NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL (STA)

Pemetrexed in the maintenance treatment of advanced non-small cell lung cancer

Prepared by Eli Lilly and Company Limited

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Contents

Abbreviations

ALP/AST/ALT	Alkaline phosphatase/ Aspartate aminotransferase/ Alanine transaminase
ASCO	American Society of Clinical Oncology
AUC	Area under the curve
BSA	Body surface area
BSC	Best supportive care
CR/PR/SD	Complete /Partial response /Stable Disease
DCR	Disease control rate
DHFR	Dihydrofolate reductase
ECOG	Eastern Cooperative Oncology Group
EQ5D	Standardised instrument used as a measure of health outcomes
ESMO	European Society for Medical Oncology
GARFT	Glycinamide ribonucleotide formyltransferase
HR	Hazard ratio
HRG	Healthcare Resource group
HRQoL	Health related Quality of Life
ICER	Incremental cost effectiveness ratio
LCSS	Lung Cancer Symptom Scale
LUCADA	Lung Cancer Data
LYG	Life years gained
NCI CTCAE	National Cancer Institute, Common Terminology Criteria for Adverse Events
NSCLC NOS	Non-small cell lung cancer not otherwise specified
NSCLC	Non-small cell lung cancer
OS	Overall survival
PFS	Progression free survival
PS	Performance status
QALY	Quality adjusted life year
RECIST	Response Evaluation Criteria in Solid Tumours
TS	Thymidylate synthase
TTF-1	Thyroid transcription factor-1, a sensitive marker for lung adenocarcinoma
TTO	Time trade off
TWS	Time to worsening of symptoms

Section A

1 Description of technology under assessment

1.1 Give the brand name, approved name and, where appropriate, therapeutic class. For devices please provide details of any different versions of the same device.

Brand Name	Alimta ®
Approved Name	Pemetrexed Disodium
Therapeutic Class	Antineoplastic, folate antagonist: folic acid analogue

1.2 Does the technology have a UK marketing authorisation/CE marking for the indications detailed in this submission? If so, please give the date on which authorisation was received. If not, please state current UK regulatory status, with relevant dates (for example, date of application and/or expected approval dates).

Pemetrexed (Alimta®) monotherapy was approved in the *maintenance* treatment of non-small cell lung cancer (NSCLC) of other than predominantly squamous histology by the European Commission on 10th July 2009.

Pemetrexed in combination with cisplatin was approved for the *first-line treatment of NSCLC* other than predominantly squamous histology and *previously treated NSCLC of other than predominantly squamous histology (i.e., second-line)* on 8th April 2008.

Pemetrexed was originally approved for *malignant pleural mesothelioma (MPM)* and second-line treatment of NCSLC in 2004.

1.3 What are the (anticipated) indication(s) in the UK? For devices, please provide the (anticipated) CE marking, including the indication for use.

NSCLC

Maintenance NSCLC

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

According to the current licence, pemetrexed maintenance treatment can only be given to patients who did not receive pemetrexed/cisplatin as first-line chemotherapy. A clinical trial on first-line pemetrexed/cisplatin followed by pemetrexed maintenance treatment, S124, is currently ongoing and results are expected in 2012.

First-line and second-line NSCLC

Pemetrexed in combination with cisplatin is indicated for the first-line treatment of patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) other than predominantly squamous cell histology. Pemetrexed as a monotherapy is indicated for the second-line treatment of patients with locally advanced or metastatic non small cell lung cancer other than predominantly squamous cell histology.

MPM

Pemetrexed is also indicated for treatment of malignant pleural mesothelioma (MPM), in combination with cisplatin.

1.4 To what extent is the technology currently being used in the NHS for the proposed indication? Include details of use in ongoing clinical trials. If the technology has not been launched, please supply the anticipated date of availability in the UK.

Pemetrexed was approved for maintenance NSCLC on 10th July 2009 and this indication has not yet been promoted in the UK. To our knowledge, pemetrexed is not currently being used in the NHS for maintenance NSCLC, outside of clinical trials.

Ongoing clinical trials

Currently, there are two Lilly sponsored clinical trials underway in the UK in the maintenance NSCLC indication - S124 and the TS study (JMIK).

S124: Multicentre, double-blind, phase III study in which patients receive four cycles of pemetrexed/cisplatin induction and are then randomised to pemetrexed plus best supportive care (BSC) or placebo plus BSC in the maintenance phase, in patients with non-squamous histology (i.e. other than predominantly squamous). The primary outcome measure is progression-free survival. Final results from this trial are expected by 2012.

TS study (thymidylate synthase, JMIK): This is a UK-only phase II single arm exploratory trial to prospectively find the correlation between progression-free survival and thymidylate synthase expression. In the trial, pemetrexed/cisplatin is given for four cycles and then pemetrexed is continued as maintenance therapy for patients with non-squamous histology. Recruitment is expected to complete by Q4 09 and preliminary results are expected at ASCO 2010.

Lilly are not aware of any other ongoing studies in the UK using pemetrexed in the maintenance NSCLC indication.

1.5 Does the technology have regulatory approval outside the UK? If so, please provide details.

Pemetrexed was approved for maintenance NSCLC by the US FDA on 6th July 2009. The licensed indication for pemetrexed in the US prescribing information is as follows:

Pemetrexed is indicated for the maintenance treatment of patients with locally advanced or metastatic non-squamous non-small cell lung cancer whose disease has not progressed after four cycles of platinum-based first-line chemotherapy.

Other than the US, pemetrexed has not been approved specifically for use in maintenance treatment of NSCLC, in any country outside the EMEA. In Japan, pemetrexed is approved for NSCLC treatment; since the label is not required to specify the setting, it follows that clinicians may prescribe pemetrexed for maintenance NSCLC.

1.6 Is the technology subject to any other form of health technology assessment in the UK? If so, what is the timescale for completion?

Ongoing assessments

Pemetrexed in combination with cisplatin in the first-line treatment of NSCLC is currently being assessed by NICE under the STA process. The Final appraisal determination (FAD) for this appraisal was published on the NICE website on the 6th August 09 and recommends pemetrexed for the first-line treatment of NSCLC in patients with a confirmed diagnosis of adenocarcinoma or large cell carcinoma.

Planned assessments

Pemetrexed in the maintenance treatment of NSCLC will be submitted to the SMC for assessment in October 2009.

Completed assessments

Pemetrexed in combination with cisplatin for the first-line treatment of NSCLC is not recommended by the SMC (June 2009, no.531/09). A re-submission is currently being made to the SMC based on a revised economic analysis.

Pemetrexed as a monotherapy for the second-line treatment of NSCLC (other than predominantly squamous cell histology) has been approved for restricted use by the SMC (September 2008, no. 342/07).

Pemetrexed as a monotherapy for second-line treatment of NSCLC was assessed by NICE but was not recommended (TA124, Aug 2007). However, this recommendation is for a patient population that is now, in part, out of licence (due to narrowing of licensed population from all NSCLC patients to patients with non-squamous NSCLC in April 2008) and TA124 is currently under consideration for review.

Pemetrexed in combination with cisplatin has been recommended by NICE as a treatment option for malignant pleural mesothelioma (MPM) (Jan 2008, TA135) and was accepted for restricted use by the SMC (July 2005, no. 192/05).

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

Formulation	Powder for concentrate for solution for infusion
Strength	100mg or 500mg glass vial
Pack Size	1 vial (single use)

1.8 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	Pemetrexed 500mg/m^2, 10-minute IV infusion on Day 1
Dosing Frequency	Every 21 days
Length of course	In the JMEN trial patients received treatment until measureable progressive disease; median number of pemetrexed cycles in the non-squamous population in JMEN was six.
Frequency of Repeat Courses	None

1.9 What is the acquisition cost of the technology (excluding VAT)? For devices, provide the list price and average selling price. 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.

Strength / List price: 500mg vial of pemetrexed / £800

100mg vial of pemetrexed / £160

1.10 What is the setting for the use of the technology?

As pemetrexed is an intravenous infusion, it will be administered under supervision of a physician in secondary care/specialist cancer centres.

1.11 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? What other therapies, if any, are likely to be administered at the same time as the intervention as part of a course of treatment?

- **For selection of patients for pemetrexed maintenance treatment, no additional radiological assessments (CT-scans or chest X-ray) will be required**.
- **The number of patients who may need additional histological/cytological tests for diagnosis prior to pemetrexed maintenance treatment is likely to be small**.
- **Patients receiving pemetrexed maintenance treatment would require radiological assessment (CT-scan or chest X-ray) every two or three treatment cycles**,
- **Concomitant vitamin supplementation is required with pemetrexed therapy.**

1. Investigations needed for patient selection

Radiological assessment

The licence for pemetrexed in maintenance NSCLC restricts its use to patients whose disease has not progressed immediately following platinum-based chemotherapy. In order to demonstrate lack of progression, patients would require a CT-scan after completion of four cycles of induction therapy. Currently, patients who respond to first-line chemotherapy usually receive a CT-scan at the second or third cycle to detect response and then at the end of treatment. Therefore, no additional radiological assessment would be required for the selection of patients eligible for pemetrexed maintenance treatment.

Pathological diagnosis

The licence for pemetrexed in NSCLC restricts its use to patients with 'other than predominantly squamous cell histology', that is adenocarcinoma, large cell carcinoma or NSCLC 'not-otherwise-specified' (NOS), referred to as 'non-squamous' in this submission.

In current clinical practice, non-squamous NSCLC is routinely identified by histological (biopsy specimens) or cytological tests, before initiating first-line treatment. Current best practice in oncology and/or biopsy sample analysis, including basic immunohistochemistry, is sufficient to make this diagnosis. Therefore the specificity of diagnosis required for patients being considered for maintenance treatment with pemetrexed is already available. These patients are not likely to undergo any further testing. In the event of uncertainty around the diagnosis, additional tests may possibly be needed prior to maintenance treatment. The proportion of patients who may require additional tests for pathological diagnosis prior to maintenance treatment with pemetrexed is expected to be small.

2. Monitoring of patients on pemetrexed maintenance treatment

Patients receiving pemetrexed maintenance treatment would require more frequent radiological assessment, to demonstrate sustained clinical benefit, than patients on a 'watch and wait' regimen. We would expect pemetrexed patients to be assessed radiologically (CT scan or chest x-ray) every two or three cycles. 'Watch and wait' patients are currently assessed clinically every one to three months with a chest x-ray, although this varies depending upon local protocols. Radiological assessment is conducted as per local protocols, but generally every three to six months or earlier if clinically indicated.

3. Concomitant medication regimen for pemetrexed

Pemetrexed is administered as a 10 minute IV infusion. Concomitant vitamin supplementation and corticosteroid administration is required, as specified in the pemetrexed summary of product characteristics (SPC).

Concomitant Medication Regimen

Vitamin Supplementation

Folic acid – Daily oral folic acid or a multivitamin containing folic acid (350-1,000µg). At least five doses of folic acid must be taken in the seven days preceding the first dose of pemetrexed. Dosing must continue during the full course of therapy and for 21 days after the last dose of pemetrexed.

Vitamin B_{12} – Intramuscular injection of vitamin B_{12} (1000µg) 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.

Corticosteroids

A corticosteroid should be given the day prior to, on the day of, and the day after pemetrexed administration.

2 Statement of the decision problem

	Final scope issued by NICE	Decision problem addressed in the submission
Population	People with advanced or metastatic (stage IIIB and IV) NSCLC, other than those with predominantly squamous histology, whose disease has not progressed following treatment with platinum-based, first-line chemotherapy	Patients with locally advanced or metastatic NSCLC of other than predominantly squamous (non-squamous) histology whose disease has not progressed [i.e., have complete response (CR), partial response (PR) or stable disease (SD)] following four cycles of induction treatment with a platinum doublet (one of the following: gemcitabine, docetaxel, paclitaxel in combination with cisplatin or carboplatin). The base case population for this submission is the licensed population: patients with non-squamous NSCLC (adenocarcinoma, large cell carcinoma or NSCLC 'not otherwise specified').
Intervention		Pemetrexed (500mg/m^2 iv infusion) administered on day 1 of a 21-day cycle, until disease progression.
Comparator(s)	Best supportive care, which may include palliative radiotherapy and corticosteroids (without maintenance therapy)	Placebo (watch and wait). Both treatment arms received BSC
Outcomes	The outcome measures to be considered include: • health-related quality of life • overall survival • progression free survival • response rates • adverse effects of treatment	• Health related quality of life • Overall survival • Progression free survival • Response rates • Adverse effects of treatment
Economic Analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services	Cost-effectiveness analysis results expressed as incremental cost per QALY gained. A cost per Life Year (cost per LY) gained analysis will also be conducted as this type of analysis is relevant in disease areas where extended survival is a key outcome of treatment. The time horizon is six years, (a lifetime model). Costs will be considered from an NHS and Personal Social Services perspective.

	perspective.	
Subgroups to be considered		Results for the non-squamous patients (licensed population) and for the sub-group of patients with adenocarcinoma are presented in this submission.
Special considerations, including issues related to equity or equality		None

Section B

3 Executive summary

Approved name, brand name, marketing status	Pemetrexed disodium Alimta ® Pemetrexed is currently marketed in the UK for first and second line NSCLC in patients of other than predominantly squamous histology and Malignant Pleural Mesothelioma. Marketing authorisation was granted for maintenance treatment of NSCLC of other than predominantly squamous histology on the 10th July 2009.
Pharmacological action of the proposed drug	Pemetrexed is a multi-targeted anti-cancer antifolate agent that exerts its action by disrupting crucial folate-dependent metabolic processes essential for cell replication.
Formulation, strength, pack size, acquisition cost price	Powder for concentrate for solution for infusion 100mg (£160) or 500mg (£800) glass vial 1 vial (single use)
The recommended course of treatment	Pemetrexed is administered at a dose of 500mg/m^2 as a 10-minute IV infusion on day 1 of a 21 day cycle. In the JMEN clinical trial, patients were treated until measureable disease progression (assessed based on RECIST criteria). In actual clinical practice, patients are most likely to receive a maximum of 15-20 treatment cycles.
The indication(s) and any restriction(s)	Pemetrexed is indicated as monotherapy for the maintenance treatment of locally advanced or metastatic NSCLC other than predominantly squamous cell histology in patients whose disease has not progressed immediately following platinum-based chemotherapy. First-line treatment should be a platinum doublet with gemcitabine, paclitaxel or docetaxel. Patients who receive pemetrexed/cisplatin as first-line treatment are not licensed to receive maintenance treatment with pemetrexed.
Histology diagnosis	Non-small cell lung cancer (NSCLC) accounts for approximately 80% of all lung cancers diagnosed. There are four main histological classifications of NSCLC: squamous cell carcinoma (33%), adenocarcinoma (25%), large cell carcinoma (4%) and 36% being NSCLC 'not-otherwise specified' (LUCADA, 2007). With widely available diagnostic techniques (biopsy and/or cytology and immunohistochemistry), it is now possible to identify NSCLC histotypes without significant cost or resource impact. The National Cancer Audit (2007) recommends routine clinical practice should aim for an optimum histological and/or cytological diagnosis of 75% of all lung cancers.

	In keeping with the scope for this appraisal, the submission relates to the licensed population for pemetrexed in maintenance NSCLC i.e., the population of patients with NSCLC 'other than predominantly squamous' (referred to as 'non-squamous') which includes the sub-groups of patients with adenocarcinoma, large cell carcinoma and NSCLC 'not otherwise specified' (NOS).
Maintenance chemotherapy of advanced NSCLC	In accordance with the licence for pemetrexed, maintenance chemotherapy in this appraisal is defined as the administration of additional chemotherapy cycles immediately on completion of four cycles of first-line (induction) chemotherapy in patients with complete / partial response / stable disease. Patients with disease progression following four cycles of induction chemotherapy are not eligible for maintenance chemotherapy. The main goal of maintenance treatment is to 'maintain' the clinical benefit achieved following first-line chemotherapy. Maintenance treatment offers the opportunity for patients to receive active treatment when tumour and symptom burden is low, patient tolerance is high and patients are of good performance status. In cancers of the breast, prostate and lymphoma, maintenance treatment is a well established concept with treatment continued until disease progression. However, in NSCLC, treatments currently used in the first and second-line setting are associated with toxicities which render them unsuitable for use in the maintenance setting. Therefore, the use of maintenance treatment in NSCLC is a relatively new concept, possible now with the tolerability profile of pemetrexed. Maintenance treatment is a new treatment paradigm which represents a significant advance in the management of patients with advanced NSCLC. In current clinical practice in the NHS, patients who do not experience disease progression following four cycles of platinum-based induction chemotherapy are not immediately offered active treatment. They undergo a period of observation ('watch and wait') and may be given best supportive care (BSC) until disease progression is detected, at which point patients may undergo second-line chemotherapy if deemed clinically appropriate. Maintenance chemotherapy with pemetrexed is proposed as an alternative to the period of 'watch and wait' that patients currently undergo in the NHS. Pemetrexed is uniquely suited to NSCLC maintenance treatment due to its favourable and manageable toxicity profile, and convenient administration schedule of a ten minute infusion every three weeks.
The main comparator(s).	Currently, pemetrexed monotherapy is the only chemotherapy licensed for the maintenance treatment of NSCLC in the UK and worldwide. There are no treatment guidelines (globally or in the UK) on the appropriate clinical assessment or treatment strategy for patients once they have completed first-line treatment. The standard of care in the NHS for responding patients after first-line chemotherapy is 'watch and

	wait' and BSC if clinically indicated. Accordingly, the comparator in the JMEN clinical trial and the economic evaluation was placebo (no active treatment), with an option to receive BSC if clinically appropriate for both arms.
Key clinical evidence	The evidence base for pemetrexed monotherapy in maintenance NSCLC consists of the phase III, multicentre, randomised, placebo-controlled, double-blind study JMEN. The study aimed to compare progression free survival (PFS), overall survival (OS), time to worsening of symptoms, disease control and adverse events in patients receiving maintenance therapy with pemetrexed plus BSC versus placebo (no active treatment) plus BSC, in patients with stage IIIB or stage IV NSCLC who had not progressed following four cycles of platinum-based induction chemotherapy. As a result, these patients were of good performance status (PS 0 or 1), similar to patients currently considered appropriate for chemotherapy treatment in England and Wales. Use of maintenance therapy in less well patients of lower performance status is not considered appropriate or anticipated in clinical practice. Results from previous studies on pemetrexed in the first-line and second-line setting showed that pemetrexed had a superior efficacy in patients with NSCLC of non-squamous histology compared to patients with squamous histology. Based on these results, a pre-specified prospective sub-group analysis was planned to evaluate the efficacy of pemetrexed plus BSC in different histological subgroups of NSCLC.
The main clinical results of the RCT	In JMEN, 663 patients were randomised 2:1 to either pemetrexed plus BSC (n=441) or placebo plus BSC (n=222). Of the ITT population 481 patients (325 on pemetrexed, 156 on placebo) had NSCLC of non-squamous histology and therefore qualify as the 'licensed population', which matches the scope for this appraisal. Pemetrexed treated non-squamous patients had a statistically significantly longer PFS than placebo treated patients (median PFS for pemetrexed 4.5 vs 2.6 months for placebo; HR 0.44; 95% CI 0.36-0.55, p<0.00001). **Pemetrexed treated non-squamous patients had a statistically significant survival benefit of 5.2 months compared to placebo treated patients** (median OS 15.5 months vs 10.3 months for placebo; HR 0.70; 95% CI 0.56-0.88, p=0.002). In the largest histology sub-type, adenocarcinoma patients, median OS was also significantly longer than placebo (pemetrexed 16.8 vs 11.5 months placebo; HR 0.73; 95% CI 0.56-0.96, p=0.026). **An increase in survival of over 5 months and median overall survival of greater than 15 months are benefits of a magnitude that have not been seen before with chemotherapy agents in NSCLC and could potentially change the outlook for patients diagnosed with advanced lung cancer.** Previous important advances in median survival in this disease in patients following first-line and second-line NSCLC, have been smaller increments of less than 2 months versus active comparators and less than 3 months versus placebo/BSC (Scagliotti 2008, Shepherd 2000, Shepherd 2005).

	Pemetrexed treated non-squamous patients had statistically significantly longer time to worsening for pain and haemoptysis compared with placebo treated patients. In general, pemetrexed was well-tolerated. The only Grade 3/4 CTC adverse events that were clinically or statistically significantly different between the pemetrexed and placebo arms were neutropenia which occurred in 2.8% of patients versus 0% (p=0.035) and fatigue which occurred in 3.7% versus 0.6% (p=0.07) in the licensed patient population.
Economic evaluation **Type of economic evaluation** **Justification for the approach used** **Pivotal assumptions underlying the model analysis** **Mean costs, outcomes and incremental ratios from the evaluation**	The evaluation of cost-effectiveness (cost-utility analysis) was based upon an economic model that utilised the trial survival data for the duration of the trial and extrapolated outcomes to a lifetime horizon (6 years) using an exponential survival function. Additional analyses based upon Weibull estimates of survival have also been provided in the sensitivity analysis. This type of model was used to replicate the results of the trial as closely as possible whilst maintaining the greatest level of transparency and simplicity in the model structure. It has been assumed that patients in clinical practice in England and Wales would receive up to a maximum of 15-20 cycles based upon normalising the distribution of cycles received in the trial and advice from clinical experts. This results in a mean number of cycles of around six, consistent with the median estimate of six recorded in the clinical trial for the licensed population. It has been assumed that patients in both arms receive BSC according to standard clinical practice. Patients on active chemotherapy are assumed not to be in receipt of radiotherapy. For the population under consideration, the licensed non-squamous population, the incremental total cost was £9,137 per patient for pemetrexed compared to placebo, and the incremental survival difference over the lifetime horizon was 5.28 months (0.44 Life Years) resulting in incremental QALYs of 0.27 per patient. The incremental cost-effectiveness ratio is £33,732 and the incremental cost per life year is £20,562.
Relevance of this submission to the End of Life supplementary criteria	Pemetrexed in the maintenance treatment of NSCLC fulfils the 'End of life' criteria. • Patients with advanced NSCLC have a short life expectancy of less than 24 months on average. In the JMEN trial, median overall survival for the licensed group, the non-squamous patients, in the untreated placebo arm was 10.3 months. Median overall survival for NSCLC patients in LUCADA is reported to be less than 8 months. • Extension to life due to pemetrexed maintenance treatment in JMEN was 5.2 months in non-squamous NSCLC patients and 5.3 months in the adenocarcinoma sub-group.

	• Currently, no other treatment is licensed /approved for maintenance treatment in NSCLC. The standard of care in NHS is 'watch and wait' plus BSC. • The total eligible population for pemetrexed maintenance treatment is 949 patients. The cumulative population across all indications for pemetrexed is also relatively small at 3,426. • The QALY weightings that would need to be applied to the cost-effectiveness ratio for pemetrexed in maintenance NSCLC for non-squamous patients compared to placebo patients based upon the submitted base case would be 1.7 in order to achieve an ICER of £20,000 cost per QALY and to 1.1 for a £30,000 cost per QALY.
Conclusion	Pemetrexed is the first tailored chemotherapy approved for use in patients with non-squamous tumours in the maintenance setting for advanced NSCLC, with an aim to maintain the clinical benefit of first-line treatment in patients who have not progressed. With an incremental survival advantage of over five months, good tolerability profile and convenient administration, pemetrexed represents a step change in the outlook and treatment paradigm for patients with advanced NSCLC.

4 Context

4.1 Please provide a brief overview of the disease/condition for which the technology is being used. Provide details of the treatment pathway and current treatment options at each stage.

Lung cancer is the second most common cancer diagnosed in the UK, with over 33,000 new cases diagnosed in England and Wales in 2006 and the leading cause of cancer death (Cancer Research UK, 2006). Lung cancer is the second most common cancer in men after prostate cancer, and the third most common cancer in women after breast and bowel cancer.

Non-small cell lung cancer (NSCLC) accounts for approximately 80% of all lung cancers diagnosed. The main sub-types of NSCLC are squamous cell carcinoma (33%), adenocarcinoma (25%), large cell carcinoma (4%), and 36% being NSCLC 'not-otherwise specified' (NOS) (LUCADA 2006). While cigarette smoking has been linked to all four types of lung cancer, the incidence of adenocarcinoma has been steadily increasing worldwide, and modifications to cigarette design are thought to be responsible for this shift in pathologic diagnosis pattern (Gabrielson et al 2006).

Survival in patients with lung cancer is poor. It was responsible for approximately 29,600 deaths in England and Wales in 2007 (Cancer Research UK, 2007). For patients with stage IIIB, only 7-9% may live for 5 years and for patients with stage IV (metastatic) cancer, only about 2-13% survive for 5 years (Cancer Research UK, 2009).

One reason for this poor prognosis is the late identification of the disease. Lung cancer is asymptomatic in the early stages and advanced disease is not amenable to curative treatment. Another reason, which explains the UK's relatively poor performance in comparison with other developed countries, is low active anti-cancer treatment rates. The National Lung Cancer Audit states that only 23.2% NSCLC patients in England and Wales received first-line chemotherapy in 2006 (LUCADA 2007).

Current treatment pathway for advanced NSCLC

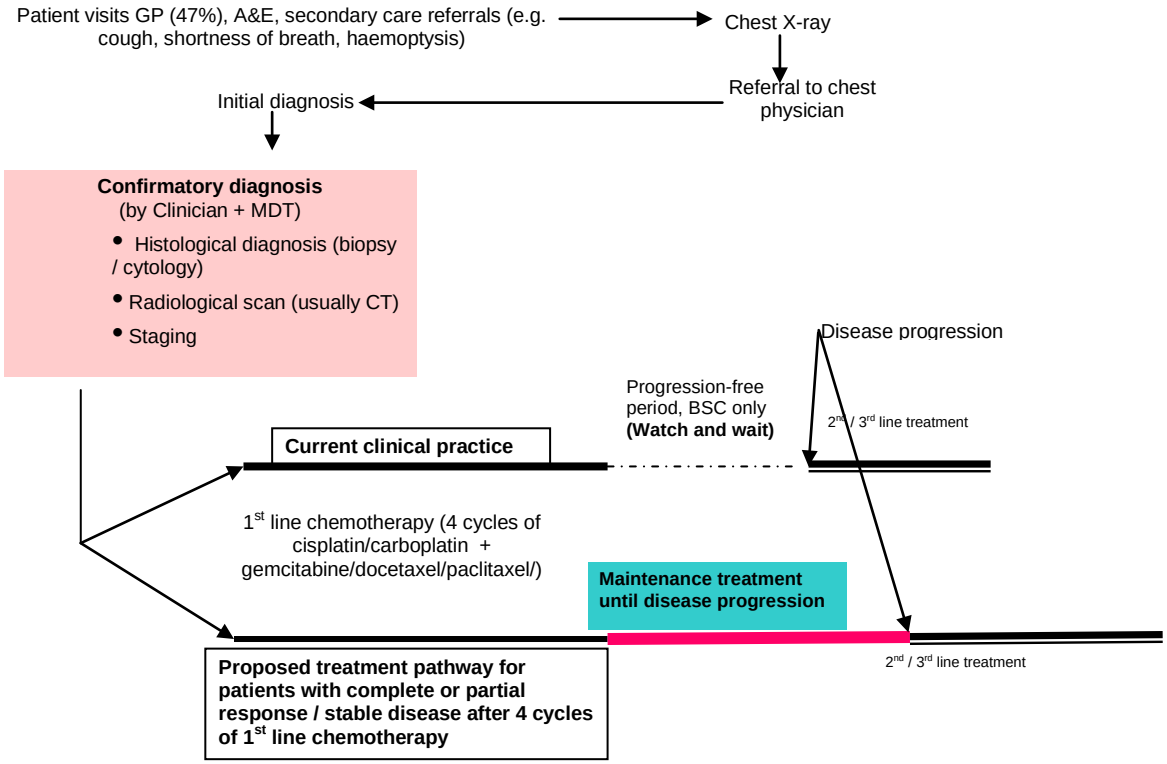
Figure 1 depicts the current treatment pathway for a patient with advanced non-small cell lung cancer in the NHS from presentation to second-line treatment.

Presentation
Almost half (47%) of all lung cancer cases analysed (22,628 from England and Wales) are referred by a primary care physician to a lung cancer specialist (part of a multidisciplinary team or MDT) following clinical suspicion. Patients may also be referred from emergency presentation or from another specialty in the same hospital.

Of the 22,628 lung cancer cases, 34% had good performance status (PS 0-1), 28.6% had poor performance status (PS 2-4); 16.8% cases were not recorded and 20.3% were missing (LUCADA 2006). Of the 10,452 cases of histologically confirmed NSCLC in LUCADA, 48% were of advanced disease (stage IIIB-IV).

The initial diagnosis by the specialist physician is followed by diagnostic confirmation of NSCLC which involves radiological assessment (usually CT-scan, or PET scan), biopsy / cytology and staging of the disease. For a proportion of patients, diagnosis is established based on clinical and/or radiological grounds only. A histological confirmation rate of at least 75% has been suggested as a reasonable benchmark of acceptable practice (LUCADA 2007). A high rate of histological confirmation rather clinical or radiological diagnosis is a good marker of the overall quality of care.

Figure 1: Treatment pathway for NSCLC in the NHS from patient presentation to second-line treatment

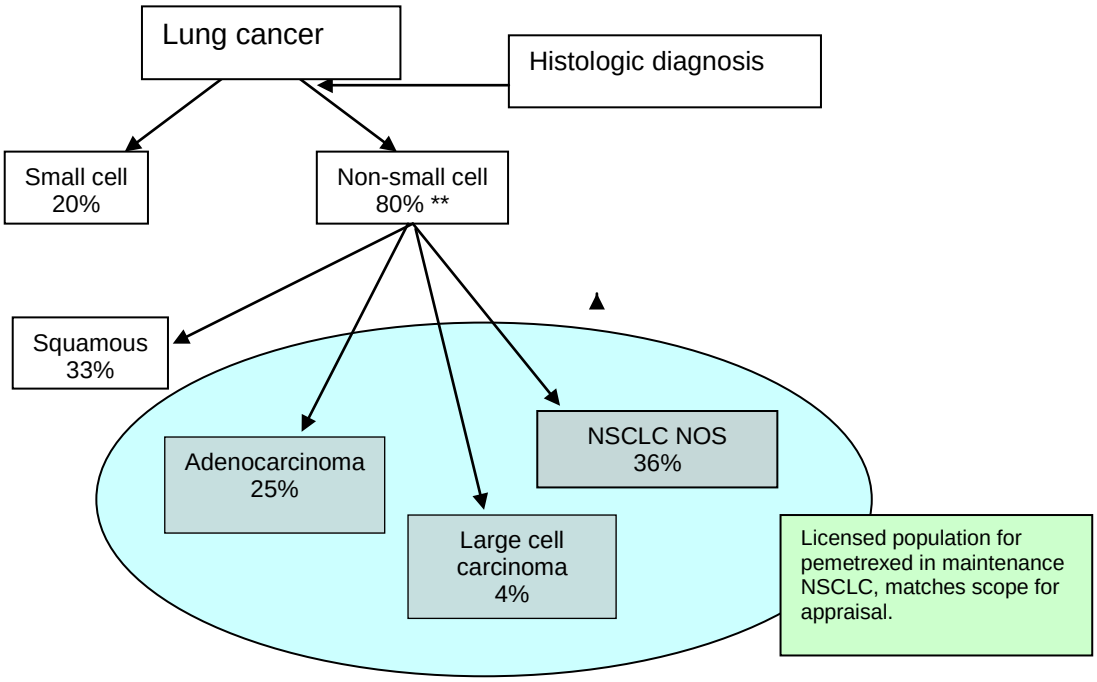


Histological diagnosis

A confirmatory diagnosis of lung cancer (either small cell or non-small cell) is required prior to initiation of anti-cancer treatment. With widely available technologies (histology, cytology, immunohistochemistry) it is now possible to diagnose to a more specific histological level (see Figure 2 for NSCLC histological subtypes) as part this NSCLC diagnosis without significant cost or resource impact. Samples are classified by morphology (e.g. what shape are the cells: square or not? Are intracellular bridges observed?) and immunohistochemistry (tests for specific markers e.g thyroid transcription factor1 – TTF1 positivity indicates a high probability of adenocarcinoma). Squamous cell carcinomas are generally easier to identify with 87% certainty reported. Adenocarcinoma may be accurately identified 80% of the time while a large cell carcinoma diagnosis may be more uncertain at 50% (Edwards et al. 2000). A diagnosis of NSCLC-NOS indicates that a specific non-squamous histologic type (e.g. adenocarcinoma or large cell carcinoma) or squamous cannot be assigned.

Histological confirmation of cancer diagnosis is currently made in 68% of patients (varies from 20% to 85%) in England and Wales (LUCADA 2007).

Figure 2: Classifications of lung cancer – histological sub-types (Travis 2004)*



***The NICE clinical guideline 24 (2005) states that non-small cell lung cancer includes squamous carcinoma 35%, adenocarcinoma 27% and large cell carcinoma 10%.**

**The remaining 2% at squamous/non-squamous level are bronchio-alveolar carcinoma and cancer *in situ.* NOS = Not otherwise specified

First-line (induction) treatment

According to LUCADA (2007), 23.2% of patients receive first-line chemotherapy in England and Wales. Platinum-based chemotherapy is the mainstay of first-line (induction) treatment options in the 70–80% of patients who present with either locally advanced or metastatic NSCLC. Current third-generation regimens (e.g. gemcitabine/cisplatin, gemcitabine/carboplatin and docetaxel/cisplatin) result in survival rates of 33% at one year and 11% at two years, with a median survival of approximately 8 months, (Schiller et al. 2002). Recently, clinical data for pemetrexed/cisplatin suggest that survival rates of 50% at one year might be achieved in patients with adenocarcinoma (Scagliotti et al. 2008). Despite these advances in therapy for patients with advanced NSCLC, the vast majority of patients will ultimately suffer disease progression within 3 to 6 months of initiating first-line therapy (Schiller et al 2002; Sandler et al 2006; Scagliotti et al 2008).

Observation ('watch and wait') phase

Currently, after completion of four cycles of first-line treatment with a platinum doublet, patients typically undergo a chemotherapy-free observation period ('watch and wait') until disease progression occurs, whereupon second-line therapy is initiated (Figure 1). During this time, patients may receive best supportive care (BSC) and are clinically assessed every one to three months and radiologically every three to six months or earlier, if clinically indicated, depending upon local protocols.

Currently, there are no treatment guidelines (globally or in the UK) on the appropriate surveillance strategy for patients once they have completed first-line treatment (i.e., what tests should be done and when, how often should patients be evaluated) (Socinski et al 2009).

Second-line treatment

Patients who receive second-line therapy are generally those who have good performance status following first-line therapy and disease progression. In current clinical practice, second-line treatment is generally initiated with docetaxel or erlotinib, upon disease progression. The response rate observed in the second-line trials is approximately 10%, with a median survival time of 6 to 8 months and 1-year survival rates of approximately 30% (Shepherd et al, 2000; Shepherd et al 2005). While second-line therapy has demonstrated improved survival and symptom palliation, only about 40% of patients in England and Wales who received first-line therapy for NSCLC go on to receive second-line therapy (Data on file_chemo_second line2009).

Pemetrexed as maintenance treatment for advanced NSCLC

Definition of maintenance treatment

In accordance with the licence for pemetrexed, in this appraisal maintenance treatment is defined as the administration of additional chemotherapy immediately after the completion of first-line (induction) chemotherapy in patients with complete / partial response or stable disease (as defined by RECIST criteria) after four cycles of induction chemotherapy. Patients who have disease progression after induction treatment are not eligible for maintenance treatment.

The goal of maintenance treatment is to maintain the clinical benefit achieved with first-line chemotherapy. Maintenance treatment is continued until disease progression.

How maintenance treatment fits into the treatment pathway explained above

Maintenance treatment is a new treatment paradigm and is proposed as an alternative for the **'watch and wait'** phase of the current treatment pathway, for patients with complete or partial response / stable disease after four cycles of first-line treatment.

Rationale for maintenance treatment

- Maintenance treatment is routinely given in current clinical practice for other cancers like breast cancer, lymphoma and prostate cancer, with treatment being continued until evidence of disease progression. Maintenance treatment for NSCLC is a relatively new concept because the chemotherapy agents used for treatment of NSCLC in the first and second-line setting have significant toxicities which may render them unsuitable for use in the maintenance NSCLC setting. Manageable toxicity and less frequent administration would translate into a more tolerable and convenient maintenance regimen for patients.

- Administration of a tolerable maintenance regimen immediately following first-line therapy may allow more patients to benefit from additional treatment while tumour and symptom burden is low, patient tolerance is high and before the inevitable deterioration in performance status and disease progression occurs.

Pemetrexed is a suitable treatment for NSCLC maintenance due to the following reasons:

- In the pemetrexed registration study in maintenance NSCLC - **JMEN**, the overall survival benefit in non-squamous patients on pemetrexed compared to placebo was 5.2 months.
- Pemetrexed treated patients also had a 1.9 month longer progression free survival.
- Pemetrexed has a favourable and manageable toxicity profile.
- Pemetrexed is easily administered as a 10-minute infusion and needs to be given only once (on day 1) during a three week cycle.

Patients eligible for pemetrexed maintenance treatment

Patients with non-squamous NSCLC with complete / partial response / stable disease (as defined by RECIST criteria) after four cycles of first-line treatment, are eligible for pemetrexed maintenance treatment.

Patients who have received pemetrexed/cisplatin as first-line treatment cannot currently receive maintenance treatment with pemetrexed. This is because the registration study for pemetrexed in maintenance NSCLC, **JMEN**, did not include patients who received first-line treatment with pemetrexed/cisplatin, since the results from study JMDB (registration study for pemetrexed/cisplatin in first-line NSCLC) were not known at the time of study initiation.

Results from an ongoing phase III randomised study (**S124**) of induction treatment with pemetrexed/cisplatin followed by maintenance treatment with pemetrexed plus BSC or placebo plus BSC are expected in 2012.

4.2 What was the rationale for the development of the new technology?

Pemetrexed was developed as an oncolytic that would have improved clinical outcomes compared to currently available therapies through extending survival in combination with an improved tolerability and administration profile.

A pivotal phase III study (JMEI) compared the efficacy and toxicity of pemetrexed versus docetaxel in the second-line treatment of patients with advanced NSCLC. JMEI demonstrated that pemetrexed resulted in clinically similar efficacy outcomes with significantly fewer side effects compared to docetaxel (Hanna et al. 2004) in the overall NSCLC population. This study led to the regulatory approval of pemetrexed for the treatment of patients with previously treated advanced NSCLC. A retrospective analysis of the Hanna et al (2004) trial showed a statistically significant treatment-by-histology interaction, suggesting that pemetrexed produced better survival in non-squamous histologies, compared with docetaxel (Scagliotti et al 2009).

Another phase III study (JMDB) established the efficacy of pemetrexed/cisplatin versus gemcitabine/cisplatin as first-line treatment of locally advanced and metastatic NSCLC. Study JMDB showed that pemetrexed plus cisplatin resulted in clinically similar efficacy outcomes with significantly fewer side effects compared to gemcitabine plus cisplatin (Scagliotti et al. 2008) in the overall NSCLC population. In the non-squamous population, improvements in OS over gemcitabine/cisplatin were observed, consistent with the statistically significant treatment-by-histology interaction. Overall survival was significantly improved for pemetrexed/cisplatin compared with gemcitabine/cisplatin in patients with non-squamous histology.

Rationale for JMEN trial assessing pemetrexed in the maintenance NSCLC setting

Pemetrexed appeared to be a good candidate to study as single-agent maintenance therapy after first-line therapy for patients with advanced NSCLC. First, single-agent pemetrexed had demonstrated anti-tumour activity in patients who progressed after first-line therapy (Hanna et al. 2004). Second, the ease of administration (a 10-minute infusion every three weeks) and the favourable and manageable toxicity profile of single-agent pemetrexed supported the investigation of pemetrexed as maintenance therapy.

4.3 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. 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.

Evidence that the efficacy of pemetrexed varies with histology has been emerging from recent clinical studies in NSCLC (JMEI, NS01, JMDB). Retrospective analyses of study JMEI showed a statistically significant treatment-by-histology interaction, suggesting that pemetrexed had better survival in non-squamous histologies and worse survival in squamous cell carcinoma, as compared to docetaxel.

Following the results of Study JMEI, new data were published that showed higher TS expression in NSCLC specimens from patients with squamous cell carcinoma, as compared to adenocarcinoma (Ceppi et al. 2006). Earlier preclinical data had correlated over-expression of TS with reduced sensitivity to pemetrexed in antifolate-resistant cell lines (Sigmond et al. 2003; Giovannetti et al. 2005). These results suggested a plausible biological hypothesis for the clinically observed results: the reduced clinical efficacy of pemetrexed in patients with predominantly squamous cell carcinoma is due to higher TS expression in these tumours.

During the course of JMEN enrolment, results from JMDB became available. These results demonstrated a statistically significant treatment-by-histology interaction favouring pemetrexed/ cisplatin, consistent with the results from JMEI. A retrospective analysis of an additional randomised study (NS01, Ohe et al 2008), showed substantially better survival for non-squamous than for squamous patients.

Based on the clinical results of three randomised studies (JMEI, JMDB, and NS01), the statistical analysis plan for JMEN was updated to include a pre-specified test for treatment-by-histology interaction and corresponding subgroup analyses. It was anticipated that the efficacy advantage for pemetrexed over placebo would be greater within the non-squamous subgroups than within the squamous subgroup.

4.4 What is the suggested place for this technology with respect to treatments currently available for managing the disease/condition?

Maintenance treatment for advanced NSCLC is a relatively new concept which is yet to be adopted in routine clinical practice (as explained under 2.1 above). UK market research data shows that (Data on file_Maintenance market research_april2009) only 3% of advanced (stage IIIB and stage IV) NSCLC patients currently receiving first-line anticancer therapy are administered maintenance treatment. Only 4% of UK clinicians sampled said they had administered maintenance treatment in the preceding four weeks. Reliable market share data for maintenance treatment is not available from the UK since the number of cases is very low and no agent other than pemetrexed is as yet licensed for maintenance NSCLC.

Currently in the NHS, patients who respond after first-line (induction) chemotherapy are not immediately given further active treatment. Induction treatment is routinely followed by a period of ‘watch and wait’ during which patients are clinically assessed every one to three months and may only receive best supportive care (BSC), as necessary. The current standard of care in the NHS for maintenance treatment of NSCLC is therefore ‘watch and wait’ plus BSC.

The JMEN trial evaluated the safety and efficacy of maintenance treatment with pemetrexed in patients with complete / partial response / stable disease following first-line therapy with a platinum-based doublet. Patients in the JMEN trial were assigned to receive either pemetrexed or ‘placebo’ (no active treatment) with both arms being administered BSC, in keeping with current clinical practice.

Treatment options for maintenance NSCLC
Currently, no pharmacologic intervention other than single agent pemetrexed has received regulatory approval as maintenance treatment immediately after first-line chemotherapy in the treatment of advanced NSCLC.

4.5 Describe any issues relating to current clinical practice, including any variations or uncertainty about best practice.

Histologic diagnosis

There is variation across England and Wales in current practice with respect to histological diagnosis of NSCLC. LUCADA reports 68% of patients had a histological diagnosis in 2006, an optimum rate of 75%, is recommended. There is some uncertainty regarding accuracy of histological diagnosis. A trial by (Edwards et al.2000) reported 87% accuracy in diagnosing squamous cell carcinoma, 80% for adenocarcinoma and 50% for large cell carcinoma. It is expected that as more therapies require this level of specificity and analysis becomes more routine, the level of accuracy will improve, more patients will be diagnosed with a specific histotype and the proportion of patients with tumours classified as NOS will decrease.

An independent retrospective review of histological classification from the JMEN trial was conducted to investigate accuracy of diagnosis in a subset of 102 patients. Histological classification was found to match in 83 of the 93 evaluable cases, i.e., investigator and independent reviewer agreed in 89.2% cases when classifying samples as non-squamous versus squamous.

Duration of maintenance therapy for advanced NSCLC

In the JMEN study, maintenance treatment with pemetrexed was continued until disease progression as measured by RECIST criteria rather than clinical opinion. The median number of treatment cycles administered in the pemetrexed arm in the ITT population was five and six for the licensed non-squamous population. A small number of patients in the trial were extreme 'outliers' in terms of duration of treatment and received a high number of treatment cycles, leading to a very skewed distribution (see Figure 6 in the Safety Section) and therefore a distorted mean of eight cycles in the licensed population. In clinical practice, patients are likely to receive a maximum of 15-20 cycles, consistent with the majority of patients (>90%) in the trial. UK clinical experts consulted believe that patients are likely to receive a maximum of ten treatment cycles.

Adoption of maintenance treatment with pemetrexed.

Since maintenance treatment of NSCLC is a new treatment paradigm, initially there may be variations in the level of adoption between cancer networks. The absence of treatment guidelines on maintenance treatment may further contribute towards variation in clinical practice. However, variations may diminish once the patient benefits in terms of increased overall survival and improved quality of life become evident.

4.6 Provide details of any relevant guidelines or protocols.

NSCLC maintenance treatment is not in either the NICE Lung cancer guideline (CG24) or the European Society for Medical Oncology (ESMO) NSCLC guidelines. This may be because maintenance therapy is a relatively new concept. In the absence of any treatment guidelines, the current standard of care worldwide for maintenance treatment of NSCLC is 'watch and wait' (plus BSC) until disease progression, when second-line therapy may be initiated.

5 Equity and equality

5.1 Identification of equity and equalities issues

Are there any issues relating to equity or equalities (consider issues relating to current legislation and any issues identified in the scope for the appraisal)?
None identified

How has the analysis addressed these issues?
[Not applicable]

6 Clinical evidence

6.1 Identification of studies

A systematic literature search was performed on 22nd May 2009 to identify studies of pemetrexed maintenance in patients with advanced NSCLC (see appendix 2 for detailed search strategy).

Since maintenance treatment is a relatively new concept and because earlier literature searches revealed that studies often report combined outcomes following first-line and maintenance treatments, and the term 'maintenance' treatment may not be consistently interpreted by different investigators, a decision was taken to keep the initial search quite broad-based, to allow all relevant studies to be included.

Articles identified through literature search of databases (Medline, Embase, Current Contents, Biosys Previews, all EBM Reviews) ASCO* abstracts and Lilly internal database	n =39 n = 3 n = 1		
		Articles excluded – Reviews, economic analysis, not NSCLC	N=26
		Articles excluded – not in English language	N=2
		Pemetrexed not mentioned in abstract	N=3
		Not advanced NSCLC	N=1
		Not maintenance treatment	N=7
Relevant RCT articles included	n = 4	(See below)	

*American Society of Clinical Oncology

6.2 Study selection

6.2.1 Complete list of RCTs

Provide a list of all RCTs that compare the intervention with other therapies (including placebo) in the relevant patient group. The list must be complete and will be validated by independent searches conducted by the assessors.
Where data from a single study have been drawn from more than one source (for example, a poster and a published report) and/or where trials are linked (for example, an open-label extension to an RCT), this should be made clear.

The search of Medline, Embase, Current Contents, Biosys Previews, all EBM Reviews did not identify any clinical trials of single agent pemetrexed in the maintenance NSCLC setting. Three abstracts were identified from an electronic search of the ASCO website (see list of relevant RCTs below). All three abstracts were pertaining to the JMEN study, which was the only clinical trial on single agent pemetrexed in the maintenance NSCLC setting identified from the internal Lilly database.

6.2.2 Inclusion and exclusion criteria

State the inclusion and exclusion criteria that were used to identify the studies detailed in the list of relevant RCTs. If additional inclusion criteria were applied to select studies that have been included in the systematic review, these need to be listed separately.
Inclusion criteria:
Randomised control trials, Phase III, pemetrexed in maintenance treatment of advanced (stage IIIB / IV) NSCLC, head-to-head comparisons vs pemetrexed, English language.

Exclusion criteria:
Phase I/II, first-line NSCLC only, second-line NSCLC only.

6.2.3 List of relevant RCTs

List all RCTs that compare the technology directly with the appropriate comparator(s) with reference to the specification of the decision problem. If there are none, state this.
In the maintenance NSCLC setting, single agent pemetrexed has been directly compared to placebo (no active treatment) with both study arms receiving BSC, in one phase III, double-blind, randomised, multicentre trial, the **JMEN** study. Three abstracts based on this study have been presented at the annual meetings of the American Society for Clinical Oncology (ASCO) in 2008 and 2009, as listed below. The full text of the JMEN study has not yet been published. This trial was identified from the Lilly internal database.

1. Belani CP, Brodowicz T, Ciuleanu T, Kim J, Krzakowski M, Laack E et al. Maintenance pemetrexed plus best supportive care versus placebo plus BSC: A randomised phase III study in advanced non-small cell lung cancer (NSCLC). J Clinical Oncology, 2009, 27:18s (suppl; abstract CRA8000).

2. Ciuleanu T, Brodowicz T, Belani C, Kim J, Krzakowski M, Laack E et al. Maintenance pemetrexed plus best supportive care versus placebo plus BSC: A phase III study. J Clinical Oncology, 2008, 26: (May 20 suppl; abstract 8011).

3. Zielinski C.C, Yang S., Santoro A., Ramlau R., Liepa A. M., Peterson P. Tolerability of pemetrexed versus placebo as a maintenance therapy in advanced non-small cell lung cancer: evidence from a large randomised study. J Clinical Oncology, 2008 (May 20 suppl; abstr 8060).

4. Clinical study report (CSR): A phase 3, double-blind, placebo-controlled study of maintenance pemetrexed plus best supportive care versus best supportive care immediately following induction treatment for advanced NSCLC.

Results of the final survival analysis from the JMEN study are reported in the addendum to the JMEN CSR, which has been provided with this submission.

Sources of clinical data in this submission include the CSR for study JMEN, and the addendum to JMEN.

6.2.4 List of relevant non-randomised controlled trials

Provide details of any non-randomised controlled trials that are considered relevant to the decision problem. Provide justification for their inclusion.
No, non-randomised trials were used in this submission

6.2.5 Ongoing studies

Provide details of relevant ongoing studies from which additional evidence is likely to be available in the next 12 months.
Currently, there is only one Lilly sponsored clinical trial underway in the UK in the maintenance NSCLC indication for which results are due within the next 12 months, the TS study (JMIK).

TS study: This is a UK-only phase II single arm exploratory trial to prospectively find the correlation between progression-free survival and thymidylate synthase expression. In the trial, pemetrexed/cisplatin is given for four cycles and then pemetrexed is continued as maintenance therapy for patients with non-squamous histology. Recruitment is expected to complete by Q4 09 and results are expected at ASCO 2010.

6.3 Summary of methodology of relevant RCTs

6.3.1 Methods

Describe the RCT design (for example, duration, degree and method of blinding, and randomisation) and interventions.
Study design
The JMEN trial was a phase III multicenter, randomised, double-blind, placebo-controlled trial of maintenance chemotherapy with pemetrexed plus BSC versus placebo (no active treatment) plus BSC**,** in patients with stage IIIB or stage IV NSCLC who have not progressed following four cycles of platinum-based induction chemotherapy. Induction regimens administered in JMEN were cisplatin or carboplatin in combination with gemcitabine, docetaxel or paclitaxel.

Study sites
The study entered 741 patients in a total of 83 centres in 20 countries worldwide (Australia, Austria, Brazil, Bulgaria, China, Croatia, the Czech Republic, Germany, Greece, Hungary, India, Italy, Korea, the Netherlands, Poland, Romania, Spain, Taiwan, Turkey and the United States). There were no centres in the UK.

Study objectives
The primary objective of this study was to compare maintenance therapy with pemetrexed plus BSC versus placebo plus BSC, in terms of objective progression-free survival (PFS) in patients with stage IIIB (with pleural effusion and/or positive supraclavicular lymph nodes) or stage IV NSCLC who have not progressed after four cycles of platinum-based induction chemotherapy.

The secondary objectives of the study included time-to-event efficacy endpoints including

- Overall survival (OS) time
- Objective tumour response rate: complete response (CR) + partial response (PR) (RECIST criteria; Therasse et al 2000, see Appendix 4 for details)
    - Complete response (CR) is defined as disappearance of all tumour lesions
    - Partial response (PR) is defined as either
        - at least a 30% decrease in the sum of the longest diameter (LD) of target lesions taking as reference the baseline sum LDs or
        - complete disappearance of target lesions, with persistence (but not worsening) of one or more non-target lesions.
- Disease control rate: CR, PR, or Stable disease (SD)
    - Stable disease (SD) is defined as absence of sufficient shrinkage to qualify for PR and absence of sufficient increase to qualify for progressive disease (a 20% increase in sum of target lesions) taking as references the smallest sum LD
- Adverse events (AEs)
- Time to worsening of symptoms (TWS) and changes in individual symptom scores and quality of life using the Lung Cancer Symptom Scale (LCSS)

An additional prospective subgroup analysis was planned to evaluate the efficacy of pemetrexed versus placebo in different histological subgroups of NSCLC. This analysis was documented in the statistical analysis plan prior to the initial datalock for progression-free survival.

Interventions

Experimental arm (pemetrexed plus BSC): Pemetrexed 500mg/m^2 on day 1 every 21 days, administered as a 10 minute infusion, plus BSC.

*Control arm (*placebo plus BSC*)*: Normal saline (0.9% sodium chloride) on day 1 every 21 days, administered as a 10 minute infusion, plus BSC.

Best supportive care (BSC): BSC was defined as treatment without a specific antineoplastic regimen and treatment was administered as considered appropriate by the prescribing physician. Acceptable BSC therapies included, but were not limited to antibiotics, antiemetics, thoracentesis, pleurodesis, blood transfusions, and/or nutritional support. Best supportive care specifically excluded anticancer surgery, immunotherapy, radiotherapy, anticancer hormonal therapy, and systemic chemotherapy in which the goal would be to either eradicate or slow the progression of the study disease.

Concomitant medications

Both experimental and control arms received prior and concomitant medication with folic acid, vitamin B_{12}, and dexamethasone.

Folic acid: 350µg -1000µg daily beginning approximately 1 to 2 weeks before the first dose of study therapy, and continuing daily until 3 weeks after the last dose of study therapy.

Vitamin B_{12}: 1000µg intramuscular injection, approximately 1 to 2 weeks before the first dose of study therapy, and approximately every 9 weeks until 3 weeks after the last dose of study therapy.

Dexamethasone: 4 mg, orally twice per day. Should be taken on the day before, the day of, and the day after each dose of study therapy.

Randomisation

Patients were randomly assigned to receive maintenance treatment with pemetrexed plus BSC or placebo plus BSC in a 2:1 ratio, in order to provide sufficient comparative data to demonstrate the superiority of pemetrexed plus BSC, while reducing patient exposure to the potentially inferior treatment with placebo plus BSC.

Randomisation was performed at a central location using a computerised, interactive, voice-activated response system (IVRS). The minimisation principle of Pocock and Simon (1975) was employed to balance assignment between treatment arms using a probability factor of 0.75, based on the following factors:

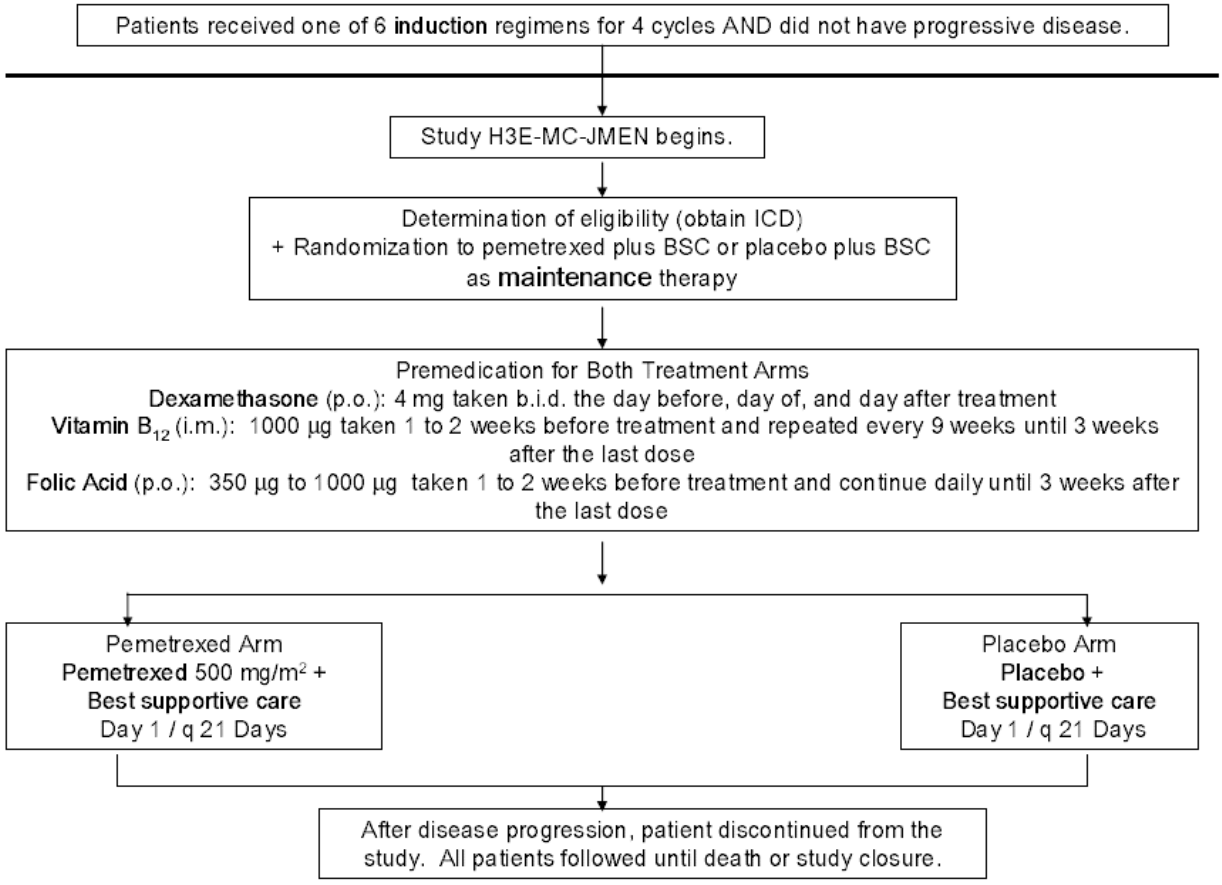
- disease stage prior to administration of induction therapy (IIIB versus IV)
- Eastern Cooperative Oncology Group (ECOG) performance status just prior to randomisation (0 versus 1)
- best tumour response to induction chemotherapy (CR/PR versus SD)
- gender (male versus female)
- previously treated brain metastases (yes versus no)
- non-platinum component of induction chemotherapy (gemcitabine versus paclitaxel versus docetaxel)

Blinding

In order to preserve the blinding of the patient and the personnel involved in patient evaluations or data collection, an unblinded third party (for example, a pharmacist) was designated. The investigator provided the necessary information to the unblinded pharmacist or designee who called the interactive voice response system (IVRS) to obtain the patient's treatment assignment. Neither the patient nor the investigator knew the treatment assignment. Study drugs were prepared by an unblinded pharmacist at each site such that the intravenous infusion bags

containing pemetrexed and placebo were visually indistinguishable. Unblinding was permitted if, in the opinion of the investigator, knowledge of treatment assignment would alter the management of a serious adverse event, otherwise physicians and patients were unblinded only at the time of disease progression. Additionally, inadvertent unblinding was not considered sufficient cause to remove the patient from the study or exclude the patient from safety or efficacy analysis.
It is unusual to have blinding in an oncology clinical trial, so this is one of the strengths of the JMEN study.

Figure 3: Summary of JMEN design (Source: Data on file_JMEN CSR Figure JMEN 9.1)



Abbreviations: b.i.d. = twice daily; BSC = best supportive care; ICD = informed consent document; i.m. = intramuscular; p.o. = oral; q = every.

6.3.2 Participants

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

Inclusion criteria

Patients were eligible to be included in the study only if they met all the following criteria:

- histologic or cytologic diagnosis of NSCLC Stage IIIB (with pleural effusion and/or positive supraclavicular lymph nodes) or Stage IV, prior to induction therapy.
- had received only one of the following induction therapies, based on 21-day cycles and lasting precisely four cycles: gemcitabine plus carboplatin, paclitaxel plus carboplatin, docetaxel plus carboplatin, gemcitabine plus cisplatin, paclitaxel plus cisplatin, or docetaxel plus cisplatin.

- documented evidence of a tumor response of CR, PR, or SD. Tumour assessment must have occured between cycle 4 (day 1) of induction therapy and the date of randomisation.
- ECOG performance status of 0 or 1
- at least 18 years of age
- adequate organ function, including the following:
    - adequate bone marrow reserve: absolute neutrophil (segmented and bands) count ≥1.5 x 109/L, platelets ≥100 x 109/L, and hemoglobin ≥9 g/dL
    - hepatic: bilirubin ≤1.5 times the upper limit of normal , ALP, ASP , and ALT ≤3.0 x upper limit of normal (ALP, AST, and ALT ≤5 x upper limit of normal are acceptable if the liver has tumour involvement)
    - renal: calculated creatinine clearance ≥45 mL/min based on the standard Cockcroft and Gault formula
- 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 4 weeks before study enrolment. Patients must have recovered from the acute toxic effects of the treatment prior to study enrolment.
- signed informed consent document on file
- male and female patients with reproductive potential must have been on an approved contraceptive method, if appropriate (for example, intrauterine device, birth control pills, or barrier device), during and for 3 months after the study. Women with childbearing potential must have had a negative serum pregnancy test within 7 days prior to study enrolment.
- estimated life expectancy of at least 12 weeks
- patient compliance and geographic proximity that allowed adequate follow-up.
- patient must have received on-study therapy no earlier than 21 days and no later than 42 days from day 1 of their last cycle of induction therapy

Exclusion criteria

Patients were excluded from the study if they met any of the following criteria

- had received prior systemic anticancer therapy excluding those listed in the inclusion criteria) including adjuvant early-stage treatment for NSCLC or any systemic treatment for any other cancer
- had received treatment within the last 30 days with a drug that had not received regulatory approval for any indication at the time of study entry
- inability to comply with protocol or study procedures
- had a serious concomitant systemic disorder that, in the opinion of the investigator, would have compromised the patient's ability to complete the study
- had a serious cardiac condition, such as myocardial infarction within 6 months, angina, or heart disease, as defined by the New York Heart Association Class III or IV
- CNS metastases (unless the patient had completed successful local therapy for CNS metastases and had been off of corticosteroids for at least 4 weeks before starting study therapy). A screening CT or MRI before enrolment in the absence of a clinical suspicion of brain metastases was not required
- 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
- concurrent administration of any other antitumor therapy
- inability to interrupt aspirin or other nonsteroidal anti-inflammatory drugs for a 5-day period (8-day period for long-acting agents, such as piroxicam).
- inability or unwillingness to take folic acid or vitamin B12 supplementation
- inability or unwillingness to take corticosteroids
- received an induction chemotherapy regimen that was not based on a 21-day cycle
- pregnant or breast feeding
- a prior malignancy other than NSCLC, carcinoma in situ of the cervix, or non-melanoma skin cancer, unless that prior malignancy was diagnosed and definitively treated at least 5 years previously with no subsequent evidence of recurrence. Patients with a history of

low-grade (Gleason score ≤6) localised prostate cancer were eligible even if diagnosed less than 5 years previously

In the JMEN trial, 745 patients were screened, of whom 741 were entered the trial and 663 were randomised to either pemetrexed plus BSC (n=441) or placebo plus BSC (n=222). The intention to treat (ITT) population consisted of all randomised patients. Although histology was not a randomisation factor, study arms were well-balanced in terms of histologic subtypes. Of the ITT population 481 patients had NSCLC of non-squamous histology and therefore qualify as the 'licensed population', which matches the scope for this appraisal. Of the 481 non-squamous patients, 325 were assigned to pemetrexed and 156 to placebo treatment. Table 1 gives the baseline demographics for the overall intention to treat (ITT) population for the JMEN trial.

Independent retrospective review of histological classification of 102 patients in the JMEN study (Data on file_JMEN_histology review, 2008)

As stated previously, the results of the JMEN study, as well as analyses of data from the JMDB and JMEI studies showed that pemetrexed had superior efficacy in non-squamous NSCLC than in squamous NSCLC. However, the qualitative and quantitative evaluation of such a treatment-by-histology interaction depends on the accuracy of the initial histological diagnosis.

To evaluate the accuracy of histologic diagnosis (squamous / non-squamous) in the JMEN study, an independent pathologist who was blinded to investigator-reported histological diagnosis, patient characteristics and treatment outcomes retrospectively reviewed 102 biopsy specimens (67 in the pemetrexed arm; 35 in the placebo arm). Of the 102 samples reviewed, 9 were not evaluable (7 in pemetrexed arm; 2 in placebo arm). Both independent and investigator review classifications were available for 93 patients (60 in pemetrexed arm; 33 in placebo arm). Histological classification was found to match in a total of 83 samples (54 in pemetrexed arm; 29 in placebo arm), i.e, there was 89.2% agreement between investigator and independent histological diagnosis when classifying samples as non-squamous versus squamous. These results confirm the high degree of diagnostic accuracy in histological diagnosis of non-squamous NSCLC in JMEN.

Table 1. Summary of baseline demographics and patient characteristics of patients in the JMEN trial – ITT population (source: Section 7.1.1 JMEN CSR addendum)

	Pemetrexed N = 441	Placebo N = 222	Total N = 663
Male n (%)	322 (73.0)	161 (72.5)	483 (72.9)
Female n (%)	119 (27.0)	61 (27.5)	180 (27.1)
Median age at randomisation (years)	60.6	60.4	60.6
Age < 65 years n (%)	294 (66.7)	149 (67.1)	443 (66.8)
Age ≥ 65 years n (%)	147 (33.3)	73 (32.9)	220 (33.2)
Ethnic origin n (%)			
Aboriginal	0 (0.0)	1 (0.5)	1 (0.2)
African	6 (1.4)	0 (0.0)	6 (0.9)
Caucasian	279 (63.3)	149 (67.1)	428 (64.6)
East Asian	104 (23.6)	50 (22.5)	154 (23.2)
Hispanic	13 (2.9)	6 (2.7)	19 (2.9)
West Asian[a]	39 (8.8)	16 (7.2)	55 (8.3)
Smoking status n (%)			
Unknown	4 (0.9)	1 (0.5)	5 (0.8)
Ever smoker	324 (73.5)	158 (71.2)	482 (72.7)
Never smoker	113 (25.6)	63 (28.4)	176 (26.5)
Disease stage prior to induction therapy[b] n (%)			
Unknown	1 (0.2)	0 (0.0)	1 (0.2)
Stage IIIB	79 (17.9)	47 (21.2)	126 (19.0)
Stage IV	361 (81.9)	175 (78.8)	536 (80.8)
ECOG performance status at randomisation[c] n (%)			
Unknown	2 (0.5)	0 (0.0)	2 (0.2)
0	176 (39.9)	85 (38.3)	261 (39.4)
1	263 (59.6)	137 (61.7)	400 (60.3)
Best tumour response to induction therapy n (%)			
Unknown	1 (0.2)	0 (0.0)	1 (0.2)
Complete response	6 (1.4)	1 (0.5)	7 (1.1)
Partial response	201 (45.6)	114 (51.4)	315 (47.5)
Stable disease	230 (52.2)	107 (48.2)	337 (50.8)
Progressive disease[d]	3 (0.7)	0 (0.0)	3 (0.5)

	Pemetrexed N = 441	Placebo N = 222	Total N = 663
Previously treated brain metastases n (%)			
Yes	33 (7.5)	18 (8.1)	51 (7.7)
No	408 (92.5)	204 (91.9)	612 (92.3)
Specific induction regimen n (%)			
Docetaxel + carboplatin	21 (4.8)	7 (3.2)	28 (4.2)
Docetaxel + cisplatin	7 (1.6)	4 (1.8)	11 (1.7)
Gemcitabine + carboplatin	107 (24.3)	48 (21.6)	155 (23.4)
Gemcitabine + cisplatin	146 (33.1)	84 (37.8)	230 (34.7)
Paclitaxel + carboplatin	132 (29.9)	59 (26.6)	191 (28.8)
Paclitaxel + cisplatin	27 (6.1)	20 (9.0)	47 (7.1)
	Histologic classification[f]		
Non-squamous carcinoma	N=325	N=156	N=481
Adenocarcinoma	222 (50.3)	106 (47.7)	328 (49.5)
Large cell carcinoma	10 (2.3)	10 (4.5)	20 (3.0)
Other[e] or indeterminate	93 (21.1)	40 (18.0)	133 (20.1)
Squamous cell carcinoma	116 (26.3)	66 (29.7)	182 (27.5)

[a]West Asian refers to patients originating from the Indian subcontinent
[b]One patient was missing disease stage status
[c]Two patients were missing performance status information
[d]Three patients were randomized but not treated due to progressive disease at the time of study entry
[e]"Other" includes patients with a primary diagnosis of NSCLC whose disease did not clearly qualify as adenocarcinoma, squamous cell carcinoma, or large cell carcinoma
[f]Expressed as percentage of ITT population

This submission will focus on the 481 patients with non-squamous NSCLC in the JMEN study, in line with the licence for pemetrexed. In the following sections, baseline demographics and efficacy outcomes are reported for the non-squamous and adenocarcinoma population. For analysis of safety, results for overall ITT population and non-squamous populations have been reported.

Summary of patient characteristics for the non-squamous population (see Table 2 below)
Overall, the histologic subgroups were well balanced with respect to baseline characteristics. Patients were predominantly Caucasian with 60% patients (195/325) in the pemetrexed arm and 62.8% (98/156) in the placebo arm. The median age of patients in pemetrexed and placebo arms was 60.6 and 60.2 years respectively. Approximately 69% patients in both arms were male (223/325 pemetrexed; 108/156 placebo), and ever smokers (224/325 pemetrexed; 107/156 placebo). Most patients had stage IV disease with 82.8% patients (269/325) in the pemetrexed arm and 80.8% (126/156) in the placebo arm. In both arms there were more patients with performance status 1 (58.5% (190/325) in the pemetrexed arm and 61.5% (96/156) in the placebo arm).

Induction treatment

There were more responders to first-line treatment in both the non-squamous and adenocarcinoma populations' placebo arms compared to pemetrexed arms. However, response to prior treatment was not found to be a significant prognostic factor, and therefore this should not have any significant impact on survival outcomes.

Gemcitabine/cisplatin, followed by gemcitabine/carboplatin and docetaxel/cisplatin were the most frequently reported induction regimens. In the pemetrexed arm 44% (143/325) of patients had

partial response and 53.5% (174/325) had stable disease compared to 50% (78/156) with partial response and 50% (78/156) with stable disease in the placebo arm.

Adenocarcinoma was the predominant histological subtype among the non-squamous NSCLC patients with 68.3% (222/325) in the pemetrexed arm and 68% (106/156) in the placebo arm, followed by other / indeterminate carcinoma with 28.6% (93/325) patients in the pemetrexed arm and 25.64% (40/156) in the placebo arm, and large cell carcinoma with 3.08% (10/325) patients in the pemetrexed arm and 6.41% (10/156) in the placebo arm.

Table 2 shows the baseline demographics for the non-squamous population from the JMEN trial.

Table 2. Summary of baseline characteristics and demographics for the non-squamous population in the JMEN study (source: Data on file_baseline_demographics_non-squamous_N481)

	Non-squamous population (N=481)		
	Pemetrexed N=325	**Placebo N=156**	**Total N=481**
Male, n (%)	223 (68.6)	108 (69.2)	331 (68.8)
Female, n (%)	102 (31.4)	48 (30.8)	150 (31.2)
Median age at randomisation (years)	60.6	60.2	
Age < 65 years, n (%)	220 (67.7)	102 (65.4)	322 (66.9)
Age ≥ 65 years, n (%)	105 (32.3)	54 (34.6)	159 (33.1)
Ethnic origin, n (%)			
Aboriginal	0 (0.0)	0 (0.0)	0 (0)
African	6 (1.8)	0 (0.0)	6 (1.2)
Caucasian	195 (60.0)	98 (62.8)	293 (60.9)
East Asian	88 (27.1)	41 (26.3)	129 (26.8)
Hispanic	8 (2.5)	3 (1.9)	11 (2.3)
West Asian[a]	28 (8.6)	14 (9.0)	42 (8.7)
Smoking status, n (%)			
Unknown	3 (0.9)	1 (0.6)	4 (0.8)
Ever smoker	224 (68.9)	107 (68.6)	331 (68.8)
Never smoker	98 (30.2)	48 (30.8)	146 (30.3)
Disease stage prior to induction therapy[b], n (%)			
Unknown	1 (0.3)	0 (0.0)	1 (0.2)
Stage IIIB	55 (16.9)	30 (19.2)	85 (17.7)
Stage IV	269 (82.8)	126 (80.8)	395 (82.1)
ECOG PS at randomisation[c], n (%)			
Unknown	2 (0.6)	0 (0.0)	2 (0.4)
0	133 (40.9)	60 (38.5)	193 (40.1)
1	190 (58.5)	96 (61.5)	286 (59.4)
Best tumour response to induction therapy, n (%)			
Unknown	1 (0.3)	0 (0.0)	1 (0.2)
Complete response	5 (1.5)	0 (0.0)	5 (1.0)
Partial response	143 (44.0)	78 (50.0)	221 (45.9)
Stable disease	174 (53.5)	78 (50.0)	252 (52.4)
Progressive disease[d]	2 (0.6)	0 (0.0)	2 (0.4)
Previously treated brain metastases, n (%)			
Yes	30 (9.2)	13 (8.3)	43 (8.9)
No	295 (90.8)	143 (91.7)	438 (91.1)

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

ECOG, Eastern Cooperative Oncology Group; PS, performance status
[a]West Asian refers to patients originating from the Indian subcontinent
[b]One patient was missing disease stage status
[c]Two patients were missing performance status information
[d]Two patients were randomised but not treated due to progressive disease at the time of study entry
Note: Baseline characteristics presented here represent the baseline characteristics of the histological subgroups subsequent to the histological reclassification of a total of three patients following the initial datalock in November 2007 (including the reclassification of one patient in the pemetrexed-treated from adenocarcinoma to squamous cell carcinoma)

The patient characteristics from the JMEN trial are difficult to compare with the patient characteristics from the LUCADA database (2007), the largest source of information on lung cancer patients in the UK. The LUCADA database includes 57% of all cases of lung cancer in England and Wales for 2006-07 but, of these, only 34% were recorded as being of good performance status, PS 0-1, the population eligible for maintenance therapy in routine clinical practice. The patients in the trial were younger with a median age of 60 years compared to a median age for LUCADA patients of 71 years. This would be expected in light of the performance status in the clinical trial being PS 0-1 as age and performance status are interrelated so the clinical trial population is likely to be broadly similar to the population treated in clinical practice with chemotherapy.

More than 60% of LUCADA patients had a histological diagnosis, but the distribution differed from JMEN, as shown in Table 3.

Table 3. Variation in histotype between England and Wales audit data (LUCADA 2007) and the JMEN trial

	Squamous cell carcinoma	**Adenocarcinoma**	**Large-cell carcinoma**	**NSCLC – NOS***
LUCADA 2007	33%	25%	4%	36%
JMEN (as percentage of overall trial population of 663 patients)	27.5%	49.5%	3%	20.1%

The main differences are in the adenocarcinoma and NSCLC-NOS groups. JMEN had a larger proportion of adenocarcinoma and fewer NSCLC-NOS than LUCADA. This is potentially due to better diagnosis in a clinical trial setting as compared to a usual care setting. The high proportion of NSCLC-NOS patients is likely to represent less than expert pathologists and/or poor samples too small for analysis. Many of these cases may be identified as adenocarcinoma on re-examination.

Table 4 below presents baseline demographics for the sub-group of patients with adenocarcinoma.

Table 4. Summary of baseline characteristics and demographics for adenocarcinoma patients (Data on file_JMEN_baseline_demographics_adeno, 2009)

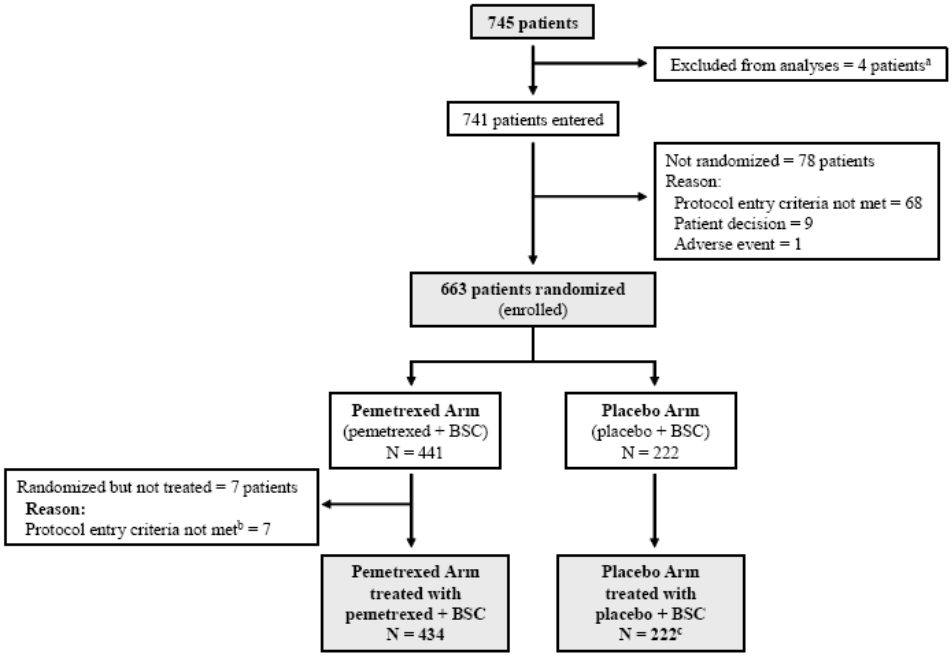
	Adenocarcinoma	
	Pemetrexed N=222	**Placebo N=106**
Male, n (%)	142 (64.0)	71 (67.0)
Female, n (%)	80 (36.0)	35 (33.0)
Median age at randomisation (years)	59.9	58.5
Age < 65 years, n (%)	154 (69.4)	73 (68.9)
Age ≥ 65 years, n (%)	68 (30.6)	33 (31.1)
Ethnic origin, n (%)		
Aboriginal	0 (0.0)	0 (0.0)
African	4 (1.8)	0 (0.0)
Caucasian	119 (53.6)	57 (53.8)
East Asian	77 (34.7)	38 (35.8)
Hispanic	3 (1.4)	2 (1.9)
West Asian[a]	19 (8.6)	9 (8.5)
Smoking status, n (%)		
Unknown	3 (1.4)	1 (0.9)
Ever smoker	137 (61.7)	64 (60.4)
Never smoker	82 (36.9)	41 (38.7)
Disease stage prior to induction therapy[b], n (%)		
Unknown	0 (0.0)	0 (0.0)
Stage IIIB	43 (19.4)	25 (23.6)
Stage IV	179 (80.6)	81 (76.4)
ECOG PS at randomization[c], n (%)		
Unknown	1 (0.5)	0 (0)
0	85 (38.3)	41 (38.7)
1	136 (61.3)	65 (61.3)
Best tumor response to induction therapy, n (%)		
Complete response	3 (1.4)	0 (0.0)
Partial response	93 (41.9)	53 (50.0)
Stable disease	124 (55.9)	53 (50.0)
Progressive disease[d]	2 (0.9)	0 (0.0)
Previously treated brain metastases, n (%)		
Yes	24 (10.8)	9 (8.5)
No	198 (89.2)	87 (91.5)
Specific induction regimen, n (%)		
Unknown		
Docetaxel + carboplatin	11 (5.0)	4 (3.8)
Docetaxel + cisplatin	3 (1.4)	2 (1.9)
Gemcitabine + carboplatin	68 (30.6)	26 (24.5)
Gemcitabine + cisplatin	71 (32.0)	37 (34.9)
Paclitaxel +carboplatin	58 (26.1)	27 (25.5)
Paclitaxel +cisplatin	11 (5.0)	10 (9.4)

ECOG = Eastern Cooperative Oncology Group; PS = performance status
[a]West Asian refers to patients originating from the Indian subcontinent
[b]No patients were missing disease stage status
[c]One patients was missing performance status information
[d]Two patients were randomized but not treated due to progressive disease at the time of study entry
Note: Baseline characteristics presented here represent the baseline characteristics of the histological subgroups subsequent to the histological reclassification of a total of three patients following the initial datalock in November 2007 (including the reclassification of one patient in the pemetrexed-treated from adenocarcinoma to squamous cell carcinoma)

6.3.3 Patient numbers

Provide details of the numbers of patients who were eligible to enter the RCT, randomised, and allocated to each treatment. Provide details of and the rationale for patients who crossed over treatment groups and/or were lost to follow up/ withdrew from the RCT. This information should be presented as a CONSORT flow chart.
A total of 745 patients were assessed for eligibility and of these, 741 patients were entered the trial and 663 patients were randomised to either pemetrexed plus BSC (n=441) or placebo plus BSC (n=222). Three patients were randomised to receive placebo but received pemetrexed treatment. These patients were analysed per protocol as per the study arm to which they were assigned.

Figure 4: CONSORT diagram for the JMEN trial (source: JMEN CSR_Addendum Fig JMEN.4.1)



Abbreviations: BSC = best supportive care; CSR = clinical study report; N = number of randomized patients.
a Patient 391-3926 was treated on study but did not undergo randomization. Patients 130-1303, 130-1313, and 687-6981 were randomized and treated, but did not have documented informed consent (refer to Section 10.2.3 of the JMEN CSR for further information).
b These 7 patients were randomized but did not receive treatment due to protocol violations (protocol entry criteria not met; refer to Section 10.2.1 of the JMEN CSR and Appendix 7.1.1. of this CSR Addendum for further information [Patients 100-1003, 100-1009, 177-1948, 212-2152, 241-2456, 420-4207, and 683-6878 were randomized, but discontinued prior to study treatment due to protocol entry criteria not met]).
c Three patients (106-8204, 212-2150, and 681-6827) were randomly assigned to placebo but received treatment with pemetrexed. These patients were analyzed per protocol according to randomized study arm (refer to Section 10.2.2 of the JMEN CSR for further information).
Sources: FQDISA11, LSDEMA11, LSDISA11.

Within 4 weeks of study entry, baseline tumour measurements were performed by imaging (CT scans or MRIs). Each patient underwent a treatment period and a follow-up period. The treatment

period consisted of treatment cycles, each 21 days long. Patients in each treatment arm were assessed clinically every 3 weeks and objectively (with radiographic imaging, using the RECIST criteria) every 2 cycles. Patients received treatment (experimental or control) until objective disease progression. The follow-up period began when the patient discontinued study treatment; follow-up included periodic tumour response evaluation until objective disease progression. Investigators followed all patients until death or study closure.

The study was conducted from March 2005 (first patient enrolled) to July 2007 (the last patient was enrolled). The last patient completed in August 2007 for the primary datalock. The database of Study JMEN was locked 3 times for analysis. The primary datalock, which measured progression-free survival (PFS), response rate (RR), disease control rate (DCR), preliminary overall survival (OS), and safety, was locked on 21 November 2007. The Safety Update (datalock 11 April 2008) was performed to assess event rates and determine if there were any new safety signals based on the additional follow-up for patients who remained on study treatment. The final OS datalock occurred on 18 December 2008.

Following the 21st November 2007 datalock but prior to the second datalock for safety update (11th April 2008), the histological classification of one patient on the pemetrexed arm was changed proactively (without query from the sponsor) by the investigative site from adenocarcinoma to squamous cell carcinoma. This patient was randomised to pemetrexed but did not receive study treatment since the patient was deemed ineligible due to inadequate organ function. The patient did not undergo scans and therefore was not included in the independently reviewed PFS population results for PFS or response. This patient was included in the squamous group for the safety update and the final OS analysis. Therefore, although the reclassification changed the grouping of this patient from the non-squamous to the squamous population, this did not impact the efficacy conclusions of this study. As a result of the histological reclassification, 481 patients (325 in the pemetrexed arm; 156 in the placebo arm) were included in the analysis of overall survival in the non-squamous group; 482 patients (326 in the pemetrexed arm; 156 in the placebo arm) were included in the analyses for PFS and RR. Baseline demographics on the final OS population of 481 patients have been reported in Table 2 and baseline demographics for the PFS population of 482 patients have been presented in Appendix 5.

6.3.4 Outcomes

Provide details of the outcomes investigated and the measures used to investigate those outcomes. Indicate which outcomes were specified in the trial protocol as primary or secondary, and whether they are relevant with reference to the specification of the decision problem.

Initially, the OS was designated as the primary endpoint for JMEN. However, the study protocol was subsequently amended as the primary endpoint was changed from OS to PFS.

Rationale for change of primary endpoint:

a. Patients with lung cancer are now living longer and receiving multiple lines of treatment with the potential to confound the interpretation of OS. Given the inclusion criteria for JMEN (stable or responding disease and an ECOG performance status of 0 or 1), these patients will likely experience longer survival times. With the availability of more effective treatments that are available today as additional lines of therapy, PFS will provide a better measure to distinguish the effectiveness of pemetrexed, prior to exposure to additional therapies. A delay in progression is expected to correlate with delayed worsening of disease-related symptoms, the evaluation of which constitutes a family of secondary endpoints in this study.

b. The double-blind placebo controlled study design of JMEN allowed for robust evaluation of PFS without requiring any changes in sample size, efficacy assumptions or statistical power of the final overall survival analysis.
Thus, the primary endpoint of the JMEN trial was progression-free survival (PFS), measured from the date of randomisation to the first date of objective disease progression or death from any cause.

Secondary endpoints include:

- Overall survival
- Time to worsening of symptoms
- Objective tumour response rate
- Adverse events
- Changes in individual symptom scores and quality of life using the Lung Cancer Symptom Scale (LCSS)

Table 5 shows the outcomes reported in the JMEN trial along with details of length of follow-up, timing of assessment and scoring methods.

Table 5. Details of outcomes reported in the JMEN trial

Outcome	Definition	Measure	Timing of assessment
Primary outcome measure			
Progression-free survival	Duration measured from the date of randomisation to the first date of progression of disease or of death from any cause	RECIST – based on computed tomography (CT), including spiral CT, scans and magnetic resonance imaging (MRI), or in some cases chest X-rays (when lesion is clearly defined and surrounded by aerated lung)	*Baseline (post-induction therapy*) : after 4 cycles of treatment and no more than 42 days after last dose of induction therapy *On study*: Repeated every 2 cycles of therapy. Assessment within 7 days prior to day 1 of each cycle *Post-study follow-up*: For patients without documented objective disease progression, approximately every 6 weeks until documented objective disease progression. Once the patient had objective disease progression, the patient was followed up approximately every 90 days until death or study closure.
Secondary outcome measures			
Overall survival	Duration measured from the date of randomisation to the date of death from any cause. For patients not known to have died as of the data-inclusion cut-off date for the analysis, overall survival was censored at the date of last prior contact.	Death	N/A
Tumour response rate	The proportion of patients per study arm with a confirmed partial response (PR) or complete response (CR).	RECIST – based on computed tomography (CT), including spiral CT, scans and magnetic resonance imaging (MRI), or in some cases chest X-rays (when lesion is clearly defined and surrounded by aerated lung)	*Baseline (post-induction therapy*) : after 4 cycles of treatment and no more than 42 days after last dose of induction therapy *On study*: Repeated every 2 cycles of therapy. Assessment within 7 days prior to day 1 of each cycle

			Post-study follow-up: For patients without documented objective disease progression, approximately every 6 weeks until documented objective disease progression *Response confirmation*: Responding pts must have had confirmatory scans performed within 6 weeks (but not less than 28 days) of the last scan. Responding pts were followed every 6 weeks (but not less than 28 days) until documented disease progression.
Time to worsening of symptoms	Measured from the date of randomisation to the first date of worsening for each of the six LCSS symptoms and three summary items; worsening was defined as a 15mm increase on the 100mm visual analogue scale. For each patient who was not known to have had a worsening (defined in this way), time to worsening of symptoms was censored at the date of the patient's last LCSS assessment.	LCSS	Baseline (prior to randomisation), once every cycle till discontinuation from study, and within 30 days of discontinuation). Assessments performed on day 21 of every cycle.
Safety	Adverse events	Adverse events were rated using the NCI CTCAE scale (Version 3.0; NCI 2003).	Baseline, before each cycle, 30 days post-therapy, and long-term (for serious AEs)
Changes in individual symptom scores and quality of life using the LCSS		LCSS	Baseline (prior to randomisation), once every cycle till discontinuation from study, and within 30 days of discontinuation). Assessments performed on day 21 of every cycle.

6.3.5 Statistical analysis and definition of study groups

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

The primary objective of this clinical trial was to compare two maintenance therapies, pemetrexed plus BSC versus placebo plus BSC, in terms of PFS. The sample size of 660 patients (pemetrexed plus BSC 440, placebo plus BSC 220) was originally selected to provide a final analysis of OS with 80% power using a one-sided alpha level of 0.025, assuming 475 events and an OS hazard ratio (HR) of 0.767. However, the study protocol was subsequently amended as the primary endpoint was changed from OS to PFS.

Using a gatekeeping strategy, nearly identical statistical assumptions were maintained, allowing for sufficient power for the final survival analysis. In order to maintain an overall one-sided alpha error probability of 0.025, the primary statistical test of progression free survival was performed after a minimum of 462 events using a nominal one-sided significance level of 0.025. For the analysis of overall survival, the one-sided a level of 0.025 was split between the preliminary and final analysis of overall survival: a nominal one-sided level of 0.00001 was spent for the preliminary analysis of overall survival, leaving a nominal level of 0.02499 to be spent for the final analysis of overall survival.

The primary statistical analysis assumed the PFS HR as approximately constant during the period of follow-up after randomisation and estimated the PFS HR from the study data using a Cox proportional hazards model (Cox 1972) with assigned treatment as the only covariate. From this Cox model, a two-tailed 95% confidence interval was used to assess the following statistical hypotheses:

- H0: PFS HR ≥ 1.00 (null hypothesis)
- HA: PFS HR < 1.00 (alternative, research hypothesis)

If the 95% confidence interval for the PFS HR falls entirely below the margin of 1.00, the null hypothesis H0 will be rejected at a nominal one-sided 0.025 significance level.

For each of the time-to-event endpoints (PFS, OS, TPD, and each of the TWS variables) the analysis estimated HRs using the Cox proportional hazards model with assigned treatment as the only covariate and compare treatment arms using the hypotheses described above.

Covariate adjusted analysis were also performed using the Cox proportional hazards model (stratified by the non-platinum component of induction therapy). The covariates considered for inclusion were:
assigned study treatment, performance status, platinum component of induction therapy, presence of previously-treated brain metastases and squamous histology. However, analysis could exclude any cofactor if there were insufficient patients representing one level of the variable, if there were insufficiently complete data collected on that variable of if that cofactor was consistently found to have no prognostic impact on the time-to-event variables under investigation.

Subgroup analysis in NSCLC histological subtypes

Evidence that the efficacy of pemetrexed varies with histology has been emerging from recent clinical studies in NSCLC. Retrospective analyses of study JMEI (pemetrexed in second-line NSCLC; Hanna et al 2004) showed a statistically significant treatment-by-histology interaction, suggesting that pemetrexed has better survival in non-squamous histologies and worse survival in squamous cell carcinoma, as compared to docetaxel in previously treated patients with advanced NSCLC. During the course of enrolment to JMEN, results from prespecified analyses from the pivotal first-line study JMDB became available. These results demonstrated a statistically significant treatment-by-histology interaction favouring pemetrexed plus cisplatin, supporting the interaction observed in JMEI. An additional randomised study (NS01) completed in 2007 in Japanese patients treated with pemetrexed, retrospectively showed substantially better survival for non-squamous than for squamous patients. Based on the results of three randomised trials (JMEI, JMDB, NS01), Lilly updated the JMEN statistical analysis plan to include a prespecified test for treatment-by-histology interaction and corresponding subgroup analyses. It was anticipated that the efficacy advantage for pemetrexed over placebo would be greater within the non-squamous subgroups than within the squamous subgroup. This analysis was documented in the statistical analysis plan prior to the initial datalock for PFS.

Cofactor adjustment was planned to account for possible imbalances between histologic subgroups in factors suspected to have a potential prognostic effect for either NSCLC or response to pemetrexed therapy. Tests for interaction were performed using multivariate Cox models stratified by the non-platinum component of induction therapy (gemcitabine versus taxane), with terms for treatment (pemetrexed versus placebo), squamous histology (no versus yes), treatment-by-histology interaction (non-squamous patients treated with pemetrexed versus all other patients), performance status (0 versus 1), response to induction therapy (CR/PR versus SD), East Asian ethnicity (yes versus no), smoking status (never smoker versus ever smoker), gender (female versus male), and age (< 65 versus ≥ 65). Based on the JMEN analyses, two other factors initially considered (platinum component [cisplatin or carboplatin] of induction therapy and the stage of disease [Stage IIIB or IV]) were omitted because they showed no tendency toward a prognostic effect.

6.3.6 Critical appraisal of relevant RCTs

NICE evaluative criteria	JMEN trial
How was allocation concealed?	Allocation concealment was ensured as randomisation for all sites involved in the study was undertaken using a computerised, interactive, voice-activated response system at a central location. An unblinded pharmacist obtained the patient's treatment assignment from this system; investigators were thus shielded from knowledge of treatment assignment.
What randomisation technique was used?	Patients were randomised to pemetrexed or placebo in a 2:1 ratio and a minimisation principle was adopted to balance patient assignment between study arms.
Was a justification of the sample size provided?	A sample size of approximately 660 patients was initially selected to provide analysis of overall survival with 80% power using a one-sided α level of 0.025, assuming 475 events and an overall survival HR of 0.767. The primary endpoint of the trial was later changed to PFS but nearly identical statistical assumptions and error control were maintained.
Was follow-up adequate?	Each patient underwent a treatment period and a follow-up period. The treatment period consisted of treatment cycles, each 21 days long, administered until disease progression. The follow-up period began when the patient discontinued study treatment; follow-up included periodic tumour response evaluation until objective disease progression. Investigators followed all patients until death

	or study closure.
Were the individuals undertaking the outcomes assessment aware of allocation?	Patients in the pemetrexed-treated arm were given pemetrexed 500 mg/m^2 via intravenous infusion on day 1 of a 21-day cycle. Patients in the placebo-treated arm received an intravenous infusion of normal saline; to maintain blinding the pemetrexed and saline infusions were prepared by an unblinded pharmacist/designee at each site such that the preparations were visually indistinguishable. Unblinding was permitted if, in the opinion of the investigator, knowledge of treatment assignment would alter the management of a serious adverse event, otherwise physicians and patients were unblinded only at the time of disease progression.
Was the design parallel-group or crossover? Indicate for each crossover trial whether a carry-over effect is likely	JMEN was a parallel-group study. However, patients who had disease progression were unblinded to study treatment and subsequent treatment was permitted at the discretion of the investigator, so some crossover did occur. Fewer patients in the pemetrexed arm received post-discontinuation therapy compared to placebo (53.2.5% vs 67.3%, p<0.001). The rate of crossover from placebo to pemetrexed was 18.5%. Survival results are not likely to have been influenced by post-study therapy given the higher rate of follow-up treatment on the placebo arm, low rate of crossover, and the balanced selection of therapies between arms.
Was the RCT conducted in the UK (or were one or more centres of the multinational RCT located in the UK)? If not, where was the RCT conducted, and is clinical practice likely to differ from UK practice?	The JMEN trial was a parallel group trial conducted at 83 investigational sites in 20 countries (Australia, Austria, Brazil, Bulgaria, China, Croatia, the Czech Republic, Germany, Greece, Hungary, India, Italy, Korea, the Netherlands, Poland, Romania, Spain, Taiwan, Turkey and the United States). There were no centres in the UK. However, the study design ensures that the trial results are very much relevant to the UK. The trial population is representative of patients with NSCLC as a whole since the inclusion/exclusion criteria for the JMEN trial was such that only patients with locally advanced or metastatic NSCLC were enrolled. The patients received induction regimens similar to what the average NSCLC patient would receive in the UK,i.e., cisplatin or carboplatin in combination with gemcitabine, docetaxel and paclitaxel . The comparator in the JMEN trial is placebo (watch and wait) plus BSC, which is the standard of care in the NHS.
How do the patients included in the RCT compare with patients who are likely to receive the intervention in the UK? Consider factors known to affect outcomes in the main indication, such as demographics, epidemiology, disease severity, setting.	Patients in JMEN were generally younger compared to the average NSCLC patient in the UK (LUCADA 2007). This was due to the inclusion criteria for the trial, which restricted patient entry to limit confounding factors. However, performance status rather than age is a prognostic factor for overall survival in NSCLC, and so this is unlikely to impact the relevance of JMEN results to UK patients. More patients in JMEN have adenocarcinoma and fewer patients have NSCLC-NOS than seen in LUCADA. This is due to better diagnosis in clinical trial compared to usual care. The proportion of adenocarcinoma patients in the UK is likely to increase with improvements in diagnostic specificity over time. Most patients in JMEN were of good performance status (PS 0-1). In LUCADA, 34% of patients were of good performance status. As mentioned previously, patients in LUCADA include those with lung cancer in general, irrespective of lines of treatment or eligibility for chemotherapy and so these patients are not necessarily representative of the average patient who would receive pemetrexed maintenance treatment, since in actual clinical practice, only patients who are relatively fit would receive chemotherapy.
For pharmaceuticals, what dosage regimens were used in the RCT? Are they within those detailed in the Summary of	See Section 6.3.1 for dosage regimens. These were as per the SPC for pemetrexed.

Product Characteristics?	
Were the study groups comparable?	The study groups were well balanced in terms of prognostic factors and other baseline characteristics and histology.
Were the statistical analyses used appropriate?	See Section 6.3.5 for a description of the statistical analysis for JMEN
Was an intention-to-treat analysis undertaken?	Yes. ITT was undertaken for efficacy and safety analysis.
Were there any confounding factors that may attenuate the interpretation of the results of the RCT(s)?	None known

6.4 Results of the relevant comparative RCTs

Treatment by histology interaction in study JMEN

A statistically significant treatment-by-histology interaction was observed in the analysis of the overall population in the JMEN trial for both progression-free survival (interaction p=0.036; HR = 0.65;) and overall survival (interaction p=0.033; HR=0.52), indicating that pemetrexed had greater efficacy in non-squamous NSCLC patients than in patients with squamous histology. This is consistent with the results of studies JMEI (second-line NSCLC) and JMDB (first-line NSCLC), which showed that the efficacy of pemetrexed is higher in patients with non-squamous histology.

Table 6. Treatment by histology interaction for PFS and OS in JMEN (source: JMEN CSR section 11.4.4.1; JMEN addendum section 4.4.2.4)

Statistic	Histology subtype	
	Non-squamous (n=481)	**Squamous (n=182)**
OS HR (95% CI)	0.66 (0.49 – 0.88)	1.28 (0.85 – 1.93)
Treatment-by-histology interaction test HR	0.52	
p value	0.033	
PFS HR (95% CI)	0.44 (0.36 – 0.55)	0.69 (0.49 – 0.98)
Treatment-by-histology interaction test	0.65	
p value	0.036	

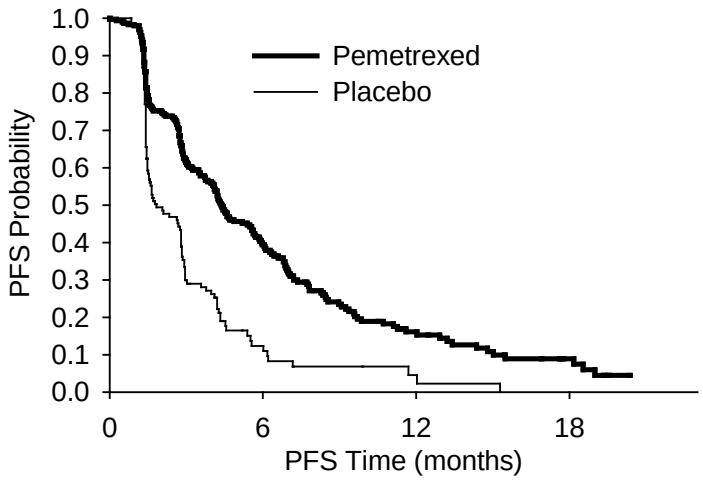
Results for non-squamous group of patients, and the sub-group of patients with adenocarcinoma are discussed below in detail.

Primary endpoint

Progression free survival

Patients in the pemetrexed arm had a significantly longer PFS as compared to patients in the placebo arm (median PFS for pemetrexed 4.5 vs 2.6 months for placebo; HR 0.44; 95% CI 0.36-0.55, p<0.00001). The most pronounced difference in survival was observed for adenocarcinoma patients (median PFS for pemetrexed 4.7 vs 2.6 months for placebo; HR 0.45; 95% CI 0.35-0.59, p<0.00001).

Figure 4: Kaplan-Meier curve of objective progression-free survival in patients with NSCLC of non-squamous histology (source: pemetrexed SPC)



Independent review of PFS for histologic population

A pre-planned, independent central review was conducted by an external vendor to assess for systematic bias in investigator assessed PFS. The vendor had no knowledge of treatment assignment. All patients with available scans, i.e., 291 patients (89%) in the pemetrexed arm and 139 (89%) patients in the placebo arm were included in the analysis. The results of the independent analysis were consistent with the investigators' analysis (median PFS for pemetrexed 4.4 vs 1.9 months for placebo; HR 0.47; 95% CI 0.37-0.60, p< 0.00001).

The analysis demonstrated that the investigator-assessed PFS was similar in terms of the relative efficacy of the two arms since the 2 estimates of the HR were very similar (0.44 and 0.47 for investigator assessed and independently reviewed respectively).

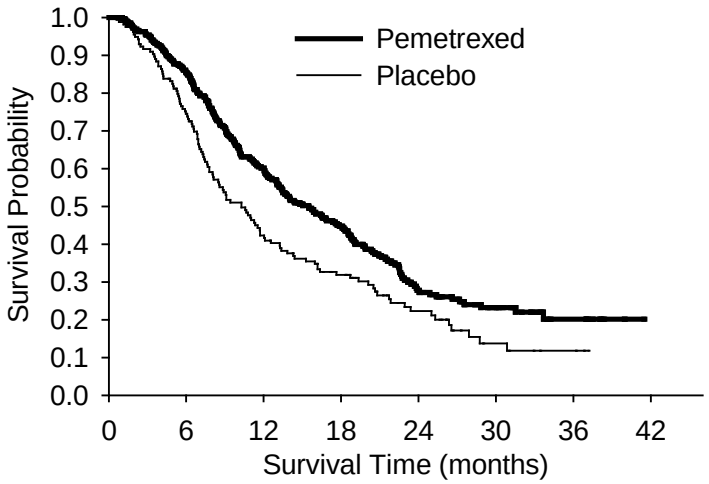
Secondary endpoints

Overall survival

For the non-squamous NSCLC population, patients in the pemetrexed arm had a significantly longer survival benefit as compared to patients in the placebo arm. Median OS for pemetrexed was 5.2 months longer as compared with placebo (15.5 months vs 10.3 months for placebo; HR 0.70; 95% CI 0.56-0.88, p=0.002). A consistent survival benefit was observed for pemetrexed treated adenocarcinoma patients too (median OS for pemetrexed 16.8 vs 11.5 months for placebo; HR 0.73; 95% CI 0.56-0.96, p=0.026).

One-year survival rates for the non-squamous population were 60% for pemetrexed compared with 42% for placebo. Two-year survival rates were 28% for pemetrexed and 22% for placebo. In the adenocarcinoma population one-year survival rates were 67% for pemetrexed and 47% for placebo. Two-year survival rates were 29% for pemetrexed and 26% for placebo. (Data on file_JMEN_survival rates2009)

Figure 5: Kaplan-Meier curve of overall survival in patients with NSCLC of non-squamous histology (source: pemetrexed SPC)



Tumour response

A significant difference in tumour response (CR +PR) was observed between treatment arms (7.4% for pemetrexed vs 1.9% for placebo; p=0.018). The disease control rate (CR + PR + SD) was also higher in the pemetrexed arm vs placebo (57.7% vs 32.7%, p<0.001). This response was achieved in patients who had already experienced complete response / partial response / stable disease in the first-line setting, so a high response in the maintenance setting would not be expected. This is consistent with clinical goals of maintenance treatment, i.e., the focus is on maintaining the clinical benefit achieved with first-line treatment.

Time to worsening of symptoms

Patients in the pemetrexed arm had significantly longer time to worsening for pain and haemoptysis compared with placebo-treated patients (median 8.4 months for pemetrexed versus 4.9 months for placebo for pain, Table 7); the median time to worsening of symptoms for haemoptysis was not calculated due to high censoring rates. There were no statistically significant differences between treatment groups in terms of time to worsening of any other symptoms including loss of appetite, fatigue, cough, dyspnoea, symptom distress and global quality of life although there were numeric trends in favour of pemetrexed..

The rates of censoring were very high for these analyses, limiting the statistical power of the findings and the ability to interpret the results in terms of patient outcomes. Clinical investigators cited concern over patient welfare as a key reason for not asking the patient to complete the HRQoL questionnaires at the follow up visit after progression. This is a common problem in clinical trials, particularly within cancer (Stephens et al 1999).

Table 7. Time to worsening of symptoms in non-squamous patients (source: JMEN CSR Table JMEN.14.13)

Individual LCSS Score	Pemetrexed Median (months) (95% CI)	Placebo Median (months) (95% CI)	HR[a] (95% CI)	p-Value [a]
Loss of appetite (n= 204)	4.27 (5.78)	4.63 (2.96-)	1.113 (0.81-1.52)	0.501
Fatigue (n=217)	3.19 (2.79-6.28)	3.09 (2.43-3.98)	0.957 (0.71-1.28)	0.770
Cough (n= 166)	7.13 (4.73-)	6.44 (3.52-15.64)	0.883 (0.63-1.24)	0.471
Dyspnea (n=179)	10.71 (4.37-)	3.55 (2.79-15.61)	0.836 (0.61-1.15)	0.271
Haemoptysis [b] (n=33)	- -	15.61 (15.61-)	0.445 (0.22-0.90)	0.024
Pain (n=183)	8.41 (5.16-12.45)	4.90 (2.79-15.61)	0.693 (0.51-0.95)	0.022
Symptom distress (n=209)	4.50 (3.65-6.08)	3.68 (2.79-15.61)	0.879 (0.65-1.19)	0.403
Interference with activity level (n=182)	7.82 (5.16-)	3.71 (2.43-15.61)	0.794 (0.58-1.09)	0.152
Global quality of life (n=188)	7.20 (4.53-15.90)	3.68 (2.79-6.28)	0.795 (0.58-1.09)	0.149

Abbreviations: CI = Confidence interval; HR = hazard ratio; LCSS = Lung Cancer Symptom Scale; N = number of randomized patients; n = number of patients with symptom; TWS = time to worsening of symptoms.

a Unadjusted HR and p-value from Cox model with treatment as the only cofactor.

b Median TWS for hemoptysis was not calculated due to the high level of censoring.

Table 8. Summary of efficacy outcomes, non-squamous NSCLC population and adenocarcinoma sub-group from the JMEN trial

	Pemetrexed	Placebo	Hazard ratio	p-value
Median PFS (months)				
Non-squamous (n=482)	*4.50*	*2.60*	*0.44 (0.36-0.55)*	*<0.00001*
Adenocarcinoma (n=329)	4.73	2.60	0.45 (0.35-0.59)	<0.00001
Median overall survival (months)				
Non-squamous (n=481)	*15.47*	*10.28*	*0.70 (0.56-0.88)*	*0.002*
Adenocarcinoma (n=328)	16.82	11.53	0.73 (0.56-0.96)	0.026
Tumour response				
Non-squamous (n=482)	*7.4*	*1.9*		*0.018*
Adenocarcinoma (n=329)	8.1	2.8		0.090
Disease control rate				
Non-squamous (n=482)	*57.7*	*32.7*		*<0.001*
Adenocarcinoma (n=329)	61.0	33.0		<0.001

Summary of efficacy of pemetrexed in maintenance NSCLC

- JMEN was a robust, well-designed trial assessing the efficacy of pemetrexed as maintenance treatment in advanced NSCLC patients with complete / partial response or stable disease following four cycles of induction treatment with cisplatin or carboplatin in combination with gemcitabine, paclitaxel or docetaxel. The comparator in this trial is the current standard of care in the NHS, i.e., 'watch and wait' (placebo) plus BSC.
- Non-squamous NSCLC patients in the pemetrexed arm had a 1.9 months longer PFS as compared to the patients in the placebo plus BSC arm (pemetrexed 4.5 months, placebo 2.6 months; hazard ratio 0.44 , CI 0.36-0.55, p<0.0001).
- Non-squamous NSCLC patients in the pemetrexed arm had a overall survival benefit of 5.2 months over patients in the placebo arm (median OS pemetrexed arm 15.5, placebo 10.3; hazard ratio 0.70, CI 0.56-0.88, p=0.002).
- Adenocarcinoma patients in the pemetrexed arm had a 2.1 months longer PFS than the placebo arm (pemetrexed arm 4.7 months, placebo 2.6 months; hazard ratio 0.45 CI 0.35-0.59, p<0.00001).
- Adenocarcinoma patients in the pemetrexed arm had an overall survival benefit of 5.3 months over the placebo arm (median OS in pemetrexed arm 16.8 vs 11.5 in placebo arm; hazard ratio 0.73, CI 0.56 – 0.96, p=0.026).
- Patients in the pemetrexed-treated arm had statistically significantly longer time to worsening for pain and haemoptysis compared with placebo-treated patients.

Relevance of the End of life criteria (supplementary advice issued to the Appraisal committee on 2nd January 2009) to this technology appraisal.

Criteria:

- *The treatment is indicated for patients with a short life expectancy, normally less than 24 months.*

Lung cancer has an enormous impact on national mortality and currently accounts for 7% of all deaths and 22% of all deaths from cancer in the UK. Survival statistics vary with the stage of the disease at diagnosis. While around 58-73% patients with early stage (stage IA) may survive at 5 years, survival statistics fall with more advanced stages of lung cancer (for which pemetrexed maintenance treatment is indicated). For patients with stage IIIB, only 7-9% may live for 5 years and for patients with stage IV (metastatic) cancer, only about 2-13% survive for 5 years (Cancer Research UK, 2009).

Median overall survival estimates for patients with untreated NSCLC are difficult to come by. According to LUCADA (2007), the median OS by network for patients with histologically confirmed NSCLC was 232 days = 7.6 months. The median OS for patients in the placebo arm of the JMEN study was 10.3 months.

- *There is sufficient evidence to indicate that the treatment offers an extension to life normally of at least an additional 3 months, compared with current NHS treatment.*

OS results
Results from the JMEN trial on pemetrexed in the maintenance setting showed that in patients with non-squamous NSCLC, pemetrexed treatment offers a median survival benefit of 5.2 months over placebo. In the sub-group of patients with adenocarcinoma, pemetrexed treatment offers a median survival benefit of 5.3 months over placebo. This magnitude of survival benefit has not been demonstrated previously and is considered particularly significant, clinically, in this difficult to treat advanced cancer.

Results from the economic model in this submission show that the mean incremental life years gained by pemetrexed maintenance treatment 5.3 months for the non-squamous population and 5 months for the adenocarcinoma sub-group.

- *No alternative treatment with comparable benefits is available through the NHS.*

Currently, there is no other agent licensed for use in the maintenance NSCLC setting. In the JMEN trial, pemetrexed was shown to be superior to placebo in the maintenance NSCLC setting in patients with tumours of non-squamous histology. The standard of care in the NHS is placebo (watch and wait) plus BSC until the disease progresses, so the use of pemetrexed represents a step change in the clinical management of patients with advanced lung cancer. Pemetrexed would provide patients with an active, well-tolerated option of care that sustains the benefit of first-line treatment, as an alternative to waiting for the disease to worsen prior to being offered additional chemotherapy.

- *The treatment is licensed or otherwise indicated for small patient populations.*

Table 9. Number of patients eligible for pemetrexed maintenance treatment in UK

Population with lung cancer in England and Wales	33,450
80% patients with lung cancer have NSCLC	26,760
80% patients have advanced NSCLC	21,408
65% patients have non-squamous NSCLC	13,915
23% get 1st line chemotherapy	3,228
74% respond to 1st line chemotherapy (including pemetrexed)	2,389
Patients excluded, not licensed for use as received pemetrexed first-line	1,440
Patients licensed and eligible to receive maintenance therapy	**949**

The above calculation assumes a response rate to first-line of 74% which is a maximum based on JMDB trial (JMDB Study Report – response in gemcitabine/cisplatin treatment arm). This would be a maximum possible estimate since data from the literature states that response rates are between 40% and 75% (Schiller 2002; Scagliotti 2008). Based on the SATURN study 46% of patients went on to receive maintenance therapy (Cappuzzo, 2009).

In addition, in actual practice, the number of patients eligible for pemetrexed maintenance treatment is likely to be below 2,389 (approximately 949, see Appendix 6 for details) since the current licence for pemetrexed precludes its use in patients who have received pemetrexed/cisplatin in first-line. This number (949 patients) is a maximum as it assumes that all eligible patients will receive pemetrexed, when in reality, not all physicians will offer or patients wish to receive maintenance therapy.

Appendix 6 shows the patients eligible to receive pemetrexed treatment across all licensed indications (i.e., maintenance NSCLC, first and second-line NSCLC and mesothelioma). The total number of patients eligible to receive pemetrexed for any indication is 3,426.

Table 10. Summary: end of life criteria - pemetrexed in maintenance NSCLC

Short life-expectancy?	Extension to life >3months?	No alternative treatment with comparable benefits?	Indication being considered affects small populations and Licensed for other indications?
Yes Median overall survival for patients with histologically confirmed NSCLC as per LUCADA (audit period 2007) = 232 days = 7.6 months Median overall survival from the placebo arm of the JMEN trial = 10.3 months	*Yes* ***OS results*** *Extension to life due to pemetrexed = 5.2 months in non-squamous NSCLC; 5.3 months in adenocarcinoma sub-group.*	*Yes* No other treatment licensed /approved for maintenance NSCLC in UK. Standard of care in NHS is placebo (watch and wait) plus BSC.	*Yes* Eligible population for maintenance indication = 949 First-line NSCLC=1,440 Second-line NSCLC= 57 Mesothelioma = 979 Total population for pemetrexed across all indications = 3,426

6.5 Meta-analysis

Not applicable

6.6 Indirect/mixed treatment comparisons

Not applicable

6.7 Safety

Give a brief overview of the safety of the technology in relation to the decision problem. Give incidence rates of adverse effects if appropriate.

Table 11 shows the mean and median number of cycles received by patients from both arms in the JMEN study, for the overall ITT population and for the non-squamous sub-group. Patients in the pemetrexed arm received a median of 5 cycles (in overall ITT population) and 6 cycles (in non-squamous sub-group), compared to a median of 3.5 cycles (in overall ITT population) and 3 cycles (in non-squamous sub-group) in the placebo arm.

In the JMEN study, maintenance treatment with pemetrexed was continued until disease progression as measured by RECIST criteria rather than clinical opinion. A small number of patients in the trial were extreme 'outliers' in terms of duration of treatment and received a high number of treatment cycles, leading to a very skewed distribution (see Figure 6). Within the overall ITT population, 48.3% of the patients in the pemetrexed arm and 27.5% patients in the placebo arm completed ≥6 cycles of maintenance therapy. The proportion of patients receiving ≥10 cycles of treatment was 25.2% on the pemetrexed arm compared to 7.1% in the placebo arm.

Figure 6: Number of cycles received by patients (%), non-squamous population

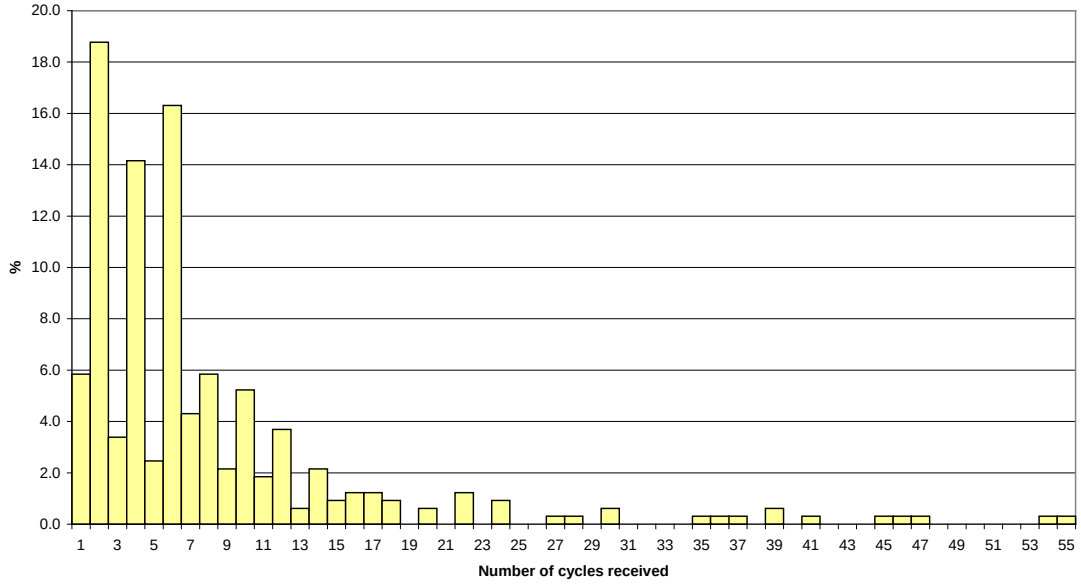


Table 11. Patient exposure to treatment in JMEN (source: Data on file_ JMEN_non-sq cycles)

No of cycles	Overall population		Non-squamous subgroup	
	Pemetrexed (n=441)	Placebo (n=222)	Pemetrexed (n=326)	Placebo (n=156)
Median	5.0	3.5	6.0	3.0
Mean	7.4	4.7	8.0	4.5
Standard Deviation	8.14	5.12	8.62	5.32
No (%) completing at least 6 cycles	213 (48.3)	61 (27.5)	175 (53.8)	39 (25.0)
No (%) completing at least 10 cycles	98 (23.4)	19 (8.6)	82 (25.2)	11 (7.1)

Hanna et al (2004; study JMEI) have characterised the safety profile for single-agent pemetrexed for patient exposures up to a median of 6 cycles. Therefore, for study JMEN, patients receiving >6 cycles were selected to define the population that received long-term exposure to pemetrexed in order to examine any potential differences in safety. No statistically significant differences were observed in the incidence of drug-related grade 3/4 toxicities when compared between patients with ≤6 and >6 cycles of exposure to pemetrexed.

Adverse events

Table 12 summarises the toxicities that were considered possibly related to study drug in > 5% of the overall patient population in study JMEN. Patients in the pemetrexed arm, not unexpectedly, exhibited higher rates of grade 3/4 toxicities in comparison with placebo treated patients. However, absolute rates were low – only 6.3% of pemetrexed- treated patients and 2.3% of placebo-treated patients had grade 3/4 toxicities. Neutropenia (p=0.006) and fatigue (p=0.001) were the only toxicities that were statistically significantly different between the pemetrexed and placebo arms in the ITT population. The difference in fatigue was not statistically significantly different in the licensed population (p=0.07)

Table 12. Percentage of patients with grade 3/4 toxicities in study JMEN, all randomised patients (source: DOF_JMEN_grade3/4AEs_ITT_non-squamous)

	Pemetrexed (n=441)	Placebo (n=222)	p-value
Haematological			
Neutropenia ‡	2.9	0	0.006
Anemia	2.7	0.5	0.070
Leukopenia	1.6	0.5	
Non-haematological			
ALT	0.2	0	
AST	0	0	
Fatigue ‡	5	0.5	0.001
Anorexia	1.8	0	
Infection	1.4	0	
Diarrhoea	0.5	0	
Nausea	0.9	0.5	0.669
Vomiting	0.2	0	1.000
Sensory neuropathy	0.7	0	
Mucositis/Stomatitis	0.7	0	
Rash	0.2	0	

* Updated safety analysis performed 6 months after initial PFS analysis.

† For the purpose of this table, a cut-off of 5% was used for inclusion of all events (all grades) where the investigator considered a possible relationship to pemetrexed.

‡ $P<0.05$ for grade 3/4 rates of neutropenia and fatigue between study arms.

As seen in study JMDB (Scagliotti 2008), safety results for histology subgroups in JMEN were consistent with the ITT population. Among the sub-groups of patients with non-squamous histology, fatigue and neutropenia were the most frequently reported toxicities. Table 13 shows the grade 3/4 toxicities for the non-squamous sub-group.

Table 13. Percentage of patients with grade 3/4 toxicities in the non-squamous sub-group (source:DOF_JMEN_grade3/4AEs_ITT_non-squamous)

Grade 3/4 toxicity	Pemetrexed (n=326)	Placebo (n=156)	p-value
Anaemia	2.5	0	0.058
Neutropenia	2.8	0	0.035
Fatigue	3.7	0.6	0.070
Nausea	0.6	0.6	1.000
Vomiting	0.3	0	1.000

Transfusions and supportive care

The overall rates of transfusions and growth factor use were low. The pattern of haematological supportive care administered in study JMEN is reflective of the difference between the study arms in the incidence of possibly study-related anaemia. Correspondingly,

significantly higher percentages of patients in the pemetrexed arm required transfusions (9.5% vs 5.9%, respectively, p=0.003) and erythropoiesis-stimulating agents (5.9% vs 1.8%, p=0.017); however, the use of colony-stimulating factors was minimal in both arms with no difference between arms (2.9% vs 3.6%, for pemetrexed and placebo respectively).

Hospitalisations

No statistically significant difference was observed between the study arms in the proportion of patient with at least 1 hospitalisation (17% of patient in the pemetrexed arm and 14.9% of patients in the placebo arm). The incidence of hospitalisations due to drug-related toxicity was higher in the pemetrexed arm compared to the placebo arm (5.2% vs 0%, p<0.001).

The proportion of patients discontinuing treatment due to adverse events was 4.8% in the pemetrexed arm compared to 1.4% in the placebo arm (p=0.027).

6.8 Non-RCT evidence

Non-RCT, both experimental and observational, evidence will be required, not just for those situations in which RCTs are unavailable, but also to supplement information from RCTs when they are available.

Inferences about relative treatment effects drawn from non-RCT evidence will necessarily be more circumspect than those from RCTs with properly controlled evidence. The bias that may be present in non-randomised data means the results should be interpreted cautiously. When possible, the use of more than one independent source of such evidence needs to be examined to gain some assurance of the validity of any conclusions drawn.

6.8.1 Details of how the relevant non-RCTs have been identified and selected

[Response]

6.8.2 Summary of methodology of relevant non-RCTs

[Response]

6.8.3 Critical appraisal of relevant non-RCTs

[Response]

6.8.4 Results of the relevant non- RCTs

[Response]

6.9 Interpretation of clinical evidence

6.9.1 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.

The treatment goals for maintenance therapy of NSCLC include maintaining the clinical benefit achieved after first-line chemotherapy, postponing disease progression and ultimately prolonging overall survival along with palliation of disease symptoms.

The evidence base for the submission, the JMEN trial, was a robust, well-designed, double-blind, phase III randomised, controlled trial comparing pemetrexed plus BSC to placebo plus BSC (i.e., "watch and wait" or no active treatment), the current standard of care in the NHS after first-line therapy with a platinum doublet. Patients were treated until disease progression. The primary end-point was PFS, with secondary endpoints of OS, response rate, disease control rate, safety and time to worsening of symptoms.

Patients in JMEN were randomised following first-line treatment with a platinum doublet (that did not include pemetrexed), and PFS was measured from the start of the maintenance treatment until the date of disease progression. The PFS results from JMEN are therefore, truly representative of the efficacy of pemetrexed during the *maintenance* phase (unlike some clinical trials where one of the first-line treatment agents itself is continued during the maintenance phase and the PFS or OS is measured from start of first-line treatment until disease progression or death). The JMEN trial and its results are therefore highly relevant to the decision problem.

In JMEN, the test for treatment-by-histology interaction was statistically significant for OS and PFS, which confirms that pemetrexed has better efficacy in patients with non-squamous histology. In the non-squamous population, pemetrexed treated patients reported a 1.9 months longer PFS and a survival benefit of 5.2 months compared to placebo plus BSC.

The objective (complete or partial) response rate in pemetrexed-treated patients was 7.4% vs 1.9% with placebo. The disease control rate was substantially higher at 57.7% in the pemetrexed arm and 32.7% in the placebo arm, reflecting the high proportion of patients with stable disease. Since these patients experienced complete / partial response or stable disease following first-line therapy, a high response rate in the maintenance setting would not be expected. This is consistent with the clinical goals of maintenance treatment where the focus is on maintaining the clinical benefit achieved from first-line chemotherapy.

In the JMEN trial, Health related quality of life was also assessed in the trial, with the help of the LCSS, which is a site-specific HRQoL questionnaire for individuals with lung cancer, widely used in oncology trials. The LCSS captures the impact of interventions on disease symptoms and patient HRQoL; it is not intended to directly capture the impact of toxicity related to treatment. Patients treated with pemetrexed reported a longer time to worsening of disease symptoms such as pain and haemoptysis. However, the rates of censoring/missing data were very high for these analyses, limiting the statistical power of the findings and the ability to interpret the results in terms of patient outcomes. Clinical investigators cited concern over patient welfare as a key reason for not asking the patient to complete the HRQoL questionnaires after disease progression.

6.9.2 Identify any factors that may influence the applicability of study results to patients in routine clinical practice; for example, how the technology was used in the trial, issues relating to the conduct of the trial compared with 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 Summary of Product Characteristics?

Population

There are differences in the JMEN trial population and the general NSCLC population in England and Wales (LUCADA 2007). The proportion of patients with adenocarcinoma was higher in the JMEN trial (49.5% of patients had adenocarcinoma histology in JMEN; in the general population, about 25% patients have adenocarcinoma).

In JMEN 67% of patients were below 65 years; most patients in general practice may be slightly older. However, since age is not reported to be a prognostic factor for survival in NSCLC (Weiss et al 2007) this is not likely affect the relevance of JMEN results to the UK NSCLC population.

Performance status is an important prognostic factor for survival in patients with NSCLC (Weiss et al 2007). The JMEN trial excluded patients with performance status >1. In LUCADA, the number of patients with PS > 1 was higher than JMEN since it included all lung cancer patients (as compared to the subset of patients given chemotherapy). In clinical practice, the proportion of patients with good performance status is likely to be higher than in LUCADA since only patients who are reasonably fit (i.e. of good performance status) are likely to get chemotherapy. LUCADA data does not present performance status by lines of treatment. Patients eligible to receive maintenance treatment with pemetrexed after having previously responded to first-line chemotherapy are likely to be fitter than patients receiving second-line NSCLC treatment.

JMEN trial design

Although none of the sites for the JMEN trial were located in the UK, the trial design ensures that the outcomes are very much relevant to the UK. Patients in the UK are routinely prescribed first-line treatment generally up to a maximum of four cycles. The induction regimens used in the trial were similar to what the average advanced NSCLC patient would receive in the UK, the most frequently prescribed regimen being gemcitabine/carboplatin and gemcitabine/cisplatin. The current standard of care in the NHS for patients who do not have disease progression post-induction treatment is 'watch and wait' – this is the comparator for pemetrexed in the JMEN trial.

Ongoing studies on pemetrexed in the UK will provide further useful data in the maintenance NSCLC setting.

Number of treatment cycles

In JMEN, patients were treated to disease progression. In routine clinical practice, this may not be feasible. According to UK clinical experts with experience of maintenance treatment, a majority of responding patients are likely to receive ten pemetrexed treatment cycles.

Choice of eligible patients: histological diagnosis

Since the licence for pemetrexed in the maintenance setting restricts the use of pemetrexed to patients with non-squamous NSCLC, this diagnosis would have to be available (if made before assigning induction chemotherapy) or performed before maintenance treatment with pemetrexed.

In order to identify appropriate patients, clinicians/pathologists will have to classify patients' histology. Identifying these patients should be possible using current best practice – which may have to become more widely disseminated. Our discussions with clinicians and

pathologists indicate there is variation between the cancer centres, partly due to the fact that, until now, it has not been necessary to sub-classify NSCLC from a therapeutic perspective as treatment outcomes did not vary with histological sub-types. The histologic typing of NSCLC is now gaining in significance and experts are confident that such sub-typing can become common practice. However, rates of accuracy in identification of adenocarcinoma, and particularly large cell carcinoma, will vary, and thus the level of tumours classified as 'NOS'. Therefore, in patients for whom it is not possible to make a confident diagnosis, maintenance treatment with pemetrexed would not be possible.

Post-discontinuation treatment
JMEN was a parallel-group study. However, patients who had disease progression were unblinded to study treatment and subsequent treatment was permitted at the discretion of the investigator, so some crossover did occur. Fewer patients in the pemetrexed arm received post-discontinuation therapy compared to placebo (53.2% vs 67.3%, p=0.004). The rate of crossover from placebo to pemetrexed was 18.5%. Survival results are not likely to have been influenced by post-study therapy given the higher rate of follow-up treatment on the placebo arm, low rate of crossover, and the balanced selection of therapies between arms.

Doses
The doses used within the study JMEN are as specified in the pemetrexed SPC.

7 Cost effectiveness

7.1 Published cost-effectiveness evaluations

7.1.1 Identification of studies

A systematic literature review was conducted using key databases in order to identify references on the cost-effectiveness of chemotherapy agents used in maintenance treatment for patients with Stage IIIB/IV NSCLC. Full details of the search are provided in Appendix 3. As some NSCLC first-line studies incorporate a maintenance component, a broad search was conducted to encompass all first-line and maintenance literature. The search was performed on the 10 November 2008. Inclusion and exclusion criteria were then applied in order to exclude studies not relevant to the decision problem. These criteria enabled articles to be retrieved that could inform the methodological approach for the economic evaluation. The inclusion/exclusion criteria are presented in full in Appendix 3.

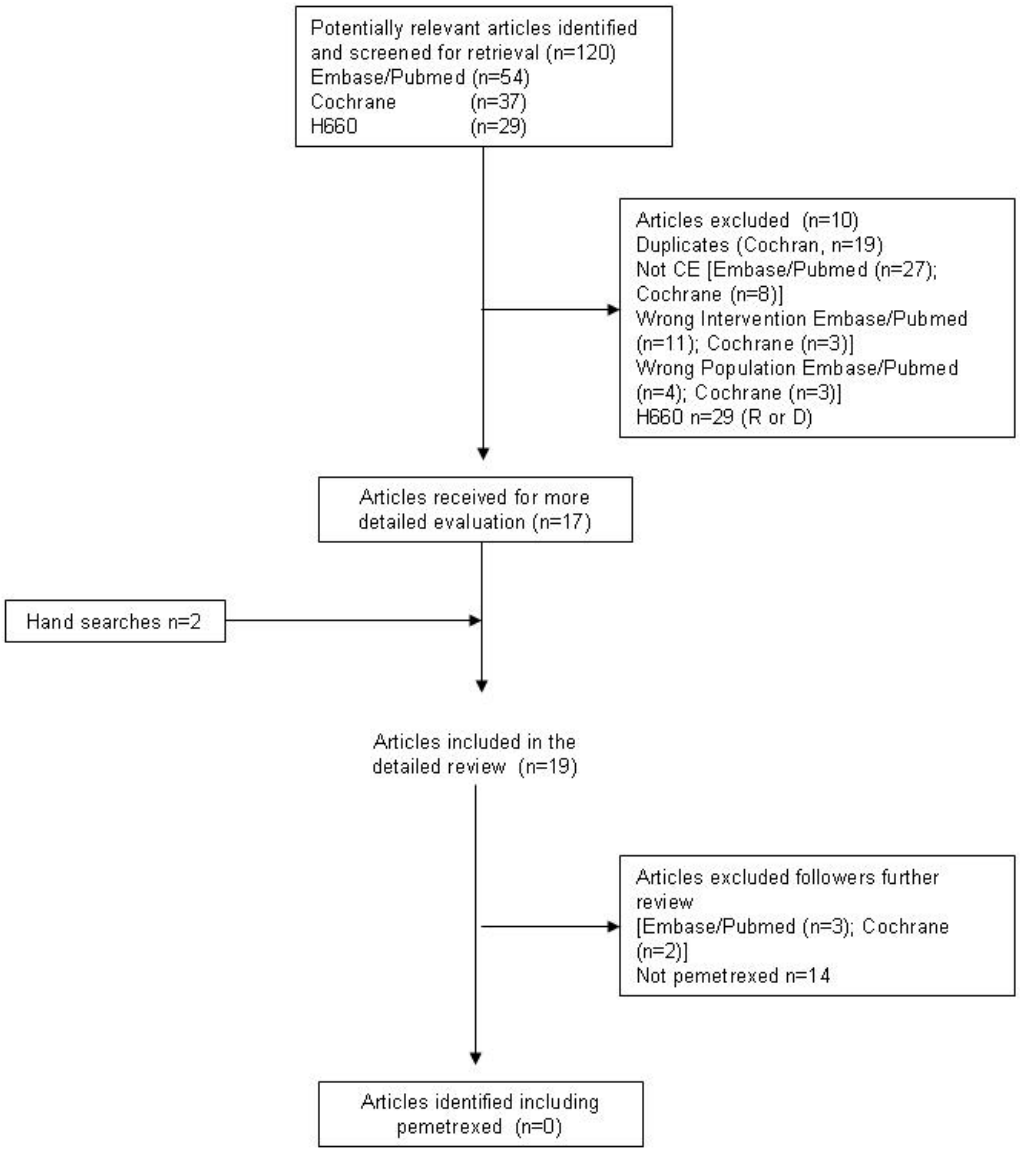
The databases searched were EMBASE, Medline, Cochrane and the Health Economics Evaluation Database (HEED), which resulted in the identification of 120 articles. One hundred and three were excluded as not meeting the inclusion/exclusion on the basis of title/abstract review. The remaining 17 abstracts were extracted for full text review. Of these five were excluded on the basis of the inclusion/exclusion criteria. In addition to the remaining 12 references, two further references were identified through hand-searching key journals.

None of the 14 papers identified were concerned with the assessment of the cost-effectiveness of pemetrexed or any other chemotherapy agent in the maintenance phase. Instead they were concerned with the assessment of the cost-effectiveness of first-line treatment of NSCLC. These references are briefly summarised in Appendix 3.

7.1.2 Description of identified studies

None of the articles identified by the literature review fitted the inclusion/exclusion criteria for maintenance therapy. Although 14 articles were identified that had some usefulness in informing the development of the economic model, as their focus was first-line chemotherapy treatment in NSCLC, rather than maintenance, they are not described here, instead they are briefly described in Appendix 3.

Figure 7: Literature review of relevant economic evaluations



7.2 De novo economic evaluation(s)

Element of health technology assessment	Reference case	Section in 'Guide to the methods of technology appraisal'
Defining the decision problem	The scope developed by the institute	5.2.5 & 5.2.6
Comparator(s)	Therapies routinely used in the NHS, including technologies regarded as current best practice	5.2.5 & 5.2.6
Perspective costs	NHS and Personal Social Services	5.2.7 to 5.2.10
Perspective benefits	All health effects on individuals	5.2.7 to 5.2.10
Type of economic evaluation	Cost-effectiveness analysis	5.2.11 to 5.2.12
Synthesis of evidence on outcomes	Bases in a systematic review	5.3
Measure of health effects	QALYs	5.4
Source of data for measurement of HRQL	Reported directly by patients and carers	5.4
Source of preference data for valuation of changes in HRQL	Representative sample of the public	5.4
Discount rate	An annual rate of 3.5% on both costs and health effects	5.6
Equity weighting	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	5.12

HRQL, health related quality of life; NHS, National Health Service; QALYs, quality-adjusted life years

7.2.1 Technology

7.2.2.1 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.

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

Pemetrexed (500mg/m^2) is administered on day one of a 21-day cycle. Treatment continues until the disease progresses (as measured by RECIST), see page 26 of clinical section for more information on RECIST.

Concomitant medications are required (SPC 2009; see Appendix 10.1):

- Folic acid – Daily oral folic acid or a multivitamin containing folic acid (350-1,000µg). At least five doses of folic acid must be taken in the seven days preceding the first dose of pemetrexed. Dosing must continue during the full course of therapy and for 21 days after the last dose of pemetrexed.
- Vitamin B_{12} – Intramuscular injection of vitamin B_{12} (1000µg) 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.
- Dexamethasone, 4mg, orally, twice daily on the day prior to, day of and day after pemetrexed administration.

7.2.2.2 Continuation rule

In the JMEN trial, patients on active treatment continued to receive chemotherapy until their disease progressed. This resulted in a mean number of cycles for the non-squamous population of 8.0 (SD 8.62; pemetrexed) and a median number of cycles of 6.0 (25^{th}-75^{th} percentile 2.5-10.0; pemetrexed). For the adenocarcinoma population the mean number of cycles was 8.6 (SD 9.30) and a median of 6.0 cycles (25^{th}-75^{th} percentile 3.0-10.0).

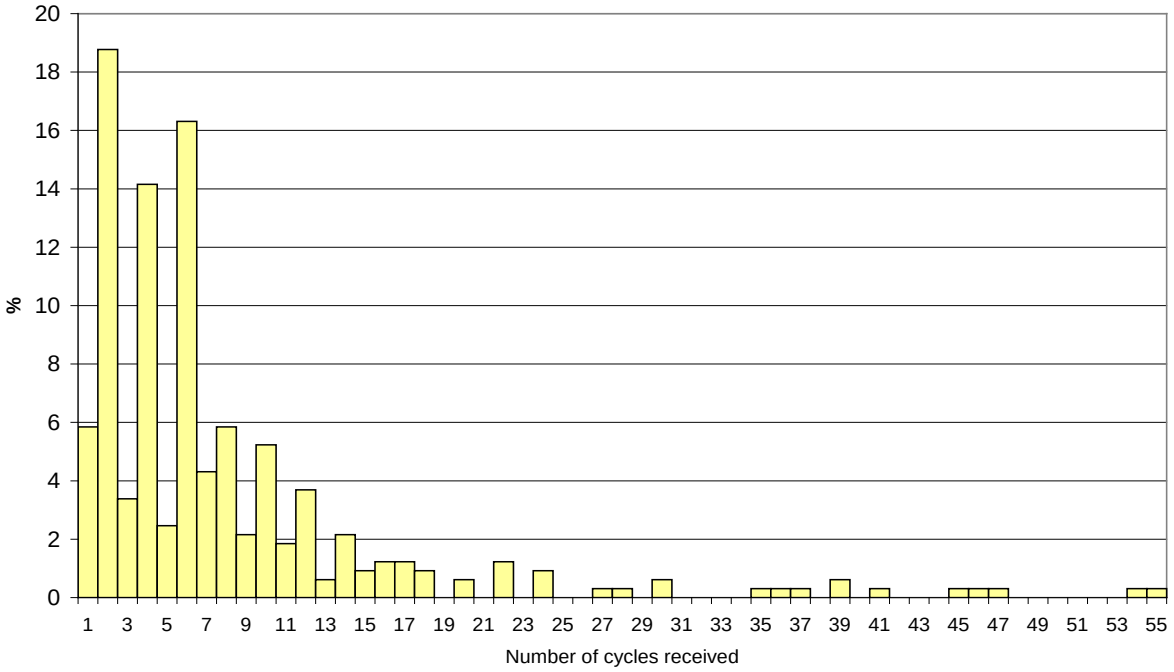
However, as can be seen in Figure 8, cycle administration in the JMEN clinical trial was highly right-skewed with a small number of extreme outliers receiving a large number of cycles while the majority of patients did not receive more than a maximum of 15-20 cycles (89%-93% patients in the trial). It is not anticipated that this pattern of highly skewed pemetrexed use would be seen in routine clinical practice in the UK. Instead, UK clinical experts consulted, have suggested that a maximum number of cycles will be adopted as experience with this therapy increases. In light of this, the economic evaluation incorporates a 'capping rule', rather than a continuation rule, to attempt to reflect likely UK practice. The capping rule sets a maximum number of cycles of pemetrexed maintenance therapy that can be administered. In the economic evaluation only costs are capped, no adjustment is made to overall survival data. No capping or continuation rule is specified in the SPC.

As pemetrexed in the maintenance phase represents a new treatment paradigm, it is difficult to estimate what a likely maximum number of cycles would be. Clinical experts have suggested a maximum of between eight and ten cycles. While this maximum number of cycles would represent approximately 75% of JMEN trial participants, those estimates result in mean values that are not reflective of the clinical trial. Therefore, a statistical approach was used and considered capping at a maximum of 1 standard deviation (SD) above the mean. This is equivalent to receiving a maximum of 17 cycles, rounded to the nearest whole cycle, and a new mean of 5.84 for the non-squamous population. The median is not affected. Using the same approach for the adenocarcinoma population, results in a maximum number of cycles of 18 and a mean of 6.16.

In the sensitivity analysis we test the effect of capping for three different scenarios: a) assuming no limit to the number of cycles provided, b) capping at two standard deviations (SD) above the mean, equivalent to 25 cycles for non-squamous patients and c) capping at 10 cycles, the 75% percentile, as per expert advice.

An alternative approach to addressing the highly skewed cycle distribution would be to use median values. In the JMEN trial the median number of cycles is six for both the non-squamous and adenocarcinoma populations. This was the approach used by Clegg et al (2001) in the HTA of chemotherapies for NSCLC. The use of medians rather than means to give an indication of central tendency, i.e. what number of cycles of chemotherapy an 'average' patient would actually receive, is useful when considering highly skewed clinical trial data. Median cycle data are also tested in the sensitivity analysis.

Figure 8: Distribution of maximum number of cycles received (data on file_JMEN_non-squamous, 2009)



7.2.2 Patients

7.2.2.1 Which patients are included in the economic evaluation?

The patient population assessed in this economic evaluation is based on JMEN trial data and consistent with the licensed population: 'patients with locally advanced or metastatic NSCLC other than predominantly squamous cell histology'. Non-squamous is used as short-hand to describe a population which includes patients with adenocarcinoma, large cell carcinoma and NSCLC not-otherwise specified (NOS). A NOS diagnosis is received if a patient is not 'predominantly' squamous but it is not possible to determine a more accurate alternative diagnosis. This may, for example, include patients with a heterogeneous tumour type.

The basecase for this submission considers the non-squamous population while the adenocarcinoma population is assessed in a sub-group analysis. Overall survival results are similar in both the non-squamous and adenocarcinoma population, see Table 14 below. Patient data from JMEN shows that adenocarcinoma accounts for the largest component of the non-squamous population (68%) in the trial, therefore differences in ICER estimates are likely to be small. For that reason, while the basecase population is non squamous NSCLC we don't anticipate a substantial difference between the non-squamous and adenocarcinoma populations.

It should be noted that because of the shape of the survival curves, adenocarcinoma has a higher median overall survival result but a lower mean overall survival result than non-squamous. In the adenocarcinoma population maximum separation of the curves is around the 50% point.

Table 14. Overall Survival by study arm for non-squamous and adenocarcinoma populations (Table JMEN4.5 CSR, addendum 2009)

	Median OS (months)	Incremental difference in OS (months)	Unadjusted HR (95%CI)	p-value
Non-squamous histology (N=481)				
Pemetrexed (n=325)	15.47	5.19	0.701 (0.56-0.88)	0.00196
Placebo (n=156)	10.28			
Adenocarcinoma (N=328)				
Pemetrexed (n=222)	16.82	5.29	0.732 (0.56-0.96)	0.02632
Placebo (n=106)	11.53			

As the data in this economic model are based on the results of the JMEN trial, it is assumed that the demographics of the patients in this economic evaluation are consistent with those of the JMEN participants. One of the most relevant criteria refers to patients' performance status. In JMEN patients were included if the had a performance status of 0/1 according to the Eastern Cooperative Oncology Group (ECOG). In line with UK NICE clinical guidelines (NICE 2005) performance status 0/1 refers to patients who are ambulatory, fitter and who are likely to derive more benefit from therapy. Patients included in the trial were those with NSCLC not amenable to surgical resection, i.e. stage IIIB/IV. Only patients who did not experience disease progression during induction (first-line) chemotherapy are eligible for pemetrexed in the maintenance phase i.e. they had to have either complete response or partial response or stable disease following four cycles of first-line/induction therapy. The baseline characteristics for the non-squamous and adenocarcinoma populations are presented on pages 33-35, clinical section.

The patient characteristics from the JMEN trial are difficult to compare with the patient characteristics from the LUCADA database (2007), the largest source of information on lung cancer patients in the UK. The LUCADA database includes 57% of all cases of lung cancer in England and Wales for 2006-07 but, of these, only 34% were recorded as being of good performance status, PS 0 or 1, the population eligible for maintenance therapy. The patients in the trial were younger with a median age of 60 years compared to a median age for LUCADA patients of 71 years. This would be expected in light of the performance status in the clinical trial being PS 0 or 1 so the clinical trial population is likely to be broadly similar to the population treated in clinical practice.

7.2.2.2 Patient subgroups

The subgroup of patients with adenocarcinoma NSCLC is explored in this submission: a subgroup identified by histological diagnosis.

Histology

Efficacy-by-histology interactions were investigated following results observed with pemetrexed in the second- and first-line treatment settings (Scagliotti 2008; Scagliotti 2009). These interactions were pre-specified as part of the JMEN trial statistical analysis plan. The histology groups in question: squamous, non-squamous, adenocarcinoma, large cell carcinoma and 'NOS' are biologically plausible sub-groups that can be identified using standard histology tests based on the World Health Organisation's Classification of lung cancer tumours (Travis 2004). They are identified by analysis of cell morphology (shape) from cytology and/or biopsy samples with immunohistochemistry (TTF1 testing) which is widely available already.

Histology practices are not standardised across the UK, meaning there is variation in practice and specificity routinely detected, however, diagnosing to this level is feasible according to clinical experts. The NICE appraisal committee in its assessment of the diagnostic specificity required for pemetrexed/cisplatin in the first-line setting concluded that such diagnosis is feasible (NICE, 2009). Efficacy-by-histology interactions and diagnostic practices are discussed in more detail in the Clinical Section.

Patients with different histotypes have a different prognosis/baseline risk, for example patients with large cell carcinoma have a poor prognosis (García-Yuste et al.2008; Moro-Sibilot 2008). It is not possible to comment on the baseline risk of those with a diagnosis of 'NOS' as, by its nature, this is a heterogeneous patient population. No baseline adjustment was made based on histology diagnosis.

Pre-specified tests for a treatment-by-histology effect were carried out using co-factor adjusted Cox models. Tests for interaction were stratified by induction therapy (gemcitabine versus paclitaxel/docetaxel) and included terms for treatment (pemetrexed versus placebo), squamous histology (no versus yes), treatment-by-squamous interaction (non-squamous pemetrexed versus all other patients), ECOG performances status (0 versus 1), induction response (CR/PR versus SD), East Asian ethnicity (yes versus no), smoking status (never versus ever), gender (female versus male), and age (< 65 versus ≥ 65). See Table 6 in the clinical section for treatment-by-histology interaction test results.

The results showed statistically significant interactions for PFS (interaction p = 0.036; HR = 0.65) and for OS (interaction p = 0.033; HR = 0.52). These tests confirmed the results seen in previous Phase III studies (Study JMEI and Study JMDB) and confirm that the treatment-by-histology interaction is not a statistical artefact (Scagliotti et al 2009).

Treatment-by histology interaction was explored for squamous versus non-squamous. Because adenocarcinoma is the largest proportion of this population it was felt not necessary to repeat the test for that population. Because "NOS" is not a group that can be pro-actively identified and is by its nature heterogeneous, it was felt inappropriate to explore NOS vs squamous. Similarly, because large cell group is so small (n=20) it was felt it wasn't appropriate to consider the interaction of large cell vs. squamous.

Other sub-groups
As well as histology based subgroups, PFS and OS were explored using a co-factor Cox model for sub-groups distinguished by: age, gender, origin, smoking status, ECOG performance status, induction platinum, and induction response. Histology was statistically different by gender for both PFS and OS. East Asian ethnicity was also statistically significant for OS. Based on these findings, no other potential sub-groups are explored in this submission.

7.2.2.3 Excluded subgroups

No key subgroups were excluded. In line with the licence, the appropriate population for this submission is non-squamous. Though JMEN collected data for squamous patients, this sub-group is off-licence and therefore has not been considered. Large cell carcinoma and 'NOS' subgroups are not considered for subgroup analysis. The large cell population in the JMEN trial is very small (n=20) and therefore it would be difficult to draw any meaningful conclusions from analysis of just 20 patients. However, the benefits of pemetrexed in this population have been shown in previous Phase III trials (e.g. JMDB, Scagliotti 2008). With regards to the 'NOS' group, it is not possible to 'proactively' identify NOS since the diagnosis is done by exclusion of other possible histotypes i.e. not a practical diagnosis in real-life. Therefore this group has also been excluded.

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

Patients enter the model at the start of maintenance therapy. Patients are only eligible for maintenance therapy if their disease has not progressed following induction/first-line treatment. Therefore, to enter the model they must have had a good response (stable disease, partial response or complete response) in the first-line setting with the aim of pemetrexed to 'maintain' this good response following completion of first-line therapy. UK clinical practice suggests patients receive a maximum of four cycles of induction therapy. Maintenance therapy is intended to start immediately after the end of first-line therapy with no delay between treatments, therefore pemetrexed monotherapy would be the fifth consecutive cycle of chemotherapy for a non-progressing patient.

Patients exit the model at death or 6 years, whichever occurs first. The choice of 6 years for the time horizon is based on modelling methodology, being the closest approximation to a life-time model possible with the patient cohort under consideration. By the 6th year more than 96% of pemetrexed patients and more than 99% of placebo patients have died. An artefact of the extrapolation function used in the model is that the number of patients alive gets infinitely smaller (ie, never actually reaches zero). In pragmatic terms however, this model is essentially a life-time model.

7.2.3 Comparator technology

The comparator in this economic evaluation is placebo. Currently, there are no other chemotherapies or biological agents licensed for the treatment of NSCLC in the maintenance phase.

Currently, after completion of four cycles of first-line treatment with a platinum doublet, patients typically undergo a chemotherapy-free observation period ("watch and wait") until disease progression occurred. During this watch and wait period patients receive appropriate best supportive care (BSC) however, no active anti-cancer therapy is given until disease progression. At disease progression, a proportion (58% in non-squamous population) receives second-line chemotherapy treatment while the remainder continue to receive BSC. After second-line treatment patients will receive appropriate BSC and terminal care.

The model starts at the time of the "watch and wait" period. Patients in both arms of the JMEN trial received best supportive care (BSC) as judged necessary by the treating physician. Therefore the comparator for the economic evaluation is placebo.

The model uses the concept of BSC from the NICE Palliative Care document. It is assumed that radiotherapy is excluded during any active chemotherapy phase consistent with the JMEN trial protocol. This is discussed in detail on page 99. The aims of BSC and active chemotherapy are quite different. According to Clegg et al (2001), BSC *'…does not attempt to prolong life or to remove (even if only temporarily) the cause of symptoms*.' In contrast pemetrexed was explicitly developed to improve quality and increase quantity of life.

At the time of this submission there are no alternative active treatments to pemetrexed indicated for the maintenance phase of patients with NSCLC. Placebo as comparator is consistent with the NICE scope.

7.2.4 Study perspective

The study perspective reflects NICE's reference case: the NHS and Personal Social Services (PSS). Direct costs associated with provision of treatment incurred by both agencies are reported. Palliative care for NSCLC patients is multi-agency, particularly as the disease progresses, including charitably funded hospices or nursing staff therefore, it is difficult to disaggregate costs to enable the exclusion of non-tax funded services. It is likely that the cost

estimates for BSC and terminal care include some element of non-tax-funded services. Indirect and intangible costs incurred by patients and their relatives are not included.

7.2.5 Time horizon

The time horizon for this analysis is six years. This takes the 29 month trial data and extrapolates it for a further 43 months, 72 months in total. This represents the year in which more than 96% of pemetrexed and more than 99% of placebo patients will have died, in both the non-squamous and adenocarcinoma populations. The method of extrapolation means patient numbers continue to get infinitely smaller however, in practical terms all patients will have died within this time frame so this is essentially a life-time model.

7.2.6 Framework

7.2.7 The purpose of this section is to provide details of the framework of the analysis. Section a) below relates to model-based evaluations, and section b) below relates to evaluations conducted alongside clinical trials. Please complete the section(s) relevant to the analysis.

a) Model-based evaluations

Questions 7.2.8.1 - 7.2.8.8 are answered in the section below. The model structure is described, including a schematic and how it represents treatment for NSCLC. Cycle length and inclusion of a half-cycle correction are described. The development of the model is described including the method of extrapolation.

All variables and assumptions used in the model are reported, as are the sources of information used to populate the model.

This economic evaluation is a single trial model. Empirical data were taken from the JMEN clinical trial and a parametric extrapolation was then applied. As such, it is not exclusively either a model-based evaluation or a non-model based evaluation but has elements of both. All relevant questions in both sections a) and b) have therefore been answered.

Model structure

The structure of the model supporting this economic evaluation is a single trial model (based on JMEN data). Empirical survival data were taken from the JMEN clinical trial and a parametric extrapolation was applied to the end of the trial data, to give a model with a six-year time horizon, of which 29 months were trial data and 43 months were extrapolated data. An extrapolation model (Drummond et al 3rd Edition 2005) was used to enable a cost-utility analysis (CUA) of pemetrexed compared to placebo in the maintenance setting to be undertaken. To maximise transparency and maintain simplicity, we also report the development of the model. Details of the selected survival distribution and the method of extrapolation are provided later in the *"Model Development"* section.

The aim of this economic evaluation was to replicate as closely as possible the overall survival outcomes from the JMEN clinical trial and to predict as accurately as possible the likely overall survival trajectory for both arms of the trial over a six-year time horizon. For this reason an extrapolation model structure was chosen. Extrapolation enables accounting of censored data. In JMEN censoring rates were 31.0% for the non-squamous population and 32.3% for the adenocarcinoma population, which are not unusual in an oncology trial but do make it difficult to extract accurate mean values from the trial results. Table 15 presents censoring rates for the non-squamous and adenocarcinoma populations. Extrapolation also

allows the modelling of what would happen were it possible to follow an entire patient cohort from initiation of maintenance treatment until death. The six-year time horizon means that over 96% of pemetrexed patients and 99% of placebo patients will have died by the sixth year making this essentially a life-time CUA.

Table 15. Censoring rates for overall survival analysis, non-squamous and adenocarcinoma patients (Table JMEN 4.5 CSR Addendum, 2009)

	N	Number of censored patients	% of censored patients
Non-squamous histology	**481**	**149**	**31.0**
Pemetrexed	325	112	34.5
Placebo	156	37	23.7
Adenocarcinoma	**328**	**106**	**32.3**
Pemetrexed	222	79	35.6
Placebo	106	27	25.5

Model development

The model was developed in five stages. These stages are described in detail below:

1 – Overall survival trial data were plotted over the duration of trial (29 months) to produce Kaplan-Meier survival curves.

2 – Parameterised curves (exponential, Weibull, log-normal) were plotted alongside to the trial data for the duration of the trial (29 months).

3 – The parameterised curves (exponential, Weibull) were extended to demonstrate parameterised survival over a six-year time horizon (72 months).

4 – Empirical data were used for the trial duration (29 months) with parameterised curves (exponential, Weibull) added to the end of the trial data to extrapolate out to a six year time horizon (an additional 43 months).

5 – Empirical data were used for the duration of the trial (29 months) with parameterised hazard function curves (exponential hazard and Weibull hazard) added to the end of the trial data to extrapolate out to a six year time horizon (an additional 43 months).

Parameterising curves

A parametric regression procedure (PROC LIFEREG in SAS) was used to estimate parameters for exponential and Weibull distributions based on individual patient level data (IPD) from the JMEN trial. The purpose of the model was to describe the underlying distribution of the 'failure time' [time to death] variable and assess the dependence of this failure time variable on the independent variable, in this case treatment with pemetrexed or placebo.

The LIFEREG procedure fits parametric models to failure time data that are right-, left- or interval-censored. JMEN OS data is predominantly right-censored data i.e., a proportion of patients were still alive at the time of datalock. The models for the response variable consist of a linear effect composed of the covariates and a random disturbance term. The distribution of the random disturbance can be taken from a class of distributions that includes both the exponential and Weibull distributions.

The model assumed for the response **y** is

$$\mathbf{y} = \mathbf{X}\beta + \sigma\epsilon$$

where **y** is a vector of response values, often the log of the failure times, **X** is a matrix of covariates or independent variables (usually including an intercept term), β is a vector of unknown regression parameters, σ is an unknown scale parameter, and ϵ is a vector of errors assumed to come from a known distribution.

The results of the parameterising of the empirical data are presented in Table 16.

Table 16. Exponential and Weibull parameters for the extrapolated curves (Data on file_JMEN_parameters_exp_nonsquam, 2009; Data on file_JMEN_parameters_exp_adeno, 2009)

	Pemetrexed		Placebo	
	Non-squamous	**Adenocarcinoma**	**Non-squamous**	**Adenocarcinoma**
Exponential (rho)	0.044623	0.0413	0.06199	0.0548
Weibull (gamma)	1.34264	1.4006	1.22926	1.31839
Weibull (exp (-z)	0.01628	0.012471615	0.03905	0.021855558

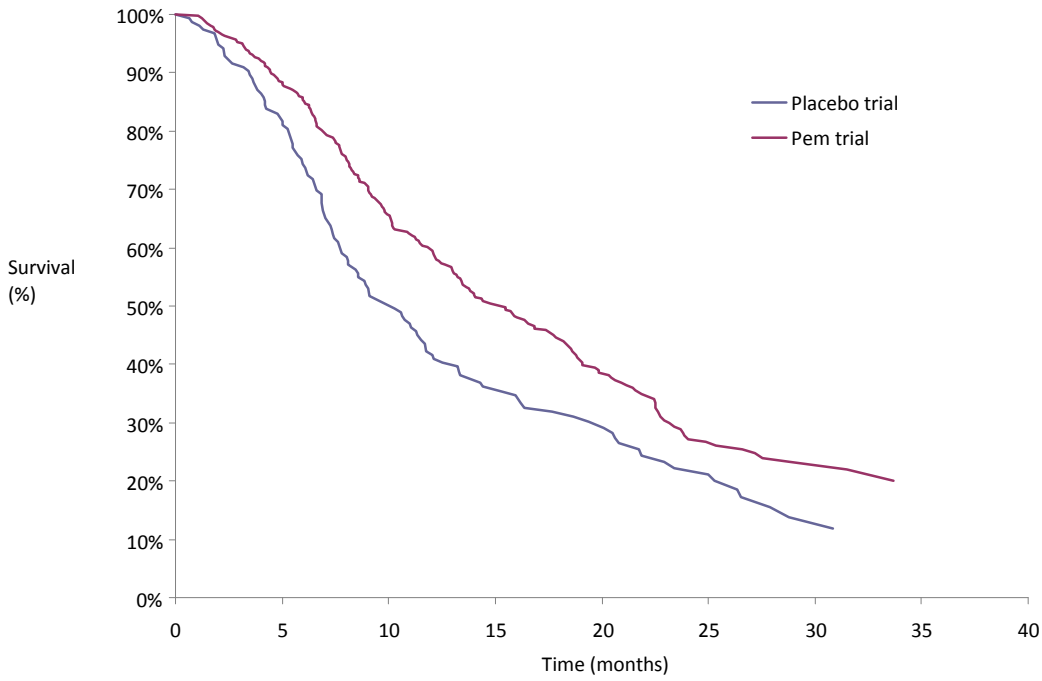
Using these outputs, exponential, Weibull and log-normal curves were compared with the trial data, see Figures 9 to 14 (log-normal not shown). Black and white curves are available in Appendix 7 for ease of reading if printing the submission in black and white.

Curve fitting

Step 1 –Trial data were plotted to produce a Kaplan-Meier survival curve

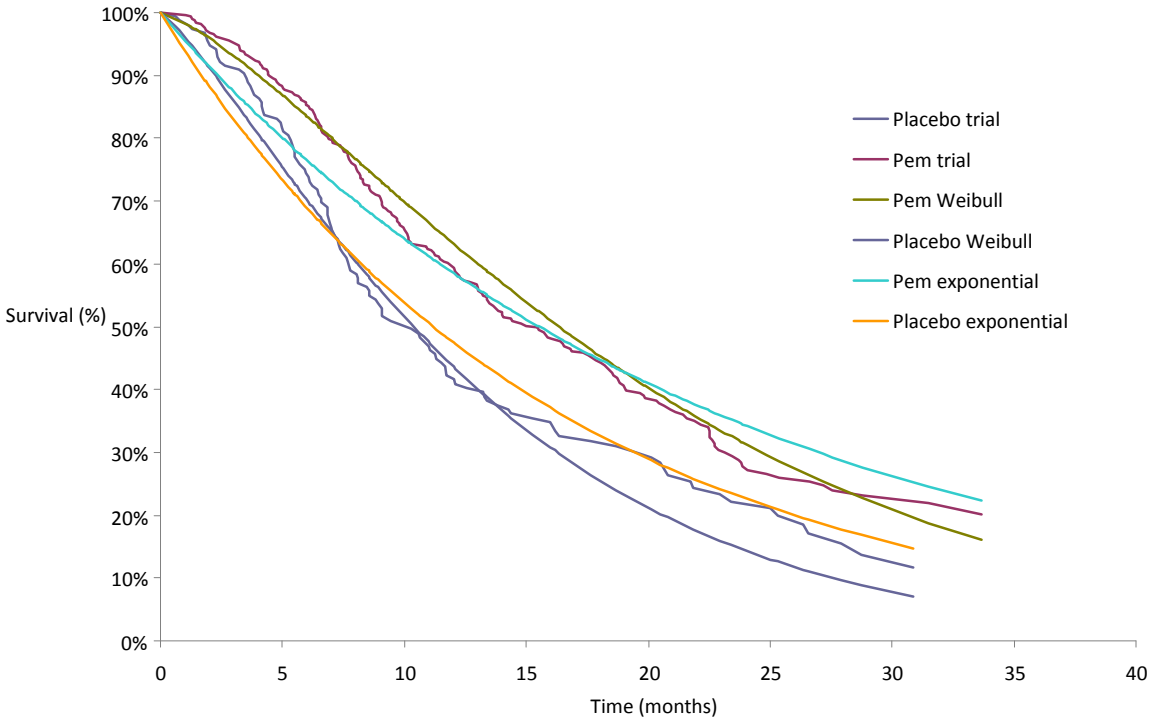
The trial data are plotted from the LIFETEST output from SAS based on JMEN IPD data, ie, the raw overall survival data from JMEN with each event (death) plotted against a time point. The time increments for these empirical data are variable depending on when the event occurred.

Figure 9: Kaplan-Meier curve for final overall survival (trial data) – non-squamous population



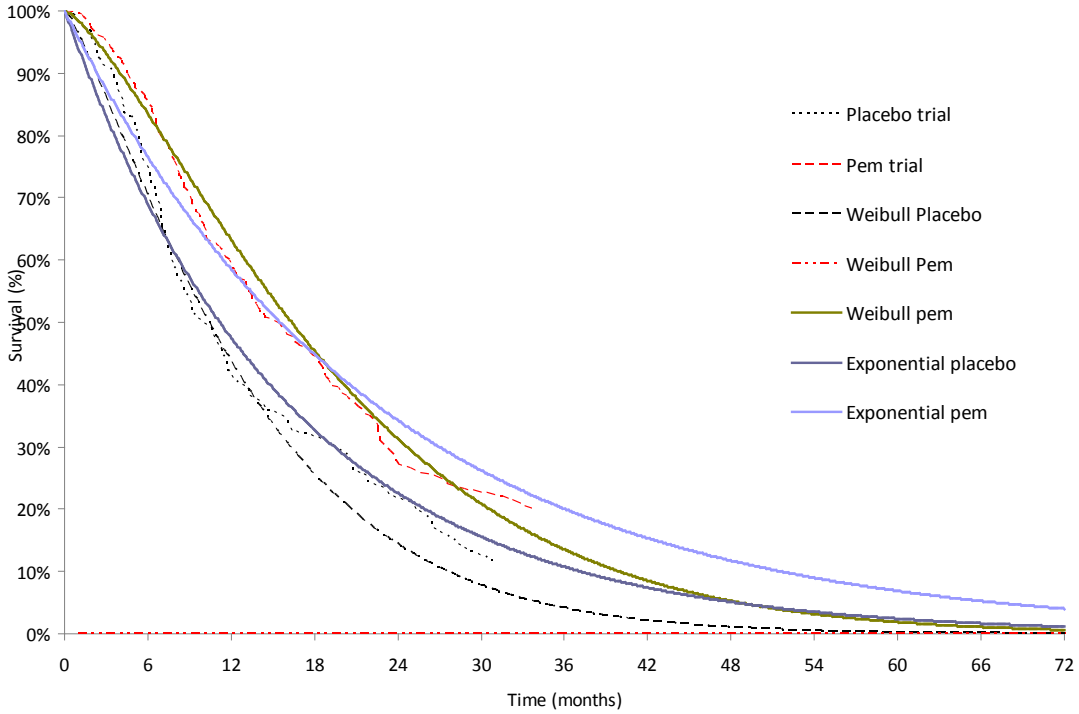
Step 2 – Exponential and Weibull distributions were compared with the trial data over the 29 month trial duration.

Figure 10: Weibull distributions and exponential distributions superimposed on trial data for the duration of the trial – non-squamous population



Step 3 – Exponential and Weibull distributions over 72 months were compared with the trial data over 29 months. However, in both steps 2 and 3, neither distribution's fit was ideal across all time points. Therefore step 4 was carried out.

Figure 11: Weibull distributions and exponential distributions for trial data extrapolated to a six year time horizon – non-squamous population

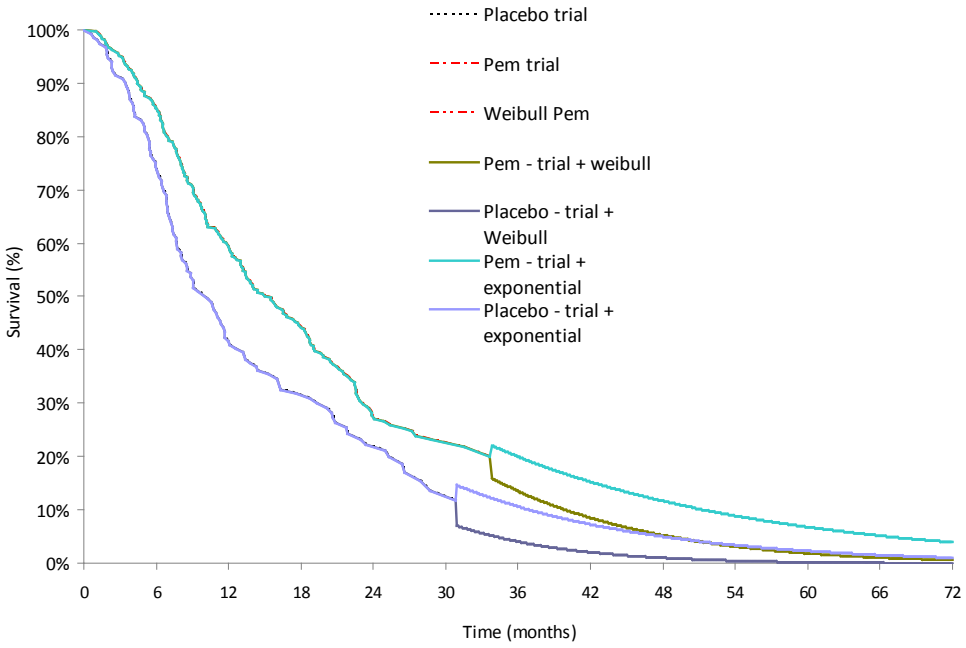


Step 4 – Empirical data were used for the 29 month duration of the trial with the exponential and Weibull parameterised curves used to extrapolate from the end of the observed data for a further 43 months. Essentially the observed trial data were used where available with the parameterised curves attached at the end to allow long-term overall survival to be projected. This is also the approach adopted by NICE's ERG in the assessment of pemetrexed in the first-line setting (NICE 2nd Appraisal Committee Meeting for Pemetrexed in the First-line setting, 24 June 2009).

In step 4 the time increments for the empirical data are as in step 1, ie, the time intervals are variable depending on when the event occurred. The parameterised data used to extrapolate beyond the end of the trial data use a constant time interval of 0.1 months. At the point where the observed data ended, the next nearest estimate of survival from the parameterised curves (which corresponded as closely as possible to the final observed time point + 0.1 months) was used to continue the survival curve. From this point on, the survival estimates from the parameterised curves were used in the subsequent 0.1 month increments.

Both the exponential and the Weibull distributions were fitted to the end of the observed trial data. However, neither produced a smooth curve (see figure12). Instead there was a 'step-up' with exponential and a 'step-down' with the Weibull curve.

Figure 12: Weibull distributions and exponential distributions for trial data extrapolated to a six year time horizon – non-squamous population



Step 5 – To address the 'step' in the curves described in the step 4, hazard functions for the exponential and the Weibull distributions were applied to the end of the empirical data. Survival data were extrapolated beyond the observed period using the specific exponential or Weibull hazard for each subsequent 0.1 month time interval. The specific hazards for each 0.1 month time interval were calculated for each of the parameterised Weibull and exponential curves using the same parameterisation as described above. As in step 4, the observed trial survival data were used until the last observed death. At the point where the observed data ended, the next nearest estimate of interval specific hazard was obtained from the parameterised curve (to best approximate the final survival time + 0.1 months). The next estimate of survival was then calculated by multiplying the probability of survival to the end of the observed study period by the probability of survival through the next 0.1 month time interval. From this point onwards, the survival estimates for each subsequent 0.1 month interval was calculated by multiplying the probability of survival to the start of the interval and the probability of surviving through the next interval.

The difference between step 4 and step 5 is the use of the parameterised survival curves. In step 4, the actual survival estimates are used beyond the end of the observed study period whereas in step 5, only the interval specific hazard is used. In step 5, the extrapolation is therefore more closely linked to the final observed survival value which is used as a basis of the future calculations (whereas in step 4 this value is not used). The difference in the approaches can be clearly seen in the curves where step 5 has a smoother tail beyond the end of the observed period whereas in step 4 there is a clear "step" between the observed and estimated survival curves.

The difference between the survival functions and the hazard function being that the exponential and Weibull functions estimate the probability that time to death is later than at some specified time (on the x-axis). Whereas, the related exponential hazard and Weibull hazard functions estimate the rate of death at a particular time point conditional on the survival until that time point or later.

Consideration was given to the most appropriate point from which to apply the modelled survival data. Based on the ERG's critique of the first-line model, Lilly explored fitting the hazard-based exponential extrapolations to the trial data once a constant linear hazard function was observed. It should be said that the exponential hazard function for the pemetrexed arm of the maintenance OS data never became constantly linear and therefore, rather than choosing an arbitrary time-point, both the Weibull and the exponential extrapolations were estimated from the end of the observed trial follow-up period using the estimated (constant) interval-specific hazard.

Figure 13: *Weibull hazard function* fitted to the end of the observed trial data for each arm – non-squamous population

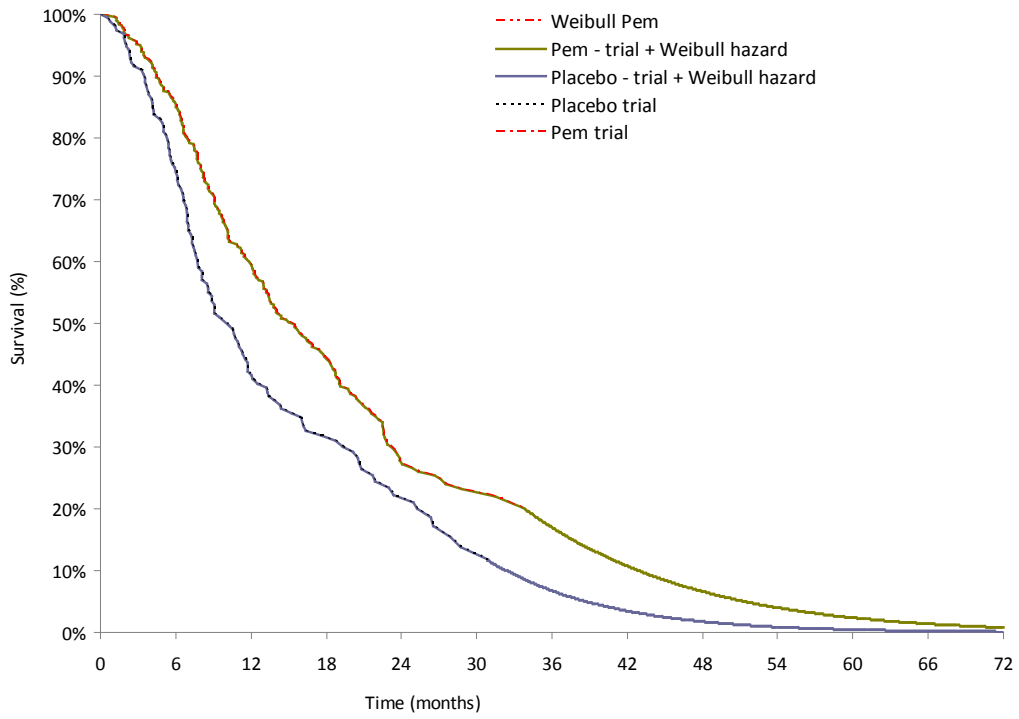
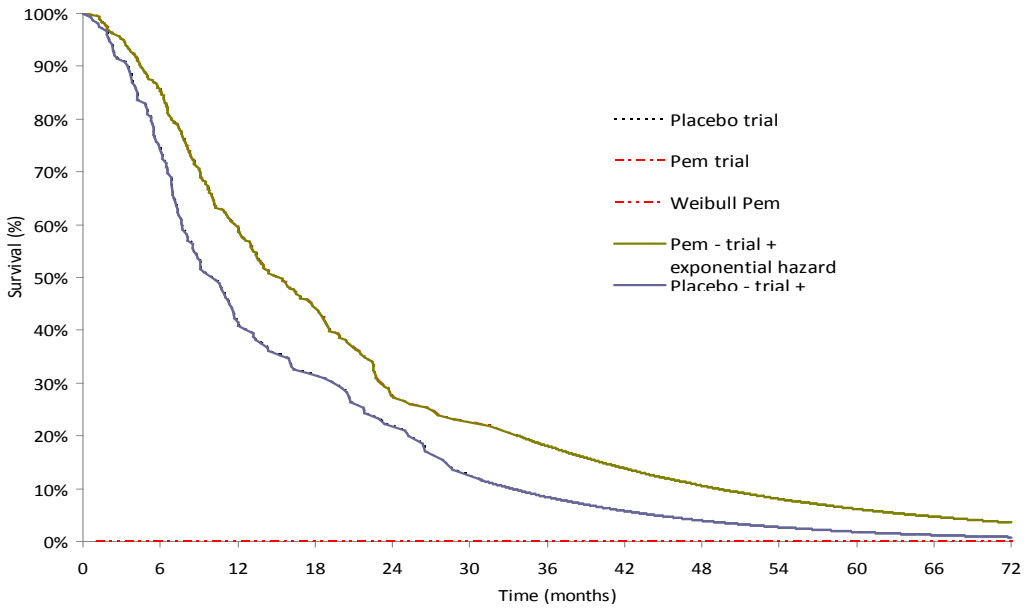


Figure 14: *Exponential hazard function* fitted to the end of the observed trial data for each arm – non-squamous population



Based on the apparent 'best-fit' for the trial and parameterised curves and the method for long-term projection used by the ERG in their consideration of pemetrexed in the first-line setting, the exponential hazard function was chosen as the basecase for the economic evaluation. Results based on the Weibull hazard extrapolation are presented in the sensitivity analysis.

Model diagram

Figure 15 is a schematic of the model. The model starts at the point patients in the JMEN trial received the first cycles of pemetrexed or placebo for the maintenance phase. While the primary endpoint of the JMEN trial was changed to be PFS, the initial powering of the trial to detect statistical significance in overall survival was maintained after the protocol was changed, through a subsequent data lock, allowing OS to be used as the primary outcome in the economic model. The model captures the key drivers of cost-effectiveness: OS, chemotherapy acquisition and administration costs, AE costs, BSC costs and utility.

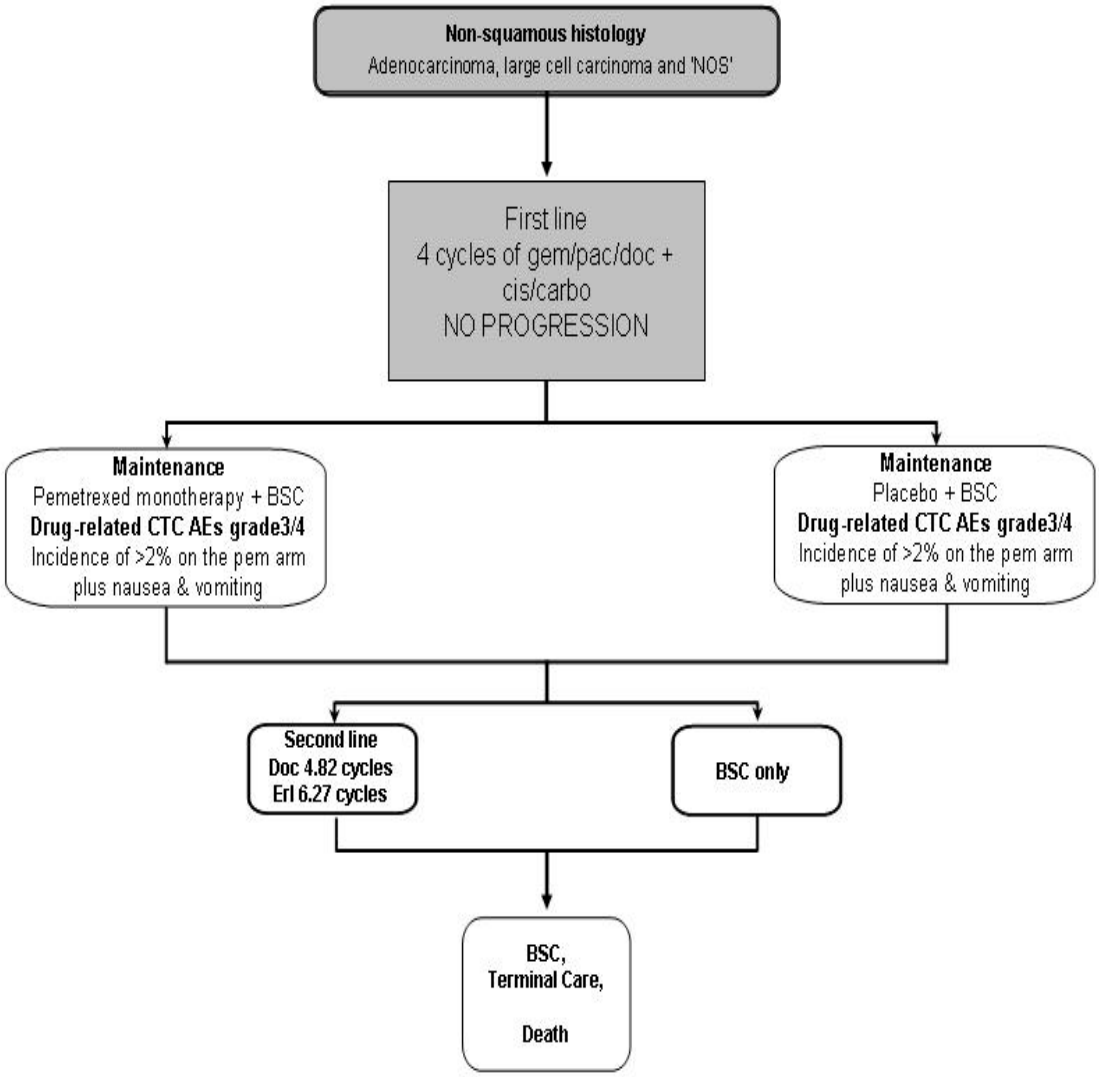
Transition through the model occurs by matching the probability/hazard of surviving from one time point to the next. As described in the *"Model Development"* section, the time point and survival data are taken directly from the trial for the first 54 cycles, the probability of survival across the remaining cycles is based on the exponential hazard function. Mean overall survival was estimated by calculating the area under the curve (AUC) of the survival functions.

The cycle length in the trial is 21 days, which corresponds to a pemetrexed chemotherapy cycle length. This extrapolation model does not model the OS data in cycles, but on the smallest time point available. However, to enable calculation of ICERs all inputs are reported in both cycle lengths and months.

A half cycle correction is used in the survival outcomes in the model. The correction is applied to the first time-point at the start of the survival curve as a result the curve is shifted by a half-cycle. No half-cycle correction is applied to the costs because a) the majority of costs are incurred at the beginning of the three week cycle b) it would have minimal effect as cycle duration is so short.

Figure 15: Treatment pathway and structure of the economic model.

The schematic below represents the treatment pathway that patients with NCSLC would go through from diagnosis to death. Patients enter the economic model in this submission at the maintenance phase (i.e. after first line treatment has been completed). This is represented in the figure below by the white boxes. Events that occur before data collection for the trial/model commences are in the grey boxes.



Treatment pathway

First-line treatment

Only patients who did not progress following four cycles of platinum-doublet chemotherapy induction (first-line) treatment were eligible for maintenance treatment. The first-line treatments received were well balanced for each arm (see Tables 2 and 3) suggesting that any difference in OS is the result of therapy received post-induction: maintenance or second-line therapy. Also, randomisation occurred after first-line therapy therefore differences between groups are controlled in that way. Therefore, first-line treatment is not included in the economic evaluation which starts, as data collection for JMEN did, at initiation of maintenance therapy. Measurement of OS commenced at the point of initiation of maintenance treatment. Final OS estimates do not include the four cycles of first-line therapy received in order to be eligible for maintenance therapy.

Maintenance treatment

Patients with stable disease, partial response or complete response after induction therapy were randomised to receive either pemetrexed monotherapy (500mg/m^2) or placebo, with BSC given as and when required on both arms. Treatment in the trial continued until disease progression, unacceptable toxicity or patient/physician choice.

A number of patients discontinued before their disease progressed. Reasons for discontinuation in the non-squamous population included subject decision (11%), adverse events (9%) and physician decision (5%). In the model these patients are captured in the OS and cycle data.

Second-line treatment

Following disease progression patients were either assigned to second-line chemotherapy or BSC. There was a statistically significant difference in the proportion of patients receiving second-line therapy by arm, 67.3% of placebo patients and 53.2% of pemetrexed patients (p=0.004) in the non-squamous population, these data were not available for the adenocarcinoma population. While some of the second-line therapies used in the trial are not available or recommended for use in second-line treatment in the UK (i.e. they do not represent usual UK practice), the type and distribution of drugs across both arms is generally well-balanced. The only exception to this is pemetrexed monotherapy as a second line therapy in the placebo arm where 18.5% of placebo patients received pemetrexed versus 0.9% in the pemetrexed arm. This bias would be expected to favour the placebo arm.

We have assumed that second-line therapies on both arms have equivalent efficacy and utility, as it is not possible to disaggregate the effect on OS of second-line treatment from maintenance treatment. In the model second-line therapy appears only as a cost. In order to adjust second-line therapies to be more consistent with UK practice we included docetaxel and erlotinib, the only therapies with market share greater than 5% and applied them in their relative proportions as reported in the most recent market share data (Data on file 2nd line market shares, 2009). This corresponds to docetaxel share of 73% and erlotinib share of 23%. It is assumed that docetaxel is provided for 4.8 cycles and erlotinib for 6.3 cycles in line with data from the ERG report and *Proposal for Provision of Erlotinib to the NHS* accompanying the erlotinib submission to NICE (NICE 2008a; NICE 2008b).

Data Inputs

The primary comparison in the economic evaluation is pemetrexed versus placebo based on data from the JMEN randomised controlled trial comparing outcomes in the maintenance setting. As a head-to-head RCT of the technology under consideration and an appropriate comparator we have addressed the preference stated in the NICE Methodology Guide for head-to-head RCT data.

The methodology guide also states the RCT should be carried out in the appropriate patient population, which the JMEN does as closely as is possible while meeting the requirements of a clinical trial to test the hypothesis under investigation without confounding variables. For that reason the patient population is slightly younger than would be expected in clinical practice, as is usual in transferring clinical trial data to the real world, but of similar performance status to the chemotherapy treated patients (PS 0/1), performance status being a key prognostic factor for survival outcomes.

The validity of the economic model was tested by comparing median OS results from the trial with median OS results from the modelled survival curves with trial survival curves; these are shown in the results sections 7.3.1 and 7.3.2.

Efficacy inputs

Overall survival (OS)

As this evaluation is concerned with assessing the cost-effectiveness of pemetrexed the appropriate primary outcome for the economic model is overall survival. Overall survival (life years gained), as indicated by being one of NICE's recommended endpoints, is a key measure of effectiveness. While progression free survival (PFS) is the primary endpoint of the trial and provides important information regarding a molecule's efficacy to the regulators, OS provides the better assessment of clinical effectiveness. Furthermore, as there is uncertainty regarding where pemetrexed has the greater survival advantage – before progression, after progression or both – it is appropriate to use an outcome that is able to capture both possibilities.

Table 17 presents median OS data. The economic model in fact uses the available observed survival data, which are provided in full in the raw data sheet in the model. However the primary end point from the trial is given here for illustrative purposes.

Table 17. Overall Survival by study arm for non-squamous and adenocarcinoma populations (Table JMEN4.5 CSR, addendum 2009)

	Median OS (mo)	Incremental difference in OS (mo)	Unadjusted HR (95%CI)	p-value
Non-squamous histology (N=481)				
Pemetrexed (n=325)	15.47	5.19	0.701 (0.56-0.88)	0.00196
Placebo (n=156)	10.28			
Adenocarcinoma (N=328)				
Pemetrexed (n=222)	16.82	5.29	0.732 (0.56-0.96)	0.02632
Placebo (n=106)	11.53			

There is a statistically significant difference in the proportion of patients receiving any second-line treatment by arm in the non-squamous population: pemetrexed = 53.2% and placebo = 67.3% (p=0.004). While the distribution of second-line therapies reported in the JMEN trial is not representative of usual UK clinical practice – for example, gefitinib is not used in the second-line setting in the UK, although in the JMEN trial it accounted for at least 10% of second-line therapy (both arms) for non-squamous and adenocarcinoma populations – therapies were well-balanced across arms. Therefore, the OS may be assumed to be applicable to UK clinical practice. There was a higher percentage of patients in the placebo arm who received pemetrexed in the second-line setting as patients would not be rechallenged with pemetrexed in the second line setting following maintenance therapy but it is one of the preferred treatment options in second-line NSCLC worldwide. Any bias of this imbalance, which is relatively small, would favour the placebo arm. Patient numbers are too small to investigate the impact of this difference in use by arm. All other second-line chemotherapies are well balanced.

Progression Free Survival (PFS)

While PFS is a clinically relevant outcome it is not explicitly modelled in this submission, instead OS is the primary economic outcome. However, as the clinical trial protocol for maintenance treatment on both arms was to treat until progression, it is assumed that PFS is essentially equivalent to the number of treatment cycles received, therefore PFS is indirectly captured in the evaluation through cycle data.

Table 18 reports median cycle duration (in cycles and converted into months) and median PFS data for comparison. Mean data are not as reliable for PFS due to censoring. Any

discrepancy between cycle data (in months) and PFS (in months) is likely to be due to patients discontinuing treatment before progression, cycle delays or timing of treatment and assessment of progression not being concurrent.

Table 18. Comparison of median cycle data with median PFS data for non-squamous population (Data on file_JMEN_nonsquam_cycles, 2009; JMEN CSR Table JMEN 11.20, 2009)

	Non-squamous population	
	Pemetrexed N=325	**Placebo N=156**
median # cycles	6.0	3.0
median cycles converted to months	4.2 months	2.1 months
Median PFS (in months)	4.5 months	2.6 months

Response rates

Response rates are less important in the maintenance setting. Patients eligible for maintenance therapy have to have already demonstrated stable disease, partial response or complete response to chemotherapy in the first-line setting. The idea of maintenance therapy is to maintain or prolong this positive response. Therefore, if these patients have already 'responded' (CR, PR, SD) in the first-line setting, it is not surprising that only 7.4% of pemetrexed and 1.9% of placebo non-squamous patients report a subsequent response in the maintenance phase. For this reason response rates have not been included in the economic model.

Adverse event data

Although resource use associated with dealing with adverse events (AEs) was collected in this international trial, it is not likely to represent UK practice: therefore AE resource use and unit costs come from the literature. The adverse event rates reported in the trial are used in the economic model to calculate a weighted average for the cost associated with drug-related adverse events applied to each arm.

Drug-related CTCAE Grade 3/4 adverse events (AEs) were included in the model if they had greater than 2% incidence rate in the JMEN trial. Nausea and vomiting is an exception which occurred with incidence rates of 0.6% (nausea) and 0.3% (vomiting) but were included as previous monotherapy studies have reported incidence rates >2% (Hanna et al. 1589-97). For simplicity these two adverse events were combined.

- Neutropenia
- Nausea and vomiting
- Fatigue
- Anaemia

Adverse event rate data from the JMEN trial are reported in Table 19 below. Data are reported separately for the intent-to-treat, non-squamous and adenocarcinoma populations although, as with pemetrexed plus cisplatin in the first-line setting there does not appear to be any difference in toxicity by histology, i.e. very similar AEs rates are reported for the three populations. While an active chemotherapy obviously has more toxicity issues than a saline placebo, the adverse event rates associated with pemetrexed are low for an active chemotherapy.

Table 19. Adverse event rate data by therapy for Grade 3/4 CTCAE drug-related toxicities for the non-squamous and adenocarcinoma population

	ITT population (n=663)		Non-squamous (n=481)		Adenocarcinoma (n=328)	
	Pemetrexed (n=441)	Placebo (n=222)	Pemetrexed (n=325)	Placebo (n=156)	Pemetrexed (n=222)	Placebo (n=106)
Neutropenia	13 (2.95%)	0 (0%)	9 (2.77%)	0 (0%)	5 (2.25%)	0 (0%)
Nausea/ Vomiting	5 (1.13%)	1 (0.45%)	3 (0.92%)	1 (0.64%)	0 (0%)	0 (0%)
Fatigue	22 (4.99%)	1 (0.45%)	12 (3.69%)	1 (0.64%)	8 (3.60%)	1 (0.94%)
Anaemia	12 (2.72%)	1 (0.45%)	8 (2.46%)	0 (0%)	4 (1.80%)	0 (0%)

Utilities

Patient reported symptoms were collected using the Lung Cancer Symptom Scale (LCSS), but no utility data were systematically collected. Therefore the utilities included in this economic model are based on the results of a literature review. A weighted mean utility is calculated, as described in detail below, and applied to each arm of the trial. Utility is tested in the one-way sensitivity analysis.

Resource use

The JMEN trial collected and reported dose data. Only minimal resource use data were collected for other aspects of the trial, for example adverse events (as mentioned above), BSC or terminal care. Resource utilisation associated with the treatment of AEs, BSC or terminal care is unlikely to be consistent across countries due to variation in health care systems. Therefore, UK focused sources for resource use and unit cost data were used to population these inputs for both arms of the model.

Unit costs

Costs relating to chemotherapy dose ((maintenance and second-line), chemotherapy administration and monitoring (maintenance and second-line), AEs, chemotherapy, BSC and terminal care were applied to give a mean cost for each arm.

Assumptions incorporated into the economic model

We have attempted to capture all assumptions incorporated into the economic model in the table below; along with a description of the assumption and its justification these are tested in the sensitivity analysis.

Table 20. Methodological/Structural Assumptions

Assumptions	Assumption Description	Justification
Structural assumptions		
Patient population	The JMEN patient population is equivalent to the eligible UK NSCLC patient population and any differences are assumed to have no impact on the outcome associated with pemetrexed or BSC treatment.	The patients in JMEN are slightly younger than those seen in clinical practice. However, based on expert clinical opinion, and use of pemetrexed of patients in similar performance status, i.e., 0/1, it is considered reasonable to accept that patients in JMEN are generally reflective of patients that would be eligible for maintenance therapy.
PFS	PFS is not modelled in this analysis. However it is assumed that PFS corresponds to the number of treatment cycles in both pemetrexed and placebo arms.	The protocol of JMEN specifies patients on both arms were treated until progression, therefore PFS is essentially equivalent to number of treatment cycles. As a result PFS is indirectly captured through cycle data. This is supported by the median cycle data with the median PFS data for non-squamous population (see Table 18)
Half-cycle correction	The correction is applied to the first time-point at the start of the survival curve.	The impact of removing the half-cycle correction is tested in the sensitivity analysis. A half-cycle correction is not applied to costs on the basis of costs being incurred at the beginning of a very short cycle
Capping rule – maximum of 17 cycles of treatment	The clinical trial cycle data are highly right-skewed with only 7-11% of patients receiving more than 20 cycles, and some extreme outliers, such as one patient who received 55 cycles. For the non-squamous population a maximum of 17 cycles is equivalent to a mean of 5.84 cycles For the adenocarcinoma population this is equivalent to a maximum of 18 cycles and a mean of 6.16	The maximum number of cycles was determined using a statistical approach. One standard deviation (SD) from the mean was assumed to be an appropriate statistical approach for which to determining the maximum number of cycles to cap. In the sensitivity analysis the effect of capping at different cycles is explored.
Capping rule	Removing the highly skewed cycle data from the model will have no effect on OS results.	Given the relatively small proportion of patients who receive >20 cycles, it is anticipated that removal of these patients from the analysis of overall survival will have minimal impact. However this is tested in the sensitivity analysis

Outcomes and adverse events		
Adverse events rates	It is assumed that only grade 3/4 CTC drug-related toxicities occurring at an incidence of >2% have significant impact upon the HRQoL of patients included in the economic model. Nausea and vomiting occurred at a lower rate than this but were included as a side-effect associated with pemetrexed in previous clinical trials.	In the assessment of an incremental cost-effectiveness it was appropriate to identify only those adverse events related to the study drug that had a measurable effect on quality of life or a high cost burden. Clinical expert opinion and review of previous NICE oncology submission for advanced NSCLC suggest that this is a reasonable assumption.
Adverse events are mutually exclusive	For simplicity of modelling a cost is applied to each adverse event rate which assumes that the AEs are mutually exclusive.	The incidence of toxicities was low in both arms so this assumption was reasonable and also borne out by clinical trial data. In addition, as was noted in the 1st line pemetrexed NICE submission, although this assumption has a minimal impact on the ICERs, any impact counts against the more toxic 'comparator', which in this case this means pemetrexed. Therefore this assumption is conservative.
Adverse events resource use	Assume that nausea and vomiting are treated in the same way	Duran et al 2008 and expert clinical opinion.
Therapies/doses		
Body surface area	The actual BSA distribution from the JMEN trial population is applied in the model as the basis for calculating dose.	BSA distribution data are taken directly from the JMEN trial (see table 24). Various BSA assumptions are tested in the sensitivity analysis.
Trial second-line therapies	It is assumed that the distribution of second-line therapies reported in the JMEN have the same efficacy as those routinely used in UK clinical practice.	A number of the treatments used in the JMEN trial are not representative of UK practice. However, with the exception of pemetrexed rates of use are similar on both arms therefore overall survival data should not differ by arm.
Choice of second-line therapy	Second-line therapies in the model are docetaxel and erlotinib.	Market share data for the UK are expected to represent usual practice in second-line. The research suggests that docetaxel is used 73% of the time and erlotinib 23% of the time in second-line setting. Positive NICE appraisals for each of these treatments support their choice as second-line therapy in the UK.

Equivalent efficacy and utility in the second line setting	It is assumed that these have no difference in efficacy or utility of second-line therapy therefore only a cost element needs to be applied. This is captured in the final OS data.	Based on the decision by NICE on erlotinib (NICE STA No 162, November 2008) it appears that docetaxel and erlotinib have equivalent cost. A conservative approach is to apply only a cost element to trial data which is controlled on each arm. This avoids any issue of differential efficacy/utility in the second-line setting.
Setting for chemotherapy administration	All chemotherapies in this economic evaluation are assumed to be given in an outpatient setting: pemetrexed, docetaxel and erlotinib.	As a 10 min IV infusion pemetrexed does not need an inpatient administration. Docetaxel monotherapy is a one hour infusion that is routinely given in the outpatient setting. Erlotinib is an oral therapy so again inpatient administration is not needed.
Costs and resources		
Cost of concomitant medication	Concomitant medication assumed to be incorporated into the HRGs	It is a principle in the reporting of HRGs that they are measured using a full-absorption costing approach. This means any component of treatment essential to or inherent within a treatment activity is included. The impact of this is tested in the sensitivity analysis.
Cost of maintenance CT scans	It is assumed that CT scans to assess whether disease has progressed during the maintenance phase are incorporated into the HRG	It is a principle in the reporting of HRGs that they are measured using a full-absorption costing approach. This means any component of treatment essential to or inherent within a treatment activity is included. This assumption is tested in the sensitivity analysis with a cost for a CT scan applied to every other cycle.

BSC	All patients receive a cost for BSC at every cycle in the model, except for the final terminal cycle.	Based on a literature review resource information for BSC was collected. BSC costs are notoriously difficult to estimate and are likely to be highly skewed. Two approaches were considered: apply the same mean cost to every cancer death or to calculate a cost per cycle and apply that to each cycle. The latter approach is more conservative and was adopted in the base case. The alternative approach is considered in the sensitivity analysis.
BSC	Radiotherapy is excluded from the pemetrexed active chemotherapy arm	Expert clinician opinion and JMEN protocol.
BSC	75% of BSC/terminal care costs are accrued in the last 3 months of life	Most patients in the UK receive comprehensive palliative care (NICE 2004). The remaining 25% of the costs were spread over the cycles between start of maintenance therapy and the cycle immediately prior to the terminal/palliative stage – i.e. the last 3 months of a patients' life.
Histological differentiation		
Histology diagnosis	It is assumed that histological diagnosis is made at the time of disease staging, before the commencement of first-line therapy.	As pemetrexed is only licensed for use in the non-squamous population, it is important to determine histology at the time of staging of disease. In an ongoing pemetrexed first-line NICE appraisal, the appraisal committee have acknowledged that histological diagnosis is reasonable to expect as pathology services in the UK are capable of conducting this diagnosis.
Utilities		
Utilities	The utility for the 'not progressed' state (i.e. maintenance phase) in pemetrexed arm is an average of the of 'response' and 'stable' states from the Nafees et al (2008) second-line utility study. (i.e. 0.66)	Since patients initiate maintenance therapy after achieving either 'response' or 'stable disease' with first line therapy the 'not-progressed' health state was assumed to be the average of the stable disease and response states from Nafees. Variations in utility of response and stable state are tested in the sensitivity analysis.

Utilities	The utility for the 'not progressed' state (i.e maintenance phase) in BSC is 0.58	In the absence of specific data, this utility estimate is assumed to be the same as 'stable with fatigue' state in the Nafees (2008) study. Variations in utility are tested in the sensitivity analysis.
Utilities following progression in maintenance phase	For patient receiving active chemotherapy as second-line treatment, a utility of 0.58 is assumed	This utility estimate is assumed to be the same as 'stable with fatigue' state in the Nafees (2008) study.
	For patient receiving BSC as second-line treatment, a utility of 0.53 is assumed.	This utility estimate is assumed to be the same as that reported by Berthelot (2000) for 2nd line treatment with BSC
	For patients receiving BSC as second-line treatment and who have previously received pemetrexed as maintenance treatment, a utility of 0.54 is assumed	Berthelot estimate for 2nd line BSC inflated to take account of better pain control with pemetrexed treatment and the benefit of being on active chemotherapy Variations in utility are tested in the sensitivity analysis.
Utility estimates	It is assumed that utility estimates from Berthelot (2000) are consistent with those in Nafees (2008) and therefore can be used together.	In the absence of data, this assumption is considered reasonable. Variations in utility of response and stable state are tested in the sensitivity analysis.
HRQoL utility increment for symptom improvement (e.g. pain control) and benefit of having had active chemotherapy	A utility of 0.54 is estimated for any BSC in the pemetrexed arm received in the first year. This is based on the Berthelot 0.53 estimate and increased by 0.01 to reflect a utility benefit associated with improvement in symptoms such as pain control and haemoptysis and the psychological benefit of receiving an active treatment.	Doyle et al 2008 report the disutility of pain to be 0.069. This is a significantly higher value than the 0.01 applied in the model. The estimate assumed is conservative but recognises the importance of symptom improvement such as pain control in this patient population
AE utilities	AEs decrements in utility do not affect the final ICER in the maintenance setting as incidence rates are so low.	This assumption is tested in the sensitivity analysis

b) Non-model-based economic evaluations

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

The economic model for this submission is based on the empirical survival data from the JMEN trial. These survival data were estimated from patient-level survival outcomes, however, the model itself doesn't contain patient-level data. Empirical survival data are used

for the first 29 months of the model with parametric extrapolations used for a further 43 months to give a time horizon of six years. For full details of how the patient level data was used to obtain survival curves and to extrapolate for the life-time horizon please refer to the *"Model Development"* section.

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

Details of the JMEN clinical trial are provided in Sections 6.3.1 to 6.3.6 and 6.4. As a head-to-head RCT of the therapy of interest and in the absence of data comparing pemetrexed to any active anti-cancer treatment in the maintenance phase, the JMEN trial was selected as being the most appropriate trial in terms of meeting the requirements described in NICE's Methodology Guide.

7.2.7.3 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?

In JMEN censoring rates were 31.0% for the non-squamous population and 32.3% for the adenocarcinoma population. For this reason and in order to bring the economic model to a life-time horizon, extrapolation of the overall survival data has been implemented. The methods for such extrapolation have been explained in detail in the *"Model Development"* Section.

With regards resource use and unit cost data, the JMEN trial collected and reported chemotherapy dose data, AE rates and brief resource use (hospitalisation rate) data associated with AEs. However, as the JMEN was an international trial and these are the inputs more prone to international variation, it was considered appropriate to use UK clinical experts and UK-focused data from the literature to address these missing data.

The JMEN trial did not collect utility data. It did use the Lung Cancer Symptom Scale (LCSS) to collect data on disease associated symptoms. The LCSS did not provide enough information to estimate utilities for this economic model, furthermore, while baseline LCSS data were relatively well collected, compliance at follow-up for data collection was poor, mainly due to investigators not wishing to provide the questionnaire to their patients to complete for compassionate reasons.

7.2.7.4 Were all relevant economic data collected for all patients in the trial? If some data (for example, resource-use or health-related utility data) were collected for a subgroup of patients in the trial, was this subgroup prespecified and how was it identified? How do the baseline characteristics and effectiveness results of the subgroup differ from those of the full trial population? How were the data extrapolated to a full trial sample?

As stated in 7.2.7.3, with the exception of the chemotherapy dose data that was obtained from JMEN, the rest of resource use data has been identified from the literature. Utility values were also derived from the literature as the information on health related quality of life in JMEN was insufficient.

There was no difference in data collection by subgroup.

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

Please refer to the “Model Development” Section previously reported for full details on the extrapolation methods used.

7.2.9 Clinical evidence

7.2.9.1 How was the baseline risk of disease progression estimated? Also state which treatment strategy represents the baseline.

Baseline risk for disease progression is based on the efficacy outcomes from JMEN trial, reported in Table 14 above.

7.2.9.2 How were the relative risks of disease progression estimated?

Relative risk for disease progression in both arms of the trial is again based on the OS data from the JMEN trial

7.2.9.3 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?

The primary outcome of the economic evaluation is overall survival. The JMEN was powered so that OS could be the primary endpoint, a protocol change part-way through the trial meant that PFS was actually the primary endpoint but statistical power was maintained for OS. Utility data were not collected as part of the JMEN trial. Therefore we have linked final OS outcomes from the trial with utility data from literature to estimate QALYs.

7.2.9.4 Were the health effects or adverse effects 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 main health and AE effects are captured in this evaluation.

The adverse events included in the model were CTC Grade 3/4 drug-related toxicities that had an incidence of more than 2% in the pemetrexed arm. These included fatigue (3.7%), neutropenia (2.8%) and anaemia (2.5%) in the non-squamous population.

Nausea and vomiting were also included in the model. Although grade 3/4 nausea/vomiting only had an incidence of 0.6% (nausea) and 0.3% (vomiting) in the non-squamous population, because higher rates have been reported in other studies of pemetrexed monotherapy, for example 2.6% (Hanna et al 2004) and they are considered adverse events associated with pemetrexed, the decision was made to include them.

As can be seen in Table 19 above there is no substantive difference in adverse events by histology group.

7.2.9.5 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?

Experts were consulted routinely during the development of the economic model.

Specifically, they suggested that radiotherapy would not be used as an adjunct therapy with active chemotherapy in any treatment phase, for this reason radiotherapy is explicitly excluded from the BSC estimates for phases of the model reporting active chemotherapy use.

Experts were also consulted to assess the number of cycles a patient would receive during maintenance phase in routine clinical practice in the UK. They suggested that 10 cycles would be a reasonable maximum for the majority of the patients.

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

For details on the assumptions used in the model please refer to Table 20 above.

7.2.10 Measurement and valuation of health effects

The value of health effects should be expressed in terms of QALYs for the appropriate time horizon. For the reference case, the measurement of changes in HRQL should be reported directly from patients and the value of changes in patients' HRQL (that is, utilities) should be based on public preferences using a choice-based method. The EQ-5D is the preferred measure of HRQL in adults. The methods to elicit EQ-5D utility values should be fully described. When EQ-5D data are not available or are inappropriate for the condition or effects of treatment, the valuation methods should be fully described and comparable to those used for the EQ-5D. Data collected using condition-specific, preference-based measures may be presented in separate analyses. The use of utility estimates from published literature must be supported by evidence that demonstrates that they have been identified and selected systematically.

All parameters used to estimate cost effectiveness should be presented clearly in tabular form and include details of data sources. For continuous variables, mean values should be presented and used in the analyses. For all variables, measures of precision should be detailed.

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

Health effects were expressed using QALYs in accordance with the NICE reference case. We also report life years as this is a clinically meaningful outcome in oncology.

7.2.10.2 Which health effects were measured and valued? Health effects include both those that have a positive impact and those with a negative impact, such as adverse events.

Utilities associated with key health states were included in the economic model. Utilities were applied to the progression-free (active chemotherapy and no active chemotherapy) and post-progression health states (active chemotherapy, no active chemotherapy and terminal disease). The mean number of maintenance treatment cycles equates to the progression-free phase, the remaining cycles from progression to death account for post-progression. A terminal utility is applied to the cycle before death. All utilities from the 2nd year onwards are discounted.

All of the adverse events in the non-squamous and adenocarcinoma population have an incidence of less than 4% and a short duration. Therefore the addition of disutilities for AEs would add complexity to the model for minimal difference in ICER. In the basecase disutilities associated with AEs are not reported, however, they are tested in the sensitivity analysis.

7.2.10.3 How were health effects measured and valued? Consideration should be given to all of the following:

- State whether the EQ-5D was used to measure HRQL or provide a description of the instrument/s used.
- Provide details of the population in which health effects were measured. Include information on recruitment of sample, sample size, patient characteristics and response rates.
- Were the data collected as part of a RCT? Refer to section 5.3 as necessary and provide details of respondents.
- How were health effects valued? If taken from the published literature, state the source and describe how and why these values were selected. What other values could have been used instead?
- Was a mapping mechanism (or 'cross-walk') generated to estimate health-related utilities of patients in the trials? Provide details of the rationale for the analysis, the instruments used, the sample from which the data were derived and the statistical properties of the mapping mechanism.
- Were health states directly valued? If so, provide details of the rationale for the analysis, the HRQL measures that were valued, the population who produced the values and full details of the methods used. Explain the rationale for the analysis and the choice of instruments used.

The JMEN study did not include any preference based HRQoL measures. The Lung Cancer Symptom Scale (LCSS) was collected at baseline, throughout the trial and at 30 days after study medication discontinuation to assess worsening of symptoms. The 30-day time-point is an approximation for post-disease progression and is expected to be associated with increased symptom burden. Time to worsening of symptoms was defined as a 15mm worsening in symptom score. Results of time to worsening of symptoms analyses numerically favoured pemetrexed (with the exception of appetite loss). Pain and haemoptysis were statistically better in the pemetrexed arm than the placebo arm (see Table x in clinical section).

Unfortunately completion of the survey was poor once patients had completed the study which led to a large amount of missing data at certain time points. Missing data is a common issue in HRQOL studies in cancer (Stephens 1999).

Therefore, as the LCSS is not a generic measure of HRQOL and there was insufficient data to conduct any mapping exercise with which to construct valid utility estimates, a literature search was conducted to identify more robust sources of utility.

The search was conducted 11 Aug 2008 with the intention of locating clinical trials in NSCLC with a first-line and/or a maintenance therapy component that reported utility values (see Appendix 8 for details of the search strategy). A total of 15 studies were identified (11 located by the literature search and four known previously to Lilly). In addition, the reference lists of each of the 15 publications were reviewed for titles which referred to HRQoL. These studies were reviewed to identify those which included an assessment of HRQoL. None of the identified studies included utility values for patients undergoing maintenance therapy.

A further literature search was conducted to identify utility weights for patients suffering from NSCLC and used EMBASE and Lilly's own database. Based on both searches a total of seven papers were identified (Table 21).

Table 21. Summary results from utility literature review

Author	Country	Participants	Method of utility derivation	Health state	Utility
Berthelot (2000)	Canada	Patients with metastatic NSCLC. Utilities derived from proxy (24 oncologists).	VAS	BSC	0.53
				Vinblastine + Cisplatin	0.52
				Vinorelbine	0.60
				Gemcitabine	0.65
				Vinorelbine + Cisplatin	0.60
				Etoposide + cisplatin	0.55
				Paclitaxel + cisplatin	0.63
Nafees (2008)	UK	Member of the general public. Utilities derived from societal-based values.	Standard gamble interview	Response	0.67
				Stable Disease	0.65
				Stable disease w/ fatigue	0.58
				Progressive Disease	0.47
Kennedy(1995)	Canada	Scenario of patients with advanced inoperable lung cancer. Non-small cell lung cancer. Utility weights derived from proxy (9 clinicians)	Scenario-based Time Trade Off (TTO) with 9 doctors	BSC	0.61 (SD +/- 0.22)
				Polychemotherapy	0.34 (SD +/- 0.30)
Manser (2006)	Australia	Patients with newly diagnosed primary lung cancer; 98% NSCLC; all stages	AQoL	Stage III NSCLC	0.67 (median)
				Stage IV NSCLC	0.68 (median)
Pimentel (2005)	Germany, UK, Finland, Netherlands, Portugal	Baseline utility weights from patients initiating first-line chemotherapy for stage III/IV NSCLC	EQ-5D (UK scoring algorithm)	Stage III/IV NSCLC in all countries at baseline	0.65 (SD=0.30)
Doyle et al (2008)(Doyle, Lloyd, and Walker 374-80)	England and Wales	101 members of general public assessed their preference for each health state (responding disease and stable disease) and impact of severe symptoms (cough, dyspnea, pain, or no additional symptoms).	VAS Standard gamble EQ-5D	**Disease state** / **Symptoms** / **Utility Value** / **Utility Value**	
				Response / No additional symptoms / 0.712 / 0.712	
				Stable disease / No additional symptoms / 0.626 / 0.626	
				Stable disease / Cough / 0.580 / 0.580	
				Stable disease / Dyspnea / 0.576 / 0.576	
				Stable disease / Pain / 0.557 / 0.557	
				Stable disease / Cough, dyspnea, and pain / 0.461 / 0.461	

Author	Country	Participants	Method of utility derivation	Health state	Utility
(Smith et al. 2166-73)	US	Patients with NSCLC (Stage III or IV) treated with Vinorelbine; Vindesine + Cisplatin; Vinorelbine + Cisplatin. 14 oncology physicians and nurses.	Method of estimate derivation not reported.	Cisplatin-containing regimens	0.60
				Vinorelbine-containing regimens	0.70

Nafees (2008), a Lilly-sponsored study designed to accompany the second-line NSCLC submission of pemetrexed to NICE, was deemed to have the most appropriate utility values of all those identified. Although the study was designed for second-line pemetrexed, considering the scarcity of applicable utility data in the literature as a whole, it was the most relevant. This paper has the advantage of being conducted to directly derive UK societal-based utility values for different tumour states of NSCLC and different toxicities commonly associated with chemotherapy treatments.

The study designed health state descriptions for stable, responding, and progressive disease and six grade 3/4 toxicities plus hair loss. These descriptions were used in brief interviews with five oncologists and five oncology nurse specialists in the UK. The resulting health states were piloted and used in a societal-based valuation study (n=100). Participants rated the health states in a standard gamble interview to derive health state utility. The health states defined are not 'line' specific, i.e. don't refer specifically to second-line therapy, therefore are applicable in the maintenance setting. The only exception to this is the definition of progression which was re-visited for the maintenance submission and deemed to be closer to a description of terminal stage disease (see box insert) and so is applied to the terminal cycle, with an estimate for 'stable with fatigue' applied to post-progression pre-terminal cycles.

Progressive

- You have a life threatening illness and your condition is getting worse.
- You have lost your appetite and have experienced significant weight loss. You experience pain and discomfort in your chest or under your ribs. You frequently have shortness of breath and breathing is often painful. You have a persistent nagging cough and sometime cough up blood. You may experience some difficulty swallowing.
- You experience severe fatigue and feel too tired to go out or to see your family and friends. It has affected your relationships with them.
- You need assistance to wash and dress yourself. You are often unable to do jobs around the house or other daily activities. You are dependent on others to do your shopping and are unable to do your usual daily activities.
- You often feel less physically attractive than you used to. You have little or no sexual drive.
- You're depressed and dying is always on your mind. You worry about how your loved ones will cope.

Data from Nafees (2008) were supplemented with data from Berthelot (2000) where the Nafees data were considered insufficient. Data from Doyle (2009) were considered in the sensitivity analysis as a way of considering the impact of pain symptom control with pemetrexed.

The relevant utility values from the Nafees paper are a) response with no adverse events, 0.67; b) stable disease with no adverse events, 0.65; c) stable disease with fatigue, 0.58; d) progressive disease, 0.47. A utility value of 0.53 for patients receiving BSC post-progression was retrieved from Berthelot (2000). Time to worsening of symptoms data from JMEN reported patients on pemetrexed had a statistically significant longer median time to paint than patients on the placebo arm (8.41 months vs 4.90 months, HR 0.445, p-value 0.022). To model the benefit improved better pain control with pemetrexed treatment, a utility increase of 0.01 was provided to patients receiving BSC in their first year post-discontinuation of pemetrexed. Doyle et al 2009, report a disutility of 0.069 associated with pain, therefore in the sensitivity analysis this is tested with a utility value of 0.599, however for the basecase a more conservative approach was taken.

Assumptions were made with respect to using these values for the health states included in the maintenance model (see Table 22) which differed to those in the Nafees study. These are discussed below.

Table 22. Utility values used in the model (adapted from Nafees (2008) and Berthelot (2000)

Health State and Adverse events within each health state	Mean utility values	Source
Not-progressed Treated with active chemotherapy (pemetrexed maintenance phase)	0.66	Nafees (2008) Average of Stable and responding health states with no AE
Not-progressed No active chemotherapy (placebo maintenance phase)	0.58	Assumed to be the same as stable with fatigue from Nafees
Progressed Receiving 2nd-line chemotherapy	0.58	Assumed to be the same as stable with fatigue from Nafees
Progressed Receiving BSC in first year (pemetrexed arm)	0.54	Berthelot estimate for 2nd line BSC inflated to take account of better pain control with pemetrexed treatment and the benefit of being on active chemotherapy
Progressed Receiving BSC all years (placebo arm) Receiving BSC 2nd year onwards (pem arm)	0.53	Berthelot estimate for 2nd line BSC
Progression - terminal cycle	0.47	Nafees (2008)

Assumptions for the Utility values

Not-progressed health state

The Nafees study did not estimate a utility value for the not-progressed health state. However, since patients initiate maintenance therapy (or placebo) after achieving either 'response' or 'stable disease' with first line therapy the not-progressed health state was assumed to be the average of the stable disease and response states from Nafees.

Progressed health state (up to the cycle before death)

Nafees estimates a utility value of 0.47 for patients in the progressive disease health state. However, this value was elicited in the context of 2nd line therapy. The health state vignette from Nafees implies that death is imminent and that patients are unable to perform most activities of daily living unassisted. The circumstances are considerably different for a patient who has progressed from maintenance therapy as these patients can live for some time with less debilitating disease. For this reason it was assumed that the utility for this health state was the same as 'stable disease with fatigue'. Fatigue was selected as it was the most common symptom of cancer reported in the JMEN trial, see Table 7.

Progressed health state (last cycle of life)

During the final stages of progression when death is imminent and health has deteriorated rapidly, a lower utility value should be applied. In order to account for this, a proportional one-off decrement for the last cycle of life was applied for every death recorded in the model equivalent to a utility of 0.47. All patients, on both arms, receive this same decrement.

7.2.10.4 Were any other generic or condition-specific preference based measures used in the clinical trials? Provide a description of the data below. The results should be considered in a sensitivity analysis (see Section 6.2.11).

No other generic or condition-specific preference based measure than Lung Cancer Symptom Scale (LCSS) was used in the clinical trial. For further details on the LCSS please refer to Sections 6.3.4. and 6.4. of the Clinical Section and 7.2.9.3 above. The LCSS did not contain enough data to explore in the sensitivity analysis.

7.2.10.5 Were any health effects excluded from the analysis? If so, why were they excluded?

No, all relevant health effects for patients with NSCLC were considered.

7.2.11 Resource identification, measurement and valuation

The following questions were merged to present the data as clearly as possible: 7.2.10.1-7.2.10.3 & 7.2.11.5.

Resource utilisation and unit costs

Utilisation rates and units costs for key resources were identified and are reported in Table 23 below. The JMEN trial collected and reported dose data but resource use data for other aspects of the trial, for example adverse events and best supportive care were not comprehensively collected or considered representative of UK practice. For this reason a range of sources of evidence were needed in addition to JMEN.

Table 23. Resource utilisation and unit cost sources

Resource	Utilisation rate data source	Unit cost data source
Medication		
Chemotherapy acquisition	JMEN trial & SPC	MIMS July (2009)
Concomitant medication (assumed to be incorporated into the NHS HRGs used but also presented to show they are relatively inexpensive).	SPC	
Administration		
Chemotherapy administration (including concomitant medication)	JMEN trial & SPC	NHS reference costs 2007-2008 (DH, 2009)
Adverse events		
Neutropenia	JMEN trial	Survey of clinical experts (Duran et al 2008), Hanna 2004
Fatigue	JMEN trial	Duran et al 2008, Hanna 2004
Nausea/vomiting	JMEN trial	Duran et al 2008, Hanna 2004
Anaemia	JMEN trial	Duran et al 2008, Hanna 2004
Best supportive care	Literature review (see Table 34 and Appendix 10).	Literature review (Table 34 and Appendix 10) & "Guidance on Cancer Services Improving Supportive and Palliative Care for Adults with Cancer; Economic Review" (NICE 2004)
Terminal care	NICE 2004	Literature review (see Table 34 and Appendix 10). & NICE 2004

Chemotherapy acquisition costs and administration dose data are taken from the trial and the therapies' SPCs with national UK prices are applied from MIMS July (2009). National HRGs are used to estimate a standard price for chemotherapy administration, based on license treatment protocol.

We considered using the chemotherapy HRGs for both procurement and delivery based on the OPCS Classification (NHS, 2009). However, because of uncertainty regarding the accuracy of some of the procurement codes, it was decided to use these data in the sensitivity analysis and use bottom up costing in the basecase. HRG costs used in the sensitivity analysis are provided in Appendix 9.

There is no standardised national level database describing resource use associated with the treatment of adverse events or best supportive/terminal/palliative care. To address the evidence gap regarding resource use associated with adverse events, Lilly commissioned a survey of clinical experts described below. The NICE/Sheffield University research was used as the basis for the BSC/palliative care resource use and costs (NICE 2004).

All unit costs in the model are the most up to date or inflated to 2008, the most up to date inflation index available from PSSRU. The unit costs for the model are based on the most up

to date UK NHS reference costs for 2007-08, which were published by the Department of Health in May 2009 (DH, 2009). BSC/palliative care costs were inflated to 2007-8 rates using the PSSRU inflation index (PSSRU 2008).

Chemotherapy

Chemotherapy list prices are used for maintenance pemetrexed and second-line chemotherapies. Prices were based on MIMS July (2009). Maintenance costs are based on the actual BSA of patients in the JMEN trial, second-line chemotherapy costs are based on a BSA of 1.7m^2 (assuming by this stage that patients have lost weight, this is also the BSA reported by Clegg et al (2001) in their HTA assessment).

Costs per vial (including wastage) are reported in the basecase with costs per mg (no wastage) tested in the sensitivity analysis, as are HRG chemotherapy procurement costs.

Administration costs are based on NHS Reference Costs 2007-08 (DH 2009) for both maintenance and second-line therapies.

Maintenance chemotherapy

The recommended dose for pemetrexed in the maintenance phase is 500mg/m^2. The BSA used in this economic evaluation is based on the actual BSA of patients in the JMEN trial, see Table 24.

Table 24. Dose data from JMEN trial based on actual distribution by BSA

Average dose and cost by BSA						
BSA	**Proportion**	**Midpoint BSA**	**Dose (mg)**	**100mg Vial**	**500mg Vial**	**Cost (vial)**
1.1-1.199	0.15%	1.15	575	1	1	£960.00
1.2-1.299	0.15%	1.25	625	2	1	£1,120.00
1.3-1.399	0.15%	1.35	675	2	1	£1,120.00
1.4-1.499	6.21%	1.45	725	3	1	£1,280.00
1.5-1.599	11.06%	1.55	775	3	1	£1,280.00
1.6-1.699	16.52%	1.65	825	4	1	£1,440.00
1.7-1.799	20.76%	1.75	875	4	1	£1,440.00
1.8-1.899	18.64%	1.85	925	0	2	£1,600.00
1.9-1.999	11.67%	1.95	975	0	2	£1,600.00
2.0-2.099	8.48%	2.05	1025	1	2	£1,760.00
2.1-2.199	4.24%	2.15	1075	1	2	£1,760.00
2.2-2.299	1.36%	2.25	1125	2	2	£1,920.00
2.3-2.399	0.45%	2.35	1175	2	2	£1,920.00
2.4-2.499	0.15%	2.45	1225	3	2	£2,080.00
Equivalent mean of		**1.79m^2**				**£1,509.58**

In the sensitivity analysis a BSA range of 1.70m^2 to 2.0m^2 is tested. The lower value is based on Clegg et al (2001; 2002) from their HTA for NSCLC, in both the first- and second-line settings, whilst the higher value was chosen as a high end range based on the BSA distribution from JMEN where almost 85% of the patients had values of 2.0m^2 or below.

A BSA of 1.82m^2 is also applied in the sensitivity analysis based on values reported in the Economic Review Group Report on pemetrexed in the first-line NSCLC setting (NICE 2009, page 58), weighted according to the ratio of males (mean BSA = 1.89m^2) to females (mean BSA of 1.65m^2) in the JMEN trial. The non-squamous population in JMEN trial was 68.6% male, the adenocarcinoma population was 64.0% male. The source of the ERG estimate is awaiting publication meaning it is not possible to confirm any factors that would affect the applicability of this BSA estimate to the model.

The distribution of BSA data from the trial equates to a mean cost per cycle of £1,509.58, calculated by multiplying the cost per vial for each BSA group by the proportion of patients in that BSA group.

Table 25. Chemotherapy unit costs (MIMS July, 2009), based on BSA distribution in JMEN trial

	Unit cost per vial	**Calculated cost per mg**	**Dose**	**Mean BSA (m^2)***	**Cost per cycle**
Maintenance Chemotherapy					
Pemetrexed (100mg vial)	£160.00	£1.60		1.79	
Pemetrexed (500mg vial)	£800.00	£1.60	500mg/m^2	1.79	£1,509.58

* Note, in this instance the cost per cycle data is not based on the mean BSA but the distribution.

Maintenance administration

Pemetrexed is a 10-minute intravenous infusion. It is assumed to be given in an outpatient setting (NHS Reference Cost Code: TCHEMTHPY_DEL_OP) on day 1 of a 21 day cycle. The cost for pemetrexed administration is taken from the NHS Reference Cost database 2007-8 prices (DH, 2009). There is no corresponding OPCS/HRG code for pemetrexed monotherapy, therefore the delivery code applied is SB12Z, 'Deliver simple parenteral chemotherapy at first attendance' as this seemed the most appropriate code to use, although the code for more complex administration is lower. Therefore, the value of pemetrexed cost per administration used in the model is £153.

Table 26. Adapted from the national schedule of reference costs 2007-08, TCHEMTHPY_DEL_OP (Chemotherapy outpatients (DH, 2009))

Currency Code	Currency Description	National Average Unit Cost
SB11Z	Deliver exclusively Oral Chemotherapy	£167
SB12Z	Deliver simple Parenteral Chemotherapy at first attendance	£153
SB13Z	Deliver more complex Parenteral Chemotherapy at first attendance	£117
SB14Z	Deliver complex Chemotherapy, including prolonged infusional treatment at first attendance	£208
SB15Z	Deliver subsequent elements of a chemotherapy cycle	£154

Concomitant medication

Premedication specified in the pemetrexed SPC include dexamethasone, folic acid and vitamin B_{12}. In this model, these costs are assumed to be incorporated into the HRGs for chemotherapy administration so are not included additionally to prevent double counting. However, they are presented here to demonstrate they are all relatively low cost, see Table 27 and therefore inclusion or exclusion would not affect the results. HRGs are developed on the principle of full-absorption costing, therefore all elements integral to the delivery of a certain activity should be captured in the related reference price.

Table 27. Concomitant medication unit costs

Concomitant therapy	Unit cost
Premedication	
Dexamethasone	£2.39
Folic Acid	£1.65
Vitamin B_{12}	£2.46

The calculation of total cost for maintenance therapy with pemetrexed based on these unit costs for acquisition and administration is shown in Table 28.

Table 28. Total maintenance chemotherapy cost per patient, based on JMEN BSA distribution

	Mean chemo acquisition cost per patient per cycle	Mean chemo admin cost per patient per cycle	Mean cost per cycle	Mean number of cycles per patient*	Mean total cost per patient
Pemetrexed (non-squamous population)	£1,509.53	£153	£1,662.53	5.84	£9,642.67
Pemetrexed (adenocarcinoma population)	£1,509.53	£153	£1,662.53	6.16	£10,264.18

*Mean number of cycles is based on capping at 1SD from the mean, maximum 17 for non-squamous and 18 for adenocarcinoma.

Second line chemotherapy

Simplified second-line costs are used in the model including only chemotherapy acquisition and administration costs.

Table 29. Second-line chemotherapy unit costs based on BSA of 1.7m^2, costs are per vial (including wastage)

	Unit cost per vial	Unit cost per mg/day	Dose	BSA	Dose /Vials required	Cost per cycle
Second-line chemotherapy						
Docetaxel (20mg vial)	£162.75	£8.14	75mg/m^2	1.7m^2	127.5mg = 1x80 + 3x20	£1,023.00
Docetaxel (80mg vial)	£534.75	£6.68	75mg/m^2	1.7m^2		
Erlotinib 150mg (30 tablets)	£1,394.96	£46.50/day	150mg/day		Assume a 21 day cycle	£976.50

For the purpose of this economic evaluation we assume that pricing scheme agreed between the manufacturers of erlotinib and the DH is in place, we understand this translates into a discount of 14.5% off the list price.

Second line administration costs

Based on the HRG reference costs (see Table 26), a code of SB14Z is applied to docetaxel (complex chemotherapy) as an hour and half infusion and a code of SB11Z is applied to erlotinib (oral administration). SB11Z is assumed to be based on a 28 day cycle (NHS 2008 OPCS chemotherapy codes) therefore is adjusted to a 21 day price for the economic model.

The calculation of total cost for second-line therapy with erlotinib and docetaxel based on the unit costs for acquisition and administration is shown in Table 29.

Table 30. Total second-line chemotherapy cost per patient,

	Mean chemo acquisition cost per patient per cycle	Mean chemo admin cost per patient per cycle	Mean cost per cycle	Number of cycles per patient*	Mean total cost per patient
Docetaxel	£1,023.00	£208	£1,231	4.9	£6,031.90
Erlotinib	£976.50	£125.25	£1,143.50	6.27	£7,169.75

Cycle data based on information the ERG and in Table 1 of Roche's proposal of arrangement for the provision of erlotinib to the National Health Service
(NICE, 2009 www.nice.org.uk/guidance/index.jsp?action=download&o=41146)

The distribution of second line chemotherapies in the model is based on the most recent market share data for products with market share greater than 5%. This equates to docetaxel having a market share of 73% and erlotinib a market share of 23% (Data on file_2ndline market share data, 2009).

Adverse Events

Adverse event rates were collected as part of the JMEN trial, however, detailed resource use data associated with the treatment of AEs were not collected. The treatment of AEs is likely to differ quite widely between different healthcare systems, therefore it is appropriate to use UK-specific costs as possible.

In order to support the pemetrexed second-line submission, Lilly commissioned a survey of clinicians to collect resource use and unit cost data relating to the treatment of adverse events and provision of best supportive care (Duran et al. 2008). Four UK clinical experts were recruited to provide information on the treatment algorithms for a range of grade 3/4 AEs. The clinicians were asked to describe the resource use associated with treating each AEs and a unit cost was then calculated. The calculation includes an estimate of medication and interventions needed, the duration of any hospitalisation and the relative proportion of care provided in an inpatient or outpatient setting. Table 31 reports the unit cost for each AE included in this economic model. Table 32 summarises how the unit cost estimate was derived based on treatment setting.

Table 31. Summary AE unit cost calculation

	HOSPITAL							
	Inpatient	%	Out-Patient	%	Day Care	%	No Treatment	%
Neutropenia	£680.00	21.10	£593.10	23.70	£710.45	6.60	£0.00	48.70
Nausea and Vomiting	£1,200.00	51.60	£20.70	36.80	£1,253.74	5.90	£0.00	5.70
Fatigue	£0	10.70	£219.80	17.70	£0.00	9.40	£0.00	62.20
Anaemia	£680.00	32.90	£593.10	20.70	£710.45	37.80	£0.00	8.50

Table 32. Adverse event resource utilisation (adapted from Duran et al.2008 and Hanna 2004)

Adverse Event	Unit cost
Neutropenia	£330.93
Nausea and Vomiting	£700.79
Fatigue	£38.90
Anaemia	£615.04

The costs of adverse events are varied in the sensitivity analysis.

Best Supportive Care & Terminal Care Costs

It is difficult to get a reliable unit cost estimate for Best Supportive Care (BSC) because the definition and understanding of what constitutes BSC varies depending on a number of factors for example: stage of disease, whose perspective (patient versus clinician, a patient might include advice on organising finances whereas a clinician's main concern is in alleviating of distressing symptoms) and what resources are available (state-funded, charity funded, informal care). Even if the perspective is agreed upon, for example a clinician's, the understanding of what constitutes BSC can vary, for example the role of radiotherapy. Clegg et al (2001; HTA p39) defined BSC as, 'care which includes the relief of symptoms by for example analgesics, but which does not attempt to prolong life or to remove (even if only temporarily) the cause of symptoms.' Clegg continues, 'The term is useful to indicate the baseline option, but may vary in its inclusions. For example, radiotherapy may be part of palliative care, by providing temporary relief of metastatic symptoms.

Lilly carried out a literature review to identify a reliable BSC estimate. Details of this are reported in Appendix 10. Table 34 presents the results from papers in which it was possible to retrieve an estimate for BSC that could be inflated to 2008 prices, the most up to date available. No attempt has been made to aggregate these costs due to variations in stage of disease, line of treatment, chemotherapies, patient demographics, geographical setting, age of publication and unit of time over which BSC was calculated. However, some surprisingly uniform results emerge. Those that reported a potentially comparable BSC cost were in the range of £3,451 to £5,048 per cancer death. As the majority of trials that report BSC reported median survival of less than 12 months, BSC costs were reported as one-offs and not adjusted to any unit of time.

Radiotherapy is potentially a large driver of BSC costs, radiotherapy costs £317 per visit (NHS Reference Cost, 2009; Outpatients TRADTHPYOP). As Clegg (2001) comments inclusion in BSC is variable, with some studies including radiotherapy as part of BSC others not. Radiotherapy was excluded from the JMEN trial on both arms. Based on expert clinical advice it was suggested that patients would not receive radiotherapy while on active chemotherapy however, some proportion would receive it if not receiving active chemotherapy. This model assumes therefore that while patients in the pemetrexed arm of the model would get BSC, they would not get radiotherapy.

The BSC and palliative care costs used in the model are based on the publication by NICE/University of Sheffield (2004) which reports the average cost of Specialist Palliative Care to be £3,236 per cancer death per year. This value was inflated to £3,451, based on an inflation index of 1.07 (PSSRU, 2008). We assumed that the bulk of this cost would be incurred in the last 3 months of life (£2588.25) with the remaining £862.75 incurred over the remaining 9 months. This is equivalent to a monthly BSC cost of £95.86 or a per cycle cost of £66.36.

The cost of BSC during maintenance treatment with pemetrexed is assumed to be £33.18 per cycle as radiotherapy is not indicated during active chemotherapy. There is also the assumption that patients receiving active chemotherapy will have better symptom control and therefore have less need for BSC. In this case, pemetrexed patients reported better pain and haemoptysis symptom control than placebo patients.

In the model the £2588.25 is applied as a cost incurred by every patient in the last cycle before death. The £66.36 estimate is applied to any other cycle in which no active chemotherapy is being given and £33.18 is applied to any cycle in which there is also treatment with an active chemotherapy. It should be noted that the assumptions used to derive these costs: last 3 months of life and previous 9 months of life, are not directly reflected in the model, i.e., the last three months costs are applied in the terminal cycle to maintain structural simplicity.

Table 33. BSC and terminal care costs used in the model (NICE 2004)

Adverse Event	Unit cost
BSC during active chemotherapy	£33.18
BSC with no active chemotherapy	£66.36
Terminal care	£2,588.25

In the sensitivity analysis we apply a constant BSC/terminal care cost to each patient of £3,451. This is on the assumption that the cost of BSC/terminal care is not a function of duration of survival but that the same volume of resources are used by terminally ill patients regardless of differences in survival.

Table 34. Results from the literature review of BSC

Author	Study	Reported cost	Comments	BSC - Adjusted to UK 2009 prices
Leighl 2002	TAX317 study.	BSC = CAN$8821.52 (1999prices) per patient death	Second-line setting	
Lees 2002	Review of gemcitabine compared with BSC and 3 other chemo regimens (300pts) Case note review	BSC = £3861 (2000 prices) per patient death	May over-estimate BSC as some chemotherapy was used in the non-BSC arm. Mostly 1st line setting	£5,048
Clegg HTA report (2001)	Review of NSCLC	BSC = £3572 per patient death (1999/2000 prices)	Measured over a 6mo period with 10% of patients still alive. Both first- and second-line setting.	£4,866
Billingham 2002	MIC2 trial 116pts in S Bham Health authority. Calculated resources x unit costs	BSC = £4076 complete data and BSC = £3933 imputed data.	Two v. similar estimates for BSC provided based on two computational methods	£4,900 (complete) £4,800 (imputed)
Clegg 2002	Paper written up on the HTA review	BSC = £3342 (1999/2000 prices)		£4,552
Maslove 2005	Big Lung Trial – 198 pts took part in the case note review. BSC pts more likely to receive palliative radiotherapy	BSC = £3595 (2000 prices) per patient death.	Had already received 1st line chemotherapy that was approximately equivalent in both arms.	£4,700
NICE palliative care review		BSC = £3,236 (2005) per cancer death per year.		£3,451

Prices adjusted using the Inflation Index reported in the PSSRU document Unit Cost of Health and Social Care (2008). Indices were: 1.36 (1999/2000); 1.31 (2000); 1.20 (2002) and 1.07 (2005)

7.2.11.4 Were resources used to treat the disease/condition included for all relevant years (including those following the initial treatment period)? Provide details and a justification for any assumptions that were made (for example, assumptions regarding types of subsequent treatment).

Yes, resources used to treat the disease were included for all years. In this model this specifically includes best supportive care and terminal care resources that are used after then first year.

7.2.11.6 What is the unit cost (excluding VAT) of the intervention(s) included in the analysis?

The unit cost for pemetrexed is £800 per 500mg vial or £160 per 100mg vial. This does not differ from the anticipated acquisition cost reported in section 1. No discounts are presented.

7.2.11.7 Does the technology require additional infrastructure to be put in place? Provide details of data sources used to inform resource estimates and values.

No, the requirement for a more specific level of histological diagnosis is something that should be possible using routine pathology practices: identification of morphology and TTF-1 immunohistochemistry, both of which are widely if not universally available now. All that needs to happen is for these skills to become routine practice. Additional immunohistochemistry tests could be carried out but are not necessary. It is likely that histological diagnosis would be made at diagnosis and staging of disease, i.e. before first-line treatment and would not need to be repeated at any later stage.

The trial protocol specified that a CT scan be performed every other cycle of maintenance in order to assess progression. According to UK clinicians consulted a CT scan would be performed every 2-3 cycles. Because HRG delivery codes are based on full-absorption costing principles we have assumed that the delivery cost for pemetrexed includes the CT scan for the basecase.

However, as reference prices are reported retrospectively, and pemetrexed is only being used in few clinical trials in the UK at the moment, we have also tested the impact of having an additional CT scan every other cycle in the sensitivity analysis. For the purposes of modelling the £92 cost of a scan (DH, 2009) was divided by two and applied every cycle. This makes a total administration cost per cycle of £204, based on the SB12Z (simple parenteral). Had SB13Z (£117 per episode) been used instead this would have equated to an administration cost of £163 per cycle, merely demonstrating that uncertainty with regards the appropriate chemotherapy OPCS/HRG coding influences ICER estimates.

7.2.11.8 Were the resources measured and valued in a manner consistent with the reference case? If not, how and why do the approaches differ?

The same method for costing the medication, administration, adverse events, BSC and terminal care were applied to pemetrexed and placebo arms.

7.2.11.9 Were resource values indexed to the current price year?

Methods for index to most appropriate year described above, PSSRU's Unit Cost compendium (PSSRU 2008) was used to derive the inflation indices.

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

All assumptions described above.

7.2.12 Time preferences

Were costs and health benefits discounted at the rates specified in NICE's reference case?

Yes, both costs and benefits were discounted at a rate of 3.5% per year.

7.2.13 Sensitivity analysis

Sensitivity analysis should be used to explore uncertainty around the structural assumptions used in the analysis. Analysis of a representative range of plausible scenarios should be presented and each alternative analysis should present separate results.

The uncertainty around the appropriate selection of data sources should be dealt with through sensitivity analysis. This will include uncertainty about the choice of sources for parameter values. Such sources of uncertainty should be explored through sensitivity analyses, preferably using probabilistic methods of analysis.

All inputs used in the analysis will be estimated with a degree of imprecision. Probabilistic sensitivity analysis is preferred for translating the imprecision in all input variables into a measure of decision uncertainty in the cost effectiveness of the options being compared.

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

7.2.13.1 Has the uncertainty around structural assumptions been investigated? Provide details of how this was investigated including a description of alternative scenarios included in the analysis.

The simple structure of this model means that as the objective of the model was to model as accurately as possible OS from the trial and extrapolate over time until all (>96-99% of) patients have died, based on the assumption that in oncology OS is the most important outcome, then there are limited structural assumptions that need to be tested in this model. However, discounting rates, half-cycle correction and time horizons have been assessed in the sensitivity analysis.

7.2.13.2 Which variables were subject to sensitivity analysis? How were they varied and what was the rationale for this?

One-Way Sensitivity Analysis - One-way sensitivity analyses have been run, using the economic model, to assess variation in the incremental cost-effectiveness ratio (ICER) outcomes and incremental benefits when ranges of values are independently considered for

the parameters described below. The rationale for the sensitivity analysis is to test the model stability and identify which variables drive the incremental cost-effectiveness ratio.

1. Costs
    - Pemetrexed chemotherapy costs reduced by 10%
    - Per mg costing
    - All DH HRG procurement and delivery costs applied
    - Flat BSC cost applied to all arms
    - No BSC applied
    - Second-line costs excluded

2. Cycles
    - Costs based on median number of cycles (6 for non-squamous; 6 for adenocarcinoma)
    - Cost based on all cycles reported in the JMEN trial
    - Capping at 2 standard deviations (equivalent to a maximum of 25 cycles)
    - Capping at 10 cycles (equivalent to a mean of 5 cycles)
    - Reduce incremental OS advantage by 9.5% to correspond to the 9.5% of patients excluded with the basecase capping rule
3. Resource use
    - Hospital days for AEs +/- 50%
4. Utility
    - Apply disutilities associated adverse events
    - Apply increment associated with better pain control from Doyle et al (2009)
5. Efficacy
    - Comparison of lower pemetrexed to upper placebo CI interval for OS
    - Comparison of upper pemetrexed to lower placebo CI interval for OS
    - *It should be noted that these data are based on the median values from the JMEN trial and are therefore not extrapolated to 6 years and do not have a parameterised function applied.*
6. Patient population
    - Mean body surface area (BSA) of 1.82m^2
    - BSA of 1.7m^2
    - BSA of 2.0m^2
    - Limit BSA so that no one receives>2 large (500mg) vials
7. Structural
    - Discounting at 0%
    - Discounting at 6%
    - Time Horizon of 3, 4 and 5 years

7.2.13.3 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'.

No. The structure of the extrapolation model does not lend itself to undertaking a PSA.

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

Not applicable for this model structure.

7.2.13.5 Is there evidence that (transition) probabilities should vary over time for the condition or disease? 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.

Not applicable for this model structure.

7.2.14 Validity

The nature of this model makes validity checking with the pivotal clinical trial quite straightforward. The only measure for validation is OS, as this is the only 'modelled' input. Results are below:

Table 35. Median overall survival – validity check of model versus JMEN trial outcomes

	Non-squamous			Adenocarcinoma		
	Pemetrexed	**Placebo**	**Increment**	**Pemetrexed**	**Placebo**	**Increment**
Trial data	15.47	10.28	5.19	16.83	11.53	5.29
Exponential hazard function	15.21	10.06	5.16	16.75	11.36	5.38

The non-squamous data very slightly underestimate survival and the adenocarcinoma data very slightly overestimate survival, but, as is not surprising for results based on trial data, the results are very similar suggesting the model has a high degree of validity.

Aside from OS data, were taken directly from the trial: mean number of cycles, dose data. AEs, BSC and terminal care costs and resource use are explored in the sensitivity analysis but as these were not collected in the clinical trial then no validity checking needs to be done.

7.3 Results

7.3.1 Provide details of the results of the analysis. In particular, results should include, but are not limited to, the following:

- costs, QALYs and incremental cost per QALY
- disaggregated results such as life years gained, costs associated with treatment, costs associated with adverse events, and costs associated with follow-up/subsequent treatment
- a statement as to whether the results are based on a probabilistic sensitivity analysis
- cost-effectiveness acceptability curves including a representation of the cost-effectiveness acceptability frontier
- scatterplots on cost-effectiveness quadrants
- a tabulation of the mean results (costs, QALYs, ICERs) the probability that the treatment is cost-effectiveness a thresholds of £20,000-£30,000 per QALY gained and the error probability.

7.3.2 Base-case analysis

7.3.2.1 What were the results of the base-case analysis?

The results that follow are for the non-squamous population. The basecase inputs for this analysis are based on capping at 17 cycles and a per vial costing of the BSA distribution in the trial. Costs for second-line treatment are included. Based on the recent agreement with NICE/DH we have assumed that docetaxel and erlotinib have equivalent efficacy and that erlotinib has an acquisition cost equivalent to a 14.5% discount off list price. The extrapolation carried out used an exponential hazard function after the end of the trial data. The time horizon is 6 years (72 months or 104 cycles). Discounting at 3.5% and a half cycle correction to outcomes are applied. A full list of basecase inputs is provided in Appendix 11.

The results for the non-squamous population are reported in Tables 36-38.

Table 36. Costs associated with different therapy options (non-squamous population)

Costs	Pemetrexed	Placebo	Incremental
Maintenance chemotherapy acquisition & administration	£9,903	£299	£9,605
Second line chemotherapy acquisition & administration	£3,570	£4,516	-£946
BSC (with chemotherapy)	£105	£847	-£743
BSC (no chemotherapy)	£1,329	£133	£1,196
Terminal care	£2,514	£2,518	-£4
Adverse events	£34	£5	£29
TOTAL COST	**£17,455**	**£8,318**	**£9,137**

Costs are based on the per cycle costs (acquisition cost of chemotherapy and administration) multiplied by the number of cycles of treatment received, plus costs for treating AEs and one-off costs (i.e. terminal care).

Health outcomes

LYGs and QALYs gained

The health benefits associated with pemetrexed are reported below.

Table 37. Health outcomes – non-squamous population

Mean benefits	Pemetrexed	Placebo	Incremental difference
Quality Adjusted Life Years (QALYs)	0.9697	0.6988	0.2709
Life Years Gained (LYG)	1.70 (20.4mo)	1.26 (15.12mo)	0.44 (5.28mo)

Incremental Cost-Effectiveness Ratio

Table 38. Cost per additional QALY and life year gained - non-squamous population

	ICER	Incr.cost per LYG
Pemetrexed vs placebo	£33,732	£20,562

These results suggest that pemetrexed monotherapy for the licensed non-squamous population is just over the maximum ICER willingness-to-pay threshold used by NICE. This result is driven by the comparator being placebo/BSC and so extremely low cost. In spite of >£9000 incremental cost difference per patient, the final ICER is close to the £30,000 willingness to pay threshold because of the very substantial survival improvement. A 50% increase in median survival compared with the placebo arm, in clinical terms, represents a step-change in survival potential in this disease area. Previous important advances in median overall survival in this disease in the second-line setting, for example, that also compare active chemotherapy to placebo, have been reported to be 2.9 months (for docetaxel versus BSC (7.5 months vs 4.6 months; Shepherd 2000)) and 2 months ((erlotinib compared with BSC (6.7 months vs 4.7 months; Shepherd 2005)).

7.3.3 Subgroup analysis

7.3.3.1 What were the results of the subgroup analysis/analyses if conducted?

Results for the adenocarcinoma population are presented in Tables 39-41 below. The results are based on capping at a maximum of 18 cycles, a per vial costing based on the BSA distribution in the JMEN trial. Second-line costs are included. The time horizon is 6 years, discounting and half cycle corrections are applied to outcomes. An exponential hazard function is the basis for the extrapolation. All inputs used in the adenocarcinoma basecase are reported in Appendix 11.

In addition, the extrapolation methodology is exponential hazard, the time horizon is six years and all chemotherapy costs are calculated on a per vial basis where relevant.

Table 39. Costs associated with different therapy options – adenocarcinoma

Costs	Pemetrexed	Placebo	Incremental
Maintenance chemotherapy acquisition & administration	£10,446	£305	£10,141
Second line chemotherapy	£3,679	£4,654	-£975
BSC (active chemo)	£71	£109	-£37
BSC no chemo)	£1,481	£1,072	£409
Terminal care	£2,429	£2,432	-£3
Adverse events	£22	£1	£21
TOTAL COST	**£18,129**	**£8,574**	**£9,554**

Costs are based on the per cycle costs (acquisition cost of chemotherapy and administration) multiplied by the number of cycles of treatment received, plus costs for treating AEs and one-off costs (i.e. terminal care).

Health outcomes

LYGs and QALYs gained

The health benefits associated with pemetrexed are reported below.

Table 40. Health outcomes – adenocarcinoma

Mean benefits	Pemetrexed	Placebo	Incremental difference
Quality Adjusted Life Years (QALYs)	1.0344	0.7917	0.2427
Life Years Gained (LYG)	1.87 (20.4mo)	1.45 (17.4mo)	0.42 (5.04mo)

Incremental Cost-Effectiveness Ratio

Table 41. Cost per additional QALY and life year gained – adenocarcinoma

	ICER	Incr.cost per LYG
Pemetrexed vs placebo	£39,364	£22,788

This final ICER of £39,364 again reflects the impact of a large cost increment as a result of comparing an active chemotherapy in a novel treatment paradigm to placebo/low cost BSC. The adenocarcinoma population reports a higher ICER than the non-squamous population, even though it had a better median OS increment, than non-squamous, for two reasons. The first is that the estimated mean OS increment is slightly lower for adenocarcinoma than non-squamous taken over the six year time horizon due to a different shaped survival curve. The second is the clinical trial cycle administration data for adenocarcinoma is even more highly right-skewed than for the non-squamous giving a higher mean number of cycles than in the non-squamous population, which contributes to this higher ICER result.

The importance of a clinically significant incremental advance in survival in both the licensed non-squamous population and the adenocarcinoma sub-group is muted because of an extremely low cost comparator. However, according to the End of Life criteria, applying appropriate QALY weights both the non-squamous and the adenocarcinoma population would come under the NICE willingness-to-pay threshold of £30,000 per incremental cost per QALY.

7.3.4 Sensitivity analyses

7.3.4.1 What were the main findings of the sensitivity analyses?

The results of the range of sensitivity analyses undertaken suggest that the model is stable and that the key drivers for the ICER result are OS, pemetrexed cost and, to a lesser extent utility.

We explore first the effect of using a different extrapolation function, presenting the results based on the Weibull hazard function. We then present a range of one-way sensitivity analyses considering key variables.

Table 42. Results from the economic evaluation using the Weibull hazard extrapolation

	Non-squamous			Adenocarcinoma		
	Pemetrexed	Placebo	Increment	Pemetrexed	Placebo	Increment
Costs						
TOTAL COST	£17,352	£8,260	£9,092	£18,034	£8,534	£9,500
Health effects						
Life Years (LY)	1.61	1.21	0.40	1.70	1.39	0.31
Quality Adjusted Life Years (QALYs)	0.9223	0.6724	0.2499	0.9794	0.7581	0.2213
Cost-effectiveness						
Incremental cost per QALY gained			£36,386			£42,922
Incremental cost per LYG			£22,526			£30,629

Scenario Analysis

Table 43. Results from the economic evaluation using the Weibull hazard extrapolation

Population	Non-squamous			Adenocarcinoma		
	Incr. benefit (QALY)	Incr. cost £	ICER =	Incr. benefit (QALY)	Incr. cost	ICER =
Scenario 1 (exponential distribution):	0.2847	£13,379	£46,992	0.2584	£14,307	£55,369
Mean number of cycles as per JMEN (8 cycles for non-squamous pop and 8.6 cycles for adeno pop)						
BSA = 1.82 m^2						
Per vial costing						
AE disutility applied to PEM						
Scenario 1 (Weibull distribution):	0.2637	£13,334	£50,564	0.2369	£14,253	£60,158
Mean number of cycles as per JMEN (8 cycles)						
BSA = 1.82 m^2						
Per vial costing						
AE disutility applied to PEM						
Scenario 2 (exponential distribution):	0.2966	£6,813	£22,972	0.2671	£7,098	£26,577
Cycles capped at 10 (equivalent to mean of 4.61 cycles for non-Squamous pop. And 4.86 cycles for Adeno pop)						
BSA = 1.8m^2						
Per mg costing						
Pain benefit in second-line (Doyle)						
No AE disutility applied to PEM						

Population	Non-squamous			Adenocarcinoma		
	Incr. benefit (QALY)	Incr. cost £	ICER =	Incr. benefit (QALY)	Incr. cost	ICER =
Scenario 2 (Weibull distribution): Cycles capped at 10 (equivalent to mean of 4.61 cycles for non-Squamous pop. And 4.86 cycles for Adeno pop) BSA = $1.8m^2$ Per mg costing Pain benefit in second-line (Doyle)	0.2756	£6,767	£24,558	0.2457	£7,044	£28,670
Scenario 3*: Mean number of cycles as per JMEN (8 cycles for non-squamous pop and 8.6 cycles for adeno pop) BSA = 1.82 m^2 Per vial costing Efficacy (lower 95%CI for Pem & upper 95%CI for BSC) AE disutility applied to PEM	0.0963	£12,970	£134,666	0.0085	£13,722	Dominated
Scenario 4* Cycles capped at 10 (equivalent to mean of 4.61 cycles for non-Squamous pop. And 4.86 cycles for Adeno pop) BSA = $1.8m^2$ Per mg costing Pain benefit in second-line (Doyle) Efficacy (upper 95%CI for Pem & lower 95%CI for BSC) No AE disutility applied to PEM	0.4876	£7,227	£14,823	0.5814	£7,616	£13,100

Table 44. Results from the economic evaluation using the Weibull hazard extrapolation

Population	Non-squamous			Adenocarcinoma		
	Incr. benefit (QALY)	Incr. cost £	ICER	Incr. benefit (QALY)	Incr. cost (£)	ICER
Scenario 1 (exponential distribution): Mean number of cycles as per JMEN (8 cycles for non-squamous pop and 8.6 cycles for adeno pop) BSA = 1.82 m^2 Per vial costing AE disutility applied to PEM	0.2847	£13,379	£46,992	0.2584	£14,307	£55,369
Scenario 1 (Weibull distribution): Mean number of cycles as per JMEN (8 cycles) BSA = 1.82 m^2 Per vial costing AE disutility applied to PEM	0.2637	£13,334	£50,564	0.2369	£14,253	£60,158
Scenario 2 (exponential distribution): Cycles capped at 10 (equivalent to mean of 4.61 cycles for non-Squamous pop. And 4.86 cycles for Adeno pop) BSA = 1.8m^2 Per mg costing Pain benefit in second-line (Doyle) No AE disutility applied to PEM	0.2966	£6,813	£22,972	0.2671	£7,098	£26,577
Scenario 2 (Weibull distribution): Cycles capped at 10 (equivalent to mean of 4.61 cycles for non-Squamous pop. And 4.86 cycles for Adeno pop) BSA = 1.8m^2 Per mg costing Pain benefit in second-line (Doyle)	0.2756	£6,767	£24,558	0.2457	£7,044	£28,670

Population	Non-squamous			Adenocarcinoma		
	Incr. benefit (QALY)	Incr. cost (£)	ICER	Incr. benefit (QALY)	Incr. cost (£)	ICER
Scenario 3*:	0.0963	£12,970	£134,666	0.0085	£13,722	Dominated
Mean number of cycles as per JMEN (8 cycles for non-squamous pop and 8.6 cycles for adeno pop)						
BSA = 1.82 m^2						
Per vial costing						
Efficacy (lower 95%CI for Pem & upper 95%CI for BSC)						
AE disutility applied to PEM						
Scenario 4*	0.4876	£7,227	£14,823	0.5814	£7,616	£13,100
Cycles capped at 10 (equivalent to mean of 4.61 cycles for non-Squamous pop. And 4.86 cycles for Adeno pop)						
BSA = 1.8m^2						
Per mg costing						
Pain benefit in second-line (Doyle)						
Efficacy (upper 95%CI for Pem & lower 95%CI for BSC)						
No AE disutility applied to PEM						

*Parameterised distributions not applicable to analyses of OS.

One-way sensitivity analysis

Table 45. One-way sensitivity analysis for the non-squamous and adenocarcinoma population

Population	Non-squamous			Adenocarcinoma		
	Incr. benefit (QALY)	Incr. cost (£)	ICER (£)	Incr. benefit (QALY)	Incr. cost (£)	ICER (£)
Base case	0.2709	**£9,137**	**£33,732**	**0.2427**	**£9,554**	**£39,364**
Costs						
Pemetrexed chemotherapy costs reduced by 10%	0.2709	£8,256	£30,477	0.2427	£8,624	£35,532
Per mg costing (based on 1.79m^2)	0.2709	£8,684	£32,059	0.2427	£9,076	£37,395
Per mg cost (based on 1.82m^2)	0.2709	£8,824	£32,577	0.2427	£9,224	£38,004
Patient population						
per vial costings:						
Mean body surface area (BSA) of 1.82m^2	0.2709	£9,665	£35,681	0.2427	£10,111	£41,658
BSA of 1.79m^2	0.2709	£8,731	£32,232	0.2427	£9,126	£37,598
BSA of 1.7m^2	0.2709	£8,731	£32,232	0.2427	£9,126	£37,598
BSA of 2.0m^2	0.2709	£9,665	£35,681	0.2427	£10,111	£41,658
per mg costings:						
BSA of 1.7m^2	0.2709	£8,264	£30,507	0.2427	£8,633	£35,568
BSA of 2.0m^2	0.2709	£9,665	£35,681	0.2427	£10,111	£41,658
Limit BSA so that no one receives>2 large vials (per vial) using trial BSA distribution data	0.2709	£8,980	£33,152	0.2427	£9,389	£38,681

All DH HRG procurement and delivery costs applied (pem = £1,829; erl = £1,829; doc = £1,670)	0.2709	£9,554	£35,270	0.2427	£9,395	£38,707
Flat BSC cost applied to all arms of £3451	0.2709	£8,787	£32,440	0.2427	£9,283	£38,245
No BSC applied (terminal cost applied)	0.2709	£8,788	£32,444	0.2427	£9,284	£38,250
No terminal or BSC costs applied	0.2709	£8,792	£32,457	0.2427	£9,287	£38,264
Same cost of BSC during active chemo as not during active chemo (ie, £66.36 for all pts at every cycle)	0.2709	£9,303	£34,344	0.2427	£9,721	£40,052
No second line chemo (set to 0% on front sheet)	0.2745	£10,059	£36,650	0.2546	£10,525	£41,343
Cycles						
Costs based on median number of cycles (6.00 for non-squamous; 6.00 for adenocarcinoma) PEM ARM ONIY	0.2720	£9,398	£34,556	0.2416	£9,294	£38,461
Median cycles pem and placebo arms (non-squam 6.00 & 3.00; adeno 6&3)	0.2760	£9,397	£34,052	0.2450	£9,293	£37,923
Cost based on all cycles reported in the JMEN trial (non-squam 8.00 pemetrexed,. 4.5 placebo; adeno=8.6 placebo 4.6)	0.2855	£12,656	£44,333	0.2592	£13,529	£52,195
Capping at 2 standard deviations (non-squam equivalent to a maximum of 25 cycles, mean of 6.44; adeno equivalent to max 27 cycles and mean of 6.8)	0.2749	£10,115	£36,789	0.2470	£10,597	£42,895
Capping at 10 cycles (equivalent to a mean of non-squam 4.61; adeno 4.86 cycles)	0.2626	£7,133	£27,168	0.2339	£7,437	£31,789
Reduce incremental OS advantage by 9.5% to correspond to the 9.5% of patients excluded with the basecase capping rule	0.1854	£8,952	£48,290	0.1513	£9,356	£61,849
Resource use						
Additional CT scan (at £92) code TRADGYOP every other cycle	0.2709	£9,406	£34,723	0.2427	£9,554	£39,364
Increase AE costs by 10%	0.2709	£9,140	£33,742	0.2427	£9,556	£39,372
Decrease AE costs by 10%	0.2709	£9,134	£33,721	0.2427	£9,552	£39,355

Utility						
Remove utility advantage attached to second line chemotherapy (everything post pgn gets equivalent of 0.53 applied)	0.2658	£9,137	£34,373	0.2379	£9,554	£40,169
Apply disutilities associated adverse events	0.2703	£9,137	£33,801	0.2445	£9,554	£39,069
Pain apply increment equivalent to Doyle's estimate (0.069 – make the utility for pem in 1st year 0.599)	0.3007	£9,137	£30,389	0.2714	£9,554	£35,201
Efficacy						
Lower pemetrexed and upper placebo values from 95%CI range (based on median trial values). Incremental difference 1.15 months non-squamous; -1.25 months adenocarcinoma *(no distribution attached to these values)*	0.0825	£8,728	£105,826	-0.007	£8,970	-£1,248,535
Upper pemetrexed and lower placebo values from 95%CI range (based on median trial values). Incremental difference 9.99 months non-squamous; 10.58 months adenocarcinoma *(no distribution attached to these values)*	0.4619	£9,552	£20,680	0.5570	£10,072	£10,072
Structural						
Discounting at 0%	0.2957	£9,191	£31,085	0.2663	£9,603	£36,063
Discounting at 6%	0.2554	£9,104	£35,641	0.2284	£9,524	£41,706
Time Horizon of 3 years	0.1946	£8,972	£46,111	0.1757	£9,381	£53,393
Time Horizon of 4 years	0.2319	£9,052	£39,043	0.2069	£9,464	£45,754
Time Horizon of 5 years	0.2559	£9,105	£35,578	0.2282	£9,519	£41,706
Half cycle correction to outcomes turned off	0.2617	£9,117	£34,834	0.2459	£9,550	£38,839

It should be noted that the OS efficacy analyses were based on trial data (95%CI), therefore only cover the duration of the trial, i.e., they are not extrapolated, there is therefore no parameterisation applied to these OS values.

The results of this one-way sensitivity analysis suggest that this model is stable and robust. For the non-squamous population the majority of ICERs fall in the range £32,000-£35,000. ICERs outside of this range are the result of taking a 3 year time horizon (£46,111), reducing the OS survival increment by 9.5% (£48,290) and using all cycles reported in the JMEN trial (£44,333). None of the analyses results in pemetrexed being dominated by placebo, none of the non-squamous results are over £50,000.

7.3.4.2 What are the key drivers of the cost effectiveness results?

Key drivers of the cost-effectiveness results are pemetrexed cost (number of treatment cycles) and to a lesser extent utility.

7.3.5 Interpretation of economic evidence

7.3.5.1 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?

This is the first economic model of a chemotherapy in the maintenance phase, as such it differs from the literature. However, the comparison of an active chemotherapy to placebo/BSC is not unusual in the second-line setting or in older first-line studies. However, because of the differences in indication it is not appropriate to make direct comparisons.

It is also difficult to compare the results of pemetrexed in the maintenance phase with older chemotherapies as the survival gain, a 35% increase in mean overall survival compared with the placebo arm, ie, compared with the current standard of practice. In this difficult to treat disease area this size of survival improvement is unusual.

The structure of the model is straightforward and has been considered in the assessment of NSCLC HTAs before (PBAC 1st line, NICE 1st line).

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

The economic evaluation is relevant to all groups of patients who could potentially use the technology. The licensed population is that in the scope for this submission, as such the results are applicable to all relevant patient groups.

7.3.5.3 What are the main strengths and weaknesses of the evaluation? How might these affect the interpretation of the results?

The simplicity of this model is both its strength and its weakness. It is transparent and easy to follow and it reflects actual trial data as closely as possible. All relevant inputs are easily viewed and assessable.

A range of different extrapolation methods were used to estimate the mean overall survival all of which produced very similar results in the range of 5.18 to 5.33 months, reinforcing the robustness of the model. The consistency seen between the JMEN clinical trial data and the model extrapolation is a reflection of the clinical study design, an international, large and well conducted clinical trial. This in combination with the various extrapolation methods derived from patient-level survival data from JMEN determine the validity of the trial, the model and the assumptions used to draw the results.

A weakness if that PFS is not perhaps realised as accurately as it could be, however, the focus on assessing effectiveness rather than drug efficacy suggests that focusing on OS is probably the better approach.

There is a slight inconsistency in the application of terminal costs. The basis for the estimates of the cost of terminal care and BSC is based on the NICE Palliative guide, adjusted to reflect that most patients receive more care in the last three months of life (75%) with the remaining costs spread on the 9 months before that. However, in this model this terminal care cost is

applied to only the final cycle. A decision made for simplicity of modelling. The effect is likely to be minimal.

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

Ideally, the model would have been developed to be able to accommodate a PSA, with the benefits of being able to see the results that a PSA provides.

Relevance of this submission to the End of Life criteria (supplementary advice issued to the Appraisal Committee on 2nd of January) – information on QALYs

Section 6.4 of the Clinical Section provides evidence with regards to the four criteria required for appraisal of "end of life" treatments in order for the supplementary advice to be applied. The NICE update report of the application of the "end of life" supplementary advice (July 2009) stipulates that if the four criteria are met, the Appraisal Committee will also consider the following:

- The impact of giving a greater weight to QALYs achieved in the later stages of terminal diseases, using the assumption that the extended survival period is experienced at the full quality of life anticipated for a healthy individual of the same age
- The magnitude of the additional weight that would need to be assigned to the QALY benefits in this patient group for the cost effectiveness of the technology to fall within the current threshold range

Table 45 below shows the QALY weightings that would be applicable in the case of pemetrexed for the maintenance treatment of NSCLC based on the economic results provided by Lilly.

In order to calculate the maximum utility value that could be achieved during the extended survival period, a value of 0.8 has been considered (Kind, 1999). This is based on the weighted health state index for a healthy individual in the 55-64 age range. The median age at randomisation for the non-squamous population was 60.6 years for pemetrexed (60.2 for placebo) and 59.9 years for the adenocarcinoma population (58.5 for placebo). Therefore the same mean utility value has been applied to both population groups.

The QALY weights obtained for the basecase non-squamous population (exponential hazard) based on the original utility values provided by Lilly in this submission are 1.12 and 1.69 for a cost-effectiveness threshold of £30,000 and £20,000 per QALY respectively. The maximum utility value obtained by assuming patients extended survival period is achieved at full health (i.e. same value as a healthy individual in the same age range) was 0.352. When this value was applied to the basecase, the QALY obtained was 0.87 and 1.29 for a £30,000 and £20,000 cost per QALY threshold respectively.

Additional criteria within the "end-of-life" supplementary advice are:

- The estimates of the extension of life are robust and can be shown or reasonably inferred from either progression free survival or overall survival (taking account of trials in which cross-over has occurred and been accounted for in the effectiveness review)
- The assumptions used in the reference case economic modelling are plausible, objective and robust

As mentioned in Section 7.2.7., the economic model uses overall survival as the main efficacy measure. Tables 46 and 47 below show the incremental overall survival obtained from the JMEN trial and from the economic modelling. A number of different methods and parametric distributions were used to assess the survival curve with the best fit (as per "*Model Development Section*"). We present below the incremental survival gain from the economic model with exponential and Weibull distributions. The data presented below prove the consistency and robustness of the overall survival obtained with pemetrexed in the

maintenance setting, reported in JMEN to be 5.2 months. The median overall survival for patients in the placebo arm of JMEN was 10.3, therefore, pemetrexed represents a 50.5% in OS increase. Maintenance treatment is a relatively new concept in the management of patients with NSCLC, with current standard of care in the NHS being “watch and wait”. Therefore, pemetrexed in this setting provides a step change in the treatment options for patients suffering from this condition.

The assumptions used in the reference case of the economic model have been reported fully in Table 23 above. The assumptions used are consistent with the decision problem, the Guide to the Methods of Technology appraisals (June, 2008), UK data for relevant inputs being therefore representative of the UK clinical practice of patients with NSCLC following induction treatment.

Tables46 and 47 below demonstrate that the overall survival outputs from the model are consistent with the median values from the JMEN trial. A range of different extrapolation methods were used to estimate the mean overall survival all of which produced very similar results in the range of 5.18 to 5.33 months, reinforcing the robustness of the model. The consistency seen between the JMEN clinical trial data and the model extrapolation is a reflection of the clinical study design, an international, large and well conducted clinical trial. This in combination with the various extrapolation methods derived from patient-level survival data from JMEN (reported in the “Model Development Section”) determine the validity of the trial, the model and the assumptions used to draw the results.

Based on the economic evaluation submitted by Lilly, pemetrexed in the maintenance phase meets the criteria for End of Life appraisal. From previous appraisals described in the End of Life Supplementary Advice report, July 2009, the QALY weights estimated by Lilly appear to be within the acceptable range.

Table 46. QALY weightings for End of Life supplementary advice

Scenario	Incremental Costs	Incremental LYG	Incremental QALYs (Original)	ICER (Original)	Incremental QALYs (maximum)	ICER (maximum QALY)	Threshold (Original QALY)		Threshold (Maximum QALY)	
							£20,000	£30,000	£20,000	£30,000
Non-squamous population										
Exponential hazard (basecase)	9,137	0.44	0.2709	33,732	0.352	25,957	1.69	1.12	1.29	0.87
Weibull hazard (sensitivity)	9,092	0.40	0.2499	36,386	0.320	28,413	1.82	1.21	1.42	0.95
Adenocarcinoma population (subgroup)										
Exponential hazard (basecase)	9,554	0.42	0.2427	39,364	0.336	28,435	1.97	1.31	1.42	0.95
Weibull harzard (sensitivity)	9,500	0.31	0.2213	42,922	0.248	38,306	2.15	1.43	1.92	1.28

Table 47. Estimates of the life extension (basecase - exponential)

Variable	Non-squamous population			Adenocarcinoma Population		
	Pemetrexed	Placebo	Difference	Pemetrexed	Placebo	Difference
Overall Survival (months)						
JMEN trial data (Median)	15.47	10.28	5.19	16.83	11.53	5.29
Model – JMEN trial duration (mean)	17.21	13.55	3.66	18.08	14.84	3.24
Model – exponential trial duration (mean)	17.69	13.76	3.90	18.53	14.96	3.57
Model – exponential 6 years (mean)	20.78	15.60	5.18	22.16	17.42	4.75
Model – JMEN trial + exponential up to 6 years (mean)	20.80	15.53	5.27	22.94	18.10	4.84
Model – JMEN trial + exponential hazard up to 6 years (mean)	20.46	15.12	5.33	22.44	17.41	5.03

Table 48. Estimates of the life extension (sensitivity – Weibull)

Variable	Non-squamous population			Adenocarcinoma Population		
	Pemetrexed	Placebo	Difference	Pemetrexed	Placebo	Difference
Overall Survival (months)						
JMEN trial data (Median)	15.47	10.28	5.19	16.83	11.53	5.29
Model – JMEN trial duration (mean)	17.21	13.55	3.66	18.08	14.84	3.24
Model – Weibull trial duration (mean)	17.61	12.53	5.08	18.60	15.42	3.19
Model – Weibull 6 years (mean)	19.21	12.96	6.25	20.30	16.45	3.85
Model – JMEN trial + Weibull up to 6 years (mean)	18.91	14.14	4.77	20.64	16.69	3.95
Model – JMEN trial + Weibull hazard up to 6 years (mean)	19.35	14.51	4.84	20.44	16.71	3.72

8 Assessment of factors relevant to the NHS and other parties

The purpose of this section is to provide an analysis of any factors relevant to the NHS and other parties that may fall outside the remit of the assessments of clinical effectiveness and cost effectiveness. This will facilitate the subsequent evaluation of the budget impact analysis. Such factors might include issues relating to service organisation and provision, resource allocation and equity, societal or ethical issues, plus any impact on patients or carers.

8.1 What is the estimated annual budget impact for the NHS in England and Wales?

The typical treatment pathway followed by a patient with NSCLC was to receive first-line treatment followed by a period of 'watch and wait'. After this period a proportion of patients would receive second-line chemotherapy. The introduction of pemetrexed as a maintenance treatment may replace this 'watch and wait' period and thus represents a new treatment paradigm which is likely to have downstream consequences in terms of subsequent lines of treatment.

We have assumed a relatively modest market share in the first year as the new treatment paradigm becomes established. The estimated annual budget impact in the first 5 years following licensing for the NHS (England and Wales) ranges from £774,783 in 2010 to £7,587,527 in 2014. The estimated budget impact is shown in Table 50.

Table 49. Annual budget impact for pemetrexed in England and Wales in the first five years post-launch

	2010	2011	2012	2013	2014
No. eligible patients	2165	1719	1273	1197	1121
Cost without pemetrexed for maintenance therapy	£8,746,610	£6,944,768	£5,142,926	£4,835,886	£4,528,845
Market share of patients	4%	21%	41%	71%	76%
No. pemetrexed patients	87	361	522	850	852
Cost with pemetrexed	£9,521,393	£10,159,671	£9,791,622	£12,405,601	£12,116,372
Net Budget Impact	**£774,783**	**£3,214,903**	**£4,648,696**	**£7,569,716**	**£7,587,527**

Note: Small discrepancies in values are due to rounding, calculations were performed in excel

8.2 What number of patients were assumed to be eligible? How was this figure derived?

The estimate for the number of new incidences of lung cancer population in 2010 is taken from Cancer Research UK which reports 33,450 new cases in 2006 for England and Wales. As the incidence of lung cancer appears relatively stable over the 5 years to 2006 (Cancer Research UK) it has been assumed that the incidence of new lung cancers will continue to be stable from 2010 – 2014.

Patients are only eligible for maintenance treatment with pemetrexed if they satisfy each of the following six criteria 1) the lung cancer is non-small cell 2) the cancer is at stage IIIB/IV 3) the histology of the cancer is non-squamous 4) the patients have been considered eligible for and received first line chemotherapy 5) the patient has not progressed during four cycles of first line therapy and is therefore likely to be of good performance status (PS 0/1), and 6) the patient has not received pemetrexed as first line chemotherapy.

Figure 16 shows the steps taken to estimate the number of patients eligible to receive pemetrexed as maintenance therapy. For each step the information source and underlying assumptions are described below.

Non small cell lung cancer

Approximately 80% of lung cancers are non-small cell (Janssen-Heijnen 2001, NICE 2005).

Stage IIIB/IV

Of the non small cell lung cancers, approximately 80% are identified/diagnosed at stage IIIB/IV (Report for Scottish Executive Health Department). It has been assumed that the proportions at this stage of disease are the same in England and Wales as in Scotland.

Non-Squamous Histology
Data from LUCADA (2007) estimates the proportion of lung cancers with non-squamous histology to be 65%. However, Curado et al (2007) estimates the proportion to be 55%. The impact of this difference on the budget impact has been assessed in a sensitivity analysis.

Patients who have received 1st line chemotherapy

The proportion of patients receiving first line therapy is assumed to be 23.2%. This figure was taken from an audit by LUCADA (2007 audit period). This can vary from region to region within England and Wales.

Estimate of patients who have received pemetrexed as first-line treatment therapy.

In Lilly's first-line submission for pemetrexed (December 2008), estimated patient numbers were presented in the budget impact section. These numbers were based on the 2005 incidence of total lung cancer (33,183 patients) and an estimated 25% of patients receiving first-line chemotherapy. This submission uses more recent figures and therefore the number of patients estimated to receive pemetrexed as first-line therapy has been revised and projected forward to years 2013 and 2014. This is important as patients who received pemetrexed/cisplatin in the first-line setting are not licensed to receive pemetrexed as maintenance therapy.

Patients who responded to 1st line chemotherapy

Response to 1st line chemotherapy has been defined as stable, partial response or complete response. The proportion of patients achieving this level of response has been estimated from a Lilly sponsored clinical trial in this population and has been estimated at 74% (JMDB Study Report – response in gem/cis treatment arm). This would be a maximum possible estimate since data from the literature states that response rates are between 40% and 75% (Schiller 2002; Scaliotti 2008). Based on the SATURN study 46% of patients went on to receive maintenance therapy (Cappuzzo, 2009). Therefore the estimated reported in the budget impact are based on the higher end of the range.

Figure 16: Algorithm for the identification of patients eligible for pemetrexed in the maintenance setting (2010 – 2014)

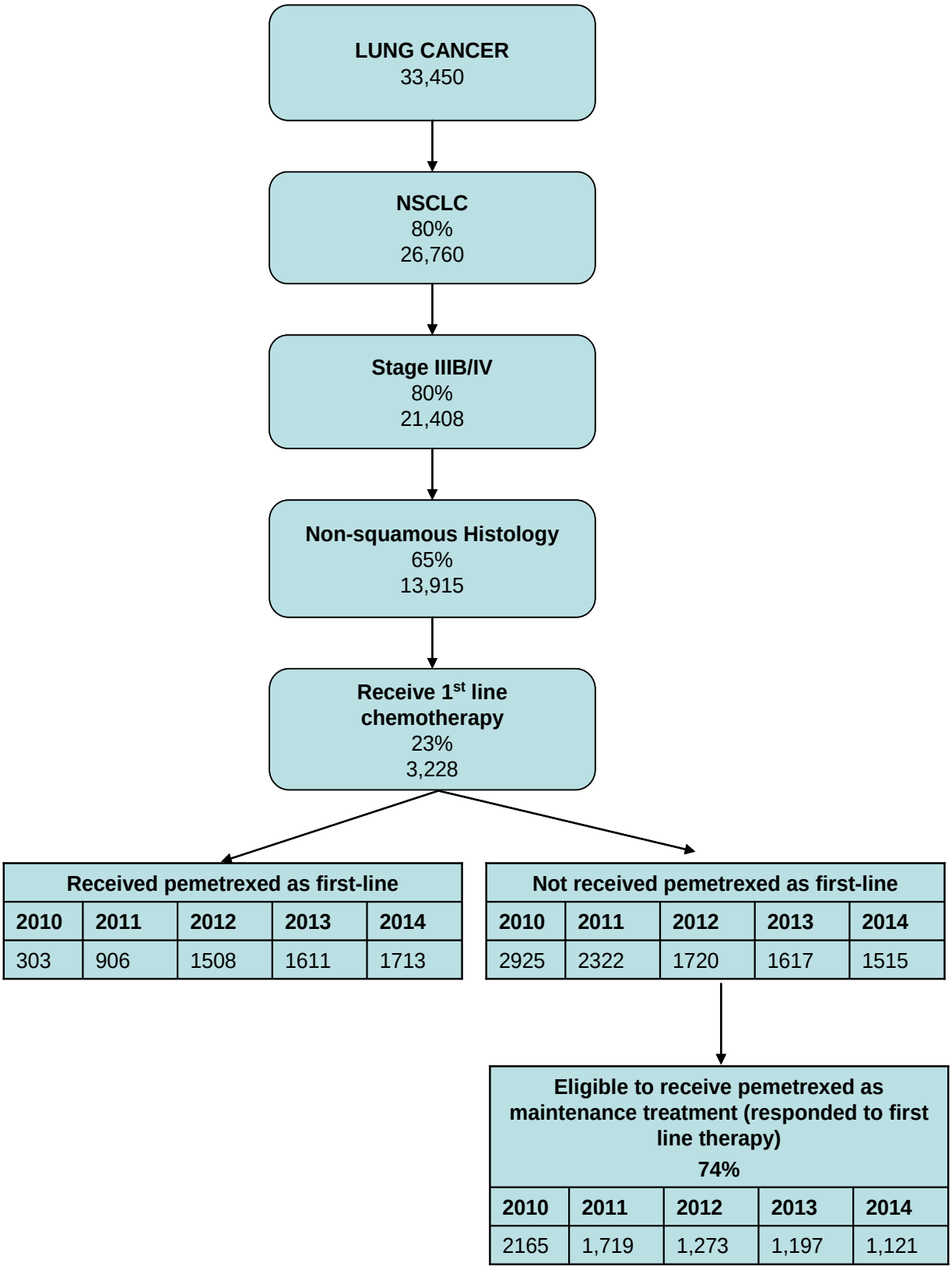


Table 50 shows the number of eligible patients for the years 2010 to 2014.

Table 50. Eligible patient population

Year	2010	2011	2012	2013	2014
Total lung cancer incidence	33,450	33,450	33,450	33,450	33,450
Number with NSCLC (80%)	26,760	26,760	26,760	26,760	26,760
No. with stage IIIB/IV (80%)	21,408	21,408	21,408	21,408	21,408
No. with non-squamous histology (65%)	13,915	13,915	13,915	13,915	13,915
Receive 1st line therapy (23%)	3,228	3,228	3,228	3,228	3,228
Patients who did not receive pemetrexed first-line	2,925	2,322	2,720	1,617	1,515
Eligible for Pemetrexed i.e. responded to 1st line therapy (74%)	2,165	1,719	1,273	1,197	1,121

The numbers of patients eligible for maintenance treatment with pemetrexed decreases over the five years as more patients receive pemetrexed in the first-line setting.

8.3 What assumption(s) were made about current treatment options and uptake of technologies?

Although the incidence of lung cancer over the last few decades has been on the decline, the incidence appears to be relatively stable from 2001 to 2006 (LUCADA 2007). Therefore, for the purposes of the budget impact analysis the assumption has been made that the yearly incidence remains the same over the period 2010 to 2014. It has been assumed that the percentage of patients receiving first-line therapy also remains stable over the five years and that the proportion responding to first-line treatment is stable.

8.4 What assumption(s) were made about market share (where relevant)?

Market share estimations have assumed the concept of maintenance therapy is fully accepted and established over a short period of time. New therapeutic options are not currently incorporated as currently none are licensed

Table 51 shows the estimated market share and patient numbers for pemetrexed as maintenance therapy.

Table 51. Market Share

Year	2010	2011	2012	2013	2014
Patients eligible for treatment with Pemetrexed	2,165	1,719	1,273	1,197	1,121
Market share	4%	21%	41%	71%	76%
No. of Pemetrexed patients	87	361	522	850	852

8.5 What unit costs were assumed? How were these calculated?

Assumptions for costs pertaining to maintenance therapy

Costs were calculated on a per vial basis (including wastage), assuming a distribution of BSA as per the trial population from JMEN and an average of 5.84 treatment cycles for

pemetrexed. BSC costs have not been incorporated, although they are included in the economic evaluation for completeness. It is difficult to establish the true budget impact for the NHS due to the multi-agency nature of BSC care and the variation in practice by physicians.

Although very few adverse events occurred in either arm of the trial, pemetrexed was associated with a higher rate than the BSC arm. Attaching costs to the adverse events resulted in an additional £7.28 per cycle cost for pemetrexed.

The cycle length and total number of cycles means that maintenance therapy and second line therapy will be completed within one year. Therefore, the budget impact analysis has assumed all costs occur within the relevant financial year.

Assumptions and costs for the 2nd line component of treatment

The introduction of pemetrexed as a maintenance treatment is likely to affect treatment practices with respect to second-line therapy. From the JMEN trial it was observed that fewer patients who received pemetrexed as maintenance therapy subsequently went on to receive second-line treatment i.e. 53.2% of pemetrexed patients received second-line therapy versus 67.3% of patients who had not received pemetrexed. Given the costs associated with second-line treatment it is important to consider these differences when estimating budget impact. It is assumed that the proportion of patients receiving second-line treatment in the UK matches that observed in the JMEN trial.

In line with the economic model the patients who received second-line treatment received either docetaxel or erlotinib. In the UK, market data shows that docetaxel and erlotinib are also favoured as second-line therapy, accounting for 64% and 24% of the market respectively. The remaining 12% is split between four other chemotherapy agents. For simplicity, we have weighted this 12% between docetaxel and erlotinib to give market shares of 73% and 27%, respectively for second-line treatment.

Patients who received active second-line line treatment are assumed to receive an average of 4.82 cycles of docetaxel or 6.27 cycles of erlotinib therapy (NICE ERG Report November 2009: TA162).

Costs for second-line treatment are calculated on a per vial or per tablet basis (including wastage) and assume patients have lost weight and therefore have a lower average BSA of $1.7m^2$ compared to first-line patients. Table 52 summarises the information presented in this section.

It is likely that the introduction of pemetrexed would have an effect on the proportion of patients receiving lines of therapy subsequent to second-line, however, as the effect is unknown it has not been considered.

Table 52. Assumptions for second-line treatment

Maintenance treatment	BSA at maintenance	No. of cycles	Receive 2nd line treatment	2nd line treatment received	No. of cycles	BSA at 2nd line
Pemetrexed	Distribution as per JMEN population (equivalent to a mean of $1.79m^2$)	5.84	53.2%	Docetaxel: 73% Erlotinib: 23%	4.82	$1.7m^2$
BSC		-	67.3%	Docetaxel: 73% Erlotinib: 23%	6.27	$1.7m^2$

Cost of administration

Costs of administration have been taken from the National schedule of reference costs 2007-08. It has been assumed that the relevant HRG code for pemetrexed is SB12Z (£153: Deliver simple parenteral chemotherapy at first attendance) and docetaxel is "SB14Z (£208: Deliver complex chemotherapy including prolonged infusional treatment at first attendance). It is assumed that the relevant HRG for Erlotinib SB11Z (£167: Deliver exclusively oral chemotherapy). Given the cycle length used in the model is 21 days the adjusted administration cost for erlotinib is £125.25.

Table 53. Chemotherapy acquisition and administration costs, based on per vial costs.

Costs	Pemetrexed	Docetaxol	Erlotinib
Chemotherapy	£1,509.58	£1,023.00	£976.47
Administration	£153.00	£208.00	£125.25
Adverse Event costs	£7.28	£0.00	£0.00
Total cost/cycle	£1,669.86	£1,176.00	£1,101.72
Mean no. of cycles	5.84	4.82	6.27
Total cost/patient	£9,751.97	£5,668.32	£6,907.80

Detailed chemotherapy treatment costs are provided in Table 54.

Table 54. Detailed chemotherapy treatment costs (MIMs July 2009)

Chemotherapy	Unit cost/(vial/pack)	Dose mg/m^2	BSA (m^2)	Cost
Pemetrexed (100mg vial)	£160	500	Distribution as per JMEN (equivalent to a mean of 1.79m^2)	£1,509.58
Pemetrexed (500mg vial)	£800	500	Distribution as per JMEN (equivalent to a mean of 1.79m^2)	
Docetaxel (20mg vial)	£162.75	75	1.7	£1,023.00
Docetaxel (80mg vial)	£534.75	75	1.7	
Erlotinib 150mg (30 tabs)*	£1,394.96	-	1.7	£976.47

*14.5% discount applied as per risk sharing scheme

Table 55 shows the total per patient costs according to the two different treatment pathways.

Table 55. Total costs associated with treatment

	Pathway	Total per patient cost
Pemetrexed	Pemetrexed followed by 53.2% of patients receiving 2nd line treatment	£12,946
BSC	BSC followed by 67.3% of patients receiving 2nd line treatment	£4,040

8.6 In addition to drug costs, consider other significant costs associated with treatment. What is the recommended treatment regime – for example, what is the typical number of visits, and does treatment involve daycase or outpatient attendance? Is there a difference between recommended and observed doses? Are there likely to be any adverse events or a need for other treatments in combination with the technology?

The budget impact analysis above accounts for the main costs observed for the treatment pathways considered.

8.7 Were there any estimates of resource savings? If so, what were they?

Fewer patients who receive pemetrexed as maintenance therapy go on to receive active 2nd line treatment than patients who receive BSC at the maintenance stage. This difference represents potential resource savings which have been accounted for above.

8.8 Are there any other opportunities for resource savings or redirection of resources that it has not been possible to quantify?

Extending the life of a patient with a terminal disease is unlikely to result in cost savings because of the extra duration of BSC required, even if less intensive BSC is required due to improved symptom control during active chemotherapy resulting in lower use of radiotherapy during active treatment.

8.9 Sensitivity analyses

Two sensitivity analyses have been conducted i.e a low case scenario and a high case scenario. Table 55 shows the results of these analyses. In the low case scenario pemetrexed is estimated to have a net budget impact in 2014 of £2,941,061. In the high case scenario the estimated net budget impact is £14,096,127.

Table 56. Summary of low and high case scenarios

Parameter	Base Case	High Case Scenario	Low Case Scenario
Proportion of patients with non-squamous histology	65%	65%	55%
No. of treatment cycles	5.84	8*	5‡
BSA (at maintenance)	BSA distribution as per JMEN (equivalent to mean BSA of 1.79m^2)	All patients have BSA of 1.9m^2	All patients have BSA of 1.7m^2
Market Share	As per table 8.4.1	Base case +25%¥	Base case -25%
Costing	Per Vial	Per Vial	Per mg
Results			
Pemetrexed cost/patient (includes 2nd line)	£12,946	£17,276	£10,475
2010 – net budget impact	£774,783	£1,429,466	£369,343
2014 – net budget impact	£7,587,527	£14,096,127	£2,941,061

* JMEN mean number of cycles, ‡ median number of cycles from JMEN, ¥ Market share is capped at 100%

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