTP(nresp)	calculated using response rate, TTP and TTP(resp)
Median TTP - responders	16.34		from response to progression

Response rate	0.11
Mean TTP - all patients	13.99
Mean TTP - responders	33.54
Mean TTP - non responders	11.68
Median TTP - non responders	8.10

converts TTP to mean and weighted averages the TTP for non responders

Response Rates: Absolute Values

Trial	Product	N	Overall Response Rates (%)
Hanna et al., (2004)	Pemetrexed 500mg/m^2	283	9.1
Shepherd et al., (2005)	Erlotinib	427	8.9
Hanna et al., (2004)	Docetaxel 75mg/m^2	288	8.8
Shepherd et al., (2000)	Docetaxel 75mg/m^2	55	5.5
Schuette et al., (2005)	Docetaxel 75mg/m^2	103	12.6
Fossella et al., (2000)	Docetaxel 75mg/m^2	120	6.7
Camps et al., (2005)	Docetaxel 75mg/m^2	129	9.3
Ramlau et al., (2006)	Docetaxel 75mg/m^2	415	5
Gridelli et al., (2004)	Docetaxel 75mg/m^2	110	2.7
Shepherd et al., (2000)	BSC	100	NR
Shepherd et al., (2005)	BSC	211	
Thatcher et al., (2005)	BSC	563	

Response Rates: Detailed Calculations Performed For Pemetrexed to Determine Response Rates

Pemetrexed	N	n	Response (%)
Hanna et al., 2004	283	26	9.19%

SE	1.72%	calculated standard error
lower	5.82%	weighted mean - 1.96 * weighted SD
upper	12.55%	weighted mean + 1.96 * weighted SD
PSA	8.59%	assumed as approximate normal distribution for mean value

Docetaxel

Number of trials	7	All trials
weighted mean	6.80%	pooled weighted mean statistic (x_w)
weighted SE	1.93%	pooled weighted SD of the mean statistic (s_w)
lower	3.01%	weighted mean - 1.96 * weighted SD
upper	10.60%	weighted mean + 1.96 * weighted SD
PSA	5.18%	assumed as approximate normal distribution for mean value

	Data from trials					Calculation of Standard Error and CI of Mean						Used for pooled variance
						var S^2	SD S	1/var $1/S^2$	CI step	U	L	(N-1) * var
	n	N	p	q	pq	pq/N	sqrt(S^2) (SE)					
Schuette et al., 2005	13	103	0.13	0.87	0.11	0.00	0.03	933.95	0.06	0.19	0.06	0.11
Fossella et al., 2000	8	120	0.07	0.93	0.06	0.00	0.02	1,928.57	0.04	0.11	0.02	0.06
Hanna et al., 2004	25	288	0.09	0.91	0.08	0.00	0.02	3,633.14	0.03	0.12	0.05	0.08
Shepherd et al., 2000	3	55	0.05	0.95	0.05	0.00	0.03	1,066.51	0.06	0.11	(0.01)	0.05
Camps et al., 2005	12	129	0.09	0.91	0.08	0.00	0.03	1,528.98	0.05	0.14	0.04	0.08
Ramlau., 2006	19	415	0.05	0.95	0.04	0.00	0.01	9,499.39	0.02	0.07	0.03	0.04
Gridelli et al., 2004	3	110	0.03	0.97	0.03	0.00	0.02	4,146.42	0.03	0.06	(0.00)	0.03

Pooled Data	0.071	arithmetic mean
	0.058	weighted by w = 1/std error
	0.068	weighted by w = N
	0.000	pooled variance of statistic - weighted by N
	0.019	pooled standard deviation (error) of statistic - weighted by N

Response Rates: Detailed Calculations Performed For Docetaxel to Determine Response Rates

Response Rates: Detailed Calculations Performed For Erlotinib to Determine Response Rates

Erlotinib	N	n	Response (%)
Shepherd et al., 2005	427	38	8.90%

SE	1.38%	calculated standard error
lower	6.20%	weighted mean - 1.96 * weighted SD
upper	11.60%	weighted mean + 1.96 * weighted SD
PSA	8.98%	assumed as approximate normal distribution for mean value

Incidence of Grade 3 / 4 Adverse Events: Absolute Values

			GRADE 3-4 ADVERSE EVENTS						
Trial	Product	N	Neutropenia	Febrile Neutropenia	Nausea / vomiting	Diarrhoea	Fatigue	Alopecia (any grade)	Rash
Hanna et al., (2004)	Pemetrexed 500mg/m^2	265	14	5	11	1	14	17	2
Shepherd et al., (2005)	Erlotinib	485	NR	NR	29	29	92	NR	44
Hanna et al., (2004)	Docetaxel 75mg/m^2	276	111	35	8	7	15	104	2
Shepherd et al., (2000)	Docetaxel 75mg/m^2	55	37	1	4	1	NR	NR	NR
Schuette et al., (2005)	Docetaxel 75mg/m^2	102	21	2	5	NR	NR	NR	NR
Fossella et al., (2000)	Docetaxel 75mg/m^2	121	65	10	5	2	NR	NR	NR
Camps et al., (2005)	Docetaxel 75mg/m^2	129	19	10	1	1	NR	80	NR
Ramlau et al., (2006)	Docetaxel 75mg/m^2	401	NR	11	11	11	17	140	NR
Gridelli et al., (2004)	Docetaxel 75mg/m^2	107	20	5	0	3	7	40	NR
Shepherd et al., (2000)	BSC	100	NR	NR	6	0	NR	NR	NR
Shepherd et al., (2005)	BSC	242	NR	NR	6	1	56	NR	0
Thatcher et al., (2005)	BSC	562	NR	NR	4	5	NR	NR	1

Incidence of Grade 3 / 4 Adverse Events: Detailed Calculations Performed For Pemetrexed – Excluding Febrile Neutropenia

Pemetrexed	N	FN	Neutropenia	Nausea/ Vomiting	Fatigue	Diarrhea	Rash	Alopecia
		n	n	n	n	n	n	n
Hanna et al., 2004	265	5	14	11	14	1	2	17
Rate of AE (%)		1.89%	5.28%	4.15%	5.28%	0.38%	0.75%	6.42%

Incidence of Grade 3 / 4 Adverse Events: Detailed Calculations Performed For Pemetrexed – Excluding Febrile Neutropenia

Docetaxel 75mg/m2		FN	Neutropenia	Nausea/ Vomiting	Fatigue	Diarrhea	Rash	Alopecia
	N	n	n	n	n	n	n	n
Schuette et al., 2005	102	2	21	5				
Fossella et al., 2000	121	10	65	5		2		
Hanna et al., 2004	276	35	111	8	15	7	2	104
Shepherd et al., 2000	55	1	37	4		1		
Camps et al,. 2005	129	10	19	1		1		80
Ramlau et al., 2006	401	11	238	11	17	11		140
Gridelli et al., 2004	107	5	20	0	7	3		40
Rate of AE (%)		12.68%	42.91%	2.85%	4.97%	2.30%	0.72%	39.87%

FN	Neutropenia	Nausea/ Vomiting	Fatigue	Diarrhea	Rash	Al
%	%	%	%	%	%	
1.96%	20.59%	4.90%				
8.26%	53.72%	4.13%		1.65%		
12.68%	40.22%	2.90%	5.43%	2.54%	0.72%	3
1.82%	67.27%	7.27%		1.82%		
7.75%	14.73%	0.78%		0.78%		6
2.74%	59.35%	2.74%	4.24%	2.74%		3
4.67%	18.69%	0.00%	6.54%	2.80%		3

Incidence of Grade 3 / 4 Adverse Events: Detailed Calculations Performed For Erlotinib – Excluding Febrile Neutropenia

Erlotinib		FN	Neutropenia	Nausea/ Vo	Fatigue	Diarrhea	Rash	Alopecia
	N	n	n	n	n	n	n	n
Shepherd et al., 2005	485			29	92	29	44	
Rate of AE (%)		0.00%	0.00%	5.98%	18.97%	5.98%	9.07%	0.00%

Incidence of Grade 3 / 4 Febrile Neutropenia: Detailed Calculations Performed For Pooling of Data – All Treatments

Pemetrexed	Total	Cycle 1	Cycle 2	Cycle 3+	Cycle 1	Cycle 2	Cycle 3+
Hanna et al., 2004	1.89%	0.00%	60.00%	40.00%	0.00%	1.13%	0.75%

Docetaxel 75mg/m2	Total	Cycle 1	Cycle 2	Cycle 3+	Cycle 1	Cycle 2	Cycle 3+
Hanna et al., 2004	12.68%	65.71%	14.29%	20.00%	8.33%	1.81%	2.54%

Erlotinib	Total	Cycle 1	Cycle 2	Cycle 3+
Shepherd et al., 2005	1.89%	0.00%	1.13%	0.75%

Treatment Discontinuation Rates: Absolute Values

Trial	Product	N	Toxicity	Consent Withdrawal
JMEI Study Report (PBAC Submission)	Pemetrexed 500mg/m^2	283	21	12
Shepherd et al., (2005)	Erlotinib	485	26	NR
JMEI Study Report (PBAC Submission)	Docetaxel 75mg/m^2	288	25	18
Shepherd et al., (2000)	Docetaxel 75mg/m^2	55	NR	NR
Schuette et al., (2005)	Docetaxel 75mg/m^2	103	10	4
Fossella et al., 2000	Docetaxel 75mg/m^2	121	7	NR
Camps et al., 2005	Docetaxel 75mg/m^2	129	9	7
Ramlau et al., 2006	Docetaxel 75mg/m^2	415	49	NR
Gridelli et al., 2004	Docetaxel 75mg/m^2	106	12	NR
Shepherd et al., (2000)	BSC	100	NR	NR
Shepherd et al., (2005)	BSC	242	4	NR
Thatcher et al., 2005	BSC	563	13	NR

Adverse Event Discontinuation Rates: Calculations Performed to Determine Pooled Data By Treatment

Pemetrexed

	N	Rate	n	SE	PSA
Hanna et al., 2004	283	0.07	21	0.0156	0.056

Docetaxel 75mg/m2

	N	Rate	n	SE	Var	Var * (N-1)
Schuette et al., 2005	103	10%	10	0.0292	0.0009	0.0868103
Fossella et al., 2000	121	6%	7	0.0212	0.0005	0.054054
Hanna et al., 2004	288	9%	25	0.0166	0.0003	0.0789951
Camps et al., 2005	129	7%	9	0.0224	0.0005	0.0643968
Ramlau et al., 2006	415	12%	49	0.0158	0.0003	0.1038803
Gridelli et al., 2004	106	11%	12	0.0308	0.0009	0.0994445

Pooled Data	0.090	arithmetic mean
	0.096	weighted by w = N
	0.000	pooled variance of statistic - weighted by N
	0.021	pooled standard deviation (error) of statistic - weighted by N
	0.088	PSA

Erlotinib

	N	Rate	n	SE	PSA
Shepherd et al., 2005	485	0.05	26	0.0102	0.060

BSC costs were sourced from table below (Lees 2002). Palliative care costs were removed (Hospice, hospitalisations) to provided total costs of £2158.

Table II. Average costs (£; 2000 values) per patient of gemcitabine plus best supportive care (BSC) or BSC alone and the incremental costs

Resource component	Gemcitabine plus BSC	BSC alone	Incremental cost
Chemotherapy drugs[a]	1525	NA	1525
Chemotherapy administration	950	NA	950
Hospitalisations	1400	1471	–71
Hospice admissions	465	231	234
Radiotherapy and surgical procedures	325	492	–167
Visits to health professionals	137	152	–15
Concomitant medications	700	1514	–814
Total costs	**5502**	**3861**	**1642**

a Patients in the BSC alone arm did receive some non-gemcitabine chemotherapy. This resource use is incorporated into the concomitant medications component.